AARP Maryland

One Park Place | Suite 475 | Annapolis, MD 21401-3475
1-866-542-8163 | Fax: 410-837-0269
aarp.org/md | md@aarp.org | twitter: @aarpmd
facebook.com/aarpmd

May 7, 2024

Maryland Prescription Drug Affordability Board
16900 Science Dr., Suite 112-114
Bowie, MD 20715

Dear PDAB Board Members:

AARP Maryland congratulates the board on moving forward with proposals to do cost reviews on prescription drugs that are widely used, very expensive, and pose extreme hardship for state residents who cannot afford them. And we support going ahead with cost reviews on all eight drugs selected if the PDAB would use as the Upper Payment Limit (UPL) for the two of those drugs that are in the initial group slated for Medicare price negotiation beginning in 2026 whatever price the federal government will pay as a result of those negotiations.

As we have noted in comments before, the approximately 850,000 AARP members in Maryland, who are 50 years old or older, have been disproportionately affected by high prices on vital Rx drugs. They need prompt assistance in affording these drugs, and the potential UPLs on key Rx drugs that are both widely used and very costly offer perhaps the best chance of furnishing this help.

With this in mind, we are concerned with some of the initial written public comments about the cost-review drugs sent to the PDAB's Stakeholder Council, on which our lead health care advocacy volunteer Jim Gutman serves as a public member. In particular, several patient-advocacy organizations that derive a substantial portion of their budgets from financial assistance made in various forms by the pharmaceutical industry are warning of problems regarding "access" to the drugs under consideration if cost reviews go ahead. In some cases, the phrasing they are using in these warnings is nearly identical to that used by pharmaceutical companies both in the past and in their most recent comments.

To be clear, there has been no evidence presented in any state pursuing cost reviews of prescription drugs that such reviews will lead to those specific drugs becoming unavailable. Indeed, there are statutes requiring pharmaceutical producers who advertise a drug in a state including via multistate television ads to continue furnishing that drug there. And contentions by pharmaceutical producers that the principal cause of affordability issues is rebates that they have to pay to middlemen in the drug-distribution process ring hollow when the industry refuses to disclose the amounts of the rebates they pay to the various entities in that process.

For those and many other reasons, AARP Maryland urges the PDAB to continue its meticulously planned development of cost-review studies that can lead to UPLs.

Sincerely,

Hank Greenberg
AARP Maryland State Director

May 10, 2024

VIA ELECTRONIC MAIL TO COMMENTS.PDAB@MARYLAND.GOV

Maryland Prescription Drug Affordability Board
16900 Science Drive, Suite 112-114
Bowie, MD 20715

Re: Comments on SKYRIZI®'s Referral to the Stakeholder Council

Dear Members of the Maryland Prescription Drug Affordability Board:

AbbVie Inc. (AbbVie or the Company) is submitting comments in response to the Maryland Prescription Drug Affordability Board's (PDAB's or the Board's) referral of AbbVie's product SKYRIZI® (risankizumab-rzaa) (SKYRIZI) to the Maryland Prescription Drug Affordability Stakeholder Council (PDASC).

As detailed further herein, given the value of SKYRIZI and its affordability to Maryland patients, AbbVie respectfully requests that SKYRIZI be removed immediately from the Board's list of drugs under consideration for cost review. We also have concerns that the Board has not adequately responded to AbbVie's requests for information pertaining to its selection of SKYRIZI and referral of the product to the PDASC. The lack of transparency regarding the Board's decision-making is contrary to the public interest, raises questions under Maryland's Administrative Procedure Act (APA) and has critically deprived AbbVie of the ability to effectively participate in the Board's selection process.

I. Background

AbbVie's mission is to discover and deliver innovative medicines and solutions that solve serious health issues today and address the medical challenges of tomorrow. We strive to have a remarkable impact on people's lives across several key therapeutic areas – immunology, oncology, neuroscience, and eye care. For nearly 20 years, AbbVie has been a leader in the field of immunology through significant investment in research and the development of new, innovative medicines and programs that meet the needs of patients, physicians, and payers.

SKYRIZI is a prescription, biologic interleukin-23 antagonist that is indicated for the treatment of: (1) moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy (approved in April 2019); (2) active psoriatic arthritis in adults (approved in January 2022); and (3) moderately to severely active Crohn's disease in adults (approved in June 2022).[1] The successful discovery, development, manufacturing, and sale of biologics like SKYRIZI is a long, expensive and uncertain process. There are unique risks and uncertainties with biologics. For example, access to and supply of necessary biological materials, such as cell lines,

[1] SKYRIZI, Full Prescribing Information, https://www.rxabbvie.com/pdf/skyrizi_pi.pdf.

may be limited and current governmental regulations restrict access to and regulate the transport and use of such materials. In addition, the development, manufacturing and sale of biologics is subject to regulations that are often more complex and extensive than the regulations applicable to other pharmaceutical products. As a result, manufacturing biologics, especially in large quantities, is often complex and may require the use of innovative technologies. Such manufacturing also requires facilities specifically designed and validated for this purpose and sophisticated quality assurance and quality control procedures. Biologics are also frequently costly to manufacture because production inputs are derived from living animal or plant material.

The U.S. Food and Drug Administration (FDA) first approved SKYRIZI (specifically, National Drug Code (NDC) 00074-2042-02) in 2019 pursuant to Biologics License Application (BLA) 761105. Since the product's initial approval, AbbVie has continued to invest substantially in research on the use of SKYRIZI to address unmet patient needs, including for rare diseases. For example, SKYRIZI has an FDA Orphan Drug Designation for the treatment of pediatric Crohn's disease (*see* Figure 1).[2] Crohn's disease is a type of inflammatory bowel disease which commonly involves the end of the small intestine and the large intestine. Children living with Crohn's disease may be affected by a delay in growth and sexual maturation, and may experience symptoms similar to those in adults including diarrhea, abdominal pain, rectal bleeding, and weight loss. AbbVie is currently sponsoring a Phase 3, multicenter study to assess the pharmacokinetics, efficacy, and safety of SKYRIZI in pediatric participants with moderately to severely active Crohn's disease.[3] The study began in December 2023, and is estimated to be completed in April 2029.

Figure 1*: *FDA Orphan Drug Designation for SKYRIZI

[2] U.S. Food and Drug Administration, Orphan Designation for Risankizumab, at https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=544716.

[3] Clinical Trials, *A Study to Assess Adverse Events, Change in Disease Activity, and How Intravenous and Subcutaneous Risankizumab Moves Through the Body of Pediatric Participants With Moderately to Severely Active Crohn's Disease*, https://clinicaltrials.gov/study/NCT05995353?term=m16-194&rank=1.

Significantly, the Board erroneously failed to include the "Orphan Drug Flag" for SKYRIZI® in the current version of its publicly available data Dashboard for the eight drugs referred to the PDASC (see Figure 2).[4]

Figure 2: FDA Excerpt of Maryland PDAB Dashboard Data for SKYRIZI

NDC11	Drug Name	Dose-Strength	Dose-Strength Unit of Measure	FDA Approval Date	Patent Expiration Date	Accelerated Approval Flag	Orphan Drug Flag	Only in Class Flag
00074-1050-01	Skyrizi	150	MG/ML	2019-04-23	.	0	0	1
00074-2042-02	Skyrizi	75	MG/0.83ML	2019-04-23	.	0	0	1
00074-2100-01	Skyrizi	150	MG/ML	2019-04-23	.	0	0	1

The Board defines the "Orphan Drug Flag" as identifying "prescription drug products listed on an FDA application that has at least one FDA Orphan Drug Designation." Per the Board's "Cost Review Eligibility and Selection Methodology" obtained by AbbVie in response to its public records request (*see* Section III, infra), this data element should "capture if a drug has any rare disease indications. Drugs can have multiple indications and only some of them may be for rare diseases. Some of these are designated but not approved indications."[5]

The Board's omission of such verifiable and publicly accessible information, coupled with other mistakes in the data set like incorrect FDA approval dates associated with two of the three SKYRIZI NDCs referred to the PDSAC[6] compounds our concerns regarding the veracity and relevance of the data and information relied upon by the Board in its selection process, which we address further in Section III.

As a threshold matter, and separate from the drug's persuasive value proposition discussed in Section II, SKYRIZI's orphan drug status provides additional support for our strong belief that SKYRIZI should be removed from the list of products the Board is considering for potential cost review.

The FDA Orphan Drug Designation is granted to drugs and biologics defined as those intended for the safe and effective treatment, diagnosis, or prevention of rare diseases or disorders that affect fewer than 200,000 people in the United States, or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment medicine.[7]

---

[4] Maryland PDAB, "Drugs Referred to the Stakeholder Council - Dashboard," at https://pdab.maryland.gov/documents/comments/drugs_referred_stakeholder_council_dashboard_2024.xlsx (last visited May 8, 2024). *See also* COMAR 14.01.04.03B(1)(d) (stating that "[t]o the extent practicable, Board staff may provide the following information for each prescription drug product in the dashboard: … (d) Whether the prescription drug product is designated by the Secretary of the FDA, under 21 U.S.C. §360bb, as a drug for a rare disease or condition").

[5] Maryland PDAB, "Cost Review Eligibility and Selection Methodology" (version provided to AbbVie on April 29, 2024).

[6] NDC 00074-2042-02 was approved pursuant to BLA761105 on April 23, 2019. NDCs 00074-1050-01 and 00074-2100-01, however, were not approved until more than two years later, on April 26, 2021, pursuant to BLA761105 S009 and S010, respectively. *See* U.S. Food and Drug Administration, Drugs@FDA: FDA-Approved Drugs Database, Biologics License Application 761105, at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=761105.

[7] 21 C.F.R. § 316.

Maryland should follow the lead of other jurisdictions that have implemented prescription drug affordability boards that generally do not select rare disease therapies for cost assessment. As such states recognize, and in addition to the variables that can complicate bringing a biologic product to market, as discussed above, the small number of patients in rare disease populations can create unique challenges for drug development and present different market considerations compared to other therapies, among other pertinent considerations. Relatedly, the currently marketed presentations of SKYRIZI are "Only in Class" and have no therapeutic equivalents identified in FDA's Orange Book. SKYRIZI has both unique clinical and economic value. It is not a suitable candidate for cost review by the Board.

II. SKYRIZI is a Valuable and Affordable Treatment Option for Maryland Patients

At AbbVie, we are driven by the potential for innovative medicines to have a remarkable impact on patients. We also recognize that innovative treatments can only make a difference if patients can get the medicines that they and their providers choose. Innovation, pricing, and access must work in harmony, which is why we are committed to ensuring that patients who need our medicines can access them. Our approach to pricing aims to drive broad and rapid access to our medicines, while addressing the world's toughest health challenges, and we price our medicines to reflect the value they bring to patients and their families, the health system and to society.[8] We also consider the affordability and accessibility of our medicines for a diverse set of stakeholders, including patients, providers, governments and other payers, as well as the long-term sustainability of our innovation and societal impact.

To these ends, we urge the Board to view the value of SKYRIZI with a patient-centric lens. As detailed herein, SKYRIZI is an effective treatment option that fulfills an unmet need for patients with autoimmune conditions. Notably, utilization of SKYRIZI relevant to the Board's selection process – *i.e.*, by "a unit of State or local government, health benefit plan, or Maryland Medical Assistance Program"[9] – is quite low relative to commercial utilization of the product. Conflating the metrics for these different payor and reimbursement environments is not appropriate for a variety of reasons addressed herein.

Additionally, because SKYRIZI is affordable to patients, as well as the broader healthcare system generally and in Maryland specifically, selection of the drug for a cost review would not further the statutory purpose of the PDAB "to protect State residents, State and local governments, commercial health plans, health care providers, pharmacies licensed in the State, and other stakeholders within the health care system from the high costs of prescription drug products."[10] Again, SKYRIZI should not be among the products considered for cost review.

A. SKYRIZI is an Important Treatment Option that Fulfills Unmet Patient Needs

[8] AbbVie, "Pricing and Access of Our Innovative Medicines (2003)," at https://www.abbvie.com/content/dam/abbvie-com2/pdfs/about/pricing-and-access-of-our-innovative-medicines.pdf.
[9] Md. Code Ann., Health-Gen. § 21-2C-14.
[10] Md. Code Ann., Health-Gen. § 21-2C-02(b).

SKYRIZI is a vital treatment option for patients with autoimmune conditions. For example, psoriasis is the most prevalent autoimmune disease in the United States, affecting 3% of the U.S. adult population, or approximately eight million Americans.[11] In addition to the visible signs of psoriasis (*e.g.*, raised plaques, scales on skin), the associated physical, emotional, mental, and social burden can negatively impact patients' quality of life.[12] Moreover, an estimated 30% of people with psoriasis will go on to develop psoriatic arthritis, which is characterized by painful swelling in the joints and reduced range of motion.[13]

Though advancements have been made in recent years for the treatment of these conditions, there remains significant need for the patients suffering from the diseases, the prescribers treating them, and entities budgeting for and covering the costs of therapies.

The effectiveness of psoriasis medicines – measured by levels of skin clearance – matters to patients. A lack of initial response to treatment or lack of sustained response to treatment results in 62% of treatment discontinuations within the first year.[14] In clinical trials, SKYRIZI has demonstrated not only high levels skin clearance for patients with psoriasis, but lasting clearance over time with the convenience of every twelve-week dosing. These results include patients who are historically more difficult to treat, such as patients who weigh more, patients with severe disease and/or patients who have been treated with prior psoriasis medications.[15,16] Importantly, SKYRIZI also has demonstrated significant improvements in patients' psoriasis symptoms, and quality of life and depression/anxiety.[17]

SKYRIZI also offers meaningful benefits over alternative treatment options; for example, SKYRIZI has a comparable safety profile to STELARA® (ustekinumab), another commonly used biologic plaque psoriasis therapy, and provides predictability and durability between doses, over time, and across patient types with standard dosing regimen.[18] SKYRIZI also provides durable

[11] National Psoriasis Foundation. Statistics. https://www.psoriasis.org/content/statistics.
[12] Boehncke WH, Schon MP. Psoriasis. Lancet. 2015;386(9997):983–994.
[13] Mease PJ, Gladman DD, Papp KA, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. Journal of the American Academy of Dermatology. 2013;69(5):729-735.
[14] Strober B, Zema CL, Holmes C, et al. Reasons for drug discontinuation among psoriasis patients in the Corrona Psoriasis Registry. Submitted to the 28th European Academy of Dermatology and Venerology. Oct 9-13, 2019; Madrid, Spain.
[15] SKYRIZI (risankizumab-rzaa) [package insert]. North Chicago, IL: AbbVie Inc.
[16] Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomized, placebo-controlled and ustekinumab-controlled phase 3 trials. Lancet. 2018;392(10148):650-661.
[17] Augustin M, Lambert J, Zema C, Thompson EHZ, Yang M, Wu EQ, Garcia-Horton V, Geng Z, Valdes JM, Joshi A, Gordon KB. Effect of Risankizumab on Patient-Reported Outcomes in Moderate to Severe Psoriasis: The UltIMMa-1 and UltIMMa-2 Randomized Clinical Trials. JAMA Dermatol. 2020 Dec 1;156(12):1344-1353. doi: 10.1001/jamadermatol.2020.3617. PMID: 33052382; PMCID: PMC7557488.
[18] Strober B, Eyerich K, Hong HC, et al. Long-term efficacy and safety of switching from ustekinumab to risankizumab: results from the open-label extension LIMMitless. Presented at: 28th European Academy of Dermatology and Venereology (EADV) Congress; October 9-13, 2019; Madrid, Spain.

skin clearance through six years,[19] as demonstrated in our clinical trials/long-term extensions as well as a favorable benefit-risk profile and predictable real-world treatment patterns with the lowest rates of dose escalation and switching rates.

In network meta-analyses, SKYRIZI had one of the most favorable long-term benefit-risk profiles, with the highest Psoriasis Area and Severity Index (PASI) response rate and lowest safety event rates compared with other treatments.[20] In the real-world, up to ~32% of patients with psoriasis taking any class of biologic dose escalated in the first 12 months after initiating treatment and 26% of patients treated with biologics switched to another treatment within 2 years of initiation. Both dose escalation and switching are treatment patterns that can lead to additional healthcare costs for payers.[21]

Psoriasis patients that dose escalated their biologic treatment had substantial annual mean per person psoriasis-related outpatient prescription pharmacy costs across treatments from $5,202 to $16,475. In addition, switching treatments within the first year of start was associated with a 28.2% higher mean total cost of care compared to patients who did not switch.[22] In the real-world, at the 30% threshold, the percentage of patients with dose escalation in the maintenance period was significantly lower with SKYRIZI (2.0%) compared with other biologics (adalimumab, ustekinumab, secukinumab, ixekizumab, and guselkumab; 17.9%, 10.0%, 15.7%, 18.0%, and 7.2%, respectively; $p < 0.0001$).[23] In addition, switch rates varied between specific biologics, with the lowest switch rates observed for patients treated with SKYRIZI at 8.5% followed by guselkumab at 15.7%, ustekinumab at 24.5%, ixekizumab at 25.1%, secukinumab at 30.4%, and adalimumab at 38.9%, over 24 months.[24]

SKYRIZI also is an important treatment option for patients with Crohn's disease (CD), a chronic, inflammatory bowel disease that affects nearly one in 100 Americans.[25] Specifically, SKYRIZI is the first advanced treatment to evaluate the impact of treatment on both clinical and endoscopic outcomes.[26] Head-to-head data compared to ustekinumab in patients with prior anti-TNF failure has shown superiority in terms of endoscopic remission at Week 48 (SEQUENCE trial) (31.8% for SKYRIZI and 16.2% for STELARA®). Secondary endpoints tested for

[19] Papp KA, et al. Long-term Safety and Efficacy of Risankizumab for the Treatment of Moderate-to-Severe Plaque Psoriasis: Final Analysis of Results From the LIMMitless Open-label Extension Trial For up to 6 Years of Follow-up. Poster 53833. Presented at the 2024 American Academy of Dermatology (AAD) Annual Meeting, March 8–12, 2024, San Diego, CA, USA

[20] Accessed at https://pubmed.ncbi.nlm.nih.gov/34862951/

[21] Bagel J, Glick B, Wu JJ, et al. Dose escalation and associated costs in biologic treatment of psoriasis based on real world data. J Med Econ. 2021;24(1):792-791 https://pubmed.ncbi.nlm.nih.gov/37154473/

[22] Wu JJ, Patel M, Li C, et al. Real world switch rates of biologics and associated costs in patients with psoriasis. Presented at the 2023 American Academy of Dermatology Annual Meeting; March 17-21, 2023; New Orleans, LA.

[23] Accessed at https://pubmed.ncbi.nlm.nih.gov/37025014/

[24] Accessed at https://pubmed.ncbi.nlm.nih.gov/37154473/

[25] Crohn's and Colitis Foundation, Overview of Crohn's Disease, https://www.crohnscolitisfoundation.org/patientsandcaregivers/what-is-crohns-disease/overview.

[26] SKYRIZI, Full Prescribing Information, *supra*.

superiority at Week 48 and included higher rates of clinical remission, steroid-free endoscopic remission, and steroid-free clinical remission at Week 48 for SKYRIZI.[27]

B. SKYRIZI is Affordable and Accessible to Patients and the Broader Healthcare System

AbbVie has comprehensive programs that enable patients, including those in Maryland, to access our medicines at prices they can afford. AbbVie offers patient support programs (PSPs) that set a new industry standard for patient service by focusing on a high-touch, highly personal, human health care experience delivered through a combination of personal interactions, digital solutions, and sophisticated data management. For example, eligible commercially insured patients may qualify for SKYRIZI Complete, which offers a Savings Card that reduces patient cost-sharing to as little as $5 per dose.[28] Additionally, under myAbbVie Assist, low-income patients who are uninsured, unemployed, or have recently lost insurance coverage may be eligible to receive SKYRIZI at no cost.[29]

AbbVie's understanding is that the PDAB is particularly interested in the cost of SKYRIZI for its state employee insurance plan members, who to our knowledge have coverage under a commercial plan/plans. If not otherwise restricted from doing so under your plans, your employees with commercial insurance coverage are eligible to apply for cost-sharing assistance from AbbVie according to program's terms and conditions. Specifically, each employee that received such assistance could pay as little as $5 per dose out of pocket.[30]

Further, we believe that the state of Maryland, for its employee insurance plan(s), may or has contracted with CVS Caremark under one of its PBM options; we are unaware due to the lack of records production to date whether the PDAB and Council has examined out of pocket cost for SKYRIZI per employee under said plan(s) and if not, we encourage you to do so.

Understanding our access programs and the individualized needs of patients, physicians, and payers is only one part of a large solution to the issue of access, and AbbVie is committed to working with all stakeholders to ensure patients receive the treatments they need to live their best life.

III. The Maryland PDAB Has Not Adequately Responded to AbbVie's Public Information Act Request, Adversely Impacting AbbVie's Ability to Effectively Participate in the Cost Review Process

By letter dated March 29, 2024, AbbVie submitted a public records request of the Maryland PDAB pursuant to the Maryland Public Information Act (PIA),[31] seeking all documents and information related to the PDAB's selection of SKYRIZI for potential cost review and its referral

[27] Peyrin-Biroulet L, Chapman JC, Colombel J-F, et al. Risankizumab versus ustekinumab for patients with moderate to severe Crohn's disease: Results from the phase 3b SEQUENCE study. Presented at the United European Gastroenterology Week (UEGW 2023), October 14-17, 2023. Copenhagen, Denmark, OP#LB01.
[28] SKYRIZI Complete, https://www.skyrizi.com/skyrizi-complete/save-on-skyrizi-costs./.
[29] myAbbVie Assist, https://www.abbvie.com/patients/patient-support/patient-assistance.html.
[30] SKYRIZI Complete, *supra*.
[31] Md. Code Ann., General Provisions §§ 4-101–4-601,

to the PDASC. The PDAB responded to AbbVie's PIA request on April 29, 2024 (the Board's Response), the same date as the PDASC's meeting to discuss SKYRIZI and the other seven drugs referred by the PDAB.

A. The Board's Response Does Not Provide Sufficient Information to Determine Why SKYRIZI Was Selected

As AbbVie will further discuss in a separate correspondence, our view is that the Board's Response to AbbVie's PIA request was inadequate for several reasons, including but not limited to the following:

- Many of the documents in the Board's Response are publicly available materials that do not directly relate to the Board's selection of SKYRIZI generally or for referral to the PDASC specifically. For example, the Board's Response includes copies of statutes, regulations, and materials posted on the PDAB's website (*e.g.*, public meeting agendas, comment letters).
- Although the Board's Response includes limited Board correspondence and documentation relating to its drug selection process, the materials are heavily redacted and do not provide insight on the Board's discussions involving SKYRIZI or other prescription drug products with similar spending and costs.
- The spreadsheets in the Board's Response are limited to information on SKYRIZI, and thus generally are not helpful in assessing why SKYRIZI was selected in comparison to other pharmaceutical products.

Critically, the documents in the Board's Response collectively — and in combination with publicly available information — fail to answer a key and valid question under Maryland's PDAB process —why SKYRIZI?

The product has clear and well-defined clinical and economic value to patients and payors alike supported by an extensive body of data, information, health care provider and patient accounts, and other highly relevant information, only a sample of which is referenced in this comment letter. SKYRIZI has an FDA Orphan Drug Designation. Two of the three SKYRZI NDCs identified by the Board have been on the market for less than five years. The drug is categorized as "Only in Class." The information included in the Board's Response does not provide a clear explanation regarding its selection criteria and how application of such criteria resulted in the Board's inclusion of SKYRIZI on the list of eight products for referral to the PDASC. In fact, we were actually provided with information that cuts the opposite way. For example, SKYRIZI's rank relative to other potentially eligible drugs more strongly supports *not* selecting SKYRIZI than it does to further justify or validate the Board's decision.

The intent of Maryland's PDAB law is "to protect State residents, State and local governments, commercial health plans, health care providers, pharmacies licensed in the State, and other stakeholders within the health care system from the high costs of prescription drug products."[32] If the Board does not provide meaningful information regarding how it determines

[32] Md. Code Ann., Health-Gen. § 21-2C-02(b).

whether a drug will lead to an affordability challenge, AbbVie and the broader public have no way to determine whether the Board is acting consistently with its charge. Conversely, if the requested information is not being shared because it simply does not exist, that fact in and of itself is significant and should be disclosed for the public to consider. Without more, the Board's selection of SKYRIZI and referral of the product to the PDASC seems arbitrary and sets a concerning precedent with respect to how patient access to effective and affordable therapies could be impacted by an ill-defined process.

B. Without Adequate Information to Understand the Board's Selection Criteria and Decision-Making Process, AbbVie is Deprived of an Ability to Meaningfully Engage in the Board's Selection Process

The requested records are critical to affording AbbVie a fair opportunity to engage with the PSADC and the PDAB about SKYRIZI. Indeed, the very purpose of the PDASC is to provide stakeholder input to assist the PDAB in its decision-making.[33] There is a member of the PDASC who specifically represents brand name drug corporations. As the manufacturer of a drug under consideration for potential cost review, AbbVie is a relevant stakeholder that must be afforded a meaningful opportunity to have its views heard.

AbbVie has serious concerns about its ability to develop and submit informed comments that effectively address the PDAB's rationale for referring SKYRIZI to the Stakeholder Council when we do not currently have meaningful insight into the methodology, standards, criteria, data, and other information underlying the PDAB's decision to select our product. Moreover, in the absence of same, we are unable to independently verify the PDAB's assessment or offer the PDASC our alternative view of the value, benefits and patient access and affordability of SKYRIZI. What the Board has made publicly available to date does not inspire confidence. For example, the PDAB's published data on patient out-of-pocket costs for the selected drugs including SKYRIZI does not seem to include manufacturer-provided copay assistance, which as highlighted above results in many patients paying as little as $5 per dose for SKYRIZI. Rather, the data appears to only represent the patient's annual prescription drug cost sharing, which includes a deductible, copay, or coinsurance defined by the patient's health insurance plan, providing an incomplete picture of a patient's actual cost.[34] Further, our understanding is that the underlying data files are limited to only privately fully-insured and self-insured non-ERISA health insurance plans for Maryland and Non-Maryland residents and do not include any ERISA plans.[35] The fact that the Board seems to rely heavily on commercial market metrics in selecting products for potential cost review when utilization in such contexts would not, pursuant to existing law, even be covered by a upper payment limit (UPL) established for a drug is also very concerning.

[33] Maryland Prescription Drug Affordability PDAB, "Prescription Drug Affordability Stakeholder Council, 2022 Stakeholder Council Meeting," at https://pdab.maryland.gov/pdab_stakeholder_2022.html ("The purpose of the Prescription Drug Affordability Stakeholder Council is to provide stakeholder input to assist the PDAB in making decisions to protect the State, its residents, and other stakeholders in the Maryland health care system").
[34] Accessed at https://pdab.maryland.gov/cost_review_process.html
[35] *Id*.

Without the benefit of the requested documents and related other information, AbbVie is unable to understand, analyze, and independently verify the methodology and underlying data that the PDAB used to identify which drugs to refer to the PDASC. At its April 29 meeting, the PDASC discussed *the drugs referred by the PDAB*; based on such discussion and its evaluation of the public comments received, the PDASC will provide input to the PDAB that will inform the PDAB's decision whether to select a drug for cost review, a process that may ultimately result in establishment of an UPL for a reviewed drug. Accordingly, we view the records request and cost review processes as necessarily linked.

At its March 25, 2024 meeting, several PDAB members expressed concerns about the quality of available data (*e.g.*, dated claims information), raising legitimate questions regarding the veracity of the data and information the PDAB relied upon to select the eight drugs referred to the PDASC. AbbVie shares these concerns, as the PDAB's product selections may not accurately reflect the eligible drugs that pose actual affordability challenges to Maryland patients. The PDAB has only provided a limited subset of data in a public dashboard which, among other issues, lacks context and complete source information.[36] The mistakes in the Board's publicly available data Dashboard substantially validates our concerns about the quality of the information upon which the Board's decision-making relies. Additionally, the PDAB's Response to AbbVie's PIA request does not provide sufficient information for AbbVie to verify the PDAB's analysis and to understand why SKYRIZI was selected over other products that the Board ranked at a higher position. Impacted stakeholders like AbbVie are, therefore, unable to engage in the cost review process fairly and fully.

AbbVie believes that it is critically important that the PDAB provide manufacturers and other key stakeholders including patients with an opportunity to provide meaningful and informed feedback during this process, and the PDASC's input for the Board consider *all* of the stakeholders it is charged with representing. Without the criteria and underlying data that the PDAB is relying on to determine which drugs are subject to a cost review, the PDASC and PDAB will not receive the information it needs for fulsome deliberations.

IV. Conclusion

We appreciate the opportunity to highlight the value and affordability of SKYRIZI to Maryland patients and payors alike. However, as noted, we are unable to comment completely nor with the benefit of full public transparency into the Board's process to date including the inability of the PDAB to produce records. **For these reasons and many others outlined in this letter, AbbVie objects to the selection of SKYRIZI and referral of the product to the PDASC, and respectfully requests that the PDAB immediately remove SKYRIZI from the list of products under consideration for potential cost review.**

[36] *See* Maryland PDAB, "Drugs Referred to the Stakeholder Council- Dashboard," at https://pdab.maryland.gov/documents/comments/drugs_referred_stakeholder_council_dashboard_2024.xlsx.

Please contact Emily Donaldson at emily.donaldson@abbvie.com with any questions.

Sincerely,

Hayden Kennedy
Vice President, Global Policy & U.S. Access Strategies
Government Affairs
On behalf of AbbVie Inc

Council 3 AFSCME MARYLAND

1410 Bush Street, Suite A

Baltimore, MD 21230

Phone: 410-547-1515

Patrick Moran – President

Maryland Prescription Drug Affordability Board
Comments on Proposed Drugs for Cost Review
May 2024

On behalf of AFSCME Maryland, thank you for the opportunity to comment. AFSCME Maryland represents 45,000 state government, higher education, and local government workers. Many of them get their health coverage through workplace plans that will be subject to any prescription drug upper payment limits established by the Maryland Prescription Drug Affordability Board.

We view affordability of prescription drugs in two primary ways: affordability to the individual and affordability to a health plan and the health system more broadly. In many ways, affordability to the individual participating in a health plan is a product of their plan design and formulary structure. Even if, for example, an individual has a flat co-pay for preferred brand name drugs, they may need a certain branded drug that is not considered preferred by their plan. Depending on the details of their plan, they could face substantial out-of-pocket costs in such cases. Regardless, even with flat co-pays, many lower- and moderate-income individuals may face difficulty affording their drugs, particularly when they need to take multiple drugs. Affordability for uninsured individuals poses a different set of questions and challenges.

It is just as important to analyze how the net price for a particular drug contributes toward premiums for health plans. To be clear, we believe a drug can pose an affordability challenge to the state, broadly, despite presenting individuals with little to no out-of-pocket burden. Anytime pharmaceutical companies set unreasonably high prices or arbitrarily raise prices on existing therapies, plans must account for the cost impact, typically through premium increases. Some plans may also shift costs to participants through higher out-of-pocket responsibilities, either for a specific drug or for a broader set of drugs.

Overall premiums for employer-sponsored health coverage have steadily increased over the past several decades, typically outpacing both inflation and employee earnings. As a simple matter, dollars that are required to fund employer-sponsored health plans are not available for other forms of compensation, whether they be wages, retirement contributions or other benefits. Today, the average total premium for family coverage is around $24,000 per year.[1] A recent analysis in JAMA shows that over a 32-year period beginning in 1988 a typical American family lost out on over

[1] https://www.kff.org/report-section/ehbs-2023-section-1-cost-of-health-insurance/

$125,000 in wages due to increasing health care premiums.[2] Taking a narrow view of compensation (wages plus health coverage), the authors show a steady increase in the percentage of compensation taken up by health benefits over this timeframe – rising from 7.9% to 17.7%. The Bureau of Labor Statistics (BLS) measures a more complete view of compensation and shows that fully 10.8% of state and local government employee compensation now pays for health benefits.[3] Likewise, the benefits consultancy Willis Towers Watson recently released an analysis showing employer-sponsored health benefits increased from 5.9% to 12.3% of payroll between 2000 and 2020.[4] While there are a host of cost drivers for employer-sponsored coverage, there is no doubt that excessive pharmaceutical pricing has contributed mightily to this trend and suppressed wages for working families. For instance, between 2022 and 2023, of drugs with prices increases, nearly half rose faster than the rate of inflation.[5]

In the attachment, we provide tables outlining premiums for the state employee health plan for calendar year 2024.[6] The plan is somewhat unique in that enrollment and premiums are separated for medical services and prescription drugs. We acknowledge we are not privy to the underlying actuarial assumptions and methodologies used to price the various plans. Just as not all employees will choose to enroll in medical coverage for any number of reasons, not all employees will choose to enroll in both medical and prescription coverage. However, we provide them simply as context to show that prescription drugs are clearly a significant portion of the cost to the state of Maryland to provide health benefits. Further, high drug prices are borne by all, including non-users of particular high-cost drugs. For example, the share of total employee-paid premiums that goes to the prescription drug benefit ranges from 26.7% (for someone also enrolled in employee + child coverage through the United PPO) to 42.2% (for someone enrolled in employee only coverage through Kaiser).

As far as the drugs proposed to undergo a cost review, we urge the Board to weigh and consider the impact on state and local government health plans and their participating members, in line with the Board's current authority. The therapeutic class of 'antidiabetics' is consistently the highest cost for the state employee health plan by a wide margin.[7] Between Q1 FY 2020 and Q1 FY 2024, spending on antidiabetic drugs increased more than 100%, from $14.5 million to $29.3 million.[8] As of Q2 FY 2024, fully 23% of all net drug spending within the plan comes from this one class.[9] Just between Q4 FY 2023 and Q2 FY 2024, the net cost per member per month (PMPM) for antidiabetics increased from $55.95 to $62.90.[10] Therefore, in particular, we believe the

---

[2] https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2813927
[3] https://www.bls.gov/news.release/pdf/ecec.pdf
[4] https://www.wtwco.com/en-us/insights/2024/04/shifts-in-benefit-allocations-among-us-employers-2000-2020
[5] https://aspe.hhs.gov/reports/changes-list-prices-prescription-drugs
[6] https://dbm.maryland.gov/benefits/Documents/2024%20Employee%20Retiree%20Rate%20Sheets.pdf
[7] https://dlslibrary.state.md.us/publications/JCR/2023/2023_54-55_2024(3).pdf
[8] https://mgaleg.maryland.gov/pubs/budgetfiscal/2025fy-budget-docs-operating-F10A02-Department-of-Budget-and-Management---Personnel.pdf
[9] https://dlslibrary.state.md.us/publications/JCR/2023/2023_54-55_2024(3).pdf
[10] https://dlslibrary.state.md.us/publications/JCR/2023/2023_54-55(b)_2023(9)(rev).pdf

antidiabetic drugs selected by the Board (Farxiga, Jardiance, Ozempic and Trulicity) warrant further scrutiny and should be prime candidates to undergo cost reviews.
In Q4 FY 2023 (the last quarter for which data has been made public), these drugs were all in the top six for total net spending among active employees[11]:

#1, Ozempic: $7.9 million.
#2, Trulicity: $2.7 million.
#3, Jardiance: $1.97 million.
#6, Farxiga: $1.0 million.

[11] https://dlslibrary.state.md.us/publications/JCR/2023/2023_54-55(b)_2023(9)(rev).pdf

2024 Monthly Premiums, Employee Paid Portion

Medical Premium - Employee Portion

	Employee Only	Employee +1	Employee + Family
CareFirst PPO	123.38	222.08	308.46
CareFirst EPO	82.34	172.82	214.10
Kaiser	82.30	172.70	213.96
United PPO	121.36	218.48	303.44
United EPO	82.84	172.30	205.44

Rx Premium - Employee Portion

	Employee Only	Employee + Child	Employee + Spouse	Employee + Family
Rx Coverage	59.98	79.72	99.56	119.98

Medical + Rx Premium - Employee Portion

	Employee Only	Employee + Child	Employee + Spouse	Employee + Family
CareFirst PPO	183.36	301.80	321.64	428.44
CareFirst EPO	142.32	252.54	272.38	334.08
Kaiser	142.28	252.42	272.26	333.94
United PPO	181.34	298.20	318.04	423.42
United EPO	142.82	252.02	271.86	325.42

Percentage of Premium Attributable to Rx

	Employee Only	Employee + Child	Employee + Spouse	Employee + Family
CareFirst PPO	32.7%	26.4%	31.0%	28.0%
CareFirst EPO	42.1%	31.6%	36.6%	35.9%
Kaiser	42.2%	31.6%	36.6%	35.9%
United PPO	33.1%	26.7%	31.3%	28.3%
United EPO	42.0%	31.6%	36.6%	36.9%

2024 Monthly Premiums, Total (Employer + Employee Contributions)

Medical Premium - Total

	Employee Only	Employee +1	Employee + Family
CareFirst PPO	616.90	1110.40	1542.30
CareFirst EPO	548.93	1152.13	1427.33
Kaiser	548.67	1151.33	1426.40
United PPO	606.80	1092.40	1517.20
United EPO	552.27	1148.67	1369.60

Rx Premium - Total

	Employee Only	Employee + Child	Employee + Spouse	Employee + Family
Rx Coverage	299.90	398.60	497.80	599.90

Medical + Rx Premium - Total

	Employee Only	Employee + Child	Employee + Spouse	Employee + Family
CareFirst PPO	916.80	1509.00	1608.20	2142.20
CareFirst EPO	848.83	1550.73	1649.93	2027.23
Kaiser	848.57	1549.93	1649.13	2026.30
United PPO	906.70	1491.00	1590.20	2117.10
United EPO	852.17	1547.27	1646.47	1969.50

Percentage of Premium Attributable to Rx

	Employee Only	Employee + Child	Employee + Spouse	Employee + Family
CareFirst PPO	32.7%	26.4%	31.0%	28.0%
CareFirst EPO	35.3%	25.7%	30.2%	29.6%
Kaiser	35.3%	25.7%	30.2%	29.6%
United PPO	33.1%	26.7%	31.3%	28.3%
United EPO	35.2%	25.8%	30.2%	30.5%

NOTE: The PPO and prescription drug plans are provided at an 80/20 premium split, with the state covering 80% of the total premium. The EPO options and the Kaiser Permanente plan are offered at an 85/15 split.

Public Comments

Maryland Prescription Drug Affordability Board

Re: Drugs Referred to the Stakeholder Council Therapeutic Alternatives

Sent Via Email comments.pdab@maryland.gov

Dear Prescription Drug Affordability Board and Staff,

Boehringer Ingelheim submits these comments in response to the Prescription Drug Affordability Board (PDAB) referring JARDIANCE ® to the Stakeholder Council. In addition, this letter includes comments on the PDAB's list of Therapeutic Alternatives for JARDIANCE®.

Founded in 1885 and independently owned ever since, Boehringer Ingelheim is a research-driven company with 53,000 employees around the world dedicated to the discovery and development of breakthrough therapies that transform lives, today and for generations to come. As a leading research-driven biopharmaceutical company, we create value through innovation in areas of high unmet medical need focused on breakthrough therapies and first in-class innovations.

Boehringer understands the scrutiny over prescription drug prices. The U.S. healthcare system is complex and often does not work for patients, especially the most vulnerable. In many cases patients face prices at the pharmacy counter that are out of reach. Policy reforms are needed that will address the root of the problem. While we understand that there is a need to find ways to concurrently reduce state budget expenditures and reduce patient out of pocket costs, we feel compelled to show our five areas of concern about using an Upper Payment Limit (UPL) as a solution.

1. A UPL Unlikely to Reduce Cost for Patients:

Simply capping the price of a prescription drug for the payor or pharmacy benefit manager (PBM) with an upper payment limit (UPL) will not directly help people at the pharmacy counter. Pharmacy counter prices are controlled by the patient's insurance plan.

Boehringer currently provides significant discounts and rebates off the list price of its medicines to insurers, pharmacy benefits managers and other parties. Unfortunately, these discounts are not always passed on to patients. As a result, patients often face high out-of-pocket costs at the pharmacy counter.

Prescription drugs subject to an UPL will likely have less ability to offer the rebates necessary to negotiate with PBMs to guarantee preferred tier access to patients. PBMs and other middlemen seek larger and larger rebates from manufacturers that rarely reach patients while claiming they are providing cost savings to their customers. Their goal is not to ensure the best patient outcome but to continue to extract rebates for formulary access. This perverse incentive means that although JARDIANCE® has proven its value to patients and health systems patients may not have access due to PBM decisions.

2. A UPL is Likely to Hurt Patient Access:

Boehringer shares your goal of ensuring patients have access to the medicines we develop. However, instituting an UPL may further restrict access for some patients. Patient access may decrease for drugs subject to an UPL because they may be placed on a less preferred tier, and this is all due to the financial incentives of the PBM and health plans. The health care system – including how payors purchase drugs – drives the misaligned incentives. Manufacturers negotiate rebates with PBMs for preferential formulary placement on tiers that provide patients with low-cost sharing. If a PBM/Payor is not satisfied with rebate negotiations, they may choose another prescription drug that is not therapeutically equivalent to the preferred drug for a given condition and put the low-rebate drug on a tier that limits patient access and is more expensive for patients or sometimes remove the drug from their formulary altogether.

3. JARDIANCE® Data Proves Its Value:

Boehringer Ingelheim's focus has always been helping to improve outcomes for adults living with a range of cardio-renal-metabolic conditions. We are confident in the value that JARDIANCE® brings to patients and the healthcare system.

JARDIANCE® is a highly utilized drug since it treats interconnected co-morbid conditions referred to as Cardio-Renal-Metabolic diseases. It is an SGLT2 inhibitor approved for type 2 diabetes and three additional indications including cardiovascular disease associated with type 2 diabetes, chronic heart failure, and chronic kidney disease (CKD).

Almost 60% of U.S. adults aged 65 years and older – more than 33.5 million Americans - have at least one cardio-renal-metabolic condition, driving significant disease burden, mortality and total overall healthcare spend.

JARDIANCE® is the number one prescribed SGLT2 inhibitor with 59 million prescriptions. Boehringer is committed to our patients and approximately 88% of JARDIANCE patients pay no more than $50 for their prescriptions due to our multiple assistance programs.

The American Rescue Plan Act removed the statutory cap on rebates resulting in some pharmaceutical manufacturers paying more than 100% in rebates on some products to Medicaid.

Peer-reviewed, published economic assessments using real-world data consistently demonstrate that JARDIANCE® lowers the total cost of care. Studies show JARDIANCE® is cost-effective in treating CKD. For commercial payers, the increased effectiveness of treating CKD with JARDIANCE® resulted in a lower cost of approximately $16,363 per patient per year for payers.[1]

Another specific example of JARDIANCE'S® value is demonstrated through Outcome Based Agreements with large health systems. For example, Boehringer entered into an Outcomes-Based Agreement with Highmark in Pennsylvania to demonstrate the value of Jardiance®. The results showed that JARDIANCE® reduced the total cost of care by 20%. Specifically, the cost of care savings was driven by a 30% reduction in the total annual medical spend for adults with type 2 diabetes and cardiovascular disease who took Jardiance compared to other anti-glycemic medications. This is just one example – there are more.

By putting a UPL in place, fewer patients will have access to JARDIANCE® due to the complexity of our healthcare system leading to higher total costs of care and patient disruption. JARDIANCE® has already proven its value by leading to better health outcomes for patients and by demonstrating overall cost savings to the healthcare system and state.

In 2015, a JARDIANCE® landmark clinical trial became one of the most significant breakthroughs in the field of diabetes care and the first ever trial for any diabetes medication to show statistically significant reduction of adverse cardiovascular outcomes in people with type 2 diabetes and established cardiovascular disease. This trial forever changed the way healthcare providers treat adults with type 2 diabetes and led to change in the professional diabetes treatment guidelines in the United States and worldwide. In 2016, FDA relied on this landmark clinical trial to approve JARDIANCE® "to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease."[2]

---

[1] National Institute of Diabetes and Digestive and Kidney Disorders. Kidney disease statistics for the United States. https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease. Updated September 2021. Accessed January 18, 2023

[2] Jardiance® (empagliflozin tablets) Prescribing Information at 1 (Dec. 2016), https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204629s008lbl.pdf.

We have continued to invest significantly in research and development that has extended the impact of JARDIANCE® to expand its use with additional patient populations. The CKD indication was the result of this continued investment.

This is a critical point because investment in drugs does not end once it is approved for one condition, research, and development (R & D) investments continue. Price control policy would negatively impact decisions to continue investing in R&D for such drugs.

4. JARDIANCE'S Focus on Health Equity:

Cardiovascular Disease is the leading cause of death in the US; and Diabetes is the eighth leading cause of death in the US. These diseases are more common among people who are members of some racial and ethnic minority groups and groups with lower socioeconomic status. [3] By enacting UPLs on drugs that treat these diseases, patients may be disadvantaged by access restrictions and changes in formulary coverage.

CKD is more common among Black and Hispanic adults, compared to White adults.[4] Additionally, health disparities in CKD are exacerbated when there is poor access to health care and health insurance. Certain racial and ethnic groups have an increased risk of type 2 diabetes and hypertension which could lead to a faster onset and progression of CKD.

Increased awareness of the importance of screening and early detection of CKD would benefit patients. In its initial stages as many as 9 in 10 adults with CKD are not aware they have the disease.[5] If left untreated CKD may progress into end-stage renal disease (ESRD) requiring dialysis or kidney transplant.[6] Those options impact quality of life and add cost to the health care system.

[3]CDC.gov. Advancing Health Equity | Diabetes | CDC; Accessed April 12, 2024.
[4] National Institute of Diabetes and Digestive and Kidney Disorders. Kidney disease statistics for the United States. https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease. Updated September 2021. Accessed January 18, 2023
[5] National Institute of Diabetes and Digestive and Kidney Disorders. Kidney disease statistics for the United States. https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease. Updated September 2021. Accessed January 18, 2023
[6] National Institute of Diabetes and Digestive and Kidney Disorders. Kidney disease statistics for the United States. https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease. Updated September 2021. Accessed January 18, 2023

5. Costs and Data Analysis Transparency

Per the state statute, the purpose of the Board is to protect state residents, state and local governments, commercial health plans, health care providers, pharmacies licensed in the state, and other stakeholders within the health care system from the high costs of prescription drugs.[7] Implementation of this misguided law in FY 2023 expended $1.4M in operational costs with another estimated $1.4M in FY 2024 for almost $3M in total costs derived from fees on manufacturers without achieving any cost savings for patients.[8] Also, these budget allocations do not include the extra costs incurred by the Maryland Health Care Commission since the law's initial inception.

These operational costs, including the data analysis to set a UPL does not solve for the stated goals of the Board, but increases the cost to manufacturers and does nothing to reduce the out-of-pocket costs for the patients or to reduce the overall healthcare costs to the state.

The lack of transparency in the data methodology calls conclusions into question since the analysis and results cannot be independently verified.

Therapeutic Alternatives

Boehringer Ingelheim submits the following statement in response to the Prescription Drug Affordability Board's request for comments for Therapeutic Alternatives for Drugs Referred to the Stakeholder Council including JARDIANCE®.

Cardiovascular Renal Metabolic (CRM) conditions are quite complex and overlapping. Many patients living with diabetes have multiple comorbidities and/or established cardiovascular (CV) risk factors.

JARDIANCE® has the following US FDA approved indications:

- To reduce the risk of CV death and hospitalization for heart failure (HF) in adults with HF
- To reduce the risk of sustained decline in eGFR, end-stage kidney disease, CV death, and hospitalization in adults with chronic kidney disease at risk of progression
- To reduce the risk of CV death in adults with type 2 diabetes mellitus and established CV disease

[7] Pena-Melnyk, D. et al., Maryland House Bill 769; 2019 Regular Session - House Bill 768 Enrolled (maryland.gov). Accessed April 12, 2024.
[8] Fiscal Digest FY 2023 (maryland.gov); Accessed April 12, 2024

- As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus

When assessing therapeutic alternatives, a drug's holistic value should be considered. In fact, JARDIANCE® recently received regulatory approval in Europe and the United States for the treatment of chronic kidney disease. Some 850 million people are estimated to suffer from this chronic disease worldwide. JARDIANCE® can now potentially help manage cardiovascular-renal-metabolic conditions of more than 1 billion people, including the most vulnerable of patients living in underserved communities.

Conclusion

Boehringer opposes government price setting programs at the federal and state level as they do not ensure lower prices for people at the pharmacy counter.

In addition, these policies can also jeopardize patient access and the ability for manufacturers to invest in future innovations.

We respectfully request you remove JARDIANCE® from further review.

Regards,

Bridget Walsh
VP, Government Affairs and Public Policy
Boehringer Ingelheim Pharmaceuticals, Inc.

COMMUNITY ACCESS NATIONAL NETWORK

Mailing Address:

Attn: Jen Laws
PO Box 3009
Slidell, LA 70459

Chief Executive Officer:

Jen Laws
Phone: (313) 333-8534
Fax: (646) 786-3825
Email: jen@tiicann.org

May 10, 2024
Maryland Prescription Drug Affordability Stakeholder Council
6900 Science Drive, Suite 112-114
Bowie, MD 20715

Dear Members of the Maryland Prescription Drug Affordability Stakeholder Council,

About CANN: The Community Access National Network (CANN) is a 501(c)(3) national nonprofit organization focusing on public policy issues relating to HIV/AIDS and viral hepatitis. CANN's mission is to define, promote, and improve access to healthcare services and supports for people living with HIV/AIDS and/or viral hepatitis through advocacy, education, and networking.

On behalf of the patients CANN serves across the nation and, in particular, Marylanders living with HIV, we write today with great concern regarding the selection of medications for "affordability review", particularly Biktarvy – an antiretroviral (ARV) medication utilized for both the treatment and prevention of HIV.

ARVs Are Not Interchangeable

Due to the nature of HIV, antiretroviral medications are not interchangeable. Non-medical switching is ill-advised and potentially detrimental to both individual patient outcomes and the health of the community. When a person is diagnosed with HIV, the process for identifying the most clinically appropriate medication is two-fold: 1) genotype-specific testing is done to ensure the medication used is effective and ARV resistance to that particular medication does not already exist and 2) patient tolerability is sufficient. Providers and counselors "walk" a patient through the necessities associated with either a daily, single tablet regimen or an every-other-month injectable medication. Should a patient experience adherence barriers, regardless if those barrier originate within their personal lives or as a by-product of payor barriers (like prior authorization), the potential developing ARV resistance manifests. Once a patient develops resistance to a particular ARV, that **ENTIRE** class, regardless of brand, is now no longer a viable treatment for that patient.

It is inappropriate and defeatist to public health goals and individual patient success to risk imposing any barrier to care, including payor prioritization based upon reimbursement rates or, more specifically, payor profitability per medication.

Patient and System "Affordability" Rests with PBM and Formulary Design, NOT Reimbursement Rates

Underappreciated under the lens of "capping reimbursement rates", are particular problems associated with for-profit Pharmacy Benefit Managers (PBMs) and their role in "extracting value" from the public health funding stream and within the entire ecosystem of both patient affordability and, more broadly, access to care.

PBMs, not manufacturers or even wholesalers, determine the charges and costs associated, formulary positioning, and administrative process which amount to burden for individual patients. This design has already had an adverse impact in relation to the drug pricing provisions of the Inflation Reduction Act (IRA). This is evidenced by Novo Nordisk's recently announced withdrawal of Levemir, an insulin product, from the United States' marketplace. In announcing the withdrawal, the manufacturer announced "significant formulary losses impacting patient access" – or more directly, PBMs withdrawing coverage of the medication because it was no longer profitable to the payor after a reduction in list price.

Imposition of an "upper payment limit" may have similar effects, regardless of particular therapy. If the Maryland PDAB or PDASC are to consider any study of "cost" or "affordability", they must first consider adverse actions already affecting patient and system affordability and how those may be compounded without more sufficient guardrails in pharmacy benefit designs.

APCD Data is Incomplete and Questionable

All Payor Claims Databases (APCD) are not a complete picture of the patient experience or costs to systems. Rather, those data are merely what payor present as justification for charges to patients. The credibility of these data, or lack thereof, is worth noting as the federal Congress and several states are currently or have historically investigated the self-dealing nature of PBMs. Indeed, AG David Yost of Ohio has lead the way in the nation on this issue and, as recently as two years ago, then-AG Jeff Landry of Louisiana investigation one of the largest PBMs and their relationship with the primary carrier for self-dealing and inflated pricing to avoid the Affordable Care Act's Medical Loss Ratio rule.

Further, these data do not sufficiently capture the provider or patient costs (both tangible and intangible) associated with prior authorizations or step therapy. These costs, while not captured by APCD data, are meaningful and considered from the patient and system lens. While challenging to capture the costs associated for patients, the American Medical Association has invested in measuring the "system" cost to providers associated with punitive pharmacy benefit design via its Prior Authorization Physician Survey. Data contained therein found that prior authorization resulted in the potential or even likelihood of treatment abandonment 80% of the time. Similarly, physician offices reported an average of nearly two full days of staff and labor per week dedicated to managing prior authorizations. This is, again, a very tangible "cost to system" which may be even more adversely affected by instituting an upper reimbursement limit.

Additionally, APCD data does not sufficiently capture denials of coverage. ADPC data does not capture rebate data and even rebate data presented by manufacturers will not capture which, how much, or if any rebates are passed onto patients or employers, absorbed as profit for PBMs, or how those rebates are used to influence formulary position and thus cost-sharing. APCD data will not capture manufacturer patient assistance program design or sufficiently tell the story of how manufacturers, government programs, or private charitable entities

cover costs and reduce burden for patients. And without extraordinary outreach to patients, the cost review process will not capture this experience in a sufficiently quantifiable way, as we saw in Colorado.

A UPL Will Harm Public Health Funding and Thus Exacerbate Health Disparities

Because of how public health is funded, both by the 340B Drug Discount Program and by Medicaid rebates (including those Federal matching dollars), singularly focused action on reimbursement rates **ONLY** threaten to harm patients and the healthcare ecosystem writ large. The value of these rebates and the quantifiable federal matching dollars which allow reinvestment into marginalized communities are realized on dollars already spent. There is NO ability to recoup these funds "after the fact", once a reimbursement rate is reduced.

Necessarily, this means, that an upper payment limit will reduce available dollars to 340B funded entities and the state's Medicaid program.

More directly, a reduction in reimbursement rate alone, rather than a comprehensive address of pharmacy benefit design, will divest from the most marginalized and most vulnerable patients, families, and communities in Maryland. Imposing an upper payment limit will harm programs funded by these mechanisms by reducing dollars available to reinvest in these programs, including but not limited to free pop-up clinics, health awareness programs, and direct service programs like those found within Federally Qualified Health Centers, and, in particular, the state's AIDS Drug Assistance Program.

Maryland's PDAB and PDASC Must Pivot to Assessing the Honest Barriers Patients Face

Because of the complex mechanisms of public health funding, the nature of counterintuitive unintended consequences associated with healthcare and public health funding, and because, ultimately, the idea of a PDAB was sold on improving access to care for Marylanders – which a UPL will not do – the PDAB and PDASC should consider requesting a broader authority, without a prescribed mechanism of action, to more sufficiently study the nature of cost drivers for patients, the healthcare ecosystem, and the state itself prior to taking ANY additional action.

Failing to "pause" will harm patients on a personal level. We've already seen this in Colorado. Indeed, despite being told for more than a year to ask the question of "what happens if the UPL is set below acquisition cost?", the Colorado PDAB failed to do so – until this month. At which in point in time, patient concerns regarding continued accessibility were only finally starting to be heard. This after more than 50 hours of meetings and testimony and tears and honest fear for the lives and well-being of their families, were Colorado patients only beginning to be heard. Marylanders deserve better than this process.

Similarly, after nearly two years of the same healthcare and public health funding concerns, the Oregon PDAB is being faced with having to answer regarding system costs associated with reduced rebate funding necessary to run public programs. Some stakeholders are attempting to negotiate additional state funding for the state's AIDS Drug Assistance Program but the concerns relative to FQHCs are yet to be addressed and they are becoming loud and clear.

It is incumbent of the Maryland PDAB to heed these warnings sooner rather than later and not repeat the failures of other states attempting the same process. These concerns are not ill-borne nor are they over-inflated,

rather they reflect the reality of the landscape as it is today. Far too much of the posturing from certain voices on your board seek to wave off the concerns associated with drug shortages or to inaccurately and over-simplify our healthcare funding process by, rather offensively, relating life-saving medications to "bread". This is dismissive of legitimate concerns and, frankly, should be its own warning to the PDAB and PDASC as to insufficient nature of the expertise currently influencing the posture of PDAB and PDASC.

You well know these things are not as simple as "bread". Patient lives are on the line.

The intentions of the PDAB and PDASC are noble. Those intentions should be respected. Patients and providers, especially those with policy expertise, deserve the same respect as we ring pertinent alarm bells or, for your benefit, share our experiences from other states engaging in the same process.

CANN looks forward tow working with the PDAB and PDASC, sharing our experiences from other state regarding PDABs, and ensuring patient experiences and voices are the highest priority of Maryland's PDAB.

Ever yours in service,

Jen Laws
President & CEO
Community Access National Network

Maryland

Comments PDAB -PDAB- <comments.pdab@maryland.gov>

Submitted for public comment: General comments about PDAB and drugs referred to the Stakeholder Council.

1 message

Patrick Mutch [redacted] Fri, May 3, 2024 at 9:28 AM
To: "comments.pdab@maryland.gov" <comments.pdab@maryland.gov>
Cc: Nora Hoban[redacted], Patrick Mutch [redacted]

Submitted for Public Comment: Maryland Prescription Drug Affordability Board

Dear Members of the Maryland Prescription Drug Affordability Board,

As President and CEO of Chase Brexton Health Care, I am writing you to express our concerns about the potentially significant negative impacts of establishing an upper payment limit on manufacturers of medications for our patients and the sustainability of our mission. These actions will decrease our 340b pharmacy savings used to care for the complex needs of the underserved populations that depend on us for access to health care. In addition, **our patients using one or more of the eight medications under review are never denied these medications and have access to a sliding fee scale and multiple other programs of support for these medications. I write today, deeply concerned with the overall negative impact of the Board's actions on our patients and with the Board's suggestion to begin a "cost review study" of Biktarvy, the antiretroviral medication used for the treatment and prevention of HIV, and Trulicity, the medication used for the treatment of diabetes.**

Who are we?

Chase Brexton Health Care is a Federally Qualified Health Center (FQHC) non-profit organization with five centers in Baltimore City, Columbia, Glen Burnie, Woodlawn (Security Square) and Easton. We serve more than 45,000 unique patients annually, most of whom are underserved and would not have any other access to health care. Of the 45,000+ patients, 45% are insured by Medicaid, and 26% are uninsured. The majority of our patients who disclose financial status live on an annual income of 200% or below the Federal poverty limit (i.e. $51,640 for a family of three). Utilizing one or more of the eight medications under study, we care for over 3,000 HIV patients and 4,700 diabetic patients and support their adherence to medications with providers, clinical pharmacists, nurses, social workers and community health workers.

Federally Qualified Health Centers were established in 1965 as part of President Lyndon Johnson's War on Poverty, serving as America's safety-net for medically under resourced areas and populations. FQHCs are tasked with maintaining an "open door" policy, providing affordable healthcare regardless of an individual's ability to pay. There are over 1,403 FQHCs throughout the United States and these organizations serve about 25 million individuals annually. Given this massive reach and the fact that Maryland is the second - and likely not the last - State to consider the task before you, I ask the Board to recognize the impact of your decision.

The 340b program, a predominant source of funds and support

Hospitals and Federally Qualified Health Centers are among the organizations recognized as covered entities under 340b federal legislation. The 340b program was established 30 years ago by the federal government to provide access to discounted medications for low-income and underinsured patients and also to provide additional resources in the form of savings to covered entities to sustain the mission of providing health

care to underserved communities. The 340b program reduces acquisition costs for medications for covered entities enabling uninsured patients to obtain discounted medications. For insured patients, 340b discounted medications enable covered entities to bill insurance companies at allowable reimbursement rates which results in savings to be reinvested in patient care and to sustain the mission. Any reduction in allowable reimbursement rates or increases in the costs of discounted medications reduces the value of the 340b savings realized by these covered entities. An upper payment limit which reduces current reimbursement rates or increases the acquisition costs of 340b discounted medications reduces the realized savings and revenues which may be reinvested into patient care, caring for the uninsured and sustaining the mission. **Covered entities invest all these savings back into supporting patient care and sustaining their missions. Imposing an upper payment limit is a threat to health equity and the missions of covered entities. All 340b entities will be negatively impacted by an upper payment limit which will likely reduce 340b savings.**

What is the impact of the Board's decision?

Federally Qualified Health Centers such as Chase Brexton Health Care have a dedicated mission to serve impoverished communities "regardless of ability to pay". We are required to offer healthcare services with sliding fee scales for patients who have significant barriers to access health care. In addition, there are other programs that support access to care and medications so that no patients go without their medications. Chase Brexton Health Care and other FQHCs utilize their 340B savings to provide the array of integrated care that includes adult and pediatric primary care, behavioral health, substance use, psychiatry, ob/gyn services, dental services, pharmacy, social services, LQBTQ affirming care, food assistance, transportation, even housing in some situations. Each center site is specifically selected due to the area being officially recognized as serving marginalized underserved communities. The 340b savings are essential to safety-net providers in reducing health care disparities, increasing access to comprehensive services, and ensuring patients have access to life saving medications. Indeed, FQHCs are some of the best stewards of the program and any reduction in the 340b savings reduces those entities' ability to serve the most marginalized of Marylanders.

In conclusion, we appreciate the very important goal of reducing patient cost burdens. **However, we respectfully ask the Board to study the potentially negative impacts to 340b covered entities before implementing any study.**

Patrick F. Mutch, President and Chief Executive Officer, Chase Brexton Health Care

CC: Nora Hoban, Chief Executive Officer, Mid-Atlantic Association of Community Health Centers

Patrick F. Mutch
President & Chief Executive Officer

Pronouns (he/him)

Chase Brexton Health Care
Because everyone's health matters.

1111 North Charles Street | Baltimore, MD 21201

[redacted]

chasebrexton.org

Our mission is to provide compassionate and integrated high quality health care that honors diversity, addresses health inequities, and advances wellness in the communities we serve.

Chase Brexton Health Care

1111 North Charles Street • Baltimore, MD 21201 • 410.837.2050 • chasebrexton.org

May 8, 2024

Submitted for Public Comment: Maryland Prescription Drug Affordability Board

Dear Members of the Maryland Prescription Drug Affordability Board:

As Chief Medical Officer and Director of the Infectious Disease Center of Excellence at Chase Brexton Health Care, I am writing to express our concerns about the potentially significant negative impact establishing an upper payment limit on manufacturers of medications would have on the treatment and reduction of HIV in Maryland. Further, challenging access to Biktarvy and having to switch patients to non-preferred drug options could result in increased costs.

There are over 31,000 people living with HIV (PWH) in Maryland. PWH are disproportionally more likely to have psychosocial barriers to care, be in a lower-than-average financial class, have other medical comorbid conditions, and have a substance use disorder. These burdens result in patients with complex care issues, including difficulty taking medications regularly, trouble remaining adherent to treatment plans, and struggles remaining in care.

Biktarvy is the most prescribed medication to treat HIV in the United States. At Chase Brexton Health Care, 60 percent of our PWH patients are on this drug. To understand why, we need to understand the basics of how HIV is treated: HIV is a virus that can quickly adjust to its environment. When exposed to medications, HIV can mutate and become resistant to such drugs, which allows the virus to survive even in the most challenging environments. With very few exceptions, HIV needs to be treated with a "cocktail," a prescription of three different drugs, and that "cocktail" needs to be taken daily as prescribed. When using three fully susceptible drugs regularly, the virus is under so much treatment pressure that it no longer can develop resistance and the treatment is successful. If the medications are not taken regularly, we refer to it as poor- or non-adherence, and the virus thrives.

Biktarvy addresses many of the HIV treatment challenges:

- First, **Biktarvy is a single tablet regimen (STR) that contains three active drugs**, effectively combining the "cocktail" into one pill, it only has to be **taken once daily**, and it **causes very few side effects** compared to most other HIV drugs. Studies have shown that the fewer pills someone needs to take and the less side effects those drugs cause, the more likely the patient is to take their medications regularly, decreasing the risk of developing resistance and treatment failure.
- Secondly, every drug has its own threshold to be able to develop resistance to the virus. Some are more forgiving to non-adherence and others are less. **Biktarvy has a high barrier to resistance compared to many other drugs** making it a very favorable drug to treat even patients who do not take their medication daily for any reason (such as ongoing substance use, or homelessness). Each time a patient develops

resistance to a drug, their treatment regimen needs to be changed. And often that results in simple single tablet regimens not being possible options anymore. This results in patients having to go on multidrug regimens, leading to increased daily pill burden and increased cost. Biktarvy is very favorable in that regard as it is less likely to fail due to development of resistance reducing the risk of patients needed to be switched to another more complex and more expensive regimen.

- Lastly, many HIV drugs tend to have many and often severe interactions with other medications. This is less of a concern for young and otherwise healthy individuals. However, compared to the general population, PWH are more likely to have other comorbid conditions, such as diabetes, hypertension, or substance use disorder. It can be challenging to find a regimen that works with the other medications an individual is taking. **Biktarvy is compatible with most commonly used medications** and makes this a favorable choice for people on other treatment regimens.

The Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV, developed by the Department of Health and Human Services (DHHS), refer to Biktarvy as the preferred drug for the treatment of HIV. The medications listed by the Maryland Prescription Drug Affordability Board as Proposed Therapeutic Alternatives, posted April 10, 2024, contains many second- and third choice drugs that are not comparable to Biktarvy. Further, most of the listed options are not considered preferred regimens by the DHHS guidelines and have specific issues making them unfavorable options for our patient population in Baltimore City.

I would like to comment on three of the listed to explain why they are less favorable and more likely to cause issues leading to treatment failure.

1. Triumeq is also an STR that contains three active drugs, including the medication abacavir. **Abacavir can cause severe/life-threatening immune hypersensitivity reactions** in certain people and requires testing prior to being prescribed to determine if it can be used safely. Further, abacavir has been shown in studies to **increase the risk of cardiovascular events**, including heart attacks and strokes making this an unfavorable choice, especially in patients with other cardiovascular comorbidities and risk factors.
2. Genvoya is an STR that contains three drugs plus one so-called booster drug. That booster drug increases the half-life of one of the drugs, allowing for patients to take Genvoya only once daily. However, that booster drug increases the half-life of many other medications as well, **causing drug-to-drug interactions** with many commonly used medications, including statins very frequently used to treat high cholesterol and steroids used to treat asthma and many other conditions. Further, the drugs **in Genvoya have a low barrier to resistance increasing the risk of drug resistant HIV mutations** if not taken regularly. Genvoya is more likely to fail due to resistance than Biktarvy.
3. Sustiva is not an STR; it is a single drug that needs to be paired with two other active agents to be a complete regimen. Increased pill burden means an increased risk of poor adherence. Further, Sustiva **is**

Chase Brexton Health Care

1111 North Charles Street • Baltimore, MD 21201 • 410.837.2050 • chasebrexton.org

one of the oldest drugs on the list, having received FDA authorization in 1998 and **is rich in side effects**, causing neuropsychiatric changes in over 50 percent of patients including insomnia, aggression, depression, anxiety, paranoia, and psychosis. All of these side effects are reasons patients may be resistant to taking Sustiva regularly, making this an outdated and unfavorable option. Sustiva also causes **drug-to-drug interactions** with many commonly used drugs, making it difficult to use in patients taking other medications. **Sustiva has a very low barrier to mutations**, making it one of the easiest HIV drugs to develop a resistance to. Finally, Sustiva was removed as a first line option from the HIV treatment guidelines years ago. With the advances in medicine today, it should not be on any preferred drug list.

Challenging access to Biktarvy and having to switch patients to non-preferred drug options could result in increased costs. If the patient is placed on non-preferred drug options, it will lead to increases in complications from drug-to-drug interaction and increases in resistance due to worsened adherence. These factors will ultimately lead to an increase in new drugs prescribed, and therefore an increase in overall cost.

The task before the Board is a delicate matter and the Board needs to consider all potential consequences. The complexities in the field of Infectious Disease medicine make this decision to reduce access to Biktarvy all the more profound. With more than 13 years of experience as an Infectious Disease doctor, I understand my patients and take immense care in prescribing medications that will provide them the most favorable outcomes and success in their treatment plan.

Biktarvy has research-proven advantages over all listed alternative options, making it a preferred choice for most patients. **It has a high barrier to resistance, is easy to take, causing minimal or no side effects which improves adherence, and causes no drug-to-drug interactions with most commonly prescribed medications.**

In thinking not only of my patients but of the treatment of HIV statewide, I would recommend careful consideration and reflection on the significant impact changing access to Biktarvy could have on HIV treatment, undetectable/untransmittable rates, and overall infection reduction within the state of Maryland.

Sincerely,

Sebastian Ruhs, MD, PhD
Infectious Disease Physician
Chief Medical Officer

CC: Patrick Mutch, CEO, Chase Brexton Health Care
Mahro Ershadi, Chief Pharmacy and Strategy Officer, Chase Brexton Health Care
Jeff Cywinski, Director of Pharmacy, Chase Brexton Health Care

Chase Brexton Health Care

Mt. Vernon Center • 1111 North Charles Street • Baltimore, MD 21201 • 410.837.2050 • chasebrexton.org

May 8, 2024

Subject: Urgent Concerns Regarding Proposal for Upper Payment Limit on Prescription Drugs

Dear Members of the Maryland Prescription Drug Affordability Board,

As the Chief Pharmacy and Strategy Officer and Director of Pharmacy, we are writing to express our profound concerns regarding the potential repercussions of implementing upper payment limits on prescription drugs for our patient population and the long-term sustainability of our mission.

The proposal to establish upper payment limits could have a significant impact on 340B pharmacy savings curtail for providing care to underserved population in Maryland. At Chase Brexton, a Federally Qualified Health Center (FQHC), we annually serve over 45,000 unique patients , the majority of whom rely on us as their primary source of healthcare. Among them are over 3,000 HIV patients and 4,700 diabetic patients, who depend on Chase Brexton for essential medications.

The ramifications of such a decision extend far beyond Chase Brexton; they threaten the entire network of FQHCs, jeopardizing health equity and our collective ability to serve marginalized communities. The 340B program was established to maximize scarce federal resources and provide more comprehensive services. It enables us to offer low-cost medications to under-insured patients and not as a profit-making endeavor. Every dollar saved through the program is reinvested back into patients' care, sustaining our mission.

The 340B drug program plays a crucial role in providing affordable medications, such as offering Humalog insulin for less than $2 per vial to eligible patients. However, when misconceptions persist, it undermines the essential services provided by FQHCs.

Chase Brexton Health Care

Mt. Vernon Center • 1111 North Charles Street • Baltimore, MD 21201 • 410.837.2050 • chasebrexton.org

We urge the Maryland Prescription Drug Affordability Board to carefully consider the far-reaching and unintended consequences of implementing upper payment limits and prioritize the healthcare needs of underserved communities in Maryland.

Sincerely,

Mahro M Ershadi, MBA, PharmD
Chief Pharmacy and Strategy Officer

Jeffrey Cywinski, RPH, ACE
Pharmacy Director

CC: Patrick Mutch
Chief Executive Officer

Sebastian Ruhs, MD, PhD
Infectious Disease Physician
Chief Medical Officer

UNIVERSITY of MARYLAND EASTERN SHORE

SCHOOL *of* PHARMACY *and* HEALTH PROFESSIONS

Dear Prescription Drug Affordability Board,

I am an AAHIV certified pharmacist practicing in the area of HIV care on the Eastern Shore of Maryland. I urge you to be very cautious with your evaluation and suggestions for modification to use of Biktarvy within the state of Maryland. As with all specialties, HIV has much nuance and recommendations should be made with consultation of those with expertise in the area.

The assessment of Biktarvy as a drug is potentially unaffordable is misguided. The reason it is at the top of the list for total dollars spent is due to its popularity, any HIV treatment with similar numbers of prescriptions would be in the exact same position before this Board.* Biktarvy is a popular drug because of its efficacy, and tolerability.[1] Biktarvy is one of 3 Single Tablet Regimens (STRs) on the DHHS guidelines list of preferred initial regimens.[1] It attained that status years ago and has replaced older regimens that are not as well tolerated. Biktarvy is a highly active combination regimen that retains activity even in the presence of some mutations.[2] It can be safely administered rapidly to patients without the need for extensive and delayed lab testing.[3] HIV treatment has progressed to a phase where we can keep people healthy on tolerable medications, as the STR with proven efficacy and tolerability, Biktarvy has become the primary treatment utilized by HIV experts.

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. Choice of ART during pregnancy should be guided by recommendations from the Perinatal Guidelines.

For people who do not have a history of CAB-LA use as PrEP, the following regimens are recommended:

INSTI plus Two NRTIs

- BIC/TAF/FTC **(AI)**[a]
- DTG/ABC/3TC **(AI)**—**if HLA-B*5701 negative**
- DTG plus (TAF or TDF)[c] plus (FTC or 3TC) **(AI)**

INSTI plus One NRTI

- DTG/3TC **(AI),** except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

For people with HIV and a history of CAB-LA use as PrEP, INSTI genotypic resistance testing should be performed before the start of ART. If treatment is begun prior to results of genotypic testing, the following regimen is recommended:

- DRV/c[b] or DRV/r with (TAF or TDF)[c] plus (FTC or 3TC)—pending the results of the genotype test **(AIII)**

DHHS Guidelines 2024: Table 6 Recommended Initial Regimens[1]

We appreciate that Triumeq and Dovato are proposed as alternatives for Biktarvy, however, the regular use of both of these medications have requirements for labs, including delays for resistance testing or genetic testing.[1] These delays in therapy can prevent uptake of treatment and have shown worse outcomes for patients. Additionally, Triumeq's massive tablet size limits its acceptability and use.[4]

Genvoya and Stribild's size are also on the larger size, however their real drawback is the CYP450-3A4 boosting agent. This booster causes many drug interactions and makes overall care for the patient difficult and at times potentially dangerous.[1] The integrase inhibitor, elvitegravir, in these medications does not have the same durability against missed doses and resistance as bictegravir, also making them less preferred regimens.[1] It should be noted, that these regimens are not less expensive than Biktarvy, but are less effective AND pose risks to the patient.

Descovy is not a complete therapy and would be the NRTI backbone of another product.[1] Commonly it would be combined with Tivicay. This is a great treatment, but it has the noted drawback of not being a STR. This creates the possibility of errors in prescribing and dispensing, which in turn, can lead to the development of resistance. This combination therapy also is more expensive that the STR of Biktarvy.

Isentress is a less potent and less robust integrase inhibitor than bictegravir and dolutegravir.[1] It also requires combination with a dual NRTI backbone like Descovy. This combination makes the overall treatment more expensive than Biktarvy.

The protease inhibitor class, including Reyataz and Prezista, requires boosting with a CYP450-3A4 inhibitor.[1] This presents problematic drug interactions to manage. Additionally, these medications are not being dosed as STRs and combined costs is approximately equivalent to the cost of Biktarvy.

Pifeltro does not have the strong activity of Biktarvy and also requires the addition of the 2 NRTI backbone like Descovy.[1] This combination is about the same cost as Biktarvy.

The only regimen suggested to be an actual cost savings is use of efavirenz along with the 2 NRTI backbone. This medication, while it has extensive experience in practice, also has an extensive adverse effect profile.[1] There are well known psychiatric contraindications to use of this medication and it can cause psychiatric adverse effects.[1,5] Most notably, would be vivid nightmares and dreams.[1,5] These often are so problematic that patients discontinue use of efavirenz.

Overall, while there are other options to the use of Biktarvy, they are not all good options, they do not really result in medication savings, and ultimately cost the system at least as much as Biktarvy. The main reason why Biktarvy costs more than all other HIV medications combined is that we use it much more extensively because it easy to use, durable and a well-tolerated product.

Sincerely,
Richard DeBenedetto, PharmD, MS, AAHIVP
Associate Professor, University of Maryland Eastern Shore
Clinical Pharmacist, Chesapeake Healthcare

References:

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Year. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Accessed 5/10/2024. [Initial Combination Antiretroviral Regimens for People with HIV]
2. Biktarvy [Package Insert]. Foster City, CA: Gilead; 2021.
3. Koenig SP, Dorvil N, Devieux JG, et al. Same-day HIV testing with initiation of antiretroviral therapy versus standard care for persons living with HIV: A randomized unblinded trial. PLoS Med. 2017;14(7):e1002357. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28742880.
4. Triumeq [Package Insert]. Research Triangle Park, NC: ViiV HEalthcare; 2014.
5. Sustiva [Package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2015.

equalityfederation

May 10, 2024

Maryland Prescription Drug Affordability Board
16900 Science Drive
Suite 112-114 Bowie, MD 20715

Re: Statement of Michael Elizabeth, Public Health Policy Strategist, Equality Federation - Submitted for Public Comment: Maryland PDAB Meeting - May 20, 2024

Dear members of the Maryland Prescription Drug Affordability Board,

My name is Michael Elizabeth (they/them), and I serve as Public Health Policy Strategist with the Equality Federation. We support our member organization in Maryland, FreeState Justice. FreeState Justice (FSJ) is Maryland's leading legal nonprofit dedicated to improving the lives of the state's over 234,000 LGBTQ+ residents.

Equality Federation is an advocacy accelerator working to achieve full equality for LGBTQ+ communities. A key component of this work is enhancing public health and HIV advocacy for communities impacted by HIV.

We have observed with concern that Biktarvy is included on Attachment A of the March 25, 2024 MD PDAB meeting materials for Preliminary Identification of Potential Drugs for Referral to the Stakeholder Council. FreeState Justice and Equality Federation join the Maryland Commission on LGBTQIA+ Affairs in strongly urging the Maryland PDAB to conduct a thorough assessment considering social and structural determinants of health before evaluating any HIV medication. This assessment should meaningfully engage Marylanders living with HIV to ensure efforts to end the HIV epidemic are successful.

Limiting treatment options and increasing the complexity of accessing life-saving HIV medication will negatively impact people living with HIV. This is especially harmful to LGBTQ+ individuals, who already face significant marginalization and barriers to healthcare. Complex HIV treatment regimens necessitate that patients and providers work in close partnership to determine optimal medication choices and achieve positive health outcomes.

People living with HIV need access to the medications prescribed to them.

Different HIV medications are not easily interchangeable. To ensure the benefits of advancements in HIV treatment, patients must be able to start, stay, or switch to the HIV treatment regimen deemed most appropriate for them, always in consultation with their healthcare provider. Any policy that restricts access to these medications or disrupts treatment for stable patients could lead to poor medication adherence, impede viral suppression, harm patient health, and even increase the risk of new HIV transmissions.

Equality Federation and FreeState Justice are eager to collaborate with the Maryland PDAB to ensure access to affordable, life-saving HIV treatment and prevention drugs without unintended negative consequences. We share the PDAB's goal of making essential treatments accessible to Marylanders and would welcome an opportunity to work together for the benefit of those living with HIV and their healthcare providers.

Sincerely,

Michael Elizabeth
Public Health Policy Strategist
Equality Federation
mike@equalityfederation.org
713.443.0509

May 10, 2024

Via email (*comments.pdab@maryland.gov*)

Maryland Prescription Drug Affordability Board
16900 Science Drive, Suite 112-114
Bowie, MD 20715

Re: Reasons Biktarvy Should Not Be Selected for a Cost Review

Dear Members of the Prescription Drug Affordability Board:

I am writing on behalf of Gilead Sciences, Inc. ("Gilead"), in response to the Prescription Drug Affordability Board's ("PDAB") recent referral of Biktarvy® to the Stakeholder Council for input into whether Biktarvy should be selected to undergo a cost review and identification of proposed therapeutic alternatives for Biktarvy®, as well as to comment on unintended consequences of a UPL, and provide process recommendations.[1] Gilead is a research-based biopharmaceutical company that discovers, develops, and commercializes innovative medicines for people with life-threatening diseases in areas of unmet medical need, and has been a leading innovator in treatments for human immunodeficiency virus (HIV) for more than 30 years.

Gilead previously submitted letters to the Maryland PDAB and Stakeholder Council explaining that Biktarvy should not be selected for cost review because Biktarvy is already affordable and accessible for Marylanders with HIV. These letters also addressed that imposing a UPL on Biktarvy could result in treatment delays and interruptions, which could also result in an increase in the amount of HIV virus in the blood, leading to worse clinical outcomes and development of resistant forms of the virus. A UPL on Biktarvy would thus not only be unnecessary in light of Biktarvy's affordability but could also result in Maryland facing increased healthcare costs and would undermine efforts to end the HIV epidemic, pose an undue risk to public health, and disproportionately affect vulnerable populations. These effects conflict with the Moore Administration's goal of ensuring health equity in Maryland.

This letter builds on the points made in Gilead's prior letters by providing additional information on:

<u>Reasons that Biktarvy is clearly differentiated from other HIV medicines:</u>

- HIV drugs have unique clinical and pharmacological qualities that need to be considered when selecting the most appropriate regimen for a person with HIV, in order to support better medication adherence, improve viral suppression, and reduce the risk of transmitting HIV.
- There is longstanding recognition in public programs that patients need access to the particular HIV medication that was prescribed for them, and that one HIV product cannot simply stand in for another.

- Biktarvy offers a single-tablet regimen that is highly effective, supports rapid start, provides a high barrier to drug resistance, and demonstrates exceptional tolerability and safety; therefore, other HIV drugs are not appropriate comparators for the cost-review process.

Reasons Biktarvy should not be selected for a cost review:

- Biktarvy is affordable and accessible to people with HIV in Maryland.
- The State is overestimating its spending on Biktarvy.
- Maryland's Medicaid program has access to unique lower drug pricing, specially determined for its low-income and disability-eligible enrollees. Policies that would disrupt Medicaid's exclusive access to protected pricing would also disrupt the stability of Maryland's Medicaid program for its most vulnerable patients.

In addition, the process of selecting drugs and conducting cost reviews should be fair, reasoned, and transparent while allowing for meaningful engagement from Gilead and other stakeholders.

***

I. HIV drugs have unique clinical and pharmacological qualities that need to be considered when selecting the most appropriate regimen for a person with HIV in order to support better patient medication adherence, improve viral suppression, and reduce the risk of transmitting HIV.

HIV is a uniquely challenging virus to treat, making HIV medicines especially poor candidates for the cost-review process. HIV aggressively replicates at a rate of one billion new viral particles per day, overwhelming and simultaneously destroying the immune system by targeting the $CD4^+$ T cells needed for a proper immune response.[2] Effectively targeting viral replication requires combining multiple drugs with different mechanisms of action, and this highly individualized approach has been critical to transforming a once-deadly disease into a manageable, chronic condition with minimal impact on life expectancy.[3]

Because of the complexity of treatment, antiretroviral therapy (ART) must be selected taking into consideration both clinical considerations and the ability of a treatment regimen to fit into an individual's overall healthcare experience and effectively support their adherence. For this reason, the U.S. Department of Health and Human Services (DHHS) *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV* states that "selection of a regimen should be individualized" for a particular patient based on factors such as virologic efficacy, toxicity, potential adverse effects, pill burden, dosing frequency, drug–drug interaction potential, resistance-test results, comorbid conditions, and childbearing potential."[4] In addition, studies show that, as people with HIV age, they are more likely to develop additional health issues and tend to develop them earlier than people who do not have HIV.[5,6] This often means they must take multiple medications and may be more prone to drug-drug interactions from medications for different conditions, particularly when their HIV medication includes certain components. When individuals take their medication as prescribed, such adherence prevents HIV from multiplying, which suppresses the HIV virus.[7] Viral suppression stops HIV infection from progressing,

helping people living with HIV stay healthy and live longer, and maintaining an undetectable viral load also effectively eliminates the risk of sexually transmitting the virus to an HIV-negative partner.[8]

Effectively managing HIV infection requires vigilance to avoid creating treatment resistant mutations, which reduce the efficacy of ART. Mutations are more likely to develop in patients with suboptimal adherence to treatment regimen and in patients who are given a regimen with a lower genetic barrier to resistance, including patients whose access to treatment is disrupted by policy interventions. Specific resistance mutations may create the need for varied combinations of medications, which may require taking more pills or otherwise be more inconvenient to take. Thus, given the possibility that resistance could develop to any single drug, it is essential to have a diverse artillery of ARTs available for all patients. The ARTs recommended by DHHS for most patients are those that effectively suppress the virus, have a high barrier to resistance, have minimal adverse events, and are simple to take. The importance of adherence, risk of transmission and HIV drug resistance means that the HIV landscape thus poses unique challenges that make the cost-review and UPL approach particularly inapt.

II. There is longstanding recognition in public programs that patients need access to the particular HIV medication that was prescribed for them, and that one HIV product cannot simply stand in for another.

The Centers for Medicare & Medicaid Services (CMS) recognizes the need for individual treatment in the context of Medicare Part D. With respect to antiretrovirals, CMS has stated there are a "number of multiple drug combinations and adjunctive therapies involved," drug protocols are subject to change, and changing drug resistance plays a role "in determining the selection of among the different antiretroviral drugs."[9] Moreover, CMS has acknowledged that "[t]he need to adjust specific combination antiretroviral therapy in real time is complex and must consider, among other things, viral sensitivity to the drugs, drug interactions, pregnancy status (if applicable), and potentially the patient's pharmacogenomic profile of the cytochrome P450 system."[10] For these reasons, CMS does not allow plans to implement any form of utilization management for antiretrovirals in Medicare Part D.

At the state level, Maryland's Integrated HIV Prevention and Care Plan for 2022-2026 identifies statewide needs to increase both community knowledge and provider education regarding treatment options (always mentioned in plural) and the benefits of ongoing HIV treatment.[11] Simply put, effective treatment regimens must take into account and be formulated according to patient-specific factors.

III. Biktarvy offers a single-tablet regimen that is highly effective, supports rapid start, provides a high barrier to drug resistance, and demonstrates exceptional tolerability and safety; therefore, other HIV drugs are not appropriate comparators for the cost-review process.

Biktarvy, a single-tablet regimen ("STR"), is an "AI" recommended treatment for most people to start on for treatment of HIV under the U.S. Department of Health and Human Services (DHHS) guidelines. Recommendations in DHHS guidelines are based on scientific evidence and expert opinion. Each recommendation statement includes a letter (A, B, or C) that represents the strength of the recommendation and a Roman numeral (I, II, or III) that represents the quality of the evidence that supports the recommendation.[12] The DHHS recommendation means that Biktarvy has demonstrated durable virologic efficacy, a favorable tolerability and toxicity profile, and is easy to use.[13] There are only three other regimens that received a "AI" recommendation for initiating HIV treatment in these guidelines, and Biktarvy has been shown to have specific advantages over each. While Maryland's PDAB statute and regulations state that certain factors regarding "therapeutic alternatives" should be considered "to the extent practicable," the proposed "therapeutic alternatives" list that the Board has identified as potential cost-comparators for Biktarvy contains regimens requiring multiple pills, medications that are not guideline-recommended, and medications that undervalue the clinical value that Biktarvy offers compared to previous generations of treatments. If the Board must use comparators for Biktarvy in the context of the State PDAB cost review, it should only focus on single-tablet regimens. Even focusing on these, Biktarvy is clearly differentiated as outlined below.

<u>Biktarvy offers a complete regimen in a single tablet</u>

In order to suppress the HIV virus, multiple antiretrovirals with different mechanisms of action must be combined to make what is considered a complete regimen. A single-tablet regimen (STR) includes multiple agents to treat HIV in one tablet and is approved as a complete regimen to treat HIV. A multi-tablet regimen, on the other hand, is one that combines multiple different medications across multiple pills taken separately, sometimes with different dosing intervals. Patients on STRs like Biktarvy have higher rates of adherence to HIV treatment and, subsequently, higher rates of achieving undetectable levels of virus in the body compared to patients on multi-tablet regimens ("MTRs").[14,15,16] This is because some patients may have difficulty adhering to complex treatment regimens due to factors such as the number of pills, dosing schedule, and dietary restrictions. As such, though MTR therapeutic alternatives may exist for a specific patient, this does not mean such alternatives represent the best choice to assure meaningful personal and public health outcomes for that patient. By improving treatment adherence and persistence, patients on STRs like Biktarvy are expected to better control their HIV, resulting in decreased rates of hospitalization and lower overall healthcare costs.[17,18,19,20,21] The majority of drugs identified by Maryland as potential alternatives for Biktarvy are not complete single tablet regimens for the treatment of HIV and therefore are inappropriate comparators.

Biktarvy supports rapid start

Biktarvy can be started immediately after HIV diagnosis— known as "rapid start" of HIV treatment—before results of recommended resistance testing or baseline laboratory testing are available.[22] Rapid start is not only associated with rapid suppression of the virus, but is also linked to individual receiving ongoing treatment for their HIV at higher rates.[23,24,25,26,27,28] Biktarvy is the only unboosted single-tablet option that is recommended by the DHHS for rapid start.[29]

Biktarvy has a high barrier to resistance

HIV can develop resistance to certain medications if they are not taken consistently and correctly, particularly with medications with a lower barrier to resistance. Once resistance develops, certain medications may no longer be effective against the resistant strain, leading to treatment failure and reduced treatment options. Biktarvy has a high barrier to resistance due to its unique pharmacokinetic and pharmacodynamic properties. For example, it is the only unboosted STR label-indicated and DHHS-recommended for patients with pre-existing M184V/I, an HIV resistance mutation seen in a large share of viruses tested for resistance in persons who have been on HIV treatment.[30]

Biktarvy is approved across broad populations

Furthermore, unlike other guideline-recommended STRs for treatment initiation, the efficacy and safety profile of Biktarvy have been evaluated in people living with HIV who have hepatitis B virus (HBV) coinfection, an infection which is 10-20 times more prevalent in the HIV population, and disproportionately prevalent in select subpopulations, such as persons who inject drugs.[31,32,33] Biktarvy is approved for individuals with end stage renal disease on chronic hemodialysis with history of treatment and pregnant women switching treatments, differentiating it from other STRs considered as potential therapeutic alternatives by the Board.[34]

For these reasons and many others, there are no true therapeutic alternatives for Biktarvy, which is uniquely proven to work across many diverse populations, with a high barrier to resistance and lower risk of producing viral resistance, and recommended for rapid start. The proposed therapeutic alternatives do not provide appropriate cost comparators for Biktarvy, as summarized in Table 1.

Finally, although the PDAB has posted a list of proposed therapeutic alternatives for Biktarvy on its website, the PDAB has not identified the criteria for selecting them. Accordingly, the basis for the identification of these drugs as therapeutic alternatives for Biktarvy is unclear. Further, because no UPL Action Plan has been published, it is unknown how the PDAB will use or consider any data concerning the proposed therapeutic alternatives. This lack of clarity limits stakeholders' ability to offer meaningful guidance.

Table 1: Biktarvy and Therapeutic Alternatives Proposed by the Board

Biktarvy and Proposed Therapeutic Alternatives	DHHS AI Recommended as Initial Regimen for Most People with HIV	DHHS Recommended Single Tablet Regimen for Rapid Start	Reported Treatment-Emergent Resistance in Clinical Trials**	DHHS Recommended for HIV & HBV coinfection
Biktarvy	Yes	Yes	None	Yes
Triumeq	Yes	No	Yes	No
Genvoya	No	No	Yes	Yes
Stribild	No	No	Yes	Yes
Dovato	Only in individuals with HIV RNA <500,000 copies/mL, with no HBV coinfection	No	Yes	No
Descovy*	Only in combination with another agent	N/A	Yes	In combination with a 3rd agent
Tivicay *	Only in combination with 2 other agents	N/A	Yes	Only if combined with tenofovir + a 3rd agent
Isentress *	No	N/A	Yes	No
Reyatz *	No	N/A	Yes	No
Prezista *	No	N/A	Yes	No
Pifeltro *	No	N/A	Yes	No
Sustiva *	No	N/A	Yes	No

*Incomplete regimens. Cells shaded in gray are NOT complete regimens and must be combined with other agents. A complete antiretroviral therapy regimen combines two to three antiretrovirals with different mechanisms of action to suppress the virus. The first five drugs on this table are combination products made up of multiple agents with different mechanisms.
** Based on Gilead studies

IV. Biktarvy is affordable and accessible to people with HIV

The PDAB's current UPL authority extends to drugs that are "[p]urchased or paid for by a unit of State or local government or an organization on behalf of a unit of State or local government," "[p]aid for through a health benefit plan on behalf of a unit of State or local government," and "[p]urchased for or paid for by the Maryland State Medical Assistance Program."[35] Below we address affordability and access in each of these market segments.

- Maryland Medicaid: Enrollees in Maryland's Medicaid program who rely on Biktarvy fill their prescriptions for no more than $1. Furthermore, Maryland Medicaid does not generally currently require a prior authorization, in which a provider must provide documentation about why a medicine is needed, before patients are able to receive medicine to treat HIV. This means that people with HIV can obtain treatment in a timely way based solely on the recommendation of their doctor and without bureaucratic hurdles.

- State or local government health benefit plan: The vast majority of individuals who are insured through Maryland's health plans for state and local government employees have access to Biktarvy on their plan's preferred brand tier. This means that these people with HIV can receive Biktarvy at the lowest cost-sharing amount for a branded drug. For instance, the State of Maryland prescription benefits administered through CVS Caremark have between $15-$25 copayment for preferred brand drugs for a 45-day supply.[36] If these individuals nonetheless face challenges affording their medicines, Gilead's Advancing Access® program may be available to reduce or eliminate out-of-pocket costs.[37]

On top of these programs, Marylanders with HIV can benefit from additional assistance through the Ryan White HIV/AIDS program (Ryan White) administered by the Health Resources and Services Administration (HRSA). Ryan White helps low-income people with HIV access medicines, medical care, and support services by providing grants to cities, states, counties, and community organizations. Ryan White has five parts, and Part B includes the AIDS Drug Assistance Program (ADAP), which supports access to medicines.[38] Maryland's AIDS Drug Assistance Program, or "MADAP," pays for HIV medicines for clients without insurance and assists individuals with insurance with copay and deductible payments. People eligible to participate in MADAP can obtain Biktarvy with a $0 copay. [39,40] To be eligible, a Maryland resident with HIV must not be on Medicaid and must earn 500 percent of the federal poverty level or less. These affordability protections are unique to HIV treatments, which makes the cost-review process uniquely unnecessary for Biktarvy and other HIV medicines.

The Maryland PDAB was set up to protect Marylanders from the high costs of prescription drugs. Based on the information presented, selecting Biktarvy for cost review would be an ineffective use of the Board's resources and time as it is already affordable for Marylanders.

V. The State is overestimating its spending on Biktarvy

The PDAB recently released a "sample database" which includes data about the eight drugs identified by the PDAB as candidates for potential cost-reviews.[41] Because the public has neither access to the data or full dashboard supporting this database nor a detailed understanding of the data sources and methodology used by the PDAB, stakeholders with analytical expertise are limited in their ability to comment on potential errors, provide missing context, or explain discrepancies between the database and other sources. This lack of disclosure of the information on which the PDAB is relying is particularly concerning because of several inconsistencies between "sample database" data and Gilead's data for Biktarvy.

- Maryland's "sample database" grossly overestimates total spend in Commercial and Medicare compared Gilead's own sales data. This is concerning because one of the selection criteria, which resulted in Biktarvy's consideration for potential cost review, is "highest total spend in the most recent available calendar year."
- Maryland did not publish Medicaid data, one of the main populations of interest for the UPL, leaving open the question of whether data being used to assess Biktarvy's affordability in this segment is also inaccurate.
- Gilead compared Biktarvy's patient out-of-pocket (OOP) costs in the "sample database" with IQVIA's Longitudinal Access and Adjudication Data (LAAD), an industry gold standard dataset for patient claims data.[42] The All-Payer Claims Database (APCD), which the Board relied on in identifying drugs for as cost review candidates, significantly overestimates final patient OOP costs. The APCD does not take accurate account of secondary benefits, such as manufacturer cost-sharing assistance, Medicare payments for dual-eligible patients, and MADAP payments that offset a portion of the patient's costs. As a result of the Board's reliance on the APCD, the Board's dashboard overestimates the patient OOP costs for Biktarvy by approximately 8 times for the commercial segment and by approximately 3 times for the Medicare Part D segment when compared to IQVIA's LAAD. Continuing to rely on the APCD in making affordability determinations would be a profound mistake, resulting in erroneous determinations.
- The "sample database" lacks consistency as the data years for each market segment is different (2022 for commercial and 2020 for Medicare). Moreover, the "sample database" does not include all data reportedly included in the non-public version of the dashboard, which purportedly included 2021 data for Medicaid.[43] This raises questions about how the board is considering "the most recent available calendar year" and weighting data from different sources and years.

These inconsistencies, lack of transparency, and inaccuracies in the "sample database" create doubt about whether Biktarvy should have been selected for potential cost review.

VI. Maryland's Medicaid program has access to unique lower drug pricing, specially determined for its low-income and disability-eligible enrollees. Policies that would disrupt Medicaid's exclusive access to protected pricing would also disrupt the stability of Maryland's Medicaid program for its most vulnerable patients.

Medicaid programs currently pay no more than the "best price" for which Biktarvy is sold to most purchasers in the United States, consistent with federal law. Under the Medicaid Drug Rebate Program, Gilead and other manufacturers enter into national rebate agreements with the federal Secretary of Health and Human Services in exchange for Medicaid coverage of their prescription drugs. Under these agreements, manufacturers provide a mandatory rebate that results in Medicaid programs receiving a net price that is no more than the lowest price at which a manufacturer sells its product in the commercial market. Certain providers that serve uninsured or underinsured people living with HIV – including Ryan White HIV/AIDS Program grantees and federally qualified health centers – also can access HIV drugs through the 340B drug discount program at a price that reflects the Medicaid "best price."

Such pricing guardrails, specific to the Medicaid program, ensure that eligible patients with low incomes have access to care. Special considerations that are unique to the Medicaid program and its enrollees inform pricing policies in this specific context. These considerations are not appropriately extended to other purchasers or payer types covering different populations, such as commercially sponsored or employer-sponsored health benefits. For example, HIV products such as Biktarvy are disproportionately provided at the Medicaid "best price" compared with other prescription drugs because HIV is more prevalent among low-income, historically marginalized, and minority populations – who are also more likely to be covered by Medicaid or receive their medicines from 340B providers. To illustrate, forty percent of nonelderly adults with HIV are covered by Medicaid, compared to only fifteen percent of nonelderly adults overall.[44] Similarly, IQVIA found that the share of sales accounted for by 340B were twice as high for antivirals as for drugs overall.[45]

If Maryland were to impose a UPL on an HIV medicine that would change the dynamics around Medicaid's access to a unique "best price," such changes would impact and potentially disrupt drug access not only for Medicaid enrollees in Maryland but possibly other patients in Maryland with different coverage as well. The impact of such changes in public policy could be particularly harmful for patients enrolled in Medicaid, in addition to being economically unsustainable for pharmacies, providers, or manufacturers, resulting in disruptions to patient access—as can be seen in other countries where government price setting has resulted in reduced patient access and comments submitted by pharmacies and community health centers.[46] And this disruption would occur without improving affordability for Marylanders with HIV because Biktarvy is already affordable to those insured by Medicaid or other populations where the UPL would apply.

Given the potential for perverse consequences, Gilead urges the PDAB to take caution and avoid disrupting care for people living with HIV by declining to select Biktarvy for cost review. Additionally, the Board should finalize and approve its UPL Action Plan as required in statute

before drugs are selected for cost reviews. This will help ensure that unintended consequences of a UPL can be further assessed.

VII. The process of selecting drugs and conducting cost reviews should be fair, reasoned, and transparent while allowing for meaningful engagement from Gilead and other stakeholders.

The PDAB and the Stakeholder Council should provide appropriate procedures for engagement with patients and other stakeholders to make reasoned cost determinations, including reasonable efforts to protect privacy and provide feasible commenting opportunities. To date, the PDAB has not established any process for patients or other stakeholders to share their experiences other than through general public comment. This process is inadequate for drugs like Biktarvy, considering public stigma often associated with HIV and the socioeconomic barriers that confront many people living with HIV. In addition, a 90-second speaking allotment for live public testimony during meetings is not enough time for stakeholders to offer substantive comments.

Moreover, the Board's opportunities for public comment arise arbitrarily and unpredictably, with comment windows often opening upon the Board's taking of certain actions (such as posting particular information on the website) that are not scheduled or announced in advance. That was the case with respect to the comment windows for letters responding to the list of proposed therapeutic alternatives and the list of drugs referred to the Stakeholder Council for input. As a result, stakeholders do not know in advance when a comment window will be open, which makes planning challenging, particularly when the Board does not update its website regularly and uses the listserv only occasionally or belatedly. Any 30-day comment period is generally too short for most stakeholders to prepare and engage meaningfully, but the uncertainty of when the 30-day period will begin and close creates additional process concerns.

The PDAB and the Stakeholder Council must also provide manufacturers with a meaningful opportunity to weigh in before the PDAB makes decisions. Manufacturers can offer a unique and valuable perspective to the PDAB. They can correct or clarify outdated or incomplete data, explain technical details, and contextualize information about the drug at issue. In selecting eight drugs for potential cost reviews, the PDAB failed to provide manufacturers and other stakeholders with an opportunity to serve this critical role. Instead, the PDAB selected drugs for discussion in private, based on a vague and unpredictable methodology, and in reliance on data that it has not made available to the public and which appears to be inaccurate. In addition to potential concerns regarding Maryland's Open Meetings Act,[47] this approach deprives manufacturers of a meaningful opportunity to comment on the inclusion of their drugs on the initial drug list. The PDAB should address this issue and ensure that Gilead has an opportunity to meaningfully participate in the selection and (if necessary) the cost review process going forward.

Lastly, the PDAB has not made recordings of its meetings available to the public, despite multiple requests by members of the Stakeholder Council and concerns raised by the General

Assembly. Other State PDABs do provide this tool. Given these potential barriers, the PDAB's current process does not allow for meaningful patient and other stakeholder engagement in the process.

***

Biktarvy is the only unboosted single tablet HIV regimen that is recommended by DHHS guidelines for use in rapid start. It better supports adherence and persistence than other HIV drugs.[48,49,50] It is also the only STR FDA-approved and DHHS-recommended for patients with pre-existing M184V/I, a common resistant mutation, in people who have been taking HIV medicines. And, unlike other guideline recommended STRs for starting treatment, Biktarvy has been studied in people living with HIV who have hepatitis B virus coinfection and pregnant women. To give people with HIV in Maryland confidence that they will be able to continue accessing Biktarvy, Gilead urges the PDAB not to select Biktarvy for a cost review.

Sincerely,

DocuSigned by:
Kristie Banks
3B4BECBA5AB74F3...

Kristie Banks
Vice President, Managed Markets
Gilead Sciences, Inc.

DocuSigned by:
Betty Chiang
DE32260A4A3E4AA...

Betty Chiang, M.D.
Vice President, Medical Affairs
Gilead Sciences, Inc.

---

[1] https://pdab.maryland.gov/documents/comments/biktarvy_proposed_therapeutic_alternatives.pdf
[2] Center for Substance Abuse Treatment. Substance Abuse Treatment for Persons With HIV/AIDS. Treatment Improvement Protocol (TIP) Series, No. 37. 2000. No. (SMA) 12-4137. Rockville, MD: Substance Abuse and Mental Health Services Administration.
[3] Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Panel on Antiretroviral Guidelines for Adults and Adolescents; 2023 Dec 6. Available from: Link
[4] HHS, Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV, G-4 (Mar. 23, 2023), https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv.
[5] Collins LF, Armstrong WS. What It Means to Age With HIV Infection: Years Gained Are Not Comorbidity Free. *JAMA Netw Open.* 2020;3(6):e208023. doi:10.1001/jamanetworkopen.2020.8023.
[6] Gross, AM, et al. Methylome-wide analysis of chronic HIV infection reveals five-year increase in biological age and epigenetic targeting of HLA. Molecular Cell. 2016, 62(2). 157-168.
[7] https://hivinfo.nih.gov/understanding-hiv/fact-sheets/hiv-treatment-adherence
[8] Eisinger RW, Dieffenbach CW, Fauci AS. HIV Viral Load and Transmissibility of HIV Infection: Undetectable Equals Untransmittable. *JAMA.* 2019 Feb 5;321(5):451-452.
[9] Medicare Program; Contract Year 2015 Policy and Technical Changes to the Medicare Advantage and the Medicare Prescription Drug Benefit Programs; Proposed Rule, 79 Fed. Reg. 1918, 1944 (Jan. 10, 2014).
[10] *Id.*

[11] Maryland Integrated HIV Prevention and Care Plan including the Statewide Coordinated Statement of Need 2022-2026; Submission to the Health Services Resource Administration HIV/AIDS Bureau and the Centers for Disease Control and Prevention Division of HIV Prevention, December 9, 2022
[12] https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/introduction?view=full
[13] https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/what-start-initial-combination?view=full.
[14] Cohen, J., Beaubrun, A., Bashyal, R., Huang A, Li J, Baser O. Real-world adherence and persistence for newly-prescribed HIV treatment: single versus multiple tablet regimen comparison among US Medicaid beneficiaries. *AIDS Res Ther*. 2020;17(1):12. Published 2020. doi.org/10.1186/s12981-020-00268-1
[15] Hines DM, Ding Y, Wade RL, Beaubrun A, Cohen JP. Treatment Adherence And Persistence Among HIV-1 Patients Newly Starting Treatment. *Patient Prefer Adherence.* 2019;13:1927-1939.
[16] Sax PE, Eron JJ, Frick A, et al. Patterns of Adherence in Bictegravir- and Dolutegravir-based Regimens. Poster presented at: Conference on Retroviruses and Opportunistic Infections; March 8-11, 2020; Boston, Massachusetts.
[17] Sutton S, Magagnoli J, Hardin J. Impact of Pill Burden on Adherence, Risk of Hospitalization, and Viral Suppression in Patients with HIV Infection and AIDS Receiving Antiretroviral Therapy. *Pharmacotherapy.* 2016; 36(4):385-401.
[18] Cohen CJ, Meyers JL, Davis KL. Association between daily antiretroviral pill burden and treatment adherence, hospitalisation risk, and other healthcare utilisation and costs in a US medicaid population with HIV. BMJ Open. 2013;3(8):e003028.
[19] Sutton S, Hardin JW, Bramley TJ, D'Souza AO, Bennett CL. Single- versus multiple-tablet HIV regimens: adherence and hospitalization risks. *American Journal of Managed Care.* 2016;22(4):242-248.
[20] Kapadia SN, Grant RR, German SB, et al. HIV virologic response better with single-tablet once daily regimens compared to multiple-tablet daily regimens. *SAGE Open Med.* 2018;6:2050312118816919.
[21] Seybolt L, Conner K, Butler I, et al. Rapid Start Leads to Sustained Viral Suppression in Young People in the South. Poster presented at Conference on Retroviruses and Opportunistic Infections; March 8-11, 2020; Boston, Massachusetts. Abstract 1073.
[22] AIDS Education & Training Center Program. Rapid (Immediate) ART Initiation & Restart: Guide for Clinicians. https://aidsetc.org/sites/default/files/resources_files/ncrc-rapid-art-6-10-21_0.pdf. Published May 2022.
[23] Gay CL, Willis SJ, Cope AB, Kuruc JD, McGee KS, Sebastian J, Crooks AM, McKellar MS, Margolis DM, Fiscus SA, Hicks CB, Ferrari G, Eron JJ; Duke-UNC Acute HIV Infection Consortium. Fixed-dose combination emtricitabine/tenofovir/efavirenz initiated during acute HIV infection; 96-week efficacy and durability. AIDS. 2016 Nov 28;30(18):2815-2822.
[24] McNulty M, Schmitt J, Friedman E, Hunt B, Tobin A, Maheswaran AB, Lin J, Novak R, Sha B, Rolfsen N, Moswin A, Rose B, Pitrak D, Glick N. Implementing Rapid Initiation of Antiretroviral Therapy for Acute HIV Infection Within a Routine Testing and Linkage to Care Program in Chicago. J Int Assoc Provid AIDS Care. 2020 Jan-Dec;19:2325958220939754.
[25] O'Shea JG, Gallini JW, Cui X, Moanna A, Marconi VC. Rapid Antiretroviral Therapy Program: Development and Evaluation at a Veterans Affairs Medical Center in the Southern United States. AIDS Patient Care STDS. 2022 Jun;36(6):219-225. doi: 10.1089/apc.2022.0039. Epub 2022 May 18.
[26] Pathela P, Jamison K, Braunstein S, et al. Initiating antiretroviral treatment for newly diagnosed HIV patients in sexual health clinics greatly improves timeliness of viral suppression. *AIDS.* 2021;35(11):1805–1812.
[27] Bacon O, Chin JC, Hsu L, et al. The Rapid ART Program Initiative for HIV Diagnoses (RAPID) in San Francisco. Presented at: Conference on Retroviruses and Opportunistic Infections; March 4-7, 2018; Boston, Massachusetts. Abstract 93.
[28] Poschman K, Spencer EC, Goldberg D, et al. Impact of HIV Test-and-Treat Initiative in Miami-Dade County, Florida. Poster Presented at: Conference on Retroviruses and Opportunistic Infections (CROI) 2019. Seattle, WA. Abstract 903.
[29] An unboosted HIV regimen refers to a regimen that doesn't include a medication called a "booster." Boosters, usually ritonavir or cobicistat, work by decreasing the hepatic metabolism of certain HIV drugs, therefore

prolonging their presence in the body. Unboosted regimens tend to have fewer drug interactions due to the fact that boosters affect not only the metabolism of HIV drugs but other medications as well.

[30] Stanford HIV Drug Resistance Database: https://hivdb.stanford.edu/cgi-bin/MutPrevBySubtypeRx.cgi.

[31] Zhou K, Terrault N. Management of Hepatitis B in Special Populations. Best Pract Res Clin Gastroenterol. 2017 June;31(3):311–320. doi: 10.1016/j.bpg.2017.06.002. Available from: Link

[32] Avihingsanon A, Lu H, Leong CL, Hung CC, Koenig E, Kiertiburanakul S, Lee MP, Supparatpinyo K, Zhang F, Rahman S, D'Antoni ML, Wang H, Hindman JT, Martin H, Baeten JM, Li T; ALLIANCE Study Team. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 and hepatitis B coinfection (ALLIANCE): a double-blind, multicentre, randomised controlled, phase 3 non-inferiority trial. Lancet HIV. 2023 Oct;10(10):e640-e652. doi: 10.1016/S2352-3018(23)00151-0. Epub 2023 Jul 23. PMID: 37494942. Available from: Link

[33] Biktarvy® [package insert]. Foster City CA: Gilead Sciences. 2022. Link

[34] BIKTARVY SmPC, Gilead Sciences, April 2023, and BIKTARVY USPI, Gilead Sciences, October 2022.

[35] Md. Code, Health-Gen. § 21-2C-14.

[36] https://dbm.maryland.gov/benefits/Documents/CVS_Caremark_Handbook.pdf

[37] https://www.gileadadvancingaccess.com/

[38] https://ryanwhite.hrsa.gov/

[39] https://health.maryland.gov/phpa/OIDPCS/Pages/MADAP.aspx

[40] https://alivemaryland.org/wp-content/uploads/2022/08/MADAP-FAQ-082922A.pdf

[41] https://pdab.maryland.gov/documents/comments/drugs_referred_stakeholder_council_dashboard_2024.xlsx

[42] Longitudinal Access and Adjudication Data (LAAD). United States: IQVIA (2020, 2022)

[43] https://pdab.maryland.gov/documents/comments/drugs_referred_stakeholder_council_dashboard_2024.xlsx, Tab "Dictionary-Eligible Drug List"

[44] Kaiser Family Foundation (March 2023), "Medicaid and People with HIV."

[45] IQVIA. The 340B Drug Discount Program: Complexity, Challenges, and Change.

[46] *See,* Richard Kane. PhRMA. New global analysis shows patient access challenges around the world. April 12, 2023. *See also,* NACDS letter to the Maryland Prescription Drug Affordability Board. Re: Upper Payment Limit Action Plan. November 13, 2023. A*lso,* Mid-Atlantic Association of Community Health Centers letter to The Honorable Pamela Beidle. Re: Senate Bill 388. February 7, 2024. https://phrma.org/en/Blog/New-global-analysis-shows-patient-access-challenges-around-the-world.

[47] *See* Md. Code Ann., Gen. Provis. § 3-301.

[48] Cohen, J., Beaubrun, A., Bashyal, R., Huang A, Li J, Baser O. Real-world adherence and persistence for newly-prescribed HIV treatment: single versus multiple tablet regimen comparison among US Medicaid beneficiaries. *AIDS Res Ther*. 2020;17(1):12. Published 2020. doi.org/10.1186/s12981-020-00268-1

[49] Hines DM, Ding Y, Wade RL, Beaubrun A, Cohen JP. Treatment Adherence And Persistence Among HIV-1 Patients Newly Starting Treatment. *Patient Prefer Adherence.* 2019;13:1927-1939.

[50] Sax PE, Eron JJ, Frick A, et al. Patterns of Adherence in Bictegravir- and Dolutegravir-based Regimens. Poster presented at: Conference on Retroviruses and Opportunistic Infections; March 8-11, 2020; Boston, Massachusetts.

Global Coalition on Aging

May 10, 2024

Re: Maryland Prescription Drug Affordability Board's Decision to Proceed with Drug Cost Reviews and Draft Upper Payment Limit Action Plan

Honorable Members of the Maryland Prescription Drug Affordability Board,

The Alliance for Health Innovation (Alliance) is a group of cross-sector stakeholders representing patients, providers, caregivers, academia, biopharmaceutical innovators, and business communities.

Led by the Global Coalition on Aging (GCOA), the Alliance is committed to establishing the importance of innovation in achieving healthy aging. We advocate for state policy solutions that support a thriving innovation sector, enabling Maryland residents and other communities to live longer and healthier lives.

We are writing to express our deep concerns about the decision to proceed with drug cost reviews and the Board's consideration of therapeutic alternatives for drugs selected for review. We are particularly troubled by the lack of clarity on how the PDAB will implement any upper payment limit (UPL) that may be established through such a review. This uncertainty could jeopardize access to life-saving medications for patients, particularly for communities disproportionately impacted by chronic and complex conditions such as HIV. Furthermore, we are concerned about the absence of clear safeguards to ensure that the perspectives of patients, caregivers, and other stakeholders are fully integrated into the review process.

Many diseases that once burdened aging populations have evolved into manageable chronic conditions due to modern, safer, and more effective treatments. These treatments allow many patients to live longer, healthier lives. Much of this progress is owed specifically to patient advocacy efforts and opportunities that patients have been given to weigh in on the value of treatments from their unique and individual perspectives. HIV is a powerful and critical example of this, as specific disadvantaged populations – such as older adults living with HIV – are even more dependent on access to innovative medicines than average. By 2030, over 70% of the HIV-positive population in the US will be over 50, and in 2021, over 53% of new HIV diagnoses in the United States were in people aged 50 and older. [1,2]

[1] Wing E. J. (2017). The Aging Population with HIV Infection. Transactions of the American Clinical and Climatological Association, 128, 131–144.
[2] Centers for Disease Control and Prevention. HIV in the United States by Age: HIV Diagnoses. https://www.cdc.gov/hiv/group/age/diagnoses.html

UPL policies typically lead to significant patient access restrictions, which disproportionally affect the disadvantaged populations these policies are meant to protect. A recent survey of healthcare payers indicates that patients would likely experience increased utilization management (UM) protocols around drugs subject to a UPL.[3] Complex UM protocols – such as prior authorization or step therapy – can compromise or delay effective treatment plans. While the PDAB has claimed that patients will receive benefits in the form of lower costs for prescription drugs, setting a UPL on treatment for HIV or any other medication would achieve neither patient affordability nor savings for the state of Maryland.

In 2021, people aged 55 and older represented 41% of the U.S. population living with HIV, with 68% of those individuals being virally suppressed.[4] People living with HIV are more likely to develop additional health issues and tend to develop them earlier compared to those who do not have HIV.[5] Threatening recent progress toward ending the HIV epidemic for older Marylanders and other patients in the state and threatening to exacerbate co-morbidities will only increase the burden on the broader healthcare system.

Patients living with HIV work closely with their providers to determine a treatment plan that works best for them. UM tactics impose significant administrative burdens on providers while forcing patients to spend precious time waiting to access the treatments best suited to their needs. One such tactic, known as non-medical switching, can be observed when a payer forces a patient on a stable regimen to switch from the treatment recommended by their provider to a cheaper medicine. Non-medical switching undermines the essential relationship between a patient and their provider. It ignores potential drug-drug interactions and side effects that could have been avoided with the recommended treatment. Conversely, improvements to HIV treatment adherence, unburdened by complex barriers to access like UM, can decrease overall hospitalization rates and lead to lower overall health system costs.

Interruptions to an individual's HIV treatment regimen can lead to impacts both at the personal and public health levels, with the potential for more significant and widespread consequences than other therapeutic areas. Ultimately, barriers to timely access to effective HIV treatments could lead to the progression of costly resistant viruses and could further complicate HIV care for older adults living with HIV and comorbid conditions.

---

[3] Partnership to Fight Chronic Disease. Health Plans Predict: Implementing Upper Payment Limits May Alter Formularies And Benefit Design But Won't Reduce Patient Costs.
https://www.fightchronicdisease.org/sites/default/files/FINAL%20PFCD%20Avalere%20PDAB%20Insurer%20Research.pdf

[4] AIDSVu. National HIV/AIDS and Aging Awareness Day 2023. https://aidsvu.org/news-updates/national-hiv-aids-and-aging-awareness-day-2023/

[5] Gross, AM, et al. Methylome-wide analysis of chronic HIV infection reveals five-year increase in biological age and epigenetic targeting of HLA. Molecular Cell.
2016, 62(2). 157-168.

Across therapeutic areas, medication nonadherence for patients living with chronic diseases is thought to generate upwards of $100 billion in preventable healthcare costs.[6] There is no doubt that out-of-pocket costs can be a significant barrier between patients and their prescription drugs. Thirty-five percent of patients abandon their treatment plan when out-of-pocket costs reach $75-$125, leading to substantial long-term health and financial consequences for the individual patient and the health care system.[7] However, in the case of HIV and its unique public health impact, there are local, state, and national safety-net programs in place to ensure that patients can access their HIV treatments. For patients covered through Medicaid and state-purchased plans, out-of-pocket costs for HIV treatments are typically between zero and three dollars.

While the PDAB has yet to establish its UPL action plan, the potential negative impacts of setting a UPL on HIV treatments – both for patients and the state more broadly – are clear. To ensure that all patients in Maryland have a pathway to longer and healthier lives, those living with and at increased risk for HIV must be afforded timely and unburdened access to the treatment options recommended by their healthcare provider.

We urge the Board to pause its activity and ensure that there is clarity on how the PDAB will implement any upper payment limit (UPL) that may be established and allow for proactive engagement with patients, caregivers, and other stakeholders to ensure that concerns about access and innovation are carefully considered to prevent access barriers from excessively impacting the most vulnerable of Marylanders.

Thank you for allowing us to share our concerns and for your commitment to finding solutions to the affordability challenges that Maryland patients face. We would be happy to discuss these concerns further or answer any questions.

Sincerely,

Michiel Peters

Michiel Peters

Head of Advocacy Initiatives, Global Coalition on Aging

[6] Kleinsinger, Fred. The Unmet Challenge of Medication Nonadherence. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6045499/
[7] IQVIA. Medicine Spending and Affordability in the U.S. https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/medicine-spending-and-affordability-in-the-us

HealthHIV

1630 Connecticut Avenue, NW, Suite 500
Washington, DC 20009

202.232.6749 | healthhiv.org

Dear Members of the Prescription Drug Affordability Stakeholder Council,

As background, **HealthHIV** is a national non-profit working with healthcare organizations, communities, and providers to advance effective HIV, HCV, STI, and LGBTQI+ health care, harm reduction, and health equity through education and training, technical assistance and capacity building, advocacy, communications, and health services research and evaluation.

And our work is purposefully connected to the broader HIV ecosystem—a network that supports not only clinical care but also the comprehensive well-being of individuals living with HIV.

The discussion regarding Biktarvy's affordability review and the potential imposition of an upper payment limit (UPL) is of genuine concern. We understand the Council's intent to make medications more affordable; however, we also recognize that the structure of such policies must carefully consider their broader impact—particularly on systems like the 340B program that are central to our public health response.

Impact on the 340B Program and the HIV Ecosystem

The 340B program is crucial for enabling covered entities, including Federally Qualified Health Centers and community-based supportive services agencies, to leverage 340B rebates and provide necessary services and medications to underserved populations. Although AIDS Drug Assistance Programs (ADAPs) are part of the ecosystem, they operate separately with their own funding mechanisms. The program's structure allows these entities to use savings from medication rebates to fund various health services—thus playing a pivotal role in our public health HIV ecosystem.

1. **Reduction in Rebate Value:**
   A UPL below current reimbursement rates could reduce the rebate values covered entities realize. This reduction directly impacts the savings and revenues these entities rely on to reinvest in public health programs. For Maryland's ADAP, which received approximately $24.494 million in state special funds FY 2022, these rebates add significant value, enabling the program to serve more patients and enhance overall access to care for individuals living below 500% of the Federal Poverty Level.

2. **Threat to Health Equity and Program Sustainability:**
   The potential reduction in rebate value due to a UPL could jeopardize the ability of programs like MD's ADAP to serve patients who critically depend on these services. For many grantees, the sustainability of their programs hinges on the 340B revenues. Any decline in these revenues threatens the very foundation of their operations and their mission to support health equity.

3. **Broader Implications for Public Health Programming:**
   Implementing a UPL could also have disproportionate effects on smaller subgrantees, such as those supported by 318 Grants, which are essential in delivering services like HIV screening and pre-exposure prophylaxis (PrEP). These entities are incredibly efficient, and their funding model is primarily based on

realizing 340B savings. This reliance on the rebate system emerged from a non-governmental response at the beginning of the epidemic. Reducing these savings could lead to significant service cuts, adversely affecting public health outcomes and undoing an ecosystem that has contributed to fewer new infections.

Enhance Understanding of HIV Treatment Affordability: Key Considerations

To fully understand the implications of a UPL on patient access to medications like Biktarvy, it is crucial to establish comprehensive access monitoring. This approach recognizes that affordability is just one dimension of access. Affordable medication that cannot be accessed by patients due to other barriers, such as delays in treatment initiation or administrative hurdles, does not truly serve public health needs.

Potential Unintended Consequences:

While Maryland has not detailed how a UPL might be implemented, it is clear that such a policy could lead to unintended consequences, including delays and interruptions in treatment. These disruptions can have far-reaching impacts—particularly for those relying on medications like Biktarvy for their HIV treatment.

If a UPL were set near the cost of multi-tablet regimens (MTRs) or even other DSHS single-tablet regimens (STRs), states and insurers might favor these less expensive regimens to contain costs. This could force patients, especially those who are stable on an STR, to switch to an MTR or a therapeutic alternative — alternatives that may not be suited, preferred, or part of the shared decision-making process. While the cost savings might look beneficial—or attractive to the payer on paper—this switch could disrupt treatment for patients who are well-managed on an STR, leading to potential adherence issues and negatively affecting viral suppression rates. *Remember this is a communicable disease.*

The economic implications of switching from STR to MTR under an UPL are highlighted by the pricing data in Table 22b of the DSHS Antiretroviral Treatment Guidelines [Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services.] And while STRs like Biktarvy are priced at $3,795 monthly, generic components of a comparable MTR are significantly cheaper, even cumulatively. If a UPL encourages the use of these cheaper MTRs, patients, especially those stable on STRs, may be forced to switch, potentially disrupting their treatment and adherence leading to poorer health outcomes.

Example

In WA state, for example, setting the 340B argument partially aside, the real-world impacts of adherence are already evident in Washington State. The *HIV antivirals annual report* [Clinical Quality and Care Transformation. (2023). HIV antivirals annual report. Engrossed Substitute Senate Bill 5187; Section 211(46); Chapter 475; Laws of 2023. Health Care Authority. December 1, 2023] indicates a trend where a switch from MTR to STR might not just be a matter of convenience but also a factor in treatment effectiveness. The report shows a 7% higher viral suppression rate among patients on STRs than those on MTRs—93% versus 86% [Clinical Quality and Care Transformation, 2023]. This difference is not merely statistical but translates into real-world patient health impacts.

To put this into perspective, based on the report's data:

- 3,848 clients were diagnosed with HIV and had at least one prescription drug claim in 2021.
- Of these, 93% on STR would mean approximately 3,579 patients achieving viral suppression.
- In contrast, 86% on MTR would translate to about 3,309 patients being virally suppressed.

This means the 7% gap accounts for about 270 patients (3,579 - 3,309) who might not achieve viral suppression due to being on MTRs instead of STRs. Implementing a UPL that could push patients from STRs to MTRs risks complicating the treatment regimen and potentially increasing the number of patients not virally suppressed by hundreds, depending on the total population size. This shift could lead to more frequent medical needs/visits, higher medical case management (and non-medical) needs, and increased overall healthcare costs—effectively setting back efforts to manage HIV more effectively and considerably in terms of people's quality of life. The report underscores the importance of considering these clinical outcomes when setting policies that affect drug payment structures. Until real-world impact considerations are monitored by this Council and PDAB, these concerns remain significant and warrant careful attention.

It must be pointed out that there are many reasons for the 7% difference: resistance issues, preference, stability, fewer side effects, shared decision-making, etc. *To be clear*, we (this Council, the PDAB) do not know the specific reasons for the 7% difference in viral suppression rates between STRs and MTRs, as stated by the Health Care Authority, but it represents a real and impactful difference nonetheless. And that warrants more review, dialogue, and transparency before any affordability review imposing a UPL is undertaken on the most widely used STR.

Weigh the Practical and Systemic Implications on Patient Care and System Efficiency
In light of the potential challenges a UPL introduces, it is crucial to prioritize patients—*particularly* those with high-acuity health issues, to prevent any disruption in their continuum of care.

The introduction of a UPL could necessitate increased involvement from non-medical and medical case managers and multidisciplinary teams to address these patients' heightened needs effectively.

This approach involves maintaining consistent patient care and managing the additional costs these supports impose on the healthcare system.

Transitioning patients from one medication to another—especially under the constraints of a UPL requires careful planning and coordination to ensure continuity of care and system efficiency. For high-acuity patients, this might mean enhanced engagement with medical case management beyond the typical scope of services provided by programs like Ryan White. These patients often need additional support to manage the transition, including more frequent consultations, personalized adherence strategies, and direct intervention by healthcare professionals to mitigate any risks associated with changing treatments.

If these 340B savings diminish due to a UPL, there could be a gap in funding for essential services and medications. The state might then face pressure to "backfill" or compensate for these financial shortfalls to ensure PWH continues to receive necessary care without disruption—disruption that, if adherence issues arise from these decisions, further

carries potential criminal liability on patients through COMAR § 18-601.1 (whereas the penalty "**subject to a fine not exceeding $2,500 or imprisonment not exceeding 3 years or both")**.

Furthermore, logistical hurdles such as ensuring the availability of new medication at local pharmacies, adjusting pickup times, and handling formulary replacements need meticulous attention to minimize disruptions to patient care. Each step, from managing the inventory of the old medication to smoothly integrating the new one, needs to be strategically planned to avoid treatment gaps, unnecessary waste, and additional strain on our healthcare resources.

These necessary adjustments and the associated costs underscore the importance of a thoughtful approach when considering the implementation of a UPL. It's about more than just the direct cost of medication; it's about ensuring a seamless transition that maintains the quality of care and life for all patients—particularly those most vulnerable. Remember, each PWH's situation is unique, and changes should be made carefully to ensure continuity of care and avoid any negative impacts on treatment outcomes.

Conclusion:

As you continue your deliberations, we urge the Council to consider the full scope of implications that a UPL on Biktarvy could have on the HIV ecosystem and the broader public health landscape in Maryland. A thoughtful approach that includes a preliminary study of access and the potential impacts on covered entities is essential.

We appreciate the opportunity to share our perspectives and look forward to engaging further with the Council on this critical issue. Thank you for considering our views as you work towards policies that balance patient protections and affordability together with the need to maintain robust and equitable public health programming.

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

14 Beacon Street
Suite 800
Boston, MA 02108
617-528-4013
www.icer.org

May 8, 2024

The Maryland Prescription Drug Affordability Board
16900 Science Drive, Suite 112-114
Bowie MD, 20715

Re: Comments on the *Drugs Referred to the Stakeholder Council*

Dear Members and Staff of Maryland's Prescription Drug Affordability Board,

The Institute for Clinical and Economic Review (ICER) is pleased to submit comments on the *Drugs Referred to the Stakeholder Council*, which were first presented at the March 25, 2024 Board meeting of Maryland's Prescription Drug Affordability Board. ICER is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders improve patient outcomes and improve affordability. Our reports are used by the Veterans Health Administration and by most Medicaid and private insurance plans to help inform their formulary determinations, support drug price negotiation, and improve access for patients. As part of the international community of value assessment organizations (sometimes referred to as health technology assessment), we also participate in many activities related to the development of methods of evidence assessment, cost- effectiveness analysis, and public deliberation that can support efforts to achieve affordable access to high-value care.

As part of our work, we have conducted assessments of two of the prescription drugs on the *Drugs Referred to the Stakeholder Council* – Skyrizi for psoriasis, and Dupixent for both asthma and atopic dermatitis. Given our expertise in this field, we believe we can offer valuable insights to help inform the Prescription Drug Affordability Board of Maryland's efforts to make prescription drugs more affordable and accessible for Marylanders.

ICER's findings on Skyrizi for Psoriasis

In 2018 ICER produced an Evidence Report on Psoriasis focused on multiple interventions for plaque psoriasis including risankizumab (Skyrizi®). As part of ICER's analyses, we utilize the ICER Evidence Rating Matrix ™ to evaluate the overall strength of evidence for a variety of outcomes. Based on the evidence in ICER's 2018 Evidence Report on Psoriasis,

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

14 Beacon Street
Suite 800
Boston, MA 02108
617-528-4013
www.icer.org

ICER rated Skyrizi "A" when compared to placebo. An ICER rating of "A" is defined as superior, meaning a high certainty of a substantial (moderate-large) net health benefit.

Additionally, as part of all analyses an ICER "health benefit price benchmark" is developed for the new intervention, which reflects prices aligned with commonly-cited long-term cost-effectiveness thresholds ranging from $100,000 to $150,000 per equal value life-year (evLY) gained. The prices represent the prices paid by insurers, net of rebates and other concessions, that would be required to reach these cost-effectiveness thresholds. In short, it is the top price range at which a health system can reward innovation and better health for patients without doing more harm than good. Further information on the ICER Health Benefit Price Benchmark (HBPB) can be found in ICER's Value Assessment Framework. For the 2018 Evidence Report on Psoriasis ICER determined the Health Benefit Price Benchmark range for Skyrizi to be $27,300 - $ 39,800 per year.

ICER's findings on Dupixent for the treatment of Asthma Associated with Type 2 Inflammation

In ICER's 2018 assessment of biologics for severe asthma one of the interventions of interest was dupilumab (Dupixent®). ICER's Health Benefit Price Benchmark (HBPB) range for Dupixent was $10,100 - $14,300 per year. At the time, a key policy recommendation from ICER was that the manufacturers should lower the prices of biologic therapies for asthma so they align with the added value they bring to patients. Based on the evidence, ICER rated Dupixent "C+" relative to stand care. The "C+" rating is defined as Comparable or Incremental, meaning moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit.

ICER's findings on Dupixent for the treatment of Atopic Dermatitis

ICER's 2021 Atopic Dermatitis Analysis found Dupixent's Health Benefit Price Benchmark (HBPB) range to be $29,000 - $39,500 per year. Using ICER Evidence Rating Matrix ™ Dupixent, for the treatment of Atopic Dermatitis, was rated "A" defined as Superior – High certainty of a substantial (moderate-large) net health benefit

One final note regarding Therapeutic Alternatives. As the Board considers appropriate therapeutic alternative for the SGLT-2 inhibitors Farxiga and Jardiance, we call your

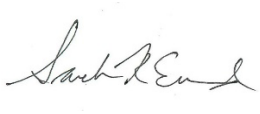
ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

14 Beacon Street
Suite 800
Boston, MA 02108
617-528-4013
www.icer.org

attention to the recently-approved SGLT-2 inhibitor Brenzavvy. Brenzavvy is being sold not through the traditional insurance system, but through entities like Mark Cuban Cost Plus Drug Company, and is offered for an annual price of $600. The transparency of the price of Brenzavvy may be a helpful data point as the Board considers its review of Farxiga and Jardiance.

We thank Maryland's Prescription Drug Affordability Board for the opportunity to comment on Skyrizi for Psoriasis and Dupixent for Asthma and Atopic Dermatitis, two of the drugs on the *Drugs Referred to the Stakeholder Council,* and are available to respond to any follow-up questions the Board may have.

Sincerely,



Sarah K. Emond, MPP
President and Chief Executive Officer
Institute for Clinical and Economic Review (ICER)
www.icer.org

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

14 Beacon Street
Suite 800
Boston, MA 02108
617-528-4013
www.icer.org

Attachments:

1. Atlas SJ, Brouwer E, Fox G, Carlson JJ, Campbell JD, Agboola F, Hansen RN, Pearson SD, Rind DM. JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, July 9, 2021. https://icer.org/assessment/atopic-dermatitis-2021/#timeline

2. Banken R, Agboola F, Ellis A, Chapman R, Segal C, Fazioli K, Ollendorf DA, Pearson SD. Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, August 3, 2018. https://icer.org/assessment/psoriasis-2018/#timeline

3. Tice JA, Walsh JME, Synott P, Kumar VM, Adair E, Rind DM, Pearson SD. Biologic Therapies for Treatment of Asthma Associate with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks; Evidence Report. Institute for Clinical and Economic Review, December 20, 2018. https://icer.org/assessment/asthma-2018/#timeline

Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.
+1.317.276.2000
www.lilly.com

May 10, 2024

By Email (*comments.pdab@maryland.gov*)

Maryland Prescription Drug Affordability Stakeholder Council
16900 Science Drive, Suite 112-114
Bowie, MD 20715

Re: Drugs Referred to the Stakeholder Council

Dear Council and Staff:

Eli Lilly and Company (Lilly") is the manufacturer of Trulicity® and submits these written comments to the Maryland Prescription Drug Affordability Stakeholder Council (the "Council") in response to Trulicity's inclusion on the "Drugs for Referral to the Stakeholder Council" listing from the Maryland Prescription Drug Affordability Board (the "Board"). Lilly urges the Council recommend that the Board not select Trulicity for a cost review under COMAR regulation 14.01.04.

Affordability for Maryland patients

Trulicity is affordable. Patients in Maryland paid an average of $2 to $39 per month for their therapy, which equates to only 0.2% to 4% of the list price[1]. This affordability stems from exceptional access provided by payers within the state, as well as affordability programs provided by Lilly: 80% to 90% access across formularies and segments (including healthcare marketplace, Medicaid and Medicare)[2]. Lilly continues to advocate for patient choice, with most patients having the ability to choose the incretin therapy that is appropriate for them with the help of their healthcare provider. This choice has maintained healthy competition in the broader incretin therapy market. We feel Trulicity is both competitively priced based on the clinical value it provides and the class in which it competes.

[1] Based on information licensed from IQVIA: IQVIA™, Real-World Evidence Claims Data for the period March 2023 - Feb 2024 reflecting estimates of real-world activity. All rights reserved. Accessed on April 23, 2024.
[2] Ibid.

Therapeutic Alternatives

As part of the Cost Review Study Process, "Trulicity Proposed Therapeutic Alternatives" was published by the Board. Lilly believes a number of drugs contained on this listing are not valid alternatives for therapy with Trulicity. Semaglutide (Ozempic), liraglutide (Victoza), exenatide (Byetta), lixisenatide (Adlyxin), exenatide-extended release (Bydureon), semaglutide (Rybelsus), tirzepatide (Mounjaro) are valid alternatives that should remain on the listing. All other products, which are not glucose-dependent insulinotropic polypeptide (GIP) receptor or glucagon-like peptide-1 (GLP-1) receptor agonist products, should be removed prior to any further comparisons in products potentially subject to a cost review.

Unintended consequence to patient access and cost

Lilly encourages the Council and the Board to be thoughtful about the process to assess cost challenges to Maryland patients and to balance the likely consequence of limiting access to patients as a result of instituting an Upper Payment Limit ("UPL"). In addition, UPLs are unlikely to impact the patient out-of-pocket experience at the pharmacy counter, which is the ultimate goal of the creation of the Board and its regulations.

Value of Trulicity® to patients[3]

Trulicity is for adults and children 10 years of age and older with type 2 diabetes used along with diet and exercise to improve blood sugar (glucose). Trulicity is also used in adults with type 2 diabetes to reduce the risk of major cardiovascular (CV) events (problems having to do with the heart and blood vessels) such as death, heart attack, or stroke in people who have heart disease or multiple cardiovascular risk factors. Trulicity is the only GLP-1 RA that provides this combination of benefits: powerful A1C reduction across 4 doses, proven CV benefit in both primary and secondary prevention patients, simply delivered.[4] In fact, in AWARD-11, Trulicity provided sustained A1C reduction at 1 year of <7%.[5] Trulicity acts like the natural human hormone, GLP-1, helping the body do what it's supposed to do naturally:

---

[3] See full Prescribing Information for Trulicity at https://uspl.lilly.com/trulicity/trulicity.html#pi
[4] Treating Adults with Type 2 Diabetes | HCP | Trulicity (dulaglutide)
[5] Clinical Trials: Lowering A1C, Weight Change & CV Data | HCP | Trulicity (dulaglutide)

reduces hepatic glucose production by decreasing glucagon secretion, slows gastric emptying and releasing glucose-dependent insulin. Reductions in fasting and postprandial serum glucose were observed as quickly as 48 hours after the first dose of Trulicity.[6]

We appreciate that the Council and the Board share our commitment to prescription drug affordability, and we are proud to lead the industry in making our products affordable. We are proud of the impact that our efforts have had on making Trulicity affordable for Maryland patients and believe the Council's review will demonstrate the meaningful impact Trulicity have had for patients with type 2 diabetes.

Sincerely,

Cynthia Ransom
Sr. Director, Government Strategy

[6] How Trulicity Works, MOA & FPG and PPG Reductions | HCP | Trulicity (dulaglutide)

MID-ATLANTIC ASSOCIATION OF
COMMUNITY HEALTH CENTERS

Dear Members of the Maryland Prescription Drug Affordability Board,

Thank you for the opportunity to provide comment. The Mid-Atlantic Association of Community Health Centers, or MACHC, is the federally designated primary care association for Maryland's sixteen community health centers that provide comprehensive primary care to more than 340,000 patients annually.

The following pages illustrate how 340B savings are vital to Maryland's federally qualified health centers and other safety-net providers, including Ryan White Clinics. The 340B program was established to stretch scarce federal resources by requiring manufacturers to sell drugs to safety-net providers at a reduced price. In addition to increasing access to affordable medications for uninsured and underinsured patients, the reimbursement from insured patients allows safety-net providers to sustain their mission and invest in important services, like medication adherence programs, OB-GYN, dental care, and nutrition services.

A cost review should consider that safety-net providers and patients could be unintentionally harmed as upper payment limits will reduce the benefit the 340B program provides. The program offers patients increased access to discounted medications and preventive care. Harming the 340B program will put safety-net providers in a dire position and likely result in reduced program capacity, ultimately exacerbating the need for primary care services and increasing emergency department usage. With Maryland's already strained hospital capacity, this would be untenable. MACHC recognizes that a drug's inclusion in a cost review study does not mean it will be subject to an upper payment limit. **However, Board action without considerable review and input from 340B providers in Maryland could result in a backslide in primary care initiatives and ultimately worsen health outcomes statewide.**

MACHC urges the Prescription Drug Affordability Board to consider the following requests:

1. Withold determinations regarding Upper Payment Limits until the impact of the loss of 340B savings is understood.
2. Work closely with 340B safety-net providers to understand how upper payment limits on these drugs will impact patient care through all levels of Maryland's health system.
3. Ensure that future upper payment limits do not harm 340B safety-net providers by establishing strategies such as exemptions or state funds to support 340B organizations.
4. Consider regulation and reform of pharmacy benefit managers and associated health insurers, given that pharmacy benefit managers determine insured patients' out-of-pocket cost and medication access.

Thank you for the opportunity to comment on this process. For additional information, please do not hesitate to reach out to me at nhoban@machc.com.

Sincerely,

Nora E. Hoban

Nora E. Hoban
Chief Executive Officer
Mid-Atlantic Association of Community Health Centers

The 340B Program

How the Program Works

A Tax Free Benefit Supporting Access to Health Care

The 340B program, established more than 30 years ago, allows safety-net providers to buy outpatient medicines for less. The program is NOT funded by taxpayers. Instead, drug companies sell drugs to providers at discounted prices in exchange for receiving payment for medications under Medicare and Medicaid. The program enables safety-net providers to stretch scarce funding to make health care more accessible. Providers use 340B savings to enhance primary and preventive programs, wraparound services, and access to medications.

Non-profit safety-net providers buy discounted medications from manufacturers that are shipped to pharmacies

Pharmacies charge insurance companies non-discounted drug prices for patients of a 340B provider

Savings equal the difference of the discount drug price and the amount insurance companies pay

Pharmacies send the savings to safety-net providers that then invest savings to increase access to care

Patients that need financial help to afford medications can receive discounts or free medications

WHAT PROVIDERS ARE ELIGIBLE TO RECEIVE 340B DISCOUNTS?

- Federally Qualified Health Centers and Look-Alikes
- Ryan White clinics and state AIDS assistance programs
- Hospitals treating a disproportionate share of low-income patients
- Critical Access & Sole Community Hospitals
- Rural Referral Centers
- Cancer and Children's Hospitals
- Other federally funded clinics

Eligible providers must register and re-enroll annually to certify compliance, and are subject to HRSA and manufacturer audits. Safety-net providers must also document compliance methods to ensure no duplicate Medicaid discounts are applied and medication is only given to existing 340B patients. Non-compliance findings result in fines, corrective action plans, and possible termination from the program.

WHO IS CONSIDERED A 340B PATIENT?

ALL PATIENTS receiving healthcare at a 340B safety-net provider are allowed to benefit from the program. For patients who may not be able to afford medications, sliding fee discounts can be applied based on patient income, family size, and other factors. Savings support service expansion, allowing more patients to access needed health care.

MACHC
Mid-Atlantic Association of Community Health Centers

340B Is A Population Health Program

The federal government created the 340B program with the expectation that safety-net providers would invest savings to support essential programs and services benefitting communities

SAFETY-NET PROVIDERS REINVEST 340B SAVINGS IN ESSENTIAL HEALTH PROGRAMS LIKE

COMMUNICABLE DISEASE PROGRAMS

The 340B program has been instrumental in ending the Hepatitis C and HIV epidemics, enabling service expansion and ability to treat more patients to reduce community impact

CANCER SCREENING AND PREVENTION

A 2018 study found 340B-participating hospitals are more likely to provide mammograms and other breast cancer screenings than non-340B hospitals (L&M Policy Research)

SUBSTANCE USE DISORDER TREATMENT

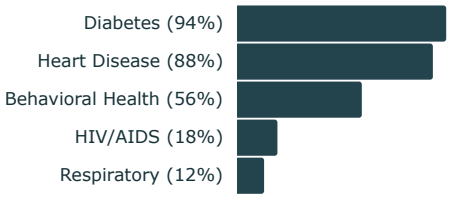
Savings from 340B allow many providers to offer comprehensive substance use treatment and detoxification services, regardless of a patient's ability to pay

MATERNAL HEALTH

Many safety-net providers invest 340B savings in pre- and perinatal programs to reduce maternal and fetal mortality & morbidity, keeping moms and babies healthy

340B IS ESSENTIAL TO TREATING AND MANAGING THE MOST COMMON CHRONIC CONDITIONS

Top Conditions Treated With 340B Drugs at Federally Qualified Health Centers



Percent of Federally Qualified Health Centers that ranked each condition as one of the top three treated with 340B medications (NACHC, 2022)

340B Medication Access Reduces Total Cost of Care | COPD Case Study

Pre-340B Participation	2.42 Visits Per Patient
Post-340B Participation	1.66 Visits Per Patient
Estimated Mean Cost Avoidance	$1012.82 Per Patient

COPD patients who received 340B discounted medications had fewer emergency department visits and hospitalizations (Taliaferro et al., 2023)

PRIMARY & PREVENTIVE CARE IS UNDERFUNDED IN THE U.S. | 340B IS CRITICAL TO AUGMENT

The U.S. has the highest per capita healthcare spending and lower life expectancy than similar economically developed countries. Strong primary care is associated with better population health, lower costs, and more equitable outcomes.

340B reduces emergency department visits, avoidable hospitalizations, and supports community health

MARYLAND LEGISLATIVE COALITION

Maryland Prescription Drug Affordability Board Comments on Proposed Drugs for Cost Review May 2024

I am submitting this comment on behalf of the Maryland Legislative Coalition (MLC), an association of activists - individuals and grassroots groups in every district in the state. We are unpaid citizen lobbyists, and our Coalition supports well over 30,000 members. We have been advocating for health care for all and affordable prescription drug prices since our inception in 2017.

Because the cost of prescription drugs for the citizens of Maryland had gotten so completely out of control, our members were happy to advocate for a first in the nation Prescription Drug Affordability Board. It was a bold step forward to stabilize prescription drug costs and keep the drug companies and insurance companies from gouging families across the state as they struggle to afford medications that they rely on to stay healthy and productive.

It has been several years since the Board was established, but due to the shortsightedness of the previous Governor, it had been languishing without full funding and without a complete roster of board members. Last year, with the help of activists, those problems were corrected.

In 2024, MLC supported legislation to expand the authority of the Prescription Drug Affordability Board through testimony and constituent emails to their legislators. The legislation would have allowed the five-member board to use upper payment limits to make high-cost medications more affordable for all Marylanders — not just those who work for state and local governments.

Almost all of our Coalition members struggle with high drug prices. They can't afford the copays. They can't afford to take medications that they need because those medications are priced out of reach. While we support the 8 drugs currently under review by the Maryland Prescription Drug Affordability Board, of particular interest is Vyvanse which appears to have more of an intergenerational impact. One of our young members has trouble finding the medication and when they do, the copay is $200/month. Without insurance, the cost can be as high as $500/month. It is unconscionable to saddle anyone with high prescription costs, especially those who have other expenses and nascent careers

MLC will continue to vehemently support the expansion of the authority of the Prescription Drug Affordability Board to include all Marylanders and more medications.

May 9, 2024

Maryland Prescription Drug Affordability Board
16900 Science Drive, Suite 112-114
Bowie, MD 20715

Re: Written comment on list of prescription drugs referred to the Stakeholder Council

Dear Members of the Prescription Drug Affordability Boad,

I write today as both the CEO of the Maryland Tech Council (the "Tech Council") and as the biotechnology representative on the Prescription Drug Affordability Board ("PDAB") Stakeholder Council. The Tech Council is a community of nearly 800 Maryland member companies that span the full range of the technology sector. Our vision is to propel Maryland to become the number one innovation economy for life sciences and technology in the nation.

Maryland is one of the leading states in the nation for the concentration of life sciences companies and jobs. The State is rich in assets that make life sciences innovation possible – with 54,000 life sciences jobs, 2,700 life sciences and biotechnology companies, world class universities, and government agencies. These companies are a critical asset to Maryland's economy. We consistently urge policymakers to bear this in mind when considering new policies that could harm our life sciences ecosystem. As a Stakeholder Council member and on behalf of the life sciences community, I am writing to note several overarching concerns about the initial list of drugs referred to the Stakeholder Council for cost reviews by the PDAB.

Principally, I want to echo several of the comments submitted to the Stakeholder Council about the lack of transparency and specificity as to how the initial eight drugs referred for cost reviews were selected. While we understand that each satisfies certain eligibility criteria from the adopted regulations, it is not clear why these drugs were selected among dozens of others that were not. Not having the methodology, additional criteria, data, or other context makes it difficult for the manufacturers of those products to respond to concerns about affordability. Publishing supplemental information about the selection process would bring additional transparency and credibility to the process.

Additionally, we urge the PDAB to consider the full picture of a patient's out-of-pocket costs when making determinations on the affordability of a drug. In discussions during April 29th Stakeholder Council meeting, it was stated that factors like patient co-pay assistance programs were not considered in the selection of these eight drugs. We do understand that it is the intent of the PDAB to consider patient assistance programs as part of the cost review process. However, we feel that not considering this information on the front end may result in companies having to undergo a burdensome cost review process and the possible imposition of an upper payment limit ("UPL") where it may not be warranted under the circumstances.

On behalf of Tech Council members in the life sciences industry, I also want to share that there is a high level of concern about what happens once a drug is considered unaffordable. Life sciences companies are spending an inordinate amount of time attempting to assess how a UPL would impact their businesses and the patients that they serve. It has been stated during multiple PDAB Stakeholder Council meetings that UPLs are just one potential tool to use if a drug presents an affordability challenge. What is unclear are what types of

other measures could be considered by the PDAB that are an alternative to UPLs. Selecting drugs without first knowing how a UPL will be applied, or what alternatives might be pursued, makes it very difficult for manufacturers to consider any unintended consequences of affordability measures and any impacts on patients and providers.

Lastly, I am taking this opportunity to again call on the PDAB to post the recordings of PDAB Board and Stakeholder Council meetings on the PDAB website for both future and prior meetings. This request has been made by me and other Stakeholder Council members on multiple occasions. To date, the PDAB has not directly addressed whether it will make prior recordings available. Publicly posting the prior recordings of these meetings would help increase transparency surrounding the PDAB's proceedings and will allow concerned patients, providers, and members of the public the opportunity to learn more about the process. We respectfully request a response on whether these recordings will be made publicly available.

Thank you for the opportunity to submit these comments.

Sincerely,

Kelly M Schulz

Kelly Schulz
CEO, Maryland Technology Council

National Eczema Association

May 10, 2024

Maryland Prescription Drug Advisory Board (MD-PDAB)
Subject Line: Drugs Referred to the Stakeholder Council Comment
Sent Via Email comments.pdab@maryland.gov

Dear MD-PDAB Board Members and Staff:

The National Eczema Association submits these comments in response to MD-PDAB's request for comments on drugs referred to the stakeholder council at the March 25, 2024 meeting. We present our concerns with the inclusion of Dupixent (dupilumab) on the referred list.

The National Eczema Association (NEA) is a non-profit, 501(c)(3) organization that is the voice for the more than 31 million Americans and their families who are living with eczema. NEA is the driving force for an eczema community fueled by knowledge, strengthened through collective action and propelled by the promise for a better future.

Eczema is the name for a group of conditions that cause the skin to become itchy, inflamed, and have rash-like lesions. Atopic dermatitis (AD) is the most common, and chronic form of eczema, affecting more than 9.6 million children[1] and about 16.5 million adults[2] of all races and ethnicities in the United States[3].

AD is a multidimensional, heterogeneous disease with significant burden that includes itch, pain, and sleep loss; social, academic, economic and lifestyle consequences; and negative effects on personal mental health as well as the health and wellness of the caregiver and family support system. More than 55% of people who are dealing with moderate to severe eczema have inadequate disease control[4 5 6].

The AD community has long-awaited treatments that can more effectively address the myriad negative disease symptoms and impacts to their quality of life. We are in the midst of a new era of care for eczema patients with several new FDA-approved groundbreaking therapies for AD, and dozens more in the drug discovery pipeline, which have the potential to be transformative in their ability to ease numerous physical, psychological, and quality of life burdens[7 8 9]. Dupilumab is one of these novel treatments and is unique in its FDA approval down to 6 months

[1] Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. J Invest Dermatol. 2011;131(1):67-73.
[2] Chiesa Fuxench ZC, Block JK, Boguniewicz M, et al. Atopic Dermatitis in America Study: A Cross-Sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. J Invest Dermatol. 2019;139(3):583-590.
[3] Hanifin JM, Reed ML, Eczema Prevalence and Impact Working Group. A population-based survey of eczema prevalence in the United States. Dermatitis. 2007;18(2):82-91.
[4] McCleary, K.K. *More Than Skin Deep 'Voice of the Patient' Report*. (2020).
[5] Simpson, E. L. *et al.* Association of Inadequately Controlled Disease and Disease Severity With Patient-Reported Disease Burden in Adults with Atopic Dermatitis. *JAMA Dermatol*. **154**, 903-912 (2018)
[6] Wei, W. et al. Extent and consequences of inadequate disease control among adults with a history of moderate to severe atopic dermatitis. *J. Dermatol*. **45**, 150-157 (2018).
[7] Drucker AM, Wang AR, Li WQ et al. The burden of Atopic Dermatitis: Summary of a report for the National Eczema Association. J Invest Dermatol. 2017;137(1):26-30.
[8] Chiesa Fuxench ZC, Block, JK, Boguniewicz M, et al. Atopic dermatitis in America study: A cross-sectional study examining the prevalence and disease burden of atopic dermatitis in the US adult population. J Invest Dermatol.2019;139(3):583-590.
[9] Silverberg J, Gelfand J, Margolis D et al. Patient burden and quality of life in atopic dermatitis in US adults. Ann Allergy Asthma Immunol. 2018;121(3):340-347.

National Eczema Association

of age. The availability of dupilumab and other newly FDA-approved treatments for AD enables patients and their healthcare providers much needed options to align on therapeutic goals and preferences and identify a treatment approach most appropriate for the unique clinical history, disease burdens, values and needs of those living with this disease.

We recognize that these groundbreaking therapies are presenting emerging coverage, access, and out-of-pocket (OOP) cost considerations for the eczema community. NEA is actively engaged in research that strives to assess and understand the real-world lived experience of AD, and how it is, or is not improving across the diverse patient and caregiver population with advances in care and treatment. Since 2019 we have conducted 10 surveys within the eczema community on the intersecting topics of OOP costs, access to care and prescription treatments, shared decision making, and mental health, among others[10]. Collectively, our research efforts have addressed numerous gaps in the understanding of the AD patient and caregiver perspective, identified notable drivers and contributors to patient burden, and illustrated concepts that require additional research to more fully elucidate their interconnectivity.

For example, our research found that 42% percent of individuals affected by AD spend at least $1,000 OOP annually for disease management[11]. This research also highlighted the significant breadth of OOP costs for AD, which included over 20 categories of medical, non-medical, and supportive care expenses. While specific data regarding the impact of prescription drug costs as a whole, or by class of drug on household finances remains a gap, our current analyses indicate that Black race, worse AD severity, having Medicaid insurance, and the use of three or more AD therapies were each found to be associated with higher OOP costs[12] [13].

Importantly however, our OOP survey also assessed costs related to prescriptions covered, and not covered by insurance, finding that 48.6% of individuals had incurred OOP expenses for a prescription which was not covered by their insurance[11]. Additional NEA research conducted in 2021 found that 50% of AD patients experienced an insurance delay/denial in the past year across all currently available AD topical and systemic therapies, with 31% of prescriptions for biologics encountering a patient-reported insurance delay/denial[14]. Our research further highlighted the other 'cost' implications to patients related to these access issues, including additional medical expenses for care (e.g., other medications, emergency/urgent care needs), disease flares, and pursuing other treatment approaches[15].

[10] Research We Do. https://nationaleczema.org/research-we-do/
[11] Smith Begolka, W., Chovatiya, R., Thibau, I.J. & Silverberg, J.I. Financial Burden of Atopic Dermatitis Out-of-Pocket Health Care Expenses in the United States. Dermatitis 32, S62-S70. 2021
[12] Chovatiya, R., Begolka, W.S., Thibau, I.J. & Silverberg, J.I. Financial burden and impact of atopic dermatitis out-of-pocket healthcare expenses among black individuals in the United States. Arch. Dermatol. Res. 2021: 10.1007/s00403-021-02282-3.
[13] Chovatiya, R., Begolka, W.S. Thibau, I.J. & Silverberg, J.I. Impact and Associations of Atopic Dermatitis Out-of-Pocket Health Care Expenses in the United States. Dermatitis. 2021. Doc: 10.1097/DER.0000000000000795.
[14] Loiselle, A.R., Thibau, I.J. & Guadalupe, M. A patient survey to identify atopic dermatitis prescription treatment access barriers. J Am Acad Dermatol. 2022: 10.1016/j.jaad.2022.06.073
[15] Chovativa, R., Begolka, W.S., Thibau, I.J. & Silverberg, J.I. The burden of atopic dermatitis polypharmacy and out-of-pocket healthcare expenses in the United States. 2022. Revolutionizing Atopic Dermatitis 2022 Conference.

National Eczema Association

We highlight the interconnectedness of cost and accessibility related to AD prescription treatments as we are concerned that additional cost and/or access issues could be an unintended consequence of MD-PDAB deliberations, should the availability of Dupixent for Maryland residents' change for those using state-based insurance plans.

In addition to the access issues already highlighted, we are additionally concerned about the potential for non-medical switching, which the NIH defines as, "a change in a stable patient's prescribed medication to a clinically distinct, non-generic, alternative for reasons other than poor clinical response, side-effects or non-adherence." Published medical literature has demonstrated multiple negative influences of non-medical switching on medical outcomes and healthcare utilization, including reduced medical adherence and poorer disease control[16] [17] [18]. Further, we are unclear how potential cost-savings to the state (i.e., establishing an upper price limit) will trickle down to alleviate patient OOP expenses and access challenges for Dupixent.

The eczema community has long-awaited these new treatments to address their significant unmet needs and improve their quality of life. We commend the MD-PDAB for their goal to reduce patient OOP costs and suggest that additional information is needed to best understand the affordability of newer medications from the perspective of the eczema community. Further, we hope that any discussion of managing costs for payers also results in transparent cost-savings for patients that does not compromise access to potentially life-changing therapies.

As you continue discussions, please consider us a resource to discuss our available data on efforts to improve patient care and address cost, coverage, and access challenges. You can reach out to Michele Guadalupe, Director of Advocacy and Access, at michele@nationaleczema.org with any questions.

Sincerely,

Julie Block, President & CEO

[16] J Mark Access Health Policy. 2020; 8(1): 1829883. Published online 2020 Oct 5. doi: 10.1080/20016689.2020.1829883
[17] Nguyen, Elaine et al. "Impact of non-medical switching on clinical and economic outcomes, resource utilization and medication-taking behavior: a systematic literature review." Current medical research and opinion vol. 32,7 (2016): 1281-90. doi:10.1185/03007995.2016.1170673
[18] Gilbert, Ileen et al. "The Impact of a Forced Non-Medical Switch of Inhaled Respiratory Medication Among Patients with Asthma or Chronic Obstructive Pulmonary Disease: A Patient Survey on Experience with Switch, Therapy Satisfaction, and Disease Control." Patient preference and adherence vol. 14 1463-1475. 20 Aug. 2020, doi:10.2147/PPA.S242215

May 10, 2024

Maryland Prescription Drug Affordability Board
16900 Science Drive Suite 112-114
Bowie, MD 20715

VIA EMAIL TO: comments.pdab@maryland.gov

Re: Drugs Referred to the Stakeholder Council Comment

Dear Maryland Prescription Drug Affordability Board:

Novo Nordisk appreciates the opportunity to submit written comments to the Maryland Prescription Drug Affordability Board (Board) regarding the inclusion of Ozempic® on a list of drugs that may be subject to a cost review. Novo Nordisk is a global healthcare company committed to improving the lives of those living with serious chronic conditions, including diabetes, hemophilia, growth disorders, and obesity. The Novo Nordisk Foundation, our majority shareholder, is among the top five largest charitable foundations in the world. Accordingly, our company's mission and actions reflect the Foundation's vision to contribute significantly to research and development that improves the lives of people and the sustainability of society.

The Board should decline to conduct a cost review of Ozempic®, as the unintended consequences of an upper payment limit (UPL) could adversely impact access to treatment and worsen health outcomes for patients living with diabetes and related chronic diseases.

Throughout our company's hundred-year history, we have had a steadfast focus on improving the lives of patients living with chronic diseases. Chronic diseases are the single biggest threat to life expectancy in the United States, erasing more than twice as many years as all car accidents, suicide, homicides, and overdoses combined. Furthermore, chronic diseases are responsible for 7 in 10 deaths each year,[1] and they are the primary reason that Americans have lower life expectancy than those in peer nations.[2] Despite these statistics, real progress in treating and preventing serious chronic diseases continues to be undermined by misguided policies that are unlikely to benefit patients. Novo Nordisk respectfully requests that the Board decline to conduct a cost review of Ozempic® for reasons summarized in greater detail below:

[1] US Centers for Disease Control and prevention. Chronic Diseases https://www.cdc.gov/chronicdisease/center/index.htm
[2] "An Epidemic of Chronic Illness is Killing Us Too Soon." Washington Post. October 3, 2023. https://www.washingtonpost.com/health/interactive/2023/american-life-expectancy-dropping/

Ozempic® *is a highly effective treatment option for Marylanders living with diabetes and co-morbid conditions.*

Diabetes imposes a particularly high lifetime burden of illness, this is in part due to its chronic nature, but also because of the serious complications that can arise if it is not managed effectively. These complications can include heart disease, stroke, kidney failure, vision loss, and nerve damage. Managing the disease requires continuous daily monitoring, medication, lifestyle changes and regular medical care, all of which contribute to an increase burden on individuals and healthcare systems. However, because of decades of research and development, people with diabetes now have highly effective new treatment options to treat and prevent complications arising from metabolic-related chronic diseases.

Ozempic® is a once weekly GLP-1 receptor agonist (RA) indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (T2D) and to reduce the risk of major adverse cardiovascular (CV) events (MACE) (CV death, non-fatal myocardial infarction (MI) or non-fatal stroke) in adults with T2D and established CV disease.[3] Our clinical trials have demonstrated Ozempic's® significant impact on diabetes and several of its comorbidities. This includes the some of the following findings: Ozempic® reducing A1C up to 2.1% in the SUSTAIN-FORTE clinical trial[4]; and a 26% relative risk reduction in MACE with a 39% reduction in rate of non-fatal stroke in SUSTAIN-6[5].

The efficacy and safety of Ozempic® was evaluated in the SUSTAIN clinical trial program. For glycemic efficacy, Ozempic® was compared to several other antidiabetic medications including sitagliptin 100 mg, exenatide ER 2 mg, insulin glargine U-100, dulaglutide 0.75 mg and 1.5 mg, canagliflozin 300 mg, and liraglutide 1.2 mg. Mean reductions in A1C from baseline ranged from 1.2%-1.5% and 1.5-1.8% for Ozempic® 0.5 mg and 1 mg, respectively, after 30 to 56 weeks of treatment, compared to 0–1.4% with placebo and active comparators. Throughout the glycemic control trials, both the 0.5 mg and 1 mg doses of Ozempic® demonstrated superior improvements in A1C vs. comparators.

Additionally, research and clinical trials have demonstrated the superiority of GLP-1 RA to other antihyperglycemic drugs in improving glycemic efficacy, reducing weight and blood pressure, and delivering a cardioprotective effect – all without the risk of hypoglycemia.[6] These drugs have transformed treatment guidelines for the management of patients with diabetes and are widely recognized as a standard of care.[7] While it is critical that patients who can benefit the most from these medications receive them, access issues persist. Recently conducted research in collaboration with Mass General Brigham[8] showed that within that healthcare system, 82.5%

[3] Ozempic® Prescribing Information. Plainsboro, NJ: Novo Nordisk Inc. https://www.novo-pi.com/ozempic.pdf
[4] Frías JP, Auerbach P, Bajaj HS et al. Efficacy and safety of once-weekly semaglutide 2.0 mg versus 1.0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomized, phase 3B trial. Lancet Diabetes Endo.
[5] 2021;9(9):563-574. doi:10.1016/S2213-8587(21)00174-1Marso SP, Bain SC, Consoli A, et al; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834-1844.
[6] Latif W, Lambrinos KJ, Rodriguez R. Compare and Contrast the Glucagon-Like Peptide-1 Receptor Agonists (GLP1RAs) [Updated 2023 Mar 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK572151/
[7] American Diabetes Association. Standards of care in diabetes—2024. Diabetes Care. 2024;47(suppl 1):S1- S321.
[8] J. Blood, Aleander et. Al., "Randomized Evaluation of a Remote Management Program to Improve Guideline-directed Medical Therapy: The Diabetes Remote Intervention to Improve Use of Evidence-based Medications (DRIVE) Trial." 7 April 2024. https://doi.org/10.1161/CIRCULATIONAHA.124.069494. Circulation. 2024;0

of patients with T2D also have a CV and/or kidney condition. Among those patients with multiple conditions, 66.9% are not receiving guideline-recommended care (either SGLT2i or GLP-1 RA therapy). Patients who are not receiving the standard of care for the treatment of diabetes are more likely to face complications that require further medical care, which subsequently places additional burdens on the patient and the healthcare system.

In 2022, the total direct medical costs associated with those living with diabetes was $307 billion[3]. Of that $307 billion, only 8%, or $24.7 billion, was associated with the costs of non-insulin antidiabetic medications such as Ozempic®. On the other hand, medical expenses such as inpatient hospital care, ER visits, and outpatient office visits accounted $169.5 billion, or 55.2% of the direct medical costs. According to the most recent Maryland Diabetes Action Plan, direct medical spending accounted for $4.29 billion in 2017.[9] GLP-1 medications hold the promise of saving the healthcare system billions of dollars over a ten-year period by reducing demand for hospital and skilled nursing care.[10]

Novo Nordisk is committed to ensuring patients living with diabetes can afford our medications, and this is a responsibility we take seriously.

At Novo Nordisk, we strive to develop sustainable affordability options that balance patient affordability, market dynamics, and evolving policy changes. Novo Nordisk contracts with payers throughout the state, offering rebates to ensure formulary placement and appropriate patient access to our medications**.** In 2023, Novo Nordisk's cumulative rebates and discounts across our entire US portfolio amounted to 74% of gross sales (75% in 2022 and 75% in 2021).[11] In addition to paying rebates in the commercial market, manufacturers are also required to pay significant statutory discounts and rebates to the government. Under the current reimbursement paradigm, rebates play a central role in how insurers manage the prescription drug benefit. A recent analysis of data from SSR Health's net price database across 10 major manufacturers showed that the gap in value between list prices and net prices (after rebates and other reductions) among brand name drugs reached $300 billion in 2022. The unweighted average discount off the list price was 53.5%, meaning that manufacturers sold their products, on average, for less than half of the list price.[12]

However, when examining the overall costs to health care systems in Maryland, the Board evaluated gross spend, i.e. the list price, which is a poor indicator of the cost of a medication for most patients and health insurers. According to a recent analysis, brand-name drugs' list prices grew at mid-single-digit rates in 2023. Net prices, however, dropped for a sixth consecutive year and by 7% after adjusting for inflation.[13] Despite the growing divergence between list and net prices, average out-of-pocket (OOP) spending for most diabetes prescriptions in the U.S. remains low. According to an analysis by IQVIA, OOP spending was less than $30 across 83%

[9] Maryland Diabetes Action Plan 2020. Diabetes Action Plan June 1 2020.pdf (maryland.gov)
[10] Alison Sexton Ward, PhD, Bryan Tysinger, PhD, PhuongGiang Nguyen, MSPH, Dana Goldman, PhD and Darius Lakdawalla, PhD. Benefits of Medicare Coverage for Weight Loss Drugs. April 18, 2023.https://healthpolicy.usc.edu/research/benefits-of-medicare-coverage-for-weight-loss-drugs/.
[11] Novo Nordisk. 2023 Annual Report. Novo Nordisk Annual Report 2023 (PDF)
[12] Fein, AJ. Gross-to-Net Bubble Update: 2022 Pricing Realities at 10 Top Drugmakers. *Drug Channels Institute*. 2023 Jun 13 [cited 2024 Jan 18]. Available from: https://www.drugchannels.net/2023/06/gross-to-net-bubble-update-2022-pricing.html
[13] Fein, AJ. U.S. Brand-Name Drug Prices Fell for an Unprecedented Sixth Consecutive Year (And Will Fall Further in 2024). https://www.drugchannels.net/2024/01/tales-of-unsurprised-us-brand-name-drug.html. January 3, 2024.

of diabetes prescriptions (based on April 2020 claims data across payers).[14] Internal data shows that 99.6% of patients in Maryland in Medicaid on average have an OOP cost of less than $5, and 82.5% of Marylanders who have commercial insurance pay less than $25 on average for Ozempic®.[15]

However, for patients who continue to struggle to afford their medication, either due to inadequate plan benefit design or a lack of coverage altogether, Novo Nordisk provides additional financial support through our affordability programs. We allow uninsured patients in financial need to access our products at no cost, and we also provide copay assistance for Ozempic® that reduces a commercially insured patient's out-of-pocket cost to as little as $25. Information about our patient assistance programs can be found at www.novocare.com. Novo Nordisk remains committed to ensuring access to our medications by reducing the out-of-pocket cost burden, simplifying a complex pricing system, and fostering better pricing predictability for the patients we serve.

A UPL could disrupt patient access to diabetes treatments in Maryland.

As demonstrated by our efforts, we share the Board's interest in making prescription drugs affordable to patients, but shortsighted policies that impose price controls will only undermine these efforts, as patient access is likely to be compromised. The largest pharmacy benefit managers (PBMs) in the US exert significant control over the treatment options available to patients.[16] Through formulary designs, PBMs direct patients to medications that can generate the highest rebates from manufacturers. A recent Government Accountability Office (GAO) report found that "…plan sponsors frequently gave preferred formulary placement to highly rebated, relatively higher-gross-cost brand-name drugs compared to lower-gross-cost competitor drugs, which generally had lower rebates".[17] Because of these perverse incentives, products subject to a UPL may be *less* attractive to insurers and PBMs relative to competitor products that can continue to offer higher rebates.

Numerous case studies underscore these unintended consequences within the prescription drug supply chain. In one recent example, a drug manufacturer launched a biosimilar of the long-acting insulin glargine at a 65% lower price relative to the reference product's wholesale acquisition cost (WAC). After little formulary uptake, the biosimilar manufacturer opted to launch a higher-priced version of the same product, with the ability to now pay rebates at a similar level to the reference product. According to an IQVIA analysis, PBMs largely favored the higher-priced version because it allowed them to generate rebate revenue.[18]

[14] IQVIA. *Diabetes Costs and Affordability in the United States*. 2020 Jun 29 [cited 2024 Feb 7]. Available from: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/diabetes-costs-and-affordability-in-the-united-states

[15] IQVIA LAAD February 2023 – January 2024.

[16] Fein AJ. "The Top Pharmacy Benefit Managers of 2021: The Big Get Even Bigger." Drug Channels. April 5, 2022. https://www.drugchannels.net/2022/04/the-top-pharmacy-benefit-managers-of.html

[17] Government Accountability Office (GAO). CMS Should Monitor Effects of Rebates on Drug Coverage and Spending. Statement of John E. Dicken, Director, Health Care Before the Subcommittee on Health, Committee on Energy and Commerce, House of Representatives. https://www.gao.gov/assets/gao-23-107056.pdf. September 19, 2023.

[18] IQVIA. Lessons from Semglee: Early Perspectives on Pharmacy Biosimilars. 2022 [cited 2024 Apr 25]. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/us/white-paper/2022/lessons-from-semglee-early-perspectives-on-pharmacy-biosimilars.pdf

Despite these risks, the Board is embarking on cost reviews with little consideration for the potentially significant unintended consequences of a resulting UPL. The Board has not taken steps to ensure that patients will be able to access products that may be subjected to a UPL. There are presently no beneficiary protections or formulary requirements for patients seeking treatment for a product that may be subjected to a UPL. This heightens the risk of downstream access barriers for patients, including an interruption in continuity of care, prior authorization hurdles in accessing a prescribed therapy, and improper utilization management tactics that force patients to switch or delay treatment.

The Board assumes that a UPL will work for Marylanders—but recent evidence suggests otherwise. UPLs fail to recognize the complex dynamics within the supply chain and are more likely to cause foreseeable harm to patients' ability to access prescribed medications.

Maintaining access to Ozempic® is crucial for patients living with T2D. With its proven effectiveness in lowering blood sugar levels and reducing the risk of cardiovascular events, Ozempic® represents a valuable treatment option for managing diabetes and improving overall health outcomes. Ensuring access to Ozempic® enables patients to benefit from its therapeutic advantages, which ultimately leads to better disease management, enhanced quality of life, and to potentially reduced health-care costs associated with diabetes-related complications.

Novo Nordisk is committed to working with patients and payers to ensure that those who benefit from our medications have access to them. Because Ozempic® is both highly effective and broadly affordable, we respectfully request that the Board not move forward with a cost review, as the unintended consequences of a UPL could upend care for thousands of Marylanders living with diabetes.

Thank you for the opportunity to provide comments and for your consideration of the issues raised in this letter. Should you have any questions or concerns, please contact Ryan Urgo, Head of Policy, at RVUR@novonordisk.com for additional information.

sanofi

May 10, 2024

Maryland Prescription Drug Affordability Board
16900 Science Drive, Suite 112-114
Bowie, MD 20715

Re: Drugs Referred to the Stakeholder Council

Dear Members of the Maryland Prescription Drug Affordability Board,

Sanofi appreciates the opportunity to submit comments to the Maryland Prescription Drug Affordability Board ("Board") on the list of drugs referred to the Stakeholder Council. For the reasons listed below, **we respectfully ask that the Board decide not to conduct any drug cost review at this time and at minimum decide not to conduct any cost review of Dupixent®.**

Dupixent, which Sanofi commercializes with its partner, Regeneron, is a biologic medication that blocks the signaling of two key sources of Type 2 inflammation (IL-4 and IL-13) and is currently indicated in the treatment of five conditions: eczema/atopic dermatitis; asthma; nasal polyps; eosinophilic esophagitis; and prurigo nodularis. Given these five indications, Dupixent's utilization is higher than if five separate drugs were developed to treat these conditions – evidence of the value it provides to the healthcare system and to patients. Dupixent was also the first advanced therapeutic approved to treat four of its five indications and remains the only approved advanced therapy down to six months of age in atopic dermatitis and one year of age in eosinophilic esophagitis, representing transformative scientific breakthroughs for patients suffering from those diseases and further demonstrating the value and innovation it brings to patients and the healthcare system.

I. Dupixent is affordable for Maryland patients

sanofi

a. Dupixent has already undergone a review by a nationally recognized, independent nonprofit healthcare research institute and was deemed cost effective

Dupixent was evaluated as part of the drug class used to treat atopic dermatitis by the Institute for Clinical and Economic Review ("ICER") at its initial launch in 2017. ICER is "an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs."[1] And ICER serves as a "non-partisan, independent, go-to resource for objective evidence about the value of health care in the US."[2] In 2017 when Dupixent launched in the market, ICER reviewed its clinical effectiveness and value. At that time, ICER "found the price of dupilimab [i.e., Dupixent] to be in line with its value."[3] ICER's Chief Medical Officer, Dr. David Rind, MD, MSc stated "Our analyses showed that dupilumab [i.e., Dupixent] offers important clinical benefit for patients with moderate-to-severe atopic dermatitis. Moreover, the drug was priced in a way that aligns well with the benefit it provides to patients."[4]

In the years following Dupixent's initial approval for atopic dermatitis, its value to the healthcare system has only increased with the approvals of four additional indications, and more indications are being studied in our research pipeline. At the same time, Sanofi has acted in line with our Pricing Principles,[5] taking reasonable price increases in the years since its launch. In fact, Sanofi has never had a product, including Dupixent, included in ICER's annual "Unsupported Price Increase Report." This determination of cost effectiveness at launch, coupled with our

---

[1] *See* Institute for Clinical and Economic Review. What is ICER? *at* https://icer.org/what-is-icer/.
[2] Id. As of 2019, twenty state Medicaid agencies reportedly used ICER data in their Medicaid drug reviews. *See* Use of Comparative Effectiveness Reviews in Medicaid Drug Reviews, *at* https://www.kff.org/other/state-indicator/use-of-comparative-effectiveness-reviews-in-medicaid-drug-reviews/?currentTimeframe=0&selectedDistributions=state-incorporates-comparative-effectiveness-review-cer-information-in-drug-coverage-reviews--cer-info-sources&sortModel=%7B%22colId%22:%22CER%20Info%20Sources%22,%22sort%22:%22asc%22%7D.
[3] Institute for Clinical and Economic Review. (2017). Atopic Dermatitis: Final Evidence Report. Retrieved from https://icer.org/wp-content/uploads/2020/10/MWCEPAC_ATOPIC_FINAL_EVIDENCE_REPORT_060717.pdf
[4] Id.
[5] *See* Sanofi 2024 Pricing Principles Report *at* https://www.sanofi.us/assets/dot-us/pages/images/our-company/Social-impact/diversity-equity-and-inclusion/employee-resource-groups/Employee-Resource-Groups/pricing-principles/Sanofi-2024-Pricing-Principles-Report.pdf (also attached in Appendix)

commitment to responsible price increases, leads to a conclusion that Dupixent remains a good value to patients and to the system and that it would be inappropriate for the Board to focus on Dupixent for a drug cost review, let alone its first drug cost review.

b. Sanofi's Copay Assistance and Patient Assistance Program are utilized by a significant percentage of Maryland patients

We understand that affordability to most patients is not about list price, but rather the price paid by the patient at the pharmacy counter. Pharmaceutical manufacturers do not control a patient's copay – that cost is determined by their health plan. Recognizing this, manufacturers do provide assistance to patients to help offset high copays that result from insurers' benefit design. Sanofi is committed to addressing this challenge and offers a copay card program for Dupixent patients in Maryland and nationwide to help ensure affordable access to this innovative treatment.[6]

In 2022, 72% of commercially insured patients in Maryland received copay assistance from Sanofi. With the Dupixent MyWay® Copay Card, which subsidizes commercially insured patients' out-of-pocket drugs costs, these patients may pay as little as $0* copay per fill of Dupixent.[7] According to our data, in 2022 the average out of pocket cost after manufacturer assistance was $38.53 per one month supply of Dupixent[8] for commercially insured patients in Maryland. All commercially insured patients are eligible for our copay card, and the enrollment process is quick and easy – as simple as filling out a form on our website.[9]

Additionally, through the Dupixent MyWay® Patient Assistance Program, qualified patients with incomes significantly above the Federal Poverty Level, up to $100,000 in income, who are uninsured or whose insurance does not cover Dupixent receive their medication at no cost.[10] The Dupixent MyWay® Support Team is available by phone 24/7 to help

[6] *Eligibility requirements and amount of assistance are subject to change. *See* Dupixent MyWay® Copay Card, *at* https://www.dupixent.com/support-savings/copay-card.
[7] *See* Dupixent Copay Card Enrollment, *at* https://www.dupixent.com/support-savings/copay-card-enrollment.
[8] Some indications may require different dosing.
[9] Id.
[10] *See* Dupixent MyWay® Program, *at* https://www.dupixent.com/support-savings/dupixent-my-way.

patients and healthcare providers to access the program.[11] 1,280 Maryland patients qualified for and received their Dupixent prescriptions at no cost through our Patient Assistance Program in 2023.

The Board should consider the breadth of these Sanofi programs, which lower or eliminate Maryland patients' out-of-pocket costs, in evaluating Dupixent's affordability. Based on the above data, Dupixent is affordable to Maryland patients, so the Board should not review this product and certainly not prioritize its review.

II. Dupixent represents exactly the type of innovation that public policy should protect

a. Dupixent has an orphan designation

Additionally, Sanofi asks the Board to consider that Dupixent's indication for eosinophilic esophagitis ("EoE") was approved as an orphan drug designation. According to the American Partnership for Eosinophilic Disorders ("APFED"), "EoE is a chronic, allergic inflammatory disease of the esophagus (the tube connecting the mouth to the stomach). It occurs when a type of white blood cell, the eosinophil, accumulates in the esophagus. The elevated number of eosinophils cause injury and inflammation to the esophagus. This damage may make eating difficult or uncomfortable, potentially resulting in poor growth, chronic pain, and/or difficulty swallowing."[12] Dupixent is the first FDA-approved therapy to treat patients with EoE. Dupixent is also currently being studied in patients with bullous pemphigoid, a rare autoimmune disease that causes painful skin blisters and many patients' disease is not adequately controlled with currently approved therapies.[13]

Medicines approved to treat rare diseases are exempt from certain laws and regulations, as a recognition that patients suffering from rare diseases can benefit only when companies are willing to assume the risks involved in orphan drug development. Other state Prescription Drug Affordability

[11] Contact 1-844-DUPIXENT (1-844-387-4936) to speak to a DUPIXENT MyWay Case Manager or representative.
[12] *See* APFED "What Are EGIDS? – About EoE" *at* https://apfed.org/about-ead/egids/eoe/.
[13] Zhao L, Wang Q, Liang G, et al. Evaluation of Dupilumab in Patients With Bullous Pemphigoid. *JAMA Dermatol.* 2023;159(9):953–960. doi:10.1001/jamadermatol.2023.2428.

Boards, such as Oregon's,[14] exempt drugs with orphan indications. The Board should follow Oregon's example in this regard and omit Dupixent and other orphan drugs from review. Any untested tampering with the economics of an orphan drug may discourage manufacturers like Sanofi from taking the financial risks necessary for orphan drug development.

b. Dupixent is still being studied in other indications that have no currently approved advanced therapies

Sanofi remains committed – and devotes significant resources – to exploring other potential disease states and patient populations that could benefit from Dupixent. A recent clinical trial showed positive results in some patients with chronic obstructive pulmonary disease ("COPD") who were treated with Dupixent.[15] There are currently no biologic products approved to treat COPD, and many COPD patients' symptoms are not well controlled with currently approved therapies.

We believe that Dupixent may also benefit patients in other indications, and strongly encourage the Board to consider the potential chilling effect that a price control could have on this type of innovation. In fact, Dupixent represents precisely the type of innovation and approach to pricing that should be encouraged in our industry – pursuing first-in-class or best-in-class medicines that have the potential to transform the practice of medicine for patients, and pricing those medicines in a manner that reflects the value they provide to patients and society.

III. The Board has provided insufficient data for a complete response and has failed to follow a reasonable process

The Board recently posted to its website incomplete data on the eight selected drugs that is simply described as a "sample database that includes non-proprietary data and data that has been approved for public display".[16] The provided chart does not address the Board's methodology, list its sources for the data it includes, describe how the Board identified the eight

[14] Or. Rev. Stat. § 646A.694 (2021).
[15] Bhatt, Surya P., et. al. (2023). Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. *New England Journal of Medicine*, 389, 205-214. DOI: 10.1056/NEJMoa2303951
[16] *See* Cost Review Study Process Updates, *at* https://pdab.maryland.gov/cost_review_process.html.

drugs it referred to the Stakeholder Council, nor show the data for any drug reviewed but not referred to the Stakeholder Council. Thus, Sanofi remains concerned that the methodology, data sources, and criteria used by the Board to identify drugs for inclusion in this list was not made available to the public and may not accurately prioritize drugs that pose actual affordability challenges for patients. For example, we note that the Board's chart includes out-of-date information, such as the Medicare patient out-of-pocket cost and spending data from 2020, which predates the Inflation Reduction Act's Medicare rebates that cap drug price increases to economy-wide inflation for that program and reduce and cap patient out-of-pocket costs. The Board should halt any consideration of a cost review until these data issues are resolved, lest the Board arbitrarily and unnecessarily pull inappropriate drugs, like Dupixent, into its cost review process.

The Board also must adequately explain why it is treating these eight drugs differently than the thousands of other drugs that were eligible for a Stakeholder Council referral. Without such an adequate explanation, the decision to refer these eight drugs for Stakeholder Council discussion was, and any decision to conduct a cost review on them would be, inherently arbitrary and unreasonable and would raise serious concerns under State and Federal law. (Sanofi recognizes that there was brief discussion of the eight drugs at the March 25, 2024 Board meeting, but this discussion did not address the factors applied or evidence considered by the Board in deciding to refer these drugs to the Stakeholder Council. Moreover, this discussion was particularly insufficient because the Board has not publicly released recordings or transcripts of this and other recent Board meetings.)

The Board has likewise failed to articulate standards for selecting drugs for cost review and has not yet established an "action plan" for determining upper payment limits ("UPLs") and/or applying UPLs in practice. Likewise, the Maryland Prescription Drug Affordability Board statute and regulations do not define key cost review terms such as "affordability challenge" or "high out-of-pocket costs," and while these authorities describe numerous factors for the Board to consider when identifying drugs for a cost review, they do not describe how to weigh them. Plus, neither the Maryland statute nor regulations articulate a standard for what would be an appropriate UPL. The Board cannot implement a reasonable and compliant cost review process without first filling these major gaps, so the Board should delay its cost review until it has done so.

Finally, the Board has given itself too little time to consider public comments in advance of the May 20, 2024 Board meeting – only 10 days to review comments regarding the eight drugs referred to the Stakeholder Council and only seven days to review comments regarding the therapeutic alternatives lists – given that meeting's agenda to select drugs for cost review and to approve lists of therapeutic alternatives. As Sanofi will note in detail in its forthcoming comments on the therapeutic alternatives identified for Dupixent, determining appropriate therapeutic alternatives requires a nuanced and complex analysis, especially for products such as Dupixent that have five approved indications. To ensure that the selected alternatives are reasonable and genuinely meet patient therapeutic needs, each potential alternative must be analyzed under many factors, including but not limited to, each drug's safety, efficacy, pharmacology, and cost-effectiveness. Even where therapeutic alternatives are available, whether and how patients respond to them will vary significantly. We do not see how the comprehensive data regarding the dozens of potential therapeutic alternatives to the eight referred drugs can reasonably be reviewed by the Board in so little time. Therefore, the Board should not vote to approve any drug for cost review or any therapeutic alternative during its meeting on the May 20, 2024.

IV. Over-emphasizing a medicine's list price will not necessarily improve patient affordability, and will likely impede patient access

The list price of a drug is not the price that most patients pay at the pharmacy counter. As noted above, a patient's copay is set by their health plan, not the manufacturer. Further, commercially insured patients' out-of-pocket costs are reduced by the drug manufacturer copayment support programs noted above, and many patients pay nothing for their drugs through patient assistance. Over-emphasizing the list price of a medicine in Maryland's cost review is unreasonable and will fail to adequately address patient access and affordability challenges. A price control will likely also have unintended consequences such as impairing patient access to their medicines and undercutting pharmaceutical innovation. We encourage the Board to consider recommendations for broader reforms that will truly make the health care system work better for all patients.

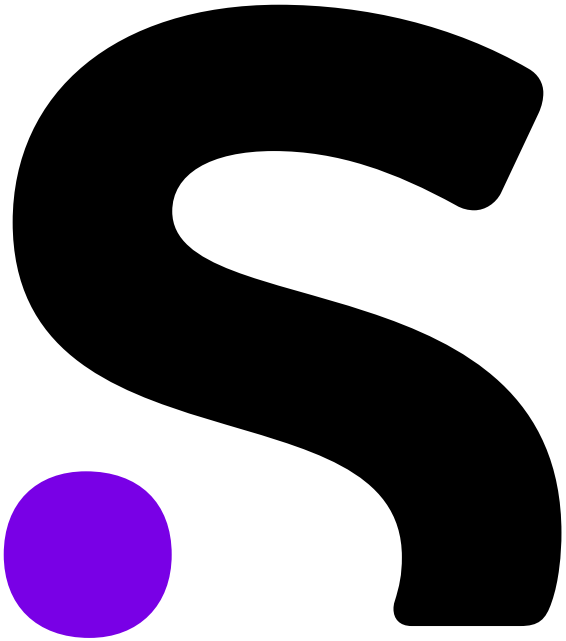
Thank you for the opportunity to provide comments and for considering our concerns. We hope that after considering this information, **the Board will decide not to conduct any drug cost review at this time, and at minimum decide not to conduct any cost review of Dupixent.**

Please feel free to contact me at deanne.calvert@sanofi.com with any questions.

Sincerely,

Deanne Calvert
Head, State Government Relations, Sanofi

APPENDIX



sanofi

2024 Pricing Principles Report

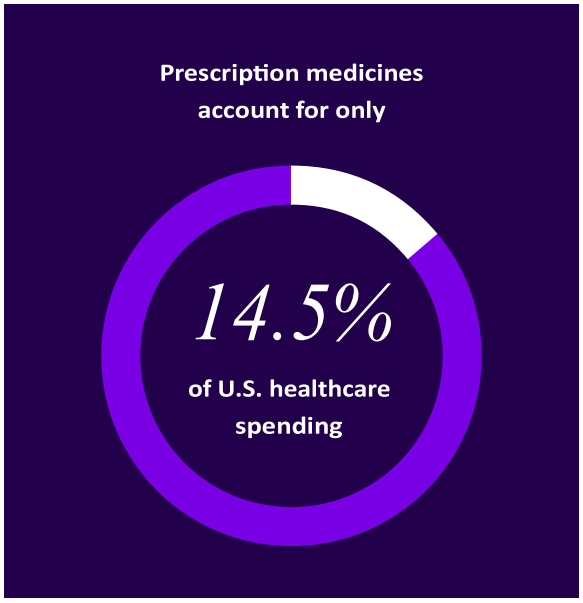
Advancing Responsible Leadership

Prescription Medicine Pricing: Our Principles and Perspectives

At Sanofi, we work passionately to help prevent, treat, and cure illness and disease, understand and solve healthcare needs of people across the world, and transform the practice of medicine.

Our focus spans a number of therapeutic areas, including:

Immunology *Rare diseases* *Rare blood disorders* *Vaccines* *RSV* *Diabetes* *Cardiovascular diseases* *Neurology* *Oncology* *Transplant*



Sanofi has a longstanding commitment to promote healthcare systems that make our treatments accessible and affordable to those in need. We understand and share concerns about the affordability of medicines for patients while also recognizing that we are only one of many stakeholders involved in healthcare delivery. In the United States, medicines are a small share – about 14.5%[1] – of total healthcare spending.

To maintain an environment that will continue to bring new healthcare solutions to patients, **we must encourage a transition to a value-driven healthcare system that provides incentives for the highestquality care.** This evolution will enable both affordable access to treatments and continued investment in medical innovation.

Sanofi is committed to helping address this challenge. While many factors, including decisions affecting patient out-of-pocket spending and insurance coverage, are controlled by other stakeholders in the U.S. healthcare delivery continuum, **we believe we have a responsibility to be a leader in addressing issues of patient access and system sustainability.** For our part, we price our medicines according to their value, while advancing broader solutions that improve patient outcomes and support affordability within the U.S. healthcare system.

1. The Altarum Institute. Projections of the Prescription Drug Share of National Health Expenditures Including Non-Retail. July 2022.

Our Pricing Principles:

Advancing Responsible Leadership in Access & Affordability

Pharmaceutical innovation brings value to patients, society, and healthcare systems. Given ongoing concerns over rising healthcare costs, our approach to pricing reflects our commitment to patient access while minimizing our contribution to overall healthcare system spending.

We, therefore, commit to both continued transparency in how we price our prescription medicines and to limit increases in prices in the United States.

The Pricing Principles we put forth focus on three pillars:

1. ***Clear rationale for pricing*** *at the time of launch of a new medicine*
2. ***Reporting of U.S. pricing actions*** *on our medicines over time*
3. ***Continued transparency in the United States*** *around our pricing decisions*

"

Responsible pricing is not just a policy; it's a promise to our patients that we will hold ourselves accountable for the life-saving medicines and vaccines we discover, develop, and bring to market.

Adam Gluck
Head, U.S. and Specialty Care
Corporate Affairs, Sanofi

Clear Rationale for Pricing

When we set the price of a new medicine, we hold ourselves to a rigorous and structured process that includes consultation with external stakeholders and considers the following factors:

A holistic assessment of value, *including:*

1. **Clinical value and outcomes**, or the benefit the medicine delivers to patients, and how well it works compared to a of care
2. **Economic value**, or how the medicine reduces the need for — and therefore spend on — other healthcare interventions
3. **Social value**, or how the medicine contributes to quality of life and productivity standard

Our assessments rely on a range of internal and external methodologies, including health technology assessment (HTA) and other analyses, that help define or quantify value and include patient perspectives and priorities.

Comparable treatments available or anticipated

We review similar current or future treatment options at the time of launch to understand the landscape within the disease areas in which our medicines or vaccines may be used.

System-wide affordability

We consider the steps we must take to promote access for patients and contribute to a more sustainable system for payors and healthcare systems.

Unique launch factors

There may be factors specific to a medicine or vaccine at the time of launch. For example, we may need to support ongoing clinical trials to reinforce the value of our medicines (e.g., longer-term outcomes studies), implement important regulatory commitments, or develop sophisticated patient support tools that improve care management and help decrease the total cost of care.

Reporting of U.S. Pricing Actions

We acknowledge our role in preserving the sustainability of our healthcare system and in limiting our contribution to U.S. healthcare spending growth.

On January 1, 2023, with the passage of the Inflation Reduction Act and the presence of other evolving market dynamics, Sanofi revised the “Limited U.S. Price Increases” policy we first established in 2017. As of 2023, our approach to pricing our medicines responsibly balances:

Our ambition to chase the miracles of science to improve people's lives and

"

Every decision we make is done with the patient in mind, ensuring that we remain a driving force for both innovation and affordability in healthcare.

Deborah Glasser
Head, Specialty Care
North America and
U.S. Country Lead

ensure patients have access to the medicines they need now and in the future;

Government policies; and

Evolving trends in the marketplace.

For any list price actions taken by Sanofi during the fiscal year 2023 on any of our medicines, the guiding principle was to adhere to a level that is consistent with our approach on responsible pricing.

Sanofi will annually disclose additional background if price actions trigger a prescription drug mandatory supplemental rebate under the Inflation Reduction Act of 2022.

Continued Transparency in the United States

To maintain an open dialogue and recognize calls for continued transparency in our pricing actions, **we will annually disclose our average aggregate U.S. list and net price changes from the prior calendar year.** These data illustrate how the U.S. healthcare system impacts the way pricing changes accrue to manufacturers versus others in the healthcare delivery continuum. The data also highlight our discrete role in the U.S. healthcare system, i.e., what we as a maker of medicines can control. We believe this information contributes to better-informed discussions to improve patient access and affordability.

While our efforts focus on securing affordable coverage of our medicines for patients, it is important to note that patient cost-sharing and coverage decisions are ultimately made by payors and employers, not manufacturers of the medicines.

Simply put, patients' out-of-pocket costs depend on how their healthcare insurance coverage is structured and the extent to which their health plan passes negotiated discounts to patients.

Our principles reflect both a desire to help our stakeholders better understand our pricing decisions and to advance a more informed discussion of issues related to the pricing of medicines.

While list prices often receive the most public attention, they do not reflect the price patients pay at the pharmacy counter, nor do they typically reflect the price Sanofi is paid for our medicines.

List prices...

our

...are not the prices typically paid by the insurers, employers, or pharmacy benefit managers who purchase medicines on behalf of patients in their respective health plans. We negotiate discounts and rebates with payors, designed to offer the healthcare system lower prices in exchange for greater access and affordability for patients with insurance.

...fail to capture the substantial mandated discounts and rebates, sometimes required by law, provided to government programs, including those provided in Medicare Part D, Medicaid, and the 340B drug pricing programs.

Net prices...

fees

...are what Sanofi receives after discounts, rebates, and paid to health plans and other parts of the healthcare system.

...take into account copay expenses that help reduce patients' prescription medicine costs.

Clear Rationale for Pricing

ALTUVIIIO® [Antihemophilic Factor (Recombinant), Fc-VWF-XTEN Fusion Protein-ehtl]

Sanofi introduced ALTUVIIIO in the United States in March 2023 for routine prophylaxis and on-demand treatment to control bleeding episodes and perioperative (surgery) management of bleeding in adults and children with hemophilia A. ALTUVIIIO is the first and only once-weekly hemophilia A treatment that delivers factor activity levels in the normal to near-normal range (over 40%) for most of the week.

Hemophilia A is a rare, lifelong condition in which the ability of a person's blood to clot properly is impaired, leading to excessive and spontaneous bleeds into joints that can result in joint damage and chronic pain, and potentially impact quality of life. The severity of hemophilia is determined by the level of clotting factor activity in a person's blood, and there is a negative correlation between risk of bleeding and factor activity levels.

A Look Back: 2023 Report Card

In May 2017, Sanofi expanded on its commitment to tackle rising healthcare costs with the introduction of our Pricing Principles. Our goal – then and now – is to promote a culture of transparency that would be adopted not only in our industry, but across healthcare – including hospitals and payors – where transparency is often sorely lacking.

Our Pricing Principles are a reflection of our unwavering dedication to providing patients with innovative and life-changing treatments while limiting costs and minimizing our contribution to healthcare spending growth.

The following report outlines our 2023 pricing decisions.

At launch, Sanofi set the U.S. list price of ALTUVIIIO at $5.11 per international unit (IU). As a weight-based dosing regimen, costs per course of ALTUVIIIO treatment will vary by patient. ALTUVIIIO is priced at parity to the annual cost of treating a Hemophilia A patient prophylactically on ELOCTATE® [Antihemophilic Factor (Recombinant), Fc Fusion Protein], another recombinant factor VIII from Sanofi, to ensure that patients have access to the improved bleed protection provided by ALTUVIIIO. Actual costs to patients, payors, and health systems are anticipated to be lower as list pricing does not reflect discounts, rebates, or patient assistance programs.

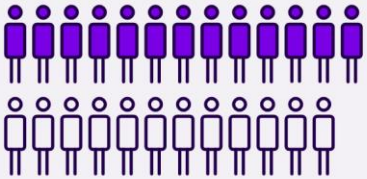
The pricing of ALTUVIIIO reflects Sanofi's commitment to responsible pricing to help ensure all appropriate patients have access to ALTUVIIIO. To set the list price of ALTUVIIIO, Sanofi considered input from payors, pharmacists, and physicians while also recognizing the experience of patients living with hemophilia A. And Sanofi is committed to demonstrating the cost-effectiveness of ALTUVIIIO via real world analyses in published posters and ongoing research.

Sanofi Patient Support Services for ALTUVIIIO is committed to helping eligible U.S. patients access the support they need. Assistance includes disease and medication education, electronic enrollment, financial support, insurance investigation paired with ePrescribing technology, and ongoing help to address barriers throughout the treatment journey.

Beyfortus® (nirsevimab-alip) 50 mg and 100 mg Injection

Sanofi, in partnership with AstraZeneca, introduced Beyfortus 50mg and 100mg Injection in the United States in September 2023. Beyfortus is the first and only long-acting monoclonal antibody indicated for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease (LRTD) in newborns and infants born during or entering their first RSV season, and for children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

At launch, Sanofi set the U.S. list price of Beyfortus at $495 per dose. The 50mg and 100mg formulations carry the same price to simplify access. For those infants who remain vulnerable through their second RSV season, they are administered 200mg (2 x 100mg injections).



Currently, there are an **estimated 25,000 patients in the United States with hemophilia A** across all severity levels, of which approximately **13,000 are treated.**

= ~1,000 patients = patients treated

Sanofi priced Beyfortus in accordance with the public health value and innovation it delivers to infants and their families, health systems, and society. The price was determined by considering a range of factors, including the prevention of RSV in infants and the cost burden of RSV-related complications and hospitalizations. As presented in economic models shared during the June 22, 2023, Advisory Committee on Immunization Practices (ACIP) meeting, Beyfortus was shown to be a cost-effective immunization over the long term. As part of the ACIP review process, vaccines undergo a rigorous cost-effectiveness analysis. Both Sanofi and the Centers for Disease Control and Prevention (CDC) conducted these analyses based on the 50mg dose, and they were disclosed and discussed in a public ACIP meeting.

The list price of Beyfortus was based on the cost-effectiveness analyses of Beyfortus for infants at the 50mg dose. This ensures that the price is reflective of the clinical benefit of Beyfortus to all infants as well as the healthcare system. As the clinical benefit is the same for both the 50mg and 100mg doses, we chose to price both equally.

Additionally, the recommendation from ACIP to include Beyfortus in the CDC's Child and Adolescent Immunization Schedule means the cost of Beyfortus is covered by private insurance plans without a co-pay in accordance with the Affordable Care Act. Moreover, Beyfortus was included in the Vaccines for Children's (VFC) program at discounted pricing of $395 per dose. This federally funded program provides vaccines at no cost to children who might not otherwise be vaccinated because of inability to pay. Because of its inclusion in the VFC program, Beyfortus will be provided at no cost to many eligible babies, supporting the goal of more equitable access. Thus, Beyfortus is available at no out-of-pocket cost to families through their insurance plans or through the VFC program. Currently coverage is in place for nearly 100% of infant lives in the United States.

[2]Leader, S., & Kohlhase, K., 2003.
[3]Zhou H., et al., 2012.
[4]Rainisch G., et al. 2020.

Reporting of U.S. Pricing Actions

In 2023, Sanofi increased the price of 48 of its 80 prescription medicines in line with our pricing principles.

Of these, we increased the list price of Enjaymo® (sutimlimab-jome) by 4.44% in January 2023. This increase resulted in a nominal penalty under the new mandatory rebate program created by the Inflation Reduction Act for the period between July 1 – September 30, 2023, the first quarter the program was in place. Triggering the nominal penalty was due to a difference between Sanofi's forecasted inflation estimate and the final calculation of the annual rate of inflation during the CMS lookback period.

In 2023, Sanofi announced significant price reductions for two of its insulin products in the United States.

The list price of Lantus® (insulin glargine injection) 100 Units/mL, our most prescribed insulin by

▼ *78%*

Similarly, the price of our short-acting insulin, Apidra® (insulin glulisine injection) 100 Units/mL by

▼ *70%*

These changes took effect January 1, 2024.

Sanofi also took six price decreases, lowering the list prices of the following vaccines in 2023 compared to December 2022:

- Tenivac® (Tetanus and Diphtheria Toxoids Adsorbed) by ▼*6.9%*
- Imovax® (Rabies Vaccine) by ▼*1.8%*
- Daptacel DTAP® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) by ▼*19.2%*
- Adacel TDAP® (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed) by ▼*9.1%*
- Acthib® [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)] by ▼*33.1%*
- Tubersol® (Tuberculin, Purified Protein Derivative) by ▼*2.6%*

Continued Transparency in the United States

U. . Portfolio Annual Aggregate Price Change from Prior Year[17]

Year	Average Aggregate List Price	Average Aggregate Net Price
2016	4.0% Increase	2.1% Decrease
2017	1.6% Increase	8.4% Decrease
2018	4.6% Increase	8.0% Decrease
2019	2.9% Increase	11.1% Decrease
2020[18]	0.2% Increase	7.8% Decrease

17 Aggregated across Sanofi's prescription portfolio.

18 Price increases or reductions that are taken mid-year may have an impact in two calendar years. In our 2019 pricing report, Sanofi announced that it took a price reduction on Admelog (insulin lispro injection) 100 Units/mL in July 2019. The 2020 carryover impact of that change is not included in the 2020 Average Aggregate List Price above. If included, the 2020 Average Aggregated List Price change vs. 2019 would have been effectively 0%, and the Average Aggregate Net Price would decrease by 8.0%.

Gross sales paid as rebates in 2023

Sanofi paid

46%

of our gross sales to payors as rebates

$5.8 Billion

in mandatory rebates to government payors as required by federal law

$9.2 Billion

in rebates negotiated with health plans and PBMs and their related fees

2021	1.5% Increase	1.3% Decrease
2022	2.6% Increase	0.4% Decrease
2023	4.3% Increase	15.7% Decrease

Sanofi's annual net price change is influenced by a number of factors, including the level of discounts, rebates, and fees paid to ensure access to our medicines, the makeup of our product portfolio, the type of health plan or program through which the medicine is dispensed (especially those with both negotiated and government-mandated rebates and discounts), and the extent of patient assistance we provide to improve the affordability of our medications.

In 2023, we experienced a 15.7% decrease in our average aggregated net price, the most significant decrease compared to any previous year since we began reporting these data. This decline was the result of a combination of the above factors, including dynamics within our insulin portfolio and heightened demand for rebates and fees from health plans and PBMs who continue to assert control over drug pricing and patient out-of-pocket costs.

The Relationship Between Prescription Drug List and Net Prices

All prescription medicines have both a list price and a net price.

The **"list price"** of a medicine often receives the most attention in public discussions, but it does not reflect the price patients pay at the pharmacy counter, nor does it reflect the amount health insurance companies pay (or that Sanofi receives).

A Look Back: Our Commitment to Patient Affordability in 2023

In too many cases Americans continue to struggle to afford their medicines due to rising out-of-pocket drug costs. Despite the policy and regulatory fervor around drug pricing, very little action has been taken to address what patients pay at the pharmacy counter – which is dictated by health plans and pharmacy benefit managers.

As part of Sanofi's commitment to enabling affordable access, we continue to invest in innovative and industry-leading savings programs that directly lower out-of-pocket costs for patients. We take responsible actions in areas where patients face the greatest need, such as access to insulin.

Sanofi provides significant discounts, rebates, and fees to different stakeholders across the healthcare value chain to ensure our medicines are accessible to patients. The **"net price"** accounts for these various discounts, rebates, and fees, accurately resulting in the amount Sanofi receives for its medicines.

List Price	—	*Discounts, Rebates, and Fees*	=	*Net Price*
(set by Sanofi using our Pricing Principles)		(provided by Sanofi to its customers, including insurers and distributors, to obtain access)		(the amount Sanofi receives for its medicines)

Payors, including pharmacy benefit managers (PBMs) and government and private insurers, ultimately decide which medicines to cover on their plans' drug formularies. Their coverage decisions are based in part on the discounts and rebates Sanofi provides for each of our medicines. Sanofi's rebates – which help to secure formulary placement on prescription coverage plans – should guarantee that patients can access and afford necessary medicines. But this is often not the case. Unfortunately, **there is no way for a pharmaceutical manufacturer like Sanofi to ensure that rebates are passed on to patients** in the form of lower copays and cost-sharing for the patient.

Insulin has long been in the spotlight as an area where the out-of-pocket burden on people with diabetes is unacceptable. This phenomenon persists in part because scrutiny has been directed toward list prices rather than ensuring that rebates, discounts, and fees are used to make insulin more affordable for patients.

The amount that Sanofi pays in discounts, rebates, and fees for our insulin products has continued to grow. In fact, the net price of insulin has fallen for nine consecutive years, making our insulins significantly less expensive for insurance plans.

The out-of-pocket burden on people with diabetes has lessened in recent years as a result of policy and other solutions that deliver direct savings to patients, which Sanofi has long championed and played a meaningful role. These solutions include Centers for Medicare & Medicaid Services' Senior Savings Model and state caps on monthly insulin copays for people enrolled in state-regulated insurance plans.

Still, too many patients struggle to pay for their insulins despite growing discounts and rebates paid by Sanofi, demonstrating the misalignment between discounts paid to payors and patients' out-of-pocket costs.

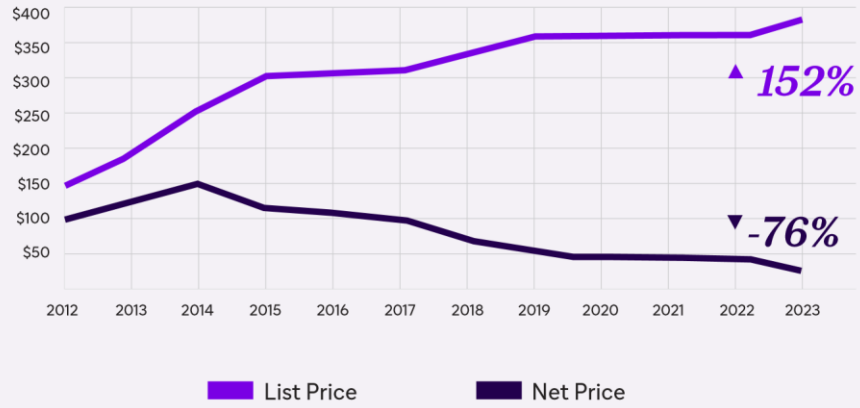
Given these affordability challenges patients face, **Sanofi has taken direct action to improve access and affordability for millions.** For example, we launched an unbranded biologic for Lantus® at 60% less than the Lantus list price in June 2022. However, despite this pioneering low-price approach, patients did not realize the full cost savings because incentives within the health system lead health plans and middlemen to favor high list prices and larger rebates. Lack of interest from health plans to include Sanofi's lower list price option on their formularies led, in part, to its discontinuation.

To further our commitment to support patients directly at the pharmacy counter and accelerate the transformation of the U.S. insulin market, Sanofi announced in March 2023 a list price reduction of Lantus (insulin glargine injection) 100 Units/mL, our most widely prescribed insulin in the United States, by 78% as well as the list price of our short-acting Apidra® (insulin glulisine injection) 100 Units/mL by 70%, both of which took effect in January 2024.

Sanofi's historic list price reduction and continued partnership with stakeholders across the drug supply chain underscore our longstanding commitment to offering affordable access to medicines.

Change in Insulin Costs Over Time

Since 2012, the net price of Sanofi insulins has declined by 76%. Despite this, health plans and others continue to spotlight changes in list prices. However, our insulins are less expensive for insurance plans year over year because of the deep discounts and higher fees we pay.



Since 2012, for people taking Lantus® (insulin glargine injection) 100 units/mL on commercial and Medicare Part D plans:

▼ Lantus Net Price Decreased 58%
(lower today than it was at launch in 2004)

▲ Average OOP Costs Increased 24%

Insulin Affordability in Action

2018

Launched Admelog® (insulin lispro injection) 100 Units/mL at a list price that was 15% lower than the reference product, which was the lowest list price of any mealtime insulin.

Introduced of Insulins Val***you*** Savings Program, allowing all who are uninsured to have access to Sanofi insulins at a single, low monthly cost.

2019

Reduced the list price of Admelog by 44% to ensure the medicine retained the lowest list price for mealtime insulin in the United States.

Expanded of Insulins Val***you*** Savings Program so all uninsured patients, regardless of income level, can access one or multiple Sanofi insulins for a fixed price of $99 per 30-day supply (for up to 10 boxes of pens and/or 10mL vials per 30-day supply).

2020

Introduced temporary changes to Sanofi Patient Connection to help those who experienced unexpected loss of income and health insurance during the COVID-19 pandemic. This included providing eligible people with immediate access to a 30-day supply of their medicines, early reordering of prescriptions, expansion of acceptable documentation for proof of income, and extension of its Temporary Patient Assistance Program.

2021

Began voluntary participation in the CMS Senior Savings Model, which gave patients who enrolled in a participating Part D plan access to Sanofi insulins for a $35-or-less copay for each 30-day prescription.

2022

Reduced the list price of Admelog by an additional 25%.

Initiated a new collaboration with Direct Relief to donate insulin and combination diabetes medicines at no cost to people living with diabetes in underserved communities.

Launched Insulin Glargine Injection 100 Units/mL (U-100) at a price 60% less than the 2022 list price of Lantus (insulin glargine injection) 100 Units/mL.

Updated our Insulins Val***you*** Savings Program to allow uninsured patients with a valid prescription to buy any combination and amount of Sanofi insulins for $35 per 30-day supply.

2023

Announced the planned list price reduction of Lantus (insulin glargine injection) 100 Units/mL by 78%, as well as the list price of Apidra (insulin glulisine injection) 100 Units/mL by 70%.

Began collaborations with GoodRx and Amazon Pharmacy to cap the cost of some Sanofi insulins at $35 a month for commercially insured patients. These collaborations, along with other third party partnerships, **led to patient savings amounting to $4.6 million in 2023.**

Bridging the Affordability Gap: Our Patient Support Programs

Sanofi takes pride in developing new life-saving medicines and ensuring access for the patients who need them most. We have developed a suite of innovative, patientinformed programs to help reduce prescription medicine costs — regardless of a person's insurance status or income level.

Each of Sanofi's programs is tailored to a specific population, and we are continually listening to patients, advocates, and caregivers to better understand additional actions we could take to address ongoing or emerging challenges. Sanofi informs patients and providers about the availability of these programs through several mediums, and we continue to seek new ways to educate the public about their availability.

"Over the years, Sanofi has taken proactive steps to address the cost of insulin, implementing innovative solutions to support the lowest out-of-pocket expenses for patients. We are proud to continue to support this community, prioritizing patient access and helping to create a more affordable health system for patients.

Olivier Bogillot
Head, North America
General Medicines, Sanofi

We remain committed to addressing pressing issues around insulin access and affordability. Sanofi was the first company to introduce a program through which uninsured patients could access one or more of our medicines at a set price. And now, our innovative and patientcentric savings programs help most people reduce the cost of our insulin medicines (Admelog, Apidra, Lantus, Toujeo, and Insulin Glargine U-300) to a price of $35 or less for a 30-day supply, regardless of income or insurance status.

We also provide free medications to qualified low- and middle-income patients as part of a number of Patient Assistance Programs across our therapuetic areas including Sanofi Patient Connection.

We continue to review and evolve our programs to better serve and improve affordability for patients.

Every patient has unique circumstances, and Sanofi has live support specialists who can be reached at *(855) 984-6302* to answer individual patient questions and navigate their unique situation to find the best resources and programs to help lower their out-of-pocket costs.

2023 Patient Support: By the Numbers

3.6 Million+
# of redemptions of assistance card

128,609
# of times Insulins a Sanofi copay Val***you*** Savings Program was used

127,369
# of patients who use of copay through patient assistance programs

$1.48 Billion+
patient savings from received free medicine assistance programs

$61.9 Million+
patient savings from use Val***you*** Savings Program

$ 1.71 Billion+
value of medicine of Insulins provided via patient assistance programs

A Look Forward: Our Position on System Transformation

Sanofi supports policy solutions that can help transform healthcare delivery to achieve lower costs and wider access for patients taking prescription medicines. Driving system savings through better, more efficient health outcomes and not blunt cost-cutting measures will require change across the healthcare continuum – including substantial reforms to benefit design in commercial and government coverage.

Broader System Reforms Are Needed to Improve Patient Outcomes & Affordability

History has shown that the **most effective changes in health policy are solutions that directly address the cost barriers patients face.**

This is especially true of major prescription drug reforms, such as the passage of the Medicare Part D drug program in 2003. Two decades later, 50.5 million Americans on Medicare now receive direct coverage for their outpatient prescriptions.

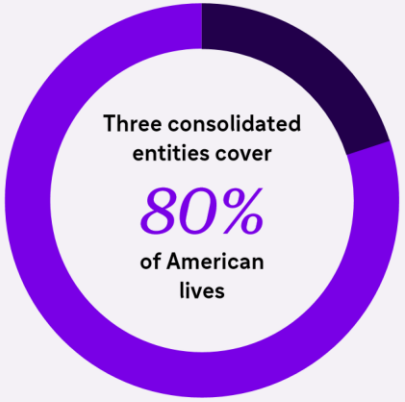
To continue delivering the shared goals of better health outcomes and ongoing treatment innovation, it is essential for policies to directly address patient cost and access barriers. This means **shifting our narrow focus on list prices to the development of solutions that can improve benefit design and balance system incentives** across many stages of prescription drug delivery.

Central to the process of medicines reaching patients are the players in the middle of drug delivery: pharmacy benefit managers (PBMs), insurers, wholesalers, specialty and retail pharmacies, and group purchasing organizations.

The U.S. health system has seen significant consolidation among these groups, which are now often owned by the same parent corporations, cycling patients between different divisions within the same company for care and reimbursement. This is especially true for specialty medicines, where PBMs steer patients toward their own specialty pharmacies.

Due to the concentration of market power among these three consolidated companies, Sanofi has had to agree to more rebates, discounts, and fees during the negotiation process to try to ensure patients are able to access our medicines. In 2023, we had a 15% increase in fees – or service charges – paid on top of negotiated rebates to PBMs and health plans in Managed Care, Medicare Part D, and Managed Medicaid agreements. In total, we paid about $1.4

Impact of Vertical Integration



Manufacturers pay significant rebates, fees and discounts to try to secure access for patients on these plans.

Yet, patients still struggle with out-of-pocket costs at the pharmacy counter.

billion more in negotiated rebates and fees than in 2022 – almost an 18% increase year-over-year.

The increased scale of these negotiated payments, on top of the substantial mandated discounts provided to government programs (e.g., Medicare Part D, Medicaid, and the 340B drug pricing programs), greatly contributed to a 15.7% decrease in our portfolio net price in 2023, the largest decrease in any previous year since we began reporting.

Additionally, insurers are more frequently applying restrictions or diversion tactics to the robust copay assistance programs provided by Sanofi and other manufacturers that are intended to help patients afford their medicines. These revenue strategies, known as **copay accumulators and maximizers or alternative funding programs, funnel manufacturer patient assistance funds into the payor's bottom lines, rather than applying them toward a patient's deductible or out-of-pocket maximum.**

These business tactics negatively impact patients as the extensive rebates and fees we pay are not translating into medication access for too many people enrolled in insurance plans. Insurers are avoiding their appropriate financial responsibility to cover their beneficiaries' medicines by shifting those costs back to patients in the form of significant out-of-pocket costs.

If policies are enacted to add oversight and accountability to protect patient interests, we can address the barriers patients face and support broader coverage and access to the medicines they need. Therefore, **Sanofi supports policies that would correct these market distortions**, including:

1. Mandating that service fees levied across the pharmaceutical supply chain (e.g., administration fees, data fees, formulary fees, etc.) are flat rather than charged as a percentage of the list price of a medicine.
2. Requiring that manufacturer rebates and discounts paid to PBMs and insurers benefit patients by lowering out-of-pocket costs at the pharmacy counter.
3. Preventing PBMs from capturing manufacturer copay assistance through diversion of funds intended to reduce patient cost-sharing or denial of coverage for their medicine.
4. Allowing patients in federal health insurance programs, such as Medicare, to access manufacturer copay assistance programs when there's no generic or biosimilar alternative available.

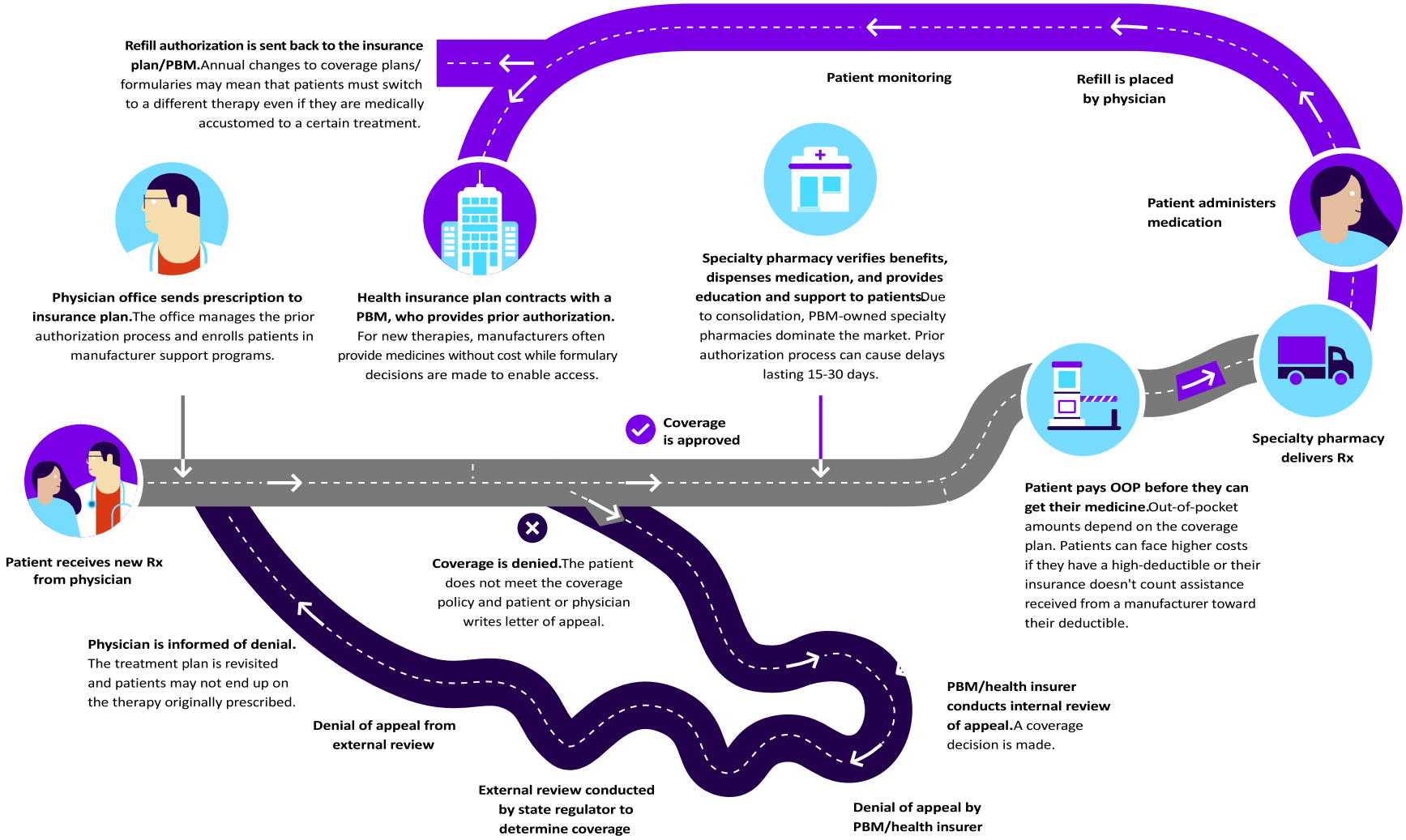
"By establishing policies that align incentives so the value driven by competition accrues to patients, we can accomplish our shared goal of lowering drug prices and patient costs, while also protecting and cultivating the entrepreneurial risk-taking necessary for pharmaceutical manufacturers to continue to discover, develop, and bring to market life-saving new medicines.

Paul Hudson
CEO, Sanofi

The Road to Access: Understanding Specialty Pharmacy Barriers

Specialty medicines – typically defined as those used to treat rare, complex or chronic conditions – require extra patient education, ongoing monitoring, adherence support, and specialized handling, such as unique medication storage or shipment requirements. As a result, these medications are not available directly over the pharmacy counter and have their own reimbursement and distribution processes.

Patients prescribed specialty medicines experience more frequent coverage restrictions despite the billions in rebates and fees that manufacturers pay to insurers



and PBMs to ensure access to medications. Implementing policies that aim to remove these barriers can help widen and accelerate access to the medicines patients need.

Health Policy Solutions That Protect Innovation While Delivering Out-of-Pocket Relief for Patients

The U.S. pharmaceutical industry has delivered unprecedented scientific breakthroughs that have changed the way we treat and prevent diseases, spanning a wide range of therapeutic areas. **Sanofi supports policy solutions that preserve drug discovery and development** while ensuring broad and affordable patient access to life-changing medicines.

While Sanofi supports the modest affordability improvements included in the Inflation Reduction Act (IRA), unfortunately, in only the first couple of years since enactment, we are already seeing the earliest signs of the negative impact the IRA may have on innovation and science.

The IRA's "negotiation" process, as written, is essentially government price setting, which will artificially influence research and development (R&D) investment decisions. This can significantly impact drug candidates that can target multiple disease areas, as the IRA's pre-price control window limits a company's ability to conduct clinical trials for regulatory approval in different indications. This could lead to as many as 139 fewer drugs developed over the next decade alone. As science is iterative, the long-term consequences could be even more dramatic, contradicting the government's other healthcare goals, including advancements in oncology treatments. If the IRA continues down this path and curtails U.S. innovation in medicines, the lack of novel treatments could lead to higher medical costs and increased hospital stays – areas of the system where both costs are high and patient burdens significant.

Without changes, **the IRA's price controls will place a thumb on the scale of science** in ways that will significantly limit scientific research, **and too many seniors will continue struggle to afford their medicines.** Sanofi supports changes to the IRA's drug pricing policies to minimize the harms to innovation and make the system work better for patients, including:

> "
>
> The IRA barely impacts patients' out-of-pocket expenses and does nothing to address other parts of the health system that limit patient access. The next phase of health reform should reverse the approach – improve the remaining 85% of the healthcare industry outside pharmaceuticals – to better address patient affordability before further impacting science and innovation.
>
> ***Adam Gluck***
> ***Head, U.S. and Specialty Care Corporate Affairs, Sanofi***

1

Modifying the current law's unscientific distinction between small molecule drugs and biologics, which will discourage the development of medicines that typically come in pill or capsule form. Small molecule drugs, which are often preferred by patients, receive four fewer years of protection before price controls compared to other forms of prescription drugs.

2

Reducing the disincentives that constrain investment in multiple indications for a drug candidate. For example, exemptions for orphan medicines should be expanded to those that treat more than one rare disease.

Accounting for value as it relates to both patients and the health system. For example, value should properly reflect the ability to lead a productive life mostly free of disease, the impact of the side effects, the cost of physician monitoring, and other clinical outcomes valued by patients and their families.

3

4

Monitoring formulary decisions by health plans to protect patient access to new medicines through frequent, adequate updates of oversight plans. Medicare should contribute to a future where providers and patients have an array of clinical choices so that the best and most appropriate innovations are available to treat patients needing such advances.

May 10, 2024

SUBMITTED VIA EMAIL TO: comments.pdab@maryland.gov

Maryland Prescription Drug Affordability Board
16900 Science Drive, Suite 112-114
Bowie, MD 20715

Re: Maryland Prescription Drug Subset List

Dear Members of the Maryland Prescription Drug Affordability Board,

On behalf of Takeda Pharmaceuticals America, Inc. ("Takeda"), I am writing regarding the inclusion of Vyvanse® (lisdexamfetamine dimesylate) on the list of drugs that the Maryland Prescription Drug Affordability Board ("PDAB") is considering for inclusion in the cost review process. We appreciate the opportunity to provide written feedback and respectfully ask that the PDAB remove Vyvanse from consideration for this review process in part because numerous generic versions of Vyvanse, covering all dosage forms and strengths of the product, have been approved and launched beginning in August 2023.[1] Of the eight products on the PDAB-approved list, Vyvanse is the only product with generic alternatives currently marketed in the United States.

Vyvanse is approved for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years and older and for adults with moderate to severe binge eating disorder (BED). Although Vyvanse was selected for consideration based on 2022 data, patent protection covering Vyvanse and the associated FDA-granted regulatory exclusivity period expired in the U.S. in August 2023. Since that time, multiple manufacturers have launched AB-rated generic versions of lisdexamfetamine dimesylate. In fact, seven AB-rated generics launched immediately after Vyvanse loss of exclusivity occurred. To date, ten manufacturers have launched generic versions of lisdexamfetamine dimesylate, covering in total all dosage forms and strengths of Vyvanse. While the pricing by generic manufacturers varies, the weighted average Wholesale Acquisition Cost (WAC) for generic manufacturers across the six months from September 2023 to February 2024, was 47% lower than the Vyvanse WAC for the same period.[2]

Generic entry following the expiration of patent exclusivity organically creates market dynamics for increased patient choice and affordability, which can also achieve the PDAB goals of greater access and equity.[3] In fact, the FDA has shown that when six or more generic manufacturers are on the market, drug prices decreased more than 95%.[4] Generics often enter the market immediately upon patent expiration and some capture as much as 90% of the market within three months of becoming available.[5]

[1] Vyvanse formulations includes seven (7) capsule strengths (10mg-70mg) and six (6) chewable tablet strengths (10mg-60mg) all of which are also now approved by the FDA in generic version.
[2] Weighted average WAC Pricing information across generics based on WAC Pricing via Price Rx Feb 2024.
[3] "Bylaws of the Maryland Prescription Drug Affordability Board," https://pdab.maryland.gov/documents/pdab_Bylaws.pdf
[4] US Food and Drug Administration, "Generic competition and drug prices," https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm129385.htm
[5] PhRMA Fact Sheet, "What is Hatch-Waxman," https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/D-F/Fact-Sheet_What-is-Hatch-Waxman_June-2018.pdf

Takeda Pharmaceuticals America, Inc.
750 9th Street, NW, Suite 575, Washington, DC 20001
(202) 649-4000

Vyvanse brand share erosion in the U.S. has been slightly milder than initially anticipated due to constraints of generic supply.[6] However, per statements made by generic manufacturers to FDA, these supply constraints are expected to begin to ease gradually over the coming months. As such, Takeda anticipates further Vyvanse brand share erosion over this timeframe, pending any additional constraints in the generics market. In the meantime, as noted in FDA's drug shortages record, Takeda is not experiencing manufacturing or supply delays for Vyvanse.[7] We remain confident in our capability to continue maintaining an adequate supply of Vyvanse to meet its U.S. forecasted demand.

Given the approval of ten AB-rated generic versions of lisdexamfetamine dimesylate and erosion of Vyvanse branded share, alternative cost containment strategies under consideration by the PDAB, such as an upper payment limit (UPL), may prove to be redundant and/or unnecessary to achieve the PDAB's affordability goals. **Therefore, we respectfully request that the PDAB remove Vyvanse from consideration for the cost review process**.

* * *

Takeda is focused on creating better health for people and a brighter future for the world. We aim to discover and deliver life-transforming treatments. Together with our partners, we aim to improve the patient experience and advance a new frontier of treatment options through our dynamic and diverse pipeline.

Thank you for considering our comments. Should you have any questions, please contact me at william.gazda@takeda.com.

Sincerely,

William M. Gazda

William Gazda
Head – US Established Brands Portfolio
Takeda Pharmaceuticals America, Inc.

[6] Takeda Quarterly Earnings Report for the Quarter Ended March 31, 2024, https://assets-dam.takeda.com/image/upload/v1715219664/Global/Investor/Financial-Results/FY2023/Q4/qr2023_q4_qfr_en.pdf
[7] FDA, "Current and Resolved Drug Shortages and Discontinuations Reported to FDA," https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Lisdexamfetamine%20Dimesylate%20Capsule&st=c

Maryland

Comments PDAB -PDAB- <comments.pdab@maryland.gov>

Drugs Referred to the Stakeholder Council Comment

Mark Varner [redacted] Thu, May 2, 2024 at 12:04 PM
To: comments.pdab@maryland.gov

Hello,

Thank you for the opportunity to provide comments to the PDAB. I am a heart transplant recipient, and transplant recipients are another group of people who have unusual medication requirements.

I am a retired Maryland state employee, and I will be losing the State's drug prescription coverage. Please see the attached article from today's Baltimore Sun for a summary.

This program provides a significant cost-reduction option for the 50,000 plus retirees. The State is moving us to a Medicare Part D plan of our choosing. The key difference between the State provided plan is that the State plan has a much larger formulary of covered medications.

Based on 2024 Medicare Part D options, my costs will increase four-fold. My cost will be thousands of dollars greater.

I note that you are considering Trulicity and Ozempic. I have taken Trulicity in the past, and have noted that Mounjaro provides better benefits. This is agreement with my clinician's observations.

I note that you are also considering Farxiga. I take that medication as well to help with kidney disease damage brought on by the transplant rejection medications that I must take to stay alive.

Mark Varner

Retired state workers slated to switch to Medicare Part D next year.pdf
2948K

JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis: Effectiveness and Value

Final Evidence Report

August 17, 2021
Updated October 14, 2022
Updated February 27, 2023

Prepared for

February 27, 2023 Update: Per ICER's guidelines on the acceptance and use of "In-Confidence" data from manufacturers of pharmaceuticals, academic-in-confidence data that was redacted in the report has been unmasked after 18 months following the date of the public ICER meeting.

New evidence regarding treatments and therapies gets published on an ongoing basis. ICER reached out to key stakeholders included in this review 12 months after the publication of this report giving them an opportunity to submit public comments regarding new relevant evidence or information on coverage that they wish to highlight. Their statements can be found here. ICER has launched ICER Analytics to provide stakeholders an opportunity to work directly with ICER models and examine how changes in parameters would affect results. You can learn more about ICER Analytics here.

ICER Staff and Consultants	The University of Washington Modeling Group
Steven J. Atlas, MD, MPH Associate Professor of Medicine Harvard Medical School, Boston Director, Practice Based Research & Quality Improvement Division of General Internal Medicine Massachusetts General Hospital **Grace E. Fox, PhD** Research Lead ICER **Foluso Agboola, MBBS, MPH** Vice President of Research ICER **Jon D. Campbell, PhD, MS** Senior Vice President for Health Economics ICER **Steven D. Pearson, MD, MSc** President ICER **David M. Rind, MD, MSc** Chief Medical Officer ICER	**Elizabeth Brouwer, PhD, MPH** Research Scientist The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute Department of Pharmacy University of Washington **Josh J. Carlson, PhD, MPH** Associate Professor The CHOICE Institute Department of Pharmacy University of Washington **Yilin Chen, MPH** PhD Student The CHOICE Institute Department of Pharmacy University of Washington **Ryan N. Hansen, PharmD, PhD** Associate Professor The CHOICE Institute Department of Pharmacy University of Washington *The role of The University of Washington is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of The University of Washington.*

DATE OF PUBLICATION: August 17, 2021

How to cite this document: Atlas SJ, Brouwer E, Fox G, Carlson JJ, Campbell JD, Agboola F, Hansen RN, Pearson SD, Rind DM. JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, July 9, 2021. https://icer.org/assessment/atopic-dermatitis-2021/#timeline

Acknowledgements: Steven Atlas served as the lead author for the report and wrote the executive summary, background, patient and caregiver perspectives, uncertainty and controversies, summary and comment, potential other benefit and contextual considerations, definitions and oversaw the comparative clinical effectiveness sections in the main report and supplemental information. Grace Fox and Foluso Agboola led the systematic review and wrote the clinical effectiveness sections in collaboration with Steven Atlas. We would like to acknowledge the work of Serina Herron-Smith and Emily Nhan who contributed to the clinical effectiveness sections. Josh Carlson, Ryan Hansen, and Elizabeth Brouwer developed the economic model and authored the cost-effectiveness sections in collaboration with Yilin Chen. Jon Campbell provided methods guidance for the cost-effectiveness modeling and authored the budget impact analysis section. David Rind and Steven Pearson provided methodologic guidance on the clinical and economic evaluations. We would like to thank Ashton Moradi for his contributions to the budget impact analysis. We also thank Maggie Houle, Liis Shea, and Zunelly Odhiambo for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 21% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Life science companies relevant to this review who participate in this program include: AbbVie, Eli Lilly, Incyte, Leo Pharma, Pfizer, Regeneron, and Sanofi. For a complete list of funders and for more information on ICER's support, please visit our independent funding webpage.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

About New England CEPAC

The New England CEPAC – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The CEPAC Panel is an independent committee of medical evidence experts from across New England, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about CEPAC is available at https://icer.org/who-we-are/people/independent-appraisal-committees/new-england-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials may differ in real-world practice settings.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer.org/wp-content/uploads/2021/01/ICER_Atopic-Dermatitis_Stakeholder-List_011521.pdf

Expert Reviewers

Wendy Smith Begolka, MBS
Vice President, Scientific and Clinical Affairs
National Eczema Association
Wendy is a salaried employee of the National Eczema Association which has received grants and sponsorship awards from a variety of industry partners.

Jonathan Silverberg, MD, PhD, MPH
Associate Professor of Dermatology
The George Washington University School of Medicine and Health Sciences
Dr. Silverberg has received honoraria as a consultant and/or advisory board member for AbbVie, Eli Lilly, Incyte, Leo Pharma, Pfizer, Regeneron, and Sanofi. He has also served as a speaker for Eli Lilly, Leo, Pfizer, and Regeneron.

Eric Simpson, MD, MCR
Professor of Dermatology
Oregon Health & Science University, School of Medicine
Dr. Simpson receives honoraria and grants from AbbVie, Eli Lilly, Incyte, Leo Pharma, Pfizer, Regeneron, and Sanofi.

Table of Contents

Executive Summary 1
1. Background 1
2. Patient and Caregiver Perspectives 3
3. Comparative Clinical Effectiveness 6
3.1. Methods Overview 6
3.2. Results for Moderate-to-Severe Population 11
Summary and Comment 23
3.3. Results for Mild-to-Moderate Population 25
Summary and Comment 29
4. Long-Term Cost Effectiveness 31
4.1. Methods Overview 31
4.2. Key Model Choices and Assumptions 32
4.3. Results 40
4.4 Summary and Comment 47
5. Contextual Considerations and Potential Other Benefits 48
6. Health Benefit Price Benchmarks 52
7. Potential Budget Impact 54
7.1. Overview of Key Assumptions 54
7.2. Results 54
8. Policy Recommendations 57

A. Background: Supplemental Information 66
A1. Definitions 66
A2. Potential Cost-Saving Measures in Atopic Dermatitis 69
B. Patient Perspectives: Supplemental Information 70
B1. Methods 70
C. Clinical Guidelines 71
D. Comparative Clinical Effectiveness: Supplemental Information 75
D1. Detailed Methods 75

D2. Network Meta-Analysis Supplemental Information 89
D3. Additional Clinical Evidence 101
Moderate-to-Severe Population 101
Adults 101
Children and Adolescents 111
Mild-to-Moderate Population 117
D4. Ongoing Studies 119
D5. Previous Systematic Reviews and Technology Assessments 124
E. Long-Term Cost Effectiveness: Supplemental Information 127
E1. Detailed Methods 127
E2. Results 129
E3. Sensitivity Analyses 132
E4. Scenario Analyses 140
E5. Prior Economic Models 148
F. Potential Budget Impact: Supplemental Information 149
Methods 149
Results 150
G. Additional Evidence Tables 154
H. Public Comments 317
I. Conflict of Interest Disclosures 326
References 329

List of Acronyms and Abbreviations Used in this Report

ADerm-IS	**Atopic Dermatitis Impact Scale**
AE	**Adverse event**
AHRQ	**Agency for Healthcare Research and Quality**
BSA	**Body surface area**
CDLQI	**Children's Dermatology Life Quality Index**
CPI	**Consumer Price Index**
DFI	**Dermatitis Family Impact questionnaire**
DLQI	**Dermatology Life Quality Index**
EASI	**Eczema Area Severity Index**
EQ-5D	**EuroQol five-dimension questionnaire**
FDA	**Food and Drug Administration**
HADS	**Hospital Anxiety and Depression Scale**
IGA	**Investigator's Global Assessment**
IL	**Interleukin**
JAK	**Janus kinase**
NICE	**National Institutes for Health and Care Excellence**
NMA	**Network meta-analysis**
PDE 4	**Phosphodiesterase 4**
PICOTS	**Population, Intervention, Comparators, Outcomes, Timing, and Settings**
POEM	**Patient-Oriented Eczema Measure**
PP-NRS	**Peak Pruritus Numerical Rating Scale**
PRISMA	**Preferred Reporting Items for Systematic Reviews and Meta-Analyses**
QALY	**Quality-adjusted life-year**
QoL	**Quality of life**
QW	**Weekly dosing regimen**
Q2W	**Every two-week dosing regimen**
RCT	**Randomized controlled trial**
SCORAD	**Scoring Atopic Dermatitis**
SLR	**Systematic literature review**
TCI	**Topical calcineurin inhibitors**
TCS	**Topical corticosteroids**
USPSTF	**US Preventive Services Task Force**
WPAI	**Workplace Productivity and Activity Impairment**
WTP	**Willingness to pay**

Executive Summary

Atopic dermatitis is a common, chronic skin condition with persistent or relapsing lesions that are itchy, inflamed, and dry. Commonly referred to as "eczema," atopic dermatitis affects both children and adults. Symptoms of itching and even skin pain vary in severity, but can affect sleep, cause psychological distress, and result in difficulty with performance at school or work.[1-3] The appearance of the skin can also lead to social embarrassment and isolation.[4] The net effect is that atopic dermatitis can have a profound effect on all aspects of patients' lives and those of their family and caregivers.[5,6] In the United States (US), atopic dermatitis is estimated to affect around 11-15% of children and 7-10% of adults.[7-10] The overall costs associated with atopic dermatitis are estimated to be $5.3 billion dollars in the US, including over $1 billion in health care costs.[11,12] Atopic dermatitis also can lead to work and productivity loss.[5]

Patients and caregivers emphasized the importance of having measures of treatment outcomes that are most meaningful to them. Itching and pain were seen as the key outcomes, but their impact on sleep, increased distraction, worry, anxiety and other aspects of life varied according to an individual's particular circumstances. For example, some patients reflected that when they were adolescents, appearance was most important to them. As they got older, other issues such as the impact on the skin in terms of pain and infections became more important. Though all recognized atopic dermatitis as a chronic condition, the importance of flares and the need to break cycles of worsening disease was also emphasized. Since many individuals also are impacted by other conditions such as asthma and allergies, and some treatments improve these conditions as well, we heard about the importance of thinking broadly about the benefits of treatments. Since itching is the most bothersome symptom for most patients, the importance of measuring the impact of treatments on itch and associated issues such as sleep disruption are needed. The importance of comprehensive outcome measures that capture the diversity and impact of atopic dermatitis over time was emphasized.

ICER reviewed dupilumab for moderate-to-severe atopic dermatitis and topical crisaborole for mild-to-moderate atopic dermatitis in 2017. A number of new biologic therapies are available or being evaluated in patients with atopic dermatitis. Tralokinumab, a monoclonal antibody that blocks IL-13 receptor binding is given subcutaneously and is under investigation for patients with moderate-to-severe atopic dermatitis. Abrocitinib, baricitinib, and upadacitinib are oral Janus kinase (JAK) inhibitors that are also being evaluated for patients with moderate-to-severe atopic dermatitis. Concerns about the safety of oral JAK inhibitors that are approved for other conditions has led the U.S. Food and Drug Administration (FDA) to extend the review period for these drugs,[13] and tralokinumab received a Complete Response Letter from the FDA requesting additional data relating to a device component used to inject tralokinumab.[14] A topical JAK inhibitor, ruxolitinib

cream, is being evaluated for patients with mild-to-moderate atopic dermatitis, and its review period has also been extended by the FDA.[15]

In the moderate-to-severe population, the four interventions all improved skin findings compared with placebo, and, where assessed, appeared to improve itch, sleep, and quality of life. Quantitative indirect comparisons across the new agents and dupilumab, as well as head-to-head comparisons between two of the agents (upadacitinib and abrocitinib) and dupilumab suggest that higher doses of upadacitinib and possibly abrocitinib are somewhat more effective than dupilumab, while baricitinib (at the doses likely to be approved) and tralokinumab are likely somewhat less effective than dupilumab; however, there is substantial uncertainty in these comparisons. Resolution of itch may occur more quickly with higher-dose abrocitinib than with dupilumab.

Safety is an important consideration with biologic therapies and, as above there have been particular concerns about the safety of oral JAK inhibitors when used for other conditions. Concerns about lack of long-term data for dupilumab, noted in ICER's 2017 report, have been alleviated over time based on published data and widespread use in clinical practice.[16] Tralokinumab is a novel inhibitor of IL-13 that works through a mechanism more similar to dupilumab than the JAK inhibitors, but lacks the same long-term safety profile of dupilumab.

An additional consideration in comparing therapies is that many patients with atopic dermatitis have comorbid atopic conditions such as asthma, and dupilumab has proven efficacy in treating certain patients with asthma or chronic rhinosinusitis.

Taking into consideration the above information on short-term benefits seen in the trials but limited data and concerns about long-term safety, especially for oral JAK inhibitors, we concluded the evidence on net health benefit for abrocitinib, baricitinib, upadacitinib, and tralokinumab compared with topical therapies alone was *promising but inconclusive* ("P/I") and compared to each other was *insufficient* ("I"). We concluded that the evidence for net health benefit for abrocitinib and upadacitinib compared with dupilumab was also *insufficient* ("I"), and that the net health benefit of baricitinib and tralokinumab were *comparable or inferior* ("C-") when compared with dupilumab.

Since the baricitinib and tralokinumab trials only included adults and abrocitinib and upadacitinib trials enrolled small numbers of patients younger than age 18, there is greater uncertainty for adolescents with the new therapies.

We compared the cost and effectiveness of abrocitinib, baricitinib, tralokinumab and upadacitinib for moderate to severe atopic dermatitis to topical emollients (standard of care) and dupilumab, over a five-year time horizon taking a health system perspective.

Estimated net prices were used for baricitinib, upadacitinib and dupilumab that are currently marketed. For abrocitinib, we used the average of the net prices of baricitinib and upadacitinib as a placeholder. For tralokinumab, we used the net price of dupilumab as a placeholder.

Table ES1 presents the incremental results from the base case cost-effectiveness analysis. Given no modeled gains in life years across the evaluated therapies, the cost per life year gained is not reported.

Table ES1. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLYG
Abrocitinib*	SoC	$148,300	NA	$148,300
Baricitinib	SoC	$71,600	NA	$71,600
Tralokinumab*	SoC	$129,400	NA	$129,400
Upadacitinib	SoC	$248,400	NA	$248,400
Dupilumab	SoC	$110,300	NA	$110,300
Abrocitinib*	Dupilumab	$303,400	NA	$303,400
Baricitinib	Dupilumab	Less Costly, Less Effective	NA	Less Costly, Less Effective
Tralokinumab*	Dupilumab	Less Costly, Less Effective	NA	Less Costly, Less Effective
Upadacitinib	Dupilumab	$1,912,200	NA	$1,912,200

evLYG: equal-value life-year gained, QALY: quality-adjusted life-year, SOC: Standard of Care

*Using a placeholder price

Note: The cost per QALY and cost per evLYG ratios were the same given that the treatments have not been shown to lengthen life.

From the cost-effectiveness base case assuming the standard of care comparator, we estimated the Health Benefit Price Benchmarks (HBPBs) for each intervention. The HBPB range for abrocitinib is $30,600 to $41,800 (discounts not presented due to placeholder price); for baricitinib, $24,400 to $29,000 (16% discount to no discount from Wholesale Acquisition Cost (WAC) needed at the $150,000 threshold); for tralokinumab from $25,700 to $35,000 (discounts not presented due to placeholder price); for upadacitinib from $30,400 to $41,500 (discounts of 35% to 53% from WAC); and for dupilumab from $29,000 to $39,500 (discounts of 6% to 31% from WAC).

Table ES2. Annual Cost-Effectiveness Health Benefit Price Benchmarks for Abrocitinib, Baricitinib, Tralokinumab, Upadacitinib, and Dupilumab versus Standard of Care

Health Benefit Measure	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Abrocitinib				
QALYs Gained	NA*	$30,600	$41,800	NA*
evLYG	NA*	$30,600	$41,800	NA*
Baricitinib				
QALYs Gained	$29,000	$24,400	$33,300	0% to 16%
evLYG	$29,000	$24,400	$33,300	0% to 16%
Tralokinumab				
QALYs Gained	NA*	$25,700	$35,000	NA*
evLYG	NA*	$25,700	$35,000	NA*
Upadacitinib				
QALYs Gained	$64,300	$30,400	$41,500	35% to 53%
evLYG	$64,300	$30,400	$41,500	35% to 53%
Dupilumab				
QALYs Gained	$41,800	$29,000	$39,500	6% to 31%
evLYG	$41,800	$29,000	$39,500	6% to 31%

WAC: wholesale acquisition cost; evLYG: equal value life year gained; QALY: quality-adjusted life year

* Not applicable (NA) as placeholder prices were used

In the mild-to-moderate population, topical ruxolitinib cream was more effective than vehicle (placebo). While ruxolitinib cream also appeared to be more effective than a medium potency topical corticosteroid, it was not compared to more potent topical corticosteroids and differences in trial designs precluded quantitative indirect comparisons across topical therapies. There is currently limited information on long-term safety of ruxolitinib cream. As a topical JAK inhibitor therapy, safety concerns are likely not as great as with oral JAK inhibitors, but there still is systemic absorption of the topical agent. Topical corticosteroids have known harms both to the skin and, particularly with higher potency preparations in children, a risk for systemic harms. Topical calcineurin inhibitors carry a "black box" warning for a potential risk for causing malignancy, although many clinical experts feel the evidence does not warrant this concern.

We assess the net health benefit for ruxolitinib cream compared with topical emollients to be *comparable or better* ("C++"). We consider the evidence for the net health benefit for ruxolitinib cream compared with other topical medications to be *insufficient* ("I").

Appraisal committee votes on questions of comparative effectiveness and value, along with key policy recommendations regarding pricing, access, and future research are included in the main report; several key policy themes are highlighted below:

- All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with atopic dermatitis are introduced in a way that will help reduce health inequities.

- Payers should only use step therapy when it provides adequate flexibility to meet the needs of the diverse range of patients with atopic dermatitis and when implementation can meet established standards of transparency and efficiency.

- Specialty societies should update treatment guidelines for patients with atopic dermatitis to reflect current treatment options in a form that is easy to interpret and use by clinicians, patients, and payers.

- Manufacturers, payers, and patient advocacy groups should support pricing and rebate reform efforts that will create better rewards for clinical and economic value while also helping patients afford access to the treatments they need.

1. Background

Atopic dermatitis is a common, chronic skin condition with persistent or relapsing lesions that are itchy, inflamed, and dry. Commonly referred to as "eczema," atopic dermatitis affects both children and adults. Symptoms of itching and even pain vary in severity, but can affect sleep, cause psychological distress, and result in difficulty with performance at school or work.[1-3] The appearance of the skin can also lead to social embarrassment and isolation.[4] The net effect is that atopic dermatitis can have a profound effect on all aspects of patients' lives and those of their family and caregivers.[5,6,17] In the United States (US), atopic dermatitis is estimated to affect around 11-15% of children and 7-10% of adults.[7-10] The overall costs associated with atopic dermatitis are estimated to be $5.3 billion dollars in the US, including over $1 billion in health care costs.[11,12] Atopic dermatitis also can lead to work and productivity loss.[5]

Atopic dermatitis is thought to be caused by changes in the barrier properties of the skin and problems with the body's immune response.[18,19] Patients with atopic dermatitis often have a family history that can also include asthma and allergic rhinitis; atopic dermatitis is also associated with socioeconomic and environmental factors.[20] Atopic dermatitis frequently begins during childhood and persists into adulthood in about 50% of affected children.[21] Diagnosed primarily by its appearance, the skin lesions can be localized or widespread, varying in their location by age, and can come and go or be persistent.[22] When acute, the appearance is of red papules and vesicles with weeping, oozing and crusting. When subacute or chronic, lesions are dry, scaly, or excoriated with skin thickening, erosions, cracking and bleeding. Disease severity is difficult to consistently define because it is based upon the amount and location of skin involved, its appearance, and the subjective impact of symptoms.

Most children with atopic dermatitis have mild disease, with 12-26% having moderate and 4-7% having severe disease.[20,23] Moderate or severe disease appears to be more common in adults.[24] The severity of atopic dermatitis can also vary by season and geographic region.[25] For all patients with atopic dermatitis, treatment includes maintaining the skin barrier with moisturizers and emollients, avoiding triggers such as heat/cold, low humidity, and known allergens.[26] Topical corticosteroids are recommended for short-term, intermittent use, and long-term maintenance may include the topical calcineurin inhibitors, tacrolimus and pimecrolimus, or the phosphodiesterase 4 (PDE-4) inhibitor, crisaborole.[27] For those with atopic dermatitis not controlled with topical therapies, phototherapy or systemic immunomodulators are used.[28] Short-term use of systemic oral corticosteroids or cyclosporine can be used to more quickly control skin disease, while oral methotrexate, azathioprine or mycophenolate mofetil can be used for long-term control. Dupilumab, an IL-4 receptor antagonist, became available in 2017, is approved in the US for those

ages six and older, and is now a commonly used systemic immunomodulator for moderate- to-severe disease.[29]

Despite available treatments, many individuals do not respond to multiple different topical and systemic therapies supporting the need for new treatment options.[30] This is especially true for children, where there is greater concern about the effects of topical and systemic corticosteroids.[31]

A number of new biologic therapies are available or being evaluated in patients with atopic dermatitis. One new target for therapy is Interleukin (IL)-13.[32] Tralokinumab, a monoclonal antibody that blocks IL-13 receptor binding is given subcutaneously and is under investigation for patients with moderate-to-severe atopic dermatitis. It received a Complete Response Letter from the FDA requesting additional data relating to a device component used to inject tralokinumab.[14]

Janus kinases (JAKs), cytoplasmic protein tyrosine kinases that are critical for signal transduction to the cell nucleus, are other new targets for therapy.[33] Oral JAK inhibitors being evaluated for patients with moderate-to-severe atopic dermatitis include abrocitinib, baricitinib, and upadacitinib. Concerns about the safety of oral JAK inhibitors that are approved for other conditions has led the U.S. Food and Drug Administration (FDA) to extend the review period for these drugs.[13] A topical JAK inhibitor, ruxolitinib cream is being evaluated for patients with mild-to-moderate atopic dermatitis. The FDA has also extended the review period for ruxolitinib cream.[15]

Table 1.1. Interventions of Interest

Intervention Generic Name (Brand Name)	Mechanism of Action	Delivery Route	Prescribing Information
Abrocitinib	JAK inhibitor	Oral	100-200mg once daily
Baricitinib (Olumiant)	JAK inhibitor	Oral	1-2mg once daily
Upadacitinib (Rinvoq)	JAK inhibitor	Oral	15-30mg once daily
Ruxolitinib Cream	JAK inhibitor	Topical	0.75-1.5% twice daily
Tralokinumab	IL-13 monoclonal antibody	Subcutaneous injection	600mg initial dose then 300mg every 2 weeks

JAK: Janus kinase, IL: interleukin

Note: There may be an option for dosing tralokinumab every four weeks in some patients.

2. Patient and Caregiver Perspectives

Discussions with individual patients, caregivers and patient advocacy groups identified important insights and perspectives. Common themes emphasized included: the considerable burden of this chronic condition on patients, caregivers and families; the diversity of the experience with atopic dermatitis especially at different times in one's life; the demands of current treatment and the need for better treatment options; the impact on all aspects of life including school, work and social/family relationships; the importance of measuring outcomes of care that are most meaningful to patients; and the high costs and affordability of care for patients and families.[34]

Though the majority of those with atopic dermatitis have a milder course that can be adequately managed with topical therapy, this perception may lead to an underappreciation of the profound effect that atopic dermatitis can have on all aspects of a patient's life. The considerable burden of atopic dermatitis reflects its chronic nature (often beginning in childhood and progressing through adolescence and into adulthood), and the unpredictability of disease flares. As such, it not only impacts the patient but also families, caregivers, friends, and relationships. The primary symptom of atopic dermatitis, itch, can lead to a host of additional problems including skin pain and infections as well as disrupting sleep and causing psychological distress including loss of self-esteem, anxiety, depression, and suicidal ideation. Because flares of the disease can lead individuals to search for some behavior or action to explain the worsening, there can be guilt, or it may lead others to blame the patient for the flare. The result is that atopic dermatitis can have a profound impact on life activities, interpersonal relationships and performance at school and work.

The impact of atopic dermatitis can vary depending on many factors, including the age of the patient, leading to a diversity of experiences. For children with atopic dermatitis, interpersonal effects can include bullying by other children and changes in family dynamics among parents and siblings associated with extra time and attention spent by caregivers focused on the patient, leading other children in a household to feel neglected. For adolescents, the impact of atopic dermatitis on appearance was emphasized, leading to self-isolation and insecurities, all affecting social interactions. Across all age groups, atopic dermatitis can impact life activities such as exercise and recreation due to their negative effects on the skin related to excessive sweating or cold/heat exposure. As an allergic condition, atopic dermatitis can also necessitate restrictions on diet that can be difficult.

As a result of the symptoms of atopic dermatitis that can lead to sleep disturbance and daytime fatigue, it can affect performance including that in school and work. For students it can affect school attendance and lead to distraction when in class, negatively impacting developmental milestones. Similarly, atopic dermatitis can affect work through missed days, decreased work

performance (presenteeism), missed promotions, limited career options, and even disability from one's chosen profession. The net result is a financial impact on individuals and families over the course of one's life in terms of educational and work advancement opportunities delayed or lost.

A wide range of deficiencies with currently available topical and systemic treatments for atopic dermatitis were noted. There was broad recognition that current therapies do not address all of the needs of patients with atopic dermatitis. The need for therapies that work quickly, provide sustained relief and are safe for long-term use were highlighted. Though some patients derive benefit from existing therapies, the considerable time and effort involved in applying topical moisturizers and wraps or traveling to and from phototherapy sessions is taxing on patients and their caregivers. Moreover, travel to receive care can be particularly demanding for patients in the US who live outside of large metropolitan areas. For those with mild to moderate disease, there is a need for new topical therapies. Topical steroids can damage skin with prolonged use, while topical calcineurin inhibitors carry a black box warning, and topical phosphodiesterase-4 (PDE-4) inhibitors have limited efficacy; these latter agents can also cause skin discomfort/burning.

For those with moderate to severe disease not adequately managed with topical therapies, oral corticosteroids are commonly used for short courses, but have well-recognized side effects, can have rebound flares when discontinued, and are avoided in younger patients. Other systemic therapies such as cyclosporin, methotrexate and other non-selective systemic immunomodulators have limited benefit and potentially serious side effects. Even dupilumab, the first biologic approved in the US for atopic dermatitis, takes time to begin working, does not help all individuals, and has side effects, such as conjunctivitis that result in some patients discontinuing use. Finally, patients and caregivers commented about the challenge of choosing therapies where the long-term effects are not completely known or may have uncommon but potentially serious side effects.

Patients and caregivers emphasized the importance of having measures of treatment outcomes that are most meaningful to them. Itching and skin pain were seen as the key outcomes, but their impact on sleep, increased distraction, worry and anxiety and other aspects of life varied according to an individual's particular circumstances. For example, some patients reflected that when they were adolescents, appearance was most important to them. As they got older, other issues such as the impact on the skin in terms of pain and infections became more important. Though all recognized atopic dermatitis as a chronic condition, the importance of flares and the need to break cycles of worsening disease was also emphasized. Since many individuals also are impacted by other conditions such as asthma and allergies, and some treatments improve these conditions as well, we heard about the importance of thinking broadly about the benefits of treatments. Since itching is the most burdensome symptom for most patients, the importance of measuring the impact of treatments on itch and associated issues such as sleep disruption are needed. The

importance of comprehensive outcome measures that capture the diversity and impact of atopic dermatitis over time was emphasized.

For many patients and parents, the high cost of care for atopic dermatitis was noted. Topical emollients and wraps are non-prescription and often not covered by health insurance. Even for those with health insurance, the affordability of care is a challenge for patients and families. The chronic nature of atopic dermatitis with copayments and deductibles for numerous doctor visits, multiple trials of different topical therapies, and phototherapy sessions add up quickly. Moreover, newer systemic therapies for atopic dermatitis are very expensive and patients and caregivers face the burden of negotiating insurance coverage policies and the potential for high out of pocket costs.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review (SLR) assessing the evidence on abrocitinib, baricitinib, tralokinumab, and upadacitinib in moderate-to-severe atopic dermatitis and ruxolitinib cream in mild-to-moderate atopic dermatitis are described in Section D1 of the Report Supplement.

Scope of Review

This SLR compares the clinical effectiveness of abrocitinib, baricitinib, tralokinumab, and upadacitinib to topical therapies, dupilumab, and each other for the treatment of moderate-to-severe atopic dermatitis in adolescents and adults. The SLR also compares ruxolitinib cream to topical therapies for the treatment of mild-to-moderate atopic dermatitis in adolescents and adults. The full PICOTS criteria are detailed in Section D1 of the Report Supplement.

Evidence Base

Moderate-to-Severe Population

A total of 58 references met our inclusion criteria for the moderate-to-severe population.[35-83] Of these, we identified five randomized controlled trials (RCTs) of abrocitinib (one phase II and four phase III),[35-37,39,40,77,84] five RCTs of baricitinib (one phase II and four phase III),[42,45,46,48] three RCTs of tralokinumab (two phase III),[63,64] five RCTs of upadacitinib (one phase II and four phase III),[69,70,80,81,83] and six RCTs of dupilumab (one phase II and five phase III) that met our inclusion criteria.[50-53,56] Of these trials, 21 enrolled adults, where 14 were placebo-controlled monotherapy trials and six were placebo-controlled combination trials that permitted background topical medication. Two head-to-head trials were identified, and these were one placebo- and active-controlled combination trial (JADE COMPARE) and one active-controlled monotherapy trial (Heads Up). Several trials solely enrolled children or adolescents, where one was a placebo-controlled monotherapy trial and two were placebo-controlled combination trials.

Trials that enrolled adults are described first, followed by trials that solely enrolled children and adolescents. Of note, only the FDA-approved dose of dupilumab was evaluated in adults (300 mg once every two weeks).

Evidence Tables G1.3-1.7 contain the key study design and baseline characteristics of each trial, while a summary is presented below in Table 3.1. Please note that blacked out data represents

academic-in-confidence data submissions. While most trials enrolled patients ≥18 years old, the pivotal trials for abrocitinib, JADE MONO-1 and JADE MONO-2, and the pivotal trials for upadacitinib, MEASURE UP 1, MEASURE UP 2, and AD-UP enrolled patients ≥12 years old. However, most patients in these trials were ≥18 years old, and we searched for evidence stratified by age. The primary endpoints of the abrocitinib trials, JADE MONO-1, JADE MONO-2, and JADE COMPARE, were measured at 12 weeks, while the remaining trials' primary endpoints were measured at 16 weeks. Trial populations were comparable with respect to age (31-41 years), duration of disease (21-28 years), and disease severity (32%-55% IGA of 4). Primary endpoints varied slightly among the trials but typically consisted of EASI 75 and/or IGA (IGA score of 0/1 or 0/1 and ≥2 points from baseline improvement).

RCTs that only enrolled children or adolescents were limited. LIBERTY AD ADOL enrolled patients 12-17 years and measured its co-primary endpoints of EASI 75 and IGA (IGA score of 0/1 and ≥2 points from baseline improvement) at 16 weeks. JADE TEEN also enrolled patients 12-17 years and measured its co-primary endpoints of EASI 75 and IGA (IGA score of 0/1 and ≥2 points from baseline improvement) at 12 weeks. In contrast, LIBERTY AD PEDS enrolled patients 6-11 years with severe atopic dermatitis and measured its primary endpoint of IGA (IGA score of 0/1) at 16 weeks.

Additional details are available in Section D3 of the Report Supplement.

Table 3.1. Overview of Placebo-controlled Monotherapy and Combination Trials of Abrocitinib, Baricitinib, Tralokinumab, Upadacitinib, and Dupilumab in Adults

Trial	Arms	Sample Size (N)	EASI (Mean)	Mean age, y	Mean Disease Duration, y	IGA Score of 4 (%)
Abrocitinib						
JADE MONO-1*	ABRO 100 mg ABRO 200 mg PBO	387	30.2	32.4	23.4	40.7
JADE MONO-2*	ABRO 100 mg ABRO 200 mg PBO	391	28.5	35.1	21.0	32.2
JADE COMPARE	ABRO 100 **mg + TCS** ABRO 200 mg **+ TCS** DUP 300 mg **+ TCS** PBO + TCS	837	30.9	37.7	22.7	35.4
Gooderham 2019	ABRO 100 mg ABRO 200 mg PBO	167	25.6	40.8	23.0[ɣ]	40.8
Baricitinib						
BREEZE-AD 1	BARI 1 mg BARI 2 mg BARI 4 mg** PBO	624	31.0	35.7	25.7	41.8
BREEZE-AD 2	BARI 1 mg BARI 2 mg BARI 4 mg** PBO	615	33.5	34.5	24.0	50.5
BREEZE-AD 5	BARI 1 mg BARI 2 mg PBO	440	27.1	39.7	23.7	41.7
BREEZE-AD 7	BARI 2 mg + TCS PBO + TCS	329	29.57	33.8	24.03	45.0
Guttman-Yassky 2018	BARI 4 mg + TCS** BARI 2 mg + TCS PBO + TCS	104	21.23 [ɣ]	36.5	22.03	NR
Tralokinumab						
ECZTRA 1	TRA 300 mg PBO	802	29.3	37.0	27.5	50.9
ECZTRA 2	TRA 300 mg PBO	794	28.9[ɣ]	32.0	25.3	49.2
ECZTRA 3	TRA 300 mg + TCS PBO + TCS	380	25.5	36.0	26.0	46.3
Upadacitinib						

Trial	Arms	Sample Size (N)	EASI (Mean)	Mean age, y	Mean Disease Duration, y	IGA Score of 4 (%)
MEASURE UP 1*	UPA 15 mg UPA 30 mg PBO	847	29.5	34.0	20.7	45.2
MEASURE UP 2*	UPA 15 mg UPA 30 mg PBO	836	29.1	33.6	24.3	54.9
AD-UP*	UPA 15 mg + TCS UPA 30 mg + TCS PBO + TCS	901	29.6	34.1	23.4	52.9
Heads Up	DUP 300 mg UPA 30 mg	692	29.8	36.8	24.3	50.2
Guttman-Yassky 2020	UPA 7.5 mg** UPA **15 mg** UPA 30 mg PBO	167	25.6	40.8	23.0ʏ	40.8
Dupilumab						
LIBERTY AD SOLO 1	DUP 300 mg Q2W DUP 300 mg QW PBO	671	30.7	38.7	26.7	48.3
LIBERTY AD SOLO 2	DUP 300 mg Q2W DUP 300 mg QW PBO	708	29.4	34.7	24.8	48.3
LIBERTY AD CHRONOS	DUP 300 mg QW + TCS * DUP 300 mg + TCS PBO + TCS	740	29.8*	31.2ʏ	26.7ʏ	47.7
Thaci 2016	DUP 300 mg Q4W DUP 300 mg Q2W DUP 300 mg QW** DUP 200 mg Q2W DUP 100 mg Q4W** PBO	379	31.9	37.0	28.0	47.3

All values are pooled by ICER. All timepoints at 16 weeks except JADE MONO-1, JADE MONO-2, (12 weeks) and COMPARE (12/16 weeks). Bolded arms were included in the network meta-analyses. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, N: total number, NR: not reported, QW: weekly, Q2W: every two weeks, Q4W: every four weeks, TCS: topical corticosteroid, TRA: tralokinumab, UPA: upadacitinib, Y: year, %: percent. *pooled estimates from this trial were in patients 12 and older, ʏmedian, **included in pooled values here, but not included in comparative clinical effectiveness evaluation.

Mild-to-Moderate Population

A total of 21 references met our inclusion criteria for the mild-to-moderate population.[73,74,85-103] Of these, we identified two phase III, placebo-controlled RCTs of ruxolitinib cream[97] and one phase IIb placebo- and active-controlled (topical triamcinolone acetonide) RCT of ruxolitinib cream.[86,87] While no new trials of crisaborole for this indication were identified since the prior ICER Report in 2017, two phase III RCTs of this agent met inclusion criteria in our previous review.[95] Differences in trial populations, outcome definitions, and length of follow-up do not permit us to quantitatively compare outcomes of trials of ruxolitinib cream with crisaborole or topical calcineurin inhibitors.

Evidence Tables G1.50-1.53 contain the key study design and baseline characteristics of each trial, while a summary is presented below in Table 3.2 for the ruxolitinib cream trials. TRuE-AD1 and TRuE-AD2 were identical phase III multicenter, double-blind, vehicle (placebo)-controlled RCTs conducted in North America and Europe among 631 and 618 patients ≥12 years old, respectively, while Kim 2020 was a phase IIb multicenter, double-blind, dosing-ranging RCT conducted in North America among 307 patients ≥18 years old. The trials had similar baseline characteristics (see Table 3.2.), and the primary endpoints of TRuE-AD1 and TRuE-AD-2 were the proportion of patients achieving IGA (score of 0/1 with ≥2-point improvement from baseline) at week eight. In contrast, the primary endpoint of Kim 2020 was the percentage change from baseline in EASI score at week four in patients treated with ruxolitinib cream 1.5% twice a day compared with placebo. Additional details are available in Section D3 of the Report Supplement.

Table 3.2. Overview of Trials of Ruxolitinib Cream

Intervention	Trial	Arms	Sample Size (N)	Treatment Duration (Weeks)	EASI (Mean)	Median Age, y	Disease Duration, y	IGA Score of 3 (%)
Ruxolitinib Cream	TRuE AD 1	Vehicle (PBO) RUX 0.75% RUX 1.5%	631	8 weeks	7.8	31.8	16	75.8
	TRuE AD 2	Vehicle (PBO) RUX 0.75% RUX 1.5%	618	8 weeks	8	34.2	16.1	74
	Phase II Kim 2020	Vehicle (PBO) RUX 1.5% BID TRI 0.1%	307	8 weeks	8.4	35.0	20.8	NR

TRuE-AD 1 and 2 enrolled patients 12 and older, while the phase II study enrolled patients 18 and older. BID: twice-daily, N: total number, NR: not reported, PBO: non-medicated cream, RUX: ruxolitinib, TRI: triamcinolone acetonide cream, Y: years, %: percent

3.2. Results for Moderate-to-Severe Population

The key clinical benefits and harms of abrocitinib, baricitinib, tralokinumab, and upadacitinib in moderate-to-severe atopic dermatitis as well as key network meta-analysis (NMA) results are described in Section 3.2. Data synthesis and quantitative analyses, such as additional NMAs, are described in Section D2 of the Report Supplement. Additional results are presented in Sections D2 and D3 of the Report Supplement.

Clinical Benefits

Abrocitinib

Abrocitinib substantially increased the likelihood of achieving EASI 75 and IGA response in a dose dependent manner compared to placebo. Results for other EASI thresholds and other patient reported outcomes were generally consistent with results for EASI 75 and IGA. In comparison with dupilumab, outcomes were similar on most measures, though outcomes with abrocitinib 200 mg were somewhat better and itch improved more at 2 weeks. Though few adolescents were included in these trials, they appeared to have similar outcomes compared to adults. Long-term data were limited.

In three monotherapy trials of abrocitinib 200 mg, 61% to 65% of patients achieved EASI 75, compared with 10%-15% in the placebo arms of those trials.[35,36,40] EASI 75 was achieved by 40%-45% of patients with abrocitinib 100 mg. Tests of statistical significance comparing abrocitinib 200 mg and 100 mg dosing were not reported. EASI 90 was achieved by 38%-52% of patients with abrocitinib 200 mg, compared with 4%-10% of patients with placebo. EASI 90 was achieved by 19%-26% of patients with abrocitinib 100 mg. IGA response, defined as an IGA score of 0 or 1 *and* an improvement of 2 points or more from baseline, was achieved by 38%-44% of patients with abrocitinib 200 mg, compared to 6%-9% with placebo. In the abrocitinib 100 mg arms, IGA response was achieved by 24%-30% of patients.

One trial compared abrocitinib 200 mg, abrocitinib 100 mg, dupilumab, and placebo in patients also treated with topical corticosteroids.[37] IGA response, as defined above, and EASI 75, both measured at week 12 were the co-primary outcomes. IGA response was achieved by 48% of patients with abrocitinib 200 mg, 37% with abrocitinib 100 mg, 37% with dupilumab, and 14% with placebo. The percentage of patients achieving EASI 75 with abrocitinib 200 mg was 70% compared with 59% with abrocitinib 100 mg, 58% with dupilumab, and 27% with placebo. Responses in the abrocitinib arms were statistically superior to placebo, but statistical significance was not reported compared to dupilumab at 12 weeks. However, at 16 weeks, there were no statistically significant differences in

EASI 75 and IGA response between the abrocitinib arms and dupilumab apart from the IGA response being greater for the abrocitinib 200 mg arm (see Report Supplement D3).

In the monotherapy trials, more patients experienced a ≥4-point improvement on the patient reported Peak Pruritus Numerical Rating Scale (PP-NRS), a measure of itching, with abrocitinib 200 mg and 100 mg than with placebo (55%-64% and 38%-50% vs. 12%-26%, respectively).[35,36,40] Concordant with the EASI and IGA results in the trial versus dupilumab, at week 16 more patients achieved a ≥4-point improvement with abrocitinib 200 mg, abrocitinib 100 mg, and dupilumab (63% and 48% and 55%), compared to placebo (29%).[37] Measurement of PP-NRS at two weeks was a key secondary outcome in this trial and abrocitinib 200 mg (49%), but not abrocitinib 100 mg (32%), was statistically superior to dupilumab (27%) for this outcome providing some evidence that resolution of itch may occur more quickly with abrocitinib 200 mg than dupilumab.

Other patient reported outcomes showed similar favorable results compared to placebo. In two monotherapy trials, patients had greater reductions from baseline on the Dermatology Life Quality Index (DLQI) with abrocitinib 200 mg (-9 to -10) and 100 mg (-7 to -8) than placebo (-4; $p<0.05$ for comparisons with both doses of abrocitinib), where a 4-point difference is considered to be clinically meaningful.[35,36,104] In those trials, patients had greater reductions from baseline on the Patient-Oriented Eczema Measure (POEM), a self-reported measure of symptom severity, with abrocitinib 200 mg (-11) and abrocitinib 100 mg (-7 to -9), compared with placebo (-4; $p<0.05$ for both comparisons with placebo), where a 3-4-point improvement is considered clinically meaningful.[105] The Scoring Atopic Dermatitis (SCORAD), an instrument combining objective measures of area and intensity with subjective symptoms including itch and sleeplessness, was also evaluated in the trials. Results showed there were greater reductions from baseline with abrocitinib 200 mg (-56% to -70%) and abrocitinib 100 mg (-46% to -50%), compared to placebo (-23% to -29%; $p<0.002$, for comparisons with both doses of abrocitinib).[40 36] In addition, pooled analysis of the monotherapy trials showed that patients had greater numeric reductions from baseline on the Hospital Anxiety and Depression Scale (HADS) with abrocitinib 200 mg and 100 mg doses than placebo for both depression and anxiety (anxiety: − 2.0 and − 1.7 vs. − 1.0; depression: − 1.7 and − 1.3 vs. − 0.1; statistical significance not reported).[106]

Similar results on patient reported outcomes were reported for the trial that compared abrocitinib to dupilumab and placebo. For example, patients had greater improvements from baseline on the DLQI with abrocitinib 200 mg (-12; 95% CI: -12 to -11), abrocitinib 100 mg (-9; 95% CI: -10 to -8), and dupilumab (-11; 95% CI: -11 to -10) compared to placebo (-6; 95% CI: -7 to -5).[104]

At the time of this report, limited long-term data for abrocitinib suggest maintenance of EASI 75, IGA response, and ≥4-point improvement on the patient reported PP-NRS at 48 weeks (See Report Supplement D3).[76,107]

Baricitinib

Baricitinib increased the likelihood of achieving EASI 75 and IGA response compared to placebo. Results for other EASI thresholds and other patient reported outcomes were generally consistent with results for EASI 75 and IGA. Differences compared to placebo were modest with baricitinib 1 mg and not always statistically significant. There are limited long-term data and baricitinib was not studied in adolescents.

We do not report baricitinib 4 mg arm trial results because this dose is not anticipated to be used in the U.S. In three monotherapy trials of baricitinib 2 mg, 18%-30% of patients achieved EASI 75, compared with 6%-9% in the placebo arms of those trials.[42,45] EASI 75 was achieved by 13%-17% of patients with baricitinib 1 mg. Tests of statistical significance comparing baricitinib 2 mg and 1 mg were not reported. EASI 90 was achieved by 9%-21% of patients with baricitinib 2 mg, compared to 3%-5% of patients with placebo. In the baricitinib 1 mg arms of those trials, 6%-9% of patients achieved EASI 90. IGA response, defined as an IGA score of 0 or 1 *and* an improvement of 2 points or more from baseline, was achieved by 11%-24% in the baricitinib 2 mg arms, compared with 5% in the placebo arms. IGA response was achieved by 9%-13% of patients with baricitinib 1 mg.

Similar incremental improvements beyond placebo were reported in two trials that compared baricitinib 2 mg with placebo in patients also treated with topical corticosteroids.[46,48] For example, 30%-43% of patients achieved EASI 75 with baricitinib 2 mg compared to 20%-23% with placebo. IGA response, as defined above, was achieved by 22%-24% of patients with baricitinib 2 mg, compared with 8%-15% of patients with placebo.

In the monotherapy trials, more patients experienced a ≥4-point improvement on the patient reported PP-NRS with baricitinib 2 mg and baricitinib 1 mg than with placebo (12%-25% and 6%-16% vs. 5%-7%, respectively).[42,45] In addition, patients had greater improvements from baseline on nighttime awakenings due to itching, as measured by the atopic dermatitis sleep scale (ADSS), with baricitinib 2 mg than placebo (-1 to -1.2 vs. -0.4 to -0.8; statistical significance not reported).[49,108,109] In one combination trial, more patients achieved a PP-NRS ≥4-point improvement with baricitinib 2 mg than placebo (38% vs. 20%).[46]

In the monotherapy trials, patients had greater reductions from baseline on the DLQI with baricitinib 2 mg and 1 mg than placebo (-4 to -7 and -5 to -6 vs. -3 to -4, respectively; $p<0.05$ for both comparisons), where a 4-point difference is considered to be clinically meaningful.[42,45,104] In these trials, patients had greater reductions from baseline on POEM with baricitinib 2 mg and 1 mg compared to placebo (-6 to -7 and -4 to -5 vs. -2 to -3, respectively; $p<0.05$ for both comparisons), where a 3-4-point improvement is considered clinically meaningful.[105]. Similarly, patients had greater reductions from baseline on SCORAD with baricitinib 2 mg than placebo in two trials that

reported this outcome (-22% to -28% vs. -13%-14%, respectively; p<0.05); differences between baricitinib 1 mg and placebo were not statistically significant.[42] In addition, patients had greater numeric reductions from baseline on HADS Anxiety (-1.9 to -2.6 vs. 0.9 to 2.0) and HADS Depression (-1.0 to -1.7 vs. 0.3 to 1.3) with baricitinib 2 mg than placebo, although statistical significance was not reported.[49,108,109] Trial results also showed a greater improvement with baricitinib 2 mg on work productivity measures (absenteeism, presenteeism, work productivity loss, and activity impairment) than placebo. [49,108,109]

One combination trial reported a greater reduction from baseline on the DLQI with baricitinib 2 mg than placebo (-8 vs. -6, respectively; p=0.022), where a 4-point improvement is considered clinically meaningful.[46,104] The phase II trial reported a greater reduction in this outcome with baricitinib 2 mg compared to placebo that did not reach statistical significance (-6 vs. -7, respectively; p>0.05).[48]

At the time of this report, limited long-term data for baricitinib suggest maintenance of EASI 75 and IGA response at 52-68 weeks. [43,44,82] These are described in greater detail in Report Supplement D3.

Tralokinumab

Tralokinumab increased the likelihood of achieving EASI 75 and IGA response compared to placebo. Results for other EASI thresholds and other patient reported outcomes were generally consistent with results for EASI 75 and IGA. There are limited long-term data and tralokinumab was not studied in adolescents.

In two placebo-controlled monotherapy trials of tralokinumab, 25%-33% of patients achieved EASI 75, compared with 11%-13% of patients in the placebo arms of those trials.[63] EASI 90 was achieved by 15%-18% of patients with tralokinumab, compared with 4%-6% of patients with placebo. IGA response, defined as an IGA score of 0 or 1, was achieved by 16%-22% of patients in the tralokinumab arms, compared with 7%-11% in the placebo arms.

In a trial in patients treated with topical corticosteroids, tralokinumab was more effective than placebo.[64] For example, the percentage of patients achieving EASI 75 with tralokinumab was 56% compared with 36% with placebo. IGA response, also defined as an IGA score of 0 or 1, was 39% with tralokinumab compared with 26% with placebo.

In the placebo-controlled monotherapy trials, more patients experienced a ≥4-point improvement on the patient reported PP-NRS with tralokinumab than with placebo (20%-25% vs. 10%, respectively).[63] Concordant with the EASI and IGA results in the combination trial, more patients achieved a ≥4-point improvement with tralokinumab than placebo (45% vs. 34%).[64]

In one of the monotherapy trials, patients had greater reductions from baseline on the DLQI with tralokinumab than placebo (-7 vs. -5; p=0.002); however, this difference is less than the difference considered clinically meaningful (4-point improvement).[63,104] In the other monotherapy trial, patients had greater reductions in this outcome with tralokinumab than placebo that also met this clinically meaningful difference (-9 vs. -5; p<0.001).[63,104] In both trials, patients had greater reductions from baseline on POEM with tralokinumab compared to placebo (-8 to -9 vs. -3 to -4; p<0.001), where a 3-4-point improvement is considered clinically meaningful.[105]. Similarly, in both trials, patients had greater reductions from baseline on SCORAD with tralokinumab than placebo (-25% to -28% vs. -14% to -15%; p<0.001). In both trials, patients had greater reductions from baseline in the weekly average of eczema-related sleep interference NRS with tralokinumab than placebo (-3 vs. -2; p=0.007). In addition, data submitted as academic-in-confidence by the manufacturer suggest a greater reduction from baseline on HADS total score with tralokinumab compared to placebo; however, the difference was not statistically different in one trial.[65] Similar results were reported for the combination trial. For example, patients had greater reductions from baseline on the DLQI with tralokinumab than placebo (-12 vs. -9; p<0.001).[64,104]

At the time of this report, long-term data for tralokinumab are limited. Data from the 36-week maintenance periods of the two placebo-controlled monotherapy trials suggest maintenance of EASI 75 and IGA responses at 52 weeks, while similar results from the 32-week maintenance period of the placebo-controlled combination trial were also reported (see Report Supplement D3).[63,64] Additionally, a lower dosing frequency of tralokinumab (300mg every 4 weeks) was evaluated among 16-week responders, and outcomes were similar but slightly worse than for those continued on the higher dose.[63]

Upadacitinib

Upadacitinib substantially increased the likelihood of achieving EASI 75 and IGA response in a dose dependent manner compared to placebo. Results for other EASI thresholds and other patient reported outcomes were generally consistent with results for EASI 75 and IGA. Compared with dupilumab, outcomes for upadacitinib 30 mg were similar or somewhat better on reported measures. Though few adolescents were included in these trials, they appeared to have similar outcomes compared to adults. No long-term data were identified.

In three monotherapy trials of upadacitinib 30 mg, 69%-80% of patients achieved EASI 75, compared with 10%-16% in the placebo arms of those trials.[69,80] In those same trials, 52%-70% achieved EASI 75 with upadacitinib 15 mg. No tests of statistical significance comparing upadacitinib 30 mg to 15 mg dosing were reported in these trials. EASI 90 was achieved by 50%-66% of patients with upadacitinib 30 mg, compared with 2%-8% of patients with placebo. Further, EASI 90 was achieved by 26%-53% of patients with upadacitinib 15 mg. IGA response, defined as an

IGA score of 0 or 1 *and* an improvement of 2 points or more from baseline, was achieved 50%-62% of patients with upadacitinib 30 mg, compared with 2%-8% of patients with placebo. In the upadacitinib 15 mg arms, 31%-48% achieved IGA response.

In a head-to-head monotherapy trial, more patients treated with upadacitinib 30 mg than dupilumab achieved EASI 75 (71% vs. 61%; p = 0.006) and EASI 90 (61% vs. 39%; p<0.001) at 16 weeks.[83] At the time of this Report, results for IGA response were not available.

In a trial that compared upadacitinib to placebo in patients also treated with topical corticosteroids, the percentage of patients achieving EASI 75 with upadacitinib 30 mg was 77% compared with 65% with upadacitinib 15 mg and 26% with placebo. [81] IGA response, as defined above, was achieved by 59% of patients with upadacitinib 30 mg, 40% with upadacitinib 15 mg, and 11% with placebo.

In the placebo-controlled monotherapy trials, more patients experienced a ≥4-point improvement on the patient reported PP-NRS with upadacitinib 30 mg and 15 mg than with placebo (53%-60% and 42%-59% vs. 6%-12%, respectively).[69,80] More patients achieved a ≥4-point improvement with upadacitinib 30 mg than dupilumab (55% vs. 36%).[83] Similarly, in the trial that compared upadacitinib to placebo in patients also treated with topical corticosteroids, more experienced achieved a ≥4-point improvement with upadacitinib 30 mg and 15 mg than placebo (64% and 52% vs. 15%).[81]

Other patient reported outcomes showed similar favorable results compared to placebo. In two of the monotherapy trials, DLQI response, defined as an improvement of 4-points or more from baseline, was achieved by 78%-82% of patients on upadacitinib 30 mg, 72%-75% of patients on upadacitinib 15 mg, compared with 28%-29% of patients on placebo. [80] In those trials, POEM response, defined as an improvement of 4-point or more from baseline, was achieved by 81%-84% of patients on upadacitinib 30 mg, 71%-75% of patients on upadacitinib 15 mg, compared with 23%-29% of patients on placebo. [80] In another trial, patients had greater reductions from baseline on POEM with upadacitinib 30 mg and 15 mg compared to placebo (-12 and -9 vs. -2, respectively; p≤0.001 for both comparisons), where a 3-4-point improvement is considered clinically meaningful.[69,105] Similarly, patients had greater reductions from baseline on SCORAD with upadacitinib 30 mg and 15 mg compared to placebo (-60% to -73% and -47% to -66% vs. -12% to -33%; p<0.001 for both comparisons). [69,80,105] In addition, greater proportions of patients achieved clinically meaningful improvement in HADS-anxiety and HADS-depression with upadacitinib 30 mg compared to placebo (49% to 56% vs. 11% to14%; p<0.0001). [80] Clinical meaningful improvement was defined in those trials as a HADS anxiety or HADS depression score of <8, assessed in patients with HADS anxiety score of ≥8 or HADS depression score of ≥8 at baseline. [80] At the time of this report, these patient-reported outcomes were not reported in the trial that compared upadacitinib to placebo in patients receiving topical corticosteroids.

No long-term evidence was identified for upadacitinib at the time of this report.

Network Meta-Analysis (NMA) Results of Monotherapy Trials

For quantitative indirect comparisons, the monotherapy placebo-controlled trials of the agents were felt to provide the most comparable results. Here, we present the NMA results of EASI 75 and EASI 90 from the monotherapy trials (15 trials). Refer to the Report Supplement D2 for more details on the methods and trials included and the results of NMA on other outcomes (EASI 50, IGA response, and PP-NRS ≥4-point improvement) on these trials. We also present information on the NMAs of combination trials (6 trials) in the Report Supplement (see Report Supplement D2).

EASI 75 and EASI 90

For the EASI NMA (15 trials), we present the results of the unadjusted random effect model, given its better fit for the model relative to the adjusted model (see Report Supplement D2). All interventions showed statistically significantly greater EASI 75 and EASI 90 responses than placebo and baricitinib 1 mg (Tables 3.4 and 3.5). Compared to placebo, interventions were 1.5 to 5.7 times more likely to achieve EASI 75 (Table 3.4) and 1.8 to 9.6 times more likely to achieve EASI 90 (Table 3.5). Upadacitinib 30 mg was more likely to achieve EASI 75 and EASI 90 than the other interventions; however, upadacitinib 30 mg was not statistically better than abrocitinib 200 mg. Additionally, there were no statistically significant differences with abrocitinib (both doses) and upadacitinib 15 mg compared to dupilumab. In comparison, dupilumab showed statistically significantly greater EASI 75 and EASI 90 responses than tralokinumab and baricitinib (both doses).

Based on the NMA, the expected proportion of patients who achieved EASI 75 was 12% for placebo, 49% for dupilumab, 40% for abrocitinib 100 mg, 58% for abrocitinib 200 mg, 19% for baricitinib 1 mg, 29% for baricitinib 2 mg, 31% for tralokinumab, 55% for upadacitinib 15 mg, and 67% for upadacitinib 30 mg (see Table 3.3).

Table 3.3: NMA Results. Proportions of patients achieving EASI 50, 75, and 90 thresholds in Monotherapy RCTs.

Treatment	EASI 50	EASI 75	EASI 90
	Median proportion (95% CrI)		
Placebo	0.21 (0.20 – 0.23)	0.12 (0.1 -0.13)	0.05 (0.04 - 0.06)
Dupilumab 300 mg Q2W	0.64 (0.58 – 0.70)	0.49 (0.42 – 0.55)	0.32 (0.27 – 0.38)
Abrocitinib 100 mg	0.55 (0.45 – 0.65)	0.40 (0.30 -0.50)	0.24 (0.17 – 0.33)
Abrocitinib 200 mg	0.73 (0.64 – 0.81)	0.58 (0.49 – 0.68)	0.41 (0.32 -0.52)
Baricitinib 1 mg	0.31 (0.25 – 0.39)	0.19 (0.14 -0.25)	0.09 (0.07 – 0.14)
Baricitinib 2 mg	0.44 (0.36 – 0.52)	0.29 (0.23 – 0.37)	0.16 (0.12 – 0.22)
Tralokinumab 300 mg	0.46 (0.38 – 0.53)	0.31 (0.24 – 0.38)	0.17 (0.13 – 0.23)
Upadacitinib 15 mg	0.70 (0.64 – 0.76)	0.55 (0.48 – 0.61)	0.38 (0.31 – 0.45)
Upadacitinib 30 mg	0.80 (0.75 – 0.84)	0.67 (0.61 – 0.73)	0.50 (0.44 -0.57)

Table 3.4. Relative Risks for EASI 75 in Monotherapy RCTs in Adults

UPA 30 mg								
1.15 (0.97-1.40)	**ABRO 200 mg**							
1.22 (1.10 -1.37)	1.06 (0.86-1.28)	**UPA 15 mg**						
1.38 (1.23-1.56)	1.20 (0.97-1.46)	1.13 (0.97-1.32)	**DUP 300mg Q2W**					
1.70 (1.34-2.23)	1.47 (1.25-1.78)	1.39 (1.08-1.85)	1.23 (0.95-1.64)	**ABRO 100 mg**				
2.18 (1.77-2.77)	1.89 (1.45-2.49)	1.79 (1.42-2.29)	1.58 (1.25-2.03)	1.29 (0.93-1.76)	**TRA 300 mg**			
2.28 (1.81-2.95)	1.97 (1.50-2.62)	1.86 (1.47-2.43)	1.64 (1.28-2.15)	1.34 (0.96-1.85)	1.04 (0.77-1.41)	**BARI 2 mg**		
3.53 (2.65-4.79)	3.06 (2.21-4.24)	2.88 (2.14-3.95)	2.54 (1.88-3.49)	2.07 (1.42-2.98)	1.61 (1.13-2.29)	1.54 (1.20-2.01)	**BARI 1 mg**	
5.71 (5.13-6.38)	4.95 (4.11-5.85)	4.67 (4.08-5.31)	4.13 (3.60-4.70)	3.36 (2.60-4.21)	2.61 (2.09-3.18)	2.50 (1.97-3.11)	1.62 (1.22-2.12)	**PBO**

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

Table 3.5. Relative Risks for EASI 90 in Monotherapy RCTs in Adults

UPA 30 mg								
1.23 (0.96-1.61)	**ABRO 200 mg**							
1.33 (1.15-1.56)	1.09 (0.81-1.43)	**UPA 15 mg**						
1.58 (1.35-1.87)	1.29 (0.96-1.69)	1.18 (0.96-1.47)	**DUP 300mg Q2W**					
2.08 (1.51-2.98)	1.70 (1.36-2.17)	1.57 (1.11-2.28)	1.32 (0.94-1.93)	**ABRO 100 mg**				
2.89 (2.19-3.95)	2.36 (1.65-3.39)	2.17 (1.60-3.0)	1.83 (1.34-2.54)	1.39 (0.91-2.09)	**TRA 300 mg**			
3.05 (2.26-4.26)	2.49 (1.72-3.61)	2.29 (1.67-3.23)	1.93 (1.39-2.71)	1.47 (0.95-2.22)	1.06 (0.71-1.55)	**BARI 2 mg**		
5.31 (3.69-7.79)	4.32 (2.85-6.56)	3.98 (2.72-5.9)	3.35 (2.28-4.99)	2.54 (1.57-4.04)	1.83 (1.17-2.84)	1.73 (1.26-2.42)	**BARI 1 mg**	
9.60 (8.32-11.17)	7.83 (6.05-9.87)	7.21 (6.0-8.6)	6.08 (5.08-7.22)	4.61 (3.29-6.25)	3.32 (2.5-4.27)	3.14 (2.32-4.14)	1.81 (1.27-2.54)	**PBO**

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

Harms

Most adverse events (AEs) and treatment-emergent adverse events (TEAEs) observed in the trials were of mild-to-moderate severity (see Report Supplement Tables D3.4-3.7). Included in the most commonly reported AEs with greater incidence than placebo were nausea, conjunctivitis, and herpetic infection. The incidence of discontinuation due to AEs or TEAEs and the incidence of serious adverse events (SAEs) were low and were generally similar among these agents.

Although the incidence of SAEs in the trials of JAK inhibitors for this indication was low, long-term data are limited and evidence from trials evaluating JAK inhibitors at longer time points for other indications suggest an increased risk of SAEs, such as reactivation of herpes zoster, malignancy, thromboembolic events, and cardiovascular events.[33] Additionally, baricitinib and upadacitinib carry black box warnings for serious infections, malignancies, and thrombosis.[110,111] More information on the harms of the interventions is available in Evidence Tables G1.42-1.47 of the Report Supplement.

At the time of the 2017 ICER Report, long-term safety for dupilumab were limited. Since then, long-term safety data over three years from an open-label extension were reported, and these results supporting the safety of dupilumab were consistent with trials of up to 52 weeks (see Tables D3.6 and D3.7 in the Report Supplement).[50,112]

Subgroup Analyses and Heterogeneity

We examined outcomes among patient subgroups of interest based on age (children 6 to 11 years old, adolescents 12-17 years old, and adults greater than 18 years old) and disease severity (moderate and severe).

Patient Age

Trials of baricitinib and tralokinumab did not include patients younger than 18 years old. One trial of abrocitinib solely enrolled patients 12-17 years old, while several trials of abrocitinib and upadacitinib trials enrolled patients 12 years and older, and data on subgroups of adolescent patients in those trials were obtained from conference presentations or manufacturers as academic-in-confidence data(see Report Supplement Tables D3).[39,41,70,77] Results from these trials were qualitatively similar to results of patients greater than 18 years old in these trials and from the dupilumab trial, LIBERTY AD ADOL,[52] which enrolled adolescent patients (see Report Supplement Tables D3.8-3.11).

Disease Severity

Subgroup analyses based on disease severity at baseline mostly provided by manufacturers as academic-in-confidence suggest qualitatively better outcomes in patients with severe disease compared to those with moderate disease with abrocitinib, baricitinib, and tralokinumab (see Evidence Tables G1.25-1.42).[39,44,65] No evidence stratified by disease severity was identified for upadacitinib.

Uncertainty and Controversies

There is no well-defined classification for "moderate-to-severe" atopic dermatitis and how it differs from those with "mild-to-moderate" disease. This results in differences in study populations among trials and the varying responses seen for those receiving placebo treatment.

Abrocitinib, baricitinib, tralokinumab, and upadacitinib are therapies with novel mechanisms of action affecting the body's immune system, and we lack adequate long-term safety data for patients with atopic dermatitis. Although SAEs were rare in the phase III atopic dermatitis trials of abrocitinib, baricitinib, and upadacitinib, worrisome side effects for oral JAK inhibitors approved and in use for other conditions have led the FDA to place boxed warnings on this class of agents. Presumably because of these concerns, the FDA announced in April 2021 that they are extending the review period for abrocitinib, baricitinib, and upadacitinib.[13]

Although patients with atopic dermatitis can have disease activity that flares and remits over time, suggesting that intermittent use of these therapies may be possible, clinical experts we spoke with felt that they will be used for long periods in patients with clinical response and tolerability.

Although tralokinumab is not a JAK inhibitor, lack of long-term data results in some concerns about safety for this novel IL-13 antagonist. Though dupilumab is an IL-4 receptor alpha antagonist, it inhibits IL-4 and IL-13 signaling and suggests that long-term safety data for dupilumab may also apply to tralokinumab.

We primarily used indirect quantitative methods (NMAs) to compare abrocitinib, baricitinib, tralokinumab, and upadacitinib to each other because there were no head-to-head studies. Such indirect analyses have more uncertainty than had the therapies been compared directly. Only two trials compared interventions to dupilumab (JADE COMPARE for abrocitinib and Heads Up for upadacitinib).

The pivotal phase II and III RCTs compared the active agents to placebo as monotherapy during the 16-week study periods (12 weeks for the abrocitinib trials). These trials represent the best evidence for the efficacy of the active therapies and were used in our primary NMA analyses. Other trials comparing these new drugs to placebo along with the use of topical steroids and/or calcineurin

inhibitors may better reflect benefit as used in routine practice since new therapy is often added to existing topical treatments. However, differences among trials that included the use of background topical therapy led us to consider these trials separately from the placebo trials in our NMA analyses. The choice of our primary NMA results using trials only with placebo and not with topical therapies likely reflects a best-case view of the benefit of these new therapies. This is supported by the lower risk ratios in the NMAs for trials that include topical therapies. We examined doses for the new therapies we anticipate may be approved for use including 1 mg of baricitinib that is recommended for rheumatoid arthritis patients with moderate renal impairment.

There is limited information available about the relative benefits and harms of these new therapies in important subgroups including patients with moderate versus severe atopic dermatitis and adolescents aged 12-17. Few trials have yet reported outcomes separately for patients with moderate versus severe atopic dermatitis at baseline, so it is uncertain whether the treatment benefit differs based upon baseline severity.

The onset of action may also differ among these drugs. Specifically, abrocitinib assessed its primary outcome at 12 weeks, whereas the other drugs used 16 weeks. In the JADE COMPARE trial of abrocitinib versus dupilumab, abrocitinib appeared to improve outcomes more quickly than dupilumab even though outcomes were similar by 16 weeks.

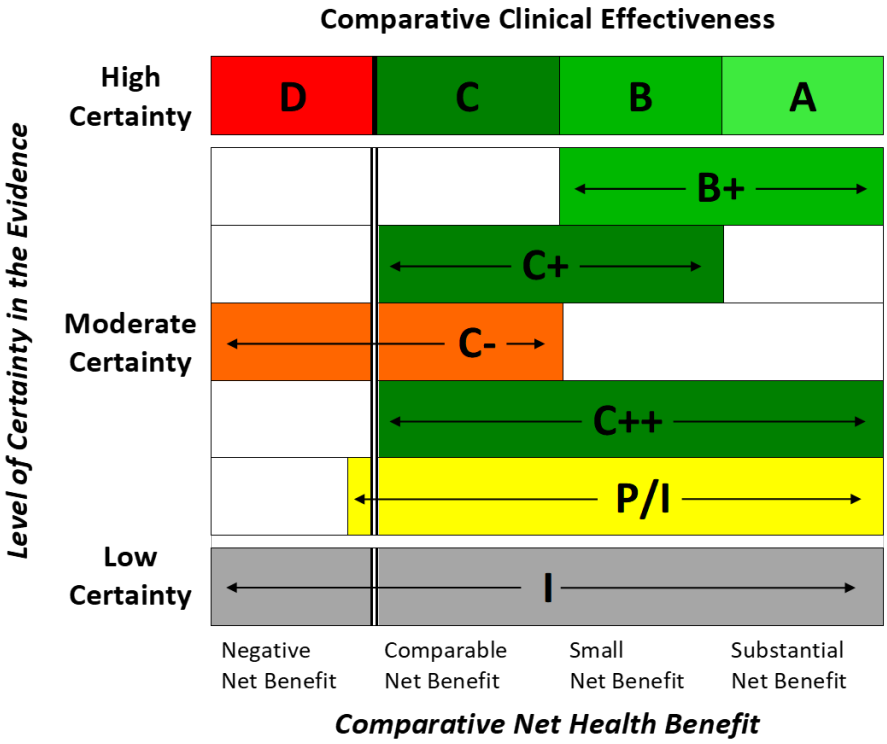
Given the large impact of atopic dermatitis in African-Americans and the importance of skin appearance on outcomes of treatment more broadly,[113] few trials included a sizable number of patients with darker skin complexions, and we are not aware of any trial that has reported outcomes among those with darker skin complexion.

Patients with atopic dermatitis often have other allergic conditions such as rhinitis and asthma. Dupilumab has been shown to be beneficial in patients with atopic dermatitis and these other conditions, but it is not known how abrocitinib, baricitinib, tralokinumab, and upadacitinib affect patients who also have allergic rhinitis or asthma.

Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.2) is provided in Section D1 of the Report Supplement.

Figure 3.2. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Results from clinical trials and from our NMAs suggest that abrocitinib, baricitinib, tralokinumab, and upadacitinib improve outcomes of patients with atopic dermatitis compared to topical emollients alone (placebo). These outcomes included improving the severity of atopic dermatitis and patient reported itch and sleep. Similar favorable results for abrocitinib, baricitinib, tralokinumab, and upadacitinib are seen in trials that permitted use of topical medications. There

appear to be some differences among these medications in terms of their effectiveness, with abrocitinib and upadacitinib having more favorable outcomes than baricitinib and tralokinumab at the doses studied in the trials.

With regard to comparisons with dupilumab, direct comparisons with abrocitinib and upadacitinib and our NMAs suggest that higher doses of upadacitinib and possibly abrocitinib are somewhat more effective than dupilumab, while baricitinib (at the doses likely to be approved) and tralokinumab are likely somewhat less effective than dupilumab. When comparing therapies, other outcomes may also be important such as many patients with atopic dermatitis have comorbid atopic conditions and dupilumab has proven benefit in treating some patients with asthma.

Though abrocitinib, baricitinib, tralokinumab, and upadacitinib appeared to have few serious harms reported from the trials of atopic dermatitis, oral JAK inhibitors approved for other indications, including baricitinib and upadacitinib, have label warnings about potentially causing serious infections, blood vessel disorders, cancer and death, and serious harms are more common at the higher doses studied. Whether certain oral JAK inhibitors or their use in patients with atopic dermatitis is associated with fewer long-term harms remains uncertain. No similar risks have been reported with tralokinumab but while it works through a mechanism more similar to dupilumab than the JAK inhibitors it lacks the same long-term safety profile of dupilumab. Moreover, for all of these medications there is uncertainty about their relative benefit and safety caused by differences in the trials with regards to patient characteristics, outcomes assessed and their timing, the indirect nature of the NMAs, and limited long-term efficacy and safety data.

In summary, for adults and adolescents with moderate-to-severe atopic dermatitis inadequately controlled with topical or systemic therapies, or for whom topical or systemic therapies are not tolerated or are medically inadvisable, we identified benefits from short-term trials of these four agents but concerns about long-term safety, especially for the oral JAK inhibitors. As such:

- We consider the evidence for the net health benefit for abrocitinib, baricitinib, tralokinumab and upadacitinib compared with topical therapies alone to be *promising but inconclusive ("P/I")*, demonstrating a moderate certainty of a small or substantial net health benefit, with a small (but nonzero) likelihood of a negative net health benefit.
- We consider the evidence for the net health benefit for abrocitinib and upadacitinib compared with dupilumab to be *insufficient ("I")*, and that the net health benefit of baricitinib and tralokinumab were *comparable or inferior ("C-")* when compared with dupilumab, demonstrating moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior.

- We consider the evidence for the net health benefit for abrocitinib, baricitinib, tralokinumab, and upadacitinib compared with each other to be *insufficient ("I")*.

We also note that for the new therapies, we have greater uncertainties for adolescents given that baricitinib and tralokinumab trials only included adults and the randomized trials of abrocitinib and upadacitinib enrolled small numbers of patients younger than age 18.

Table 3.6. Evidence Ratings

Treatment	Comparator	Evidence Rating
Abrocitinib	Topical therapies alone	P/I
Baricitinib	Topical therapies alone	P/I
Tralokinumab	Topical therapies alone	P/I
Upadacitinib	Topical therapies alone	P/I
Abrocitinib	Dupilumab	I
Baricitinib	Dupilumab	C-
Tralokinumab	Dupilumab	C-
Upadacitinib	Dupilumab	I
Abrocitinib, Baricitinib, Tralokinumab, Upadacitinib	To each other	I

3.3. Results for Mild-to-Moderate Population

Clinical Benefits

The key clinical benefits and harms of ruxolitinib cream in the mild-to-moderate population are described in Section 3.3. Additional evidence is presented in Sections D2 and D3 of the Report Supplement (see Report Supplement Tables D3.12-3.13 and Evidence Tables G1.48-1.64.)

Our 2017 Report found inadequate evidence to assess the relative efficacy of crisaborole with the other topical therapies for mild-to-moderate atopic dermatitis including topical calcineurin inhibitors and topical corticosteroids. Trials of crisaborole found modest improvement compared to vehicle (placebo). For example, in pooled analyses of two trials of crisaborole, Investigator's Static Global Assessment (ISGA) response, defined as an ISGA score of 0 or 1 *and* an improvement of 2 points or more from baseline, was moderately higher in the crisaborole arms, compared with the placebo arms at day 29 (32% vs. 22%). NMA results comparing crisaborole to pimecrolimus, a topical calcineurin inhibitor, showed a trend towards improvement in IGA response with pimecrolimus (risk ratio: 0.61; 95% CrI: 0.10 to 2.28). However, time periods and versions of IGA scales differed between the trials, and the credible interval was wide. Further, an SLR suggested pimecrolimus was less effective than topical tacrolimus or moderate potency topical corticosteroids.[114]

Ruxolitinib Cream

Ruxolitinib cream substantially increased the likelihood of achieving EASI 75, EASI 90, and IGA response in a dose dependent manner compared to vehicle (placebo). Results for other EASI thresholds and other patient reported outcomes were generally consistent with results for EASI 75 and IGA. Compared with topical corticosteroids, outcomes for ruxolitinib cream were better on reported measures. Results for adolescents were similar to adults and long-term data were limited.

We identified two monotherapy trials (TRuE-AD1 & TRuE-AD2) comparing ruxolitinib cream to vehicle (placebo). Both trials enrolled patients ≥12 years old; most of the patients were ≥18 years old (80%-81%). In addition, we identified a placebo- and active-controlled trial that enrolled patients ≥18 years old.

In TRuE-AD1 and 2, 62% of patients achieved EASI 75 in the ruxolitinib cream 1.5% arms, compared with 14%-25% of patients in the vehicle (placebo) arms at week eight.[97] EASI 75 was achieved by 52%-56% of patients with ruxolitinib cream 0.75%. EASI 90 was achieved by 43%-44% of patients in the ruxolitinib cream 1.5 arms, compared with 4%-10% of patients in the vehicle (placebo) arms. In the ruxolitinib cream 0.75% arms, 35%-38% of patients achieved this outcome. IGA response, defined as an IGA score of 0 or 1 and an improvement of 2 points or more from baseline, was achieved by 51%-54% of patients in the ruxolitinib cream 1.5% arms, compared with 8%-15% of patients in the vehicle (placebo) arms. IGA response was achieved by 39%-50% of patients with ruxolitinib cream 0.75%.

More patients experienced a ≥4-point improvement on the patient reported PP-NRS with ruxolitinib cream 1.5% and 0.75% dosing than with vehicle (placebo) (51%-52% and 40%-43% vs. 15%-16%, respectively).

Other patient reported outcomes showed similar favorable results compared to vehicle (placebo). In pooled analyses, patients had greater reductions from baseline on the DLQI with ruxolitinib cream 1.5% (-7) and ruxolitinib cream 0.75% (-7) than vehicle (placebo) (-3.1; $p<0.0001$ for comparisons with both doses of ruxolitinib cream), where a 4-point difference is considered to be clinically meaningful.[99,104] Patients also had greater reductions from baseline on POEM with ruxolitinib cream 1.5% and 0.75% compared to vehicle (placebo) (-11 and -11 to vs. –4.2, respectively; $p<0.0001$ for both comparisons), where a 3-4-point improvement is considered clinically meaningful.[99,105]. More patients experienced a ≥6-point improvement on the Patient Reported Outcomes Measurement Information System (PROMIS) Short Form-Sleep Disturbance Score with ruxolitinib cream 1.5% and 0.75% dosing than vehicle (placebo) (22%-26% and 21% vs. 10%-19%%, respectively; $p<0.05$ for both comparisons).[115] Similarly, patients had greater reductions

from baseline on SCORAD with ruxolitinib cream 1.5% and 0.75% dosing than vehicle (placebo) (-67% and -63% vs. -30.4%; p<0.0001).

In a monotherapy trial that compared ruxolitinib cream to topical triamcinolone acetonide (a medium potency topical corticosteroid) and vehicle (placebo), there were numerical improvements with ruxolitinib cream compared to triamcinolone acetonide cream for EASI 75, IGA response (as defined above), and change from baseline in itch NRS scores.[86,87] However, no tests of statistical significance were reported (see Table D3.12 in the Report Supplement).

Results for HADS Anxiety and Depression were not reported in any trials of ruxolitinib cream.

The 52-week long-term extension studies of TRuE-AD1 and TRuE-AD2, designed to primarily evaluate the long-term safety of ruxolitinib, suggest maintenance of IGA response at 52 weeks (see Report Supplement D3).[73]

Harms

All TEAEs were of mild-to-moderate severity (see Report Supplement Table D3.13). The most commonly reported TEAEs included application site burning and pruritus, and the incidence of these TEAEs was lower in the ruxolitinib cream arms than vehicle (placebo). In contrast, the incidence of serious TEAEs was generally similar between the arms. Further, discontinuation incidence due to TEAEs was lower in the ruxolitinib cream arms compared to placebo and triamcinolone acetonide cream. More information on the harms of ruxolitinib cream is available in Evidence Tables G1.59-1.60 of the Report Supplement.

Subgroup Analyses and Heterogeneity

We examined outcomes among patient subgroups of interest based on age (children 6 to 11 years old, adolescents 12-17 years old, and adults greater than 18 years old), disease severity (mild and moderate), and race.

Patient Age

No trials of ruxolitinib cream enrolled children. Subgroup analyses of adolescent patients from trials that enrolled patients 12 years and older suggest qualitatively similar results to the overall population, though the proportion of patients 12-17 years old in these trials was small (see Evidence Tables G1.61-1.64).[101]

Disease Severity

Subgroup analyses based on disease severity at baseline suggest qualitatively better outcomes in patients with moderate disease compared to those with mild disease (see Evidence Tables G1.61-1.64).[97]

Race

In a presentation of pooled data from two trials, IGA response with ruxolitinib appeared somewhat greater in white than black patients.[101] With the two doses (1.5% and 0.75%), the percentages of white patients who achieved IGA treatment success at week eight were 57.3% and 49.7% versus 12.2% with vehicle (placebo); in black patients, these results were 38.1% and 31.4% versus 11.5%. Results in Asians and other races appeared more similar to the results in white patients.

Uncertainty and Controversies

Although ruxolitinib cream is a topical JAK inhibitor and concern for side effects may be lower, systemic absorption still occurs and its role for the long-term management of patients with mild-moderate atopic dermatitis, especially in children and adolescents, is uncertain and will also require long-term assessment of safety outcomes. Perhaps reflecting concerns about systemic JAK inhibitors and potential systemic absorption of topical JAK inhibitors, the FDA announced in June 2021 that they are extending the review period for ruxolitinib cream by three months.[15] Trial designs did not allow for quantitative indirect comparisons between topical ruxolitinib and other topical therapies. The only head-to-head trial was in comparison with a medium potency topical corticosteroid which would be expected to have lower efficacy than more potent topical therapies.

The effectiveness of ruxolitinib cream in patients with darker skin complexions may be somewhat less, supporting the need for trials in broader populations.[101]

Summary and Comment

In two phase III trials of ruxolitinib cream versus topical emollients alone (placebo), patients receiving ruxolitinib cream had improved outcomes at the two doses studied. A single phase II trial of ruxolitinib cream included a topical steroid comparator. While outcomes appeared to favor ruxolitinib cream compared to topical triamcinolone acetonide, no tests of statistical significance were reported, and it was not compared with more potent topical corticosteroids. Side effects of ruxolitinib cream were similar to or better than vehicle (placebo), though long-term safety remains uncertain. In summary:

- We consider the evidence for the net health benefit for ruxolitinib cream compared with topical emollients to be *comparable or better ("C++")*, demonstrating a moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit.
- We consider the evidence for the net health benefit for ruxolitinib cream compared with other topical medications to be *insufficient ("I")*.

New England CEPAC Votes

Table 3.7. New England CEPAC Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
Patient Population for questions 1-4: *Adults with moderate-to-severe atopic dermatitis whose disease has either not responded adequately to topical therapies, or for whom topical therapies have not been tolerated, or are medically inadvisable. Usual care in such patients is defined as use of topical emollients and avoidance of exacerbating factors. Given the currently available evidence:*		
Is the evidence adequate to demonstrate that the net health benefit of **abrocitinib** added to usual care is superior to that provided by usual care alone?	8	5
Is the evidence adequate to demonstrate that the net health benefit of **baricitinib** added to usual care is superior to that provided by usual care alone?	7	6
Is the evidence adequate to demonstrate that the net health benefit of **upadacitinib** added to usual care is superior to that provided by usual care alone?	9	4
Is the evidence adequate to demonstrate that the net health benefit of **tralokinumab** added to usual care is superior to that provided by usual care alone?	11	2
Patient Population for Questions 5*: Adolescents and Adults with mild-to-moderate atopic dermatitis.*		
Given the currently available evidence, Is the evidence adequate to demonstrate that the net health benefit of **ruxolitinib cream** is superior to that provided by topical emollients alone?	12	1

Based on the evidence in the clinical trials and ongoing concerns about long-term safety with oral JAK inhibitors, the panel votes were split as to the net health benefit of abrocitinib, baricitinib, and upadacitinib in adults with moderate to severe atopic dermatitis. The panel voted that tralokinumab had adequate evidence of net health benefit in this setting.

For adolescent and adult patients with mild-to-moderate atopic dermatitis, the panel voted that ruxolitinib cream has adequate evidence of net health benefit compared with topical emollients alone. The panel focused on the clinical effectiveness and the safety profile of ruxolitinib cream.

4. Long-Term Cost Effectiveness

4.1. Methods Overview

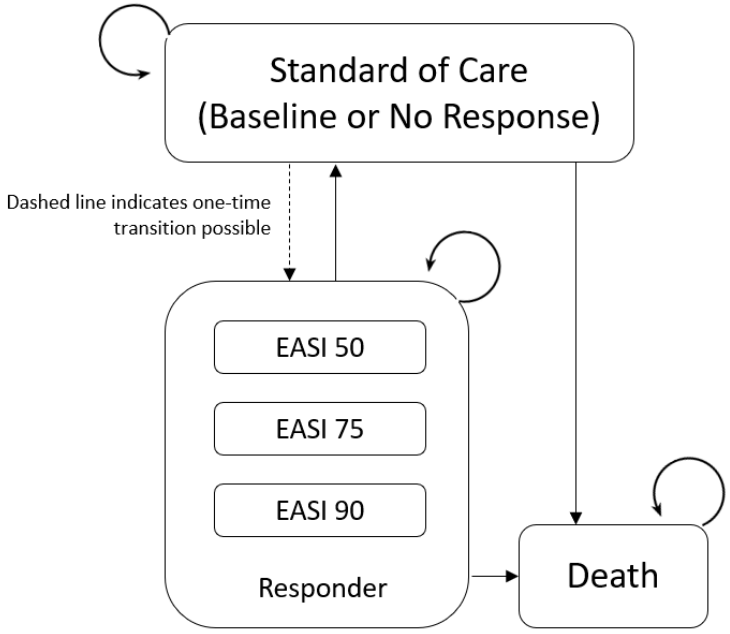
We adapted the Markov model from ICER's 2017 report on dupilumab for this evaluation, with the adaptation informed by key clinical trials and prior relevant economic models.[116] Costs and outcomes were discounted at 3% per year.

The model focused on an intention-to-treat analysis, with a hypothetical cohort of adult patients with moderate-to-severe atopic dermatitis being treated with abrocitinib, baricitinib, tralokinumab and upadacitinib compared to dupilumab, or emollients (representing standard of care). Model cycle length was 16 weeks based on common response evaluation time points, prior published economic models, and clinical data.

We developed a Markov model with health states based on treatment response. Treatment response was measured by the Eczema Area and Severity Index (EASI) score.[117] Health states were categorized by the percent decrease in EASI score from baseline after a patient begins an intervention: 50%-74% decrease (EASI 50), 75%-89% decrease (EASI 75), 90%-99% decrease (EASI 90), or less than 50% decrease (no response).

Patients enter the model in the non-responder state and then may remain in non-response or transition to a responder state (EASI 50-74, 75-89, or 90-100) in the first cycle. Once in a response state, patients were not allowed to transition between responder categories. Patients could transition back to the non-responder state as they discontinued treatment, for any reason. Patients could also transition from any health state to death. Patients remained in the model until the end of the time horizon of five years or death. We assumed that atopic dermatitis disease and treatment did not affect mortality.

Figure 4.1. Model Structure



EASI: Eczema Area Severity Index;
Schematic note: Standard of care indicates topical emollients only (not topical corticosteroids). Patients in the standard of care state, either at baseline or after discontinuing therapy, are assumed to have an EASI score of less than 50.

4.2. Key Model Choices and Assumptions

Below is a list of key model choices:

- Each therapy was included at one dosage, which is either the most commonly used dosage or the most effective dosage (if two doses have equal effects, we modeled the lower dose).
- We modeled one line of active therapy to focus the cost-effectiveness analyses on the available clinical data for the interventions of interest.
- The model used 16-week cycles and included a half-cycle correction for all cycles.
- Base case costs included direct medical costs by health state, drug costs, and any costs associated with administration or monitoring.
- Mortality in each health state was based on age- and gender-specific US mortality rates (all-cause).

- Due to no assumed differences in mortality across treatments and no assumed time variation on a treatment's benefits after the measurement of treatment response, we used a 5-year time horizon for the base case model and tested the horizon duration in a scenario analysis.
- All health states were weighted by a single set of health state utility values from pooled manufacturer data to derive quality-adjusted life-years (QALYs).
- Costs and outcomes were discounted annually at 3%.
- Change in peak pruritus numerical rating scale (PP-NRS), impact on sleep items within the disease-specific patient-reported outcomes (POEM, SCORAD, and ADerm-IS), and impact on anxiety/depression (HADS) were assessed in the clinical review and were considered as part of a cost consequences analysis alongside the cost-utility findings from the model.

Our model includes several assumptions stated below.

Table 4.1. Key Model Assumptions

Assumption	Rationale
Transitions to the response state occur after one cycle.	Patients are typically evaluated for treatment response after approximately 16 weeks.
Patients do not change response levels after the initial response while on treatment	There are limited data on sustained changes between response levels.
After transitioning off treatment, quality of life and costs are equivalent to a patient who was eligible for treatment but never treated	There is limited evidence that treatment for atopic dermatitis alters the course of the condition after treatment has ceased
Patients on only topical treatment who are responders (achieve ≥EASI50 after the first cycle) transition to non-response at a rate equivalent to discontinuation rates for placebo patients in the relevant clinical trials	Patients in the placebo arms of the considered clinical trials were allowed to utilize emollients, and thus the recurrence rate in the placebo arms is expected to mirror that of patients treated with topicals. We did not consider discontinuation rates of trials where patients were allowed to use topical corticosteroids.
Among responders, discontinuation rates do not vary by responder level	There is limited evidence supporting differential discontinuation by response level or over time.
Atopic dermatitis disease and treatments do not affect mortality	There is limited evidence suggesting an effect on mortality. We assume the modeled patient population excludes patients for whom JAK inhibitors could affect mortality (those over 50 years of age with a cardiovascular risk factor).

Treatment Population

The modeled base case analysis utilized a hypothetical cohort of patients with moderate-to-severe atopic dermatitis in the U.S. being treated with abrocitinib, baricitinib, tralokinumab, or upadacitinib, compared to dupilumab or emollients (representing standard of care). We pooled trial data from these treatments to derive demographic details for the cohort, which included a mean age of 35.8 years and 44% of the cohort being female. The patient population is assumed to exclude patients over 50 with increased cardiovascular risk, as JAK inhibitors will likely not be approved in that population.

Model Inputs

Transition Probabilities

We utilized the results of the NMA of placebo-controlled monotherapy trials to inform the treatment-specific transitions to each responder health state in the first model cycle. The overall percentage of responders was as follows: 73% for abrocitinib, 44% for baricitinib, 46% for tralokinumab, 80% for upadacitinib, 64% for dupilumab, and 21% for standard of care.

Table 4.2. Initial Response Health State Transition Probabilities

Drug	EASI 50-74	EASI 75-99	EASI 90+	Total Responders
Abrocitinib	14.32%	17.05%	41.10%	72.47%
Baricitinib	14.65%	12.96%	16.50%	44.11%
Tralokinumab	14.82%	13.29%	17.44%	45.55%
Upadacitinib	12.68%	16.70%	50.43%	79.81%
Dupilumab	15.32%	16.61%	31.94%	63.87%
Standard of Care	9.6%	6.5%	5.3%	21.4%

EASI: Eczema Area Severity Index

We utilized treatment specific per-cycle treatment discontinuation rates for the first year after initial treatment and then for all subsequent years over the model time horizon where data was available. Per cycle discontinuation rates were derived from long-term follow-up data for patients who achieved a minimum of EASI 50 at their initial 16-week evaluation. Treatment discontinuation for any reason resulted in transitioning to the non-responder health state. Long-term discontinuation data for atopic dermatitis patients were not available for upadacitinib; in the absence of data provided on the discontinuation rate for responders after 16 weeks, we assumed a rate equal to the highest rate within the class.

Table 4.3. Discontinuation Rates

Drug	Year 1	Year 2+	Source
Abrocitinib	3.76%	3.76%	JADE COMPARE
Baricitinib	7.44%	7.44%	BREEZE-AD3
Tralokinumab	5.04%	5.04%	ECZTRA 2
Upadacitinib	7.44%	7.44%	BREEZE-AD3 (proxy)
Dupilumab	3.77%	4.87%	LIBERTY AD-SOLO CONTINUE; LIBERTY AD OLE
Standard of Care	25.40%	25.40%	ECZTRA 1 & 2

EASI: Eczema Area Severity Index

Health State Utilities

We derived pooled health state utilities for each health state (Baseline, <EASI 50, EASI 50-74, EASI 75-89, and EASI 90-100) from manufacturer submitted data. We estimated utility values for each health state by combining estimates from the treatments with disaggregated data by health state and weighting by the number of study participants. Utility data were not disaggregated by moderate and severe subpopulations. We considered therapy-specific health state utility values to capture benefit beyond EASI score, however the available evidence did not support differential utility scores by treatment. To capture the benefits during patients' first 16 weeks on therapy, the utilities in the first cycle were calculated as a weighted average with half the time assumed to be spent at baseline utility and the other half assumed to be in a responder state for those who transitioned in the subsequent cycle. Utility for the health state of EASI 0-49 was applied to only the first model cycle to represent patients who took the therapy during the initial 16-week trial period and may have derived some benefit from the therapy despite not reaching the responder status of EASI 50. It is assumed that after discontinuing therapy, patients return to the non-responder state utility.

Table 4.4. Health State Utilities

Health State	Value	Source
Non-responder	0.6	ECZTRA 1 & 2, MEASURE UP 1 & 2, AD UP, SOLO 1 & 2
EASI 0-49	0.71	
EASI 50-74	0.80	
EASI 75-89	0.85	
EASI 90-100	0.88	

EASI: Eczema Area Severity Index

Patient Reported Outcomes

Inputs in the cost-consequence analysis were derived from manufacturer submitted data, including one measure of itch (PP-NRS), three measures for sleep (POEM, SCORAD, and ADerm-IS), and one measure of anxiety/depression (HADS). These analyses were included if data were provided for the mean score at baseline and for each responder category. Data were available for tralokinumab (PP-NRS, POEM, SCORAD, HADS) and upadacitinib (PP-NRS, Aderm-IS). The model output was the mean score and incremental mean score versus SoC over the model time horizon. Measures of change in other patient reported outcomes were considered but ultimately not included in the cost-consequence modeling due to lack of data by health state.

Table 4.5. Patient Reported Outcomes

	PP-NRS	PP-NRS	POEM (Sleep)	SCORAD (Sleep)	ADerm-IS (sleep)	HADS (anxiety/ depression)
Drug	**Tralokinumab**	**Upadacitinib**	**Tralokinumab**	**Tralokinumab**	**Upadacitinib**	**Tralokinumab**
Pooled Baseline*	7.5	7.5	3.3	6.7	18.5	12.59
EASI 50	4.7	5.2	2	3.8	9.4	-3.4
EASI 75	3.6	4.2	1.5	2.3	6.2	-4.55
EASI 90	2.6	3.1	1	1.5	3.6	-4.96
Source for pooled baseline	ECZTRA 1, 2, MEASURE UP 1, 2, AD UP, BREEZE AD5, MONO1-2, COMPARE	ECZTRA 1, 2, MEASURE UP 1, 2, AD UP, BREEZE AD5, MONO1-2, COMPARE	ECZTRA 1, 2	ECZTRA 1, 2	Measure Up1, 2, and AD Up	LP0162-1326/1339/1325
Source for drug-specific scores	ECZTRA 1, 2	MEASURE UP 1, 2, and AD UP	ECZTRA 1, 2	ECZTRA 1, 2	Measure Up1, 2, and AD Up	LP0162-1326/1339/1325

*Pooled baseline estimates include all trials with a baseline estimate for each measure. Health state-specific measures are presented where data was available; drugs without health state specific PRO measures are not presented in this table.

ADerm-IS: Atopic Dermatitis Impact Scale, EASI: Eczema Area Severity Index, PP-NRS: Peak Pruritis Numeric Rating Scale, POEM, Patient-Oriented Eczema Measure, SCORAD: Scoring Atopic Dermatitis; HADS, hospital anxiety and depression scale;

Mortality

Gender- and age-specific background mortality from the Centers for Disease Control and Prevention U.S.-specific tables was used for all-cause mortality rates, and was uniformly applied across all health states.[118]

Cost Inputs

Drug Costs

For included therapies that are currently marketed, we obtained net pricing estimates from SSR Health, LLC, which combine data on unit sales with publicly disclosed US sales figures that are net of discounts, rebates, patient assistance programs, and concessions to wholesalers and distributors, to derive a net price. We estimated net prices by comparing the four-quarter averages (i.e., 3rd quarter of year 2019 through 2nd quarter of 2020) of both net prices and wholesale acquisition cost (WAC) per unit to arrive at a mean discount from WAC for the drug. Finally, we applied this average discount to the most recent available WAC (Redbook accessed March 9, 2021) to arrive at an estimated net price per unit.

For abrocitinib, we used the average of the net prices of baricitinib and upadacitinib as a placeholder price. For tralokinumab, we used the net price of dupilumab as a placeholder price and assume that it is used every two weeks in the base case. No known corroborated analyst pricing is available for either abrocitinib or tralokinumab. Placeholder prices will be updated in future versions of the report as pricing information becomes available.

Table 4.6. Drug Costs

Drug	WAC per Dose	Discount from WAC*	Net Price per Dose	Net Price per Year
Abrocitinib (200 mg qd)†	$127.65	17%	$113.34	$41,397.44
Baricitinib (Olumiant™, 2 mg qd)	$79.28	33%	$53.12	$19,402.08
Tralokinumab (300 mg q2w)†	$1,601.70	26%	$1,193.27	$31,131.56
Upadacitinib (Rinvoq™, 30 mg qd)	$176.02	1%	$173.56	$63,392.79
Dupilumab (Dupixent®, 300 mg 2qw)	$1,601.70	26%	$1,193.27	$31,131.56

*SSR Health, LLC, was used for estimating discounts from wholesale acquisition cost
†Using placeholder prices

Non-Drug Costs

Direct Medical Costs

We used annual direct medical cost estimates from manufacturer provided data derived from IBM Watson MarketScan claims database. Claims were analyzed from years 2011-2018, and costs were updated from 2018 to 2021 US dollars using the US Bureau of Labor Statistics CPI inflation calculator, which include all non-drug direct health care costs.[119] Subcutaneous injectables were assumed to also incur a one-time cost for self-injection training and monitoring. We did not find evidence of any serious adverse events occurring in >5% of subjects among any of the clinical trials, therefore we did not include adverse event costs in the model.

Table 4.7. Direct Medical Health State Costs

	Value	Source
Annual Health State Costs		
Non-responder	$18,588.62	Data provided by manufacturer
EASI 50-74	$10,100.58	
EASI 75-89	$8,910.17	
EASI 90+	$8,595.68	
One-time SC Training and Monitoring Costs		
Office visit/self-injection training	$23.00	CPT 99211
General practitioner visit	$57.00	CPT 99212
Blood panel	$7.77	CPT 85025

CPT: current procedural terminology codes, SC: subcutaneous
All costs in 2021 USD

4.3. Results

Base Case Results

The total discounted costs, quality-adjusted life years (QALYs), life years (LYs), and equal value of life years gained (evLYG) over the five-year time horizon are presented in Table 4.9. We note that there are not currently available prices for abrocitinib and tralokinumab, and thus the cost estimates and incremental cost-effectiveness ratios are based on placeholder prices. In a cohort of patients with moderate-to-severe atopic dermatitis who received a single treatment beyond emollients for up to 5 years, baricitinib had the lowest drug cost and total cost, $26,900 and $105,300, respectively, compared to upadacitinib at $151,300 and $219,700 as the highest drug and total costs, respectively. Abrocitinib generated the highest QALYs, 3.59, followed by upadacitinib and dupilumab, with 3.51 and 3.47, respectively. Abrocitinib's higher QALYs was due to having the second highest percent of overall responders and a lower discontinuation rate versus comparators.

Table 4.9. Discounted Results for the Base Case for each Treatment and Standard of Care

Treatment	Drug Cost	Total Cost	QALYs (same as evLYGs)	Life Years	PP-NRS†	POEM (sleep)†	SCORAD (sleep)†	ADerm-IS (sleep)†	HADS (depression and anxiety)†
Abrocitinib*	$113,200	$178,400	3.59	4.85	NA	NA	NA	NA	NA
Baricitinib	$26,900	$105,300	3.23	4.85	NA	NA	NA	NA	NA
Tralokinumab*	$51,700	$127,700	3.29	4.85	-1.11	-0.52	-1.23	NA	-1.23
Upadacitinib	$151,300	$219,700	3.51	4.85	-1.65	NA	NA	-5.75	NA
Dupilumab	$72,400	$141,900	3.47	4.85	NA	NA	NA		NA
Standard of Care (Topicals)	$-	$87,800	2.98	4.85	-0.15	-0.08	-0.19	-0.55	-0.19

ADerm-IS: Atopic Dermatitis Impact Scale, NA: not available, PP-NRS: Peak Pruritis Numeric Rating Scale, POEM: Patient-Oriented Eczema Measure, QALY: quality-adjusted life-year, evLYG: equal-value life-year gained, SCORAD: Scoring Atopic Dermatitis; HADS: hospital anxiety and depression scale;

*Using a placeholder price

†Average change in PRO score from pooled baseline over model time horizon

Results of the cost-consequence analysis, which reflect the average change in each patient reported outcome (PRO) score from a pooled baseline over the 5-year time horizon, are also reported in Table 4.9. Incremental results can be found in Supplement table E2.1.

Table 4.10 presents the incremental results from the base case analysis, which include incremental cost-effectiveness ratios for incremental cost per LY gained, incremental cost per QALY gained, and incremental cost per evLYG gained. Given no modeled gains in life years across the evaluated therapies, the cost per life year gained is not reported.

Table 4.10. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLYG
Abrocitinib*	SoC	$148,300	NA	$148,300
Baricitinib	SoC	$71,600	NA	$71,600
Tralokinumab*	SoC	$129,400	NA	$129,400
Upadacitinib	SoC	$248,400	NA	$248,400
Dupilumab	SoC	$110,300	NA	$110,300
Abrocitinib*	Dupilumab	$303,400	NA	$303,400
Baricitinib	Dupilumab	Less Costly, Less Effective	NA	Less Costly, Less Effective
Tralokinumab*	Dupilumab	Less Costly, Less Effective	NA	Less Costly, Less Effective
Upadacitinib	Dupilumab	$1,912,200	NA	$1,912,200

evLYG: equal-value life-year gained, QALY: quality-adjusted life-year, SOC: Standard of Care

*Using a placeholder price

Note: The cost per QALY and cost per evLYG ratios were the same given that the treatments have not been shown to lengthen life.

Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Across all modeled comparisons, the health state utility values were identified as the most influential model parameters on the incremental cost-effectiveness ratios, followed by the drug cost, initial transition probabilities, non-responder direct costs, and discontinuation rates. The Report Supplement contains tornado diagrams for each of the modeled comparisons.

Probabilistic sensitivity analyses were also be performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results, contained in the Report Supplement. From the PSA simulations, we estimated the probability of a drug being cost-effective across a range of incremental cost-effectiveness ratios ($50,000, $100,000, $150,000, and $200,000 per QALY), presented in Table 4.11 versus standard of care. PSA results indicated that included therapies had 0% estimated probability of being cost-effective versus dupilumab at an ICER threshold of $200,000 or less. We also performed threshold analyses for drug costs across a range of incremental cost-effectiveness ratios ($50,000, $100,000, $150,000, and $200,000 per QALY), available in the Report Supplement.

Table 4.11. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Each treatment versus SoC

Cost-Effectiveness Threshold	Abrocitinib*	Baricitinib	Tralokinumab*	Upadacitinib	Dupilumab
$50,000	0%	45%	12%	0%	0%
$100,000	3%	74%	43%	0%	38%
$150,000	49%	85%	65%	3%	76%
$200,000	82%	90%	75%	25%	92%

*Based on placeholder prices

Scenario Analyses

We conducted five scenario analyses for the report. First, we calculated a modified societal perspective by adding productivity loss associated with moderate-to-severe atopic dermatitis by health state. Second, we extended the time horizon to lifetime, but maintained the single line of treatment. Third, we adjusted the model for abrocitinib to be initially evaluated at 12-weeks rather than 16 weeks to reflect the JADE MONO-1 and -2 clinical trials. Fourth, we adjusted the model to reflect outcomes for combination therapy with topical corticosteroids. Finally, we adjusted the model for tralokinumab patients achieving EASI 75 or above after 16 initial weeks of therapy to reduce dosing frequency from every 2 weeks to every 4 weeks to reflect arms of the ECZTRA3 clinical trial.

The total discounted costs, quality-adjusted life years (QALYs), life years (LYs), and equal value of life years gained (evLYG) over the five-year time horizon under the modified societal perspective are presented in Table E4.2 in the Report Supplement. The drug costs and patient outcomes remained the same compared to the base case, and the table shows the base case total costs for comparison. The total cost from the modified societal perspective versus the base case increased by 10-26% for the interventions and 36% for standard of care.

Table E4.3 in the Report Supplement presents the incremental results from the modified societal perspective scenario analysis, which include incremental cost-effectiveness ratios for incremental cost per LY gained, incremental cost per QALY gained, and incremental cost per evLYG. Incremental cost-effectiveness ratios from the modified societal perspective versus the base case when applying the standard of care comparator decreased by 7% to 22% across the therapies evaluated, but did not lead to therapies crossing cost-effectiveness thresholds (i.e., $50, $100, or $150,000 per QALY), with the exception of dupilumab which became cost-effective at the $100,000 per QALY threshold.

Table E4.5 in the Report Supplement presents the incremental results from the lifetime time horizon scenario analysis, which include incremental cost-effectiveness ratios for incremental cost per LY gained, incremental cost per QALY gained, and incremental cost per evLYG gained. Incremental cost-effectiveness ratios from the lifetime time horizon versus the base case five-year horizon when applying the standard of care comparator decreased by 4% to 13% across the therapies evaluated, but did not lead to therapies crossing cost-effectiveness thresholds (i.e., $50, $100, or $150,000 per QALY).

Table E4.6 in the Report Supplement presents the effect of changing the initial model cycle for abrocitinib from 16-weeks to 12-weeks to better reflect the JADE MONO-1 and -2 clinical trials. This scenario had minimal effect on QALYs, life-years, or equal-value life-years. In a five-year time horizon, this switch would decrease drug cost and total costs by 1.4% and 0.9%, respectively, and decrease ICER versus SoC by 1%; ICER versus dupilumab would increase by 0.2%. These outcomes are based on a placeholder price for abrocitinib and will be updated.

Table E4.8 in the Report Supplement presents the total results for the combination therapy scenario analysis, which include drug costs, total costs, QALYs, life-years, and evLYG. Drug costs and total costs were higher in the combination therapy scenario for all therapies, with increases ranging from 6-36%. Total costs decreased by 2% for those on standard of care. QALYs increased 2-4% across all therapies and SoC in the combination therapy scenario. Incremental cost-effectiveness results (Table E4.9) were all nominally larger (9-14%) in the combination therapy scenario when compared to standard of care/placebo but remained in the same order of cost effectiveness. Abrocitinib was the only therapy to cross a cost-effectiveness threshold (exceeded $150,000 for combination therapy, assuming a placeholder price). When compared to dupilumab, both baricitinib and

tralokinumab remained less costly and less effective, however dupilumab switched to dominate upadacitinib (dupilumab being less costly and more effective than upadacitinib) in the combination therapy scenario.

Table E4.10 in the Report Supplement presents the results of scenario that allowed 50% of patients who achieved EASI 75 or above on tralokinumab to switch from Q2 to Q4 week dosing, which reflects data from the . This scenario had no effect on QALYs, life-years, or equal-value life-years. In a five-year time-horizon assuming concurrent TCS therapy in both arms, drug and total costs would decrease by 15% and 8%, respectively. The ICER would decrease by 20% compared to SoC, however tralokinumab would remain less costly and less effective when compared to dupilumab. Because the clinical trial informing the analysis allowed patients to use concurrent TCS therapy, these results are most comparable to the scenario analysis of combination therapy.

Threshold Analyses

Annual prices necessary to reach cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY compared to standard of care are listed in Table 4.12.

Table 4.12. QALY-Based Threshold Analysis Results

	Annual WAC	Annual Net Price	Annual Price to Achieve $50,000 per QALY	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY
Abrocitinib	$46,600*	$41,400*	$19,400	$30,600	$41,800
Baricitinib	$29,000	$19,400	$15,600	$24,400	$33,300
Tralokinumab	$41,800*	$31,100*	$16,400	$25,700	$35,000
Upadacitinib	$64,300	$63,400	$19,300	$30,400	$41,500
Dupilumab	$41,800	$31,100	$18,400	$29,000	$39,500

QALY: quality-adjusted life-year, WAC: wholesale acquisition price

*Based on a Placeholder Price

Model Validation

We used several approaches to validate the model. We provided preliminary model structure, methods and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model, as needed. We varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. Specifically, we tested all mathematical functions in the model to ensure they were consistent with the report (and Report Supplement materials) and used extreme and null input values to ensure the model was producing findings

consistent with expectations. Finally, model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Uncertainty and Controversies

As with any modeling exercise, there are limitations to be considered when evaluating these findings. First, we extrapolated clinical trial efficacy beyond the length of time that the trials were conducted, which assumes continued effectiveness (along with adherence to treatment). Next, we assumed that levels of EASI response are associated with differences in health-related quality of life. However, there may be differential effects of the treatments modeled on conditions such as itch and sleep that are not completely captured by generic quality of life instruments. However, available data did not support the use of treatment specific utilities. Additionally, there may be incremental effects of some of these treatments on quality of life in sub-populations of people with atopic dermatitis, such as those with co-occurring asthma or chronic rhinosinusitis, which are not explicitly captured in the current model.

We only had discontinuation data beyond one year for dupilumab, and assumed that the discontinuation rates for the other treatments were the same as year 1 in years 2-5. However, we note that we selected a 5-year time horizon for the base case in part to reduce the impact of these assumptions. Further, atopic dermatitis specific discontinuation rates were not available for upadacitinib and we therefore assumed that the discontinuation rate was equal to the highest rate within the class. We also assumed that patient response to treatment was fixed after 16 weeks, allowing neither further improvement nor waning of efficacy, other than capturing discontinuation. This assumption was based on the lack of data demonstrating changes in either direction.

We excluded SAEs that occurred in less than 5% of the trial population. However, we note there are some rare SAEs from the phase III JAK inhibitor clinical trials that may impact both costs and patient health-related quality of life.

Finally, the NMA analyses that informed our effectiveness estimates in the model were derived from phase II and III RCTs that compared the treatments of interest to placebo with only the added use of topical emollients at 16 weeks. We provided results for the use of these products in combination with topical steroids as a scenario analysis. Furthermore, the NMA's produced estimates with wide confidence intervals and there may be additional uncertainty regarding the comparative effectiveness of these treatments.

4.4 Summary and Comment

Using a Markov model, we compared the cost and effectiveness of four emerging therapies for moderate to severe atopic dermatitis to skin emollients and an approved biologic, dupilumab, over a five-year time horizon taking a health system perspective. It is important to note that the JAK inhibitor class has been associated with some rare but serious clinical adverse events which are not captured in the current model but would carry the potential to impact both costs and outcomes in those patients who experience them.

While drug prices are not currently available for two therapies (abrocitinib and tralokinumab), we found abrocitinib to produce the most QALYs (3.59) of therapies considered and baricitinib to produce the fewest (3.23). Compared to SoC with emollients only, baricitinib was cost-effective at a $100,000/QALY threshold, abrocitinib and tralokinumab were cost-effective at a $150,000/QALY threshold (using placeholder prices), dupilumab was cost-effective at a $150,000/QALY threshold, and upadacitinib would need to decrease its WAC per dose cost from $176 to $113 in order to be cost-effective at $150,000/QALY threshold. Compared to dupilumab, baricitinib and tralokinumab were found to be less costly and less effective whereas abrocitinib (using a placeholder price) and upadacitinib did not meet commonly cited cost-effectiveness thresholds.

5. Contextual Considerations and Potential Other Benefits

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

Table 6.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on the severity of the condition being treated	Patients, caregivers, advocacy groups and clinical experts all identified a need for new therapeutic options for patients with atopic dermatitis, especially those with more severe disease who are either unresponsive or intolerant of existing therapies.
Magnitude of the lifetime impact on individual patients of the condition being treated	Atopic dermatitis is a chronic condition that usually begins in childhood and can continue throughout the course of a patient's life broadly affecting physical, psychosocial, and emotional health. As such it can affect childhood development, school achievement and performance in the workplace.
There is uncertainty about the long-term risk of serious side effects	Though trials of abrocitinib, baricitinib and upadacitinib in atopic dermatitis showed few serious side effects, oral JAK inhibitors when used for other conditions include black box warnings for serious infections, malignancies, and clotting disorders.

Table 6.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	New therapies for atopic dermatitis that improve the appearance, symptoms and complications of atopic dermatitis may help improve quality of life across a range of different outcomes including social interactions with family, friends and other relations, educational achievement, and work performance. However, it is uncertain whether abrocitinib, baricitinib, tralokinumab and upadacitinib will improve education or work outcomes.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	For children and adolescents with atopic dermatitis, the care required often involves family members and other caregivers. The impact of atopic dermatitis and the demands of treatment fall not only on the patient, but also their caregivers. As such, new therapies for atopic dermatitis offer the possibility of improving the quality of life for the caregivers as well as for patients.
Patients' ability to manage and sustain treatment given the complexity of regimen	The potential of new oral therapies such as abrocitinib, baricitinib and upadacitinib to improve outcomes for patients with atopic dermatitis may also decrease the complexity of care. The need for topical therapies that are time-consuming to apply, phototherapies that require multiple treatment visits or medications that are delivered by injection all increase the complexity of care. Though oral JAK inhibitors are likely to be given along with topical therapies they are likely to reduce the complexity of a patient's regimen if effective. For those responding to an initial every two week schedule, tralokinumab dosing decreased to every four weeks in some patients could potentially affect real world adherence.
Health inequities	The high costs of treatments for atopic dermatitis, especially newer agents, may exacerbate existing health inequities.
These interventions offer novel mechanisms of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	Abrocitinib, baricitinib, tralokinumab and upadacitinib represent new therapies that reflect translational research in which improved understanding of the mechanisms of disease have led to new therapies.

New England CEPAC Votes

At the public meeting, the New England CEPAC deliberated and voted on the relevance of specific potential other benefits and contextual considerations on judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework.

When making judgments of overall long-term value for money, what is the relative priority that should be given to *any* effective treatment for atopic dermatitis, on the basis of the following contextual considerations:

Contextual Consideration	Very Low Priority	Low priority	Average priority	High priority	Very high priority
Acuity of need for treatment of individual patients based on the severity of the condition being treated	0	0	6	6	1
Magnitude of the lifetime impact on individual patients of the condition being treated	0	0	3	9	1

For the acuity of need for treatment, the panel voted that any effective treatment should be given average or high priority due to the severity of the disease. The magnitude of lifetime impact on individual patients received a majority vote of "high priority;" the panel emphasized the chronic nature of atopic dermatitis which can start early in a person's life, often in adolescence.

For questions 8-12, considering the average effects of the new systemic therapies as a group, what are the relative effects of the new therapies versus usual care (use of topical emollients and avoidance of exacerbating factors) on the following outcomes that inform judgment of the overall long-term value for money.

Potential Other Benefit or Disadvantage	Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
Patients' ability to achieve major life goals related to education, work, or family life	0	0	0	4	9
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	0	0	6	7
Society's goal of reducing health inequities	0	1	7	4	1
What are the relative effects of the JAK inhibitors as a class versus dupilumab on patients' ability to manage and sustain treatment given the complexities of the regimens?	0	0	4	8	1
What are the relative effects of tralokinumab versus dupilumab on patients' ability to manage and sustain treatment given the complexities of the regimens?	0	0	8	5	0

The panel voted that the new systemic therapies would have a minor or major positive effect on both the patients' and their caregivers' quality of life. At the same time, the panel concluded that it is difficult to assess these therapies' impact on society's goal of reducing health inequities – high prices and any access limitations might negatively impact certain populations more severely than others. When talking about adherence and patients' ability to sustain a treatment given the complexities of the regimens, the panel voted that the oral JAK inhibitors may have a minor positive effect as oral therapies. When comparing tralokinumab and dupilumab, which are both given by subcutaneous injection, the panel voted that there would be no difference, or a minor positive difference, on the patients' ability to manage the treatments.

6. Health Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) for the annual cost of treatment with the interventions when compared to standard of care alone are presented in Table 6.1 below. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLYG gained. Because of the assumption that atopic dermatitis and assessed therapies do not have an impact on mortality, calculated QALYs Gained and evLYGs are equal in this model. Using the broadest set of figures derived from these thresholds, we arrive at a HBPB for abrocitinib from $30,600 to $41,800; for baricitinib $24,400 (no discount needed at the $150,000 threshold); for tralokinumab, $25,700 to $35,000; for upadacitinib, $30,400 to $41,500; and for dupilumab, $29,000 to $39,500. Discounts from WAC to reach threshold prices for abrocitinib and tralokinumab are not applicable as they are currently based on placeholder WAC prices and should be updated when WAC pricing is established.

Table 6.1. Annual Cost-Effectiveness Health Benefit Price Benchmarks for Abrocitinib, Baricitinib, Tralokinumab, Upadacitinib, and Dupilumab versus Standard of Care

Health Benefit Measure	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Abrocitinib				
QALYs Gained	NA*	$30,600	$41,800	NA*
evLYG	NA*	$30,600	$41,800	NA*
Baricitinib				
QALYs Gained	$29,000	$24,400	$33,300	0% to 16%
evLYG	$29,000	$24,400	$33,300	0% to 16%
Tralokinumab				
QALYs Gained	NA*	$25,700	$35,000	NA*
evLYG	NA*	$25,700	$35,000	NA*
Upadacitinib				
QALYs Gained	$64,300	$30,400	$41,500	35% to 53%
evLYG	$64,300	$30,400	$41,500	35% to 53%
Dupilumab				
QALYs Gained	$41,800	$29,000	$39,500	6% to 31%
evLYG	$41,800	$29,000	$39,500	6% to 31%

WAC: wholesale acquisition cost; evLYG: equal value life year gained; QALY: quality-adjusted life year

* Not applicable (NA) as placeholder prices were used

New England CEPAC Votes

Table 6.2. New England CEPAC Votes on Long-Term Value for Money at Current Prices

Question	Low long-term value for money at current prices	Intermediate long-term value for money at current prices	High long-term value for money at current prices
Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with **baricitinib** versus usual care?	0	7	6
Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with **upadacitinib** versus usual care?	10	3	0

The panel voted on two therapies which already have a known price as they are approved for other indications. The majority of the panel voted that baricitinib represents either an "intermediate" or "high" value for money at current prices. The incremental cost-effectiveness ratio for baricitinib was $71,600 per QALY gained.

The majority of the panel voted that upadacitinib represents a "low" value for money at current prices. The incremental cost-effectiveness ratio for upadacitinib was $248,400 per QALY gained.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

ICER used results from the cost-effectiveness model to estimate the potential total budgetary impact of each drug that awaits US regulatory approval (abrocitinib, baricitinib, tralokinumab, and upadacitinib) for moderate-to-severe atopic dermatitis. We used the WAC, an estimate of net price, and the three threshold prices (at $50,000, $100,000, and $150,000 per QALY) for each drug in our estimates of budget impact. Consistent with the cost-effectiveness analysis, abrocitinib was assigned a placeholder net price equal to the average between baricitinib and upadacitinib's annual net prices. Similarly, tralokinumab was assigned a placeholder net price equal to dupilumab's annual net price. Placeholder prices will be updated in future versions of the report as actual pricing information becomes available.

The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

ICER's methods for estimating potential budget impact are described in detail in the Report Supplement Section F. For this analysis, we calculated the budget impact of new treatments (abrocitinib, baricitinib, tralokinumab, and upadacitinib) given these treatments' displacement of dupilumab plus usual care (assumed 10% mix) and usual care alone (90% mix) and by assigning 103,200 new individuals to each new treatment per year (for five years).

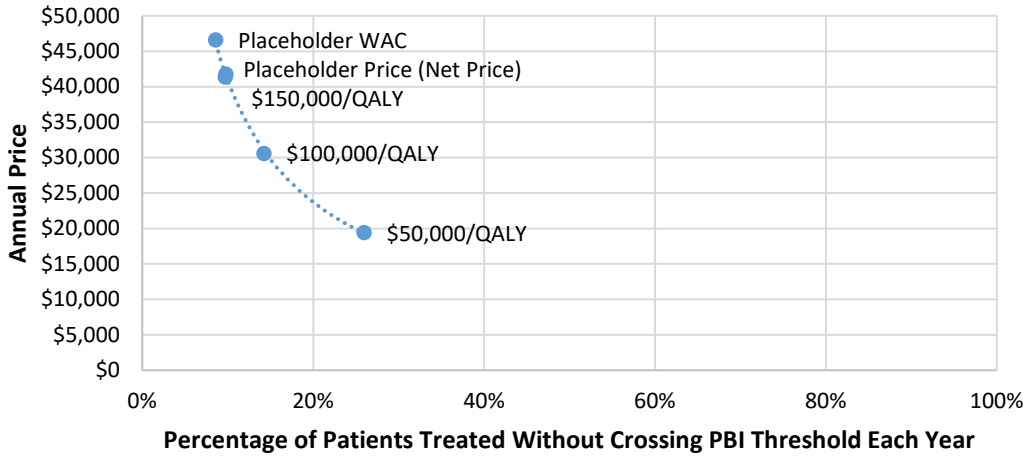
7.2. Results

Report Supplement Section F displays the average annual per patient budget impact findings across the five unit prices (WAC, discounted WAC, and the prices that achieve three different cost-effectiveness thresholds) for abrocitinib, baricitinib, tralokinumab, and upadacitinib. Further, Report Supplement Section F details the cumulative per-patient budget impact estimates for abrocitinib, baricitinib, tralokinumab, and upadacitinib.

Figures 7.1 – 7.4 illustrate the potential budget impact of abrocitinib, baricitinib, tralokinumab, and upadacitinib treatment of the eligible population, based on the respective five different unit prices (WAC, discounted WAC, and the prices that achieve three different cost-effectiveness thresholds). Upon removing the placeholder prices and across all four treatments, the range of the percentage of those treated without crossing the potential budget impact annual threshold was between 8%

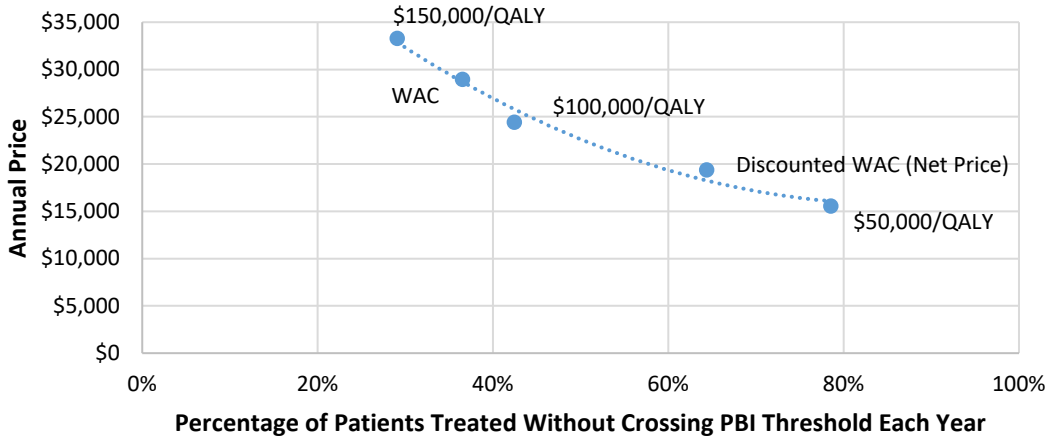
and 79% for all prices evaluated (WAC unit price to the maximum price to achieve $50,000 per QALY).

Figure 7.1. Budgetary Impact of Abrocitinib*



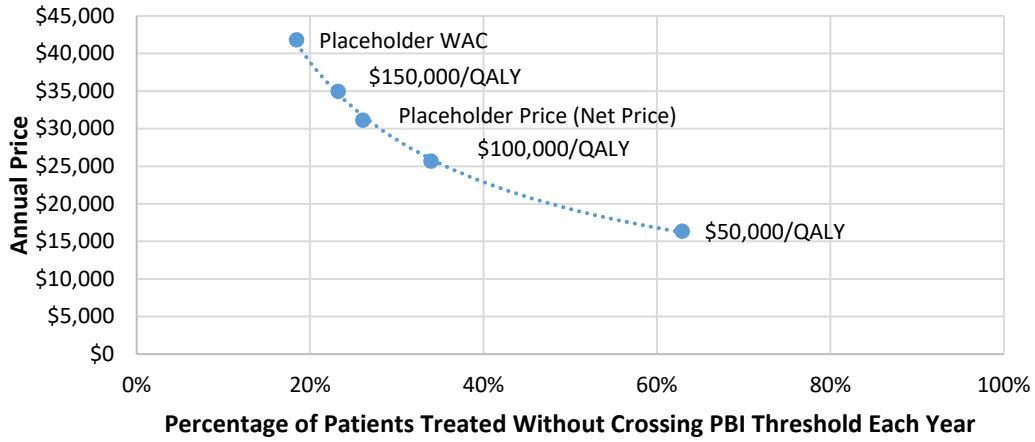
PBI: potential budget impact, QALY: quality-adjusted life-year, WAC: wholesale acquisition price
*Based on placeholder prices

Figure 7.2. Budgetary Impact of Baricitinib



PBI: potential budget impact, QALY: quality-adjusted life-year, WAC: wholesale acquisition price

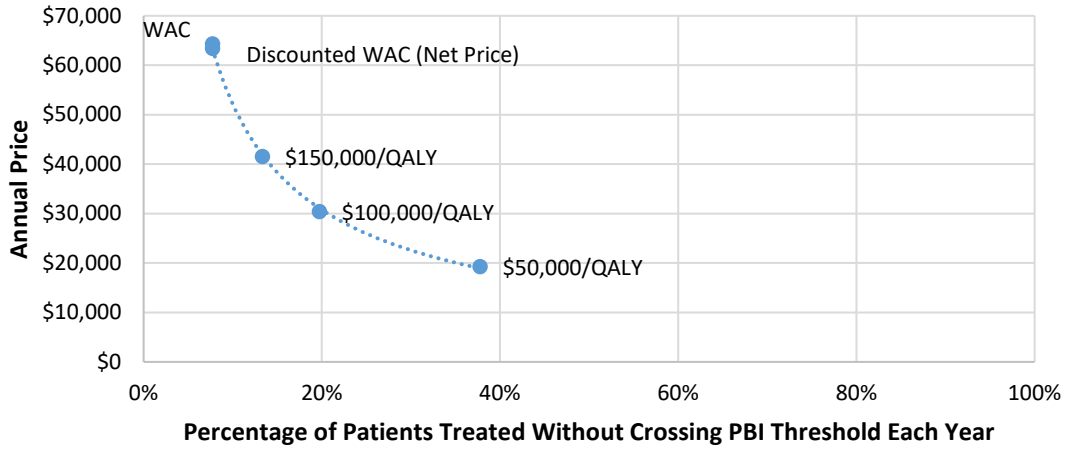
Figure 7.3. Budgetary Impact of Tralokinumab*



PBI: potential budget impact, QALY: quality-adjusted life-year, WAC: wholesale acquisition price

*Based on placeholder prices

Figure 7.4. Budgetary Impact of Upadacitinib



PBI: potential budget impact, QALY: quality-adjusted life-year, WAC: wholesale acquisition price

8. Policy Recommendations

Following its deliberation on the evidence, the Comparative Effectiveness Public Advisory Council engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on the use of oral abrocitinib, baricitinib, and upadacitinib, topical ruxolitinib cream, and subcutaneous tralokinumab. The policy roundtable members included three patient advocates, two clinical experts, two payers, and three representatives from the drug maker(s). The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

All Stakeholders

All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with atopic dermatitis are introduced in a way that will help reduce health inequities.

Safe and effective treatment for atopic dermatitis, especially for those with moderate to severe disease, remains a significant unmet health care need. Efforts are needed to ensure that new therapies for atopic dermatitis such as oral abrocitinib, baricitinib, and upadacitinib, topical ruxolitinib cream, and subcutaneous tralokinumab, improve the health of patients and families and do not aggravate existing health inequities. Clinical experts and patients highlighted that the high cost of new therapies may worsen disparities in accessing care. This may be due to lack of health insurance that limits access to specialists and the new therapies that they prescribe, or high deductible payments even for those with insurance may result in steep out of pocket costs. The cost of care is not the only factor that may contribute to health inequities. Our clinical experts noted that the appearance of the skin is a key contributor to measures of disease severity, and individuals with darker skin types may be assessed as having less severe skin involvement. Since educational materials often include photos of individuals with atopic dermatitis who have lighter skin types, those with darker skin may be more likely to be misdiagnosed.

To address these concerns:

<u>Manufacturers should take the following actions:</u>

- Follow the precedent of responsible pricing set by Sanofi/Regeneron with dupilumab and set the price for new treatments for atopic dermatitis in fair alignment with added benefits for patients.

- Take steps necessary to include a more diverse patient population in clinical trials, including adequate number of patients with ethnic and racial backgrounds who have darker skin types.

Payers should take the following actions:

- Ensure that benefit designs developed in conjunction with employers and other plan sponsors do not create requirements for out-of-pocket spending that create major barriers to appropriate access for vulnerable patients

Clinical specialty societies should take the following actions:

- Develop and disseminate educational materials and create measurable goals to demonstrate that clinicians are aware of the challenges of diagnosing atopic dermatitis in patients with darker skin types.

Payers

The large number of patients with varying levels of severity of atopic dermatitis, combined with the potential for side effects and the high annual prices for newer generation treatments, will lead payers to develop prior authorization criteria and to consider other limits on utilization.

Perspectives on specific elements of cost sharing and coverage criteria for oral abrocitinib, baricitinib, and upadacitinib, topical ruxolitinib cream, and subcutaneous tralokinumab within insurance coverage policy are discussed below.

Coverage Criteria

- **Age:** Age criteria are likely to follow the FDA label for each drug and will not be expanded to cover earlier ages in the case of drugs not approved for adolescents or children. Similarly, although there may be greater uncertainty in outcomes for younger patients, it seems unlikely that payers will use clinical trial eligibility criteria to narrow coverage if the FDA approval includes treatment of adolescents. Payers should have efficient mechanisms for clinicians to seek coverage exceptions for patients with serious unmet need who are near the cutoff for the age necessary for coverage.

- **Clinical eligibility**: There is no clear consensus on how to operationalize a definition of the FDA indication for treatment of patients with "moderate to severe" atopic dermatitis. The severity of atopic dermatitis can vary substantially over time and, from a patient's perspective, can include a complex combination of intensity of itch, location, body surface

area involvement, and degree of skin impairment. Some payers will allow clinician attestation, whereas others will adopt criteria based on clinical trial eligibility. Given the variability of patient phenotype and lack of familiarity among clinicians with scoring systems used in clinical trials, it is advisable for payers to create a broad, clinically relevant definition inclusive of multiple specific measures of disease intensity, e.g. "any of the following: BSA ≥ 10%, IGA ≥ 3, EASI ≥ 16," or "affected BSA ≥ 10% OR involvement of body sites that are difficult to treat with prolonged topical corticosteroid therapy (e.g. hands, feet, face, neck, scalp, genitals/groin, skin folds) or severe itch that has been unresponsive to topical therapies."

- In addition to a definition of severity, payers are likely to require that patients have received an adequate trial of topical therapy, e.g. a 30-day trial of prescription topical corticosteroid and/or topical calcineurin inhibitor OR the use of these medications is not medically advisable (as occurs with eyelid involvement). Payers should not require that this trial of topical agent(s) be immediately prior to the requested prescription; medical records indicating prior trial of topical therapy be sufficient.

- Potential criteria requiring prior use of phototherapy or systemic off-label treatment with agents like methotrexate is covered in the section on step therapy below.

- Ruxolitinib cream, if approved by the FDA, will likely have an indication for treatment of "mild to moderate" atopic dermatitis. The clinical criteria for coverage may be based on clinical trial eligibility (BSA ≥ 3% excluding scalp OR IGA 2-3) but will also likely require prior use of topical corticosteroids or calcineurin inhibitors. Another indication could be allowing the use of ruxolitinib cream in patients with severe atopic dermatitis for areas that do not clear adequately with systemic therapies.

- **Exclusion criteria**: There are no special medical comorbidities at this time that would serve as exclusion criteria for these treatments.

- **Duration of coverage and renewal criteria**: Initial coverage will likely be for a period of six to 12 months, which is long enough for dose titration, assessment of side effects, or disease progression.

- Clinical experts and payers felt that it would be appropriate to require attestation for continuation of therapy. The timing of such renewal may depend to some extent upon the specific therapy. For example, oral JAK inhibitors appear to have a quicker onset of action than biologics such as dupilumab or tralokinumab. Patients and clinicians felt that requiring submission of outcome measures to support continuation was not needed. For biologics that are given by injection, patients reported that they would not want to continue use in

the absence of improvement. For JAK inhibitors, given the potential for uncommon but serious side effects, long-term use in the absence of considerable benefit may also be unlikely. Most clinical experts suggested a three- to six-month period prior to renewal to be appropriate.

- **Provider restrictions**: Clinical experts agreed that it is reasonable to restrict prescriptions for dupilumab, abrocitinib, baricitinib, tralokinumab and upadacitinib to dermatologists or allergy specialists. Some payers may consider allowing prescription by generalist physicians able to work in consultation with specialists. The new therapies for moderate to severe atopic dermatitis require knowledge about evaluating and treating patients that most primary care clinicians are unlikely to have. Specialty clinicians are better suited to identify patients who are most likely to benefit, provide sufficient information for patients to make a well-informed decision, and monitor for response and side effects. Ruxolitinib cream may be covered with less restrictions on prescriber qualifications, but because it may be used in younger patients some payers may still wish to limit prescribing, at least initially, to specialists or generalist clinicians working in consultation with specialists.

Step Therapy

Payers should only use step therapy when it provides adequate flexibility to meet the needs of diverse patients and when implementation can meet high standards of transparency and efficiency.

Clinical experts and patient representatives stated that delayed and restricted access to treatment due to step therapy requirements for patients with moderate to severe atopic dermatitis is common. While it is possible to tailor step therapy in a clinically responsible fashion, it is often administered with documentation burdens and inadequate procedures for exceptions that make step therapy a source of great frustration and the cause of poor outcomes for some patients due to the discontinuation of medicine/missed doses. A particular area of concern raised by patients involved requirements to re-step through previously failed therapies when insurance changed.

Payers establishing step therapy with less expensive, off-label systemic agents and/or phototherapy should allow patients and clinicians to choose from multiple options rather than require patients to try multiple options.

Currently available specialty society guidelines are out of date and updated versions are expected in the coming year that may help shape policies regarding appropriate step therapy. Clinical experts at the ICER meeting stated that it may be reasonable for payers to require patients to step through a less expensive off-label systemic therapy, but these therapies have well-known adverse effects

and limited efficacy data that make it clinically inappropriate to require patients to attempt trials with all options prior to obtaining coverage for one of the newer agents. Prior agents include cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, and interferon gamma. Cyclosporine may be a reasonable first-line agent for some patients, but the risk of renal toxicity requires patients to switch to another treatment after 6-12 months, so patients should not be required to try this agent after having an inadequate response to another systemic agent such as methotrexate that may be used for longer term use.

It is reasonable to include phototherapy as an option for first-step therapy, but lack of availability in many locations makes it inappropriate for payers to require patients to try phototherapy before receiving coverage for other options. The only exception would be a health plan/system that can provide good access to phototherapy at an out-of-pocket expense comparable to medication treatment options.

If multiple agents for severe atopic dermatitis are approved, payers should make available at least one biologic (dupilumab and/or tralokinumab) and at least one oral JAK inhibitor given how different these classes are in their onset of action and their risk profile. Clinician experts emphasized that the heterogeneity of atopic dermatitis and the challenges in defining and measuring disease severity support the need for having access to a range of different therapies. Specifically, clinical experts did not feel it would be appropriate to use step therapy that makes only one treatment available as the first step agent across biologics and oral JAK inhibitors. Some patients only have severe disease on a seasonal basis, making continual biologic treatment potentially less desirable than periodic use of a JAK inhibitor. Similarly, patients with asthma or more year-round severity are better candidates for biologic treatment. Clinical experts therefore strongly urged that at least one agent from both classes be available within any step therapy policy.

For ruxolitinib cream use in patients with mild to moderate atopic dermatitis, policy round table participants felt that stepping through other topical therapies such as a corticosteroid or calcineurin inhibitor was reasonable. Some clinical experts felt that since ruxolitinib cream may be used for younger patients as a steroid sparing medication, requiring stepping through a more potent topical steroid may not be appropriate. Manufacturers, Payers and Patient Advocacy Groups

Support pricing and rebate reform efforts that will create better rewards for clinical and economic value while also helping patients access and afford the treatments they need

It is widely recognized that the high prices of new prescription medications limit access to patients who may benefit from their use. Current pricing for medications is complex and the practice of using rebates and other methods to obscure the price of a therapy makes it difficult to assess whether the price being paid is in line with its effectiveness. Manufacturers and payers during the policy round table highlighted the potential impact of value-based pricing as helping to promote

transparency, affordability and promote access to new therapies. For example, upadacitinib has a much higher price after estimated rebates than other treatments, and it is possible that this drug can compete with a higher price largely because its manufacturer can tie formulary placement to rebates provided by other drugs made by that same manufacturer. This phenomenon, commonly known as "rebate walls," may in some cases provide an overall lower net cost to the payer, but it may only drive up the bubble between the list price and the net price for the benefit of pharmacy benefit managers and/or wholesalers, and it also creates true barriers to competition for new agents that have fewer indications or which are not made by companies that have other products whose rebates can be bundled together in negotiation. Unfortunately, there are no easy solutions to the role of rebates in the current system, but policy round table participants agreed that the federal government, plan sponsors, and other policy makers should work together to try to develop new approaches, such as indication-specific pricing, that can be piloted to create a pathway toward an end to the dominant role of bundled rebates.

Specialty Societies

Update treatment guidelines for patients with atopic dermatitis to reflect current treatment options in a form that is easy to interpret and use by clinicians, patients, and payers

Clinical societies should update their practice guidelines for managing patients with mild to moderate and moderate to severe atopic dermatitis to include newer therapies such as abrocitinib, baricitinib, dupilumab, tralokinumab and upadacitinib. Payers base their coverage decisions and integration of utilization tools to a great extent on clinical guidelines. The American Academy of Dermatology last updated it guidelines for the treatment of atopic dermatitis in 2014. The Joint Task Force on Practice Parameters for Allergy and Immunology, comprised of the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma, and Immunology issued updated treatment guidelines for atopic dermatitis in 2012. Current guidelines do not include newer approved agents for patients with atopic dermatitis such as dupilumab, approved by the FDA in 2017 or crisaborole cream, approved by the FDA in 2016; guidelines also do not discuss newer therapies that have not yet received FDA approval, such as IL-13 receptor antagonists and JAK inhibitors.

Policy round table participants highlighted that guidelines should not only provide information on options to be used by clinicians and patients for shared decision making, but also offer pragmatic advice about how to select specific therapies for specific subgroups. Payers expressed the need for updated guidelines from clinical societies with detailed guidance to permit meaningful stepped therapy approaches that permit reasonable clinical exceptions. For example, guidelines should distinguish use of agents in adolescents versus adults where there may be differences in the willingness to accept small but potentially serious risks and the need for rapid onset of

improvement.

Manufacturers and Researchers

Establish long-term registries that can be used to assess the benefits and harms of chronic use of oral JAK inhibitors for patients with atopic dermatitis

Concerns about uncommon but potentially serious risks of oral JAK inhibitors such as serious infections, cancer, blood clots and cardiovascular events when used for other conditions have led to boxed warnings. Whether these harms will also be seen when used in patients with moderate to severe atopic dermatitis requires larger, long-term follow-up studies that assess not only the durability of response but these infrequent risks among individuals using oral JAK inhibitors versus other biologic therapies such as dupilumab. Even the topical JAK inhibitor, ruxolitinib cream, has topical absorption and may warrant long-term follow-up, especially since it may be used in younger individuals. Even if it is not associated with systemic toxicity, topical ruxolitinib cream use might increase the risk of skin cancers.

Conduct research that directly compares real-world treatment options and sequential treatment effectiveness

Multiple stakeholders expressed concerns about the lack of information directly comparing new treatments and the need for active comparator trials. With the potential for having multiple newer therapeutic options that work through different mechanisms for patients with mild to moderate and moderate to severe atopic dermatitis, there is a great need for pragmatic research trials that compare different medications as they will be used by patients and clinicians in real world settings. Appropriate head-to-head trials would inform decision making by patients and clinicians. Trials that compare multiple treatment options, sequences and combinations are needed to identify comparative effectiveness, durability of benefit, and adverse effects. For example, trials should compare the net benefits of different oral JAK inhibitors or the tolerability and acceptance of oral versus injectable therapies for patients with moderate to severe disease.

Support the development of improved measures of disease severity and outcomes that are meaningful to patients

Clinical experts identified the lack of standard definitions of disease severity in atopic dermatitis as a challenge to identifying homogeneous patient populations for inclusion in clinical trials. We also heard from patient advocacy groups that endpoints used in clinical trials do not always measure what is most important to patients and families. For example, many endpoint measures focus on the appearance of the skin, something that may be important for an adolescent or young adult, but

may be less important for older patients. Though there are measures of itch, sleep, and interference in quality of life, these outcomes are not yet combined in ways that reflect the heterogeneity needed. Moreover, they are rarely translated into utility measures that can be incorporated into cost effectiveness analyses. Patient groups can take a leading role in collecting real-world data, as well as collaborating with researchers, manufacturers, and regulators to define a core set of severity and outcome measures and then in promoting their use in all clinical trials.

Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

The primary outcomes in the pivotal trials studied include investigator assessed responses:

1. E***czema Area Severity Index score (EASI):***[120] This instrument represents a modification of the general schema used in the psoriasis area and severity index (PASI). The total score for the EASI ranges from 0 to a maximum of 72 with higher scores indicating greater severity. Total scores represent a sum of severity scores from four body regions (head and neck, upper extremities, trunk, and lower extremities). The score for each body region includes an assessment of severity for the four signs of erythema, induration/papulation/edema, excoriations, and lichenification. These are each assigned a score of 0 to 3 (None, mild, moderate, severe, respectively). These are added up for each anatomic region and multiplied by the percentage area involved and a proportionate body surface area assigned to each of the four body regions. The percentage area involved for each of the four body regions are assigned a proportional score from 0 to 6 (where 0= no eruption, 1 = ≤10%, 2 = 10-29%, 3 – 30-49%, 4 = 50-69%, 5= 70-89%, and 6 = 90-100%). The proportionate body surface areas assigned to adults are 10% for the head and neck (20% for children), 20% for the upper extremities (same for children), 30% for trunk (same for children) and 50% for lower extremities (30% for children). Outcomes are assessed as the change in EASI response from baseline and are categorized as the percent improvement as noted below. The EASI-75 response is most commonly used as the primary outcome end point.

- **EASI-50**: a percentage improvement of EASI score from baseline that is ≥ 50%
- **EASI-75**: a percentage improvement of EASI score from baseline that is ≥ 75%
- **EASI-90**: a percentage improvement of EASI score from baseline that is ≥ 90%

2. ***Investigator's Global Assessment (IGA):***[121] This clinician-reported outcome measure provides an overall assessment of the severity of a patient's atopic dermatitis at a specific time point. There are different versions of the instrument with the most common using a 5- or 6- point rating scale. The 5-point scale ranges from 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), to 4 (severe). The 6-point scale ranges from 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), 4 (severe) to 5 (very severe). In many trials the primary response outcome or IGA response is defined as a score of 0 or 1 on the IGA. The IGA response can also include an improvement from baseline of ≥2 points. Other cutoffs used in studies include ≥3 or ≥4 points.

3. ***Peak Pruritus Numerical Rating Scale (PP-NRS):***[122] Itch (or pruritus) represents a key symptom for patients with atopic dermatitis and can be intense, persistent, and debilitating. This scale was developed to assess one dimension of pruritis, its severity. It is a single self-reported item designed to measure the severity of pruritis or peak pruritus, or 'worst' itch, over the previous 24 hours using an 11-point scale. The item asks: 'On a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable", how would you rate your itch at the worst moment during the previous 24 hours?' Improvement from baseline can be reported using a number of different cut points including, ≥2, ≥3, or ≥4 points

4. ***Scoring Atopic Dermatitis (SCORAD):***[123] Developed and validated by the European Task Force on Atopic Dermatitis, SCORAD is a composite severity index that combines objective symptoms (extent and intensity, and subjective criteria (pruritis and sleep loss). The extent of atopic dermatitis is expressed as the skin surface area involved. The intensity includes 6 specific symptoms: erythema, edema/papulation, oozing/crusts, excoriations, lichenification and dryness of the involved skin. These are rated from none (0), mild (1), moderate (2) or severe (3) for each item. The subjective symptoms are assessed using a visual analogue scale where 0 is no itch (or no sleeplessness) and 10 is the worst imaginable itch (or sleeplessness). The SCORAD index ranges from 0 to 103, with higher scores indicating worse severity.

5. ***Dermatology Life Quality Index (DLQI):***[124] The DLQI is a 10-item, validated dermatology specific quality of life assessment instrument used in clinical practice and clinical trials. It assesses six domains including: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and adverse effects of treatment. Nine items have four response options: "not at all," "a little," "a lot," and "very much." One item asks about whether work or study has been prevented, and then (if "yes") to what degree has the skin condition been a problem ("a lot," "a little," or "not at all"). Individual items are summed to obtain a total score that can range from 0 to 30, with higher scores indicating worse health-related quality of life. Suggested interpretation of DLQI score for 0-1 indicates no impact, 2-5 indicates small impact, 6-10 indicates moderate impact, 11-20 indicates large impact and 21-30 indicates an extremely large impact on health-related quality of life for the skin condition.

6. ***Children's Dermatology Life Quality Index (CLDQI):***[125] A version of the DLQI questionnaire designed to measure the impact of skin disease on the lives of children ages 4 to 16 years.

7. ***Patient-Oriented Eczema Measure (POEM):***[105] This simple, validated questionnaire assesses patient's symptoms and impact of atopic dermatitis in children and adults. It asks about symptoms over the prior week and includes seven questions about itch, sleep disturbance and whether the skin is weeping/oozing, cracked, flaking, dry/rough, or bleeding. These are rated from "no days," "1-2 days", "3-4 days", "5-6 days", or "every day". POEM scores range from 0 to 28 with higher

scores indicating worse disease severity and the minimal clinically important difference has been reported to be 3-4.

8. ***Atopic Dermatitis Impact Scale (ADerm-IS):***[126] It includes three items (difficulty falling asleep, level of impact on sleep, burden of waking up at night) to be completed daily, assessing impact on sleep over the previous 24 h, and seven items (limitations in household activities, physical activities, social activities, difficulty concentrating, feeling self-conscious, embarrassed, sad) completed weekly to assess overall impact over the past 7 days. Responses are on an 11-point numeric rating scale from 0 "not [present]" to 10 "extremely [present]". Responses are on an 11-point numeric rating scale from 0 "not [present]" to 10 "extremely [present]".

9. ***Dermatitis Family Impact Questionnaire (DFI):***[127] A disease-specific measure to assess the impact of atopic dermatitis on the quality of life of parents and family members of affected children.

10. ***Hospital Anxiety and Depression Scale (HADS):*** Likert scale used to detect states of anxiety and depression; anxiety and depression subscales each with 7 items.

11. ***Work Productivity and Activity Impairment for Atopic Dermatitis (WPAI-AD):***[128] The WPAI, a validated instrument is used to measure impairment in work productivity and daily activities. The questionnaire consists of six questions assessing the past 7 days: employment status (yes/no), work time missed due to atopic dermatitis (hours), work time missed due to other reasons (hours), actual work time (hours), impact of atopic dermatitis on work productivity while at work (0-10 point scale) and impact of atopic dermatitis on activities outside of work (0-10 point scale). Four scores are derived: absenteeism (percentage of time missed from work due to health), presenteeism (percentage of impairment while at work due to health), work productivity loss (aggregate of absenteeism and presenteeism) and activity impairment (percentage of impairment in daily activities due to health). Higher scores indicate a higher level of impairment. Higher scores indicate a higher level of impairment.

A2. Potential Cost-Saving Measures in Atopic Dermatitis

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). These services are ones that would not be directly affected by therapies for atopic dermatitis (e.g., caregiver/family burden), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of atopic dermatitis beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with atopic dermatitis that could be reduced, eliminated, or made more efficient. No suggestions were received.

B. Patient Perspectives: Supplemental Information

B1. Methods

In developing and executing this report, we received valuable input from individual patients and patient advocacy groups throughout the scoping and evidence development process. We received public comments on our draft scoping document from the following patient advocacy organizations: the National Eczema Association, the International Eczema Council, and the Allergy and Asthma Network. We also conducted a focus group with three patients and three caregivers that was arranged through the National Eczema Association. These interviews with patients and caregivers helped to illustrate the diversity of experiences of patients living with atopic dermatitis, as well as highlighted the health outcomes that were most important to them.

C. Clinical Guidelines

American Academy of Dermatology

Guidelines of care for the management of atopic dermatitis[28]

The American Academy of Dermatology issued updated and expanded clinical guidelines for the treatment of atopic dermatitis in 2014, based on the initial guidelines that were published in 2004. These guidelines were developed by a working group of experts in the field who used an evidence-based approach to discuss diagnosis, assessment, safety, and efficacy of available treatments for atopic dermatitis.

Treatment with Topical Therapies

Non-pharmacologic treatments are recommended to maintain and prevent flares. These interventions include moisturizers, bathing practices (i.e., limited use of non-soap cleansers, subsequent moisturization), and wet-wrap therapy for those with moderate-to-severe atopic dermatitis. Wet wrap therapy can also be used in conjunction with topical corticosteroids during flares. These methods serve to minimize the severity of atopic dermatitis and reduce the amount of pharmacologic intervention needed.

Topical pharmacologic treatments are recommended to treat atopic dermatitis in patients that do not respond to the above interventions. These include topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI), both of which are used for the treatment and management of adults and adolescent atopic dermatitis patients. TCS are recommended for both active and maintenance therapy in patients that have not had success in controlling symptoms with non-pharmacologic interventions. TCI are recommended as a second-line therapy if TCS has failed to control symptoms.

While other topical treatments exist for the maintenance of atopic dermatitis symptoms, they are not recommended lines of therapy. These topical therapies include antimicrobials, antiseptics, and antihistamines.

Treatment with Phototherapy and Systemic Agents

The American Academy of Dermatology recommends phototherapy as a second-line treatment for atopic dermatitis in children and adults, as well as maintenance therapy in cases of chronic disease. It can be used as monotherapy or in combination with other topical therapies. While it is considered a low-risk treatment, it is important to consider adverse events when used in

conjunction with other drugs. Phototherapy treatment is contingent on several patient factors, including availability, cost, skin type, and medical history.

The prescription of systemic agents for atopic dermatitis patients warrants several considerations related to disease contraindications, quality of life, and severity. Systemic treatment is recommended for patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled by topical regimens and phototherapy. The recommended off-label systemic therapies indicated by the guidelines include cyclosporine, azathioprine, and methotrexate. Mycophenolate mofetil and interferon gamma are also indicated as alternative off-label therapies for atopic dermatitis. The minimal effective dose of each systemic therapy should be used when treating patients. The guidelines also recommend against the use of systemic corticosteroids, as there are concerns with associated short- and long-term adverse events.

Use of Adjunctive Therapies

It is recommended that patient education always be included in conventional therapy. The use of TCS or TCI can also be used to prevent relapse after the disease has been stabilized.

Joint Task Force on Practice Parameters for Allergy and Immunology

Atopic Dermatitis: A practice parameter update 2012[129]

The Joint Task Force on Practice Parameters for Allergy and Immunology issued an update in 2012 to their 2004 treatment guidelines for atopic dermatitis. The task force was comprised of the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma, and Immunology. In these suggestions for practice, the joint task force presents recommendations for first line management and treatment of atopic dermatitis, as well as guidance for severe cases that are more difficult to treat.

First Line Management and Treatment of Atopic Dermatitis

It is recommended that clinicians treat patients using a systematic approach, and the intensity of management and treatment should be determined by severity of the disease. Recommended treatments include skin hydration, topical anti-inflammatory medications, antipruritic therapy, antibacterial measures, and elimination of any environmental factors that may be exacerbating illness. Some of these common irritants include soaps, toiletries, wools, and chemicals that tend to trigger the itch-scratch cycle. Food allergies may also be considered as triggers for infants and children with atopic dermatitis.

Regardless of the severity of illness, it is imperative for clinicians to educate patients and family members on the chronic nature of the disease. Treating clinicians should review disease

exacerbating factors with their patients, as well as the safety and side effects of any prescribed medications.

Treatment of Severe Cases of Atopic Dermatitis

For severe cases of atopic dermatitis, it is recommended that patients are treated with systemic immunomodulating agents, such as cyclosporine, mycophenolate mofetil, azathioprine, interferon gamma, and corticosteroids. Wet dressings can also be used in combination with topical corticosteroids. However, it is important to note the potential serious adverse events associated with these drugs, and the risks and benefits should be discussed with the patient. Phototherapy can also be utilized as a means of treatment, particularly narrow-band UBV, which has been proven to be most effective in the U.S. For extremely severe cases of atopic dermatitis, hospitalization is recommended, as this could potentially remove a patient from environmental allergens and lessen the effects of disease associated stressors, such as sleep deprivation.

Investigative approaches to treating and managing atopic dermatitis are not recommended, as there is currently insufficient data to prove effectiveness. Examples of these interventions include intravenous immunoglobin, omalizumab, and rituximab.

National Institute for Health and Care Excellence (NICE)

Dupilumab for Treating Moderate to Severe: Recommendations[130]

NICE released recommendations for use of dupilumab in 2018. Dupilumab is recommended as an option for treating moderate to severe atopic dermatitis in adults after not responding to at least one other systemic therapy such as cyclosporin, methotrexate, azathioprine, and mycophenolate, or if these are contraindicated or not tolerated. Response should be assessed at 16 weeks and therapy should be stopped if there has not been an adequate response. This is considered at least a 50% reduction in the EASI score (EASI 50) and at least a 4-point reduction in the DLQI, both compared to prior to starting treatment. The recommendation notes that skin color should be taken into account and clinical adjustments made if appropriate when assessing the EASI since it may affect the score. For the DLQI, adjustments can be made if appropriate to account for any physical, psychological, sensory, or learning disabilities, or communication difficulties that could affect patient responses.

Baricitinib for Treating Moderate to Severe: Recommendations[130]

NICE released recommendations for use of baricitinib in March 2021. Baricitinib has similar recommendations as for dupilumab; adults with moderate to severe atopic dermatitis not responding to at least one other systemic therapy such as cyclosporin, methotrexate, azathioprine, and mycophenolate, or if these are contraindicated or not tolerated. Response should be assessed from 8 weeks and baricitinib should be stopped if there has not been an adequate response at 16 weeks, using the same criteria as for dupilumab.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The populations of focus for the review were:

1. Adults and children with moderate-to-severe atopic dermatitis whose disease has either not responded adequately to topical therapies or for whom topical therapies have not been tolerated or are medically inadvisable

2. Adults and children with mild-to-moderate atopic dermatitis

Additionally, based on the availability of data, we included evidence stratified by age (children: <12 years, adolescents: ≥12 years to <18 years, and adults: ≥18 years), duration (≤16 weeks and >16 weeks), and disease severity (mild, moderate, and severe).

Interventions

The interventions of interest included the following JAK inhibitors and monoclonal antibodies:

Moderate-to-severe atopic dermatitis (Population 1):

- Abrocitinib (Pfizer)
- Baricitinib (Olumiant©, Eli Lilly)
- Upadacitinib (Rinvoq©, AbbVie)
- Tralokinumab (Leo Pharma)

Note that each of these therapies may be used alone or with topical therapies (including emollients with or without a topical corticosteroid or calcineurin inhibitor)

Mild-to-moderate atopic dermatitis (Population 2):

- Ruxolitinib cream (Incyte)

Comparators

For moderate-to-severe atopic dermatitis (Population 1) we compared the interventions to:

- Dupilumab
- Each other
- Topical therapies (including emollients with or without a topical corticosteroid or calcineurin inhibitor)

We had initially included methotrexate as a comparator, but after additional input from clinical experts and other stakeholders we have not included comparisons with methotrexate in the report due to differences in study design, populations, and outcomes.

For mild-to-moderate atopic dermatitis (Population 2) we compared the intervention to:

- Topical emollient therapy alone
- Topical corticosteroids
- Topical calcineurin inhibitors
- Crisaborole cream

Outcomes

The outcomes of interest are described in the list below.

- Patient-reported pruritus or itching
- Eczema Area and Severity Index (EASI); 50, 75, and 90 or relative change from baseline
- Investigator's Global Assessment (IGA)
- Sleep
- Scoring Atopic Dermatitis (SCORAD) Score
- Patient-Oriented Eczema Measure (POEM)
- Dermatology Life Quality Index (DLQI)
- Children's Dermatology Life Quality Index (CDLQI)
- Anxiety and depression (e.g., Hospital Anxiety and Depression Scale [HADS])
- European Quality of Life-5 Dimensions (EQ-5D)
- Measures of productivity (e.g., Work Productivity and Activity Impairment Questionnaire [WPAI])
- Other patient-reported symptom and quality of life measures

- Safety
    - Adverse events (AEs)
    - Treatment-emergent adverse events (TEAEs)
    - Serious adverse events (SAEs)
    - Discontinuation due to AEs
    - Thrombotic events
    - Infections (serious, skin, herpetic)
    - Hematological abnormalities
    - Malignancy
        - Non-melanocytic skin cancer
    - All-cause mortality

Timing

Evidence on intervention effectiveness was derived from studies of at least four weeks duration.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for atopic dermatitis followed established best research methods.[131,132] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[133] The PRISMA guidelines include a checklist of 27 items described further in Table D1.1.

Table D1.1. PRISMA 2009 Checklist

Checklist Items		
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from

conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/grey-literature-policy/). Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer-review.org/use-of-in-confidence-data/).

Table D1.2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials (Interventions)*

1	observational study.pt.
2	exp case-control studies/
3	exp cohort studies/
4	exp cross-over studies/
5	exp matched-pair analysis/
6	multicenter study.pt.
7	1 or 2 or 3 or 4 or 5 or 6
8	randomized controlled trial.pt.
9	controlled clinical trial.pt.
10	randomized.ab.
11	placebo.ab.
12	drug therapy.fs.
13	randomly.ab.
14	trial.ab.
15	groups.ab.
16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	comparative study.pt. or compare.ab,ti. or compares.ab,ti. or compared.ab,ti. or comparing.ab,ti. or comparison.ab,ti. or comparison.ab,ti. or comparative.ab,ti. or effective.ab,ti. or effectiveness.ab,ti. or versus.ab,ti. or vs.ab,ti.
18	7 and 17
19	16 or 18
20	exp animals/
21	humans.sh.
22	20 not 21
23	19 not 22
24	limit 23 to English language
25	(case reports or comment or congresses or editorial or letter or review).pt.
26	24 not 25
27	exp Eczema/ or eczema.mp.
28	exp Dermatitis, Atopic/
29	neurodermatitis.mp. or exp Neurodermatitis/
30	exp Dermatitis/ or dermatitis.mp.
31	27 or 28 or 29 or 30

32	Exp Abrocitinib/ or abrocitinib.mp.
33	(abrocitinib or "pf04965842" or pf04965842 or "pf 4965842" or pf4965842).ti,ab.
34	Exp baricitinib/ or baricitinib.mp.
35	(baricitinib or "incb 028050" or incb028050 or "incb 28050" or "ly 3009104" or ly3009104 or olumiant).ti,ab.
36	Exp upadacitinib/ or upadacitinib.mp.
37	(upadacitinib or "abt 494" or abt494 or rinvoq or "upadacitinib hemihydrate" or "upadacitinib hydrate" or "upadacitnib tartrate").ti,ab.
38	Exp tralokinumab/ or tralokinumab.mp.
39	(tralokinumab or "cat354" or cat354 or "cat-354").ti,ab.
40	Exp Ruxolitinib/ or ruxolitinib.mp.
41	(ruxolitinib or "incb 018424" or incb018424 or "incb 18424" or incb18424 or jakafi or jakavi or "ruxolitinib maleate" or "ruxolitinib phosphate").ti,ab.
42	32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43	31 and 42
44	26 and 43

***Search last updated on May 26, 2021.**

Table D1.3. Search Strategy Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials (Comparators)*

1	observational study.pt.
2	exp case-control studies/
3	exp cohort studies/
4	exp cross-over studies/
5	exp matched-pair analysis/
6	multicenter study.pt.
7	1 or 2 or 3 or 4 or 5 or 6
8	randomized controlled trial.pt.
9	controlled clinical trial.pt.
10	randomized.ab.
11	placebo.ab.
12	drug therapy.fs.
13	randomly.ab.
14	trial.ab.
15	groups.ab.
16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	comparative study.pt. or compare.ab,ti. or compares.ab,ti. or compared.ab,ti. or comparing.ab,ti. or comparison.ab,ti. or comparison.ab,ti. or comparative.ab,ti. or effective.ab,ti. or effectiveness.ab,ti. or versus.ab,ti. or vs.ab,ti.
18	7 and 17
19	16 or 18

20	exp animals/
21	humans.sh.
22	20 not 21
23	19 not 22
24	limit 23 to english language
25	(case reports or comment or congresses or editorial or letter or review).pt.
26	24 not 25
27	exp Eczema/ or eczema.mp.
28	exp Dermatitis, Atopic/
29	neurodermatitis.mp. or exp Neurodermatitis/
30	exp Dermatitis/ or dermatitis.mp.
31	27 or 28 or 29 or 30
32	dupilumab.mp.
33	(dupilumab or dupixent or "regn 668" or regn688 or "sar 231893" or sar231893).ti,ab
34	crisaborole.mp
35	(eucrisa or an2728 or 'an-2728').ti,ab
36	32 or 33 or 34 or 35
37	limit 38 to yr=2017-2021
38	31 and 37
39	26 and 38

***Search last updated on May 26, 2021.**

Table D1.4. Cochrane Database of Systematic Reviews*

1	eczema.mp.
2	neurodermatitis.mp.
3	dermatitis.mp.
4	atopic dermatitis'.mp.
5	1 or 2 or 3 or 4
6	abrocitinib.mp.
7	(abrocitinib or "pf04965842" or pf04965842 or "pf 4965842" or pf4965842).ti,ab.
8	baricitinib.mp.
9	(baricitinib or "incb 028050" or incb028050 or "incb 28050" or "ly 3009104" or ly3009104 or olumiant).ti,ab.
10	upadacitinib.mp.
11	(upadacitinib or "abt 494" or abt494 or rinvoq or "upadacitinib hemihydrate" or "upadacitinib hydrate" or "upadacitnib tartrate").ti,ab.
12	tralokinumab.mp.
13	(tralokinumab or "cat354" or cat354 or "cat-354").ti,ab.
14	ruxolitinib.mp.

15	(ruxolitinib or "incb 018424" or incb018424 or "incb 18424" or incb18424 or jakafi or jakavi or "ruxolitinib maleate" or "ruxolitinib phosphate").ti,ab.
16	methotrexate.mp
17	(amethopterin or 'methotrexate hydrate' or mexate).ti,ab
18	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19	dupilumab.mp.
20	(dupilumab or dupixent or "regn 668" or regn688 or "sar 231893" or sar231893).ti,ab
21	crisaborole.mp
22	(eucrisa or an2728 or 'an-2728').ti,ab
23	('topical corticosteroid$' or 'topical emollient$' or 'topical therp$').mp
24	calcineurin inhibitor$'.mp.
25	19 or 20 or 21 or 22 or 23 or 24
26	limit 25 to dd=20200201-20210121
27	18 or 26
28	5 and 27

***Search last updated on May 26, 2021.**

Table D1.5. Search Strategy of EMBASE SEARCH (Interventions)*

#1	'eczema'/exp OR eczema
#2	'atopic dermatitis'/exp OR 'atopic dermatitis'
#3	'neurodermatitis'/exp OR neurodermatitis
#4	'dermatitis'/exp OR dermatitis
#5	#1 OR #2 OR #3 OR #4
#6	'abrocitinib'/exp OR abrocitinib
#7	abrocitinib:ti,ab OR 'pf 04965842':ti,ab OR pf04965842:ti,ab OR 'pf 4965842':ti,ab OR pf4965842:ti,ab
#8	'baricitinib'/exp OR baricitinib
#9	baricitinib:ti,ab OR 'incb 028050':ti,ab OR 'incb 28050':ti,ab OR 'ly 3009104:ti,ab' OR olumiant:ti,ab
#10	'upadacitinib'/exp OR upadacitinib
#11	upadacitinib:ti,ab OR 'abt 494':ti,ab OR rinvoq:ti,ab OR 'upadacitinib hemihydrate':ti,ab OR 'upadacitinib hydrate':ti,ab OR 'upadacitinib tartrate':ti,ab
#12	'tralokinumab'/exp OR tralokinumab
#13	tralokinumab:ti,ab OR 'cat 354':ti,ab OR 'cat-354':ti,ab OR cat354:ti,ab
#14	'ruxolitinib'/exp OR ruxolitinib
#15	ruxolitinib:ti,ab OR 'incb 018424':ti,ab OR 'incb 18424':ti,ab OR 'incb 424':ti,ab OR jakafi:ti,ab OR jakavi:ti,ab OR 'ruxolitinib maleate':ti,ab OR 'ruxolitinib phosphate':ti,ab
#16	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17	#5 AND #16
#18	random*:ti OR placebo*:ti OR 'single blind*':ti OR 'double blind*':ti OR 'triple blind*':ab,ti
#19	'cohort analysis'/de OR 'cohort analysis'
#20	'longitudinal study'/de OR 'longitudinal study'

#21	'prospective study'/de OR 'prospective study'
#22	'follow-up'/de OR 'follow-up'
#23	'case control study'/de OR 'case control study'
#24	'matched-pair analysis'/de OR 'matched-pair analysis'
#25	'cross-over study'/de OR 'cross-over study'
#26	'cohort*':ti,ab
#27	'case* and control*':ti,ab
#28	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
#29	'compar*':ti,ab
#30	'effective*':ti,ab
#31	'versus':ti,ab
#32	'vs.':ti,ab
#33	#29 OR #30 OR #31 OR #32
#34	#28 AND #33
#35	#18 OR #34
#36	#17 AND #35
#37	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#38	#36 NOT #37
#39	#38 AND [english]/lim
#40	#39 NOT [medline]/lim

***Search last updated on May 26, 2021.**

Table D1.6. Search Strategy of EMBASE SEARCH (Comparators)*

#1	'eczema'/exp OR eczema
#2	'atopic dermatitis'/exp OR 'atopic dermatitis'
#3	'neurodermatitis'/exp OR neurodermatitis
#4	'dermatitis'/exp OR dermatitis
#5	#1 OR #2 OR #3 OR #4
#6	'dupilumab'/exp OR dupilumab
#7	dupilumab:ti,ab OR dupixent:ti,ab OR 'regn 668':ti,ab OR regn668:ti,ab OR 'sar 231893':ti,ab OR sar231893:ti,ab
#8	'crisaborole'/exp OR crisaborole
#9	eucrisa:ti,ab OR staquis:ti,ab OR 'an 2728':ti,ab OR 'an-2728':ti,ab OR an2728:ti,ab
#10	#6 OR #7 OR #8 OR #9
#11	#5 AND #10
#12	random*:ti OR placebo*:ti OR 'single blind*':ti OR 'double blind*':ti OR 'triple blind*':ab,ti
#13	'cohort analysis'/de OR 'cohort analysis'
#14	'longitudinal study'/de OR 'longitudinal study'
#15	'prospective study'/de OR 'prospective study'
#16	'follow-up'/de OR 'follow-up'
#17	'case control study'/de OR 'case control study'
#18	'matched-pair analysis'/de OR 'matched-pair analysis'

#19	'cross-over study'/de OR 'cross-over study'
#20	'cohort*':ti,ab
#21	'case* and control*':ti,ab
#22	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23	'compar*':ti,ab
#24	'effective*':ti,ab
#25	'versus':ti,ab
#26	'vs.':ti,ab
#27	#23 OR #24 OR #25 OR #26
#28	#22 AND #27
#29	#12 OR #28
#30	#11 AND #29
#31	#30 NOT ('animal experiment'/de OR 'animal model'/de OR 'case report'/de OR 'human cell'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#32	#31 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp)
#33	#32 AND [2017-2021]/py
#34	#33 NOT [medline]/lim
#35	#34 AND [english]/lim

***Search last updated on May 26, 2021.**

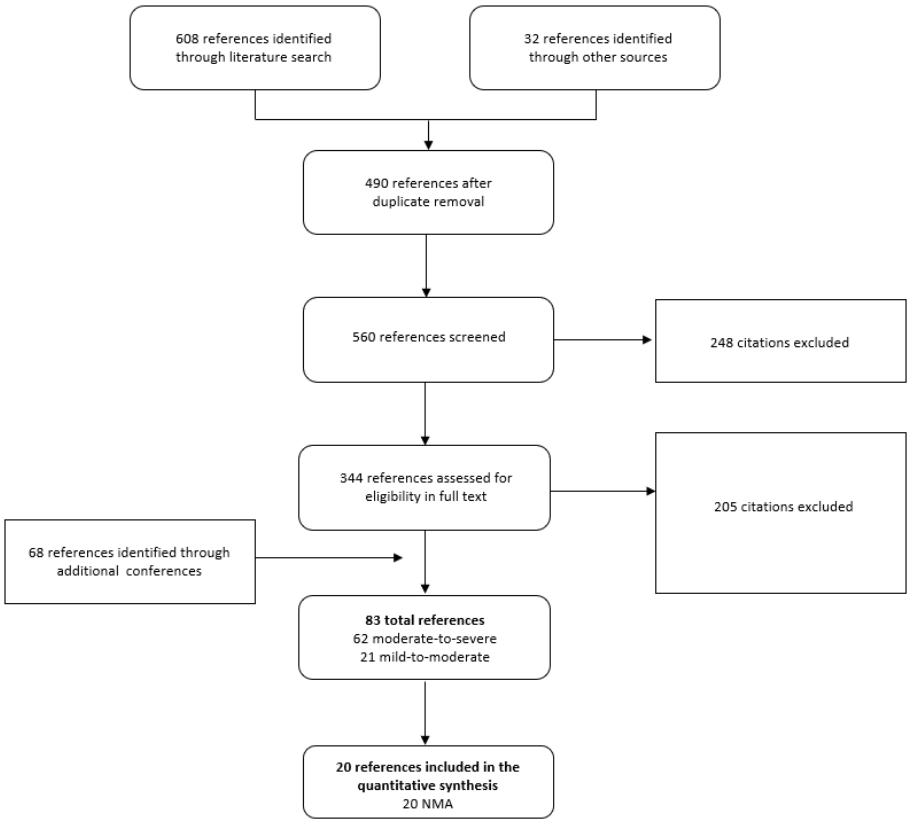
Table D1.7. Search Strategy of EMBASE SEARCH (Systematic Reviews)*

#1	'eczema'/exp OR 'eczema' OR 'eczema'/exp OR eczema
#2	'atopic dermatitis'/exp OR 'atopic dermatitis'
#3	'neurodermatitis'/exp OR neurodermatitis
#4	'dermatitis'/exp OR dermatitis
#5	#1 OR #2 OR #3 OR #4
#6	'abrocitinib'/exp OR abrocitinib
#7	abrocitinib:ti,ab OR 'pf 04965842':ti,ab OR pf04965842:ti,ab OR 'pf 4965842':ti,ab OR pf4965842:ti,ab
#8	baricitinib'/exp OR baricitinib
#9	baricitinib:ti,ab OR 'incb 028050':ti,ab OR 'incb 28050':ti,ab OR 'ly 3009104:ti,ab' OR olumiant:ti,ab
#10	'upadacitinib'/exp OR upadacitinib
#11	upadacitinib:ti,ab OR 'abt 494':ti,ab OR rinvoq:ti,ab OR 'upadacitinib hemihydrate':ti,ab OR 'upadacitinib hydrate':ti,ab OR 'upadacitinib tartrate':ti,ab
#12	'tralokinumab'/exp OR tralokinumab
#13	tralokinumab:ti,ab OR 'cat 354':ti,ab OR 'cat-354':ti,ab OR cat354:ti,ab
#14	'ruxolitinib'/exp OR ruxolitinib
#15	ruxolitinib:ti,ab OR 'incb 018424':ti,ab OR 'incb 18424':ti,ab OR 'incb 424':ti,ab OR jakafi:ti,ab OR jakavi:ti,ab OR 'ruxolitinib maleate':ti,ab OR 'ruxolitinib phosphate':ti,ab
#16	'methotrexate'/exp OR methotrexate
#17	aminopterin:ti,ab OR mtx:ti,ab OR rasuvo:ti,ab OR otrexup:ti,ab OR xatmep:ti,ab OR trexall:ti,ab
#18	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	'dupilumab'/exp OR dupilumab

#20	dupilumab:ti,ab OR dupixent:ti,ab OR 'regn 668':ti,ab OR regn668:ti,ab OR 'sar 231893':ti,ab OR sar231893:ti,ab
#21	'crisaborole'/exp OR crisaborole
#22	eucrisa:ti,ab OR staquis:ti,ab OR 'an 2728':ti,ab OR 'an-2728':ti,ab OR an2728:ti,ab
#23	'calcineurin inhibitor$':ti,ab
#24	steroid:ti,ab OR topical:ti,ab OR 'topical emollient$':ti,ab OR 'topical corticosteroid$':ti,ab
#25	#19 OR #20 OR #21 OR #22 OR #23 OR #24
#26	#5 AND #25
#27	#26 AND [1-2-2020]/sd
#28	#5 AND #18
#29	#27 OR #28
#30	#29 AND ([systematic review]/lim OR [meta analysis]/lim)
#31	#30 AND [humans]/lim
#32	#31 NOT [medline]/lim

***Search last updated on May 26, 2021.**

Figure D1.1. PRISMA Flow Chart Showing Results of Literature Search for Abrocitinib, Baricitinib, Tralokinumab, Upadacitinib, and Ruxolitinib Cream



Study Selection

We performed screening at both the abstract and full-text levels. According to the inclusion and exclusion criteria described earlier, a single investigator screened all abstracts identified through electronic searches. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full-text appraisal. One investigator reviewed full papers and provided justification for the exclusion of each excluded study.

Data Extraction and Quality Assessment

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (Table D3.1 and D3.6.[134] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all-important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Figure 3.2 of the Report).[135]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. We performed an assessment of publication bias for abrocitinib, baricitinib, upadacitinib, tralokinumab, and ruxolitinib cream using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published and did not find any evidence of publication bias.

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see section D3) and synthesized qualitatively in the body of the review. In addition, we evaluated the comparative efficacy of abrocitinib, baricitinib, upadacitinib, tralokinumab, and dupilumab for adults ≥ 18 years old with moderate-to-severe atopic dermatitis by means of network meta-analysis (NMA), where feasible. Based on data availability, our NMA evaluated IGA, EASI 50, EASI 75, EASI 90, and PP-NRS ≥4-point improvement outcomes at 12 and 16 weeks. Network Meta-Analysis Supplemental Information below (Section D2) contains a detailed description of the NMA methods. Due to inconsistent or limited data reporting, other outcomes were only described narratively in the body of the report or in Section D3 of the Report Supplement.

D2. Network Meta-Analysis Supplemental Information

NMA Methods

We evaluated the feasibility of conducting quantitative synthesis by exploring the differences in study populations, study design, analytic methods, and outcome assessment for each outcome of interest. Trials deemed sufficiently similar in terms of population, intervention type, duration, and outcome definitions were included in the NMAs. While most trials that met the NMA eligibility criteria enrolled patients ≥18 years old, the pivotal trials of abrocitinib (JADE MONO-1 and JADE MONO-2) and the pivotal trials for upadacitinib (MEASURE UP 1, MEASURE UP 2, and AD-UP) enrolled patients ≥12 years old. In order to analyze all trials in a comparable fashion in a single network, we searched for subgroup evidence stratified by age on these trials. We received confidential data from the manufacturers for trials where the subgroup data by age were not publicly presented.

Based on data availability, we developed quantitative, indirect comparisons of abrocitinib, baricitinib, upadacitinib, tralokinumab, and dupilumab using a Bayesian network meta-analysis (NMA) for IGA, EASI 50, EASI 75, EASI 90, and PP-NRS ≥4-point improvement at 12 and 16 weeks in patients ≥18 years old. The primary endpoints of the abrocitinib trials, JADE MONO-1, JADE MONO-2, and JADE COMPARE, were measured at 12 weeks, while the remaining trials' primary endpoints were measured at 16 weeks. IGA and PP-NRS ≥4-point outcomes were analyzed as dichotomous outcomes ("yes" or "no") using a binomial likelihood and log link. EASI outcomes were analyzed as ordered categorical data with up to four distinct groups: i.e., EASI<50, EASI 50, EASI 75, and EASI 90, representing a reduction in the Eczema Area Severity Index (EASI) of less than 50%, at least 50%, at least 75%, and at least 90% respectively. Using the EASI outcomes reported in studies, we created mutually exclusive groups by re-classifying the data as <50, 50-74, 75-89, ≥90. Therefore, a multinomial likelihood model with a probit link with methods from the National Institute for Health and Clinical Excellence Decision Support Unit was used.[136]

Given the expected differences in the clinical efficacy of treatment in the monotherapy trials and combination trials, separate networks of the monotherapy trials and combination trials were developed. We explored both random- and fixed-effects models for each network and compared the goodness of fit to the data. We considered the model with the lowest deviance information criterion (DIC) to have the "best" fit to the data. We used fixed-effects models for the NMAs of the combination trials, given the limited data available for each network. Adjusting for placebo response in an NMA design is frequently performed to control for differences in population characteristics and baseline risk. We considered placebo adjustment for all NMAs and reported results where the adjusted NMA model provided a better fit of the data. The model with placebo

adjustment was considered a better fit if the regression coefficient was statistically significant and there was a reduction in between-trial heterogeneity.

Binomial NMAs were conducted using the IndiRect NMA platform (CRG-EVERSANA, 2020™). Multinomial NMAs were conducted using JAGS software (version 4.3.0) via R using the R2jags package. For all analyses, we used noninformative prior distributions for all model parameters. We initially discarded the first 50,000 iterations as "burn-in" and base inferences on an additional 50,000 iterations using three chains. Convergence of chains was through visual examination of the Brook–Gelman–Rubin diagnostic and historical plots. League tables were presented for the treatment effects (RR of each drug versus each other and placebo, along with 95% credible intervals (95% CrI). Table D2.1 lists the NMAs we conducted and the details of the model, and Table X lists the trials included in our NMAs as well as reasons for exclusion of trials.

Table D2.1. NMAs Conducted & Presented

Outcome	Trial Type	Model	Number of trials
EASI	a) Monotherapy only b) Combination only	Multinomial with probit link	a) 15 b) 6
IGA	a) Monotherapy only b) Combination only	Binomial with log link	a) 14 b) 6
PP-NRS≥4-point	a) Monotherapy only b) Combination only	Binomial with log link	a) 14 b) 5

Table D2.2. Network Meta-Analysis Inputs for Monotherapy NMAs (All data inputs are in adults 18 and older)

Trial	Wk	Arm	IGA Response		PP-NRS≥4 Response		EASI Scores 50		75		90	
			N	n	N	n	N	n	N	n	N	n
JADE MONO-1	12	ABRO 200 mg	120	58	121	68	153	116	120	78	153	59
		ABRO 100 mg	122	28	122	44	156	90	122	47	156	29
		PBO	60	4	60	11	76	17	60	7	76	4
JADE MONO-2	12	ABRO 200 mg	140	53	140	75	154	123	139	85	154	58
		ABRO 100 mg	139	42	141	67	155	106	139	62	155	37
		PBO	70	7	70	8	77	15	70	8	77	3
Gooderham 2019	12	ABRO 200 mg	48	21	44	28	48	38	48	31	48	21
		ABRO 100 mg	54	16	50	25	54	30	54	22	54	14
		PRO	52	3	51	13	52	14	52	8	52	5
ECZTRA 1	16	TRA 300 mg	601	95	594	119	601	250	601	150	601	87
		PBO	197	14	194	20	197	42	197	25	197	8
ECZTRA 2	16	TRA 300 mg	591	131	575	144	591	295	591	196	591	108
		PBO	201	22	200	19	201	41	201	23	201	11
MEASURE UP 1	16	UPA 30 mg	243	148	238	145	285	244	243	192	285	188
		UPA 15 mg	239	119	234	125	281	217	239	166	281	149
		PBO	241	21	233	26	281	83	241	43	281	22
MEASURE UP 2	16	UPA 30 mg	247	125	246	150	282	232	247	180	282	163
		UPA 15 mg	243	93	240	103	276	206	243	144	276	116
		PBO	242	12	238	24	278	79	242	32	278	14
Heads Up	16	UPA 30 mg	NR	NR	340	188	348	276	348	247	348	211
		DUP 300 mg	NR	NR	336	120	344	248	344	210	344	133
Guttman-Yassky 2020	16	UPA 30 mg	42	21	36	19	42	35	42	29	42	21
		UPA 15 mg	42	13	32	19	42	30	42	22	42	11
		PBO	41	1	35	2	41	9	41	4	41	1
BREEZE-AD 1	16	BARI 2 mg	123	14	100	12	123	37	123	23	123	13
		BARI 1 mg	127	15	105	11	127	32	127	22	127	11
		PBO	249	12	222	16	249	38	249	22	249	12
BREEZE-AD 2	16	BARI 2 mg	123	13	106	16	123	34	123	22	123	11
		BARI 1 mg	125	11	100	6	125	23	125	16	125	8
		PBO	244	11	213	10	244	30	244	15	244	6
BREEZE-AD 5	16	BARI 2 mg	146	35	131	33	146	51	146	43	146	30
		BARI 1 mg	147	19	132	21	147	29	147	19	147	11
		PBO	147	8	123	7	147	19	147	12	147	5
SOLO 1	16	DUP 300 mg Q2W	244	85	213	87	224	154	224	115	224	80
		PBO	224	23	212	26	224	55	224	33	224	17
SOLO 2	16	DUP 300 mg Q2W	233	84	225	81	233	152	233	103	233	70

Trial	Wk	Arm	IGA Response		PP-NRS≥4 Response		EASI Scores 50		75		90	
			N	n	N	n	N	n	N	n	N	n
		PBO	236	20	221	21	236	52	236	28	236	17
THACI 2016	16	DUP 300 mg Q2W	64	19	NR	NR	64	50	64	34	64	19
		PBO	61	1	NR	NR	61	18	61	7	61	2

ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, N: total number, NR: not reported, Q2W: every two weeks, TCS: topical corticosteroid, TRA: tralokinumab, UPA: upadacitinib, Wk: week

Table D2.3. Network Meta-Analysis Inputs for Combination Therapy NMAs (All data inputs are in adults 18 and older)

Trial	Wk	Arm	IGA Response		PP-NRS≥4 Response		EASI Scores 50		75		90	
			N	n	N	n	N	n	N	n	N	n
JADE COMPARE*	16	ABRO 200 mg	221	105	172	108	221	193	221	157	221	108
		ABRO 100 mg	230	80	168	79	229	186	229	138	229	87
		DUP 300 mg	232	90	189	108	232	195	232	152	232	90
		PBO	124	16	94	27	124	71	124	38	124	14
ECZTRA 3*	16	TRA 300 mg + TCS	252	98	249	113	252	200	252	141	252	83
		PBO + TCS	126	33	126	43	126	73	126	45	126	27
AD-UP*	16	UPA 30 mg + TCS	260	150	258	168	297	262	260	201	297	187
		UPA 15 mg + TCS	261	107	252	134	300	244	261	172	300	128
		PBO + TCS	264	30	256	39	304	124	264	68	304	40
BREEZE-AD7*	16	BARI 2 mg + TCS	109	26	97	37	109	70	109	47	109	18
		PBO + TCS	109	16	104	21	109	45	109	25	109	15
Guttman-Yassky 2018*	16	BARI 2 mg + TCS	37	8	NR	NR	37	21	37	11	37	7
		PBO + TCS	49	4	NR	NR	49	18	49	10	49	3
LIBERTY AD CHRONOS*	16	DUP 300 mg Q2W + TCS	106	41	102	60	106	85	106	73	106	42
		PBO + TCS	315	39	299	59	315	118	315	73	315	35

ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, N: total number, NR: not reported, Q2W: every two weeks, TCS: topical corticosteroid, TRA: tralokinumab, UPA: upadacitinib, Wk: week

Figure D2.1. Network Figure. Monotherapy Trials

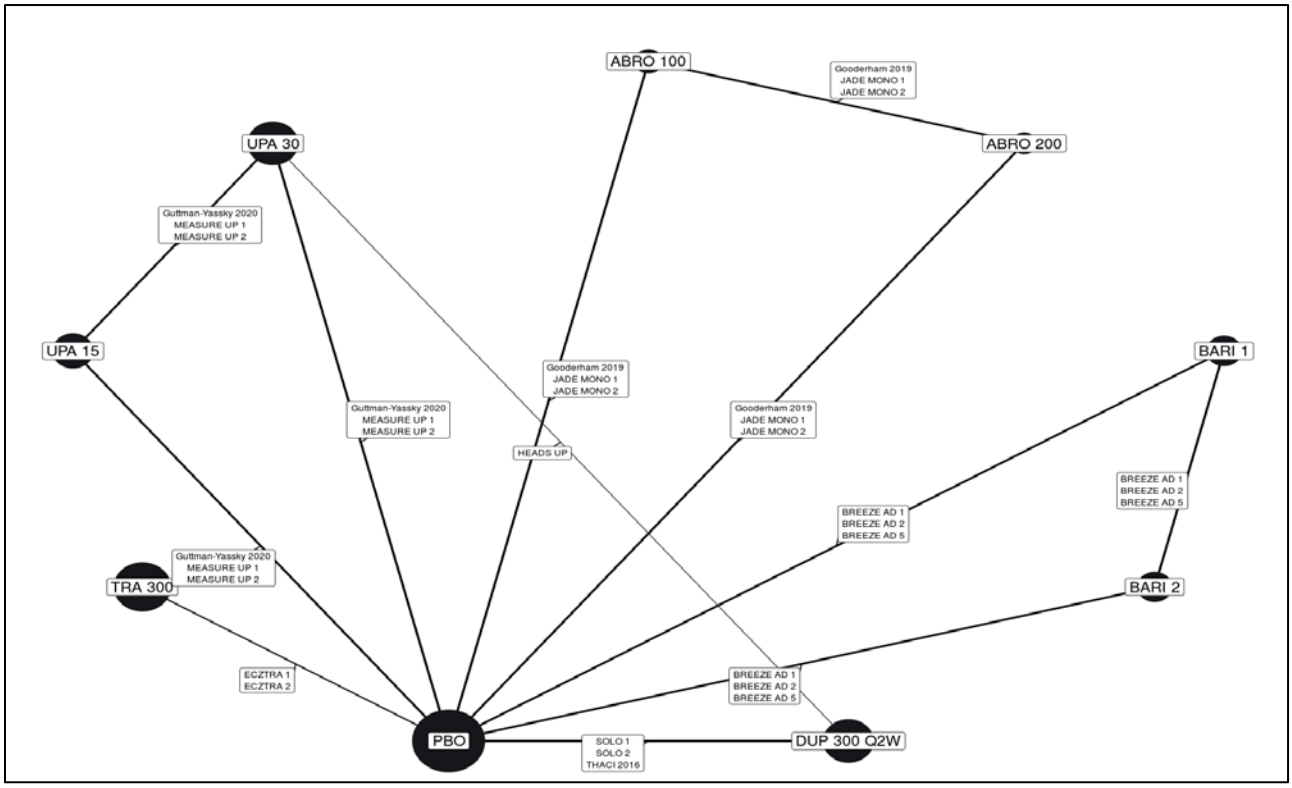
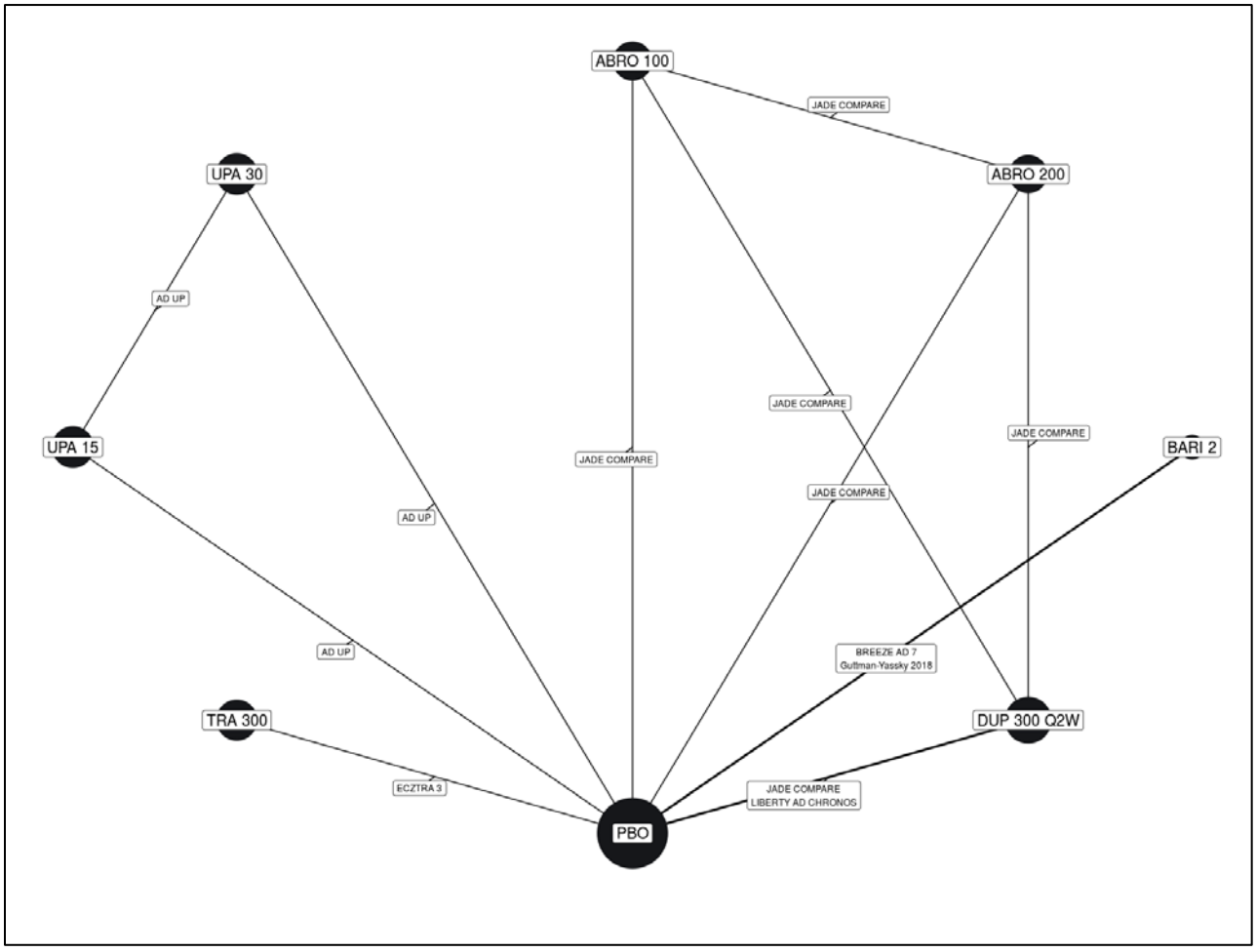


Figure D2.2. Network Figure. Combination Trials



Network Meta-Analysis Results: Monotherapy RCTs

For the EASI NMA, the unadjusted model (DIC: 195) was associated with improved fit compared to the adjusted model (DIC: 203); the estimated regression coefficient was not significant in the adjusted model (-0.33; 95% CrI: -1.18 to 0.54), and the interstudy SD with was increased in magnitude from 0.05 (95% CrI: 0.002–0.16) to 0.007 (95% CrI: 0.004–0.18) with placebo adjustment. For the IGA (DIC:231) and PP-NRS≥4-point improvement (DIC: 243) models, the unadjusted models were also associated with a better fit relative to the adjusted model (the interstudy SD followed a similar trend as presented for EASI model). Therefore, we presented the result of the unadjusted models for all outcomes.

EASI 50 (15 trials): Results were similar to EASI 75 and EASI 90 presented in the body of the report. All interventions showed statistically significantly greater EASI 50 responses than placebo and baricitinib 1 mg (Table D2.4). Upadacitinib 30 mg was more likely to achieve EASI 50 compared to dupilumab. However, there were no statistically significant differences with abrocitinib (both

doses) and upadacitinib 15 mg compared to dupilumab. In comparison, dupilumab showed a statistically significantly greater EASI 50 response than tralokinumab and baricitinib (both doses).

IGA (14 trials): Results were similar to EASI responses. All interventions showed statistically significantly higher efficacy on IGA, as defined in the trials, compared to placebo (Table D2.5). Upadacitinib 30 mg was more likely to achieve IGA response compared to all interventions. However, upadacitinib 30 mg was not statistically better than abrocitinib 200 mg. Additionally, there were no statistically significant differences with abrocitinib (both doses), upadacitinib 15 mg, and baricitinib 2 mg compared to dupilumab. In comparison, dupilumab showed statistically significantly greater IGA response compared to tralokinumab and baricitinib 1 mg.

PP-NRS≥4-point improvement (14 trials): While a clinically meaningful improvement in PP-NRS ranges from an improvement of 2-4-points, the available data for the interventions is almost entirely comprised of ≥4-point improvement. Apart from baricitinib 1 mg, the remaining interventions showed statistically significant responses compared to placebo (Table D2.6). Further, there was no statistically significant differences between abrocitinib (both doses), baricitinib 2mg, tralokinumab, upadacitinib (both doses) compared to dupilumab.

Table D2.4. Relative Risks for EASI 50 in Monotherapy RCTs in Adults

UPA 30 mg								
1.10 (0.98-1.26)	ABRO 200 mg							
1.14 (1.07-1.24)	1.04 (0.90-1.19)	UPA 15 mg						
1.25 (1.15-1.36)	1.14 (0.98-1.30)	1.09 (0.98-1.22)	DUP 300mg					
1.45 (1.22-1.77)	1.32 (1.17-1.52)	1.27 (1.05-1.56)	1.16 (0.97-1.44)	ABRO 100 mg				
1.75 (1.50-2.10)	1.59 (1.31-1.95)	1.53 (1.29-1.84)	1.40 (1.18-1.69)	1.21 (0.95-1.53)	TRA 300 mg			
1.81 (1.53-2.20)	1.64 (1.34-2.02)	1.58 (1.32-1.93)	1.45 (1.20-1.77)	1.25 (0.97-1.59)	1.03 (0.82-1.30)	BARI 2 mg		
2.54 (2.04-3.23)	2.31 (1.80-2.98)	2.22 (1.77-2.85)	2.03 (1.61-2.60)	1.75 (1.31-2.31)	1.45 (1.10-1.91)	1.40 (1.15-1.73)	BARI 1 mg	
3.74 (3.46-4.05)	3.40 (2.98-3.82)	3.26 (2.97-3.58)	2.99 (2.71-3.29)	2.58 (2.12-3.04)	2.14 (1.80-2.47)	2.07 (1.72-2.43)	1.47 (1.17-1.82)	PBO

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

Table D2.5. Relative Risks for IGA in Monotherapy RCTs in Adults

UPA 30 mg								
1.29 (1.09 -1.57)	UPA 15 mg							
1.44 (0.95-2.26)	1.12 (0.7-1.8)	ABRO 200 mg						
1.85 (1.28-2.64)	1.43 (0.94-2.11)	1.29 (0.77-2.06)	DUP 300mg					
2.33 (1.4-3.98)	1.8 (1.04-3.18)	1.61 (1.21-2.19)	1.26 (0.72-2.28)	ABRO 100 mg				
2.96-1.89-4.73)	2.29 (1.41-3.72)	2.06 (1.12-3.67)	1.6 (0.97-2.75)	1.28 (0.65-2.45)	BARI 2 mg			
3.97 (2.54-6.31)	3.07 (1.88-4.99)	2.75 (1.54-4.94)	2.15 (1.31-3.6)	1.7 (0.89-3.28)	1.34 (0.74-2.42)	TRA 300 mg		
4.08 (2.48-6.69)	3.16 (1.86-5.29)	2.83 (1.5-5.26)	2.2 (1.28-3.89)	1.75 (0.87-3.53)	1.37 (0.92-2.06)	1.03 (0.55-1.9)	BARI 1 mg	
8.77 (6.81-11.17)	6.78 (5.02-8.99)	6.07 (3.89-9.14)	4.72 (3.49-6.64)	3.77 (2.21-6.23)	2.95 (1.92-4.51)	2.2 (1.47-3.3)	2.16 (1.35-3.4)	PBO

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

Table D2.6. Relative Risks for PP-NRS≥4-point improvement in Placebo-controlled Monotherapy Trials in Adults

UPA 30 mg								
1.02 (0.71-1.56)	DUP 300mg							
1.1 (0.78-1.56)	1.08 (0.65-1.69)	UPA 15 mg						
1.19 (0.72-2.1)	1.17 (0.67-2.04)	1.09 (0.63-1.97)	ABRO 200 mg					
1.68 (0.95-3.2)	1.65 (0.88-3.11)	1.53 (0.83-3.02)	1.4 (0.92-2.23)	ABRO 100 mg				
1.87 (1.03-3.59)	1.83 (0.96-3.53)	1.7 (0.91-3.39)	1.56 (0.79-3.16)	1.11 (0.52-2.36)	BARI 2 mg			
2.16 (1.14-4.58)	2.12 (1.06-4.43)	1.97 (1.01-4.28)	1.81 (0.87-3.95)	1.29 (0.58-2.94)	1.16 (0.52-2.68)	TRA 300		
2.94 (1.5-6.18)	2.87 (1.4-6.03)	2.67 (1.32-5.78)	2.45 (1.14-5.38)	1.75 (0.77-4.02)	1.57 (0.88-2.86)	1.35 (0.55-3.29)	BARI 1 mg	
4.99 (3.5-6.85)	4.89 (3.22-6.72)	4.54 (2.99-6.58)	4.18 (2.54-6.22)	2.96 (1.66-4.83)	2.66 (1.47-4.44)	2.29 (1.17-4.08)	1.69 (0.86-3.11)	PBO

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

Network Meta-Analysis Results: Combination RCTs

Choice of Model: As noted above, we presented the results of the fixed-effect model for the combination therapy NMAs given the limited number of studies available for this network. Model fit information presented in Table D2.7 shows that the fixed effect models fit equally well or better compared to the random-effect model.

NMA Results: In general, the results for the combination therapy NMAs, provided more conservative estimates of the relative efficacies of these drugs versus placebo, although they followed a similar ranking order as the monotherapy NMAs. All interventions showed statistically significantly greater responses than placebo on all outcomes (Table D2.9 – D2.13). Table D2.8 presents the expected proportions of patients that achieved EASI 50,75 and 90 for each intervention.

Table D2.7. Model fit information on Combination therapy NMAs

Model Fit	Fixed effect Model	Random effect Model
EASI (multinomial model)		
Deviance Information Criterion (DIC)	79.8	79.6
Total Residual Deviance (vs. 60 data points)	64.9	63.3
IGA (binomial model)		
Deviance Information Criterion (DIC)	103.3	104.9
Total Residual Deviance (vs. 15 data points)	13.6	14.2
PP-NRS≥4-point improvement		
Deviance Information Criterion (DIC)	96.8	96.8
Total Residual Deviance (vs. 13 data points)	14	14

Table D2.8 NMA Results. Proportions of patients achieving EASI 50, 75, and 90 thresholds in Combination RCTs.

Treatment	EASI 50	EASI 75	EASI 90
	Median proportion (95% CrI)		
Placebo	0.44 (0.41 – 0.47)	0.24 (0.22 – 0.27)	0.10 (0.09 – 0.12)
Dupilumab 300 mg Q2W	0.79 (0.73 – 0.84)	0.61 (0.54 – 0.68)	0.39 (0.32 – 0.46)
Abrocitinib 100 mg	0.75 (0.68 – 0.82)	0.56 (0.47 – 0.65)	0.34 (0.26 – 0.43)
Abrocitinib 200 mg	0.83 (0.77 – 0.88)	0.66 (0.58 – 0.74)	0.44 (0.35 – 0.54)
Baricitinib 2 mg	0.62 (0.52 -0.72)	0.41 (0.31 – 0.52)	0.21 (0.14 – 0.30)
Tralokinumab 300 mg	0.63 (0.53 – 0.72)	0.42 (0.33 – 0.52)	0.22 (0.15 – 0.30)
Upadacitinib 15 mg	0.83 (0.77 – 0.88)	0.67 (0.59 – 0.74)	0.44 (0.36 – 0.53)
Upadacitinib 30 mg	0.91 (0.87 – 0.94)	0.80 (0.73 – 0.85)	0.60 (0.52 – 0.69)

Table D2.9. Relative Risks for EASI 50 in Combination RCTs in Adults

UPA 30 mg							
1.10 (1.02-1.19)	ABRO 200 mg						
1.10 (1.05-1.16)	1.00 (0.91-1.09)	UPA 15 mg					
1.15 (1.07-1.25)	1.05 (0.98-1.12)	1.05 (0.96-1.14)	DUP 300mg				
1.21 (1.11-1.35)	1.10 (1.02-1.20)	1.10 (1.00-1.24)	1.05 (0.98-1.14)	ABRO 100 mg			
1.45 (1.27-1.71)	1.32 (1.14-1.57)	1.32 (1.15-1.57)	1.26 (1.09-1.49)	1.20 (1.02-1.43)	TRA 300 mg		
1.47 (1.27-1.76	1.33 (1.14-1.61)	1.33 (1.15-1.61)	1.27 (1.09-1.54)	1.21 (1.02-1.48)	1.01 (0.82-1.26)	BARI 2 mg	
2.09 (1.96-2.25)	1.91 (1.75-2.06)	1.91 (1.77-2.06)	1.82 (1.68-1.96)	1.73 (1.56-1.90)	1.44 (1.23-1.64)	1.43 (1.20-1.65)	PBO

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

Table D2.10. Relative Risks for EASI 75 in Combination RCTs in Adults

UPA 30 mg							
1.20 (1.05-1.38)	ABRO 200 mg						
1.20 (1.09-1.32)	1.00 (0.85-1.17)	UPA 15 mg					
1.30 (1.14-1.49)	1.09 (0.97-1.22)	1.09 (0.93-1.26)	DUP 300mg				
1.42 (1.21-1.69)	1.18 (1.04-1.36)	1.18 (0.99-1.43)	1.09 (0.96-1.25)	ABRO 100 mg			
1.90 (1.53-2.45)	1.58 (1.25-2.07)	1.58 (1.26-2.07)	1.46 (1.15-1.90)	1.34 (1.03-1.76)	TRA 300 mg		
1.93 (1.52-2.55)	1.60 (1.25-2.15)	1.61 (1.26-2.15)	1.47 (1.15-1.97)	1.36 (1.04-1.84)	1.01 (0.73-1.42)	BARI 2 mg	
3.26 (2.91-3.65)	2.72 (2.35-3.11)	2.72 (2.39-3.09)	2.50 (2.21-2.83)	2.30 (1.94-2.68)	1.72 (1.35-2.11)	1.69 (1.30-2.12)	PBO

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

Table D2.11. Relative Risks for EASI 90 in Combination RCTs in Adults

UPA 30 mg							
1.36 (1.06-1.72)	ABRO 200 mg						
1.36 (1.17-1.60)	1.00 (0.77-1.29)	UPA 15 mg					
1.56 (1.25-1.94)	1.14 (0.95-1.37)	1.15 (0.90-1.45)	DUP 300mg				
1.77 (1.37-2.34)	1.30 (1.07-1.61)	1.30 (0.99-1.76)	1.14 (0.93-1.41)	ABRO 100 mg			
2.74 (1.98-3.97)	2.01 (1.41-2.98)	2.01 (1.43-2.96)	1.76 (1.24-2.57)	1.54 (1.05-2.31)	TRA 300 mg		
2.80 (1.97-4.20)	2.05 (1.41-3.15)	2.06 (1.42-3.11)	1.79 (1.24-2.71)	1.58 (1.06-2.45)	1.02 (0.64- 1.66)	BARI 2 mg	
5.82 (4.90-6.94)	4.29 (3.43-5.27)	4.29 (3.52-5.21)	3.74 (3.09-4.51)	3.28 (2.55-4.16)	2.13 (1.51-2.88)	2.08 (1.43-2.88)	PBO

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

Table D2.12. Relative Risks for IGA response in Combination RCTs in Adults

UPA 30 mg							
1.26 (0.95-1.71)	ABRO 200 mg						
1.36 (1.15-1.63)	1.08 (0.76-1.52)	UPA 15 mg					
1.53 (1.15-2.04)	1.21 (1-1.47)	1.13 (0.8-1.57)	DUP 300mg				
1.7 (1.23-2.43)	1.35 (1.09-1.7)	1.25 (0.86-1.85)	1.11 (0.89-1.42)	ABRO 100 mg			
2.54 (1.62-4.08)	2.01 (1.23-3.36)	1.87 (1.13-3.12)	1.66 (1.02-2.78)	1.49 (0.87-2.59)	BARI 2 mg		
2.83 (1.9-4.27)	2.24 (1.44-3.49)	2.08 (1.35-3.25)	1.85 (1.2-2.88)	1.66 (1.02-2.68)	1.11 (0.62-2.01)	TRA 300 mg	
4.61 (3.68-5.75)	3.65 (2.76-4.78)	3.39 (2.57-4.42)	3.02 (2.32-3.9)	2.71 (1.94-3.69)	1.82 (1.12-2.88)	1.63 (1.11-2.35)	PBO

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

Table D2.13. Relative Risks for PP-NRS≥4-point improvement in Combination RCTs in Adults

UPA 30 mg							
1.16 (1.04-1.31)	ABRO 200 mg						
1.24 (1.01-1.56)	1.07 (0.85-1.37)	UPA 15 mg					
1.32 (1.1-1.6)	1.14 (0.91-1.41)	1.06 (0.89-1.25)	DUP 300mg				
1.69 (1.3-2.26)	1.46 (1.09-1.99)	1.36 (1.1-1.71)	1.28 (1.04-1.61)	ABRO 100 mg			
1.81 (1.29-2.7)	1.56 (1.08-2.35)	1.45 (0.98-2.24)	1.37 (0.94-2.09)	1.07 (0.69-1.71)	BARI 2 mg		
2.37 (1.75-3.29)	2.04 (1.47-2.89)	1.91 (1.34-2.74)	1.79 (1.28-2.55)	1.4 (0.93-2.1)	1.31 (0.8-2.1)	TRA 300 mg	
3.36 (2.86-3.95)	2.89 (2.39-3.48)	2.7 (2.13-3.35)	2.54 (2.09-3.07)	1.99 (1.48-2.6)	1.86 (1.23-2.66)	1.42 (1.03-1.91)	PBO

Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in grey signify that the 95% credible interval does not contain one. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, PBO: placebo, TRA: tralokinumab, UPA: upadacitinib, Q2W: every two weeks

D3. Additional Clinical Evidence

This section starts by providing additional clinical evidence for patients with moderate-to-severe atopic dermatitis presented by drug. Evidence is first presented for adults and then for adolescents and children. Next, we provide additional clinical evidence for patients with mild-to-moderate atopic dermatitis in short-term placebo-controlled trials of adults and adolescents. At the time of this report, no long-term evidence for ruxolitinib cream was identified.

Moderate-to-Severe Population

Adults

Abrocitinib

Two placebo-controlled monotherapy trials of abrocitinib enrolled patients ≥12 years old (JADE MONO-1 & 2). [35,36] Results of the subgroup of patients ≥18 years old in these trials (74%-85% of the trial population) showed that 61%-65% of patients achieved EASI 75 with abrocitinib 200 mg, compared to 11%-12% in the placebo arms of those trials. [35,36] [35,36] In this subgroup of patients, 39%-45% achieved EASI 75 with abrocitinib 100 mg. The percentages of patients in this subgroup that achieved IGA response with abrocitinib 200 mg were 38%-48%, 23%-30% with abrocitinib 100 mg, and 7%-10% with placebo.

As described in the report, one trial compared abrocitinib 200 mg, abrocitinib 100 mg, dupilumab, and placebo in adult patients also treated with topical corticosteroids (JADE COMPARE). [37] While results at 12 weeks are described in the report, results at 16 weeks are presented here. The percentage of patients achieving EASI 75 with abrocitinib 200 mg was 71% compared with 60% with abrocitinib 100 mg, 66% with dupilumab, and 31% with placebo. [37] The percentage of patients achieving IGA with abrocitinib 200 mg was 48% compared with 35% with abrocitinib 100 mg, 39% with dupilumab, and 13% with placebo. [37] There were no statistically significant differences in EASI 75 and IGA response between the abrocitinib arms and dupilumab at 16 weeks. [37]

We identified one long-term trial of abrocitinib (JADE EXTEND).[76] JADE EXTEND is an ongoing, open-label extension study that evaluated continuous treatment with abrocitinib 100 mg or abrocitinib 200 mg in adults with moderate to severe atopic dermatitis who had participated in previous abrocitinib trials (JADE MONO-1, JADE MONO-2, JADE COMPARE). Results at week 48 showed the response rates on IGA (200 mg: 40%, 100 mg: 29%) and EASI 75 (200 mg: 62%, 100 mg: 46%) were sustained.

Baricitinib

We identified two long-term trials of baricitinib (BREEZE-AD3 and BREEZE-AD6). BREEZE-AD3 was a four-year blinded extension trial in which patients who achieved at least a partial response (IGA score of ≥2) at 16 weeks in originating trials were continued on baricitinib 2 mg for at least 52 weeks for a total of 68 weeks of continuous treatment. Week 68 results obtained from the manufacturer as academic-in-confidence suggest maintenance of EASI 75 and IGA response at 68 weeks. [43,44]

BREEZE-AD6 is an ongoing, 52-week, open-label, single-arm extension study that evaluated the long-term efficacy of continuous treatment with baricitinib 2 mg in adults with moderate to severe atopic dermatitis classified as non-responders or partial responders at week-16 in BREEZE-AD5 RCT.[82] The use of topical corticosteroids was permitted after Week 16 in BREEZE-AD5 and throughout BREEZE-AD6.[82] Results showed some improvement in EASI 75, IGA, and DLQI≤5 responses at 52 weeks (EASI: 49%, IGA:31%, DLQI≤5: 45%) compared to week 16 (EASI: 40%, IGA:27%, DLQI≤5: 45%).[82]

Tralokinumab

In the two placebo-controlled monotherapy trials of tralokinumab (ECZTRA 1 and 2), patients were followed up for 52 weeks.[63] After the 16-week initial treatment periods of ECZTRA 1 and 2, patients who achieved response (IGA score of 0 or 1 or EASI 75) were rerandomized to tralokinumab 300 every two weeks or every four weeks, or placebo for a 36-week maintenance period. Results are presented in Table D3.3 below.

In ECZTRA 3, the placebo-controlled trial of tralokinumab conducted in patients treated with topical corticosteroids, patients were followed up for 32 weeks.[64] Similar to ECZTRA 1 and 2, patients who achieved response (IGA score of 0 or 1 or EASI 75) at 16 weeks in ECZTRA 3 were rerandomized and followed up to the end of the study. Results are presented in Table D3.3 below.

In addition, we identified one 268-week ongoing, open-label, single-arm extension study of tralokinumab (ECZTEND).[78] ECZTEND evaluated the efficacy of continuous treatment with tralokinumab in adults with moderate to severe atopic dermatitis who had participated in previous tralokinumab trials (ECZTRA 1, 2,3, and 5). Interim results at week 56 showed the response rates on IGA (41.7%), EASI 50 (79.7%), EASI 75 (68.4%), and EASI 90 (51.1%) were sustained.[78] Safety events were consistent with what was observed in the originating trials.

Upadacitinib

Two placebo-controlled monotherapy trials of upadacitinib (MEASURE UP 1 &2) and one placebo-controlled combination trial (AD-UP) of upadacitinib enrolled patients ≥12 years old. [81] [80] In the

monotherapy trials, the EASI and IGA responses in the subgroup of patients ≥18 years old were consistent with what was observed in the overall population. At week 16, 72%-79% of patients in the subgroup of patients ≥18 years old EASI 75 with upadacitinib 30 mg, compared to 13%-17% in the placebo arms of those trials.[79] In this subgroup of patients, 59%-69% achieved EASI 75 with upadacitinib 15 mg.[79] The percentages of patients in this subgroup that achieved IGA response with upadacitinib 30 mg were 51%-61%, 38%-50% with upadacitinib 15 mg, and 5%-9% with placebo.[79]

Similarly, in the combination trial that compared upadacitinib to placebo in patients also treated with topical corticosteroids, the EASI and IGA responses in the subgroup of patients ≥18 years old were consistent with what was observed in the overall population.[81] At week 16, the percentage of patients achieving EASI 75 in the subgroup of patients ≥18 years old with upadacitinib 30 mg was 77% compared with 66% with upadacitinib 15 mg and 26% with placebo.[79] IGA response was achieved by 58% of patients with upadacitinib 30 mg, 41% with upadacitinib 15 mg, and 11% with placebo.[79]

Dupilumab

We identified two long-term Phase III trials of dupilumab (LIBERTY AD SOLO-CONTINUE and LIBERTY AD CHRONOS). In LIBERTY AD SOLO-CONTINUE, dupilumab was compared to placebo. LIBERTY AD CHRONO is a combination trial that compared dupilumab plus topical corticosteroid to topical corticosteroid alone. In both trials, patients who achieved response (IGA score of 0 or 1 or EASI 75) at 16 weeks in the originating trials were rerandomized to dupilumab 300 mg weekly, every two weeks, every four weeks, or every eight weeks, or placebo for 36 weeks. After completion, patients were followed up for up to 12 weeks or enrolled in an open-label extension (OLE). Results of LIBERTY AD SOLO-CONTINUE and LIBERTY AD CHRONOS are presented in Table D3.3.

Additional Outcome Tables

Table D3.1 Key Outcomes in Placebo-controlled Monotherapy Trials in Adults

Trial	Arm	Timepoint	EASI 50	EASI 75	EASI 90	IGA	PP-NRS[†]	SCORAD[‡]
Abrocitinib								
JADE MONO-1[¥]	ABRO 200 mg	12 weeks	76.0	63.0	39.0	44.0	57.2	NR
	ABRO 100 mg		58.0	40.0	19.0	24.0	38.0	NR
	PBO		22.0	12.0	5.0	8.0	15.0	NR
JADE MONO-2[¥]	ABRO 200 mg	12 weeks	79.9	61.0	37.7	38.1	55.3	NR
	ABRO 100 mg		68.4	44.5	23.9	28.4	45.2	NR
	PBO		19.5	10.4	3.9	9.1	11.5	NR
Gooderham 2019	ABRO 200 mg	16 weeks	79.2	64.6	52.1	43.8	63.6	-69.7
	ABRO 100 mg		55.6	40.7	25.9	29.6	50.0	-49.2
	PBO		26.9	15.4	9.6	5.8	25.5	-29.0
Baricitinib								
BREEZE-AD 1	BARI 2 mg	16 weeks	30.1	18.7	10.6	11.4	12.0	-21.5
	BARI 1 mg		25.0	17.3	8.7	11.8	10.5	-18.9
	PBO		15.3	8.8	4.8	4.8	7.2	-13.4
BREEZE-AD 2	BARI 2 mg	16 weeks	27.6	17.9	8.9	10.6	15.1	-27.8
	BARI 1 mg		18.4	12.8	6.4	8.8	6.0	-20.2
	PBO		12.3	6.1	2.5	4.5	4.7	-13.4
BREEZE-AD 5	BARI 2 mg	16 weeks	34.9	29.5	20.5	24.0	25.2	NR
	BARI 1 mg		19.7	12.9	7.5	12.9	15.9	NR
	PBO		12.9	8.2	3.4	5.4	5.7	NR
Tralokinumab*								
ECZTRA 1	TRA 300 mg	16 weeks	41.6	25.0	14.5	15.8	20.0	-25.2
	PBO		21.3	12.7	4.1	7.1	10.3	-14.7
ECZTRA 2	TRA 300 mg	16 weeks	49.9	33.2	18.3	22.2	25.0	-28.1
	PBO		20.4	11.4	5.5	10.9	9.5	-14.0
Upadacitinib								
MEASURE UP 1[¥]	UPA 30 mg	16 weeks	NR	80.0	66.0	62.0	60.0	NR
	UPA 15 mg		NR	70.0	53.0	48.0	52.0	NR
	PBO		NR	16.0	8.0	8.0	12.0	NR
MEASURE UP 2[¥]	UPA 30 mg	16 weeks	NR	73.0	58.0	52.0	60.0	NR
	UPA 15 mg		NR	60.0	42.0	39.0	42.0	NR
	PBO		NR	13.0	5.0	5.0	9.0	NR
Heads Up	UPA 30 mg	16 weeks	NR	71	60.6	NR	55.3	NR
	DUP 300 mg		NR	61.1	38.7	NR	35.7	NR
Phase II Guttmann-Yassky 2020	UPA 30 mg	16 weeks	83.3	69.0	50.0	50.0	52.8	-60.4
	UPA 15 mg		71.4	52.4	26.2	31.0	59.4	-46.9
	PBO		22.0	9.8	2.4	2.4	5.7	-12.4
Dupilumab[¶]								
LIBERTY AD SOLO 1	DUP 300 mg Q2W	16 weeks	69.0	51.0	36.0	38.0	41.0	-57.7
	PBO		25.0	15.0	8.0	10.0	12.0	-29.0
	DUP 300 mg Q2W	16 weeks	65.0	44.0	30.0	36.0	36.0	-51.1

Trial	Arm	Timepoint	EASI 50	EASI 75	EASI 90	IGA	PP-NRS[†]	SCORAD[‡]
LIBERTY AD SOLO 2	PBO		22.0	12.0	7.0	8.0	10.0	-19.7
Thaci 2016	DUP 300 mg Q2W	16 weeks	78.0	52.8	29.8	30.0	NR	-51.2
	PBO		30.0	11.09	3.5	2.0	NR	-13.8

All values in the table are percentages. BARI 4 mg, DUP 300 mg QW, DUP 200 mg, and DUP 100 mg doses were excluded from the network meta-analyses. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, TRA: tralokinumab, UPA: upadacitinib. [†]PP-NRS ≥4, [‡]LSM change from baseline, *reported adjusted mean change from baseline in SCORAD, [¶]reported LSM percentage change from baseline in SCORAD, [ɣ]data were from patients ages 12 and older.

Table D3.2. Key Outcomes in Placebo-controlled Combination Trials in Adults (Short-term)

Trial	Arm	Timepoint	EASI 50	EASI 75	EASI 90	IGA	PP-NRS[†]	SCORAD[‡]
Abrocitinib								
JADE COMPARE	ABRO 200 mg + TCS	16 weeks	87.3	71	48.9	47.5	62.8	NR
	ABRO 100 mg + TCS		81.2	60.3	38	34.8	47.0	NR
	DUP 300 mg + TCS		84.1	65.5	38.8	38.8	57.1	NR
	PBO + TCS		57.3	30.6	11.3	12.9	28.7	NR
Baricitinib								
BREEZE-AD7	BARI 2 mg + TCS	16 weeks	64.2	43.1	16.5	23.9	38.1	-29.9
	PBO + TCS		41.3	22.9	13.8	14.7	20.2	-21.4
Guttman-Yassky 2018	BARI 2 mg + TCS	16 weeks	56.8	29.7	18.9	21.6	NR	-23.87
	PBO + TCS		36.7	20.4	6.1	8.2	NR	-11.89
Tralokinumab								
ECZTRA 3	TRA 300 mg + TCS	16 weeks	79.4	56.0	32.9	38.9	45.4	-37.7
	PBO + TCS		57.9	35.7	21.4	26.2	34.1	-26.8
Upadacitinib								
AD-UP[§]	UPA 30 mg + TCS	16 weeks	NR	77.0	NR	59.0	64.0	NR
	UPA 15 mg +TCS		NR	65.0	NR	40.0	52.0	NR
	PBO + TCS		NR	26.0	NR	11.0	15.0	NR
Dupilumab								
LIBERTY AD CHRONOS	DUP 300 mg + TCS	16 weeks	80.0	69.0	40.0	39.0	59.0	-62.1
	PBO + TCS		37.0	23.0	11.0	12.0	20.0	-31.8

All values in the table are percentages. BARI 4 mg, DUP 300 mg QW, DUP 200 mg, and DUP 100 mg doses were excluded from the NMA. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, TRA: tralokinumab, TCS: topical corticosteroids, UPA: upadacitinib. [†]PP-NRS ≥4, [‡]LSM change from baseline, *reported adjusted mean change from baseline in SCORAD, [§]results are from patients ages 12 and older, [¶]reported LSM percentage change from baseline in SCORAD.

Table D3.3. Key Outcomes in Long-term Comparative Trials

Trial	Arm	Timepoint	EASI 50	EASI 75	EASI 90	IGA	PP-NRS[†]	SCORAD[‡]
Tralokinumab								
ECZTRA 1	TRA 300 mg Q2W	52 weeks[§]	NR	59.6	NR	51.3	NR	NR
	TRA 300 mg Q4W		NR	49.1	NR	38.9	NR	NR
	PBO		NR	33.3	NR	47.4	NR	NR
ECZTRA 2	TRA 300 mg Q2W	52 weeks[§]	NR	55.8	NR	59.3	NR	NR
	TRA 300 mg Q4W		NR	51.4	NR	44.9	NR	NR
	PBO		NR	21.4	NR	25	NR	NR
ECZTRA 3	TRA 300 mg Q2W + TCS (non-responders)	32 weeks	NR	55.8	NR	30.5	NR	NR
	TRA 300 mg Q2W +TCS (TRA responders)		98.6	92.5	72.5	89.6	NR	NR
	TRA 300 mg Q4W + TCS (TRA responders)		91.3	90.8	63.8	77.6	NR	NR
Dupilumab								
AD SOLO 1-CONTINUE	DUP 300 mg Q2W or QW	36 weeks	39.8	30.4	18.2	14.3	12.8	-2.7
	PBO		73.4	71.6	64.7	54.0	49.1	-4.3
LIBERTY AD CHRONOS	DUP 300 mg + TCS Q2W	52 weeks	79	65	51	36	51	-66.2
	PBO + TCS		30	22	16	13	13	-34.1

All values in the table are percentages. Includes trials only in adults 18 and older. DUP 300 mg QW + TCS dose was excluded from the table. DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, TCS: topical corticosteroids, TRA: tralokinumab. [†]PP-NRS ≥4, [‡]LSM change from baseline, [¶]reported LSM percentage change from baseline in SCORAD.

Harms

Summaries of the harms are provided in Section 3.2 of the Report. Tables presenting key harms from the short-term RCTs are presented in Tables 3.4 and 3.5. For responders in re-randomized long-term monotherapy trials (Table D3.6), harms were uncommon though slightly more patients on active treatment discontinued therapy due to side effects. Additional reports of conjunctivitis and herpetic infections were similar among those receiving active therapy or placebo. For patients in long-term combination trials (Table D3.7), harms leading to discontinuation were uncommon and similar or slightly higher for patients receiving placebo. Other adverse effects were also similar among treatment arms.

Table D3.4. Key Harms in Placebo-controlled Monotherapy Trials of Adults (Short-term)

Trial	Arm	Timepoint	Any AEs	TEAEs	D/C Due to AE	SAE	Conjunctivitis	Nausea	Herpetic Infection
Abrocitinib									
JADE MONO-1[§]	ABRO 200 mg	12 weeks	78	NR	6	3	2.6	20.0	3.9[¥]
	ABRO 100 mg		69	NR	6	3	2.6	9.0	4.5[¥]
	PBO		57	NR	9	4	0	3.0	1.3[¥]
JADE MONO-2[§]	ABRO 200 mg	12 weeks	NR	65.8	3.2	1.3	NR	14.2	1.3[#]
	ABRO 100 mg		NR	62.7	3.8	3.2	NR	7.6	1.3[#]
	PBO		NR	53.8	12.8	1.3	NR	2.6	1.3[#]
Gooderham 2019	ABRO 200 mg	16 weeks	NR	68.9	16.5	3.6	NR	14.5	0**
	ABRO 100 mg		NR			5.4	NR	1.8	3.6**
	PBO		NR			3.6	NR	1.8	2.8**
Baricitinib									
BREEZE-AD1	BARI 2 mg	16 weeks	NR	NR	0.8	0	1.6*	NR	3.3[††]
	BARI 1 mg		NR	NR	1.6	0.8	0.8*	NR	5.5[††]
	PBO		NR	NR	1.6	2.4	1.6*	NR	1.2[††]
BREEZE-AD2	BARI 2 mg	16 weeks	NR	NR	2.4	2.4	1.6*	NR	5.7[††]
	BARI 1 mg		NR	NR	5.6	7.3	4.8*	NR	4.8[††]
	PBO		NR	NR	0.8	3.7	0.8*	NR	4.5[††]
BREEZE-AD5	BARI 2 mg	16 weeks	NR	NR	2.8	1.4	NR	3.4	1.4[‡‡]
	BARI 1 mg		NR	NR	2.7	0.7	NR	2.0	2.7[‡‡]
	PBO		NR	NR	2.7	2.1	NR	2.1	0.6[‡‡]
Tralokinumab									
ECZTRA 1	TRA 300 mg	16 weeks	76.4	NR	3.3	3.8	7.1[†]	NR	0.5[¶¶]
	PBO		77	NR	4.1	4.1	2[†]	NR	1[¶¶]
ECZTRA 2	TRA 300 mg	16 weeks	61.5	NR	1.5	1.7	3[†]	NR	0.3[¶¶]
	PBO		66	NR	1.5	2.5	1.5[†]	NR	2.5[¶¶]
Upadacitinib									
MEASURE UP 1[§]	UPA 30 mg	16 weeks	NR	NR	NR	2.8	NR	3.5	4[¥¥]
	UPA 15 mg		NR	NR	NR	2.1	NR		
	PBO		NR	NR	NR	2.8	NR		0[¥¥]
MEASURE UP 2[§]	UPA 30 mg	16 weeks	NR	NR	NR	2.5	NR		2[¥¥]
	UPA 15 mg		NR	NR	NR	1.8	NR		1[¥¥]
	PBO		NR	NR	NR	2.9	NR		2[¥¥]
Phase II Guttmann-Yassky 2020	UPA 30 mg	16 weeks	76	NR	4.8	0	NR	7.1	0[¥¥]
	UPA 15 mg		63	NR	7.5	2.4	NR	2.5	0[¥¥]
	PBO		79	NR	9.5	2.5	NR	1.4	0[¥¥]
Dupilumab									

Trial	Arm	Timepoint	Any AEs	TEAEs	D/C Due to AE	SAE	Conjunctivitis	Nausea	Herpetic Infection
LIBERTY AD SOLO 1	DUP 300 mg Q2W	16 weeks	73	NR	2	3	4.8[‡]	NR	7[##]
	PBO		65	NR	1	5	0.9[‡]		4[##]
LIBERTY AD SOLO 2	DUP 300 mg Q2W	16 weeks	65	NR	1	13	3.8[‡]		4[##]
	PBO		72	NR	2	2	0.4[‡]		3[##]
Thaci 2016	DUP 300 mg Q2W	16 weeks	NR	78	6	NR	5[¶]	2	8[¥]
	PBO		NR	80	5	NR	3[¶]	7	2[¥]

All values in the table are percentages. AE: adverse event, D/C: discontinuation, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, SAE: serious adverse event, TEAE: treatment-emergent adverse event. [§]results are from patients ages 12 and older, *conjunctivitis/keratitis, [†]conjunctivitis, conjunctivitis bacterial, conjunctivitis viral and conjunctivitis allergic, [‡]conjunctivitis of unspecified cause, allergic, bacterial and viral conjunctivitis, and atopic keratoconjunctivitis, [¶]conjunctival infections, irritations, and inflammation, [¥]oral herpes, herpes simplex, eczema herpeticum, herpes virus infection, and herpes zoster, [#]eczema herpeticum and herpes zoster, **eczema herpeticum and treatment-emergent herpes simplex, [††]herpes simplex, [‡‡]herpes zoster and herpes simplex, [¶¶]eczema herpeticum, [¥¥]herpes zoster, [##]herpes viral infection, including oral herpes, herpes simplex, eczema herpeticum, herpes virus infection, herpes zoster, ophthalmic herpes simplex, genital herpes, herpes ophthalmic, and herpes simplex otitis externa.

Table D3.5. Key Harms in Placebo-controlled Combination Trials of Adults (Short-term)

Trial	Arm	Timepoint	Any AEs	TEAEs	D/C due to AEs/TEAEs	SAE	Conjunctivitis	Nausea	Herpetic Infection
Abrocitinib									
JADE COMPARE	ABRO 200 mg	16 weeks	61.9	NR	4.4	0.9	1.3	11.1	1.8
	ABRO 100 mg		50.8	NR	2.5	2.5	0.8	4.2	0.8
	DUP 300 mg		50	NR	3.3	0.8	6.2	2.9	0
	PBO		53.4	NR	3.8	3.8	2.3	1.5	0
Baricitinib									
BREEZE-AD7	BARI 2 mg + TCS	16 weeks	NR	56	0	1.8	NR	NR	6.4
	PBO + TCS		NR	38	0.9	3.7	NR	NR	3.7
Guttman-Yassky 2018	BARI 2 mg + TCS	16 weeks	NR	45.9	2.7	NR	0	NR	0
	PBO + TCS		NR	49	10.2	NR	2	NR	0
Tralokinumab									
ECZTRA 3	TRA 300 mg + TCS	16 weeks	71.4	NR	2.4	0.8	11.1	0	5‡
	PBO + TCS		66.7	NR	0.8	3.2	3.2	0.79	6‡
Upadacitinib									
AD-UP	UPA 30 mg + TCS	16 weeks	NR	NR	0	1.3	NR	NR	1.3
	UPA 15 mg + TCS		NR	NR	0	2.3	NR	NR	1
	PBO + TCS		NR	NR	0	3	NR	NR	NR

All values in the table are percentages. No short-term safety data available for BREEZE-AD7, Guttman-Yassky 2018, AD-UP, and LIBERTY AD CHRONOS. ABRO: abrocitinib, AE: adverse event, BARI: baricitinib, D/C: discontinuation, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, SAE: serious adverse event, TCS: topical corticosteroids, TEAE: treatment-emergent adverse event, TRA: tralokinumab, UPA: upadacitinib. ‡eczema herpeticum.

Table D3.6. Key Harms in Placebo-controlled Monotherapy Trials of Adults (Long-term)

Trial	Arm	Timepoint	Any AEs	TEAEs	D/C Due to AE	SAE	Conjunctivitis	Nausea	Herpetic Infection
Baricitinib									
BREEZE-AD3	BARI 2 mg	NR	NR	NR	NR	NR	NR	NR	NR
Tralokinumab									
ECZTRA 1	TRA 300 mg Q2W	36 weeks	79.4	NR	1.5	1.5	8.8*	NR	0.0‡
	TRA 300 mg Q4W		69.7	NR	1.3	3.9	6.6*	NR	0.0‡
	PBO		71.4	NR	0.0	0.0	5.7*	NR	0.0‡
ECZTRA 2	TRA 300 mg Q2W	36 weeks	68.1	NR	2.2	0.0	8.8*	NR	1.1‡
	TRA 300 mg Q4W		62.9	NR	1.1	3.4	5.6*	NR	0.0‡
	PBO		69.6	NR	0.0	0.0	6.5*	NR	0.0‡
Dupilumab									
AD SOLO 1-CONTINUE	DUP 300 mg Q2W or QW	36 weeks	NR	81.7	3.7	NR	4.9†	NR	6.1¶
	PBO		NR	70.7	0.0	NR	5.4†	NR	6.6¶

All values in the table are percentages. Includes trials only in adults 18 and older. Dupilumab 300 mg Q8W and Q4W doses were not included in the table. AE: adverse event, BARI: baricitinib, D/C: discontinuation, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, SAE: serious adverse event, TEAE: treatment-emergent adverse event, TRA: tralokinumab. *conjunctivitis bacterial, conjunctivitis viral and conjunctivitis allergic, †conjunctivitis, conjunctivitis bacterial, conjunctivitis viral, conjunctivitis allergic, and atopic keratoconjunctivitis, ‡eczema herpeticum, ¶herpes simplex virus infection, oral herpes infection, ophthalmic herpes infection.

Table D3.7. Key Harms in Placebo-controlled Combination Trials of Adults (Long-term)

Trial	Arm	Timepoint	Any AEs	TEAEs	D/C Due to AEs/TEAEs	SAE	Conjunctivitis	Nausea	Herpetic Infection
ECZTRA 3	TRA Q2W + TCS (TRA non-responders)	16-32 weeks	65.3	NR	1.1	2.1	4.2*	3.2	5‡
	TRA 300 mg Q2W + TCS (TRA responders)		69.6	NR	0	4.3	4.3*	4.3	4‡
	TRA Q4W +TCS (TRA responders)		59.4	NR	1.4	0	1.4*	5.8	6‡
	PBO Q2W + TCS (PBO responders)		63.4	NR	2.4	2.4	2.4*	0	2‡
LIBERTY AD CHRONOS	DUP 300 mg Q2W + TCS	52 2eeks	88	NR	2	4	14†	NR	7¶
	PBO + TCS		84	NR	8	5	8†	NR	8¶

All values in the table are percentages. AE: adverse event, D/C: discontinuation, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, SAE: serious adverse event, TEAE: treatment-emergent adverse event, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib. *conjunctivitis, conjunctivitis allergic, and conjunctivitis viral, conjunctivitis allergic, †conjunctivitis bacterial, atopic keratoconjunctivitis, and conjunctivitis, ‡oral herpes and eczema herpeticum, oral herpes, herpes simplex, herpes virus infection, herpes zoster, eczema herpeticum, genital herpes, ¶herpes ophthalmic, ophthalmic herpes simplex, and ophthalmic herpes zoster.

Children and Adolescents

Additional clinical evidence for children and adolescents are presented below. For adolescents, our literature search identified trials for abrocitinib, upadacitinib, and dupilumab. Only trials of dupilumab were identified for children, and all of these included topical medications in all groups. Our literature search did not identify any baricitinib or tralokinumab trials in children or adolescents.

Abrocitinib

As noted in Section 3.2 of the Report, trials of abrocitinib included adolescents and adults.

Though two placebo-controlled monotherapy trials of abrocitinib enrolled patients ≥12 years old (JADE MONO-1 &2), a small fraction of the patients in these trials were ≥12-17 years old (15%-26%).[35,36] One trial of abrocitinib solely enrolled patients 12-17 years old and included use of

topical medications in all arms (JADE TEEN). [39,41,77] While results of these trials in adolescents are briefly described in the Report, additional results and a table of key results are presented here.

In the two placebo-controlled monotherapy trials that enrolled patients ≥12 years old (JADE MONO-1 &2), 55%-60% of patients <18 years old achieved EASI 75, compared to 0%-13% in the placebo arms of those trials. [35,36] In this subgroup of patients, 44% achieved EASI 75 with abrocitinib 100 mg. The percentages of patients achieving IGA response, defined as an IGA score of 0 or 1 and an improvement of 2 points or more from baseline, with abrocitinib 200 mg were 27%-40%, 13%-27% with abrocitinib 100 mg, and 0%-13% with placebo.

In the placebo-controlled combination trial that solely enrolled adolescents (JADE TEEN), more patients in the abrocitinib arms achieved EASI 75 and IGA response at 12 weeks compared to the placebo arm (see Table D3.9).[39,77]

At the time of this Report, no long-term data for abrocitinib in adolescents were identified.

Upadacitinib

As noted in Section 3.2 of the Report, trials of upadacitinib included adolescents and adults.

Two placebo-controlled monotherapy trials (MEASURE UP 1 &2) and one placebo-controlled combination trial (AD-UP) of upadacitinib enrolled patients ≥12 years old; however, few patients in these trials were ≥12-17 years old (12%-15%).[81] [80] While results of these trials in adolescents are briefly described in the Report, additional results and a table of key results are presented here.

In the two placebo-controlled monotherapy trials that enrolled patients ≥12 years old (MEASURE UP 1 &2), 75%-83% of patients <18 years old achieved EASI 75 on upadacitinib 30 mg, compared to 8%-13% in the placebo arms of those trials. [79] In this subgroup of patients, 67%-71% achieved EASI 75 with upadacitinib 15 mg. The percentages of patients achieving IGA response, defined as an IGA score of 0 or 1 and an improvement of 2 points or more from baseline, with upadacitinib 30 mg were 63%-69%, 38%-42% with upadacitinib 15 mg, and 3%-8% with placebo (See Table D3.8). [79]

In the combination trial that compared upadacitinib to placebo in patients also treated with topical corticosteroids (AD-UP), 77% of patients <18 years old achieved EASI 75 on upadacitinib 30 mg, compared to 30% in the placebo arms.[79] IGA response was achieved by 65% of patients with upadacitinib 30 mg, 31% with upadacitinib 15 mg, and 8% with placebo (See Table D3.9). [79]

At the time of this report, no long-term data for upadacitinib in adolescents were identified.

Dupilumab

We identified one OLE of dupilumab in a subgroup in children with severe atopic dermatitis,[137] and one OLE of dupilumab in children with severe atopic dermatitis and adolescents with moderate-to-severe atopic dermatitis.[58,59] At the time of this report, the OLE of dupilumab have been published. Results for the phase IIa OLE were obtained from a conference abstract and clinicaltrials.gov. Results are presented in Table D3.9.

Additional Tables of Outcomes

Table D3.8. Key Outcomes in Placebo-controlled Monotherapy Trials in Adolescents (Short-term)

Population of Interest	Trial	Arm	Timepoint	EASI 50	EASI 75	EASI 90	IGA	PP-NRS†	SCORAD‡
12-17 years	**Abrocitinib**								
	JADE MONO-1*	ABRO 200 mg	12 weeks	69.7	54.5	30.3	27.3	47.8	-47.4
		ABRO 100 mg		61.8	44.1	20.6	26.5	33.3	-45.1
		PBO		12.5	12.5	7.1	12.5	7.1	-20.9
	JADE MONO-2*	ABRO 200 mg	12 weeks	86.7	60.0	33.3	40.0	84.6	-51.3
		ABRO 100 mg		56.3	43.8	12.5	12.5	20	-32.7
		PBO		0	0.0	0	0.0	12.5	-14.4
	Upadacitinib								
	MEASURE UP 1*	UPA 30 mg	16 weeks	85.7	83.3	73.8	69.0	54.8	NR
		UPA 15 mg		76.2	71.4	42.9	38.1	45.0	NR
		PBO		35	7.5	2.5	7.5	15.4	NR
	MEASURE UP 2*	UPA 30 mg	16 weeks	80	74.3	65.7	62.5	50.0	NR
		UPA 15 mg		75.8	66.7	45.5	42.4	33.3	NR
		PBO		33.3	13.9	0	2.8	2.8	NR
	Dupilumab								
	LIBERTY AD ADOL	DUP 200/300 mg Q2W	16 weeks	61	41.5	23.2	24.4	36.6	-51.6¶
		DUP 300 mg Q4W		54.8	38.1	19.0	17.9	26.5	-47.5¶
		PBO		12.9	8.2	2.4	2.4	4.8	-17.6¶

All values in the table are percentages. No monotherapy trials were conducted in the children population. ABRO: abrocitinib, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, UPA: upadacitinib. *subgroup of the trial population, †PP-NRS ≥4, ‡mean change from baseline, ¶LSM percentage change from baseline.

Table D3.9. Key Outcomes in Placebo-controlled Combination Trials of Children and Adolescents (Short- and Long-term)

Population of Interest	Trial	Arm	Timepoint	EASI 50	EASI 75	EASI 90	IGA	PP-NRS†	SCORAD‡
6-11 years	**Dupilumab**								
	LIBERTY AD PEDS	DUP 300 mg Q4W + TCS	16 weeks	91	69.7	41.8	32.8	50.8	-62.4¶
		DUP 100/200 mg Q2W + TCS		82.8	67.2	30.3	29.5	58.3	-60.2¶
		PBO + TCS		43.1	26.8	7.3	11.4	12.3	-29.8¶
	LIBERTY AD PED OLE*	DUP 4 mg/kg + TCS	16 weeks	93	73	33	40	69	-62
		DUP 2 mg/kg + TCS		94	59	41	35	53	-61
		DUP 4 mg/kg + TCS	52 weeks	94	75	44	25	69	-67
		DUP 2 mg/kg + TCS		94	94	71	76	65	-79
	Phase 2a AD-1412*	DUP 4 mg/kg + TCS	12 weeks	NR	NR	NR	21.1	NR	-46.9
		DUP 2 mg/kg + TCS		NR	NR	NR	16.7	NR	-57.5
12-17 years	**Abrocitinib**								
	JADE TEEN	ABRO 200 mg + TCS	12 weeks	87.1	72	45.9	46.2	55.4	-42.9
		ABRO 100 mg + TCS		87.6	68.5	41.9	41.6	52.6	-40.9
		PBO +TCS		69.1	41.5	18.1	24.5	29.8	-30.2
	Upadacitinib								
	AD-UP	UPA 30 mg + TCS	16 weeks	NR	75.7	NR	64.9	54.5	NR
		UPA 15 mg + TCS		NR	56.4	NR	30.8	41.7	NR
		PBO + TCS		NR	30.0	NR	7.5	13.2	NR
	Dupilumab								
	LIBERTY AD PED-OLE*	**Baseline weight <60 kg**							
		Overall	52 weeks	NR	86	NR	36.5	NR	NR
		Baseline weight ≥60 kg							
		Overall	52 weeks	NR	76.5	NR	49	NR	NR
	Phase 2a AD-1412*	DUP 4 mg/kg + TCS	12 weeks	NR	NR	NR	35	NR	-43.4
		DUP 2 mg/kg + TCS		NR	NR	NR	10	NR	-47.7

All values in the table are percentages. ABRO: abrocitinib, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, TCS: topical corticosteroids. *subgroup of the trial population, †PP-NRS ≥4, ‡mean percentage change from baseline, ¶LSM percentage change from baseline.

Harms

Table D3.10. Key Harms in Placebo-controlled Monotherapy Trials of Adolescents

Population of Interest	Trial	Arm	Timepoint	Any AEs	TEAEs	D/C Due to AE	SAE	Conjunctivitis	Nausea	Herpetic Infection
Dupilumab										
12-17 years	LIBERTY AD ADOL	DUP 200/300 mg Q2W	16 weeks	NR	72	0[†]	0[†]	9.8	NR	1.2[¶]
		DUP 300 mg Q4W		NR	63.9	0[†]	0[†]	10.8	NR	4.8[¶]
		PBO		NR	69.4	1.2[†]	1.2[†]	4.7	NR	3.5[¶]

All values in the table are percentages. No placebo-controlled trials were conducted in the children population. **There were no available safety data for adolescent subgroups in JADE MONO-1, JADE MONO-2, MEASURE UP 1, and MEASURE UP 2.** ABRO: Abrocitinib, AE: adverse event, D/C: discontinuation, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, SAE: serious adverse event, TEAE: treatment-emergent adverse event, UPA: upadacitinib. *subgroup of the trial population, [†]based on TEAE, [¶]herpes viral infection.

Table D3.11. Key Harms in Placebo-controlled Combination Trials of Children and Adolescents

Population of Interest	Trial	Arm	Timepoint	Any AEs	TEAEs	D/C Due to AE	SAE	Conjunctivitis	Nausea	Herpetic Infection
6-11 years	**Dupilumab**									
	LIBERTY AD PEDS	DUP 300 mg Q4W + TCS	16 weeks	NR	65	0[†]	1.7[†]	6.7[‡]	NR	1.7[¶]
		DUP 100/200 mg Q2W + TCS		NR	67.2	1.6[†]	0[†]	14.8[‡]	NR	3.3[¶]
		PBO +TCS		NR	73.3	1.7[†]	1.7[†]	4.2[‡]	NR	5[¶]
	LIBERTY AD PED-OLE*	DUP 4 mg/kg + TCS	52 weeks	NR	100	0[†]	19[†]	31	NR	50[#]
		DUP 2 mg/kg + TCS		NR	94	0[†]	12[†]	5	NR	12
	Phase 2a AD-1412*	DUP 4 mg/kg + TCS	20 weeks	NR	NR	NR	10.53	5.26	10.53	5.26[§]
		DUP 2 mg/kg + TCS		NR	NR	NR	0	0	0	5.56[§]
12-17 years	**Abrocitinib**									
	JADE TEEN	ABRO 200 mg + TCS	12 weeks	NR	62.8	2.1	2.1	NR	NR	NR
		ABRO 100 mg + TCS		NR	56.8	1.1	0	NR	NR	NR
		PBO +TCS		NR	52.1	2.1	2.1	NR	NR	NR
	Dupilumab									
	LIBERTY AD PED-OLE*	DUP 200/300 mg Q2W	52 weeks	NR	74.4	0.9[†]	0.9[†]	8.7[¥]	NR	NR
		DUP 300 mg Q4W		NR	72.2	0[†]	3.8[†]		NR	NR
	Phase 2a AD-1412*	DUP 4 mg/kg + TCS	20 weeks	NR	NR	NR	5	0	0	5[§]
		DUP 2 mg/kg + TCS		NR	NR	NR	5	0	0	0[§]

All values in the table are percentages. ABRO: abrocitinib, AE: adverse event, D/C: discontinuation, DUP: dupilumab, mg: milligram, NR: not reported, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, SAE: serious adverse event, TCS: topical corticosteroids, TEAE: treatment-emergent adverse event. *subgroup of the trial population, [†]based on TEAE, [‡]conjunctivitis cluster, [¶]herpes viral infection, [#]herpes viral infection and herpes simplex, [§]herpes viral infection, herpes simplex, and oral herpes, [¥]treatment-emergent narrow conjunctivitis.

Mild-to-Moderate Population

Ruxolitinib Cream

We identified two 52-week long-term trials of ruxolitinib conducted in patients with atopic dermatitis who had participated in TRuE-AD1 and TRuE-AD2 studies.[73] Patients were followed up for 8-weeks in TRuE-AD1 and TRuE-AD2 trials and followed up for additional 44 weeks in the extension studies.[73] Patients on ruxolitinib cream in the originating trials remained on their regimen during the long-term extension period, while patients in the vehicle (placebo) arms were re-randomized 1:1 to ruxolitinib cream 1.75% or ruxolitinib cream 1.75%.[73] During the extension studies, patients were instructed to stop treatment three days after clearance of atopic dermatitis lesions and restart treatment at the first sign of recurrence. At week 52, IGA response was achieved by 72%-80% and 60%-77% of patients on 1.5% and 0.75% ruxolitinib cream.[73]

Additional Table of Outcomes

While most results for the ruxolitinib cream trials are described in Section 3.3 of the Report, a table of key results is presented here.

Table D3.12. Key Outcomes for Ruxolitinib Cream[86,87,97]

Trial	Arm	Timepoint	EASI 50	EASI 75	EASI 90	IGA	PP-NRS†	SCORAD‡
Ruxolitinib Cream								
TRuE AD 1	RUX 1.5%	8 weeks	NR	62.1	44.3	53.8	52.2	NR
	RUX 0.75%		NR	56.0	38.1	50.0	40.4	NR
	PBO		NR	24.6	9.5	15.1	15.4	NR
TRuE AD 2	RUX 1.5%	8 weeks	NR	61.8	43.4	51.3	50.7	-67.3**
	RUX 0.75%		NR	51.5	35.1	39.0	42.7	-62.9**
	PBO		NR	14.4	4.2	7.6	16.3	-30.4**
Phase II Kim 2020*	RUX 1.5%	4 weeks	NR	56.0	26.0	38.0	62.5	NR
	TRI 0.1%		NR	47.1	13.7	25.5	19.4	NR
	PBO		NR	17.3	5.8	7.7	11.1	NR

All values in the table are percentages. RUX: ruxolitinib cream, TRI: topical triamcinolone acetonide, NR: not reported, PBO: placebo.

*Results from additional RUX arms are presented in Evidence Tables G1.48-1.64.

**Results from a pooled analysis of TRuE AD 1 and 2.

Harms

Summaries of the harms are provided in Section 3.3 of the Report. A table presenting key harms from the trials are presented here.

Table D3.13. Key Harms for Ruxolitinib Cream[86,87,97]

Trial	Arm	Timepoint	Any TEAE	Study Drug-Related TEAE	Serious TEAE	D/C Due to TEAEs	Application Site Burning	Application Site Pruritis
Ruxolitinib Cream (short-term)								
TRuE AD 1	RUX 1.5%	8 weeks	28.9	5.5	0.8	1.2	0.8	0.0
	RUX 0.75%		29.4	6.0	0.4	1.2	0.0	0.8
	PBO		34.9	12.7	1.6	4.0	1.6	1.6
TRuE AD 2	RUX 1.5%	8 weeks	23.6	4.5	0.4	0.0	0.8	0
	RUX 0.75%		29.4	3.2	1.2	0.4	0.8	0.8
	PBO		32.3	9.7	0.0	2.4	6.5	3.2
Phase II Kim 2020*	RUX 1.5%	8 weeks	24	6.0	NR	0.0	NR	NR
	TAC 0.1%		33.3	2.0	NR	2.0	NR	NR
	PBO		32.7	9.6	NR	1.9	NR	NR
Ruxolitinib Cream (Long-term)								
TRuE AD 1 & 2 (Pooled)	RUX 1.5%	52 weeks	53.8	2.9	1.3	0	2.1 - 2.2/100 patient-years**	
	RUX 0.75%		60.1	4.7	2.3	2.1	3.5 - 4.7/100 patient-years**	
	PBO to RUX 1.5%		57.6	6.1	1.0	0	NR	NR
	PBO to RUX 0.75%		53.5	2.0	5.0	0	NR	NR

All values in the table are percentages. D/C: discontinuation, NR: not reported, PBO: vehicle (placebo), RUX: ruxolitinib cream, TAC: topical triamcinolone acetonide, TEAE: treatment-emergent adverse event.

*The incidences of adverse events at four weeks were not reported.

**Presented as application site reactions

D4. Ongoing Studies

Figure D4.1. Ongoing Studies

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
Abrocitinib					
Study of Abrocitinib Compared with Dupilumab in Adults with Moderate to Severe Atopic Dermatitis on Background Topical Therapy Pfizer NCT04345367	Phase IIIb, randomized, double-blind, multi-center N=600	Arm 1 Abrocitinib 200 mg + TCS Arm 2 Dupilumab 300 mg + TCS	**Inclusion** 18 years of age or older Diagnosis of chronic atopic dermatitis for at least 6 months Recent history of inadequate response to treatment with medicated topical therapy for AD or have required systemic therapies for control of their disease **Exclusion** Acute or chronic abnormality Increased risk of developing thromboembolism Unwilling to discontinue current medications Prior treatment with JAK inhibitors or IL-4 or IL-13	Change in PP-NRS4 Change in EASI-90 at week 4	July 14th, 2021
Study to Evaluate Efficacy and Safety of PF-04965842 With or Without Topical Medications in Subjects Aged 12 years and older with Moderate to Severe Atopic Dermatitis (JADE EXTEND) Pfizer NCT03422822	Phase III, randomized, quadruple masking, Long-term extension study N=3000	Arm 1 Initial treatment period: Abrocitinib 100 mg For patients, whose dose was changed from abrocitinib 100 mg to placebo, placebo was administered for remainder of study Secondary treatment period: Abrocitinib 100 mg	**Inclusion** Aged 12 and older Must have completed a qualifying parent study **Exclusion** Other acute or chronic medical conditions Currently have active forms of inflammatory diseases Ongoing adverse event from parent study	Treatment-emergent adverse events Serious adverse events	December 1, 2023

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
		Arm 2 Initial treatment period: Abrocitinib 200 mg For patients, whose dose was changed from abrocitinib 200 mg to placebo, placebo was administered for remainder of study Secondary treatment period: Abrocitinib 200 mg			
Study to Investigate Efficacy and Safety of PF-0465842 in Subjects Aged 12 Years and Older with Moderate to Severe Atopic Dermatitis with the Option of Rescue Treatment in Flaring Subjects Pfizer NCT03627767	Phase III, randomized withdrawal, double-blind N=1231	Arm 1 Abrocitinib 100 mg Arm 2 Abrocitinib 200 mg Arm 3 Placebo	**Inclusion** 12 years or older with a minimum weight of 40kg Diagnosed with atopic dermatitis Recent history of inadequate response or inability to tolerate topical AD treatments **Exclusion** Prior treatment with JAKs Other active non-AD inflammatory diseases	Loss of response (week 12 to 52)	October 2020
Tralokinumab					
Effects of Tralokinumab Treatment of Atopic Dermatitis on Skin Barrier Function Prof. Dr. Stephan Weidinger NCT04556461	Phase II, open-label, mono-center N=16	Tralokinumab 600 mg loading dose followed by 300 mg every 2 weeks	**Inclusion** Aged 18 and older with atopic dermatitis Subjects with a recent history of inadequate response to treatment with topical medications EASI score >12	Change in trans epidermal water loss (skin barrier function)	March 2022

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
			Exclusion Concurrent enrollment in another clinical trial Previous enrollment in a tralokinumab trial Subjects with mild atopic dermatitis		
Long-term Extension Trial in Subjects with Atopic Dermatitis Who Participated in Previous Tralokinumab Trials (ECZTEND) LEO Pharma NCT03587805	Phase III, open-label, long-term extension N=1125	Tralokinumab	**Inclusion** Completed the treatment period(s) of one of the parent trials Stable dose of emollient twice daily **Exclusion** Any condition requiring permeant discontinuation of the trial treatment Patients who participated in a parent trial and experienced a serious adverse event related to the treatment	IGA score of 0 or 1 EASI 75	September 13, 2021
Tralokinumab in Combination with Topical Corticosteroids in Japanese Subjects with Moderate to Severe Atopic Dermatitis (ECZTRA 8) LEO Pharma NCT04587453	Phase 3, randomized, double-blind N=100	Arm 1 Tralokinumab + topical corticosteroids Arm 2 Placebo + topical corticosteroids	**Inclusion** Japanese subject aged 18 years and above with AD for at least 1 year AD involvement of 10% or more of body surface area Applied a stable dose of emollient twice a day **Exclusion** Subjects who cannot take TCS Concomitant conditions Known primary immunodeficiency disorder Previous treatment with systemic immunosuppressive drugs, JAKs, or TCS.	IGA score of 0 or 1 EASI 75	September 2021
Upadacitinib					
Open-Label Extension Study of Upadacitinib in Adult Patients	Phase IIIb, single group	Upadacitinib	**Inclusion**	Adverse Events	November 24, 2021

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
with moderate to Severe Atopic Dermatitis AbbVie NCT04195698	assessment, open-label N=600		Successfully completed concomitant treatment in M16-046 study **Exclusion** Use of prohibited medications		
Evaluation of Upadacitinib in Adolescent and Adult Patients with Moderate to Severe Atopic Dermatitis AbbVie NCT03569293	Phase III, randomized, quadruple masked N=912	Arm 1 Upadacitinib dose A Arm 2 Upadacitinib dose B Arm 3 Placebo	**Inclusion** Chronic atopic dermatitis Moderate to severe AD Candidate for systemic therapy **Exclusion** Prior exposure to JAK inhibitor Other active skin disease	EASI 75 vIGA-AD score of 0 or 1	May 24, 2023
A Study to Evaluate Upadacitinib in Combination with Topical Steroids in Adolescent and Adult Participants with Moderate to Severe AD AbbVie NCT03568318	Phase III, randomized, double-blind N=969	Arm 1 Upadacitinib A + topical corticosteroids Arm 2 Upadacitinib B + topical corticosteroids Arm 3 Placebo + corticosteroids	**Inclusion** Chronic atopic dermatitis Moderate to severe AD Candidate for systemic therapy **Exclusion** Prior exposure to JAK inhibitor Other active skin disease	EASI 75 vIGA-AD score of 0 or 1	June 30, 2023
A Study to Evaluate the Pharmacokinetics, Safety, and tolerability of Upadacitinib in Pediatric patients with Severe AD AbbVie NCT03646604	Open-label N=40	Arm 1 Ages 6 to 12 on low dose UPA Arm 2 Ages 6 to 12 on high dose UPA Arm 3 Ages 2 to 6 on low dose UPA Arm 4 Ages 2 to 6 on high dose UPA Arm 5	**Inclusion** Ages 2 months to 12 years of age Severe AD **Exclusion** Prior exposure to JAK	Maximum plasma concentration Oral Clearance	November 28, 2024

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
		Ages 6 months to 2 years on low dose UPA Arm 6 Ages 6 months to 2 years on high dose UPA			
A Study to Evaluate Upadacitinib in Adolescents and Adult Subjects with Moderate to Severe AD (Measure UP 2) AbbVie NCT03607422	Phase III, randomized, double-blind N=916	Arm 1 UPA dose A Arm 2 UPA dose B Arm 3 Placebo	**Inclusion** Moderate to severe AD Chronic AD for at least 3 years Ages 12 to 18 Documented history of inadequate response to topical corticosteroids or topical calcineurin inhibitor **Exclusion** Prior exposure to JAK inhibitor Other skin disease Unwilling to discontinue current medications	EASI75 vIGA-AD score of 0 or 1	July 25, 2023
A Study to Evaluate the Safety of Upadacitinib In Combination with Topical Steroids in Adolescent and Adult Participants with Moderate to Severe AD AbbVie NCT03661138	Phase III, randomized, double-blind N=272	Arm 1 UPA dose A + topical corticosteroids Arm 2 UPA dose B + topical corticosteroids Arm 3 Placebo + topical corticosteroids	**Inclusion** Active moderate to severe AD Candidate for systemic therapy **Exclusion** Prior use of a JAK inhibitor Unwilling to discontinue current medications	Adverse events	February 25, 2022

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies). There are no on-going trials for baricitinib or dupilumab.

D5. Previous Systematic Reviews and Technology Assessments

We identified seven systematic literature reviews (SLRs) evaluating systemic treatments for patients with moderate-to-severe atopic dermatitis, three of which are summarized below. We did not identify any SLRs that assessed ruxolitinib in atopic dermatitis.

Silverberg, J. I., et al. (2021). "Comparative efficacy and safety of systemic therapies used in moderate-to-severe atopic dermatitis: a systematic literature review and network meta-analysis" [138]

This systematic literature review and NMA evaluated the comparative efficacy and safety of several systemic therapies, including oral JAK inhibitors, IL-13 antagonists, and IL-31 antagonists, in adolescents and adults with moderate-to-severe atopic dermatitis. The medications assessed included abrocitinib, baricitinib, dupilumab, lebrikizumab, nemolizumab, tralokinumab and upadacitinib. Investigators identified 19 phase II and phase III RCTS, published before October 2019, to include in their analysis, which comprised of 11 monotherapy and 8 combination trials. Outcomes were analyzed separately for monotherapy and combination therapies (i.e., systemic therapies plus topical corticosteroids). For the monotherapy trials, upadacitinib 30 mg consistently had the highest response rate on all EASI measures, followed by abrocitinib 200 mg and upadacitinib 15 mg. Additionally, upadacitinib 30 mg and abrocitinib 200 mg demonstrated superiority over dupilumab 300 mg, both doses of baricitinib, and nemolizumab. A similar trend was observed for IGA response; however, no data were identified for upadacitinib for IGA response. For the combination therapy NMA, both doses of abrocitinib, dupilumab 300 mg, nemolizumab 30 mg, and lebikizumab 125 mg, had the highest response rates for all EASI measures. Additionally, abrocitinib 200 mg demonstrated superiority over baricitinib, tralokinumab, and dupilumab. On IGA, abrocitinib 200 mg, dupilumab 300 mg, nemolizumab 30 mg, and abrocitinib 100 mg, had the highest response rates. Upadacitinib was not included in the combination therapy NMA. For safety events, in the monotherapy and combination therapy RCTs, none of the treatments had adverse events that were statistically different from placebo; but most treatment arms had numerically higher probabilities of TEAEs than placebo arms. However, the probability of AE leading to discontinuation was generally lower in the treatment arms. There was no statistically significant difference between the active treatments on safety events.

Drucker, A.M., et al. (2020). "Systemic Immunomodulatory Treatments for Patients with Atopic Dermatitis: A Systematic Review and Network Meta-analysis"

Investigators conducted a systematic review assessing the efficacy and safety of systemic immunomodulatory treatments for patients with moderate-to-severe atopic dermatitis. 39 RCTs for 20 different medications, including abrocitinib, baricitinib, dupilumab, tralokinumab, upadacitinib, methotrexate, and other immunosuppressants, antagonists, and monoclonal antibodies, were included in their network meta-analysis. A total of 6360 patients were included, the mean sample size for each RCT was 60 (4-319) patients, and the mean/median age ranged between 6 and 44 years. Eligibility criteria included patients with moderate-to-severe atopic dermatitis, a systemic immunomodulatory therapy as the treatment of focus, and an outcome assessment time point of eight weeks or more. An NMA was performed for each outcome, including change from baseline in EASI, POEM, DLQI, and itch, withdrawals due to adverse events, and frequency of serious adverse events. Data were pooled for trials with 8–16-week treatment timepoints, and trials with greater than 16-week treatment time points were not analyzed.

Multiple drug doses, including dupilumab 300 mg Q2W, baricitinib 2 mg and 4 mg daily, tralokinumab 150 mg Q2W, and 300 mg Q2W had a statistically significant reduction in EASI score compared to placebo, with dupilumab 300 mg Q2W having the highest amount of certainty (mean difference [MD]: -11.3; 95% CrI: 9.7 to 13.1).

When assessing changes in clinical signs of atopic dermatitis among drugs that are already used in clinical practice, it was found that all current drugs were more effective than placebo in clearing atopic dermatitis clinical signs, but with low certainty. When comparing these drugs, dupilumab 300 Q2W and cyclosporine high-dose were more effective in clearing atopic dermatitis signs than methotrexate and azathioprine.

Dupilumab 300 mg Q2W was the only drug that demonstrated clinically meaningful improvements in both POEM (MD: -7.5; 95% CrI: -11.6 to -3.6) and DLQI outcomes (MD: -4.8; 95% CrI: -5.8 to -3.7), with high certainty, while abrocitinib 100 mg and 200 mg, and upadacitinib 15 mg and 30 mg had significant improvements with lower certainty. Additionally, only dupilumab 300 mg Q2W had a statistically significant improvement in the mean change in PP-NRS, relative to placebo, with high certainty. Cyclosporine, dupilumab, methotrexate, and azathioprine could not be compared to each other for the itch outcome due to imprecise estimates.

Safety could not be robustly assessed due to the overall low rates of adverse events. Investigators identified potential limitations in their systematic review, including heterogeneity from incorporating trials that also used background topical medication therapy, using trials that varied in the definition of disease severity, and the lack of head-to-head trials in this analysis.

Siegels, D., et al. (2020). "Systemic Treatments in the Management of Atopic Dermatitis: A Systematic Review and Meta-Analysis"

An SLR and a MA were conducted to evaluate systemic treatments for moderate-to-severe atopic dermatitis. Investigators identified 50 RCTs for 13 different approved treatments in Europe, as of February 2020, to include in their meta-analysis. The medications included baricitinib, dupilumab, methotrexate, upadacitinib, corticosteroids, and other monoclonal antibodies and immunosuppressants. The total patient population was 6681, a majority of which were in dupilumab trials (n=3529), and the average sample size for most trials was less than 100 patients. Thirty trials were conducted in adult populations. One trial was in adolescents, one trial assessed their treatment in children, and 18 trials had age groups inconsistent with the investigators' defined populations of focus.

Meta-analyses could be calculated only for dupilumab, azathioprine, baricitinib, and cyclosporine, as the other trials' evidence had higher risks of bias (RoB). Out of these treatments, dupilumab trials in adults with a dosage of 300 mg Q2W had the most robust and highest quality evidence due to the large number of trials and patients. All dupilumab doses in the trials demonstrated superiority to placebo in EASI 75 and mean change from baseline in EASI, SCORAD, PP-NRS, POEM, cDLQI (in adolescents), and DLQI (in adults). Cumulative safety data for dupilumab indicated that adverse events for dupilumab and placebo were equal and greater than 50% in incidence rates, with conjunctivitis and injection-site reactions being the most common concerns.

Investigators reported that uncertainty limited the evaluation of safety and efficacy of the other treatments' trials. Limitations included lack of published RCTs, most of the included RCTs having a high risk of bias, a relatively low number of patients in most trials, and inclusion of older trials.

E. Long-Term Cost Effectiveness: Supplemental Information

E1. Detailed Methods

Table E.1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	☐	☐	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	

Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[139]

Target Population

The target population for the economic evaluation is adult (aged 18 years or older) patients with moderate-to-severe atopic dermatitis. We pooled across treatment-specific population characteristics in order to estimate the population characteristics used within the model.

Table E.2. Baseline Population Characteristics

	Pooled Population Used in Model
Mean Age	36.5
Percent Female	43.7%
Percent Severe Disease	45.9%
Source	Weighted averages from drug trials[140-142 69 63,64,143-145]Weighted averages from drug trials[140-142 69 63,64,143-145]

Treatment Strategies

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

- Abrocitinib (Pfizer)
- Baricitinib (Olumiant™, Eli Lilly)
- Upadacitinib (RINVOQ™, AbbVie)
- Tralokinumab (LEO Pharma)

Comparators

Each intervention of interest is compared pairwise with each comparator. The comparators for these interventions were expected to be:

- Dupilumab (Dupixent™, Sanofi)
- Topical therapies (including emollients, with or without topical corticosteroid or calcineurin inhibitor)

Topical therapies, including emollients, topical corticosteroids, and calcineurin inhibitors, are a commonly used treatment for atopic dermatitis. Dupilumab was approved for treating moderate-to-severe atopic dermatitis in 2017, becoming the only approved alternative treatment for patients beyond the topical therapies. These two groups represent the predominantly used available treatment options for patients with moderate-to-severe atopic dermatitis.

E2. Results

Table E2.1. presents the incremental costs and benefits of each therapy compared to standard of care and dupilumab as measured by the Peak Pruritis Numerical Rating Scale (PP-NRS), and the sleep scores for the POEM, SCORAD, and ADerm-IS measures. The average incremental change in score over the five-year time horizon is presented where data was available by health state, as no commonly meaningful threshold or translation for these measurements was identified.

Table E2.1. Incremental Cost-Consequence Results for the Base Case

Treatment	Comparator	Incremental Cost	Incremental QALYs gained (same as evLYG)	Incremental Gain in Average PP-NRS†	Incremental Gain in Average POEM (Sleep)†	Incremental Gain in Average SCORAD (Sleep)†	Incremental Gain in Average ADerm-IS (Sleep)†	Incremental Gain in Average HADS (Anxiety and Depression)†
Abrocitinib*	SoC	$90,600	0.61	NA	NA	NA	NA	NA
Baricitinib	SoC	$17,500	0.26	NA	NA	NA	NA	NA
Tralokinumab*	SoC	$39,900	0.32	-0.96	-0.44	-1.04	NA	-1.04
Upadacitinib	SoC	$131,800	0.53	-1.50	NA	NA	-5.21	NA
Dupilumab	SoC	$54,000	0.50	NA	NA	NA	NA	NA
Abrocitinib*	Dupilumab	$36,500	0.12	NA	NA	NA	NA	NA
Baricitinib	Dupilumab	Less Costly	Less Effective	NA	NA	NA	NA	NA
Tralokinumab*	Dupilumab	Less Costly	Less Effective	NA	NA	NA	NA	NA
Upadacitinib	Dupilumab	$77,800	0.03	NA	NA	NA	NA	NA

ADerm-IS: Atopic Dermatitis Impact Scale, NA: not available, POEM: Patient-Oriented Eczema Measure, QALY: quality-adjusted life year, evLYG: equal-value life-year gained, PP-NRS: Peak Pruritis Numeric Rating Scale, SCORAD: Scoring Atopic Dermatitis; HADS, hospital anxiety and depression scale;

*Using a placeholder price

†Difference in average change in score from pooled baseline

Description evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy. [146]

2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).

3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.

4. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.

5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.

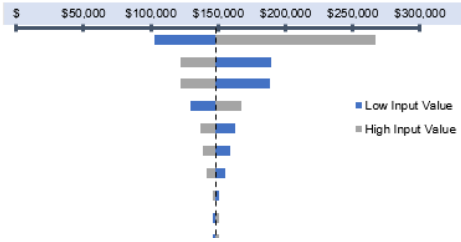
6. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

E3. Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per addition QALY for each modeled treatment. Across all modeled comparisons, the health state utility values were identified as the most influential model parameters on the incremental cost-effectiveness ratios, followed by the initial transition probabilities, non-responder direct costs, and discontinuation rates. Figures E3.1 to E3.9 display the results of the one-way sensitivity analyses performed on each modeled comparison.

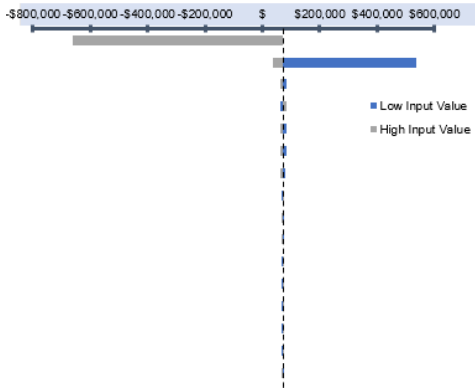
Figure E3.1 Tornado Diagram for Abrocitinib versus Standard of Care



Parameter	Low Input Value	ligh Input Valu	Low Result	High Result
Utility of non-responder state (off treatment) - Soc/Placebo	0.54	0.66	102666	267228
Utility of achieving EASI 90 (on treatment) - Abrocitinib	0.79	0.97	189226.2	121984.8
Utility of non-responder state (off treatment) - Abrocitinib	0.54	0.66	188868.9	122133.7
Cost per dose - Net price - Abrocitinib	102.01	124.67	129802	166881
Utility of achieving EASI 75 (on treatment) - Abrocitinib	0.76	0.93	162375.5	136540.0
Utility of achieving EASI 50 (on treatment) - Abrocitinib	0.72	0.88	159272.1	138814.4
Annual Direct Cost - Non-Responder	16729.76	20447.48	155469	141214
Probability of initial transition EASI 90 - Abrocitinib	0.37	0.45	151079.3	145951.5
Utility of achieving EASI 50 (on treatment) - Soc/Placebo	0.72	0.88	146058	150697
Annual Direct Cost - EASI 90	7736.11	9455.25	146360	150323

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

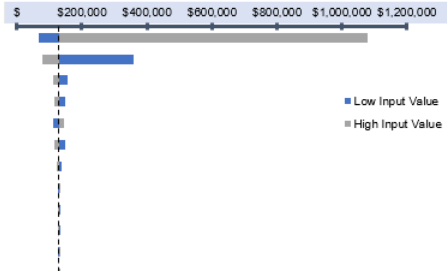
Figure E3.2 Tornado Diagram for Baricitinib versus Standard of Care



Parameter	Low Input Value	ligh Input Valu	Low Result	High Result
Utility of non-responder state (off treatment) - Soc/Placebo	0.54	0.66	33943	-662224
Utility of non-responder state (off treatment) - Baricitinib	0.54	0.66	535387.4	38338.9
Utility of achieving EASI 90 (on treatment) - Baricitinib	0.79	0.97	86237.5	61143.1
Cost per dose - Net price - Baricitinib	47.81	58.43	60597	82510
Utility of achieving EASI 50 (on treatment) - Baricitinib	0.72	0.88	82992.1	62886.6
Utility of achieving EASI 75 (on treatment) - Baricitinib	0.76	0.93	82147.8	63380.2
Annual Direct Cost - Non-Responder	16729.76	20447.48	79034	64074
Utility of achieving EASI 50 (on treatment) - Soc/Placebo	0.72	0.88	68873	74452
Risk of discontinuation - SoC	0.23	0.28	74281.2	69354.5
Probability of initial transition EASI 90 - Baricitinib	0.15	0.18	73729.6	69598.7
Utility of achieving EASI 75 (on treatment) - Soc/Placebo	0.76	0.93	69608	73611
Utility of achieving EASI 90 (on treatment) - Soc/Placebo	0.79	0.97	69916	73270
Annual Direct Cost - EASI 90	7736.11	9455.25	70148	72959
Risk of discontinuation - Baricitinib	0.07	0.08	70303.4	72833.6
Utility of achieving <EASI 50 (first cycle) - Soc/Placebo	0.64	0.78	70325	72827
Probability of initial transition EASI 75 - Baricitinib	0.12	0.14	72830.6	70368.6
Annual Direct Cost - EASI 50	9090.52	11110.64	70324	72784

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

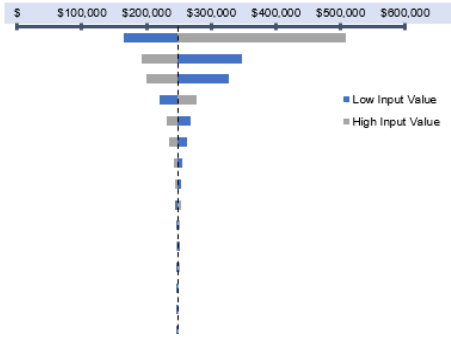
Figure E3.3 Tornado Diagram for Tralokinumab versus Standard of Care



Parameter	Low Input Value	high Input Valu	Low Result	High Result
Utility of non-responder state (off treatment) - Soc/Placebo	0.54	0.66	68843	1079007
Utility of non-responder state (off treatment) - Tralokinuma	0.54	0.66	357713.6	79007.4
Utility of achieving EASI 90 (on treatment) - Tralokinumab	0.79	0.97	155284	110953
Utility of achieving EASI 50 (on treatment) - Tralokinumab	0.72	0.88	148596.3	114640.3
Cost per dose - Net price - Tralokinumab	1073.94	1312.6	112694	146162
Utility of achieving EASI 75 (on treatment) - Tralokinumab	0.76	0.93	147472	115318
Annual Direct Cost - Non-Responder	16729.76	20447.48	136914	121943
Utility of achieving EASI 50 (on treatment) - Soc/Placebo	0.72	0.88	125547	133557
Risk of discontinuation - SoC	0.23	0.28	132707.8	126759.3
Probability of initial transition EASI 90 - Tralokinumab	0.16	0.19	132463.2	126694.9
Utility of achieving EASI 75 (on treatment) - Soc/Placebo	0.76	0.93	126617	132367
Utility of achieving EASI 90 (on treatment) - Soc/Placebo	0.79	0.97	127065	131881

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

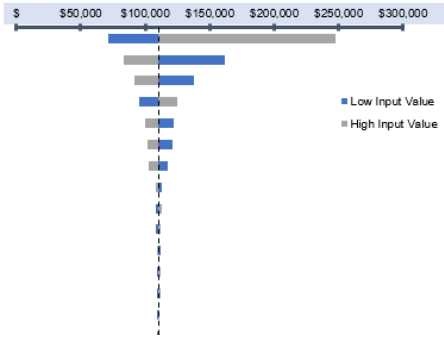
Figure E3.4 Tornado Diagram for Upadacitinib versus Standard of Care



Parameter	Low Input Value	high Input Valu	Low Result	High Result
Utility of non-responder state (off treatment) - Soc/Placebo	0.54	0.66	164320	508651
Utility of non-responder state (off treatment) - Upadacitinib	0.54	0.66	348031	193112
Utility of achieving EASI 90 (on treatment) - Upadacitinib	0.79	0.97	327231	200171
Cost per dose - Net price - Upadacitinib	156.2	190.92	219899	276893
Utility of achieving EASI 75 (on treatment) - Upadacitinib	0.76	0.93	269098	230652
Utility of achieving EASI 50 (on treatment) - Upadacitinib	0.72	0.88	262915	235396
Annual Direct Cost - Non-Responder	16729.76	20447.48	255371	241421
Probability of initial transition EASI 90 - Upadacitinib	0.45	0.55	253352.4	244135.9
Utility of achieving EASI 50 (on treatment) - Soc/Placebo	0.72	0.88	244010	252943
Utility of achieving EASI 75 (on treatment) - Soc/Placebo	0.76	0.93	245231	251644
Risk of discontinuation - SoC	0.23	0.28	251620.2	245733.1
Utility of achieving EASI 90 (on treatment) - Soc/Placebo	0.79	0.97	245738	251112
Annual Direct Cost - EASI 90	7736.11	9455.25	246203	250589
Utility of achieving <EASI 50 (first cycle) - Soc/Placebo	0.64	0.78	246407	250417
Risk of discontinuation - Upadacitinib	0.07	0.08	246855.9	249958.5
Probability of initial transition EASI 50 - Placebo/SoC	0.09	0.11	247140.9	249662.1

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

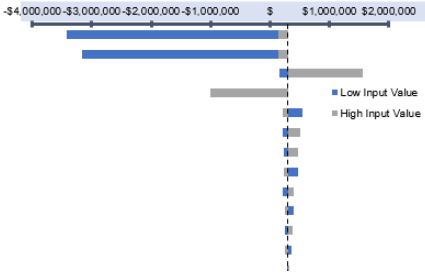
Figure E3.5 Tornado Diagram for Dupilumab versus Standard of Care



Parameter	Low Input Value	high Input Valu	Low Result	High Result
Utility of non-responder state (off treatment) - Soc/Placebo	0.54	0.66	70958	247334
Utility of non-responder state (off treatment) - Dupilumab	0.54	0.66	162211	83534
Utility of achieving EASI 90 (on treatment) - Dupilumab	0.79	0.97	137503	92052
Cost per dose - Net price - Dupilumab	1073.94	1312.6	95522	125034
Utility of achieving EASI 75 (on treatment) - Dupilumab	0.76	0.93	122434	100318
Utility of achieving EASI 50 (on treatment) - Dupilumab	0.72	0.88	120731	101491
Annual Direct Cost - Non-Responder	16729.76	20447.48	117519	103037
Probability of initial transition EASI 90 - Dupilumab	0.29	0.35	112654.0	108180.7
Utility of achieving EASI 50 (on treatment) - Soc/Placebo	0.72	0.88	108172	112468
Annual Direct Cost - EASI 90	7736.11	9455.25	108493	112063
Risk of discontinuation - SoC	0.23	0.28	112095.9	108779.6
Utility of achieving EASI 75 (on treatment) - Soc/Placebo	0.76	0.93	108758	111842
Utility of achieving EASI 90 (on treatment) - Soc/Placebo	0.79	0.97	109002	111585
Utility of achieving <EASI 50 (first cycle) - Soc/Placebo	0.64	0.78	109323	111251
Annual Direct Cost - EASI 75	8019.15	9801.19	109396	111161

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

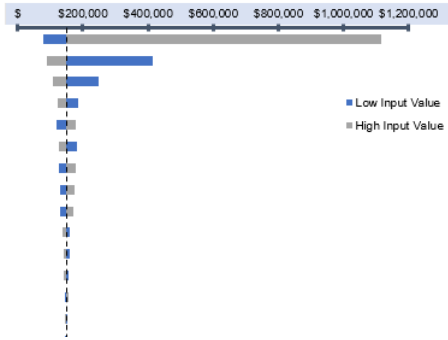
Figure E3.6. Tornado Diagram for Abrocitinib versus Dupilumab



Parameter	Low Input Value	high Input Valu	Low Result	High Result
Utility of non-responder state (off treatment) - Abrocitinib	0.54	0.66	-3429419.6	145252.0
Utility of achieving EASI 90 (on treatment) - Abrocitinib	0.79	0.97	-3160624.7	144730.6
Utility of achieving EASI 90 (on treatment) - Dupilumab	0.79	0.97	167938	1566339
Utility of non-responder state (off treatment) - Dupilumab	0.54	0.66	131674	-998458
Utility of achieving EASI 75 (on treatment) - Abrocitinib	0.76	0.93	540174.9	210892.9
Utility of achieving EASI 75 (on treatment) - Dupilumab	0.76	0.93	216010	509275
Utility of achieving EASI 50 (on treatment) - Dupilumab	0.72	0.88	224275	468562
Utility of achieving EASI 50 (on treatment) - Abrocitinib	0.72	0.88	465353.1	225018.0
Cost per dose - Net price - Abrocitinib	102.01	124.67	209310	397395
Probability of initial transition EASI 90 - Abrocitinib	0.37	0.45	404543.7	254010.4
Probability of initial transition EASI 90 - Dupilumab	0.29	0.35	257092.0	380996.8
Cost per dose - Net price - Dupilumab	1073.94	1312.6	363445	243259
Probability of initial transition EASI 75 - Dupilumab	0.15	0.18	280553.4	332178.1

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

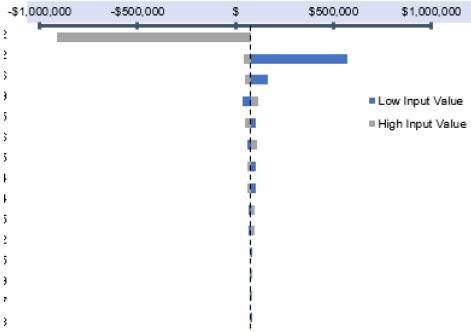
Figure E3.7 Tornado Diagram for Baricitinib versus Dupilumab



Parameter	Low Input Value	high Input Valu	Low Result	High Result
Utility of non-responder state (off treatment) - Baricitinib	0.54	0.66	79830.1	1117767.5
Utility of non-responder state (off treatment) - Dupilumab	0.54	0.66	414433	90840
Utility of achieving EASI 90 (on treatment) - Dupilumab	0.79	0.97	246744	106741
Utility of achieving EASI 75 (on treatment) - Dupilumab	0.76	0.93	185949	124325
Cost per dose - Net price - Dupilumab	1073.94	1312.6	119500	178535
Utility of achieving EASI 50 (on treatment) - Dupilumab	0.72	0.88	180232	127019
Utility of achieving EASI 90 (on treatment) - Baricitinib	0.79	0.97	127328.9	179611.5
Utility of achieving EASI 50 (on treatment) - Baricitinib	0.72	0.88	130961.1	172849.2
Utility of achieving EASI 75 (on treatment) - Baricitinib	0.76	0.93	131989.3	171090.0
Cost per dose - Net price - Baricitinib	47.81	58.43	159978	138057
Probability of initial transition EASI 90 - Dupilumab	0.29	0.35	159612.2	140767.3
Annual Direct Cost - Non-Responder	16729.76	20447.48	156020	142015
Probability of initial transition EASI 90 - Baricitinib	0.15	0.18	143133.7	155565.2
Risk of discontinuation - Baricitinib	0.07	0.08	153807.7	144859.3
Probability of initial transition EASI 75 - Baricitinib	0.12	0.14	145055.2	153285.7

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

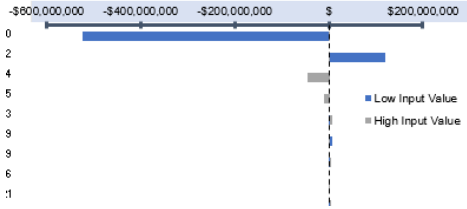
Figure E3.8 Tornado Diagram for Tralokinumab versus Dupilumab



Parameter	Low Input Value	high Input Valu	Low Result	High Result
Utility of non-responder state (off treatment) - Tralokinuma	0.54	0.66	37274.5	-913850.5
Utility of non-responder state (off treatment) - Dupilumab	0.54	0.66	573516	41684
Utility of achieving EASI 90 (on treatment) - Dupilumab	0.79	0.97	167005	50643
Cost per dose - Net price - Dupilumab	1073.94	1312.6	37875	117563
Cost per dose - Net price - Tralokinumab	1073.94	1312.6	106170	49268
Utility of achieving EASI 90 (on treatment) - Tralokinumab	0.79	0.97	60571	108410
Utility of achieving EASI 75 (on treatment) - Dupilumab	0.76	0.93	106188	61288
Utility of achieving EASI 50 (on treatment) - Dupilumab	0.72	0.88	101432	62993
Utility of achieving EASI 50 (on treatment) - Tralokinumab	0.72	0.88	63739.7	99552.9
Utility of achieving EASI 75 (on treatment) - Tralokinumab	0.76	0.93	64335	98134
Annual Direct Cost - Non-Responder	16729.76	20447.48	84545	70893
Annual Direct Cost - EASI 90	7736.11	9455.25	75313	80125
Probability of initial transition EASI 50 - Dupilumab	0.14	0.17	75673.6	79540.6
Probability of initial transition EASI 50 - Tralokinumab	0.13	0.16	79431.2	75810.3
Utility of achieving <EASI 50 (first cycle) - Tralokinumab	0.64	0.78	76469.4	79010.2

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Figure E3.9 Tornado Diagram for Upadacitinib versus Dupilumab



Parameter	Low Input Value	high Input Valu	Low Result	High Result
Utility of achieving EASI 75 (on treatment) - Upadacitinib	0.76	0.93	-523407060	954356
Probability of initial transition EASI 90 - Upadacitinib	0.45	0.55	120218472.8	1056211.4
Utility of achieving EASI 50 (on treatment) - Dupilumab	0.72	0.88	936001	-44526563
Utility of achieving EASI 75 (on treatment) - Dupilumab	0.76	0.93	870749	-9754196
Probability of initial transition EASI 90 - Dupilumab	0.29	0.35	1125055.9	7402901.6
Utility of achieving EASI 50 (on treatment) - Upadacitinib	0.72	0.88	6840672	1111442
Risk of discontinuation - Upadacitinib	0.07	0.08	1349859.0	3386682.9
Utility of achieving EASI 90 (on treatment) - Dupilumab	0.79	0.97	564887	-1380550
Probability of initial transition EASI 75 - Dupilumab	0.15	0.18	1443250.2	2875866.7

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E.3. Results of Probabilistic Sensitivity Analysis for Interventions versus Standard of Care and Dupilumab

PSA Results: Credible Ranges for the Incremental Cost-Effectiveness Ratios						
	Intervention		Comparator		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Abrocitinib vs SoC						
Total Costs	$184,796.41	($171,640 - $199,554)	$87,294.14	($78,966 - $95,735)	$97,502.27	($92,674 - $103,819)
Total QALYs	3.63	(3.44 - 3.82)	2.99	(2.72 - 3.26)	0.65	(0.56 - 0.71)
ICER					$150,587.32	($129,766 - $185,250)
Baricitinib vs SoC						
Total Costs	$102,520.36	($94,665 - $110,261)	$87,294.14	($78,966 - $95,735)	$15,226.22	($15,699 - $14,525)
Total QALYs	3.18	(2.93 - 3.41)	2.99	(2.72 - 3.26)	0.19	(0.15 - 0.21)
ICER					$80,212.86	($76,177 - $100,000)
Tralokinumab vs SoC						
Total Costs	$119,605.79	($111,474 - $128,004)	$87,294.14	($78,966 - $95,735)	$32,311.65	($32,268 - $32,508)
Total QALYs	3.22	(3.00 - 3.45)	2.99	(2.72 - 3.26)	0.23	(0.18 - 0.27)
ICER					$138,765.04	($118,531 - $174,722)
Upadacitinib vs SoC						
Total Costs	$225,978.46	($208,645 - $243,601)	$87,294.14	($78,966 - $95,735)	$138,684.31	($129,679 - $147,866)
Total QALYs	3.56	(3.31 - 3.76)	2.99	(2.72 - 3.26)	0.57	(0.50 - 0.59)
ICER					$244,292.28	($220,579 - $296,778)
Dupilumab vs SoC						

PSA Results: Credible Ranges for the Incremental Cost-Effectiveness Ratios						
Total Costs	$145,143.99	($135,673 - $154,619)	$87,294.14	($78,966 - $95,735)	$57,849.84	($56,707 - $58,884)
Total QALYs	3.51	(3.30 - 3.70)	2.99	(2.72 - 3.26)	0.52	(0.44 - 0.57)
ICER					$111,171.08	($98,772 - $133,717)
Abrocitinib vs Dupilumab						
Total Costs	$184,796.41	($171,640 - $199,554)	$145,143.99	($135,673 - $154,619)	$39,652.42	($35,968 - $44,934)
Total QALYs	3.63	(3.44 - 3.82)	3.51	(3.30 - 3.70)	0.13	(0.12 - 0.14)
ICER					$311,948.32	($256,828 - $374,276)
Baricitinib vs Dupilumab						
Total Costs	$102,520.36	($94,665 - $110,261)	$145,143.99	($135,673 - $154,619)	-$42,623.63	(-$44,359 - -$41,007)
Total QALYs	3.18	(2.93 - 3.41)	3.51	(3.30 - 3.70)	-0.33	(-0.37 - -0.30)
ICER					Less Costly, Less Effective	Less Costly, Less Effective
Tralokinumab vs Dupilumab						
Total Costs	$119,605.79	($111,474 - $128,004)	$145,143.99	($135,673 - $154,619)	-$25,538.19	(-$26,616 - -$24,199)
Total QALYs	3.22	(3.00 - 3.45)	3.51	(3.30 - 3.70)	-0.29	(-0.30 - -0.26)
ICER					Less Costly, Less Effective	Less Costly, Less Effective
Upadacitinib vs Dupilumab						
Total Costs	$225,978.46	($208,645 - $243,601)	$145,143.99	($135,673 - $154,619)	$80,834.47	($72,973 - $88,981)
Total QALYs	3.56	(3.31 - 3.76)	3.51	(3.30 - 3.70)	0.05	(0.01 - 0.06)
ICER					$1,707,871.35	($5,293,659 - $1,537,610)

ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life-year, SoC: standard of care

Figure E3.4. Results of Probabilistic Sensitivity Analysis for Cost Effectiveness at Different Thresholds

	Vs SoC				
Cost-Effectiveness Threshold	**Abrocitinib***	**Baricitinib**	**Tralokinumab***	**Upadacitinib**	**Dupilumab**
$50,000	0%	45%	12%	0%	0%
$100,000	3%	74%	43%	0%	38%
$150,000	49%	85%	65%	3%	76%
$200,000	82%	90%	75%	25%	92%
	Vs Dupilumab				
Cost-Effectiveness Threshold	**Abrocitinib***	**Baricitinib**	**Tralokinumab***	**Upadacitinib**	
$50,000	0%	0%	0%	0%	
$100,000	0%	0%	0%	0%	
$150,000	0%	0%	0%	0%	
$200,000	0%	0%	0%	0%	

SoC: standard of care

E4. Scenario Analyses

Scenario Analysis 1 – Modified Societal Perspective

We included productivity loss due to moderate-to-severe AD as indirect costs by health state. We derived estimates by health state using responses to the Workplace Productivity and Activity Impairment (WPAI) questionnaire, collected in the upadacitinib clinical trials. The work productivity loss percentage scores were multiplied by the average annual US wages from the US Social Security Administration and adjusted to per-cycle values.[147]

Table E4.1. Scenario Analysis Inputs – Productivity Loss

Health State	Value	Source
Non-responder	$6629.31	MEASURE UP 1 & 2
EASI 50	$4041.48	
EASI 75	$3130.95	
EASI 90	$1598.39	

EASI: Eczema Area Severity Index, SE: standard error

The total discounted costs, quality-adjusted life years (QALYs), life years (LYs), and equal value of life years gained (evLYG) over the five-year time horizon under the modified societal perspective are presented in Table E4.2 The drug costs and patient outcomes remained the same compared to the base case, and the table shows the base case total costs for comparison. The total cost from the modified societal perspective versus the base case increased by 10-26% for the interventions and 36% for standard of care.

Table E4.2. Results for the Modified Societal Perspective Scenario Analysis

Treatment	Base Case Total Cost	Scenario Total Cost	QALYs	Life Years	evLYGs
Abrocitinib*	$178,400	$199,700	3.59	4.85	3.59
Baricitinib	$105,300	$132,800	3.23	4.85	3.23
Tralokinumab*	$127,700	$154,200	3.29	4.85	3.29
Upadacitinib	$219,700	$242,100	3.51	4.85	3.51
Dupilumab	$141,900	$165,300	3.47	4.85	3.47
Standard of Care	$87,800	$119,100	2.98	4.85	2.98

*Using a placeholder price

Table E4.3 presents the incremental results from the modified societal perspective scenario analysis, which include incremental cost-effectiveness ratios for incremental cost per LY gained, incremental cost per QALY gained, and incremental cost per evLYG gained. Incremental cost-effectiveness ratios from the modified societal perspective versus the base case when applying the standard of care comparator decreased by 7% to 22% across the therapies evaluated.

Table E4.3. Incremental Cost-Effectiveness Ratios for the Modified Societal Perspective Analysis

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLYG
Abrocitinib*	SoC	$133,900	$-	$133,900
Baricitinib	SoC	$58,100	$-	$58,100
Tralokinumab*	SoC	$115,900	$-	$115,900
Upadacitinib	SoC	$233,700	$-	$233,700
Dupilumab	SoC	$96,200	$-	$96,200
Abrocitinib*	Dupilumab	$287,700	$-	$287,700
Baricitinib	Dupilumab	Less Costly, Less Effective	$-	Less Costly, Less Effective
Tralokinumab*	Dupilumab	Less Costly, Less Effective	$-	Less Costly, Less Effective
Upadacitinib	Dupilumab	$1,890,300	$-	$1,890,300

SOC: Standard of Care; QALY: quality adjusted life-year; evLYG: equal value life year gained;

*Using a placeholder price

Scenario Analysis 2 – Lifetime Time Horizon

We extended the model time horizon from 5 years to lifetime in this scenario to capture longer term value, though we note that only one line of treatment was modeled in order to focus on the comparisons of interest.

Table E4.4. Results for the Lifetime Time Horizon Scenario

Treatment	Drug Cost	Total Cost	QALYs	Life Years	evLYGs
Abrocitinib*	$200,631	$585,944	15.82	24.31	15.82
Baricitinib	$34,302	$448,118	15.01	24.31	15.01
Tralokinumab*	$77,924	$485,329	15.19	24.31	15.19
Upadacitinib	$195,831	$597,035	15.39	24.31	15.39
Dupilumab	$112,250	$509,336	15.49	24.31	15.49
Standard of Care	$0	$426,060	14.67	24.31	14.67

eVLYG: equal-value life-years gained, QALY: quality-adjusted life-year

*Using a placeholder price

Table E4.5. Incremental Cost-Effectiveness Ratios for the Lifetime Time Horizon Scenario

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLYG
Abrocitinib*	SoC	$136,784	$-	$136,784
Baricitinib	SoC	$63,159	$-	$63,159
Tralokinumab*	SoC	$113,150	$-	$113,150
Upadacitinib	SoC	$237,668	$-	$237,668
Dupilumab	SoC	$100,408	$-	$100,408
Abrocitinib*	Dupilumab	$224,072	$-	$224,072
Baricitinib	Dupilumab	Less Costly, Less Effective	$-	Less Costly, Less Effective
Tralokinumab*	Dupilumab	Less Costly, Less Effective	$-	Less Costly, Less Effective
Upadacitinib	Dupilumab	Dominated	$-	Dominated

SOC: Standard of Care

*Using a placeholder price

Table E4.5 presents the incremental results from the lifetime time horizon scenario analysis, which include incremental cost-effectiveness ratios for incremental cost per LY gained, incremental cost per QALY gained, and incremental cost per evLYG gained. Incremental cost-effectiveness ratios from the lifetime time horizon versus the base-case five-year horizon when applying the standard of care comparator decreased by 4% to 13% across the therapies evaluated. Compared to dupilumab, upadacitinib became dominated in the lifetime scenario.

Scenario Analysis 3 – Abrocitinib with a 12-week Initial Cycle

In phase III trials JADE MONO-1 and 2, Abrocitinib and placebo arms were evaluated at 12-weeks rather than 16-weeks (therapies were evaluated at 16 weeks in JADE COMPARE and in every other trial for included AD therapies). In the base-case model, Abrocitinib's initial impact on patients was evaluated at the end of the first 16-week cycle. To test the impact of this assumption, we built a scenario where Abrocitinib patients were evaluated at 12 weeks. Decreasing the initial cycle from 16-weeks to 12-weeks had no effect on total QALYs or life-years; changes in drug costs drove changes in total costs and ICERs by small amounts presented in table E4.6.

Table E4.6. Effect of 12-week Initial Cycle on Dupilumab Costs

Abrocitinib Outcomes	Base Case (16-week initial cycle)	Alternative Scenario (12-week initial cycle)	% Difference
Drug Cost	$113,174	$111,631	-1.4%
Total Cost	$178,362	$176,762	-0.9%
ICER vs SoC	$148,341	$146,927	-1.0%
ICER vs Dupilumab	$303,352	$302,661	-0.2%

ICER: incremental cost-effectiveness ratio, SoC: standard of care

Scenario Analysis 4 – Combination therapy with topical corticosteroids

Several clinical trials for emerging atopic dermatitis therapies allowed patients to use topical corticosteroids (TCS) in combination with the therapies being assessed, including JADE COMPARE, ECZTRA 3, AD UP, BREEZE AD 7, LIBERTY AD CHRONOS, and Guttmann-Yassky (2018). The use of TCS changes clinical outcomes and is therefore assessed in a scenario analysis separate from the base case analysis. Initial response health state transition probabilities, reported in Table E4.7, were derived from a fixed effects network meta-analysis using data from the aforementioned studies. In addition to differential initial health state transitions, we assumed that patients would use one 60 ml tube of over-the-counter mometasone furoate (a common brand of TCS) per 16-week cycle, whose average wholesale price was $57 (NDC 68462-0385-02)[148].

Drug costs and total costs were higher in the combination therapy scenario for all therapies, with increases ranging from 6-36%. Total costs decreased by 2% for those on standard of care plus TCS. QALYs increased 2-4% across all therapies and SoC in the combination therapy scenario.

Incremental cost-effectiveness results were all nominally larger (9-14%) in the combination therapy scenario when compared to standard of care/placebo but remained in the same order of cost effectiveness. No therapies changed relationship to a cost-effectiveness threshold. When compared to dupilumab, both baricitinib and tralokinumab remained less costly and less effective, however dupilumab switches to dominate upadacitinib in the combination therapy scenario.

Table E4.7. Initial Response Health State Transition Probabilities from the Network Meta-Analysis of Combination Therapy Trials

Treatment	EASI<50	EASI 50-74	EASI 75-89	EASI 90-100
Placebo	56%	19%	14%	10%
Abrocitinib 200 mg	17%	17%	22%	44%
Baricitinib 2 mg	38%	21%	20%	21%
Tralokinumab 300 mg	37%	21%	20%	22%
Upadacitinib 30 mg	9%	12%	19%	60%
Dupilumab 300 mg Q2W	21%	18%	22%	39%

Table E4.8. Results for the Combination Therapy Scenario

Treatment	Drug Cost†	Total Cost	QALYs	Life Years	evLYGs
Abrocitinib*	$128,700	$191,200	3.7	4.8	3.7
Baricitinib	$36,500	$111,200	3.3	4.8	3.3
Tralokinumab*	$69,000	$140,800	3.4	4.8	3.4
Upadacitinib	$171,600	$237,600	3.6	4.8	3.6
Dupilumab	$88,300	$153,800	3.6	4.8	3.6
Standard of Care	$-	$86,300	3.0	4.8	3.0

eVLYG: equal-value life-years gained, QALY: quality-adjusted life-year

*Using a placeholder price; †TCS included as a health state cost, not a drug cost

Table E4.9. Incremental Cost-Effectiveness Ratios for the Combination Therapy Scenario

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLYG
Abrocitinib	SoC	$163,400	$-	$163,400
Baricitinib	SoC	$81,800	$-	$81,800
Tralokinumab	SoC	$142,600	$-	$142,600
Upadacitinib	SoC	$270,600	$-	$270,600
Dupilumab	SoC	$120,600	$-	$120,600
Abrocitinib	Dupilumab	$452,900	$-	$452,900
Baricitinib	Dupilumab	Less Costly, Less Effective	$-	Less Costly, Less Effective
Tralokinumab	Dupilumab	Less Costly, Less Effective	$-	Less Costly, Less Effective
Upadacitinib	Dupilumab	Dominated (More Costly, Less Effective)	$-	Dominated (More Costly, Less Effective)

SOC: Standard of Care

*Using a placeholder price

Scenario Analysis 5 – A portion of responding patients on Tralokinumab switch from q2w to q4w

In a double-blind, placebo+TCS controlled phase III trial (ECZTRA3), patients who achieved EASI 75 and/or clear or almost clear skin after 16 weeks of treatment with tralokinumab every two weeks plus TCS were able to switch to dosing every four weeks. As the cost of treatment would decrease for those taking tralokinumab therapy less frequently, we employed a scenario analysis to assess the potential impact of this dosing schedule on cost-effectiveness estimates.

In ECZTRA3 clinical trial, patients who achieved IGA score of 0 or 1 and/or a minimum of an EASI75 score at the end of the 16-week trial period were rerandomized to receive an equal tralokinumab dose every 4 weeks (Q4W) or every 2 weeks (Q2W). In this scenario analysis, we assume no differential outcomes between the two dosing arms in the model as treatment response at week 32 was comparable between the two dosing arms (92.5% maintained a minimum EASI75 in the Q2W trial arm compared to 90.8% in the Q4W trial arm). We assume in this scenario analysis that 50% of patients achieving EASI75 or higher will switch to Q4W dosing; we make this assumption based on the manufacturer's analysis of the clinical trial data recognizing this is an estimate pending real world data. Because the clinical trial informing the analysis allowed patients to use concurrent TCS therapy, these results are only comparable to the scenario analysis of combination therapy.

The result for this scenario, where all patients achieving EASI75 or higher after the initial 16-week trial period switch to a Q4W dosing regimen, resulted in a 15% decrease in drug costs over a 5-year time horizon and an 8% decrease in total costs. Versus standard of care, tralokinumab's ICER decreased 20% to $115,000 per additional QALY gained, however the therapy was still less effective and less costly than dupilumab. There were no changes in cost-effectiveness threshold categorization.

Table E4.10. Effect of dosing change on Tralokinumab costs

Tralokinumab Outcomes	Base Case (all patients Q2W +TCS)	Alternative Scenario (all patients ≥EASI75 Q4W +TCS)*	% Difference
Drug Cost	$69,044	$58,401	-15%
Total Cost	$140,776	$130,132	-8%
ICER vs SoC	$142,646	$114,765	-20%
ICER vs Dupilumab	Less Costly, Less Effective	Less Costly, Less Effective	NA

Q2W: dosed once every two weeks; Q4W: dosed once every four weeks;

*Switch to Q4W in scenario occurs after initial 16-week trial period and is dependent on their response at 16 weeks

E5. Prior Economic Models

The results of the cross validation showed that our model results were similar to other available atopic dermatitis models. We identified two published economic evaluations of dupilumab for treatment of moderate to severe atopic dermatitis.[149,150] No prior economic evaluations of abrocitinib, baricitinib, upadacitinib, or tralokinumab were found.

Researchers in the US developed a 16-week decision tree linked to a Markov model estimating a price range in which dupilumab plus emollients would be considered cost-effective compared to emollients only (SOC) in adult patients with moderate to severe AD, using efficacy data form SOLO trials.[149] Their analysis used a US payer perspective over a lifetime horizon. The model included two health states, with patients who achieved ≥EASI 75 improvement after 16-week trial continuing on dupilumab, and non-responders switching to and remaining on SOC. After 4-month cycles, dupilumab patients could either continue to respond or transition to SOC or die. They applied utility values change from baseline in the model, with 0.21 for patients on dupilumab, 0.03 for patients on SOC, and 0.25 for non-responders. They found that dupilumab produced 1.12 more QALYs than SOC (15.95 vs 14.83) and $32,089 additional non-dupilumab drug costs ($299,449 vs $331,538). Although their model did not generate an incremental cost-effectiveness ratio, the QALYs and lifetime non-dupilumab drug costs estimates are similar to ours.

Costanzo and colleagues estimated the cost effectiveness of dupilumab plus SOC vs SOC in the Italian adult population with severe AD, using a 1-year decision tree followed by a lifetime horizon Markov model.[150] Their analysis adopted the Italian National Health Service perspective, with utility values of 0.66 at baseline for both groups, 0.95 for dupilumab and 0.78 for SOC after week 16, and 0.78 for non-responder group. They found that dupilumab generated 2.42 more QALYs than SOC (16.96 vs 14.57), with an incremental cost-effectiveness ratio of € 33,263 per QALY gained. The results from their analyses are not directly comparable to the results of the cost-effectiveness analysis presented in this report, due to different severity of disease in two populations. However, it is interesting to note that the utility values of dupilumab used in their study are slightly higher than values used in our model. Whereas we used same utility values to dupilumab and SOC, ranging from 0.81 to 0.89 for responders and 0.60 for non-responder.

In the 2017 ICER report, we estimated the cost effectiveness of dupilumab for moderate-to-severe AD compared to usual care over a lifetime horizon from a US health system perspective.[116] We found that dupilumab produced 1.91 more QALYs than usual care (16.28 vs 14.37), with an incremental cost-effectiveness ratio of $101,830 per QALY gained. The model results in this analysis were similar to the prior ICER report.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapies (i.e., usual care, dupilumab) for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment. To estimate the size of the potential candidate populations for treatment, we used inputs from the US market leading biologic therapy, dupilumab, across the following age categories (12-17 years old; and 18 and older).[151] We note that limitations exist in using cost-effectiveness model findings within the adult population for estimating the potential budget impact within younger ages but consider those limitations to be outweighed by a comprehensive approach that includes all eligible age categories. For adults (18 years and older), evidence suggests 1,675,000 US individuals have moderate-to-severe uncontrolled disease and are eligible for treatment.[151] For adolescents (age 12-17), evidence suggests 389,000 US individuals have moderate-to-severe uncontrolled disease and are eligible for treatment.[151] For the purposes of this analysis, we summed across the two age categories and assumed that 20% of these patients would initiate new treatments in each of the five years, or 412,800 patients per year.

Consistent with the ICER Reference Case, we calculated the budget impact of new treatments (abrocitinib, baricitinib, tralokinumab, and upadacitinib) given these treatments' displacement of dupilumab and usual care. We assigned an equal distribution of annually eligible individuals for each of the four treatments (abrocitinib, baricitinib, tralokinumab, and upadacitinib) = 412,800 / 4 = 103,200 new individuals per treatment per year (for five years). Per the ICER Reference Case, we assumed that all the dupilumab users switch over to each of the four new treatments in the potential budget impact analyses. We assumed that approximately 2.5% of those adolescents and adults eligible in the US are currently taking dupilumab (approximately 51,600) based on reports that over 100,000 US patients have started dupilumab.[152] This assumption results in a 10% mix of dupilumab and 90% mix of usual care alone upon which each new treatment is evaluated.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[153,154] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

The five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $819 million per year for new drugs for 2019-2020.

Results

Table F.1 illustrates the per-patient budget impact results in more detail, for:

- Abrocitinib WAC ($46,600* per year), discounted WAC ($41,400* per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY ($41,800, $30,600, and $19,400 per year, respectively) compared to usual care;
- Baricitinib WAC ($29,000 per year), discounted WAC ($19,400 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY ($33,300, $24,400, and $15,600 per year, respectively) compared to usual care;
- Tralokinumab WAC ($41,800*per year), discounted WAC ($31,100* per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY ($35,000, $25,700, and $16,400 per year, respectively) compared to usual care and;
- Upadacitinib WAC ($64,300 per year), discounted WAC ($63,400 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY ($41,500, $30,400, and $19,300 per year, respectively) compared to usual care.

* Based on placeholder prices that were assumed for abrocitinib and tralokinumab. Interpret findings with caution.

We note that dupilumab is considered a part of usual care and therefore not displayed as a standalone result.

Table F1. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon

	Average Annual Per Patient Budget Impact				
	WAC*	**Discounted WAC***	**$150,000/QALY**	**$100,000/QALY**	**$50,000/QALY**
Abrocitinib vs. usual care	$31,200	$27,600	$27,300	$18,800	$10,300
Baricitinib vs. usual care	$8,600	$5,000	$10,700	$7,400	$4,100
Tralokinumab vs. usual care	$16,500	$11,700	$13,100	$9,100	$5,000
Upadacitinib vs. usual care	$38,300	$38,400	$22,400	$15,200	$8,100

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

* Placeholder prices were assumed for abrocitinib and tralokinumab. Interpret findings with caution.

Figures F.1-F.4 illustrate the cumulative per-patient budget impact calculations for abrocitinib, baricitinib, tralokinumab, and upadacitinib compared to usual care (including 10% of patients treated with dupilumab), based on the net prices used within the cost-effectiveness analysis. We suggest caution in interpreting the potential budget impact of abrocitinib and tralokinumab due to the placeholder annual net prices assumed. We observed the general trend of decreasing year over year per treated patient potential budget impacts due to treatment discontinuation over time. Year 4 in the cost-effectiveness model included an additional model cost cycle compared to the other years . The same year 4 method was applied across evaluated treatments and for usual care and therefore, we did not smooth over the year-by-year cumulative findings.

Figure F1. Cumulative Net Cost Per Patient Treated with Abrocitinib for Five Years at Placeholder $41,400 per Year Price*

* Placeholder prices were assumed. Interpret findings with caution.

Figure F2. Cumulative Net Cost Per Patient Treated with Baricitinib for Five Years at $19,400 per Year Price

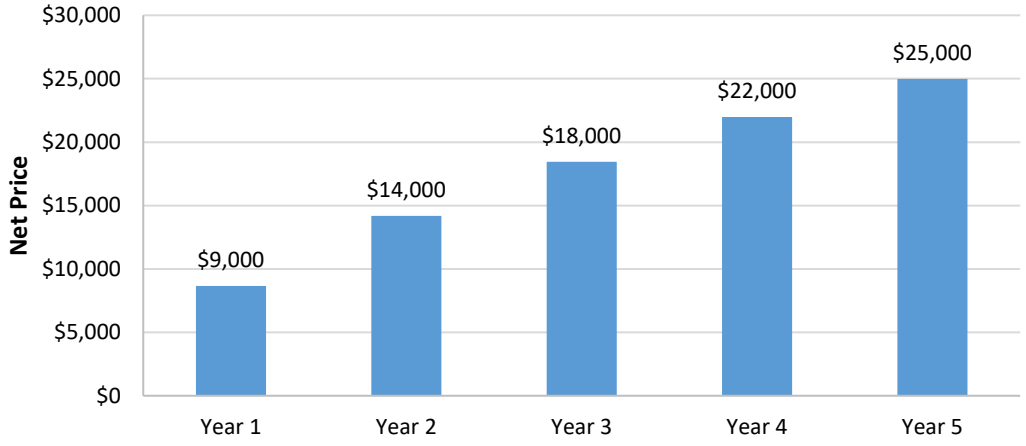
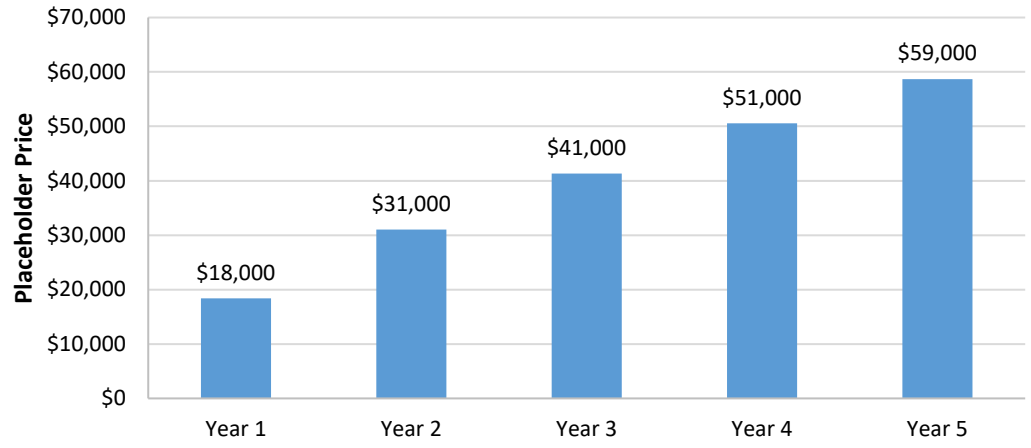


Figure F3. Cumulative Net Cost Per Patient Treated with Tralokinumab for Five Years at Placeholder $31,100 per Year Price*



* Placeholder prices were assumed. Interpret findings with caution.

Figure F4. Cumulative Net Cost Per Patient Treated with Upadacitinib for Five Years at $63,400 per Year Price

G. Additional Evidence Tables

Moderate to Severe Population

Table G1.1. Study Quality Table[35-37,40,42,45,46,48,50,51,56,63,64,69,80,81]

Trial	Comparable Groups	Non-differential Follow-up	Patient/ Investigator Blinding	Clear Definition of Intervention	Clear Definition of Outcomes	Selective Outcome Reporting	Measurements Valid	Intention-to-treat Analysis	Approach to Missing Data	USPSTF Rating
Abrocitinib										
JADE MONO-1	Yes	Yes	Yes	Yes	Yes	No	Yes	No	MI	Good
JADE MONO-2	Yes	No	Yes	Yes	Yes	No	Yes	No	MI	Good
JADE COMPARE	Yes	Yes	Yes	Yes	Yes	No	Yes	No	NRI	Good
Gooderham 2019	Yes	No	Yes	Yes	Yes	No	Yes	No	MI*	Fair
Baricitinib										
BREEZE-AD1	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MI and NRI	Good
BREEZE-AD2	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MI and NRI	Good
BREEZE-AD5	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MM**	Good
BREEZE-AD7	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MM	Good
Guttman-Yassky 2018	Yes	No	Yes	Yes	Yes	No	Yes	Yes	MM	Good
Tralokinumab										
ECZTRA 1	Yes	Yes	Yes	Yes	Yes	No	Yes	No	NRI and MI	Good
ECZTRA 2	Yes	Yes	Yes	Yes	Yes	No	Yes	No	NRI and MI	Good
ECZTRA 3	Yes	Yes	Yes	Yes	Yes	No	Yes	No	NRI and MI	Good

Trial	Comparable Groups	Non-differential Follow-up	Patient/ Investigator Blinding	Clear Definition of Intervention	Clear Definition of Outcomes	Selective Outcome Reporting	Measurements Valid	Intention-to-treat Analysis	Approach to Missing Data	USPSTF Rating
Upadacitinib										
MEASURE Up 1	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NRI and MM	Good
MEASURE Up 2	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NRI and MM	Good
AD-UP	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NRI and MM	Good
Guttman-Yassky 2020	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	LOCF and NRI	Good
Dupilumab										
LIBERTY AD SOLO 1	Yes	Yes	Yes	Yes	Yes	No	Yes	No	MI, LOCF and NRI	Good
LIBERTY AD SOLO 2	Yes	Yes	Yes	Yes	Yes	No	Yes	No	MI, LOCF and NRI	Good
LIBERTY AD CHRONOS	Yes	Yes	Yes	Yes	Yes	No	Yes	No	MI	Good
Thaci 2016	Yes	Yes	Yes	Yes	Yes	No	Yes	No	LOCF and NRI	Good

Includes only published RCTs. LOCF: last observation carried forward, MI: multiple imputation, MM: mixed-effects model, NRI: non-responder imputation.
*Mixed-effects model repeated measure and generalized linear mixed model assumption, **Mixed-effects model repeated measure.

Table G1.2 Key Features

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
Abrocitinib					
Phase III JADE MONO-1[35,75,155] Simpson 2020 Lancet + Simpson 2021 RAD Abstract	N= 387 Ages 12+ with moderate to severe atopic dermatitis DB, PC, RCT	Once-daily oral administration in one of the following doses for 12 weeks: •Abrocitinib 200 mg •Abrocitinib 100 mg •Placebo	**Prohibited medication:** concomitant topical therapies (corticosteroids, calcineurin inhibitors, tars, antibiotic creams, and topical antihistamines) •If receiving non-AD related concomitant medications, must be on stable regimen. •Prior drug/non-drug treatment, concomitant drug and non-drug treatment summarized according to CaPS	•Age: ≥ 12 years with minimum body weight of 40 kg •Diagnosis of atopic dermatitis (AD) for at ≥1 year and current status of moderate to severe disease (≥ the following scores: BSA 10%, IGA 3, EASI 16, Pruritus NRS severity 4 • Inability to tolerate topical AD treatments or require systemic treatments for AD control	•Unwilling to discontinue current AD medications prior to study or require treatment with prohibited medications during study •Prior treatment with JAK inhibitors •Other active non-AD skin diseases •Medical history including thrombocytopenia, coagulopathy, or platelet dysfunction, current or history of certain infections, cancer, lymphoproliferative disorders
Phase III JADE MONO-2[36,75,156] Silverberg 2020 JAMA Dermatology	N=391 Ages 12+ with moderate to severe atopic dermatitis DB, PC, RCT	Once-daily oral administration in one of the following doses for 12 weeks: •Abrocitinib 200 mg •Abrocitinib 100 mg •Placebo	**Permitted medication: O**ral antihistamines and topical non-medicated emollients **Prohibited medication:** Concomitant use of topical (corticosteroids, calcineurin inhibitors, tars, antibiotic creams, or topical antihistamines) or systemic therapies for AD	•Age: ≥12 years with minimum body weight of 40 kg •Diagnosis of atopic dermatitis (AD) for at ≥1 year and current status of moderate to severe disease (≥ the following scores: BSA 10%, IGA 3, EASI 16, Pruritus NRS severity 4 •Recent history of inadequate response or inability to tolerate topical AD treatments or require systemic treatments for AD control	•Unwilling to discontinue current AD medications prior to study or require treatment with prohibited medications during study •Prior treatment with JAK inhibitors •Other active non-AD skin diseases •Medical history including thrombocytopenia, coagulopathy, or platelet dysfunction, current or history of certain infections, cancer, lymphoproliferative disorders

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
Phase III JADE TEEN[39,41,77,84] Pfizer data on file + Eichenfield 2021 AAAI Abstract + Eichenfield 2021 RAD Abstract	N=285 Ages 12-17 with moderate to severe atopic dermatitis DB, PC, RCT	Once-daily oral administration in one of the following doses for 12 weeks: •Abrocitinib 200 mg •Abrocitinib 100 mg •Placebo	**Permitted medication:** background topical therapy **Permitted medication:** NR	•Age: ≥12-17 years with minimum body weight of 40 kg •Diagnosis of atopic dermatitis (AD) for at ≥1 year and current status of moderate to severe disease (≥ the following scores: BSA 10%, IGA 3, EASI 16, Pruritus NRS severity 4	•Acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation •Unwilling to discontinue current AD medications prior to the study or require treatment with prohibited medications during the study •Prior treatment with JAK inhibitors •Other active non-AD inflammatory skin diseases or conditions affecting skin •Medical history including thrombocytopenia, coagulopathy or platelet dysfunction, malignancies, current or history of certain infections, lymphoproliferative disorders, and other medical conditions at the discretion of the investigator
Phase III JADE COMPARE[37,39] Bieber 2021 NEMJ + Pfizer data on file	N= 837 Adults 18+ with moderate to severe atopic dermatitis DB, PC, RCT	•Abrocitinib (200 mg) + placebo Q2W (to Week 16)→abrocitinib (200 mg) (Week 20) •Abrocitinib (100 mg) + placebo Q2W (to Week	Permitted/provided: non-medicated emollients at least twice a day and medicated topical therapy such as corticosteroids, calcineurin inhibitors, or PDE4 inhibitors, as per protocol guidance, to treat active lesions during study.	•18+ diagnosed with AD for ≥1 year and current status of moderate to severe disease (≥ the following scores: BSA 10%, IGA 3, EASI 16, Pruritus NRS severity 4) •Documented recent history (within 6 months before screening) of inadequate	•Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior •Medical history including thrombocytopenia, coagulopathy or platelet

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
		16) →abrocitinib (100 mg) (Week 20) •Dupilumab (300 mg; with a 600 mg loading dose at baseline) + placebo once-daily to Week 16) →placebo once-daily (Week 20) •Placebo + dupilumab Q2W (to Week 16) →abrocitinib (100 mg) (Week 20) •Placebo + dupilumab Q2W (to Week 16) →abrocitinib (200 mg) (Week 20) Placebo (to week 16) → placebo (week 20)	If receiving concomitant medications for any reason other than AD, must be on a stable regimen prior to Day 1 and through the duration of the study	response to treatment with medicated topical therapy for AD for at least 4 weeks, or who have required systemic therapies for control of their disease. •Must be willing and able to comply with standardized background topical therapy	dysfunction, Q wave interval abnormalities, current or history of certain infections, cancer, lymphoproliferative disorders •Other active nonAD inflammatory skin diseases or conditions affecting skin •Prior treatment with JAK inhibitors •Previous treatment with dupilumab •Unwilling to discontinue current AD medications prior to study or require treatment with prohibited medications during study
Phase III JADE EXTEND[76,107] Reich 2021 Abstract and Shi 2021 Abstract	N=1116 Ages 12+ moderate to severe AD	•Abrocitinib 200-mg •Abrocitinib 100-mg	NR	•Patients ages 12+ and meets minimum body weight •Must have completed full treatment period or the full rescue treatment period of a qualifying Parent study OR must have completed the full open-label run-in period in B7451014 and did not meet	•Other acute or chronic medical or psychiatric condition including recent (within the past year) or behavior or laboratory abnormality that may interfere with the study •Currently have active forms of other inflammatory

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
				the protocol-specified response criteria at Week 12 •Must avoid prolonged exposure to the sun, tanning booths, sun lamps or other ultraviolet light sources	skin diseases, i.e., not AD or have evidence of skin conditions (e.g., psoriasis, seborrheic dermatitis, Lupus) •Discontinued from treatment early in a qualifying Parent study OR triggered a discontinuation criterion at any point during the qualifying Parent study which in the opinion of the investigator, or sponsor, is an ongoing safety concern •Ongoing AE in the qualifying Parent study that is an ongoing safety concern
Phase IIb[40,157] Gooderham 2019	N= 267 Ages 18 to 75 with a clinical diagnosis of moderate to severe atopic dermatitis	Abrocitinib 10 mg Abrocitinib 30 mg **Abrocitinib 100 mg** **Abrocitinib 200 mg** **Placebo**	**Permitted medication:** oral antihistamines and nonmedicated emollient (CeraVe lotion [CeraVe]; or Aquaphor [Beiersdorf Inc]) and sunscreen (both provided by the sponsor) **Prohibited:** systemic or topical medication	Adults aged 18 to 75 years with a clinical diagnosis of moderate to severe AD (percentage of affected body surface area [%BSA] ≥10; Investigator's Global Assessment [IGA] score ≥3; and Eczema Area and Severity Index [EASI] score ≥12) for 1 year or more before day 1 of the study and inadequate response to topical medications (topical corticosteroids or topical calcineurin inhibitors) for 4 weeks or more (based on investigator's judgment) or inability to receive topical	Patients who had used topical corticosteroids or topical calcineurin inhibitors within 1 week of the first dose of study drug were excluded

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
				treatment within 12 months before the first dose of study drug because it was medically inadvisable	
Baricitinib					
Phase III BREEZE-AD1[42,108] Simpson 2020 BJD	Adults 18+ with moderate to severe AD DB, PC, RCT	Daily dose for 16 weeks: •Baricitinib 4 mg (High) •Baricitinib 2 mg (Mid) •Baricitinib mg (Low) •Placebo	**Provided/required:** emollient **Prohibited:** intra-articular corticosteroid injection, parenteral corticosteroids, JAK inhibitor treatment, monoclonal antibody	• Diagnosed with moderate to severe Atopic Dermatitis for ≥ 12 months • Inadequate response or intolerance to existing topical medications within 6 months of screening • Willing to discontinue certain treatments for eczema (such as systemic and topical treatments during a washout period) • Agree to use emollients daily	•History of other concomitant skin conditions, skin disease or eczema herpeticum •Currently experiencing a skin infection or illness that requires or is being treated with topical or systemic antibiotics or corticosteroids •Prior treatment of: oral JAK inhibitor, parenteral corticosteroids injection, or intra-articular corticosteroid injection, within 2 weeks prior to study entry or 6 weeks prior to randomization •Have high blood pressure •Had major surgery within the past 8 weeks •Have experienced any of the following within 12 weeks of screening: VTE, myocardial infarction (MI), unstable ischemic heart disease, stroke, heart failure.

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
					•Have a history of recurrent (≥ 2) VTE or are considered at high risk of VTE •Have a history or presence of cardiovascular, respiratory, hepatic, liver, gastrointestinal, endocrine, hematological, neurological, lymphoproliferative disease or neuropsychiatric disorders •Have a current or recent clinically serious viral, bacterial, fungal, or parasitic infection including herpes zoster, tuberculosis.

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
Phase III BREEZE-AD2[42,109] Simpson 2020 BJD	Adults 18+ with moderate to severe AD DB, PC, RCT	Daily dose for 16 weeks: •Baricitinib 4 mg (High) •Baricitinib 2 mg (Mid) •Baricitinib 1 mg (Low) •Placebo	**Provided/required:** emollient **Prohibited:** intra-articular corticosteroid injection, parenteral corticosteroids, JAK inhibitor treatment, monoclonal antibody	• Diagnosed with moderate to severe Atopic Dermatitis for ≥ 12 months • Inadequate response or intolerance to existing topical medications within 6 months of screening • Willing to discontinue certain treatments for eczema (such as systemic and topical treatments during a washout period) • Agree to use emollients daily	•History of other concomitant skin conditions, skin disease or eczema herpeticum •Currently experiencing a skin infection or illness that requires or is being treated with topical or systemic antibiotics or corticosteroids •Prior treatment of: oral JAK inhibitor, parenteral corticosteroids injection, or intra-articular corticosteroid injection, within 2 weeks prior to study entry or 6 weeks prior to randomization •Have high blood pressure •Had major surgery within the past 8 weeks •Have experienced any of the following within 12 weeks of screening: VTE, myocardial infarction (MI), unstable ischemic heart disease, stroke, heart failure. •Have a history of recurrent (≥ 2) VTE or are considered at high risk of VTE •Have a history or presence of cardiovascular, respiratory, hepatic, liver, gastrointestinal, endocrine, hematological, neurological,

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
					lymphoproliferative disease or neuropsychiatric disorders •Have a current or recent clinically serious viral, bacterial, fungal, or parasitic infection including herpes zoster, tuberculosis.

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
Phase III BREEZE-AD3[43,44] Eli Lilly Oct 31, 2020 (Press release) + Eli Lilly data on file	Adults 18+ with moderate to severe AD DB, PC, RCT	•Baricitinib 4 mg •Baricitinib 2 mg •Placebo	**Not reported**	• Have completed the final active treatment visit for an originating study eligible to enroll participants directly into study BREEZE-AD3 OR • Meet criteria for NCT03334396 or NCT03334422.	• Had investigational product permanently discontinued at any time during a previous baricitinib study. • Had temporary investigational product interruption continue at the final study visit of a previous baricitinib study and, in the opinion of the investigator, this poses an unacceptable risk for the participant's participation in the study.

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
Phase III BREEZE-AD5[44,45,49] Simpson 2021 JAAD + Eli Lilly data on file	N=440 Adults 18+ with moderate to severe AD DB, PC, RCT	Daily dose for 16 weeks: •Baricitinib 2 mg (Mid) •Baricitinib 1 mg (Low) •Placebo	Not reported	• Diagnosed with moderate to severe Atopic Dermatitis for ≥12 months, including all of the following: • EASI score ≥16 • IGA score of ≥3 • ≥10% of BSA involvement • Inadequate response or intolerance to existing topical medications within 6 months of screening • Willing to discontinue certain treatments for eczema (such as systemic and topical treatments during a washout period) • Agree to use emollients daily	• Currently experiencing or have a history of other concomitant skin conditions (e.g., psoriasis or lupus erythematosus), or a history of erythrodermic, refractory, or unstable skin disease that requires frequent hospitalizations and/or intravenous treatment for skin infections • History of eczema herpeticum within 12 months, and/or a history of 2 or more episode of eczema herpeticum in the past • Participants who are currently experiencing a skin infection that requires treatment, or is currently being treated, with topical or systemic antibiotics • Any serious illness that is anticipated to require the use of systemic corticosteroids or otherwise interfere with study participation or require active frequent monitoring (e.g., unstable chronic asthma) • Treated with the following therapies: • Monoclonal antibody

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
					for less than 5 half-lives before randomization • Received prior treatment with any oral JAK inhibitor less than 4 weeks before randomization • Received any parenteral corticosteroid administered by IM or IV injection within 6 weeks of planned randomization or are anticipated to require parenteral injection of corticosteroids during the study • Have had an intra-articular corticosteroid injection within 6 weeks of planned randomization • Probenecid at the time of randomization that cannot be discontinued for the duration of the study • Have high blood pressure • Had major surgery within the past 8 weeks • Have experienced any of the following within 12 weeks of screening: MI, unstable ischemic heart disease, stroke, or New York Heart Association Stage III/IV heart failure • Have a history of VTE, or are considered at high risk

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
					for VTE • Have a history or presence of cardiovascular, respiratory, hepatic, chronic liver disease gastrointestinal, endocrine, hematological, neurological, lymphoproliferative disease or neuropsychiatric disorders or any other serious and/or unstable illness • Have a current or recent clinically serious viral, bacterial, fungal, or parasitic infection including herpes zoster, tuberculosis.

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
Phase III BREEZE-AD6[82] Simpson 2021 RAD Abstract	Adults 18+ with moderate to severe AD who completed the first 16 weeks of BREEZE-AD5	Baricitinib 2 mg QD + TCS	TCS permitted	• Have not participated in a Study JAIW (NCT03435081) • Have moderate to severe AD, including all of the following: EASI score ≥16, IGA score of ≥3, 10%- 50% BSA involvement • Have had inadequate response or intolerance to existing topical (applied to the skin) medications within 6 months preceding screening. • Are willing to discontinue certain treatments for eczema (such as systemic and topical treatments) • Agree to use emollients daily.	•Are currently experiencing or have a history of other concomitant skin conditions (e.g., psoriasis or lupus erythematosus) •A history of eczema herpeticum within 12 months •Skin infection requiring treatment with topical or systemic antibiotics. •Have been treated with the following therapies: monoclonal antibody for less than 5 half-lives before randomization, any oral JAK inhibitor less than 4 weeks before randomization, any parenteral corticosteroid administered by intramuscular or intravenous injection within 6 weeks of planned randomization •Have high blood pressure characterized by a repeated systolic blood pressure >160 millimeters of mercury (mm Hg) or diastolic blood pressure >100 mm Hg. •Have experienced any of the following within 12 weeks of screening: myocardial infarction (MI), unstable ischemic heart

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
					disease, stroke, or NYHA Stage III/IV heart failure •Have a history of VTE, cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, hematological, neurological, lymphoproliferative disease or neuropsychiatric disorders •Have a current or recent clinically serious viral, bacterial, fungal, or parasitic infection including herpes zoster, tuberculosis
Phase III BREEZE-AD7 Reich 2020[46,47] Reich 2020 JAMA	≥18 years of age, moderate-to-severe atopic dermatitis DB, PC, RCT	•Baricitinib 4 mg QD + TCS •Baricitinib 2 mg QD + TCS •Placebo QD + TCS	All patients received moderate- and/or low potency TCS (such as 0.1% triamcinolone cream and 2.5% hydrocortisone ointment, respectively) for active lesions; topical calcineurin inhibitors and/or crisaborole, in countries where approved, could be used in place of TCS, with guidance to limit use to areas considered inadvisable for TCS	≥18 years of age, moderate-to-severe atopic dermatitis (IGA 3 or 4), inadequately controlled by topical treatment or medically inadvisable, AD ≥1 year	~VTE or MACE w/l 12 weeks of screening; history of recurrent or high risk VTE; serious comorbid condition requiring systemic corticosteroids; history of alcohol or drug abuse; laboratory abnormalities
Phase II[48] Guttmann-Yassky 2018 JAAD	≥18 years of age, moderate-to-severe atopic dermatitis DB, PC, RCT	•Baricitinib 4 mg QD + TCS •Baricitinib 2 mg QD + TCS •Placebo QD + TCS	Triamcinolone was used throughout the study according to the labeling or as recommended by the investigator	≥18 years of age; moderate-to-severe atopic dermatitis; EASI ≥12; BSA ≥10%; disease duration ≥2 years; Inadequate response to emollients, TCS, systemic corticosteroids, or immunosuppressants; study conducted in US and Japan	History of TB, HIV, HepC, HepB; Pregnant or nursing females; participants not agreeing to use adequate contraception; serious comorbid condition that could interfere with study

Trial	Patient Population	Interventions	Concomitant Therapy	Inclusion Criteria	Exclusion Criteria
					participation; certain vaccines

Tralokinumab					
Phase III ECZTRA 1[63,65] Wollenburg 2020 British Journal of Dermatology + LeoPharma data on file	N= 802 Adults 18+ with moderate to severe atopic dermatitis	**Pre-initial treatment (day 0):** • Tralokinumab 600 mg loading dose **Initial treatment period (16 weeks):** • Tralokinumab 300 mg injection (2 injections of 150 mg each) Q2W • Placebo Q2W **Maintenance treatment period (36 weeks):** • Tralokinumab 300 mg injection Q2W • Tralokinumab 300 mg injection Q4W • Placebo	**Provided:** patients instructed to use emollient twice daily	•Age 18+ •Diagnosis of AD for ≥1 year •Subjects who have a recent history of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable. •AD involvement of ≥10% body surface area at screening and baseline. •EASI≥12 screening, ≥16 at baseline •IGA≥3 •Applied a stable dose of emollient twice daily for at least 14 days before randomization	•Active dermatologic conditions that may confound the diagnosis of AD. •Use of tanning beds or phototherapy 6 weeks prior to randomization. •Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to randomization. •Treatment with TCS and/or TCI within 2 weeks prior to randomization. •Active skin infection within 1 week prior to randomization. •Clinically significant infection 4 weeks prior to randomization. •A helminth parasitic infection within 6 months prior study entry. •Tuberculosis requiring treatment within the 12 months prior to screening. •Known primary immunodeficiency disorder. •Positive HepB or HepC

Phase III ECZTRA 2[63,65] Wollenburg 2020 British Journal of Dermatology + LeoPharma data on file	N= 794 Adults 18+ with moderate to severe atopic dermatitis DB, PC, RCT	**Pre-initial treatment (day 0):** • tralokinumab 600 mg loading dose **Initial treatment period (16 weeks):** • tralokinumab 300 mg injection (2 injections of 150 mg each) Q2W • placebo Q2W **Maintenance treatment period (36 weeks):** • tralokinumab 300 mg injection Q2W • tralokinumab 300 mg injection Q4W • placebo	**Provided:** patients instructed to use emollient twice daily	•Age 18+ •Diagnosis of AD for ≥1 year •Subjects who have a recent history of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable. •AD involvement of ≥10% body surface area at screening and baseline. •EASI≥12 screening, ≥16 at baseline •IGA≥3 •Applied a stable dose of emollient twice daily for at least 14 days before randomization	•Active dermatologic conditions that may confound the diagnosis of AD. •Use of tanning beds or phototherapy 6 weeks prior to randomization. •Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to randomization. •Treatment with TCS and/or TCI within 2 weeks prior to randomization. •Active skin infection within 1 week prior to randomization. •Clinically significant infection 4 weeks prior to randomization. •A helminth parasitic infection within 6 months prior study entry. •Tuberculosis requiring treatment within the 12 months prior to screening. •Known primary immunodeficiency disorder. •Positive HepB or HepC

Phase III ECZTRA 3 (with TCS)[64,65] Silverberg 2020 British Journal of Dermatology + LeoPharma data on file	N=380 Adults 18+ with moderate-to-severe atopic dermatitis DB, PC, RCT	**Pre-initial treatment (day 0):** •tralokinumab 600 mg injection **Initial treatment period (16 weeks)** •tralokinumab 300 mg injection Q2W + optional TCS •placebo Q2W + optional TCS **Maintenance treatment period (32 weeks)** •tralokinumab 300 mg injection Q2W + optional TCS •tralokinumab 300 mg injection Q4W + optional TCS •placebo Q2W + TCS	**permitted/provided:** TCS, emollient	•Age 18+ •Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD. •History of AD for ≥1 year. •Subjects who have a recent history of inadequate response to treatment with topical medications. •AD involvement of ≥10% body surface area at screening and baseline. •Stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomization.	•Subjects for whom TCS are medically inadvisable •Active dermatologic conditions that may confound AD diagnosis •Use of tanning beds or phototherapy within 6 weeks prior to randomization. •Treatment with systemic immunosuppressive/immunomodulating drugs or systemic corticosteroid within 4 weeks prior to randomization. •Treatment with TCS, topical calcineurin inhibitors (TCI), or topical phosphodiesterase 4 (PDE-4) inhibitor within 2 weeks prior to randomization. •Receipt of any marketed biological therapy including dupilumab or investigational biologic agents. •Active skin infection within 1 week prior to randomization. •Helminth parasitic infection within 6 months prior to study start •Tuberculosis requiring treatment within the 12 months prior to screening. •Known primary immunodeficiency disorder.

Phase III ECZTEND[78] Blauvelt 2021 RAD Abstract	N=1175 Patients 18+ who participated in previous tralokinumab clinical trials	Tralokinumab 300 mg Q2W	Optional TCS	• Completed the treatment period(s) of one of the parent trials: LP0162-1325, -1326, -1339, -1341 or -1342 • Able and willing to self-administer tralokinumab treatment (or have it administered by a caregiver) at home after the initial 3 injection visits at the trial site • Stable dose of emollient twice daily (or more, as needed) for at least 14 days before baseline	• More than 20 weeks have elapsed since the subject received the last injection of investigational medicinal product (IMP) in the parent trial • Subjects who, during the parent trial, developed an AE or SAE related to tralokinumab that led to temporary discontinuation of trial treatment • Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to baseline • Treatment with topical phosphodiesterase 4 inhibitors within 2 weeks prior to baseline • A helminth parasitic infection • Tuberculosis requiring treatment within 12 months prior to screening
Upadacitinib					
Phase III MEASURE UP 1[71,80] Guttman-Yassky 2021 Lancet + Simpson 2021 AAD VMX Abstract	N= 847 Ages 12-75 years with moderate to severe AD DB, PC, RCT	**Week 1-16:** • Upadacitinib 30 mg • Upadacitinib 15 mg • Placebo **After Week 16**: • Upadacitinib 30 mg • Upadacitinib 15 mg	**Prohibited medications:** UV light therapy, JAK inhibitors, systemic or topical, bleach baths (if more than 2x/week during study), topical treatments for AD	• Active moderate to severe atopic dermatitis defined by EASI, IGA, BSA, and pruritus • Candidate for systemic therapy or have recently required systemic therapy for atopic dermatitis	• Prior exposure to any JAK inhibitor • Unable or unwilling to discontinue current AD treatments prior to study • Requirement of prohibited medications during the study • Other active skin diseases/infections requiring systemic treatment or would interfere with appropriate assessment of atopic dermatitis lesions

Phase III MEASURE UP 2[71,80] Guttman-Yassky 2021 Lancet + Simpson 2021 AAD VMX Abstract	N= 836 Ages 12-75 years with moderate to severe AD DB, PC, RCT	**Week 1-16:** • Upadacitinib 30 mg • Upadacitinib 15 mg • Placebo **After Week 16:** • Upadacitinib 30 mg • Upadacitinib 15 mg	**Prohibited medications:** UV light therapy, JAK inhibitors, systemic or topical, bleach baths (if more than 2x/week during study), topical treatments for AD	• Active moderate to severe atopic dermatitis defined by EASI, IGA, BSA, and pruritus • Candidate for systemic therapy or have recently required systemic therapy for atopic dermatitis	• Prior exposure to any JAK inhibitor • Unable or unwilling to discontinue current AD treatments prior to study • Requirement of prohibited medications during the study • Other active skin diseases/infections requiring systemic treatment or would interfere with appropriate assessment of atopic dermatitis lesions
Phase III AD-UP (with TCS)[71,81] Reich 2021 Lancet + Simpson 2021 AAD VMX Abstract	N~901 Ages 12-75 with moderate to severe AD DB, PC, RCT	**Week 1-16** • Upadacitinib 30 mg + topical corticosteroids (TCS) • Upadacitinib 15 mg + TCS • Placebo + TCS **After Week 16:** • Upadacitinib 30 mg + TCS • Upadacitinib 15 mg + TCS	**TCS** prohibited meds, no details	• Active moderate to severe atopic dermatitis defined by EASI, IGA, BSA, and pruritus • Candidate for systemic therapy or have recently required systemic therapy for atopic dermatitis • Able to tolerate topical corticosteroids for atopic dermatitis lesions	• Prior exposure to any JAK inhibitor • Unable or unwilling to discontinue current AD treatments prior to study • Requirement of prohibited medications during the study • Other active skin diseases/infections requiring systemic treatment or would interfere with appropriate assessment of atopic dermatitis lesions

Phase IIIb Heads Up[70,83] Blauvelt 2021 JAMA Dermatology + AbbVie data on file	N= 692 Adults 18 and older with moderate to severe AD MC, RCT, DB, DD, AC	**Dose for 24 weeks** *Arm 1* Upadacitinib 30 mg daily (oral) Placebo *Arm 2* Dupilumab 300 mg every other week (subcutaneous) Placebo	**Permitted:** topical emollients **Prohibited Medications:** JAK inhibitors, prior dupilumab use, TCS, TCIs	Patients 18 and older with moderate to severe AD Participant has active moderate to severe atopic dermatitis (AD) defined by Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), Body Surface Area (BSA) and pruritus. Participant is a candidate for systemic therapy or have recently required systemic therapy for AD.	Participant has prior exposure to Janus Kinase (JAK) inhibitor. Participant has prior exposure to dupilumab. Participant is unable or unwilling to discontinue current AD treatments prior to the study. Participant has requirement of prohibited medications during the study. Participant has other active skin diseases or skin infections requiring systemic treatment or would interfere with appropriate assessment of AD lesions. Female participant who is pregnant, breastfeeding, or considering pregnancy during the study.
Phase IIb[69,158] Guttman-Yassky 2020 Allergy and Immunology + Reich 2021 RAD Abstract	N=167 Ages 18-75 years with moderate to severe AD DB, PC, RCT	**Week 1-16 (period 1):** •upadacitinib 30 mg QD •upadacitinib 15 mg QD •upadacitinib 7.5 mg QD •placebo **Week 16-88 (period 2 - rerandomization stratified by EASI**	**Permitted:** emollient, orally administered antibiotics for superficial skin infections **Prohibited medications:** Concomitant medications for the treatment of AD, JAK inhibitors (other than upadacitinib) and other non-biologic systemic treatments for AD; all biologic therapies, corticosteroids, phototherapy, extensive	•Atopic dermatitis with a diagnosis confirmed by a dermatologist and onset of symptoms at least 1 year prior to Baseline. •Moderate to severe atopic dermatitis defined by EASI≥16, BSA≥10% and IGA score≥ 3 at the Baseline visit.	•Prior exposure to any systemic or topical Janus kinase (JAK) inhibitor (including but not limited to tofacitinib, baricitinib, ruxolitinib, and filgotinib). •Treatment with topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin within 10 days prior to the Baseline visit. •Prior exposure to dupilumab or exposure to systemic therapies for AD including corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4

		75 response at week 16): •upadacitinib 30 mg QD •upadacitinib 15 mg QD •upadacitinib 7.5 mg QD •placebo	light exposure that could have affected study outcomes; all topical therapies, investigational drugs, live vaccines, cannabis, and strong inducers and inhibitors of cytochrome P450 3A; and traditional Chinese medicine	•Documented history (within 1 year prior to the screening visit) of inadequate response to treatment with topical corticosteroids (TCS), or topical calcineurin inhibitors (TCI), or for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks). •Twice daily use of an additive-free, bland emollient for at least 7 days prior to Baseline.	(PDE4)-inhibitors and mycophenolate mofetil within 4 weeks prior to Baseline. •Prior exposure to any investigational systemic treatment within 30 days or 5 half-lives (whichever is longer) of the Baseline visit

Dupilumab					
Phase III LIBERTY AD SOLO 1[51] Simpson 2016 NEMJ	≥18 years of age, moderate-to-severe atopic dermatitis DB, PC, RCT	**Dosing until week 16:** Dupilumab monotherapy 300 mg/wk, s.c.(n=223) dupilumab 300 mg s.c. every other week alternating with placebo (n=224) Placebo (n=224)	**Prohibited:** Prohibited concomitant medications included topical glucocorticoids and calcineurin inhibitors, immunomodulating biologic agents, systemic glucocorticoids, and nonsteroidal systemic immunosuppressants. Also prohibited procedures: Phototherapy, tanning bed or booth, and major elective surgeries **Permitted/allowed**: Concomitant topical glucocorticoids and calcineurin inhibitors were allowed only as rescue therapy	≥18 years of age, moderate-to-severe atopic dermatitis (IGA 3 or 4), inadequately controlled by topical treatment or medically inadvisable, AD ≥3 years	• Treatment with an investigative drug within 8 weeks or within 5 half-lives • Treatment with immunosuppressive/immunomodulatory drugs or phototherapy for atopic dermatitis within 4 weeks of baseline • Treatment with topical corticosteroids or topical calcineurin inhibitors within 1 week of baseline • Regular use (>2 visits per week) of a tanning booth/parlor within 4 weeks of the baseline visit • Planned or anticipated use of any prohibited medications and procedures during study treatment • Known or suspected history of immunosuppression, including history of invasive opportunistic infections, HIV, HepC or presence of any condition listed as criteria for discontinuation of drug and history of malignancies • Presence of skin comorbidities that may interfere with study assessments

Phase III LIBERTY AD SOLO 2[51] Simpson 2016 NEMJ	≥18 years of age, moderate-to-severe atopic dermatitis DB, PC, RCT	**Dosing until week 16:** Dupilumab monotherapy 300 mg/wk, s.c.(n=239) Dupilumab 300 mg s.c. every other week alternating with placebo (n=233) Placebo (n=236)	**Prohibited:** Prohibited concomitant medications included topical glucocorticoids and calcineurin inhibitors, immunomodulating biologic agents, systemic glucocorticoids, and nonsteroidal systemic immunosuppressants. Also prohibited procedures: Phototherapy, tanning bed or booth, and major elective surgeries **Permitted/allowed**: Concomitant topical glucocorticoids and calcineurin inhibitors were allowed only as rescue therapy	≥18 years of age, moderate-to-severe atopic dermatitis (IGA 3 or 4), inadequately controlled by topical treatment or medically inadvisable, AD ≥3 years	same as SOLO 1

Phase III LIBERTY AD CHRONOS[50] Blauvelt 2017 Lancet	≥18 years of age, moderate-to-severe atopic dermatitis DB, PC, RCT	**Day 1 (Loading dose)** •Dupilumab 600 mg •placebo **Day 1-Week 16** •Dupilumab 300 mg QW + TCS •Dupilumab 300 mg Q2W + TCS •Placebo QW + TCS	**provided during study:** TCS (medium/low potency) w/ or w/o TCIs (where inadvisable for TCS) **Permitted concomitant meds:** any medications other than those that were prohibited **Prohibited concomitant medications:** live (attenuated) vaccine, immunomodulating biologics, investigational drugs, wet wraps, any omed for AD interfering with efficacy outcomes or affect evaluation for AD severity, major elective surgical procedures, or tanning in a bed/booth.	•Chronic atopic dermatitis (AD) present for 3+ years before screening •Documented recent history (within 6 months before the screening visit) of inadequate response to a sufficient course of outpatient treatment with topical AD meds •IGA score ≥3, on the IGA scale of 0–4, BSA affected ≥10%, EASI score of ≥16, PP-NRS average score ≥3 •Applied moisturizers at least twice daily for the 7 days before randomization	•Participation in a prior dupilumab clinical trial •Important side effects of topical medication (e.g., intolerance to treatment, hypersensitivity reactions, significant skin atrophy, systemic effects) •Used any of these treatments within 4 weeks before baseline, or condition likely to require treatment during first 2 weeks of study treatment: Immunosuppressive/immunomodulating drugs (e.g., systemic steroids, cyclosporine, mycophenolate-mofetil, Janus kinase inhibitors, IFN-γ, azathioprine, methotrexate, etc., Phototherapy for AD •Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit •History or current positive HIV •Positive HepB or HepC antibody at the screening visit •Active or acute infection requiring systemic treatment within 2 weeks before baseline visit •Known or suspected history of immunosuppression
Phase III AD SOLO-CONTINUE[54] Worm 2019 JAMA	N= 422 re-randomized patients from SOLO to SOLO-CONTINUE Dupilumab-treated patients who has achieved IGA score of 0 or	Re-randomized 2:1:1:1 **Original regimen** (300 mg QW or Q2W) or **Less frequency** (300 mg Q4W or Q8W)	Patients were required to apply moisturizers 2 or more times daily throughout the study.	Received dupilumab in the SOLO studies and achieved IGA 0/1 or EASI75 at week 16.	Did not completed SOLO study or did not achieve primary endpoint.

	1 or 75% or greater improvement I EASI at week 16 during the SOLO studies. DB, PC, RCT	or **Placebo**			
Phase IIb Thaci 2016[56,57] Thaci 2016 Lancet + Simpson 2016 JAAD	18 and older with moderate to severe atopic dermatitis N= 380 DB, PC, RCT, dose ranging	Dupilumab 300 mg once a week (n = 63) **Dupilumab 300 mg every 2 weeks (n= 64)** **Dupilumab 200 mg every 2 weeks (n = 61)** **Dupilumab 300 mg every 4 weeks (n= 65)** Dupilumab 100 mg every 4 weeks (n = 65) **Placebo once a week (n = 61)**	**Prohibited concomitant medications**: topical calcineurin inhibitors, topical corticosteroids, prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin, systemic corticosteroids, systemic treatment for AD with an immunosuppressive /immunomodulating agent (e.g., cyclosporin, mycophenolate-mofetil, azathioprine, methotrexate, interferon-gamma, or other biologics); allergen immunotherapy; live (attenuated vaccine); or investigational drug other than dupilumab.	adults (aged ≥18 years) diagnosed with moderate-to-severe atopic dermatitis for at least 3 years not adequately controlled by topical treatments, or for whom topical treatment was inadvisable, Eczema Area and Severity Index (EASI), score 12 or higher at screening and 16 or higher at baseline; Investigator's Global Assessment (IGA) score of 3 or higher at screening and baseline; atopic dermatitis involvement of 10% or more of body surface area	previous treatment with dupilumab; active acute or chronic infections; use of topical treatments for atopic dermatitis (other than bland emollients) within 1 week of baseline; systemic immunosuppressive or immunomodulating drugs within 4 weeks of baseline; or significant comorbidities or laboratory abnormalities

				at screening and baseline	

AC: active controlled, AD: atopic dermatitis, AE: adverse event, BSA: body surface area, CD19: Cluster of Differentiation 19, DB: double-blind, DD: double dummy, HepB: hepatitis B, HepC: hepatitis C, HIV: human immunodeficiency virus, IFN-γ: interferon gamma, IMP: investigational medicinal product, kg: kilogram, JAK: Janus kinase, LT: long-term, MACE: major adverse cardiovascular event, MC: multi-center, mg: milligram, MI: myocardial infarction n: number, mm Hg: millimeter of mercury, N: total number, NR: not reported, NRS: numerical rating scale, NYHA: New York Heart Association Functional Classification, OL: open-label, OLE: open-label extension, PC: placebo-controlled, PDE4: Phosphodiesterase-4, QD: once daily, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, RCT: randomized control trial, s.c.: subcutaneous, TB: tuberculosis, TCI: topical calcineurin inhibitors, TCS: topical corticosteroids, VTE: venous thromboembolism.

Table G1.3. Baseline Characteristics I [35-37,39,40,42,44-48,50,51,54,56,63,64,67,69,76-78,80-84,107]

Study Name	Arms	N	Age (years)		Male		White		Disease duration (years)		Disease Severity, n (%)			
											Moderate		Severe	
			mean	SD	n	%	n	%	Mean	SD	n	%	n	%
Abrocitinib														
JADE MONO-1	PBO	77	31.5	14.4	49	64	62	81	22.5	14.4	46	60	31	40
	ABRO 100 mg	156	32.6	15.4	90	58	113	72	24.9	16.1	92	59	64	41
	ABRO 200 mg	154	33	17.4	81	53	104	68	22.7	14.5	91	59	63	41
JADE MONO-2	PBO	78	33.4	13.8	47	60.3	40	51.3	21.7	14.3	52	66.7	26	33.3
	ABRO 100 mg	158	37.4	15.8	94	59.5	101	63.9	21.1	14.8	107	67.7	51	32.3
	ABRO 200 mg	155	33.5	14.7	88	56.8	91	58.7	20.5	14.8	106	68.4	49	31.6
	Overall	391	35.1	15.1	229	58.6	232	59.3	21	14.7	265	67.8	126	32.2
JADE TEEN	PBO	96	Median: 14	IQR: 13.5 to 16.5	44	45.8	56.0	58.3	10.5	4.8	57	59.4	39	40.6
	ABRO 100 mg	95	Median: 16	IQR: 14 to 17	45	47.4	52.0	54.7	9.8	5.4	57	60	38	40
	ABRO 200 mg	94	Median: 15	IQR: 13 to 16	56	59.6	52.0	55.3	9.7	5.3	61	64.9	33	35.1
	Overall	285	Median: 15	IQR: 13 to 17	145	50.9	160	56.1	Median: 11.6	IQR: 4.9 to 14.2	175	61	110	39
JADE COMPARE	PBO	131	37.4	15.2	77	58.8	87	66.4	21.4	14.4	88	67.2	43	32.8
	ABRO 100 mg	238	37.3	14.8	120	50.4	182	76.5	22.7	16.3	153	64.3	85	35.7
	ABRO 200 mg	226	38.8	14.5	104	46	161	71.2	23.4	15.6	138	61.1	88	38.9
	DUP 300 mg	242	37.1	14.6	108	44.6	176	72.7	22.8	14.8	162	66.9	80	33.1
	Total	837	37.7	14.7	409	48.9	606	72.4	22.7	15.4	541	64.6	296	35.4
JADE EXTEND Subgroup 1[†]	ABRO 100 mg	595	Median: 32	Range: 12-83	340	57.1	NR	NR	22.7	15.2	384	64.5	211	35.5
	ABRO 200 mg	521	Median: 32	Range: 12-80	277	53.2	NR	NR	22.3	15	322	61.8	199	38.2
JADE EXTEND Subgroup 2[‡]	ABRO 100 mg	130	NR	NR	NR	NR	NR	NR	24.2	15	87	66.9	43	33.1
	ABRO 200 mg	73	NR	NR	NR	NR	NR	NR	23.6	15.6	47	64.4	26	35.6

Study Name	Arms	N	Age (years)		Male		White		Disease duration (years)		Disease Severity, n (%)			
											Moderate		Severe	
			mean	SD	n	%	n	%	Mean	SD	n	%	n	%
Phase IIb Gooderham 2019	PBO	56	42.6	15.1	21	37.5	40	71.4	Median: 25.6	Range: 1.1 to 67.1	34	61.8	21	38.2
	ABRO 100 mg	56	41.1	15.6	31	55.4	40	71.4	Median: 23.8	Range: 1.1 to 66.7	29	52.7	26	47.3
	ABRO 200 mg	55	38.7	17.6	28	50.9	37	67.3	Median 19.6	Range: 1.9 to 68.8	34	63	20	37
Baricitinib														
BREEZE-AD1	PBO	249	35	12.6	148	59.4	147	59.5	26	15.5	NR	NR	105	42.2
	BARI 1 mg	127	36	12.4	78	61.4	74	58.3	27	14.9	NR	NR	53	41.7
	BARI 2 mg	123	35	13.7	82	66.7	75	61	25	14.6	NR	NR	52	42.3
	BARI 4 mg	125	37	12.9	83	66.4	70	56.5	25	14.9	NR	NR	51	40.8
BREEZE-AD2	PBO	244	35	13	154	63.1	169	69.3	25	13.9	NR	NR	121	49.6
	BARI 1 mg	125	33	10	80	64	85	68	24	12.7	NR	NR	63	50.8
	BARI 2 mg	123	36	13.2	65	52.8	85	69.1	24	13.8	NR	NR	62	50.4
	BARI 4 mg	123	34	14.1	82	66.7	82	66.7	23	14.8	NR	NR	63	51.2
BREEZE-AD3 (LTE)	BARI 2 mg	54	32.8	12.7	28	51.9	NR	NR	NR	NR	36	66.7	18	33.3
BREEZE-AD5	PBO	147	39	17	80	54	80	55	23	17	86	59	61	41
	BARI 1 mg	147	40	17	75	51	86	59	24	17	85	58	62	42
	BARI 2 mg	146	40	15	69	47	85	58	24	16	85	58	61	42
BREEZE-AD6	BARI 2 mg	146	39.7	15	69	47.3	85	58.2	23.9	15.9	85	58.2	61	41.8
BREEZE-AD7	PBO + TCS	109	33.7	13.2	71	65	46	42	22	12.2	NR	NR	48*	44
	BARI 2 mg + TCS	109	33.8	12.8	70	64	50	46	24.6	14.8	NR	NR	50	46
	BARI 4 mg + TCS	111	33.9	11.4	75	68	54	49	25.5	13.2	NR	NR	50	45
Phase II Guttman-Yassky 2018	PBO + TCS	49	Median: 35	IQR: 28.0 to 48.0	24	49	23	47	Median: 17.7	IQR: 7.3 to 29.5	NR	NR	NR	NR
	BARI 2 mg + TCS	37	Median: 42	IQR: 26.0 to 52.0	22	59	20	54	Median: 26.4	IQR: 18.3 to 40.5	NR	NR	NR	NR

Study Name	Arms	N	Age (years)		Male		White		Disease duration (years)		Disease Severity, n (%)			
											Moderate		Severe	
			mean	SD	n	%	n	%	Mean	SD	n	%	n	%
	BARI 4 mg + TCS	38	Median: 32.5	IQR: 26.0 to 48.0	22	58	18	47	Median: 22.0	IQR: 6.4 to 30.7	NR	NR	NR	NR
Tralokinumab														
ECZTRA 1	PBO	199	Median: 37.0	IQR: 26.0 to 49.0	123	61.8	138	69.3	Median: 28.0	IQR: 18.0 to 41.0	NR	NR	102	51.3
	TRA 300 mg	603	Median: 37.0	IQR: 27.0 to 48.0	351	58.2	426	70.6	Median: 27.0	IQR: 19.0 to 38.0	NR	NR	305	50.6
ECZTRA 2	PBO	201	Median: 30.0	IQR: 23.0 to 46.0	114	56.7	123	61.2	Median: 25.0	IQR: 18.0 to 36.0	NR	NR	101	50.2
	TRA 300 mg	593	Median: 34.0	IQR: 25.0 to 48.0	359	60.5	374	63.1	Median: 25.5	IQR: 17.0 to 39.0	NR	NR	286	48.2
ECZTRA 2 Subgroup[¶]	PBO	91	38.9	15.9	46	50.5	46	50.5	30.2	16.8	52	57.1	39	42.9
	TRA 300 mg	270	40.2	15.7	147	54.4	148	54.8	29.7	16.4	153	56.7	117	43.3
ECZTRA 3	PBO + TCS	127	Median: 34.0	IQR: 24.0 to 50.0	84	66.1	85	66.9	Median: 26.0	IQR: 18.0 to 39.0	66	52	60	47.2
	TRA 300 mg + TCS	253	Median: 37.0	IQR: 28.0 to 52.0	125	49.4	203	80.2	Median: 27.0	IQR: 17.0 to 39.0	136	53.8	116	45.8
	Overall	380	Median: 36.0	IQR: 27.0 to 51.0	209	55	288	75.8	Median: 26.0	IQR: 17.0 to 39.0	202	53.2	176	46.3
ECZTEND	Overall	1174	Median: 38	IQR: 27 to 50	675	57.5	NR	NR	Median: 27.0	IQR: 18 to 40	NR	NR	NR	NR
Upadacitinib														
MEASURE UP 1	PBO	281	34.4	Range: 12 to 75	144	51.2	182	64.8	21.3	15.3	156	55.5	125	44.5
	UPA 15 mg	281	34.1	Range: 12 to 74	157	55.9	182	64.8	20.5	15.9	154	54.8	127	45.2
	UPA 30 mg	285	33.6	Range: 12 to 75	155	54.4	191	67	20.4	14.3	154	54	131	46
MEASURE UP 2	PBO	278	33.4	Range: 13 to 71	154	55.4	195	70.1	21.1	13.6	125	45	153	55

Study Name	Arms	N	Age (years)		Male		White		Disease duration (years)		Disease Severity, n (%)			
											Moderate		Severe	
			mean	SD	n	%	n	%	Mean	SD	n	%	n	%
	UPA 15 mg	276	33.3	Range: 12 to 74	155	56.2	184	66.7	25.8	5.6	126	45.7	150	54.3
	UPA 30 mg	282	34.1	Range: 12 to 75	162	57.4	198	70.2	25.9	5.8	126	44.7	156	55.3
AD-UP	PBO + TCS	304	34.3	Range: 12 to 75	178	58.6	225	74	24.3	15.2	141	46.4	163	53.6
	UPA 15 mg + TCS	300	32.5	Range: 13 to 74	179	59.7	204	68	22.9	13.9	143	47.7	157	52.3
	UPA 30 mg + TCS	297	35.5	Range: 12 to 75	190	64	218	73.4	23.1	16.1	140	47.1	157	52.9
Heads Up	DUP 300 mg	344	36.9	14.1	194	56.4	NR	NR	25	14.8	171	49.7	173	50.3
	UPA 30 mg	348	36.6	14.6	183	52.6	NR	NR	23.5	14.7	174	50	174	50
Phase IIb Guttman-Yassky 2020	PBO	41	39.9	17.5	24	58.5	28	68.3	26.8	18.8	18	44	23	56
	UPA 7.5 mg	42	41.5	15.4	28	66.7	24	57	30.4	18.1	29	69	13	31
	UPA 15 mg	42	38.5	15.2	30	71.4	21	50	22.6	15.8	19	45	23	55
	UPA 30 mg	42	39.9	15.3	22	52.4	23	55	24.2	13.6	31	74	11	26
Dupilumab														
SOLO 1	PBO	224	Median: 39	IQR: 27 to 50.5	118	53	146	65	Median: 28	IQR: 19 to 40	NR	NR	110	49
	DUP 300 mg Q2W	224	Median: 38	IQR: 27.5 to 48.0	130	58	155	69	Median: 26	IQR: 17 to 40	NR	NR	108	48
	DUP 300 mg QW	223	Median: 39	IQR: 27 to 51	142	64	149	67	Median: 26	IQR: 16 to 42	NR	NR	106	48
SOLO 2	PBO	236	Median: 35	IQR: 25 to 47	132	56	156	66	Median: 26	IQR: 18 to 39	NR	NR	115	49
	DUP 300 mg Q2W	233	Median: 34.0	IQR: 25 to 46	137	59	165	71	Median: 24.5	IQR: 18 to 36	NR	NR	115	49

Study Name	Arms	N	Age (years)		Male		White		Disease duration (years)		Disease Severity, n (%)			
											Moderate		Severe	
			mean	SD	n	%	n	%	Mean	SD	n	%	n	%
	DUP 300 mg QW	239	Median: 35	IQR: 25 to 46	139	58	168	70	Median: 24	IQR: 17 to 37	NR	NR	112	47
LIBERTY AD CHRONOS	PBO + TCS	315	Median: 34.0	IQR: 25 to 45	193	61	208	66	Median: 26	IQR: 17 to 38	168	53	147	47
	DUP 300 mg + TCS Q2W	106	Median: 40.5	IQR: 28 to 49	62	58	74	70	Median: 28	IQR: 20 to 44	53	50	53	50
	DUP 300 mg + TCS QW	319	Median: 34.0	IQR: 26 to 45	191	60	208	65	Median: 26	IQR: 18 to 39	172	54	147	46
AD SOLO-CONTINUE	PBO	83	37	IQR: 27 to 46	51	61.4	54	65.1	NR	NR	1	1.2	0	0
	DUP 300 mg Q8W	84	35	IQR: 26 to 46.5	51	60.7	56	66.7	NR	NR	2	2.4	0	0
	DUP 300 mg Q4W	86	36	IQR: 24 to 49	43	50	64	74.4	NR	NR	6	7	0	0
	DUP 300 mg QW/Q2W	169	36	IQR: 26 to 48	82	48.5	124	73.4	NR	NR	3	1.8	0	0
Phase IIb Thaci 2016	PBO QW	61	37.2	13.1	40	66	NR	NR	29.8	13.5	32	53	29	48
	DUP 200 mg	61	35.8	14.9	36	59	NR	NR	25.2	12.8	31	51	30	49
	DUP 300 mg	64	39.4	12.1	41	64	NR	NR	30.5	15.8	34	53	30	47
	DUP 300 mg	65	36.2	10.7	40	62	NR	NR	26.5	11.4	37	57	28	43

ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, IQR: interquartile range, kg: kilogram, LTE: long-term extension, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, SD: standard deviation, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *N=108, †JADE MONO-1 & 2 and JADE COMPARE subgroup, ‡JADE COMPARE dupilumab nonresponder subgroup, ¶North American subgroup.

Table G1.4 Baseline Characteristics II[35-37,39,40,42,44-48,50,51,54,56,63,64,67,69,76-78,80-84,107]

Study Name	Arms	N	EASI score		% BSA affected		SCORAD		Itch or PP-NRS	
			mean	SD	mean	SD	mean	SD	mean	SD
Abrocitinib										
JADE MONO-1	PBO	77	28.7	12.5	47.4	22.7	64.5	13.2	7	1.8
	ABRO 100 mg	156	31.3	13.6	50.8	23.4	67.1	13.7	6.9	2
	ABRO 200 mg	154	30.6	14.1	49.9	24.4	64.3	13.1	7.1	1.9
JADE MONO-2	PBO	78	28	10.2	48.2	20.8	64.3	12.4	6.7	1.9
	ABRO 100 mg	158	28.4	11.2	48.7	21.4	63.8	11.4	7.1	1.6
	ABRO 200 mg	155	29	12.4	47.7	22.3	64.1	13.1	7	1.6
	Overall	391	28.5	11.5	48.2	21.6	64	12.3	7	1.7
JADE TEEN	PBO	96	29.2	12.7	45.8	22.4	Median: 68.3	IQR: 57.9 to 78.7	7.2	1.7
	ABRO 100 mg	95	31	12.8	51.2	21.7	Median: 67.2	IQR: 57.4 to 77.4	7	1.8
	ABRO 200 mg	94	29.5	12.2	48.7	21.7	Median: 66.1	IQR: 56.4 to 76.4	6.8	2
	Overall	285	Median: 25.6	IQR: 20.0 to 37.7	Median: 45.5	IQR: 31.3 to 66.0	Median: 66.9	IQR: 56.7 to 77.7	Median: 7.0	IQR: 6 to 8
JADE COMPARE	PBO	131	31	12.6	48.9	24.9	67.9	12	7.1	1.8
	ABRO 100 mg	238	30.3	13.5	48.1	23.1	66.8	13.8	7.1	1.7*
	ABRO 200 mg	226	32.1	13.1	50.8	23	69.3	12.7	7.6	1.5
	DUP 300 mg	242	30.4	12	46.5	22.1	67.9	11.4	7.3	1.7*
	Total	837	30.9	12.8	48.5	23.1	67.9	12.6	7.3	1.7
JADE EXTEND Subgroup 1[†]	ABRO 100 mg	595	29.6	12.4	48.6	22.8	NR	NR	48.6	22.8
	ABRO 200 mg	521	30.9	13.2	49.5	23.4	NR	NR	49.5	23.4
JADE EXTEND Subgroup 2[‡]	ABRO 100 mg	130	29.6	11.2	45.4	21.2	NR	NR	7.4	1.7
	ABRO 200 mg	73	31.2	12.4	47.9	22.9	NR	NR	7.2	1.6
	PBO	56	25.4	12.9	40.1	22.3	65	12.1	7.6	1.8
	ABRO 100 mg	56	26.7	11.8	41.9	22.3	65.4	13.7	7.4	2.2

Study Name	Arms	N	EASI score		% BSA affected		SCORAD		Itch or PP-NRS	
			mean	SD	mean	SD	mean	SD	mean	SD
Phase IIb Gooderham 2019	ABRO 200 mg	55	24.6	13.5	38	23.3	62.7	13.7	6.9	2.7

Baricitinib										
BREEZE-AD1	PBO	249	32	13	53	23.1	68	14	NR	NR
	BARI 1 mg	127	29	11.8	47	21.2	66	14.4	NR	NR
	BARI 2 mg	123	31	11.7	50	22.1	68	13	NR	NR
	BARI 4 mg	125	32	12.7	52	21.8	68	12.9	NR	NR
BREEZE-AD2	PBO	244	33	12.8	52	21.7	68	12.7	NR	NR
	BARI 1 mg	125	33	12.7	55	21.9	67	12.9	NR	NR
	BARI 2 mg	123	35	16	55	26.1	69	13.3	NR	NR
	BARI 4 mg	123	33	12.7	54	21.5	68	13.6	NR	NR
BREEZE-AD3 (LTE)	BARI 2 mg	54	24.9	8.72	38.3	18.13	62.2	12.04	6.1	2.19
BREEZE-AD5	PBO	147	27	11	41.5	23	63.9	12.24	7	2.4
	BARI 1 mg	147	27.7	12	41.4	23	NR	NR	7.2	2
	BARI 2 mg	146	26.6	11	39.7	22	63.95	12.43	7.3	2.1
BREEZE-AD6	BARI 2 mg	146	26.6	11.4	NR	NR	6.5	3.1	7.7[¥]	2.1
BREEZE-AD7	PBO + TCS	109	28.5	12.3	48.1	24.4	66.6	13.8	7.4	1.7
	BARI 2 mg + TCS	109	29.3	11.9	50.6	21.6	66.8	14	7	2.1
	BARI 4 mg + TCS	111	30.9	12.6	52.1	23.3	68.3	13.2	7	2
Phase II Guttman-Yassky 2018	PBO + TCS	49	Median: 22.1	IQR: 15.3 to 28.0	NR	NR	Median: 55	IQR: 44.9 to 63.8	Median: 7	IQR: 6 to 8
	BARI 2 mg + TCS	37	Median: 22.1	IQR: 16.8 to 32.3	NR	NR	Median: 53.3	IQR: 49.9 to 61.1	Median: 6	IQR: 5 to 8
	BARI 4 mg + TCS	38	Median: 19.5	IQR: 13.7 to 25.9	NR	NR	Median: 57.6	IQR: 49.5-64.9	Median: 6.5	IQR: 4 to 8
Tralokinumab										
ECZTRA 1	PBO	199	Median: 30.3	IQR: 22.0 to 41.5	Median: 52.5	IQR: 31.0 to 77.0	Median: 70.8	IQR: 63.8 to 81.0	Median: 7.9	IQR: 6.9 to 8.7
	TRA 300 mg	603	Median: 28.2	IQR: 21.3 to 40.0	Median: 50.0	IQR: 33.0 to 70.0	Median: 69.2	IQR: 61.5 to 79.1	Median: 7.9	IQR: 6.7 to 8.9
	Overall	802	NR	NR	NR	NR	NR	NR	NR	NR

ECZTRA 2	PBO	201	Median: 29.6	IQR: 20.6 to 41.4	Median: 50.0	IQR: 31.0 to 74.0	Median: 69.9	IQR: 61.9 to 79.1	Median: 8.1	IQR: 7.1 to 9.0
	TRA 300 mg	593	Median: 28.2	IQR: 19.8 to 40.8	Median: 50.0	IQR: 31.0 to 74.0	Median: 69.5	IQR: 60.5 to 79.1	Median: 8.0	IQR: 7.0 to 9.0
	Overall	794	NR	NR	NR	NR	NR	NR	NR	NR
ECZTRA 2 Subgroup¶	PBO	91	29.9	13.1	45.2	23.6	69	11.8	8.1	1.3
	TRA 300 mg	270	27.9	11.8	43.5	23.5	67.1	11.3	8	1.5
ECZTRA 3	PBO	127	Median: 26.5	IQR: 19.9 to 39.3	Median: 40.0	IQR: 26.0 to 74.0	Median: 67.9	IQR: 59.4 to 79.0	Median: 8.0	IQR: 7.0 to 9.0
	TRA 300 mg	253	Median: 24.7	IQR: 18.4 to 35.9	Median: 41.0	IQR: 30.0 to 63.0	Median: 66.2	IQR: 57.6 to 76.3	Median: 8.0	IQR: 6.6 to 8.7
	Overall	380	Median: 25.5	IQR: 19.2 to 37.1	Median: 41.0	IQR: 28.0 to 69.5	Median: 66.5	IQR: 57.9 to 77.6	Median: 8.0	IQR: 6.6 to 8.9
ECZTEND	Overall	1174	Median: 4.7	IQR: 1.8 to 11.7	Median: 44.5	IQR: 30 to 67	Median: 30.2	IQR: 18.7 to 45	NR	NR
Upadacitinib										
MEASURE UP 1	PBO	281	28.8	12.6	45.7	21.6	66.1	12.9	7.5	1.8
	UPA 15 mg	281	30.6	12.8	48.5	22.2	68.2	12.6	7.4	1.8
	UPA 30 mg	285	29	11.1	47	22	67.3	12.5	7.5	1.7
MEASURE UP 2	PBO	278	29.1	12.1	47.6	22.7	67.9	12.1	7.5	1.9
	UPA 15 mg	276	28.6	11.7	45.1	22.4	66.6	12.5	7.2	1.8
	UPA 30 mg	282	29.7	12.2	47	23.2	66.7	13	7.4	1.7
AD-UP	PBO + TCS	304	30.3	13	48.6	23.1	NR	NR	7.1	1.6
	UPA 15 mg + TCS	300	29.2	11.8	46.7	21.6	NR	NR	7.1	1.8
	UPA 30 mg + TCS	297	29.7	11.8	48.5	23.1	NR	NR	7.4	1.6
Heads Up	DUP 300 mg	344	28.8	11.5	44.4	22.8	NR	NR	7.5	1.7
	UPA 30 mg	348	30.8	12.5	48.2	24	NR	NR	7.4	1.6
Phase IIb Guttman-Yassky 2020	PBO	41	32.6	14.5	45.7	22.8	NR	NR	6.5	1.9
	UPA 7.5 mg	42	31.4	15.8	46.9	24.9	NR	NR	6.8	1.8
	UPA 15 mg	42	31.4	12.3	50.6	21.5	NR	NR	6.4	1.7
	UPA 30 mg	42	28.2	11.6	42.1	20.4	NR	NR	6.3	2.1
Dupilumab										

SOLO 1	PBO	224	Median: 31.8	IQR:22.2 to 43.8	Median: 57	IQR: 37.4 to 77	Median: 67.0	IQR: 58.0 to 77.6	Median: 7.7	IQR: 6.2 to 8.6
	DUP 300 mg Q2W	224	Median: 30.4	IQR: 21.5 to 40.8	Median: 53.4	IQR: 37.4 to 72.5	Median: 65.1	IQR: 56.5 to 77.4	Median: 7.6	IQR: 5.9 to 8.7
	DUP 300 mg QW	223	Median: 29.8	IQR: 22.0 to 41.2	Median: 54.5	IQR: 39.0 to 73	Median: 65.9	IQR: 57.2 to 75.8	Median: 7.7	IQR: 6.0 to 8.7
SOLO 2	PBO	236	Median: 30.5	IQR: 22.1 to 41.7	Median: 53.3	IQR: 34.0 to 72.8	Median: 68.9	IQR: 58.6 to 78.5	Median: 7.7	IQR: 6.5 to 9.0
	DUP 300 mg Q2W	233	Median: 28.6	IQR: 21.0 to 40.1	Median: 50.0	IQR: 36.0 to 68.0	Median: 67.8	IQR: 57.3 to 76.7	Median: 7.8	IQR: 6.7 to 8.9
	DUP 300 mg QW	239	Median: 29.0	IQR: 21.2 to 41.8	Median: 50.0	IQR: 34.0 to 69.0	Median: 67.4	IQR: 58.4 to 77.9	Median: 7.8	IQR: 6.3 to 8.9
LIBERTY AD CHRONOS	PBO + TCS	315	Median: 29.6	IQR: 22.2 to 40.8	Median: 55.0	IQR: 40 to 75	Median: 64.1	IQR: 55.9 to 76.1	Median: 7.6	IQR: 6.3 to 8.6
	DUP 300 mg + TCS Q2W	106	Median: 30.9	IQR: 22.3 to 41.6	Median: 58.8	IQR: 43.5 to 78.5	Median: 69.7	IQR: 60.4 to 79.8	Median: 7.7	IQR: 6.6 to 8.5
	DUP 300 mg + TCS QW	319	Median: 29.0	IQR: 21.6 to 40.7	Median: 52.0	IQR: 36 - 71.5	Median: 65.3	IQR: 55.2 to 76.3	Median: 7.4	IQR: 6.0 to 8.6
AD SOLO-CONTINUE	PBO	83	2.5	2.3	8.1	8.2	16.8	10	2.8	2.1
	DUP 300 mg Q8W	84	2.3	2.3	7.9	9	17.1	9.4	2.7	2.3
	DUP 300 mg Q4W	86	2.8	3.3	9.3	10.5	17.5	10.6	3.1	2.2
	DUP 300 mg QW/Q2W	169	2.6	2.9	7.9	9	17.1	10.5	2.8	1.9
Phase IIb Thaci 2016	PBO QW	61	32.9	13.8	51.1	24	67.1	13.6	6.34	1.83
	DUP 200 mg Q2W	61	32.9	15.5	50.8	23	68.3	14.0	6.98	2.32
	DUP 300 mg Q2W	64	33.8	14.5	53.2	25	68.5	12.6	6.74	2.07
	DUP 300 mg Q4W	65	29.4	11.5	48.7	24	67.2	12.3	6.84	1.85

ABRO: abrocitinib, BARI: baricitinib, BSA: body surface area, DUP: dupilumab, IQR: interquartile range, kg: kilogram, LTE: long-term extension, mg: milligram, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, SD: standard deviation, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *N=241, [†]JADE MONO-1 & 2 and JADE COMPARE subgroup, [‡]JADE COMPARE dupilumab nonresponder subgroup, [¶]North American subgroup, [¥]SCORAD pruritus.

Table G1.5. Baseline Characteristics III[35-37,39,40,42,44-48,50,51,54,56,63,64,67,77,78,80-82,84]

Study Name	Arms		N	DLQI		CDLQI		POEM	
			N	mean	SD	N	mean	SD	mean	SD
Abrocitinib										
JADE MONO-1	PBO	77	NR	13.9	7.3	NR	13.6	7	19.9	6.1
	ABRO 100 mg	156	NR	14.6	6.5	NR	11.7	6.6	19.5	6.5
	ABRO 200 mg	154	NR	14.6	6.8	NR	13.2	5.5	19.6	5.9
JADE MONO-2	PBO	78	70	15	7.1	8	10.1	3.8	19.2	5.5
	ABRO 100 mg	158	140	15.4	7.3	16	13.8	5.8	20.9	5.7
	ABRO 200 mg	155	139	14.8	6	15	12.9	5.7	19.7	5.7
	Overall	391	349	15	6.8	39	12.7	5.4	20.1	5.7
JADE TEEN	PBO	96	NA	NA	NA	96	Median: 14.0	IQR: 9.0 to 19.0	Median: 21.0	IQR: 16.0 to 24.0
	ABRO 100 mg	95	NA	NA	NA	95	Median: 14.0	IQR: 10.0 to 19.0	Median: 21.0	IQR: 16.0 to 24.0
	ABRO 200 mg	94	NA	NA	NA	94	Median: 13.0	IQR: 8.0 to19.0	Median: 20.0	IQR: 15.0 to 24.0
	Overall	285	NA	NA	NA	285	Median: 14.0	IQR: 9.0 to19.0	Median: 20.0	IQR: 15.0 to 24.0
JADE COMPARE	PBO	131	131	15.2	6.9	NR	NR	NR	20.4	6.1
	ABRO 100 mg	238	238	15.5	6.4	NR	NR	NR	20.9	5.5
	ABRO 200 mg	226	226	16.3	6.6	NR	NR	NR	21.5	5.3
	DUP 300 mg	242	242	15.6	6.7	NR	NR	NR	21.1	5.5
	Total	837	837	15.7	6.6	NR	NR	NR	21.1	5.5
Baricitinib										
BREEZE-AD1	PBO	249	249	14	7.4	NA	NA	NA	21	5.6
	BARI 1 mg	127	127	13	6.8	NA	NA	NA	20	5.6
	BARI 2 mg	123	123	13	7.7	NA	NA	NA	21	5.6
	BARI 4 mg	125	125	14	7.1	NA	NA	NA	21	5.6

Study Name	Arms		N	DLQI			CDLQI		POEM	
			N	mean	SD	N	mean	SD	mean	SD
BREEZE-AD2	PBO	244	244	15	8.1	NA	NA	NA	21	6.3
	BARI 1 mg	125	125	15	8.1	NA	NA	NA	20	6.5
	BARI 2 mg	123	123	14	7.7	NA	NA	NA	21	6
	BARI 4 mg	123	123	14	8.4	NA	NA	NA	20	6.3
BREEZE-AD3 (LTE)	BARI 2 mg	54	54	11.4	6.88	NA	NA	NA	17.6	6.15
BREEZE-AD5	PBO	147	147	15	7	NA	NA	NA	20.5	6.48
	BARI 1 mg	147	147	15	7	NA	NA	NA	NR	NR
	BARI 2 mg	146	146	15	8	NA	NA	NA	21.7	5.35
BREEZE-AD6	BARI 2 mg	146	146	15	7.6	NA	NA	NA	NR	NR
BREEZE-AD7	PBO + TCS	109	109	15	7.9	NA	NA	NA	20.9	6.7
	BARI 2 mg + TCS	109	109	15	7.7	NA	NA	NA	21	6.3
	BARI 4 mg + TCS	111	111	14.7	7.9	NA	NA	NA	21.4	6
Phase II Guttman-Yassky 2018	PBO + TCS	49	49	Median: 15.0	IQR: 10.0 to 19.0	NA	NA	NA	Median: 20.0	IQR: 17.0 to 23.0
	BARI 2 mg + TCS	37	37	Median: 10.0	IQR: 7.0 to 17.0	NA	NA	NA	Median: 17.0	IQR: 12.0 to 25.0
	BARI 4 mg + TCS	38	38	Median: 11.0	IQR: 8.0 to 17.0	NA	NA	NA	Median: 20.5	IQR: 11.0 to 26.0
Tralokinumab										
ECZTRA 1	PBO	199	NR	Median: 16.0	IQR: 13.0 to 22.0	NA	NA	NA	Median: 24.0	IQR: 20.0 to 27.0
	TRA 300 mg	603	NR	Median: 17.0	IQR: 12.0 to 22.0	NA	NA	NA	Median: 24.0	IQR: 20.0 to 27.0
	Overall	802	NR	NR	NR	NA	NA	NA	NR	NR
ECZTRA 2	PBO	201	NR	Median: 18.0	IQR: 12.5 to 24.0	NA	NA	NA	Median: 24.0	IQR: 20.0 to 27.5

Study Name	Arms	N	DLQI			CDLQI			POEM	
			N	mean	SD	N	mean	SD	mean	SD
	TRA 300 mg	593	NR	Median: 18.0	IQR: 13.0 to 23.0	NA	NA	NA	Median: 24.0	IQR: 20.0 to 27.0
	Overall	794	NR	NR	NR	NA	NA	NA	NA	NA
ECZTRA 2 Subgroup *	PBO	91	NR	17.3	7.8	NA	NA	NA	NA	NA
	TRA 300 mg	270	NR	17.5	7.2	NA	NA	NA	NA	NA
ECZTRA 3	PBO + TCS	127	125	Median: 18.0	IQR: 12.0 to 23.0	NA	NA	NA	Median: 24.0	IQR: 20.0 to 27.0
	TRA 300 mg + TCS	253	250	Median: 18.0	IQR: 12.0 to 23.0	NA	NA	NA	Median: 23.0	IQR: 20.0 to 26.0
	Overall	380	375	Median: 18.0	IQR: 12.0 to 23.0	NA	NA	NA	Median: 23.0	IQR: 20.0 to 27.0
ECZTEND	Overall	1174	1174	Median: 5	IQR: 2 to 10	NA	NA	NA	Median: 12	IQR: 6 to 18
Upadacitinib										
MEASURE UP 1	PBO	281	NR	17	6.8	NR	NR	NR	21.5	5.3
	UPA 15 mg	281	NR	16.2	7	NR	NR	NR	21.2	4.8
	UPA 30 mg	285	NR	16.4	7	NR	NR	NR	21.4	5.1
MEASURE UP 2	PBO	278	NR	17.1	7.2	NR	NR	NR	21.9	5.2
	UPA 15 mg	276	NR	16.9	7	NR	NR	NR	21.2	5.1
	UPA 30 mg	282	NR	16.7	6.9	NR	NR	NR	21.8	4.8
AD-UP	PBO + TCS	304	NR	16.3	7	NR	NR	NR	21.5	5.1
	UPA 15 mg + TCS	300	NR	16.4	7.2	NR	NR	NR	21	5
	UPA 30 mg + TCS	297	NR	17.1	7	NR	NR	NR	21.5	5.3
Dupilumab										
SOLO 1	PBO	224	224	Median: 14.0	IQR: 9.0 to 20.0	NA	NA	NA	Median: 21.0	IQR: 16.0-25.0
	DUP 300 mg Q2W	224	224	Median: 13.0	IQR: 8.0 to 19.0	NA	NA	NA	Median: 21.0	IQR: 16.0 to 25.0

Study Name	Arms	N		DLQI		CDLQI			POEM	
			N	mean	SD	N	mean	SD	mean	SD
	DUP 300 mg QW	223	223	Median: 14.0	IQR: 8.0 to 20.0	NA	NA	NA	Median: 22.0	IQR: 17.0 to 26.0
SOLO 2	PBO	236	236	Median: 15.0	IQR: 9.0 to 22.0	NA	NA	NA	Median: 23.0	IQR: 17.0 to 26.0
	DUP 300 mg Q2W	233	233	Median: 15.0	IQR: 10.0 to 21.0	NA	NA	NA	Median: 21.0	IQR: 18.0 to 25.0
	DUP 300 mg QW	239	239	Median: 16.0	IQR: 10.0 to 22.0	NA	NA	NA	Median: 21.0	IQR: 18.0 to 26.0
LIBERTY AD CHRONOS	PBO + TCS	315	315	Median: 14	IQR: 9 to 20	NA	NA	NA	Median: 20	IQR: 16 to 25
	DUP 300 mg + TCS Q2W	106	106	Median: 13.5	IQR: 8 to 20	NA	NA	NA	Median: 21	IQR: 16 to 25
	DUP 300 mg + TCS QW	319	319	Median: 14	IQR: 8 to 20	NA	NA	NA	Median: 20	IQR: 16 to 25
AD SOLO-CONTINUE	PBO	83	NR	3.4	4.3	NA	NA	NA	6.1	5.4
	DUP 300 mg Q8W	84	NR	3	3.8	NA	NA	NA	6.8	5.9
	DUP 300 mg Q4W	86	NR	3.2	3.9	NA	NA	NA	6.1	5.1
	DUP 300 mg QW/Q2W	169	NR	3.4	4.2	NA	NA	NA	6.4	5.3
Phase IIb Thaci 2016	PBO QW	61	61	12.8	6.2	NA	NA	NA	NR	NR
	DUP 200 mg Q2W	61	61	15	7.1	NA	NA	NA	NR	NR
	DUP 300 mg Q2W	64	64	14.5	7.2	NA	NA	NA	NR	NR
	DUP 300 mg Q4W	65	65	13.3	7.3	NA	NA	NA	NR	NR

None of these baseline characteristics were available in JADE EXTEND, Phase IIb Gooderham 2019, Heads Up, and Phase IIb Guttman-Yassky 2020. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, IQR: interquartile range, kg: kilogram, LTE: long-term extension, mg: milligram, N: total number, NA: not applicable, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, SD: standard deviation, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib. *North American subgroup.

Table G1.6. Baseline Characteristics IV[36,44-47,50,51,54,80]

Study Name	Arms	N	Total HADS		HADS Anxiety		HADS Depression	
			mean	SD	mean	SD	mean	SD
Abrocitinib								
JADE MONO-2	PBO	78	NR	NR	6	3.7	4.4	3.3
	ABRO 100 mg	158	NR	NR	5.5	4.2	4.1	4
	ABRO 200 mg	155	NR	NR	5.9	3.9	4	3.7
	Overall	391	NR	NR	5.7	4	4.1	3.8
Baricitinib								
BREEZE-AD3 (LTE)	BARI 2 mg	NR	NR	NR	5.8	4.2	4.3	3.73
BREEZE-AD5	PBO	147	NR	NR	7	4.34	4.8	3.85
	BARI 1 mg	147	NR	NR	NR	NR	NR	NR
	BARI 2 mg	146	NR	NR	7	4.37	5.2	4.32
BREEZE-AD7	PBO + TCS	109	NR	NR	6.8	4.3	5.8	4.3
	BARI 2 mg + TCS	109	NR	NR	6.4	4	5.3	3.7
	BARI 4 mg + TCS	111	NR	NR	6.7	4.4	5.5	4.1
Upadacitinib								
MEASURE UP 1	PBO	281	NR	NR	7.2	4.4	5	4
	UPA 15 mg	281	NR	NR	7.5	4	5.2	3.9
	UPA 30 mg	285	NR	NR	7.4	4.4	5.2	4.2
MEASURE UP 2	PBO	278	NR	NR	7.5	4.3	5.8	4.1
	UPA 15 mg	276	NR	NR	7.2	4.2	5.3	4.2
	UPA 30 mg	282	NR	NR	7.6	4.3	5.9	4.1
Dupilumab								
SOLO 1	PBO	224	Median:12	IQR: 6.0 to 17.0	NR	NR	NR	NR

Study Name	Arms	N	Total HADS		HADS Anxiety		HADS Depression	
			mean	SD	mean	SD	mean	SD
	DUP 300 mg Q2W	224	Median: 11	IQR: 6.0 to 17.0	NR	NR	NR	NR
	DUP 300 mg QW	223	Median: 12	IQR: 6.0 to 17.5	NR	NR	NR	NR
SOLO 2	PBO	236	Median: 12	IQR: 7.0 to 19.0	NR	NR	NR	NR
	DUP 300 mg Q2W	233	Median: 13	IQR: 8.0 to 19.0	NR	NR	NR	NR
	DUP 300 mg QW	239	Median: 14	IQR: 8.0 to 20.0	NR	NR	NR	NR
LIBERTY AD CHRONOS	PBO + TCS	315	Median: 11	IQR:6.0 to 18.0	NR	NR	NR	NR
	DUP 300 mg + TCS Q2W	106	Median: 12.5	IQR: 7.0 to 18.0	NR	NR	NR	NR
	DUP 300 mg + TCS QW	319	Median: 12.0	IQR:7.0 to 18.0	NR	NR	NR	NR
AD SOLO-CONTINUE	PBO	83	5.9	6.4	NR	NR	NR	NR
	DUP 300 mg Q8W	84	7.1	6.9	NR	NR	NR	NR
	DUP 300 mg Q4W	86	7.3	7.5	NR	NR	NR	NR
	DUP 300 mg QW/Q2W	169	6.4	5.9	NR	NR	NR	NR

None of these baseline characteristics were available in JADE MONO-1, JADE TEEN, JADE COMPARE, JADE EXTEND, Phase IIb Gooderham 2019, BREEZE-AD1, BREEZE-AD2, BREEEZE-AD6, Phase II Guttman-Yassky 2018, ECZTRA 1, ECZTRA 2, ECZTRA 3, ECZTEND, AD-UP, Heads Up, Phase IIb Guttman-Yassky 2020, and Phase IIb Thaci 2016. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, IQR: interquartile range, LTE: long-term extension, mg: milligram, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, SD: standard deviation, TCS: topical corticosteroids.

Table G1.7. Baseline Characteristics: Previous Treatments[35-37,46,63,64,67]

Study Name	Arms	N	Previous Treatment(s)							
			Any previous treatment		Topical corticosteroids		Topical agents alone		Systemic agents	
			n	%	n	%	n	%	n	%
Abrocitinib										
JADE MONO-1	PBO	77	77	100	NR	NR	34	44	41	53
	ABRO 100 mg	156	155	99	NR	NR	69	44	78	50
	ABRO 200 mg	154	154	100	NR	NR	82	53	68	44
JADE MONO-2	PBO	78	78	100	NR	NR	46	59	32	41
	ABRO 100 mg	158	157	99.4	NR	NR	87	55.1	70	44.3
	ABRO 200 mg	155	153	98.7	NR	NR	93	60	60	38.7
	Overall	391	388	99.2	NR	NR	226	57.8	162	41.4
JADE COMPARE	PBO	131	131	100	NR	NR	83	63.4	48	36.6
	ABRO 100 mg	238	238	100	NR	NR	139	58.4	99	41.6
	ABRO 200 mg	226	225	99.6	NR	NR	122	54.0	103	45.6
	DUP 300 mg	242	241	99.6	NR	NR	129	53.3	112	46.3
	Total	837	835	99.8	NR	NR	473	56.5	362	43.2
Baricitinib										
BREEZE-AD7	PBO + TCS	109	NR	NR	101	93	NR	NR	NR	NR
	BARI 2 mg + TCS	109	NR	NR	100	92	NR	NR	NR	NR
	BARI 4 mg + TCS	111	NR	NR	103	93	NR	NR	NR	NR
Tralokinumab										
ECZTRA 1	PBO	199	197	99	195	98	NR	NR	NR	NR
	TRA 300 mg	603	598	99.2	591	98	NR	NR	NR	NR
ECZTRA 2	PBO	201	201	100	200	99.5	NR	NR	NR	NR
	TRA 300 mg	593	591	99.7	584	98.5	NR	NR	NR	NR
	PBO	91	NR	NR	91	100	NR	NR	NR	NR

Study Name	Arms	N	Previous Treatment(s)							
			Any previous treatment		Topical corticosteroids		Topical agents alone		Systemic agents	
			n	%	n	%	n	%	n	%
ECZTRA 2 Subgroup*	TRA 300 mg	270	NR	NR	269	99.6	NR	NR	NR	NR
ECZTRA 3	PBO + TCS	127	127	100	122	96.1	NR	NR	NR	NR
	TRA 300 mg + TCS	253	253	100	251	99.2	NR	NR	NR	NR
	Overall	380	380	100	373	98.2	NR	NR	NR	NR
Upadacitinib										
AD-UP	PBO + TCS	304	157	52	NR	NR	NR	NR	NR	NR
	UPA 15 mg + TCS	300	171	57	NR	NR	NR	NR	NR	NR
	UPA 30 mg + TCS	297	172	58	NR	NR	NR	NR	NR	NR

None of these baseline characteristics were available in JADE TEEN, JADE EXTEND, Phase IIb Gooderham 2019, BREEZE-AD1, BREEZE-AD2, BREEZE-AD3, BREEZE-AD5, BREEZE-AD6, Phase II Guttman-Yassky 2018, ECZTEND, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase IIb Guttman-Yassky 2020, LIBERTY AD SOLO 1 and SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD SOLO-CONTINUE, and Phase IIb Thaci 2016. No trials reported on previous treatment use with crisaborole. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, Q2W: every two weeks, Q4W: every four weeks, TCS: topical corticosteroids, TRA: tralokinumab, %: percent. *North American subgroup.

Table G1.8. Short-Term Efficacy Outcomes: IGA Response Rates[35-37,40,42,45,46,48,50,51,56,63,64,67,69,80,81,84]

Study Name	Arms	N	IGA response					
			n	N	%	Diff from PBO	95% CI	p value
Abrocitinib								
JADE MONO-1	**Week 12**							
	PBO	77	6	76	8	REF	REF	REF
	ABRO 100 mg	156	37	156	24	15.8	6.8 to 24.8	0.0037
	ABRO 200 mg	154	67	153	44	36	26.2 to 45.7	<0.0001
JADE MONO-2	PBO	78	7	77	9.1	REF	REF	REF
	ABRO 100 mg	158	44	155	28.4	19.3	9.6 to 29.0	0.0008

Study Name	Arms	N	IGA response					
			n	N	%	Diff from PBO	95% CI	p value
	ABRO 200 mg	155	59	155	38.1	28.7	18.6 to 38.8	<0.0001
JADE TEEN	PBO	96	23	94	24.5	REF	REF	REF
	ABRO 100 mg	95	37	89	41.6	16.7	3.5 to 29.9	0.0147
	ABO 200 mg	94	43	93	46.2	20.6	7.3 to 33.9	0.003
JADE COMPARE	PBO	131	18	129	14	REF	REF	REF
	ABRO 100 mg	238	86	235	36.6	23.1	14.7 to 31.4	<0.001
	ABRO 200 mg	226	106	219	48.4	34.8	26.1 to 43.5	<0.001
	DUP 300 mg	242	88	241	36.5	22.5	14.2 to 30.9	NR
	Week 16							
	PBO	131	16	124	12.9	REF	REF	REF
	ABRO 100 mg + PBO→ABRO 100 mg	238	80	230	34.8	22.1	13.7 to 30.5	<0.001
	ABRO 200 mg + PBO→ABRO 200 mg	226	105	221	47.5	35	26.3 to 43.7	<0.001
	DUP 300 mg + Oral PBO→PBO	242	90	232	38.8	25.6	17.1 to 34.1	NR
Phase IIb Gooderham 2019	**Week 12**							
	PBO	52	3	52	5.8	REF	0.0 to 12.1	REF
	ABRO 100 mg	54	16	54	29.6	NR	17.5 to 41.8	<0.001
	ABRO 200 mg	48	21	48	43.8	NR	29.7 to 57.8	<0.001
Baricitinib								
BREEZE-AD1	**Week 16**							
	PBO	249	12	249	4.8	REF	NR	REF
	BARI 1 mg	127	15	127	11.8	7.0	7.3 to 18.6	0.014
	BARI 2 mg	123	14	123	11.4	6.6	6.9 to 18.2	0.02
	BARI 4 mg	125	21	125	16.8	12.0	11.3 to 24.3	<0.001
BREEZE-AD2	PBO	244	11	244	4.5	REF	2.5 to 7.9	REF
	BARI 1 mg	125	11	125	8.8	4.3	5.0 to 15.1	0.108
	BARI 2 mg	123	13	123	10.6	6.1	6.3 to 17.2	0.042

Study Name	Arms	N	IGA response					
			n	N	%	Diff from PBO	95% CI	p value
	BARI 4 mg	123	17	123	13.8	9.3	8.8 to 21.0	0.003
BREEZE-AD5	PBO	147	8	147	5.4	NR	NR	NR
	BARI 1 mg	147	19	147	12.9	NR	NR	NR
	BARI 2 mg	146	35	146	24	NR	NR	≤0.001
BREEZE-AD7	PBO + TCS	109	16	109	14.7	REF	REF	NR
	BARI 2 mg + TCS	109	26	109	23.9	9.2	NR	NR
	BARI 4 mg + TCS	111	34	111	30.6	15.9	NR	NR
Phase II Guttman-Yassky 2018	PBO + TCS	49	4	49	8.2	REF	NR	REF
	BARI 2 mg + TCS	37	8	37	21.6	13.4	NR	0.115
	BARI 4 mg + TCS	38	8	38	21.1	12.9	NR	0.118
Tralokinumab								
ECZTRA 1	**Week 16**							
	PBO	197	14	197	7.1	REF	REF	REF
	TRA 300 mg	601	95	601	15.8	8.6	4.1 to 13.1	0.002
ECZTRA 2	PBO	201	22	201	10.9	REF	REF	REF
	TRA 300 mg	591	131	591	22.2	11.1	5.8 to 16.4	<0.001
ECZTRA 2 Subgroup[†]	PBO	91	13	91	14.3	REF	REF	REF
	TRA 300 mg	270	70	270	25.9	RD: 11.7	3.0 to 20.4	0.021
ECZTRA 3	PBO + TCS	126	33	126	26.2	REF	REF	REF
	TRA 300 mg + TCS	252	98	252	38.9	12.4	2.9 to 21.9	0.015

Upadacitinib								
MEASURE UP 1	**Week 16**							
	PBO	281	22	281	8	NR	NR	REF
	UPA 15 mg	281	135	281	48	NR	NR	<0.001
	UPA 30 mg	285	177	285	62	NR	NR	<0.001
MEASURE UP 2	PBO	278	14	278	5	NR	NR	REF
	UPA 15 mg	276	108	276	39	NR	NR	<0.001
	UPA 30 mg	282	147	282	52	NR	NR	<0.001
AD-UP	PBO + TCS	304	33	304	11	REF	REF	REF
	UPA 15 mg + TCS	300	120	300	40	28.5	22.1 to 34.9	<0.001
	UPA 30 mg + TCS	297	175	297	59	47.6	41.1 to 54.0	<0.001
Phase IIb Guttman-Yassky 2020	**Week 8**							
	PBO	41	0	41	0*	NR	NR	NR
	UPA 7.5 mg	42	7	42	16.7*	NR	NR	NR
	UPA 15 mg	42	10	42	23.4*	NR	NR	NR
	UPA 30 mg	42	22	42	52.2*	NR	NR	NR
	Week 16							
	PBO	41	1	41	2.4	NR	NR	REF
	UPA 15 mg	42	13	42	31	NR	NR	<0.001
	UPA 30 mg	42	21	42	50	NR	NR	<0.001
Dupilumab								
SOLO 1	**Week 16**							
	PBO	224	23	224	10	NR	NR	NR
	DUP 300 mg Q2W	224	85	224	38	NR	NR	NR
	DUP 300 mg QW	223	83	223	37	NR	NR	NR
SOLO 2	PBO	236	20	236	8	NR	NR	NR
	DUP 300 mg Q2W	233	84	233	36	NR	NR	NR
	DUP 300 mg QW	239	87	239	36	NR	NR	NR
LIBERTY AD CHRONOS	PBO + TCS	315	39	315	12	REF	REF	REF
	DUP 300 mg + TCS Q2W	106	41	106	39	26	16.3 to 36.3	<0.0001
	DUP 300 mg + TCS QW	319	125	319	39	27	20.3 to 33.3	<0.0001

Phase IIb Thaci 2016	PBO QW	61	1	61	2	REF	REF	REF
	DUP 200 mg Q2W	61	17	61	28	26.2	14.5 to 37.9	<0.0001
	DUP 300 mg Q2W	64	19	64	30	28	16.4 to 39.7	<0.0001
	DUP 300 mg Q4W	65	14	65	22	19.9	9.4 to 30.4	0.0004

Short-term data on IGA were not available in Heads Up. ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, NS: not significant, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, RD: risk difference, REF: reference, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *digitized estimate, †North American subgroup.

Table G1.9. Short-Term Efficacy Outcomes: EASI75[35-37,40,42,45,46,48,50,51,56,63,64,67,69,80,81,83,84]

Study Name	Arms	N	EASI 75					
			n	N	%	Diff from PBO	95% CI	p value
Abrocitinib								
JADE MONO-1	**Week 12**							
	PBO	77	9	76	12	REF	REF	REF
	ABRO 100 mg	156	62	156	40	27.9	17.4 to 38.3	<0.0001
	ABRO 200 mg	154	96	153	63	51	40.5 to 61.5	<0.0001
JADE MONO-2	PBO	78	8	77	10.4	REF	REF	REF
	ABRO 100 mg	158	69	155	44.5	33.9	23.3 to 44.4	<0.0001
	ABRO 200 mg	155	94	154	61	50.5	40.0 to 60.9	<0.0001
JADE TEEN	PBO	96	66	94	41.5	REF	REF	REF
	ABRO 100 mg	95	78	89	68.5	26.5	13.1 to 39.8	0.0002
	ABO 200 mg	94	81	93	72	29.4	16.3 to 42.5	<0.0001
JADE COMPARE	PBO	131	35	129	27.1	REF	REF	REF
	ABRO 100 mg	238	138	235	58.7	31.9	22.2 to 41.6	<0.001
	ABRO 200 mg	226	154	219	70.3	43.2	33.7 to 52.7	<0.001
	DUP 300 mg	242	140	241	58.1	30.9	21.1 to 40.6	REF

	Week 16							
	PBO	131	38	124	30.6	REF	REF	REF
	ABRO 100 mg + PBO→ABRO 100 mg	238	138	229	60.3	29.7	19.5 to 39.9	<0.001
	ABRO 200 mg + PBO→ABRO 200 mg	226	157	221	71	40.4	30.4 to 50.4	<0.001
	DUP 300 mg + Oral PBO→PBO	242	152	232	65.5	34.7	24.6 to 44.8	NR
Phase IIb Gooderham 2019	**Week 12**							
	PBO	52	8	52	15.4	REF	REF	NR
	ABRO 100 mg	54	22	54	40.7	3.86	1.8 to 8.4	NR
	ABRO 200 mg	48	31	48	64.6	9.51	4.3 to 21.2	NR
Baricitinib								
BREEZE-AD1	**Week 16**							
	PBO	249	22	249	8.8	REF	REF	REF
	BARI 1 mg	127	22	127	17.3	8.5	11.7 to 24.8	0.0032
	BARI 2 mg	123	23	123	18.7	9.9	12.8 to 26.5	0.006
	BARI 4 mg	125	31	125	24.8	16.0	18.1 to 33.0	<0.001
BREEZE-AD2	PBO	244	15	244	6.1	REF	3.8 to 9.9	REF
	BARI 1 mg	125	16	125	12.8	6.7	8.0 to 19.8	0.046
	BARI 2 mg	123	22	123	17.9	11.8	12.1 to 25.6	<0.001
	BARI 4 mg	123	26	123	21.1	15.0	14.9 to 29.2	<0.001
BREEZE-AD5	PBO	147	12	147	8.2	NR	NR	REF
	BARI 1 mg	147	19	147	12.9	NR	NR	NS
	BARI 2 mg	146	43	146	29.5	NR	NR	≤0.001
BREEZE-AD7	PBO + TCS	109	25	109	22.9	REF	NR	NR
	BARI 2 mg + TCS	109	47	109	43.1	20.2	NR	NR
	BARI 4 mg + TCS	111	53	111	47.7	24.8	NR	NR
	PBO + TCS	49	10	49	20.4	REF	NR	REF
	BARI 2 mg + TCS	37	11	37	29.7	9.3	NR	0.319

Phase II Guttman-Yassky 2018	BARI 4 mg + TCS	38	13	38	34.2	13.8	NR	0.148
Tralokinumab								
ECZTRA 1	**Week 16**							
	PBO	197	25	197	12.7	REF	REF	REF
	TRA 300 mg	601	150	601	25	12.1	6.5 to 17.7	<0.001
ECZTRA 2	PBO	201	23	201	11.4	REF	REF	REF
	TRA 300 mg	591	196	591	33.2	21.6	15.8 to 27.3	<0.001
ECZTRA 2 Subgroup[†]	PBO	91	14	91	15.4	REF	REF	REF
	TRA 300 mg	270	109	270	40.4	RD: 25.0	15.6 to 34.4	<0.001
ECZTRA 3	PBO + TCS	126	45	126	35.7	REF	REF	REF
	TRA 300 mg + TCS	252	141	252	56	20.2	9.8 to 30.6	<0.001
Upadacitinib								
MEASURE UP 1	**Week 16**							
	PBO	281	45	281	16	NR	NR	REF
	UPA 15 mg	281	197	281	70	NR	NR	<0.001
	UPA 30 mg	285	228	285	80	NR	NR	<0.001
MEASURE UP 2	PBO	278	36	278	13	NR	NR	REF
	UPA 15 mg	276	166	276	60	NR	NR	<0.001
	UPA 30 mg	282	206	282	73	NR	NR	<0.001
AD-UP	PBO + TCS	304	79	304	26	NR	NR	REF
	UPA 15 mg + TCS	300	195	300	65	NR	NR	<0.001
	UPA 30 mg + TCS	297	229	297	77	NR	NR	<0.001
Heads Up	DUP 300 mg	344	210	344	61.1	REF	NR	REF
	UPA 30 mg	348	247	348	71	10	NR	0.006
Phase IIb Guttman-Yassky 2020	**Week 8**							
	PBO	41	3	41	7.3	NR	NR	REF
	UPA 7.5 mg	42	13	42	31	NR	NR	0.004
	UPA 15 mg	42	22	42	52.4	NR	NR	<0.001
	UPA 30 mg	42	34	42	81	NR	NR	<0.001

	Week 16							
	PBO	41	4	41	9.8	NR	NR	REF
	UPA 15 mg	42	22	42	52.4	NR	NR	<0.001
	UPA 30 mg	42	29	42	69	NR	NR	<0.001
Dupilumab								
SOLO 1	**Week 16**							
	PBO	224	33	224	15	NR	NR	NR
	DUP 300 mg Q2W	224	115	224	51	NR	NR	NR
	DUP 300 mg QW	223	117	223	52	NR	NR	NR
SOLO 2	PBO	236	28	236	12	NR	NR	NR
	DUP 300 mg Q2W	233	103	233	44	NR	NR	NR
	DUP 300 mg QW	239	115	239	48	NR	NR	NR
LIBERTY AD CHRONOS	PBO + TCS	315	73	315	23	REF	REF	REF
	DUP 300 mg + TCS Q2W	106	73	106	69	46	35.7 to 55.7	<0.0001
	DUP 300 mg + TCS QW	319	204	319	64	41	33.7 to 47.8	<0.0001
Phase IIb Thaci 2016	PBO QW	61	7	NR	11.09*	NR	NR	0.147
	DUP 200 mg Q2W	61	34	NR	55.5*	NR	NR	<0.0001
	DUP 300 mg Q2W	64	34	NR	52.8*	NR	NR	<0.0001
	DUP 300 mg Q4W	65	32	NR	48.6*	NR	NR	<0.0001

ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, NS: not significant, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, RD: risk difference, REF: reference, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *digitized estimate, †North American subgroup.

Table G1.10. Short-Term Efficacy Outcomes: EASI 50 and 90[35-37,40,42,45,46,48,50,51,56,63,64,69-71,80,81,83,84]

Study Name	Arms	N	EASI 50						EASI 90					
			n	N	%	Diff from PBO	95% CI	p value	n	N	%	Diff from PBO	95% CI	p value
Abrocitinib														
JADE MONO-1	**Week 12**													
	PBO	77	17	76	22	REF	REF	NR	4	76	5	REF	REF	NR
	ABRO 100 mg	156	90	156	58	35.3	23.3 to 47.4	NR	29	156	19	13.3	5.4 to 21.2	NR
	ABRO 200 mg	154	116	153	76	53.5	42.0 to 65.0	NR	59	153	39	33.4	24.3 to 42.5	NR
JADE MONO-2	PBO	78	15	77	19.5	REF	REF	NR	3	77	3.9	REF	REF	REF
	ABRO 100 mg	158	106	155	68.4	48.7	37.2 to 60.1	NR	37	155	23.9	20.1	11.9 to 28.3	≤0.0001
	ABRO 200 mg	155	123	154	79.9	60.1	49.1 to 71.0	NR	58	154	37.7	33.5	24.6 to 42.5	≤0.0001
JADE TEEN	PBO	96	66	94	69.1	NR	NR	NR	17	94	18.1	NR	NR	NR
	ABRO 100 mg	95	78	89	87.6	NR	NR	NR	37	89	41.6	NR	NR	NR
	ABO 200 mg	94	81	93	87.1	NR	NR	NR	46	93	49.5	NR	NR	NR
JADE COMPARE	**Week 16**													
	PBO	131	71	124	57.3	NR	NR	NR	14	124	11.3	NR	NR	NR
	ABRO 100 mg + PBO→ABRO 100 mg	238	186	229	81.2	NR	NR	NR	87	229	38	NR	NR	NR
	ABRO 200 mg + PBO→ABRO 200 mg	226	193	221	87.3	NR	NR	NR	108	221	48.9	NR	NR	NR
	DUP 300 mg + Oral PBO→PBO	242	195	232	84.1	NR	NR	NR	90	232	38.8	NR	NR	NR
	Week 12													
	PBO	52	14	52	26.9	REF	REF	NR	5	52	9.6	REF	REF	NR

Study Name	Arms	N	EASI 50						EASI 90					
			n	N	%	Diff from PBO	95% CI	p value	n	N	%	Diff from PBO	95% CI	p value
Phase IIb Gooderham 2019	ABRO 100 mg	54	30	54	55.6	3.8	OR: 1.7 to 6.5	NR	14	54	25.9	3.2	1.3 to 7.9	NR
	ABRO 200 mg	48	38	48	79.2	9.7	OR: 4.5 to 20.9	NR	21	48	43.8	9.3	3.8 to 22.5	NR
Baricitinib														
	Week 16													
BREEZE-AD1	PBO	249	38	249	15.3	REF	NR	REF	12	249	4.8	REF	REF	REF
	BARI 1 mg	127	32	127	25.0	9.7	NR	<0.05	11	127	8.7	3.9	NR	NS
	BARI 2 mg	123	37	123	30.1	14.8	NR	<0.001	13	123	10.6	5.8	NR	<0.05
	BARI 4 mg	125	52	125	41.6	26.3	NR	<0.001	20	125	16.0	11.2	NR	<0.001
BREEZE-AD2	PBO	244	30	244	12.3	REF	NR	REF	6	244	2.5	REF	1.1 to 5.3	REF
	BARI 1 mg	125	23	125	18.4	6.1	NR	NS	8	125	6.4	3.9	3.3 to 12.1	0.053
	BARI 2 mg	123	34	123	27.6	15.3	NR	<0.001	11	123	8.9	6.4	5.1 to 15.3	0.007
	BARI 4 mg	123	36	123	29.3	17.0	NR	<0.001	16	123	13.0	10.5	8.2 to 20.1	<0.001
BREEZE-AD5	PBO	147	19	147	12.9	NR	8.4 to 19.3	NR	5	147	3.4	NR	1.5 to 7.7	NR
	BARI 1 mg	147	29	147	19.7	NR	14.1 to 26.9	NS	11	147	7.5	NR	4.2 to 12.9	NR
	BARI 2 mg	146	51	146	34.9	NR	27.7 to 43	≤0.001	30	146	20.5	NR	14.8 to 27.8	<0.001
BREEZE-AD7	PBO + TCS	109	45	109	41.3	REF	NR	REF	15	109	13.8	REF	NR	NR
	BARI 2 mg + TCS	109	70	109	64.2	22.9	NR	NR	18	109	16.5	2.7	NR	NR
	BARI 4 mg + TCS	111	78	111	70.3	29	NR	NR	27	111	24.3	10.5	NR	NR
	PBO + TCS	49	18	49	36.7	REF	NR	REF	3	49	6.1	REF	NR	REF

Study Name	Arms	N	EASI 50						EASI 90					
			n	N	%	Diff from PBO	95% CI	p value	n	N	%	Diff from PBO	95% CI	p value
Phase II Guttman-Yassky 2018	BARI 2 mg + TCS	37	21	37	56.8	20.1	NR	0.065	7	37	18.9	12.8	NR	0.092
	BARI 4 mg + TCS	38	23	38	60.5	23.8	NR	0.027	8	38	21.1	15	NR	0.052
Tralokinumab														
ECZTRA 1	**Week 16**													
	PBO	197	42	197	21.3	REF	REF	REF	8	197	4.1	REF	REF	REF
	TRA 300 mg	601	250	601	41.6	20.1	13.3 to 26.8	<0.001	87	601	14.5	10.3	6.4 to 14.1	<0.001
ECZTRA 2	PBO	201	41	201	20.4	REF	REF	REF	11	201	5.5	REF	REF	REF
	TRA 300 mg	591	295	591	49.9	29.3	22.5 to 36.1	<0.001	108	591	18.3	12.7	8.3 to 17.0	<0.001
ECZTRA 3	PBO + TCS	126	73	126	57.9	REF	REF	REF	27	126	21.4	REF	REF	REF
	TRA 300 mg + TCS	252	200	252	79.4	21.3	11.3 to 31.3	<0.001	83	252	32.9	11.4	2.1 to 20.7	0.022
Upadacitinib														
MEASURE UP 1	**Week 16**													
	PBO	281	83	281	29.6	NR	NR	REF	22	281	8	NR	NR	REF
	UPA 15 mg	281	217	281	77.2	NR	NR	≤0.001	149	281	53	NR	NR	<0.001
	UPA 30 mg	285	244	285	85.6	NR	NR	≤0.001	188	285	66	NR	NR	<0.001
MEASURE UP 2	PBO	278	79	278	28.4	NR	NR	REF	14	278	5	NR	NR	- REF
	UPA 15 mg	276	206	276	74.6	NR	NR	≤0.001	116	276	42	NR	NR	<0.001
	UPA 30 mg	282	232	282	82.1	NR	NR	≤0.001	163	282	58	NR	NR	<0.001
AD-UP	PBO + TCS	304	124	304	40.9	NR	NR	REF	40	304	13.2	REF	9.4 to 17.0	REF
	UPA 15 mg + TCS	300	244	300	81.4	NR	NR	≤0.001	128	300	42.8	28.5	22.1 to 34.9	<0.001
	UPA 30 mg + TCS	297	262	297	88.1	NR	NR	≤0.001	187	297	63.1	49.9	43.3 to 56.4	<0.001

Study Name	Arms	N	EASI 50						EASI 90					
			n	N	%	Diff from PBO	95% CI	p value	n	N	%	Diff from PBO	95% CI	p value
Heads Up	DUP 300 mg	344	248	344	72.1	NR	67.3 to 76.8	REF	133	344	38.7	REF	NR	REF
	UPA 30 mg	348	276	348	79.3	NR	75 to 83.5	0.026	211	348	60.6	21.8	NR	<0.001
Phase IIb Guttman-Yassky 2020	**Week 8**													
	PBO	41	9	41	22	NR	NR	REF	0	41	0	NR	NR	REF
	UPA 7.5 mg	42	23	42	54.8	NR	NR	<0.001	4	42	9.5	NR	NR	0.051
	UPA 15 mg	42	30	42	71.4	NR	NR	<0.001	11	42	26.2	NR	NR	<0.001
	UPA 30 mg	42	39	42	92.9	NR	NR	<0.001	19	42	45.2	NR	NR	<0.001
	Week 16													
	PBO	41	9	41	22	NR	NR	REF	1	41	2.4	NR	NR	REF
	UPA 15 mg	42	30	42	71.4	NR	NR	<0.001	11	42	26.2	NR	NR	<0.01
	UPA 30 mg	42	35	42	83.3	NR	NR	<0.001	21	42	50	NR	NR	<0.001
Dupilumab														
SOLO 1	**Week 16**													
	PBO	224	55	224	25	NR	NR	NR	17	224	8	NR	NR	NR
	DUP 300 mg Q2W	224	154	224	69	NR	NR	NR	80	224	36	NR	NR	NR
	DUP 300 mg QW	223	136	223	61	NR	NR	NR	74	223	33	NR	NR	NR
SOLO 2	PBO	236	52	236	22	NR	NR	NR	17	236	7	NR	NR	NR
	DUP 300 mg Q2W	233	152	233	65	NR	NR	NR	70	233	30	NR	NR	NR
	DUP 300 mg QW	239	146	239	61	NR	NR	NR	73	239	31	NR	NR	NR
LIBERTY AD CHRONOS	PBO + TCS	315	118	315	37	REF	REF	REF	35	315	11	REF	REF	REF
	DUP 300 mg + TCS Q2W	106	85	106	80	43	33.5 to 52.0	<0.0001	42	106	40	29	18.6 to 38.5	<0.0001
	DUP 300 mg + TCS QW	319	249	319	78	41	33.6 to 47.6	<0.0001	138	319	43	32	25.7 to 38.6	<0.0001

Study Name	Arms	N	EASI 50						EASI 90					
			n	N	%	Diff from PBO	95% CI	p value	n	N	%	Diff from PBO	95% CI	p value
Phase IIb Thaci 2016	PBO QW	61	18	61	30	NR	NR	REF	2	61	3.5*	NR	NR	0.0242
	DUP 200 mg Q2W	61	38	61	62	NR	NR	0.0003	19	61	31.1*	NR	NR	<0.0001
	DUP 300 mg Q2W	64	50	64	78	NR	NR	<0.0001	19	64	29.8*	NR	NR	<0.0001
	DUP 300 mg Q4W	65	46	65	71	NR	NR	<0.0001	19	65	28.8*	NR	NR	<0.0001

Short-term data on EASI 50 and EASI 90 were not available in JADE COMPARE at 12 weeks. ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, NS: not significant, OR: odds ratio, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, REF: reference, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *digitized estimate.

Table G1.11. Short-Term Efficacy Outcomes: PP-NRS ≥4-Point Change [35-37,39,40,42,45,46,48,50,51,56,63,64,69-71,80,81,83,84]

Study Name	Arms	N	Itch or PP-NRS (≥4-point improvement from baseline)							
			n	N	%	Change from baseline	SD	Diff from PBO	95% CI	p value
Abrocitinib										
	Week 12									
JADE MONO-1	PBO	77	11	74	15	NR	NR	REF	REF	REF
	ABRO 100 mg	156	55	147	38	NR	NR	22.5	10.3 to 34.8	0.0003
	ABRO 200 mg	154	84	147	57.2	NR	NR	41.7	29.6 to 53.9	<0.0001
JADE MONO-2	PBO	78	9	76	11.5	NR	NR	REF	4.1 to 19.0	REF
	ABRO 100 mg	158	71	156	45.2	NR	NR	33.7	22.8 to 44.7	<0.0001
	ABRO 200 mg	155	85	153	55.3	NR	NR	43.9	32.9 to 55.0	<0.0001
JADE TEEN	PBO	96	25	84	29.8	LSM: -2.7	NR	REF	REF	REF
	ABRO 100 mg	95	40	76	52.6	LSM: -3.7	NR	22.8	8 to 37.7	0.0035

Study Name	Arms	N	Itch or PP-NRS (≥4-point improvement from baseline)							
			n	N	%	Change from baseline	SD	Diff from PBO	95% CI	p value
	ABRO 200 mg	94	41	74	55.4	LSM: -3.9	NR	25.6	10.6 to 40.6	0.0013
JADE COMPARE	PBO	131	35	121	29	NR	NR	NR	NR	NR
	ABRO 100 mg	238	105	221	48	NR	NR	NR	NR	NR
	ABRO 200 mg	226	137	217	63	NR	NR	NR	NR	NR
	DUP 300 mg	242	122	224	54	NR	NR	NR	NR	NR
	Week 16									
	PBO	131	27	94	28.7	LSM: -30.3	NR	NR	NR	NR
	ABRO 100 mg	238	79	168	47.0	LSM: -49.1	NR	17.9	9.5 to 26.3	0.0002
	ABRO 200 mg	226	108	172	62.8	LSM: -64.1	NR	34.9	26 to 43.7	<.0001
	DUP 300 mg	242	108	189	57.1	LSM: -58.5	NR	5.2	-2.9 to 13.4	0.2084
Phase IIb Gooderham 2019	**Week 12**									
	PBO	52	13	51	25.5	NR	NR	REF	REF	NR
	ABRO 100 mg	54	25	50	50	NR	NR	OR: 2.8	1.4 to 5.8	NR
	ABRO 200 mg	48	28	44	63.6	NR	NR	OR: 5.1	2.4 to 10.8	NR
Baricitinib										
BREEZE-AD1	**Week 16**									
	PBO	249	16	222	7.2	NR	NR	REF	1.2 to 5.8	REF
	BARI 1 mg	127	11	105	10.5	NR	NR	3.3	6.0 to 17.8	0.246
	BARI 2 mg	123	12	100	12.0	NR	NR	4.8	7.0 to 19.8	0.169
	BARI 4 mg	125	23	107	21.5	NR	NR	14.3	14.8 to 30.2	<0.001
BREEZE-AD2	PBO	244	10	213	4.7	NR	NR	REF	2.6 to 8.4	REF
	BARI 1 mg	125	6	100	6.0	NR	NR	1.3	2.8 to 122.5	0.505
	BARI 2 mg	123	16	106	15.1	NR	NR	10.4	9.5 to 23.1	0.002
	BARI 4 mg	123	20	107	18.7	NR	NR	14.0	12.4 to 27.1	<0.001
BREEZE-AD5	PBO	147	7	123	5.7	NR	NR	NR	NR	REF
	BARI 1 mg	147	21	132	15.9	NR	NR	NR	NR	≤0.05
	BARI 2 mg	146	33	131	25.2	NR	NR	NR	NR	≤0.001

Study Name	Arms	N	Itch or PP-NRS (≥4-point improvement from baseline)							
			n	N	%	Change from baseline	SD	Diff from PBO	95% CI	p value
BREEZE-AD7	PBO + TCS	109	21	104	20.2	LSM: -27*	SE: 3.4	REF	NR	REF
	BARI 2 mg + TCS	109	37	97	38.1	LSM: -43.4*	SE: 3.3	17.9	NR	0.002
	BARI 4 mg + TCS	111	44	100	44	LSM: -51.2*	SE: 3.3	23.8	NR	<0.001
Phase II Guttman-Yassky 2018	PBO + TCS	49	NR	NR	NR	LSM: -1.72	SE: 0.44	NR	NR	NR
	BARI 2 mg + TCS	37	NR	NR	NR	LSM: -2.61	SE: 0.47	NR	NR	NR
	BARI 4 mg + TCS	38	NR	NR	NR	LSM: -2.22	SE: 0.46	NR	NR	NR
Tralokinumab										
ECZTRA 1	**Week 16**									
	PBO	197	20	194	10.3	-1.7	SE: 0.21	REF	REF	REF
	TRA 300 mg	601	119	594	20	-2.6	SE: 0.11	9.7	4.4 to 15.0	0.002
ECZTRA 2	PBO	201	19	200	9.5	-1.6	SE: 0.21	REF	REF	REF
	TRA 300 mg	591	144	575	25	-2.9	SE: 0.11	15.6	10.3 to 20.9	<0.001
ECZTRA 2 Subgroup‡	PBO	91	13	90	14.4	-1.9†	SE: 0.3†	REF	REF	REF
	TRA 300 mg	270	77	264	29.2	-3.1†	SE: 0.2†	RD: 14.9	5.9 to 23.9	0.005
ECZTRA 3	PBO + TCS	126	43	126	34.1	-2.9	SE: 0.21	REF	REF	REF
	TRA 300 mg + TCS	252	113	249	45.4	-4.1	SE: 0.15	11.3	0.9 to 21.6	0.037
Upadacitinib										
MEASURE UP 1	**Week 16**									
	PBO	281	32	272	11.8	LSM: 26.1*	SE: 5.24†	REF	REF	REF
	UPA 15 mg	281	143	274	52.2	LSM: 62.8*	SE: 4.37†	40.5	33.5 to 47.5	≤0.001
	UPA 30 mg	285	171	285	60	LSM: 72*	SE:4.37†	48.2	41.3 to 55.0	≤0.001
MEASURE UP 2	PBO	278	25	274	9.1	LSM: 17*	SE: 2.81†	REF	REF	REF
	UPA 15 mg	276	113	270	41.9	LSM: 51.2*	SE: 2.34†	32.6	25.8 to 39.4	≤0.001
	UPA 30 mg	282	167	280	59.6	LSM: 66.5*	SE: 2.34†	50.4	43.8 to 57.1	≤0.001
AD-UP	PBO + TCS	304	44	294	15	25.1	SE: 3.4	REF	10.9 to 19.0	REF
	UPA 15 mg + TCS	300	149	288	51.7	58.1	SE: 3.4	36.8	29.7 to 43.8	≤0.001
	UPA 30 mg + TCS	297	186	291	63.9	66.9	SE: 2.91	48.8	41.9 to 55.7	≤0.001

Study Name	Arms	N	Itch or PP-NRS (≥4-point improvement from baseline)							
			n	N	%	Change from baseline	SD	Diff from PBO	95% CI	p value
Heads Up	DUP 300 mg	344	120	336	35.7	-49	2	REF	NR	REF
	UPA 30 mg	348	188	340	55.3	-66.9	1.9	-17.8	NR	<0.001
Phase IIb Guttman-Yassky 2020	**Week 8**									
	PBO	41	2	37	5.5[†]	LSM: -6.7*	SE: 7.5	NR	NR	REF
	UPA 7.5 mg	42	13	40	32.1[†]	LSM: -35.5*	SE: 7.3	NR	NR	0.002
	UPA 15 mg	42	22	37	58.8[†]	LSM: -45.1*	SE: 7.3	NR	NR	<0.001
	UPA 30 mg	42	27	42	63.7[†]	LSM: -73.1*	SE: 7.1	NR	NR	<0.001
	Week 16									
	PBO	41	2	35	5.7	LSM: -9.7*	SE: 8.3	NR	NR	REF
	UPA 15 mg	42	19	32	59.4	LSM: -48*	SE: 8.1	NR	NR	<0.001
	UPA 30 mg	42	19	36	52.8	LSM: -68.9*	SE: 7.8	NR	NR	<0.001
Dupilumab										
SOLO 1	**Week 16**									
	PBO	224	26	212	12	LSM: -26.1*	SE: 3	NR	NR	NR
	DUP 300 mg Q2W	224	87	213	41	LSM: -51*	SE: 2.5	NR	NR	NR
	DUP 300 mg QW	223	81	201	40	LSM: -48.9*	SE: 2.6	NR	NR	NR
SOLO 2	PBO	236	21	221	10	LSM: -15.4*	SE: 3	NR	NR	NR
	DUP 300 mg Q2W	233	81	225	36	LSM: -44.3*	SE: 2.3	NR	NR	NR
	DUP 300 mg QW	239	89	228	39	LSM: -48.3*	SE: 2.4	NR	NR	NR
LIBERTY AD CHRONOS	PBO + TCS	315	59	299	20	LSM: -2.1	SE: 0.1	REF	REF	REF
	DUP 300 mg + TCS Q2W	106	60	102	59	LSM: -4.1	SE: 0.2	39	28.5 to 49.7	<0.0001
	DUP 300 mg + TCS QW	319	150	295	51	LSM: -4.1	SE: 0.1	31	23.8 to 38.4	<0.0001
Phase IIb Thaci 2016	PBO QW	61	NR	NR	NR	LSM: -5.2*	SE: 4.8	NR	NR	NR
	DUP 200 mg Q2W	61	NR	NR	NR	LSM: -34.1*	SE: 4.7	NR	NR	NR
	DUP 300 mg Q2W	64	NR	NR	NR	LSM: -40.1*	SE: 4.5	NR	NR	NR

Study Name	Arms	N	Itch or PP-NRS (≥4-point improvement from baseline)							
			n	N	%	Change from baseline	SD	Diff from PBO	95% CI	p value
	DUP 300 mg Q4W	65	NR	NR	NR	LSM: -32.6*	SE: 4.5	NR	NR	NR

ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, LSM: least squares mean, mg: milligram, n: number, N: total number, NR: not reported, OR: odds ratio, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, RD: risk difference, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *percent change, †digitized estimate, ‡North American subgroup.

Table G1.12. Short-Term Efficacy Outcomes: SCORAD [35-37,39,40,42,45,46,48,50,51,56,63,64,69-71,80,81,84,155,156]

Study Name	Arms	N	SCORAD					
			N	Change from baseline	SD	Diff from PBO	95% CI	p value
Abrocitinib								
JADE MONO-1	**Week 12**							
	PBO	77	75	LSM: -13.6	95% CI: -18.3 to -9	REF	REF	REF
	ABRO 100 mg	156	150	LSM: -27	95% CI: -30.2 to -23.7	-13.3	-19 to -7.7	<0.0001
	ABO 200 mg	154	151	LSM: -35.5	95% CI: -38.7 to -32.3	-21.9	-27.5 to -16.3	<0.0001
JADE MONO-2	PBO	78	78	LSM: -22.7	95% CI: -30.4 to -15.1	REF	REF	REF
	ABRO 100 mg	158	158	LSM: -45.8	95% CI: -50.9 to -40.7	-23.1	-32.3 to -13.9	<0.0001
	ABO 200 mg	155	155	LSM: -56.2	95% CI: -61.2 to -51.1	-33.4	-42.6 to -24.3	<0.0001
JADE TEEN	PBO	96	96	LSM: -30.2	95% CI: -33.9 to -26.4	NR	NR	NR
	ABRO 100 mg	95	95	LSM: -40.9	95% CI: -44.7 to -37.2	NR	NR	NR
	ABO 200 mg	94	93	LSM: -42.9	95% CI: -46.7 to -39.1	NR	NR	NR
JADE COMPARE	PBO	131	131	LSM: -23	NR	NR	NR	NR
	ABRO 100 mg	238	238	LSM: -36.6	NR	NR	NR	NR
	ABRO 200 mg	226	226	LSM: -44.9	NR	NR	NR	NR
	DUP 300 mg	242	242	LSM: -39.7	NR	NR	NR	NR
	Week 16							
	PBO	131	123	NR	95% CI: 5.1 to 16.0	NR	NR	NR
	ABRO 100 mg + PBO→ABRO 100 mg	238	228	NR	95% CI:21.0 to 32.5	NR	NR	NR
	ABRO 200 mg + PBO→ABRO 200 mg	226	221	NR	95% CI: 33.8 to 46.7	NR	NR	NR
	DUP 300 mg + Oral PBO→PBO	242	231	NR	95% CI:23.6 to 35.3	NR	NR	NR
Phase II Gooderham 2019	**Week 12**							
	PBO	52	52	-29	95% CI: -36.6 to -21.3	NR	NR	REF
	ABRO 100 mg	54	54	-49.2	95% CI: -56.4 to -42.0	NR	NR	0.002
	ABRO 200 mg	48	48	-69.7	95% CI: -76.9 to -62.5	NR	NR	<0.001

Study Name	Arms	N	SCORAD					
			N	Change from baseline	SD	Diff from PBO	95% CI	p value
Baricitinib								
BREEZE-AD1	**Week 16**							
	PBO	249	249	LSM: -13.5	SE: 2	REF	REF	REF
	BARI 1 mg	127	127	LSM: -18.9	SE: 2.5	-9.1	-11.6 to 0.9	0.093
	BARI 2 mg	123	123	LSM: -21.5	SE: 2.4	-12.7	-14.0 to -1.9	0.01
	BARI 4 mg	125	125	LSM: -28.3	SE: 2.1	-23.0	-20.5 to -9.1	<0.001
BREEZE-AD2	PBO	244	244	LSM: -13.4	SE: 2.3	REF	REF	REF
	BARI 1 mg	125	125	LSM: -20.2	SE: 2.8	-11.3	-14 to 0.3	0.059
	BARI 2 mg	123	123	LSM: -27.8	SE: 2.6	-21.6	-21.3 to -7.6	<0.001
	BARI 4 mg	123	123	LSM: -27.5	SE: 2.4	-22.7	-20.7 to -7.6	<0.001
BREEZE-AD7	PBO + TCS	109	109	LSM: -21.4	SE: 1.9	REF	REF	REF
	BARI 2 mg + TCS	109	109	LSM: -29.9	SE: 1.9	-8.5	-13.7 to -3.2	0.002
	BARI 4 mg + TCS	111	111	LSM: -35.8	SE: 1.8	-14.8	-19.6 to -9.1	<0.001
Phase II Guttman-Yassky 2018	PBO + TCS	49	49	LSM: -11.9	SE: 2.9	REF	NR	REF
	BARI 2 mg + TCS	37	37	LSM: -23.9	SE: 3.0	-23	NR	<0.01
	BARI 4 mg + TCS	38	38	LSM: -26.5	SE: 3.0	-31	NR	<0.001
Tralokinumab								
ECZTRA 1	**Week 16**							
	PBO	197	NR	-14.7	SE: 1.8	REF	REF	REF
	TRA 300 mg	601	NR	-25.2	SE: 0.9	-10.4	-14.4 to -6.5	<0.001
ECZTRA 2	PBO	201	NR	-14	SE: 1.8	REF	REF	REF
	TRA 300 mg	591	NR	-28.1	SE: 0.9	-14	-18 to -10.1	<0.001
ECZTRA 2 Subgroup[†]	PBO	91	NR	-16	NR	REF	REF	REF
	TRA 300 mg	270	NR	-29	NR	LSM: -13.7	-19.3 to -8.0	<0.001
ECZTRA 3	PBO + TCS	126	NR	-26.8	SE: 1.8	REF	REF	REF
	TRA 300 mg + TCS	252	NR	-37.7	SE: 1.3	-10.9	-15.2 to -6·6	<0.001

Upadacitinib								
MEASURE UP 1	**Week 16**							
	PBO	281	125	-32.7	95% CI: -37.3 to -28.1	REF	REF	REF
	UPA 15 mg	281	239	-65.7	95% CI: -69.2 to -62.2	-33.0	-38.4 to -27.6	<0.001
	UPA 30 mg	285	253	-40.4	95% CI: -76.5 to -69.7	-40.4	-45.8 to -35.0	<0.001
MEASURE UP 2	PBO	278	142	-28.4	95% CI: -33.3 to -23.5	REF	REF	REF
	UPA 15 mg	276	246	-29.5	95% CI: -61.8 to '54.0	-29.5	-35.2 to -23.7	<0.001
	UPA 30 mg	282	250	-68.4	95% CI: -72.4 to ;64.4	-40.0	-45.8 to -34.2	<0.001
Phase IIb Guttman-Yassky 2020	**Week 8**							
	PBO	41	33	LSM: -7*	SE: 5.8	NR	NR	REF
	UPA 7.5 mg	42	39	LSM: -35.4*	SE: 5.5	NR	NR	<0.001
	UPA 15 mg	42	36	LSM: -44.1*	SE: 5.7	NR	NR	<0.001
	UPA 30 mg	42	40	LSM: -65.3*	5.5	NR	NR	<0.001
	Week 16							
	PBO	41	33	LSM: -12.4*	SE: 6.0	NR	NR	REF
	UPA 15 mg	42	36	LSM: -46.9*	SE: 5.8	NR	NR	<0.001
	UPA 30 mg	42	40	LSM: -60.4*	SE: 5.7	NR	NR	<0.001
Dupilumab								
SOLO 1	**Week 16**							
	PBO	224	NR	LSM: -29*	SE: 3.2	NR	NR	NR
	DUP 300 mg Q2W	224	NR	LSM: -57.7*	SE: 2.1	NR	NR	NR
	DUP 300 mg QW	223	NR	LSM: -57*	SE: 2.1	NR	NR	NR
SOLO 2	PBO	236	NR	LSM: -19.7*	SE: 2.5	NR	NR	NR
	DUP 300 mg Q2W	233	NR	LSM: -51.1*	SE: 2	NR	NR	NR
	DUP 300 mg QW	239	NR	LSM: -53.5*	SE: 2	NR	NR	NR
LIBERTY AD CHRONOS	PBO + TCS	315	315	LSM: -31.8*	SE: 1.55	NR	NR	REF
	DUP 300 mg + TCS Q2W	106	106	LSM: -62.1*	SE: 2.61	NR	NR	<0.0001
	DUP 300 mg + TCS QW	319	319	LSM: -63.3*	SE: 1.53	NR	NR	<0.0001
Phase IIb Thaci 2016	PBO QW	61	61	LSM: -13.8*	SE: 4.1	REF	REF	REF
	Dupilumab 200 mg Q2W	61	61	LSM: -46.0*	SE: 4.1	-32.2	-42.9 to -21.6	<0.0001

	DUP 300 mg Q2W	64	64	LSM: -51.2*	SE: 4.1	-37.4	-47.9 to -26.9	<0.0001
	DUP 300 mg Q4W	65	65	LSM: -48.8*	SE: 4.0	-35.0	-45.4 to -24.6	<0.0001

Short-term data on SCORAD were not available in BREEZE-AD5, AD-UP, and Heads Up. ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, LSM: least squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, REF: reference, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, SD: standard deviation, SE: standard error, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib. *percent change, †North American subgroup.

Table G1.13. Short-Term Efficacy Outcomes: DLQI and CDLQI[35-37,39,40,42,45,46,48,50,51,56,63,64,69-71,80,81,84]

Study Name	Arms	N	DLQI						CDLQI			
			N	Change from baseline	SD	Diff from PBO	95% CI	p value	N	Change from baseline	95% CI	p value
Abrocitinib												
JADE MONO-1	**Week 12**											
	PBO	77	60	LSM: -4.2	95% CI: -5.9 to -2.5	REF	REF	NR	16	LSM: -3.9	REF	NR
	ABRO 100 mg	156	121	LSM: -7	95% CI: -8.1 to -5.8	–2·8	-4.8 to -0.8	NR	32	LSM: -6.4	-5.2 to 0.1	NR
	ABRO 200 mg	154	119	LSM: -9.1	95% CI: -10.3 to -8.0	–4·9	-6.9 to -2.9	NR	32	LSM: -7.5	-6.2 to -0.9	NR
JADE MONO-2	PBO	78	70	LSM: -3.9	NR	REF	-5.3 to -2.4	NR	8	LSM: -2.7	-6.1 to 0.8	NR
	ABRO 100 mg	158	140	LSM: -8.3	NR	−4.4 (−6.2 to −2.7)	-9.3 to -7.3	NR	16	LSM: -4.8	-7.2 to -2.5	NR
	ABRO 200 mg	155	139	LSM: -9.8	NR	−5.9 (−7.7 to −4.2)	-10.7 to -8.8	NR	15	LSM: -9.7	-12.1 to -7.4	NR
JADE TEEN	PBO	96	NA	NA	NA	NA	NA	NA	96	LSM: -6.3	-7.4 to -5.3	NR
	ABRO 100 mg	95	NA	NA	NA	NA	NA	NA	95	LSM: -8.6	-9.6 to -7.5	NR
	ABO 200 mg	94	NA	NA	NA	NA	NA	NA	94	LSM: -8.7	-9.7 to -7.6	NR
JADE COMPARE	PBO	131	131	LSM: -6.2	95% CI: -7.1 to -5.3	NR	NR	NR	NA	NA	NA	NA
	ABRO 100 mg	238	238	LSM: -8.7	95% CI: -9.4 to -8	NR	NR	NR	NA	NA	NA	NA
	ABRO 200 mg	226	226	LSM: -11	95% CI: -11.7 to -10.3	NR	NR	NR	NA	NA	NA	NA

Study Name	Arms	N	DLQI						CDLQI			
			N	Change from baseline	SD	Diff from PBO	95% CI	p value	N	Change from baseline	95% CI	p value
	DUP 300 mg	242	241	LSM: -9.9	95% CI: -10.6 to -9.2	NR	NR	NR	NA	NA	NA	NA
	Week 16											
	PBO	131	131	LSM: -6.2	95% CI: -7.1 to -5.2	NR	NR	NR	NA	NA	NA	NA
	ABRO 100 mg + PBO→ABRO 100 mg	238	238	LSM: -9	95% CI: -9.7 to -8.4	NR	NR	NR	NA	NA	NA	NA
	ABRO 200 mg + PBO→ABRO 200 mg	226	226	LSM: -11.7	95% CI:-12.4 to -11.1	NR	NR	NR	NA	NA	NA	NA
	DUP 300 mg + Oral PBO→PBO	242	241	LSM: -10.8	95% CI: -11.4 to -10.1	NR	NR	NR	NA	NA	NA	NA
Baricitinib												
BREEZE-AD1	**Week 16**											
	PBO	249	249	-2.5	NR	REF	NR	REF	NA	NA	NA	NA
	BARI 1 mg	127	127	-4.6	NR	-2.1	NR	<0.05	NA	NA	NA	NA
	BARI 2 mg	123	123	-4.3	NR	-1.8	NR	<0.05	NA	NA	NA	NA
	BARI 4 mg	125	125	-6.8	NR	-4.3	NR	<0.001	NA	NA	NA	NA
BREEZE-AD2	PBO	244	244	-3.4	NR	REF	NR	REF	NA	NA	NA	NA
	BARI 1 mg	125	125	-5.1	NR	-1.7	NR	NS	NA	NA	NA	NA
	BARI 2 mg	123	123	-7.4	NR	-4.0	NR	<0.001	NA	NA	NA	NA
	BARI 4 mg	123	123	-7.6	NR	-4.2	NR	<0.001	NA	NA	NA	NA
BREEZE-AD5	PBO	147	28	-4.0	1.0	NR	NR	NR	NA	NA	NA	NA
	BARI 1 mg	147	47	-5.5	0.8	NR	-3.9 to 0.9	NR	NA	NA	NA	NA
	BARI 2 mg	146	63	-7.5	0.7	NR	-5.8 to -1.2	<0.001	NA	NA	NA	NA
BREEZE-AD7	PBO + TCS	109	89	LSM: -5.6	SE: 0.6	REF	REF	REF	NA	NA	NA	NA
	BARI 2 mg + TCS	109	99	LSM: -7.5	SE: 0.6	-1.9	-3.6 to -0.3	0.022	NA	NA	NA	NA

Study Name	Arms	N	DLQI						CDLQI			
			N	Change from baseline	SD	Diff from PBO	95% CI	p value	N	Change from baseline	95% CI	p value
	BARI 4 mg + TCS	111	99	LSM: -8.9	SE: 0.9	-3.3	-4.9 to -1.7	<0.001	NA	NA	NA	NA
Phase II Guttman-Yassky 2018	PBO + TCS	49	49	-6.3	0.8	NR	NR	REF	NA	NA	NA	NA
	BARI 2 mg + TCS	37	37	-6.9	0.9	NR	NR	NS	NA	NA	NA	NA
	BARI 4 mg + TCS	38	38	-8.0	0.9	NR	NR	NS	NA	NA	NA	NA
Tralokinumab												
ECZTRA 1	**Week 16**											
	PBO	197	197	-5	SE: 0.6	REF	REF	REF	NA	NA	NA	NA
	TRA 300 mg	601	601	-7.1	SE: 0.3	-2.1	-3.4 to -0.8	0.002	NA	NA	NA	NA
ECZTRA 2	PBO	201	201	-4.9	SE: 0.6	REF	REF	REF	NA	NA	NA	NA
	TRA 300 mg	591	591	-8.8	SE: 0.3	-3.9	-5.2 to -2.6	<0.001	NA	NA	NA	NA
ECZTRA 2 Subgroup*	PBO	91	NR	-5	NR	REF	REF	REF	NA	NA	NA	NA
	TRA 300 mg	270	NR	-9	NR	LSM: -3.9	-5.8 to -2.0	<0.001	NA	NA	NA	NA
ECZTRA 3	PBO + TCS	126	126	-8.8	SE: 0.6	REF	REF	REF	NA	NA	NA	NA
	TRA 300 mg + TCS	252	252	-11.7	SE: 0.4	-2.9	-4.3 to -1.6	<0.001	NA	NA	NA	NA
Upadacitinib												
MEASURE UP 1	**Week 16**											
	PBO	281	NR		NR	NR	NR	NR	NR	NR	NR	NR
	UPA 15 mg	281	NR		NR	NR	NR	NR	NR	NR	NR	NR
	UPA 30 mg	285	NR		NR	NR	NR	NR	NR	NR	NR	NR
MEASURE UP 2	PBO	278	NR		NR	NR	NR	NR	NR	NR	NR	NR
	UPA 15 mg	276	NR		NR	NR	NR	NR	NR	NR	NR	NR
	UPA 30 mg	282	NR		NR	NR	NR	NR	NR	NR	NR	NR
Dupilumab												
SOLO 1	**Week 16**											

Study Name	Arms	N	DLQI						CDLQI			
			N	Change from baseline	SD	Diff from PBO	95% CI	p value	N	Change from baseline	95% CI	p value
	PBO	224	224	-5.3	0.5	NR	NR	NR	NA	NA	NA	NA
	DUP 300 mg Q2W	224	224	-9.3	0.4	NR	NR	NR	NA	NA	NA	NA
	DUP 300 mg QW	223	223	-9	0.4	NR	NR	NR	NA	NA	NA	NA
SOLO 2	PBO	236	236	-3.6	0.5	NR	NR	NR	NA	NA	NA	NA
	DUP 300 mg Q2W	233	233	-9.3	0.4	NR	NR	NR	NA	NA	NA	NA
	DUP 300 mg QW	239	239	-9.5	0.4	NR	NR	NR	NA	NA	NA	NA
LIBERTY AD CHRONOS	PBO + TCS	315	315	LSM: -5.3	SE: 0.3	NR	NR	REF	NA	NA	NA	NA
	DUP 300 mg + TCS Q2W	106	106	LSM: -9.7	SE: 0.5	NR	NR	<0.0001	NA	NA	NA	NA
	DUP 300 mg + TCS QW	319	319	LSM: -10.5	SE: 0.3	NR	NR	<0.0001	NA	NA	NA	NA
Phase IIb Thaci 2016	PBO QW	61	61	2.6	SE: 7.3	REF	REF	REF	NA	NA	NA	NA
	Dupilumab 200 mg Q2W	61	61	-43.3	SE: 7.2	-45.9	-64.6 to -27.2	<0.0001	NA	NA	NA	NA
	DUP 300 mg Q2W	64	64	-39.6	SE: 7.0	-42.3	-60.6 to -23.9	<0.0001	NA	NA	NA	NA
	DUP 300 mg Q4W	65	65	-37.4	SE: 6.9	-40.1	-58.3 to -21.9	<0.0001	NA	NA	NA	NA

Short-term data on DLQI and CDLQI were not available in Phase IIb Gooderham 2019, AD-UP, Heads Up, and Phase IIb Guttman-Yassky 2020. ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, LSM: least squares mean, mg: milligram, N: total number, NA: not applicable, NR: not reported, NS: not significant, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib. *North American subgroup.

Table G1.14. Short-Term Efficacy Outcomes: POEM[35-37,39,40,42,45,46,48,50,51,56,63,64,69-71,80,81,84]

Study Name	Arms	Sample Size (N)	POEM					
			N	Change from baseline	SD	Diff from PBO	95% CI	p value
Abrocitinib								
JADE MONO-1	**Week 12**							
	PBO	77	77	-3.7	95% CI: -5.5 to -1.9	NR	NR	REF
	ABRO 100 mg	156	153	-6.8	95% CI: -8.0 to -5.6	-3.1	-5.2 to -0.9	NR
	ABRO 200 mg	154	153	-10.6	95% CI: -11.8 to -9.4	-6.9	-9.0 to -4.7	NR
JADE MONO-2	PBO	78	78	-3.6	95% CI: -5.3 to -1.9	NR	-5.3 to -1.9	REF
	ABRO 100 mg	158	156	-8.7	95% CI: -9.9 to -7.5	-5.1 (-7.2 to -3.1)	-9.9 to -7.5	NR
	ABRO 200 mg	155	154	-11	95% CI: -12.1 to -9.8	-7.4 (-9.5 to -5.3)	-12.1 to -9.8	NR
JADE COMPARE	PBO	131	131	-5.1	95% CI: -6.3 to -3.9	NR	NR	NR
	ABRO 100 mg	238	238	-9.6	95% CI: -10.1 to -8.6	NR	NR	NR
	ABRO 200 mg	226	226	-12.6	95% CI: -13.6 to -11.7	NR	NR	NR
	DUP 300 mg	242	241	-10.8	95% CI: -11.7 to -9.9	NR	NR	NR
	Week 16							
	PBO	131	131	-5	95% CI: -6.3 to -3.8	NR	NR	NR
	ABRO 100 mg + PBO→ABRO 100 mg	238	238	-9.2	95% CI: -10.1 to -8.2	NR	NR	NR
	ABRO 100 mg + PBO→ABRO 100 mg	226	226	-12.5	95% CI:-13.4 to -11.6	NR	NR	NR
	DUP 300 mg + Oral PBO→PBO	242	241	-10.8	95% CI:-11.8 to -9.9	NR	NR	NR
Baricitinib								
BREEZE-AD1	**Week 16**							
	PBO	249	72	-2.7	SE: 0.8	NR	NR	REF
	BARI 1 mg	127	53	-5.3	SE: 0.9	-2.6	NR	<0.05
	BARI 2 mg	123	52	-6.3	SE: 0.9	-3.6	NR	<0.01
	BARI 4 mg	125	70	-7.8	SE: 0.8	-5.1	NR	<0.001

Study Name	Arms	Sample Size (N)	POEM					
			N	Change from baseline	SD	Diff from PBO	95% CI	p value
BREEZE-AD2	PBO	244	52	-1.5	NR	REF		REF
	BARI 1 mg	125	34	-3.9	NR	-2.4	NR	NS
	BARI 2 mg	123	40	-7.1	NR	-5.6	NR	<0.001
	BARI 4 mg	123	48	-7.6	NR	-6.1	NR	<0.001
BREEZE-AD5	PBO	147	147	-2.7	NR	NR	NR	NR
	BARI 1 mg	147	147	-4.6	NR	NR	-4.9 to 1.1	NR
	BARI 2 mg	146	146	-7.4	NR	NR	-7.7 to -1.8	<0.001
BREEZE-AD7	PBO + TCS	109	109	-5.6	0.8	REF	REF	REF
	BARI 2 mg + TCS	109	109	-8.5	0.7	-2.9	-5.0 to -0.8	0.006
	BARI 4 mg + TCS	111	111	-10.8	0.7	-5.2	-7.3 to -3.2	<0.001
Phase II Guttman-Yassky 2018	PBO + TCS	49	49	-3.5	NR	NR	NR	REF
	BARI 2 mg + TCS	37	37	-6.4	NR	NR	NR	NS
	BARI 4 mg + TCS	38	38	-7.5	NR	NR	NR	<0.01
Tralokinumab								
ECZTRA 1	**Week 16**							
	PBO	197	197	-3	0.66	REF	REF	REF
	TRA 300 mg	601	601	-7.6	0.35	-4.5	-6.0 to -3.1	<0.001
ECZTRA 2	PBO	201	201	-3.7	0.66	REF	REF	REF
	TRA 300 mg	591	591	-8.8	0.33	-5.1	-6.5 to -3.6	<0.001
ECZTRA 3	PBO + TCS	126	126	-7.8	0.66	REF	REF	REF
	TRA 300 mg + TCS	252	252	-11.8	0.46	-0.4	-5.6 to -2.4	<0.001
Upadacitinib								
Phase IIb Guttman-Yassky 2020	**Week 16**							
	PBO	41	41	1.6	1.4	NR	NR	REF
	UPA 15 mg	42	42	8.6	1.4	NR	NR	≤0.001
	UPA 30 mg	42	42	12.3	1.4	NR	NR	≤0.001

Study Name	Arms	Sample Size (N)	POEM					
			N	Change from baseline	SD	Diff from PBO	95% CI	p value
Dupilumab								
SOLO 1	**Week 16**							
	PBO	224	224	-5.1	0.7	NR	NR	NR
	DUP 300 mg Q2W	224	224	-11.6	0.5	NR	NR	NR
	DUP 300 mg QW	223	223	-11	0.5	NR	NR	NR
SOLO 2	PBO	236	236	-3.3	0.6	NR	NR	NR
	DUP 300 mg Q2W	233	233	-10.2	0.5	NR	NR	NR
	DUP 300 mg QW	239	239	-11.3	0.5	NR	NR	NR
LIBERTY AD CHRONOS	PBO + TCS	315	315	-4.7	0.4	NR	NR	REF
	DUP 300 mg + TCS Q2W	106	106	-12.4	0.6	NR	NR	<0.0001
	DUP 300 mg + TCS QW	319	319	-12.5	0.4	NR	NR	<0.0001
Phase IIb AD-1021	PBO QW	61	61	LSM: -1.1	SE: 0.9	NR	NR	REF
	Dupilumab 200mg Q2W	61	61	LSM: -10.4	SE: 0.9	NR	NR	<0.0001
	DUP 300mg Q2W	64	64	LSM: -9.8	SE: 0.9	NR	NR	<0.0001
	DUP 300mg Q4W	65	65	LSM: -9.9	SE: 0.9	NR	NR	<0.0001

Short-term data on POEM were not available in JADE TEEN, Phase IIb Gooderham 2019, MEASURE UP 1, MEASURE UP 2, AD-UP, and Heads Up. ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, LSM: least squares mean, mg: milligram, N: total number, NR: not reported, NS: not significant, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib.

Table G1.15. Short-Term Efficacy Outcomes: Total HADS[42-46,48,50-56,60,64-66,70,155]

Study Name	Arms	N	Total HADS					
			N	Change from baseline	SD	Diff from PBO	95% CI	p value
Abrocitinib								
JADE MONO-1	**Week 12**							
	PBO	77	77	LSM: -0.2	-0.8 to 0.4	REF	REF	REF
	ABRO 100 mg	156	156	LSM: -1.4	-1.8 to -0.9	-1.1	-19 to -0.4	0.0028
	ABRO 200 mg	154	154	LSM: -1.8	-2.2 to -1.4	-1.6	-2.3 to -0.9	<0.001
Baricitinib								
BREEZE-AD7	**Week 16**							
	PBO + TCS	109	109	LSM: -3.2	0.6	REF	REF	REF
	BARI 2 mg + TCS	109	109	LSM: -4.8	0.5	-1.6	-3.1 to -0.1	0.042
	BARI 4 mg + TCS	111	111	LSM: -5.1	0.5	-1.9	-3.5 to -0.4	0.011
ECZTRA 1	**Week 16**							
	PBO	197	197	NR	NR	NR	NR	NR
	TRA 300 mg	601	601	NR	NR	NR	NR	NR
ECZTRA 2	PBO	201	201	NR	NR	NR	NR	NR
	TRA 300 mg	591	591	NR	NR	NR	NR	NR
ECZTRA 3	PBO + TCS	126	126	NR	NR	NR	NR	NR
	TRA 300 mg + TCS	252	252	NR	NR	NR	NR	NR
Dupilumab								
SOLO 1	**Week 16**							
	PBO	224	224	-3	0.7	NR	NR	NR
	DUP 300 mg Q2W	224	224	-5.2	0.5	NR	NR	NR
	DUP 300 mg QW	223	223	-5.2	0.5	NR	NR	NR
SOLO 2	PBO	236	236	-0.8	0.4	NR	NR	NR

Study Name	Arms	N	Total HADS					
			N	Change from baseline	SD	Diff from PBO	95% CI	p value
	DUP 300 mg Q2W	233	233	-5.1	0.4	NR	NR	NR
	DUP 300 mg QW	239	239	-5.8	0.4	NR	NR	NR
LIBERTY AD CHRONOS	PBO + TCS	315	315	-3.6	0.34	NR	NR	REF
	DUP 300 mg + TCS Q2W	106	106	-4.9	0.56	NR	NR	0.03
	DUP 300 mg + TCS QW	319	319	-5.2	0.33	NR	NR	0.0004
Phase IIb Thaci 2016	PBO QW	61	61	LSM: 0	SE: 0.8	NR	NR	REF
	DUP 200 mg Q2W	61	61	LSM: -4	SE: 0.8	NR	NR	0.0002
	DUP 300 mg Q2W	64	64	LSM: -4.3	SE: 0.8	NR	NR	<0.0001
	DUP 300 mg Q4W	65	65	LSM: -2.7	SE: 0.8	NR	NR	0.0103

Short-term data on total HADS were not available in JADE MONO 2, JADE TEEN, JADE COMPARE, Phase IIb Gooderham 2019, BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, Phase II Guttman-Yassky 2018, ECZTRA 1, ECZTRA 2, ECZTRA 3, MEASURE UP 1, MEASURE UP 2, Heads Up, AD-UP, and Phase IIb Guttman-Yassky 2020. BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, LSM: least squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids.

Table G1.16. Short-Term Efficacy Outcomes: HADS Anxiety[35-37,39,46,50-56,60,63-66,69,84,155,157]

Study Name	Arms	HADS Anxiety					
		N	Change from baseline	SD	Diff from PBO	95% CI	p value
Abrocitinib							
JADE MONO-1	**Week 12**						
	PBO	76	LSM: -1	95% CI: -1.7 to -0.4	REF	REF	REF
	ABRO 100 mg	152	LSM: -1.6	95% CI: -2.0 to -1.1	-0.5	-1.3 to 0.2	0.1675
	ABRO 200 mg	152	LSM: -2.1	95% CI: -2.5 to -1.6	-1	-1.8 to -0.3	0.0085
JADE MONO-2	PBO	78	LSM: −0.6	95% CI: −1.3 to 0.2	REF	REF	REF
	ABRO 100 mg	156	LSM: −1.6	95% CI: −2.1 to −1.1	-1.0	-1.9 to -0.1	NR
	ABRO 200 mg	153	LSM: −1.7	95% CI: −2.2 to −1.2	-1.1	-2.0 to -0.2	NR

Study Name	Arms	HADS Anxiety					
		N	Change from baseline	SD	Diff from PBO	95% CI	p value
JADE TEEN	PBO	96	LSM: -2.1	95% CI: -2.7 to -1.5	NR	NR	NR
	ABRO 100 mg	95	LSM: -2	95% CI: -2.6 to -1.4	NR	NR	NR
	ABRO 200 mg	94	LSM: -2.4	95% CI: -3 to -1.8	NR	NR	NR
JADE COMPARE	PBO	131	LSM: -0.4	95% CI: -0.9 to 0.1	REF	REF	REF
	ABRO 100 mg	238	LSM: -1.2	95% CI: -1.5 to -0.8	-0.7	-1.4 to -0.1	NR
	ABRO 200 mg	226	LSM: -1.6	95% CI: -2.0 to -1.2	-1.2	-1.8 to -0.5	NR
	DUP 300 mg	241	LSM: -1.4	95% CI: -1.7 to -1.0	-1	-1.6 to -0.3	NR
	Week 16						
	PBO	131	LSM: -0.4	95% CI: -0.9 to 0.1	NR	NR	NR
	ABRO 100 mg	238	LSM: -1.2	95% CI: -1.6 to -.8	NR	NR	NR
	ABRO 200 mg	226	LSM: -2.0	95% CI: -2.4 to -1.6	NR	NR	NR
	DUP 300 mg	241	LSM: -1.5	95% CI: -1.9 to -1.1	NR	NR	NR
Gooderham 2019	**Week 12**						
	PBO	36	-2.6	3.01	NR	NR	NR
	ABRO 100 mg	43	-2.8	3.71	NR	NR	NR
	ABRO 200 mg	46	-2.5	3.51	NR	NR	NR
Baricitinib							
BREEZE-AD7	**Week 16**						
	PBO + TCS	109	-1.9	0.3	REF	REF	REF
	BARI 2 mg + TCS	109	-2.7	0.3	-0.8	-1.6 to 0	0.051
	BARI 4 mg + TCS	111	-2.8	0.3	-0.9	-1.7 to -0.1	0.028
Dupilumab							
SOLO 1	**Week 16**						
	PBO	NR	NR	0.7	NR	NR	NR
	DUP 300 mg Q2W	NR	NR	0.5	NR	NR	NR
	DUP 300 mg QW	NR	NR	0.5	NR	NR	NR
SOLO 2	PBO	NR	NR	0.4	NR	NR	NR
	DUP 300 mg Q2W	NR	NR	0.4	NR	NR	NR
	DUP 300 mg QW	NR	NR	0.4	NR	NR	NR

Study Name	Arms	HADS Anxiety					
		N	Change from baseline	SD	Diff from PBO	95% CI	p value
Phase IIb Thaci 2016	PBO QW	61	LSM: -0.4	SE: 0.4	NR	NR	REF
	DUP 200 mg Q2W	61	LSM: -1.9	SE: 0.4	NR	NR	0.0062
	DUP 300 mg Q2W	64	LSM: -2.2	SE: 0.4	NR	NR	0.0011
	DUP 300 mg Q4W	65	LSM: -1.3	SE: 0.4	NR	NR	0.0808

Short-term data on HADS Anxiety were not available in BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, Phase II Guttman-Yassky 2018, ECZTRA 1, ECZTRA 2, ECZTRA 3, MEASURE UP 1, MEASURE UP 2, AD-UP, Heads Up, Phase IIb Guttman-Yassky 2020, and LIBERTY AD CHRONOS. ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, LSM: least squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids.

Table G1.17. Short-Term Efficacy Outcomes: HADS Depression[35-37,39,46,50-56,60,63-67,84,155,157]

Study Name	Arms	HADS Depression					
		N	Change from baseline	SD	Diff from PBO	95% CI	p value
Abrocitinib							
JADE MONO-1	**Week 12**						
	PBO	76	LSM: -0.2	95% CI: -0.8 to 0.4	REF	REF	REF
	ABRO 100 mg	152	LSM: -1.4	95% CI: -1.8 to -0.9	-1.1	-1.9 to -0.4	0.0028
	ABRO 200 mg	152	LSM: -1.8	95% CI: -2.2 to -1.4	-1.6	-2.3 to -0.9	<0.0001
JADE MONO-2	PBO	78	0.3	95% CI: -0.3 to 0.9	REF	REF	REF
	ABRO 100 mg	156	-1.0	95% CI: -1.5 to -0.6	-1.3	-2.1 to -0.6	NR
	ABRO 200 mg	153	-1.4	95% CI: -1.8 to -1.0	-1.7	-2.5 to -0.9	NR
JADE TEEN	PBO	96	96	LSM: -1	95% CI: -1.5 to -0.5	NR	NR
	ABRO 100 mg	95	95	LSM: -1.4	95% CI: -1.9 to -0.8	NR	NR
	ABRO 200 mg	94	94	LSM: -1.2	95% CI: -1.7 to -0.6	NR	NR
JADE COMPARE	PBO	131	LSM: -0.3	95% CI: -0.7 to 0.2	REF	REF	REF
	ABRO 100 mg	238	LSM: -1.3	95% CI: -1.6 to -0.9	-1	-1.6 to -0.4	NR
	ABRO 200 mg	226	LSM: -1.6	95% CI: -1.9 to -1.2	-1.3	-1.9 to -0.7	NR
	DUP 300 mg	241	LSM: -1.3	95% CI: -1.6 to -0.9	-1	-1.6 to -0.4	NR
	Week 16						
	PBO	131	LSM: -0.3	95% CI: -0.8 to 0.2	NR	NR	NR

Study Name	Arms	HADS Depression					
		N	Change from baseline	SD	Diff from PBO	95% CI	p value
	ABRO 100 mg	238	LSM: -1	95% CI: -1.4 to -0.7	NR	NR	NR
	ABRO 200 mg	226	LSM: -1.6	95% CI: -1.9 to -1.2	NR	NR	NR
	DUP 300 mg	241	LSM: -1.2	95% CI: -1.5 to -0.8	NR	NR	NR
Gooderham 2019	**Week 12**						
	PBO	36	-0.9	3.96	NR	NR	NR
	ABRO 100 mg	43	-2.4	3.74	NR	NR	NR
	ABRO 200 mg	46	-1.8	3.9	NR	NR	NR
Baricitinib							
BREEZE-AD7	PBO + TCS	109	-1.3	0.3	REF	REF	REF
	BARI 2 mg + TCS	109	-2.1	0.3	-0.7	-1.6 to 0.1	0.083
	BARI 4 mg + TCS	111	-2.3	0.3	-1	-1.0 to -0.2	0.016
Dupilumab							
Phase IIb Thaci 2016	**Week 16**						
	PBO QW	61	LSM: 0.4	SE: 0.5	NR	NR	REF
	DUP 200 mg Q2W	61	LSM: -2	SE: 0.5	NR	NR	<0.0001
	DUP 300 mg Q2W	64	LSM: -2	SE: 0.4	NR	NR	<0.0001
	DUP 300 mg Q4W	65	LSM: -1.4	SE: 0.4	NR	NR	0.0036

Short-term data on HADS Depression were not available in BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, Phase II Guttman-Yassky 2018, ECZTRA 1, ECZTRA 2, ECZTRA 3, MEASURE UP 1, MEASURE UP 2, AD-UP, Heads Up, Phase IIb Guttman-Yassky 2020, LIBERTY AD SOLO 1 and SOLO 2, and LIBERTY AD CHRONOS.
ABRO: abrocitinib, BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, LSM: least squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids.

Table G1.18. Long-Term Efficacy Outcomes: IGA Response Rates[43,44,50,54,55,63-65,76,78,82,107,158,159]

Study Name	Arms	N	IGA response					
			n	N	%	Diff from PBO	95% CI	p value
Abrocitinib								
JADE EXTEND Subgroup 1*	**Week 48**							
	ABRO 100 mg	595	84	287	29.1	NR	NR	NR
	ABRO 200 mg	521	99	250	39.5	NR	NR	NR
	Week 48 (Responders)							
	ABRO 100 mg	NR	49	92	53.3	NR	NR	NR
	ABRO 200 mg	NR	78	136	57.4	NR	NR	NR
	Week 24 (Nonresponders)							
	ABRO 100 mg	NR	65	290	22.4	NR	NR	NR
	ABRO 200 mg	NR	59	221	26.7	NR	NR	NR
	Week 48 (Nonresponders)							
	ABRO 100 mg	NR	49	224	21.9	NR	NR	NR
	ABRO 200 mg	NR	47	172	27.3	NR	NR	NR
JADE EXTEND Subgroup 2†	**Week 32**							
	ABRO 100 mg	130	25	71	35.2	NR	NR	NR
	ABRO 200 mg	73	17	36	47.2	NR	NR	NR
Baricitinib								
BREEZE-AD3	**Week 32**							
	BARI 2 mg	54	34	54	63	NR	NR	NR
	Week 40							
	BARI 2 mg	54	31	54	57.4	NR	NR	NR
	Week 68							
	BARI 2 mg	54	52	54	59.3	NR	NR	NR
BREEZE-AD6	**Week 16**							
	BARI 2 mg	146	39	146	27	NR	NR	NR
	Week 32							

Study Name	Arms	N	IGA response					
			n	N	%	Diff from PBO	95% CI	p value
	BARI 2 mg	146	56	146	38.2	NR	NR	NR
	Week 52							
	BARI 2 mg	146	46	146	31.3	NR	NR	NR
Tralokinumab								
ECZTRA 1	**Week 52 (Maintenance Period)**							
	PBO	35	9	19	47.4	REF	REF	REF
	TRA 300 mg Q2W	68	20	39	51.3	6	-21.8 to 33.7	0.68
	TRA 300 mg Q4W	76	14	36	38.9	-9.5	-37.1 to 18.0	0.50
ECZTRA 2	PBO	46	7	28	25	REF	REF	REF
	TRA 300 mg Q2W	91	32	54	59.3	34.1	13.4 to 54.9	0.004
	TRA 300 mg Q4W	89	22	49	44.9	19.9	-1.2 to 40.9	0.084
ECZTRA 1 and 2 OLE (Initial nonresponders)	TRA 300 mg Q2W + TCS	686	138	686	20.1	NR	NR	NR
	TRA 300 mg Q2W + TCS (no response at week 24 group)	NR	NR	NR	13.9	NR	NR	NR
ECZTRA 3	**Week 32 (Maintenance Period)**							
	TRA 300 mg Q2W + TCS (TRA nonresponders)	95	NR	NR	30.5	NR	22.2 to 40.4	NR
	TRA 300 mg Q2W + TCS (TRA responders)	69	NR	NR	89.6	NR	77.8 to 99.5	NR
	TRA 300 mg Q4W + TCS (TRA responders)	69	NR	NR	77.6	NR	64.1 to 87.0	NR
ECZTEND	**Week 56**							
	TRA 300 mg Q2W (Week 56 Cohort)	612	255‡	612	41.7	NR	NR	NR
	TRA 300 mg Q2W (2-year Cohort)	345	NR	NR	NR	NR	NR	NR
Upadacitinib								
Phase IIb Guttman-Yassky 2020	**Week 16**							
	PBO→PBO	8	0	8	0	NR	NR	NR
	UPA 7.5 mg→PBO	13	3	13	7.7	NR	NR	NR
	UPA 15 mg→PBO	17	11	17	47.1	NR	NR	NR

Study Name	Arms	N	IGA response					
			n	N	%	Diff from PBO	95% CI	p value
	UPA 30 mg→PBO	13	10	13	61.5	NR	NR	NR
	PBO→UPA 30 mg	1	0	1	0	NR	NR	NR
	UPA 7.5 mg→UPA 7.5 mg	11	1	11	9.1	NR	NR	NR
	UPA 15 mg→UPA 15 mg	12	3	12	25	NR	NR	NR
	UPA 30 mg→UPA 30 mg	3	0	3	0	NR	NR	NR
	START OF RESCUE W/ UPA 30mg							
	PBO→PBO	8	0	8	0	NR	NR	NR
	UPA 7.5 mg→PBO	13	0	13	0	NR	NR	NR
	UPA 15 mg→PBO	17	0	17	0	NR	NR	NR
	UPA 30 mg→PBO	13	0	13	0	NR	NR	NR
	PBO→UPA 30 mg	1	0	1	0	NR	NR	NR
	UPA 7.5 mg→UPA 7.5 mg	11	0	11	0	NR	NR	NR
	UPA 15 mg→UPA 15 mg	12	0	12	0	NR	NR	NR
	UPA 30 mg→UPA 30 mg	3	0	3	0	NR	NR	NR
	8 WEEKS POST-RESCUE							
	PBO→PBO	8	4	8	50	NR	NR	NR
	UPA 7.5 mg→PBO	12	7	12	58.3	NR	NR	NR
	UPA 15 mg→PBO	16	15	16	93.8	NR	NR	NR
	UPA 30 mg→PBO	13	9	13	69.2	NR	NR	NR
	PBO→UPA 30 mg	1	0	1	0	NR	NR	NR
	UPA 7.5 mg→UPA 7.5 mg	10	1	10	10	NR	NR	NR
	UPA 15 mg→UPA 15 mg	9	2	9	22.2	NR	NR	NR
	UPA 30 mg→UPA 30 mg	3	0	3	0	NR	NR	NR
Dupilumab								
LIBERTY AD CHRONOS	**Week 52**							
	PBO + TCS	264	33	264	13	REF	REF	REF
	DUP 300 mg + TCS Q2W	89	32	89	36	24	12.7 to 34.2	<0.0001

Study Name	Arms	N	IGA response					
			n	N	%	Diff from PBO	95% CI	p value
	DUP 300 mg + TCS QW	270	108	270	40	28	20.4 to 34.6	<0.0001
AD SOLO-CONTINUE	**Week 36**							
	PBO	83	9	63	14.3	NR	NR	NR
	DUP 300 mg Q8W	84	21	64	32.8	NR	NR	NR
	DUP 300 mg Q4W	86	29	66	43.9	NR	NR	NR
	DUP 300 mg QW/Q2W	169	68	126	54	NR	NR	NR

Long-term data on IGA were not available in Heads Up long-term outcomes. BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, LTE: long-term extension, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, REF: reference, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, TCS: topical corticosteroids, TRA: tralokinumab, %: percent. *JADE MONO-1 & 2 and JADE COMPARE subgroup, [†]JADE COMPARE dupilumab nonresponder subgroup, [‡]Non-responder imputation.

Table G1.19. Long-Term Efficacy Outcomes: EASI 75[43,44,50,54,55,63-65,76,78,82,83,107,158,159]

Study Name	Arms	N	EASI 75					
			n	N	%	Diff from PBO	95% CI	p value
Abrocitinib								
JADE EXTEND Subgroup 1*	**Week 48**							
	ABRO 100 mg	595	132	289	45.9	NR	NR	NR
	ABRO 200 mg	521	155	252	61.7	NR	NR	NR
	Week 48 (Responders)							
	ABRO 100 mg	NR	106	153	69.3	NR	NR	NR
	ABRO 200 mg	NR	147	208	70.7	NR	NR	NR
	Week 24 (Nonresponders)							
	ABRO 100 mg	NR	91	203	44.8	NR	NR	NR
	ABRO 200 mg	NR	68	126	54	NR	NR	NR
	Week 48 (Nonresponders)							
	ABRO 100 mg	NR	58	165	35.2	NR	NR	NR
	ABRO 200 mg	NR	48	101	47.5	NR	NR	NR
JADE EXTEND Subgroup 2†	**Week 32**							
	ABRO 100 mg	130	21	31	67.7	NR	NR	NR
	ABRO 200 mg	73	16	20	80	NR	NR	NR
Baricitinib								
BREEZE-AD3	**Week 32**							
	BARI 2 mg	54	40	54	74.1	NR	NR	NR
	Week 40							
	BARI 2 mg	54	45	54	83.3	NR	NR	NR
	Week 68							
	BARI 2 mg	54	44	54	81.5	NR	NR	NR
BREEZE-AD6	**Week 16**							
	BARI 2 mg	146	58	146	40	NR	NR	NR

Study Name	Arms	N	EASI 75					
			n	N	%	Diff from PBO	95% CI	p value
	Week 32							
	BARI 2 mg	146	75	146	51.4	NR	NR	NR
	Week 52							
	BARI 2 mg	146	71	146	48.6	NR	NR	NR
Tralokinumab								
ECZTRA 1	**Week 52 (Maintenance period)**							
	PBO	35	10	30	33.3	REF	REF	REF
	TRA 300 mg Q2W	68	28	47	59.6	21.2	-0.2 to 42.6	0.056
	TRA 300 mg Q4W	76	28	57	49.1	11.7	-8.7 to 32.0	0.27
ECZTRA 2	PBO	46	9	42	21.4	REF	REF	REF
	TRA 300 mg Q2W	91	43	77	55.8	33.7	17.3 to 50.0	<0.001
	TRA 300 mg Q4W	89	37	74	51.4	30	13.7 to 46.4	0.001
ECZTRA 1 and 2 OLE (Initial nonresponders)	686	294	686	42.9	NR	NR	NR	NR
	NR	NR	NR	25.7	NR	NR	NR	NR
ECZTRA 3	**Week 32 (Maintenance period)**							
	TRA 300 mg Q2W + TCS (TRA nonresponders)	95	NR	NR	55.8	NR	45.8 to 65.4	NR
	TRA 300 mg Q2W + TCS (TRA responders)	69	NR	NR	92.5	NR	83.7 to 96.8	NR
	TRA 300 mg Q4W + TCS (TRA responders)	69	NR	NR	90.8	NR	81.5 to 95.7	NR
ECZTEND	**Week 56**							
	TRA 300 mg Q2W (Week 56 Cohort)	612	425‡	612	69.4	NR	NR	NR
	TRA 300 mg Q2W (2-year Cohort)	345	272‡	345	78.8	NR	NR	NR
Upadacitinib								
Heads Up	**Week 24**							
	DUP 300 mg	344	205	344	59.5	NR	NR	NR
	UPA 30 mg	348	223	348	64.2	NR	NR	NR
Phase IIb Guttman-Yassky 2020	**Week 16**							

Study Name	Arms	N	EASI 75					
			n	N	%	Diff from PBO	95% CI	p value
	PBO→PBO	8	0	8	0	NR	NR	NR
	UPA 7.5 mg→PBO	13	3	13	23.1	NR	NR	NR
	UPA 15 mg→PBO	17	11	17	64.7	NR	NR	NR
	UPA 30 mg→PBO	13	10	13	76.9	NR	NR	NR
	PBO→UPA 30 mg	1	0	1	0	NR	NR	NR
	UPA 7.5 mg→UPA 7.5 mg	11	1	11	9.1	NR	NR	NR
	UPA 15 mg→UPA 15 mg	12	6	12	50	NR	NR	NR
	UPA 30 mg→UPA 30 mg	3	2	3	66.7	NR	NR	NR
	START OF RESCUE W/ UPA 30 mg							
	PBO→PBO	8	0	8	0	NR	NR	NR
	UPA 7.5 mg→PBO	13	0	13	0	NR	NR	NR
	UPA 15 mg→PBO	17	0	17	0	NR	NR	NR
	UPA 30 mg→PBO	13	0	13	0	NR	NR	NR
	PBO→UPA 30 mg	1	0	1	0	NR	NR	NR
	UPA 7.5 mg→UPA 7.5 mg	11	0	11	0	NR	NR	NR
	UPA 15 mg→UPA 15 mg	12	0	12	0	NR	NR	NR
	UPA 30 mg→UPA 30 mg	3	0	3	0	NR	NR	NR
	8 WEEKS POST-RESCUE							
	PBO→PBO	8	4	8	50	NR	NR	NR
	UPA 7.5 mg→PBO	12	7	12	58.3	NR	NR	NR
	UPA 15 mg→PBO	16	15	16	93.8	NR	NR	NR
	UPA 30 mg→PBO	13	9	13	69.2	NR	NR	NR
	PBO→UPA 30 mg	1	1	1	100	NR	NR	NR
	UPA 7.5 mg→UPA 7.5 mg	10	3	10	30	NR	NR	NR
	UPA 15 mg→UPA 15 mg	9	5	9	55.6	NR	NR	NR
	UPA 30 mg→UPA 30 mg	3	1	3	33.3	NR	NR	NR
Dupilumab								

Study Name	Arms	N	EASI 75					
			n	N	%	Diff from PBO	95% CI	p value
LIBERTY AD CHRONOS	**Week 52**							
	PBO + TCS	264	57	264	22	REF	REF	REF
	DUP 300 mg + TCS Q2W	89	58	89	65	44	32.5 to 54.7	<0.0001
	DUP 300 mg + TCS QW	270	173	270	64	43	34.9 to 50.1	<0.0001
AD SOLO-CONTINUE	**Week 36**							
	PBO	83	24	79	30.4	NR	NR	NR
	DUP 300 mg Q8W	84	45	82	54.9	NR	NR	NR
	DUP 300 mg Q4W	86	49	84	58.3	NR	NR	NR
	DUP 300 mg QW/Q2W	169	116	162	71.6	NR	NR	NR

BARI: baricitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, LTE: long-term extension, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, REF: reference, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *JADE MONO-1 & 2 and JADE COMPARE subgroup, [†]JADE COMPARE dupilumab nonresponder subgroup, [‡]non-responder imputation (NRI).

Table G1.20. Long-Term Efficacy Outcomes: EASI 50 and 90[50,54,55,64,65,76,78,83,107]

Study Name	Arms	N	EASI 50						EASI 90					
			n	N	%	Diff from PBO	95% CI	p value	n	N	%	Diff from PBO	95% CI	p value
Abrocitinib														
JADE EXTEND Subgroup 1*	**Week 48**													
	ABRO 100 mg	595	NR	NR	NR	NR	NR	NR	84	289	29.2	NR	NR	NR
	ABRO 200 mg	521	NR	NR	NR	NR	NR	NR	103	252	40.7	NR	NR	NR
JADE EXTEND Subgroup 2†	**Week 32**													
	ABRO 100 mg	130	NR	NR	NR	NR	NR	NR	27	68	39.7	NR	NR	NR
	ABRO 200 mg	73	NR	NR	NR	NR	NR	NR	22	37	59.5	NR	NR	NR
Tralokinumab														
ECZTRA 3	**Week 32 (Maintenance period)**													
	TRA 300 mg Q2W + TCS (TRA nonresponders)	95	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	TRA 300 mg Q2W + TCS (TRA responders)	69	NR	NR	98.6	NR	NR	NR	NR	NR	72.5	NR	NR	NR
	TRA 300 mg Q4W + TCS (TRA responders)	69	NR	NR	91.3	NR	NR	NR	NR	NR	63.8	NR	NR	NR
ECZTEND	**Week 56**													
	TRA 300 mg Q2W (Week 56 Cohort)	612	488‡	612	79.6	NR	NR	NR	313	612	51.1	NR	NR	NR
	TRA 300 mg Q2W (2-year Cohort)	345	314‡	345	91	NR	NR	NR	195	345	56.5	NR	NR	NR
Upadacitinib														
Heads Up	**Week 24**													
	DUP 300 mg	344	NR	NR	NR	NR	NR	NR	164	344	47.6	NR	NR	NR

Study Name	Arms	N	EASI 50						EASI 90					
			n	N	%	Diff from PBO	95% CI	p value	n	N	%	Diff from PBO	95% CI	p value
	UPA 30 mg	348	NR	NR	NR	NR	NR	NR	193	348	55.6	NR	NR	NR
Dupilumab														
LIBERTY AD CHRONOS	**Week 52**													
	PBO + TCS	264	79	264	30	REF	REF	REF	41	264	16	REF	REF	REF
	DUP 300 mg + TCS Q2W	89	70	89	79	49	38.6 to 58.9	<0.0001	45	89	51	35	23.8 to 46.3	<0.0001
	DUP 300 mg + TCS QW	270	189	270	70	40	32.3 to 47.9	<0.0001	137	270	51	35	27.8 to 42.6	<0.0001
AD SOLO-CONTINUE	**Week 36**													
	PBO	83	33	83	39.8	NR	NR	NR	10	55	18.2	NR	NR	NR
	DUP 300 mg Q8W	84	46	84	54.8	NR	NR	NR	16	49	32.7	NR	NR	NR
	DUP 300 mg Q4W	86	52	86	60.5	NR	NR	NR	33	56	58.9	NR	NR	NR
	DUP 300 mg QW/Q2W	169	124	169	73.4	NR	NR	NR	75	116	64.7	NR	NR	NR

Long-term data on EASI 50 and EASI 90 were not available for the following long-term trials: BREEZE-AD3, BREEZE-AD6, ECZTRA 1, ECZTRA 2, and Phase IIb Guttman-Yassky 2020. CI: confidence interval, Diff: difference, DUP: dupilumab, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every eight weeks, REF: reference, TCS: topical corticosteroids, TRA: tralokinumab, %: percent. *JADE MONO-1 & 2 and JADE COMPARE subgroup, †JADE COMPARE dupilumab nonresponder subgroup, ‡last observation carried forward (LOCF).

Table G1.21. Long-Term Efficacy Outcomes: PP-NRS ≥4-Point Change[50,54,76,83,107,158]

Study Name	Arms	N	Itch or PP-NRS (≥4 point improvement from baseline)					
			n	N	%	Diff from PBO	95% CI	p value
Abrocitinib								
JADE EXTEND	**Week 48**							
	ABRO 100 mg	595	105	280	37.6	NR	NR	NR

Study Name	Arms	N	Itch or PP-NRS (≥4 point improvement from baseline)					
			n	N	%	Diff from PBO	95% CI	p value
Subgroup 1*	ABRO 200 mg	521	125	246	50.9	NR	NR	NR
	Week 48 (Responders)							
	ABRO 100 mg	NR	63	122	51.6	NR	NR	NR
	ABRO 200 mg	NR	116	168	69	NR	NR	NR
	Week 24 (Nonresponders)							
	ABRO 100 mg	NR	63	195	32.3	NR	NR	NR
	ABRO 200 mg	NR	57	138	41.4	NR	NR	NR
	Week 48 (Nonresponders)							
	ABRO 100 mg	NR	38	142	26.8	NR	NR	NR
	ABRO 200 mg	NR	31	101	30.7	NR	NR	NR
JADE EXTEND Subgroup 2†	**Week 32**							
	ABRO 100 mg	130	17	45	37.8	NR	NR	NR
	ABRO 200 mg	73	17	22	77.3	NR	NR	NR
Upadacitinib								
Heads Up	**Week 24**							
	DUP 300 mg	344	141	336	41.9	NR	NR	NR
	UPA 30 mg	348	171	340	50.2	NR	NR	NR
Phase IIb Guttman-Yassky 2020	**Week 16**							
	PBO→PBO	8	0	6	0	NR	NR	NR
	UPA 7.5 mg→PBO	13	3	12	25	NR	NR	NR
	UPA 15 mg→PBO	17	9	14	64.3	NR	NR	NR
	UPA 30 mg→PBO	13	9	10	90	NR	NR	NR
	PBO→UPA 30 mg	1	0	1	0	NR	NR	NR
	UPA 7.5 mg→UPA 7.5 mg	11	3	11	27.3	NR	NR	NR
	UPA 15 mg→UPA 15 mg	12	7	10	70	NR	NR	NR
	UPA 30 mg→UPA 30 mg	3	0	3	0	NR	NR	NR

Study Name	Arms	N	Itch or PP-NRS (≥4 point improvement from baseline)					
			n	N	%	Diff from PBO	95% CI	p value
	START OF RESCUE W/ UPA 30mg							
	PBO→PBO	8	0	6	0	NR	NR	NR
	UPA 7.5 mg→PBO	13	3	13	23.1	NR	NR	NR
	UPA 15 mg→PBO	17	0	14	0	NR	NR	NR
	UPA 30 mg→PBO	13	0	10	0	NR	NR	NR
	PBO→UPA 30 mg	1	1	1	100	NR	NR	NR
	UPA 7.5 mg→UPA 7.5 mg	11	3	11	27.3	NR	NR	NR
	UPA 15 mg→UPA 15 mg	12	5	10	50	NR	NR	NR
	UPA 30 mg→UPA 30 mg	3	0	3	0	NR	NR	NR
	8 WEEKS POST-RESCUE							
	PBO→PBO	8	4	6	66.7	NR	NR	NR
	UPA 7.5 mg→PBO	12	7	12	58.3	NR	NR	NR
	UPA 15 mg→PBO	16	12	14	85.7	NR	NR	NR
	UPA 30 mg→PBO	13	8	10	80	NR	NR	NR
	PBO→UPA 30 mg	1	1	1	100	NR	NR	NR
	UPA 7.5 mg→UPA 7.5 mg	10	5	11	45.4	NR	NR	NR
	UPA 15 mg→UPA 15 mg	9	8	10	80	NR	NR	NR
	UPA 30 mg→UPA 30 mg	3	2	3	66.7	NR	NR	NR
Dupilumab								
LIBERTY AD CHRONOS	**Week 52**							
	PBO + TCS	264	32	249	13	REF	REF	REF
	DUP 300 mg + TCS Q2W	89	44	86	51	38	27.0 to 49.7	<0.0001
	DUP 300 mg + TCS QW	270	97	249	39	26	18.8 to 33.5	<0.0001
AD SOLO-CONTINUE	**Week 36**							
	PBO	83	10	78	12.8	NR	NR	NR
	DUP 300 mg Q8W	84	21	79	26.6	NR	NR	NR

Study Name	Arms	N	Itch or PP-NRS (≥4 point improvement from baseline)					
			n	N	%	Diff from PBO	95% CI	p value
	DUP 300 mg Q4W	86	27	82	32.9	NR	NR	NR
	DUP 300 mg QW/Q2W	169	78	159	49.1	NR	NR	NR

Long term data on PP-NRS were not available for the following long-term trials: BREEZE-AD3, BREEZE-AD6, ECZTRA 1, ECZTRA 2, ECZTRA 3, and ECZTEND. CI: confidence interval, Diff: difference, DUP: dupilumab, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, REF: reference, TCS: topical corticosteroids, %: percent. *JADE MONO-1 & 2 and JADE COMPARE subgroup, †JADE COMPARE dupilumab nonresponder subgroup.

Table G1.22. Long-Term Efficacy Outcomes: SCORAD[50,54]

Study Name	Arms	N	SCORAD			
			N	Change from baseline	SD	p value
Dupilumab						
LIBERTY AD CHRONOS	**Week 52**					
	PBO + TCS	264	NR	LSM: -34.1*	SE: 1.88	REF
	DUP 300 mg + TCS Q2W	89	NR	LSM: -66.2*	SE: 3.14	<0.0001
	DUP 300 mg + TCS QW	270	NR	LSM: -66.1*	SE: 1.85	<0.0001
LIBERTY AD SOLO-CONTINUE	**Week 36**					
	PBO	83	NR	-2.7†	0.3	NR
	DUP 300 mg Q8W	84	NR	-3.3†	0.3	NR
	DUP 300 mg Q4W	86	NR	-4.2†	0.2	NR
	DUP 300 mg QW/Q2W	169	NR	-4.3†	0.2	NR

Long-term data on SCORAD were not available for the following long-term trials: JADE EXTEND, BREEZE-AD3, BREEZE-AD6, ECZTRA 1, ECZTRA 2, ECZTRA 3, ECZTEND, Heads Up, and Phase IIb Guttman-Yassky 2020. There were no Difference vs. placebo or 95% confidence intervals available for long-term SCORAD. CI: confidence interval, Diff: difference, DUP: dupilumab, LSM: least squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids. *percent change, †SCORAD sleep loss.

Table G1.23. Long-Term Efficacy Outcomes: DLQI[50,54,64]

Study Name	Arms	N	DLQI			
			N	Change from baseline	SD	p value
Tralokinumab						
ECZTRA 3	**Week 32 (Maintenance period)**					
	TRA 300 mg Q2W + TCS (TRA nonresponders)	95	95	-9.81	0.94*	NR
	TRA 300 mg Q2W + TCS (TRA responders)	69	69	-14.2	1.16*	NR
	TRA 300 mg Q4W + TCS (TRA responders)	69	69	-13.64	1.13*	NR
Dupilumab						
LIBERTY AD CHRONOS	**Week 52**					
	PBO + TCS	264	264	LSM: -5.6	SE: 0.36	REF
	DUP 300 mg + TCS Q2W	89	89	LSM: -10.9	SE: 0.59	<0.0001
	DUP 300 mg + TCS QW	270	270	LSM: -10.7	SE: 0.36	<0.0001
AD SOLO-CONTINUE	**Week 36**					
	PBO	83	NR	-3.1	0.52	NR
	DUP 300 mg Q8W	84	NR	-1.5	0.46	NR
	DUP 300 mg Q4W	86	NR	-0.3	0.48	NR
	DUP 300 mg QW/Q2W	169	NR	0.2	0.33	NR

Long-term data on DLQI were not available for the following long-term trials: JADE EXTEND, BREEZE-AD3, BREEZE-AD6, ECZTRA 1, ECZTRA 2, ECZTEND, Heads Up, and Phase IIb Guttman-Yassky 2020. There were data available for CDLQI and no Difference vs. placebo or 95% confidence interval data available for long-term DLQI. DUP: dupilumab, LSM: least squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids, TRA: tralokinumab. *digitized estimate.

Table G1.24. Long-Term Efficacy Outcomes: POEM[50,54]

Study Name	Arms	N	POEM			
			N	Change from baseline	SD	p value
Dupilumab						
LIBERTY AD CHRONOS	**Week 52**					
	PBO + TCS	264	264	LSM: -5.3	SE: 0.5	REF
	DUP 300 mg + TCS Q2W	89	89	LSM: -13.7	SE: 0.8	<0.0001
	DUP 300 mg + TCS QW	270	270	LSM: -12.7	SE: 0.5	<0.0001
LIBERTY AD SOLO-CONTINUE	**Week 36**					
	PBO	83	NR	-7	0.9	NR
	DUP 300 mg Q8W	84	NR	-2.8	0.8	NR
	DUP 300 mg Q4W	86	NR	-0.8	0.7	NR
	DUP 300 mg QW/Q2W	169	NR	0.3	0.6	NR

Long-term data on DLQI were not available for the following long-term trials: JADE EXTEND, BREEZE-AD3, BREEZE-AD6, ECZTRA 1, ECZTRA 2, ECZTRA 3, ECZTEND, Heads Up, and Phase IIb Guttman-Yassky 2020. CI: confidence interval, Diff: difference, DUP: dupilumab, LSM: least squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, REF: reference, SD: standard deviation, SE: standard error, TCS: topical corticosteroids.

Table G1.25. Outcomes by subgroup: IGA stratified by age[35,36,39,53,60,79]

Study Name	Arms	Category	IGA					
			N	n	%	Diff from PBO	95% CI	p value
Abrocitinib								
JADE MONO-1	**Week 12**							
	PBO	<18 years	16	2	12.5	NR	NR	NR
	ABRO 100 mg		34	9	26.5	NR	NR	NR
	ABRO 200 mg		33	9	27.3	NR	NR	NR
	PBO	≥18 years	60	4	6.7	NR	NR	NR
	ABRO 100 mg		122	28	23	NR	NR	NR
	ABRO 200 mg		120	58	48.3	NR	NR	NR
JADE MONO-2	PBO	<18 years	7	0	0	REF	REF	NR
	ABRO 100 mg		16	2	12.5	12.5	-11.7 to 36.7	NR
	ABRO 200 mg		15	6	40	40	9.4 to 70.6	NR
	PBO	≥18 years	70	7	10	REF	REF	NR
	ABRO 100 mg		193	42	30.2	20.2	9.8 to 30.6	NR
	ABRO 200 mg		140	53	37.9	27.9	17.2 to 38.5	NR
Upadacitinib								
MEASURE UP 1	**Week 16**							
	PBO	Adults	241	21	8.6	NR	NR	REF
	UPA 15 mg		239	119	49.9	NR	NR	<0.001
	UPA 30 mg		243	148	60.8	NR	NR	<0.001
	PBO	Adolescents	40	3	7.5	NR	NR	REF
	UPA 15 mg		42	16	38.1	NR	NR	<0.001
	UPA 30 mg		42	29	69	NR	NR	<0.001
MEASURE UP 2	PBO	Adults	242	12	5	NR	NR	REF
	UPA 15 mg		243	93	38.3	NR	NR	<0.001
	UPA 30 mg		247	125	50.5	NR	NR	<0.001

Study Name	Arms	Category	IGA					
			N	n	%	Diff from PBO	95% CI	p value
	PBO	Adolescents	36	1	2.8	NR	NR	REF
	UPA 15 mg		33	14	42.4	NR	NR	<0.001
	UPA 30 mg		35	22	62.5	NR	NR	<0.001
AD-UP	PBO + TCS	Adults	264	30	11.4	NR	NR	REF
	UPA 15 mg + TCS		261	107	40.9	NR	NR	<0.001
	UPA 30 mg + TCS		260	150	57.7	NR	NR	<0.001
	PBO + TCS	Adolescents	40	3	7.5	NR	NR	REF
	UPA 15 mg + TCS		39	12	30.8	NR	NR	<0.01
	UPA 30 mg + TCS		37	24	64.9	NR	NR	<0.001

Data on IGA stratified by age were not available in JADE TEEN, JADE COMPARE, JADE EXTEND, Phase IIb Gooderham 2019, BREEZE-AD1, BREEZE-AD2, BREEZE-AD3, BREEZE-AD5,BREEZE-AD6, BREEZE-AD7, Phase II Guttman-Yassky 2018, ECZTRA 1, ECZTRA 2, ECZTRA 3, ECZTEND, Heads Up, Phase IIb Guttman-Yassky 2020, LIBERTY AD SOLO 1 and SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD SOLO-CONTINUE, and Phase IIb Thaci 2016. ABRO: abrocitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, REF: reference, %: percent.

Table G1.26. Outcomes by subgroup: IGA stratified by Disease Severity[39,44,65]

Study Name	Arms	Category	Sample Size (N)	IGA					
				N	n	%	Diff from PBO	95% CI	p value
Abrocitinib									
JADE MONO 2	**Week 12**								
	PBO	Moderate (3)	NR	51	6	11.8	NR	NR	NR
	ABRO 100 mg		NR	106	32	30.2	NR	NR	NR
	ABRO 200 mg		NR	106	45	42.5	NR	NR	NR
	PBO	Severe (4)	NR	26	1	3.8	NR	NR	NR
	ABRO 100 mg		NR	49	12	24.5	NR	NR	NR
	ABRO 200 mg		NR	49	14	28.6	NR	NR	NR
JADE MONO 1	PBO	Moderate (3)	NR	45	5	11.1	NR	NR	NR
	ABRO 100 mg		NR	92	24	26.1	NR	NR	NR
	ABRO 200 mg		NR	91	48	52.7	NR	NR	NR
	PBO	Severe (4)	NR	31	3	3.2	NR	NR	NR
	ABRO 100 mg		NR	64	13	20.3	NR	NR	NR
	ABRO 200 mg		NR	62	19	30.6	NR	NR	NR
JADE COMPARE	Week 16								
	PBO	Moderate (3)	NR	82	14	17.1	NR	NR	NR
	ABRO 100 mg		NR	149	60	40.3	NR	NR	NR
	ABRO 200 mg		NR	134	66	49.3	NR	NR	NR
	DUP 300 mg		NR	158	69	43.7	NR	NR	NR
	PBO	Severe (4)	NR	42	2	4.8	NR	NR	NR
	ABRO 100 mg		NR	81	20	24.7	NR	NR	NR
	ABRO 200 mg		NR	87	39	44.8	NR	NR	NR
	DUP 300 mg		NR	74	21	28.4	NR	NR	NR
Tralokinumab									
ECZTRA 1	**Week 16**								
	PBO	Moderate (3)	95	95	10	10.5	REF	REF	REF
	TRA 300 mg		296	296	71	24	13.5	5.78 to 21.26	0.0043
	PBO	Severe (4)	102	102	4	3.9	REF	REF	REF
	TRA 300 mg		305	305	24	7.9	3.9	-0.8 to 8.7	0.168
ECZTRA 2	PBO	Moderate (3)	100	100	17	17	REF	REF	REF
	TRA 300 mg		305	305	86	28.2	11.5	2.7 to 20.29	0.0207
	PBO	Severe (4)	101	101	5	5	REF	REF	REF

Study Name	Arms	Category	Sample Size (N)	IGA					
				N	n	%	Diff from PBO	95% CI	p value
	TRA 300 mg		286	286	45	15.7	10.7	4.67 to 16.64	0.0057
ECZTRA 3	PBO + TCS	Moderate (3)	66	66	25	37.9	REF	REF	REF
	TRA 300 mg + TCS		136	136	63	46.3	8.5	-5.89 to 22.9	0.2552
	PBO + TCS	Severe (4)	60	60	8	13.3	REF	REF	REF
	TRA 300 mg + TCS		116	116	35	30.2	16.8	4.81 to 28.8	0.0141
Baricitinib									
BREEZE-AD5	**Week 16**								
	PBO	Moderate (3)	86	86	7	8.1	REF	REF	REF
	BARI 1 mg		NR	NR	NR	NR	NR	NR	NR
	BARI 2 mg		85	85	23	27.1	18.9	7.6, 30.0	NR
	PBO	Severe (4)	61	61	1	1.6	REF	REF	REF
	BARI 1 mg		NR	NR	NR	NR	NR	NR	NR
	BARI 2 mg		61	61	12	19.7	18	7.3, 29.7	NR

Data on IGA stratified by disease severity were not available in AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD7, Phase 2 Guttman-Yassky 2020, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL , Phase 2b AD-1021 Thaci 2016, LIBERTY AD PED-OLE, and Phase 2a AD-1412 Pediatric OL. ABRO: abrocitinib, AIC: academic in confidence, BARI: baricitinib, CI: confidence interval, DUP: dupilumab, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, REF: reference, TCS: topical corticosteroids, TRA: tralokinumab, %: percent.

Table G1.27. Outcomes by subgroup: EASI 75 Stratified by Age[35,36,60-62,79]

Study Name	Arms	Category	N	EASI 75					
				N	n	%	Diff from PBO	95% CI	p value
Abrocitinib									
JADE MONO-1	**Week 12**								
	PBO	<18 years	8	16	2	12.5	NR	NR	NR
	ABRO 100 mg		17	34	15	44.1	NR	NR	NR
	ABRO 200 mg		15	33	18	54.5	NR	NR	NR
	PBO	≥18 years	70	60	7	11.7	NR	NR	NR

Study Name	Arms	Category	N	EASI 75					
				N	n	%	Diff from PBO	95% CI	p value
	ABRO 100 mg		141	122	47	38.5	NR	NR	NR
	ABRO 200 mg		140	120	78	65	NR	NR	NR
JADE MONO-2	PBO	<18 years	17	7	0	0	REF	REF	NR
	ABRO 100 mg		34	16	7	43.8	43.8	13.5 to 74.0	NR
	ABRO 200 mg		33	15	9	60	60	29.4 to 90.6	NR
	PBO	≥18 years	60	70	8	11.4	REF	REF	NR
	ABRO 100 mg		122	139	62	44.6	33.2	22.0 to 44.3	NR
	ABRO 200 mg		121	193	85	61.2	49.7	38.7 to 60.7	NR
Upadacitinib									
MEASURE UP 1	**Week 16**								
	PBO	Adults	241	241	43	17.7	NR	NR	REF
	UPA 15 mg		239	239	166	69.3	NR	NR	<0.001
	UPA 30 mg		243	243	192	79.1	NR	NR	<0.001
	PBO	Adolescents	40	40	3	8.3	NR	NR	REF
	UPA 15 mg		42	42	30	71.4	NR	NR	<0.001
	UPA 30 mg		42	42	35	83.3	NR	NR	<0.001
MEASURE UP 2	PBO	Adults	242	242	32	13.2	NR	NR	REF
	UPA 15 mg		243	243	144	59.3	NR	NR	<0.001
	UPA 30 mg		247	247	180	72.7	NR	NR	<0.001
	PBO	Adolescents	36	36	5	13.9	NR	NR	REF
	UPA 15 mg		33	33	22	66.7	NR	NR	<0.001
	UPA 30 mg		35	35	26	74.5	NR	NR	<0.001
AD-UP	PBO + TCS	Adults	264	264	68	25.9	NR	NR	REF
	UPA 15 mg + TCS		261	261	172	65.8	NR	NR	<0.001

Study Name	Arms	Category	N	EASI 75					
				N	n	%	Diff from PBO	95% CI	p value
	UPA 30 mg + TCS		260	260	201	77.3	NR	NR	<0.001
	PBO + TCS	Adolescents	40	40	12	30	NR	NR	REF
	UPA 15 mg + TCS		39	39	22	56.4	NR	NR	<0.05
	UPA 30 mg + TCS		37	37	28	75.7	NR	NR	<0.001

Data on EASI 75 stratified by age were not available in JADE TEEN, JADE COMPARE, JAD EXTEND, Phase IIb Gooderham 2019, BREEZE-AD1, BREEZE-AD2, BREEZE-AD3, BREEZE-AD5, BREEZE-AD6, BREEZE-AD7, Phase II Guttman-Yassky 2018, ECZTRA 1, ECZTRA 2, ECZTRA 3, ECZTEND, Heads Up, Phase IIb Guttman-Yassky 2020, LIBERTY AD SOLO 1 and SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD SOLO-CONTINUE, and Phase IIb Thaci 2016. ABRO: abrocitinib, CI: confidence interval, Diff: difference, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, REF: reference, UPA: upadacitinib, %: percent.

Table G1.28. Outcomes by subgroup: EASI 75 Stratified by Disease Severity[39,44,55,65]

Study Name	Arms	Category	Sample Size (N)	EASI 75					
				N	n	%	Diff from PBO	95% CI	p value
Abrocitinib									
JADE MONO-2	**Week 12**								
	PBO	Moderate (3)	NR	51	6	11.8	NR	NR	NR
	ABRO 100 mg		NR	106	50	47.2	NR	NR	NR
	ABRO 200 mg		NR	106	69	65.1	NR	NR	NR
	PBO	Severe (4)	NR	26	2	7.7	NR	NR	NR
	ABRO 100 mg		NR	49	19	38.8	NR	NR	NR
	ABRO 200 mg		NR	48	25	52.1	NR	NR	NR
JADE MONO 1	PBO	Moderate (3)	NR	45	5	11.1	NR	NR	NR
	ABRO 100 mg		NR	92	43	46.7	NR	NR	NR
	ABRO 200 mg		NR	91	59	64.8	NR	NR	NR

	PBO	Severe (4)	NR	31	4	12.9	NR	NR	NR
	ABRO 100 mg		NR	64	19	29.7	NR	NR	NR
	ABRO 200 mg		NR	62	37	59.7	NR	NR	NR
JADE COMPARE	**Week 16**								
	PBO	Moderate (3)	NR	82	29	35.4	REF	REF	REF
	ABRO 100 mg		NR	148	91	61.5	NR	NR	NR
	ABRO 200 mg		NR	134	92	68.7	NR	NR	NR
	DUP 300 mg		NR	158	106	67.1	NR	NR	NR
	PBO	Severe (4)	NR	42	9	21.4	REF	REF	REF
	ABRO 100 mg		NR	81	47	58	NR	NR	NR
	ABRO 200 mg		NR	87	65	74.7	NR	NR	NR
	DUP 300 mg		NR	74	46	62.2	NR	NR	NR
Tralokinumab									
ECZTRA 1	**Week 16**								
	PBO	Moderate (3)	95	95	14	14.7	REF	REF	REF
	TRA 300 mg		296	296	98	33.1	18.3	9.57 to 27.05	0.0005
	PBO	Severe (4)	102	102	11	10.8	REF	REF	REF
	TRA 300 mg		305	305	52	17	6.3	-0.92 to 13.43	0.1247
ECZTRA 2	PBO	Moderate (3)	100	100	17	17	REF	REF	REF
	TRA 300 mg		305	305	114	37.4	20.7	11.6 to 29.75	0.0001
	PBO	Severe (4)	101	101	6	5.9	REF	REF	REF
	TRA 300 mg		286	286	82	28.7	22.5	15.52 to 29.41	<0.0001
ECZTRA 3	PBO + TCS	Moderate (3)	66	66	29	43.9	REF	REF	REF
	TRA 300 mg + TCS		136	136	78	57.4	13.5	-1.07 to 28.09	0.0724
	PBO + TCS	Severe (4)	60	60	16	26.7	REF	REF	REF
	TRA 300 mg + TCS		116	116	63	54.3	27.6	13.11 to 42.17	0.0005
Baricitinib									

BREEZE-AD5	**Week 16**								
	PBO	Moderate (3)	86	86	9	10.5	REF	REF	REF
	BARI 1 mg		NR	NR	NR	NR	NR	NR	NR
	BARI 2 mg		85	85	29	34.1	23.7	11.3, 35.3	NR
	PBO	Severe (4)	61	61	3	4.9	REF	REF	REF
	BARI 1 mg		NR	NR	NR	NR	NR	NR	NR
	BARI 2 mg		61	61	14	23	18.0	5.8, 30.4	NR
Dupilumab									
POOLED RESULTS: SOLO 1, SOLO 2, Phase 2b AD-1021	**Week 16**								
	PBO	Moderate (3)	NR	266	47	17.1	REF	REF	REF
	DUP 300 mg Q2W		NR	268	157	58.6	40.91	33.44 to 48.38	<0.0001
	PBO	Severe (4)	NR	254	21	8.3	REF	REF	REF
	DUP 300 mg Q2W		NR	253	95	37.5	29.28	22.42 to 36.14	<0.0001

Data on EASI 75 stratified by disease severity were not available in Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD7, Phase 2 Guttman-Yassky 2018, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL, Phase 2b AD-1021 Thaci 2016, LIBERTY AD PEDS, Phase 2a AD-1412 Pediatric OL, and LIBERTY AD PED-OLE. ABRO: abrocitinib, AIC: academic in confidence, BARI: baricitinib, CI: confidence interval, DUP: dupilumab, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, Q2W: every two weeks, REF: reference, TCS: topical corticosteroids, TRA: tralokinumab, %: percent.

Table G1.29. Outcomes by subgroup: EASI 50 and 90 Stratified by Age[39,55,65,75]

Study Name	Arms	Category	EASI 50				EASI 90			
			N	n	%	p value	N	n	%	p value
Abrocitinib										
JADE MONO-1	**Week 12**									
	PBO	<18 years	16	2	12.5	NR	16	2	12.5	NR
	ABRO 100 mg		34	21	61.8	NR	34	7	20.6	NR
	ABRO 200 mg		33	23	69.7	NR	33	10	30.3	NR
	PBO	≥18 years	60	15	25	NR	60	2	3.3	NR
	ABRO 100 mg		122	69	56.6	NR	122	22	18	NR
	ABRO 200 mg		120	93	77.5	NR	120	49	40.8	NR
JADE MONO-2	PBO	<18 years	7	0	0	NR	7	0	0	NR
	ABRO 100 mg		16	9	56.3	NR	16	2	12.5	NR
	ABRO 200 mg		15	13	86.7	NR	15	5	33.3	NR
	PBO	≥18 years	70	15	21.4	NR	70	3	4.3	NR
	ABRO 100 mg		139	97	69.8	NR	139	35	25.2	NR
	ABRO 200 mg		139	110	79.1	NR	139	53	38.1	NR
Upadacitinib										
MEASURE UP 1	**Week 16**									
	PBO	Adults	241	69	28.6	REF	241	22	9.1	REF
	UPA 15 mg		239	185	77.4	<0.001	239	131	54.8	<0.001
	UPA 30 mg		243	208	85.6	<0.001	243	156	64.2	<0.001
	PBO	Adolescents	40	14	35	REF	40	1	2.5	REF
	UPA 15 mg		42	32	76.2	<0.001	42	18	42.9	<0.001
	UPA 30 mg		42	36	85.7	<0.001	42	31	73.8	<0.001
MEASURE UP 2	PBO	Adults	242	67	27.7	REF	242	15	6.2	REF
	UPA 15 mg		243	181	74.5	<0.001	243	102	42	<0.001
	UPA 30 mg		247	204	82.6	<0.001	247	142	57.5	<0.001

Study Name	Arms	Category	EASI 50				EASI 90			
			N	n	%	p value	N	n	%	p value
	PBO	Adolescents	36	12	33.3	REF	36	0	0	REF
	UPA 15 mg		33	25	75.8	<0.001	33	15	45.5	<0.001
	UPA 30 mg		35	28	80	<0.001	35	23	65.7	<0.001
AD-UP	PBO + TCS	Adults	264	105	39.9	REF	264	33	12.5	NR
	UPA 15 mg + TCS		261	216	82.8	<0.001	261	112	43	NR
	UPA 30 mg + TCS		260	229	88	<0.001	260	161	62.1	NR
	PBO + TCS	Adolescents	40	19	47.5	REF	40	7	NR	NR
	UPA 15 mg + TCS		39	28	71.8	0.023	39	16	NR	NR
	UPA 30 mg + TCS		37	33	89.2	<0.001	37	26	NR	NR

Data on EASI 50 and EASI 90 stratified by age were not available for JADE TEEN, JADE COMPARE, JADE EXTEND, Phase IIb Gooderham 2019, BREEZE-AD1, BREEZE-AD2, BREEZE-AD3, BREEZE-AD5, BREEZE-AD6, BREEZE-AD7, Phase II Guttman-Yassky 2018, ECZTRA 1, ECZTRA 2, ECZTRA 3, ECZTEND, Heads Up, Phase IIb Guttman-Yassky 2020, LIBERTY AD SOLO 1 and SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD SOLO-CONTINUE, and Phase IIb Thaci 2016. ABRO: abrocitinib, CI: confidence interval, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, UPA: upadacitinib, %: percent.

Table G1.30. Outcomes by subgroup: EASI 50 and 90 Stratified by Disease Severity[39,44,55,65]

Study Name	Arms	Category	EASI 50						EASI 90					
			N	n	%	Diff from PBO	95% CI	p value	N	n	%	Diff from PBO	95% CI	p value
Abrocitinib														
JADE MONO-2	**Week 12**													
	PBO	Moderate (3)	51	12	23.5	NR	NR	NR	51	2	3.9	NR	NR	NR
	ABRO 100 mg		106	74	69.8	NR	NR	NR	106	29	27.4	NR	NR	NR
	ABRO 200 mg		106	90	84.9	NR	NR	NR	106	44	41.5	NR	NR	NR

	PBO	Severe (4)	26	3	11.5	NR	NR	NR	26	1	3.8	NR	NR	NR
	ABRO 100 mg		49	32	65.3	NR	NR	NR	49	8	16.3	NR	NR	NR
	ABRO 200 mg		48	33	68.8	NR	NR	NR	48	14	29.2	NR	NR	NR
JADE MONO-1	PBO	Moderate (3)	45	12	26.7	NR	NR	NR	45	3	6.7	NR	NR	NR
	ABRO 100 mg		92	58	63	NR	NR	NR	92	17	18.5	NR	NR	NR
	ABRO 200 mg		91	70	76.9	NR	NR	NR	91	39	42.9	NR	NR	NR
	PBO	Severe (4)	31	5	16.1	NR	NR	NR	31	1	3.2	NR	NR	NR
	ABRO 100 mg		64	32	50	NR	NR	NR	64	12	18.8	NR	NR	NR
	ABRO 200 mg		62	46	74.2	NR	NR	NR	62	20	32.3	NR	NR	NR
JADE COMPARE	**Week 16**													
	PBO	Moderate (3)	82	49	59.8	NR	NR	NR	82	12	14.6	NR	NR	NR
	ABRO 100 mg		148	123	83.1	NR	NR	NR	148	61	41.2	NR	NR	NR
	ABRO 200 mg		134	115	85.8	NR	NR	NR	134	61	45.5	NR	NR	NR
	DUP 300 mg		158	133	84.2	NR	NR	NR	158	66	41.8	NR	NR	NR
	PBO	Severe (4)	42	22	52.4	NR	NR	NR	42	2	4.8	NR	NR	NR
	ABRO 100 mg		81	63	77.8	NR	NR	NR	81	26	32.1	NR	NR	NR
	ABRO 200 mg		87	78	89.7	NR	NR	NR	87	47	54	NR	NR	NR
	DUP 300 mg		74	62	83.8	NR	NR	NR	74	24	32.4	NR	NR	NR
Tralokinumab														
ECZTRA 1	**Week 16**													
	PBO	Moderate (3)	95	24	25.3	REF	REF	REF	95	5	5.3	REF	REF	REF
	TRA 300 mg		296	154	52	26.8	16.53 to 36.99	<0.001	296	64	21.6	16.3	9.94 to 22.7	0.0002
	PBO	Severe (4)	102	18	17.6	REF	REF	REF	102	3	2.9	REF	REF	REF
	TRA 300 mg		305	96	31.5	13.8	4.92 to 22.74	0.0066	305	23	7.5	4.6	0.24 to 8.95	0.0984
ECZTRA 2	PBO	Moderate (3)	100	26	26	REF	REF	REF	100	8	8	REF	REF	REF

	TRA 300 mg		305	166	54.4	28.6	18.41 to 38.84	<0.001	305	70	23	15.1	8.06 to 22.17	0.0009
	PBO	Severe (4)	101	15	14.9	REF	REF	REF	101	3	3	REF	REF	REF
	TRA 300 mg		286	129	45.1	30	21.02 to 39.05	<0.001	286	38	13.3	10.2	5.01 to 15.36	0.0041
ECZTRA 3	PBO + TCS	Moderate (3)	66	46	69.7	REF	REF	REF	66	16	24.2	REF	REF	REF
	TRA 300 mg + TCS		136	104	76.5	6.7	-6.49 to 19.89	0.3094	136	48	35.3	11.1	-2.15 to 24.26	0.1151
	PBO + TCS	Severe (4)	60	27	45	REF	REF	REF	60	11	18.3	REF	REF	REF
	TRA 300 mg + TCS		116	96	82.8	37.7	23.55 to 51.79	<0.001	116	35	30.2	11.8	-1.18 to 24.84	0.0922
Baricitinib														
BREEZE-AD5	**Week 16**													
	PBO	Moderate (3)	86	16	18.6	REF	REF	REF	86	4	4.7	REF	REF	REF
	BARI 1 mg		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	BARI 2 mg		85	36	42.4	23.7	10.0, 36.4	NR	85	19	22.4	17.7	7.6, 28.0	NR
	PBO	Severe (4)	61	3	4.9	REF	REF	REF	61	3	4.9	REF	REF	REF
	BARI 1 mg		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	BARI 2 mg		61	15	24.6	19.7	7.2, 32.2	NR	61	14	23	18	5.8, 30.4	NR
Dupilumab														
POOLED RESULTS: SOLO 1, SOLO 2, Phase 2b AD-1021	**Week 16**													
	PBO	Moderate (3)	266	79	29.7	REF	REF	REF	266	25	9.4	REF	REF	REF
	DUP 300 mg Q2W		268	200	74.6	44.93	37.36 to 52.50	<0.0001	268	110	41	31.65	24.79 to 38.50	<0.0001
	PBO	Severe (4)	254	46	18.1	REF	REF	REF	254	11	4.3	REF	REF	REF

	DUP 300 mg Q2W		253	156	61.7	43.55	35.91 to 51.19	<0.0001	253	59	23.3	18.99	13.21 to 24.77	<0.0001

Data on EASI 50 and EASI 90 stratified by disease severity were not available for AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD7, Phase 2 Guttman-Yassky 2018, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL, Phase 2b AD-1021 Thaci 2016, LIBERTY AD PEDS, LIBERTY AD PED-OLE, and Phase 2a AD-1412 Pediatric OL. ABRO: abrocitinib, AIC: academic in confidence, BARI: baricitinib, CI: confidence interval, DUP: dupilumab, IQR: interquartile range, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, Q2W: every two weeks, REF: reference, TCS: topical corticosteroids, TRA: tralokinumab, %: percent.

Table G1.31. Outcomes by subgroup: PP-NRS Change from Baseline and ≥3- or ≥4-Point Change Stratified by Age[39,53,55,75]

Study Name	Arms	Category	Itch or PP-NRS Change from Baseline			PP-NRS ≥4-point Change		
			N	Change from baseline	SD	N	≥4-point Change	
							n	%
Abrocitinib								
JADE MONO-1	**Week 12**							
	PBO	<18 years	NR	-6	NR	14	1	7.1
	ABRO 100 mg		NR	-34.2	NR	27	9	33.3
	ABRO 200 mg		NR	-47.8	NR	23	11	47.8
	PBO	≥18 years	NR	-22.7	NR	47	9	19.1
	ABRO 100 mg		NR	-41.9	NR	88	32	36.4
	ABRO 200 mg		NR	-60.4	NR	101	57	56.4
JADE MONO-2	PBO	<18 years	NR	-7.8	NR	8	1	12.5
	ABRO 100 mg		NR	-28.4	NR	15	3	20
	ABRO 200 mg		NR	-69.4	NR	13	11	84.6
	PBO	≥18 years	NR	-20.6	NR	63	7	11.1
	ABRO 100 mg		NR	-45.8	NR	124	59	47.6
	ABRO 200 mg		NR	-55.5	NR	121	64	52.9
Upadacitinib								
MEASURE UP 1	**Week 16**							
	PBO	Adults	241	NR	NR	233	26	11.2
	UPA 15 mg		239	NR	NR	234	125	53.4
	UPA 30 mg		243	NR	NR	238	145	60.9
	PBO	Adolescents	40	NR	NR	39	6	15.4
	UPA 15 mg		42	NR	NR	40	18	45
	UPA 30 mg		42	NR	NR	42	23	54.8
MEASURE UP 2	PBO	Adults	242	NR	NR	238	24	10.1
	UPA 15 mg		243	NR	NR	240	103	42.9

Study Name	Arms	Category	Itch or PP-NRS Change from Baseline			PP-NRS ≥4-point Change		
			N	Change from baseline	SD	N	≥4-point Change	
							n	%
	UPA 30 mg		247	NR	NR	246	150	61
	PBO	Adolescents	36	NR	NR	36	1	2.8
	UPA 15 mg		33	NR	NR	30	10	33.3
	UPA 30 mg		35	NR	NR	34	17	50
AD-UP	PBO + TCS	Adults	264	NR	NR	256	39	15.2
	UPA 15 mg + TCS		261	NR	NR	252	134	53.2
	UPA 30 mg + TCS		260	NR	NR	258	168	65.1
	PBO + TCS	Adolescents	40	NR	NR	38	5	13.2
	UPA 15 mg + TCS		39	NR	NR	15	36	41.7
	UPA 30 mg + TCS		37	NR	NR	33	18	54.5

Data on PP-NRS change from baseline and ≥4-point change stratified by age were not available in JADE TEEN, JADE COMPARE, JADE EXTEND, Phase IIb Gooderham 2019, BREEZE-AD1, BREEZE-AD2, BREEZE-AD3, BREEZE-AD5, BREEZE-AD6, BREEZE-AD7, Phase II Guttman-Yassky 2018, ECZTRA 1, ECZTRA 2, ECZTRA 3, ECZTEND, Heads Up, Phase IIb Guttman-Yassky 2020, LIBERTY AD SOLO 1 and SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD SOLO-CONTINUE, and Phase IIb Thaci 2016. No data on PP-NRS≥3 or p-values were reported. ABRO: abrocitinib, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, SD: standard deviation, %: percent.

Table G1.32. Outcomes by subgroup: PP-NRS Change from Baseline Stratified by Disease Severity[39,44,65]

Study Name	Arms	Category	Itch or PP-NRS Change from Baseline						
			N	Change from baseline	SD	p value	Diff from PBO	95% CI	p value
Abrocitinib									
JADE MONO-2	**Week 12**								
	PBO	Moderate (3)	NR	-26.5	NR	NR	NR	NR	NR
	ABRO 100 mg		NR	-41.4	NR	NR	NR	NR	NR
	ABRO 200 mg		NR	-59.1	NR	NR	NR	NR	NR
	PBO	Severe (4)	NR	-6.4	NR	NR	NR	NR	NR

	ABRO 100 mg		NR	-49.2	NR	NR	NR	NR	NR
	ABRO 200 mg		NR	-53.1	NR	NR	NR	NR	NR
JADE MONO-1	PBO	Moderate (3)	NR	-22.7	NR	NR	NR	NR	NR
	ABRO 100 mg		NR	-40.8	NR	NR	NR	NR	NR
	ABRO 200 mg		NR	-62.6	NR	NR	NR	NR	NR
	PBO	Severe (4)	NR	-17.4	NR	NR	NR	NR	NR
	ABRO 100 mg		NR	-35.6	NR	NR	NR	NR	NR
	ABRO 200 mg		NR	-50	NR	NR	NR	NR	NR
Tralokinumab									
ECZTRA 1	**Week 16**								
	PBO	Moderate (3)	NR	-2	2.18	NR	NR	NR	NR
	TRA 300 mg		NR	-3.1	2.53	NR	NR	NR	NR
	PBO	Severe (4)	NR	-2.3	2.28	NR	NR	NR	NR
	TRA 300 mg		NR	-3.2	2.38	NR	NR	NR	NR
ECZTRA 2	PBO	Moderate (3)	NR	-2.2	2.52	NR	NR	NR	NR
	TRA 300		NR	-3	2.57	NR	NR	NR	NR
	PBO	Severe (4)	NR	-1.5	2.38	NR	NR	NR	NR
	TRA 300 mg		NR	-3.2	2.45	NR	NR	NR	NR
ECZTRA 3	PBO + TCS	Moderate (3)	NR	-3.3	2.54	NR	NR	NR	NR
	TRA 300 mg + TCS		NR	-3.8	2.47	NR	NR	NR	NR
	PBO + TCS	Severe (4)	NR	-3.1	2.63	NR	NR	NR	NR
	TRA 300 mg + TCS		NR	-4.5	2.3	NR	NR	NR	NR
Baricitinib									
BREEZE-AD5	**Week 16**								
	PBO	Moderate (3)	NR	-1.34	0.321	NR	REF	REF	REF
	BARI 1 mg		NR	NR	NR	NR	NR	NR	NR
	BARI 2 mg		NR	-2.58	0.28	NR	-1.24	-2.08, -0.41	NR
	PBO	Severe (4)	NR	-2.08	0.495	NR	REF	REF	REF
	BARI 1 mg		NR	NR	NR	NR	NR	NR	NR

	BARI 2 mg		NR	-3.47	0.35	NR	-1.39	-2.58, -0.21	NR

Data on PP-NRS change from baseline stratified by age were not available in JADE COMPARE, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD7, Phase 2 Guttman-Yassky 2018, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL, Phase 2b AD-1021 Thaci 2016, LIBERTY AD PEDS, LIBERTY AD PED-OLE, and Phase 2a AD-1412 Pediatric OL. ABRO: abrocitinib, AIC: academic in confidence, BARI: baricitinib, CI: confidence interval, mg: milligram, N: total number, NR: not reported, PBO: placebo, REF: reference, SD: standard deviation, TCS: topical corticosteroids, TRA: tralokinumab.

Table G1.33. Outcomes by subgroup: PP-NRS ≥2-Point Change Stratified by Disease Severity[44,65]

Study Name	Arms	Category	Itch or PP-NRS ≥2-point Change					
			N	≥2-point Change		Diff from PBO	95% CI	p value
				n	%			
Tralokinumab								
ECZTRA 1	**Week 16**							
	PBO	Moderate (3)	93	26	28	REF	REF	REF
	TRA 300 mg		294	117	39.8	11.9	1.13 to 22.65	0.0382
	PBO	Severe (4)	102	18	17.6	REF	REF	REF
	TRA 300 mg		304	96	31.6	14	5.11 to 22.84	0.0057
ECZTRA 2	PBO	Moderate (3)	100	25	25	REF	REF	REF
	TRA 300 mg		301	142	47.2	22.4	12.23 to 32.59	<0.0001
	PBO	Severe (4)	100	15	15	REF	REF	REF
	TRA 300 mg		283	113	39.9	24.6	15.70 to 33.59	<0.0001
ECZTRA 3	PBO + TCS	Moderate (3)	66	37	56.1	REF	REF	REF
	TRA 300 mg + TCS		136	96	70.6	14.5	0.25 to 28.68	0.043
	PBO + TCS	Severe (4)	60	27	45	REF	REF	REF

	TRA 300 mg + TCS		115	86	74.8	29.8	14.94 to 44.58	<0.0001
Baricitinib								
BREEZE-AD5	**Week 16**							
	PBO	Moderate (3)	NR	10	12.3	REF	REF	NR
	BARI 1 mg		NR	NR	NR	NR	NR	NR
	BARI 2 mg		NR	31	38.3	25.9	12.7, 38.1	NR
	PBO	Severe (4)	NR	6	10.2	REF	REF	NR
	BARI 1 mg		NR	NR	NR	NR	NR	NR
	BARI 2 mg		NR	22	38.6	28.4	13.0, 42.5	NR

Data on on ≥2-point change in PP-NRS stratified by disease severity were not available in JADE MONO-1, JADE MONO-2, JADE COMPARE, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD7, Phase 2 Guttman-Yassky 2018, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL, Phase 2b AD-1021 Thaci 2016, LIBERTY AD PEDS, LIBERTY AD PED-OLE, and Phase 2a AD-1412 Pediatric OL. AIC: academic in confidence, BARI: baricitinib, CI: confidence interval, mg: milligram, n: number, N: total number, PBO: placebo, REF: reference, TCS: topical corticosteroids, TRA: tralokinumab, %: percent.

Table G1.34. Outcomes by subgroup: PP-NRS ≥3-Point Change Stratified by Disease Severity[44]

Study Name	Arms	Category	Itch or PP-NRS ≥3-point Change					
			N	≥3-point Change		Diff from PBO	95% CI	p value
				n	%			
Baricitinib								
BREEZE-AD5	**Week 16**							
	PBO	Moderate (3)	NR	6	7.6	REF	REF	NR
	BARI 1 mg		NR	NR	NR	NR	NR	NR
	BARI 2 mg		NR	19	25	17.4	5.8, 28.9	NR
	PBO	Severe (4)	NR	4	7	REF	REF	NR
	BARI 1 mg		NR	NR	NR	NR	NR	NR
	BARI 2 mg		NR	21	38.6	29.8	14.9, 43.5	NR

Data on on ≥3-point change in PP-NRS stratified by disease severity were not available in in JADE MONO-1, JADE MONO-2, JADE COMPARE, ECZTRA 1, ECZTRA 2, ECZTRA 3, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD7, Phase 2 Guttman-Yassky 2018, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL, Phase 2b AD-1021 Thaci 2016, LIBERTY AD PEDS, LIBERTY AD PED-OLE, and Phase 2a AD-1412 Pediatric OL. AIC: academic in confidence, BARI: baricitinib, CI: confidence interval, mg: milligram, n: number, N: total number, PBO: placebo, %: percent, REF: reference.

Table G1.35. Outcomes by subgroup: PP-NRS ≥4-Point Change Stratified by Disease Severity[39,44,65]

Study Name	Arms	Category	Itch or PP-NRS ≥4-point Change					
			N	≥4-point Change		Diff from PBO	95% CI	P value
				n	%			
Abrocitinib								
JADE MONO-2	**Week 12**							
	PBO	Moderate (3)	48	6	12.5	NR	NR	NR
	ABRO 100 mg		92	42	45.7	NR	NR	NR
	ABRO 200 mg		90	51	56.7	NR	NR	NR
	PBO	Severe (4)	23	2	8.7	NR	NR	NR
	ABRO 100 mg		47	20	42.6	NR	NR	NR
	ABRO 200 mg		44	24	54.5	NR	NR	NR
JADE MONO-1	PBO	Moderate (3)	36	7	19.4	NR	NR	NR
	ABRO 100 mg		66	25	37.9	NR	NR	NR
	ABRO 200 mg		74	41	55.4	NR	NR	NR
	PBO	Severe (4)	25	3	12	NR	NR	NR
	ABRO 100 mg		49	16	32.7	NR	NR	NR
	ABRO 200 mg		50	27	54	NR	NR	NR
Tralokinumab								
ECZTRA 1	**Week 16**							
	PBO	Moderate (3)	92	14	15.2	REF	REF	REF
	TRA 300 mg		291	80	27.5	12.2	3.26 to 21.15	0.018

	PBO	Severe (4)	102	24	23.5	REF	REF	REF
	TRA 300 mg		303	84	27.7	4.2	-5.38 to 13.82	0.4032
ECZTRA 2	PBO	Moderate (3)	100	22	22	REF	REF	REF
	TRA 300 mg		293	86	29.4	7.5	-2.02 to 17.09	0.1431
	PBO	Severe (4)	100	17	17	REF	REF	REF
	TRA 300 mg		282	84	29.8	12.8	3.63 to 21.9	0.0132
ECZTRA 3	PBO + TCS	Moderate (3)	66	25	37.9	REF	REF	REF
	TRA 300 mg + TCS		134	58	43.3	5.4	-9.04 to 19.83	0.4688
	PBO + TCS	Severe (4)	60	21	35	REF	REF	REF
	TRA 300 mg + TCS		115	57	49.6	14.5	-0.55 to 29.65	0.0668
Baricitinib								
BREEZE-AD5	**Week 16**							
	PBO	Moderate (3)	69	4	5.8	REF	REF	NR
	BARI 1 mg		NR	NR	NR	NR	NR	NR
	BARI 2 mg		74	16	21.6	15.8	4.5, 27.0	NR
	PBO	Severe (4)	54	3	5.6	REF	REF	NR
	BARI 1 mg		NR	NR	NR	NR	NR	NR
	BARI 2 mg		57	17	29.8	24.3	10.2, 37.6	NR

Data on on ≥4-point change in PP-NRS stratified by disease severity were not available in in JADE COMPARE, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD7, Phase 2 Guttman-Yassky 2018, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL, Phase 2b AD-1021 Thaci 2016, LIBERTY AD PEDS, LIBERTY AD PED-OLE, and Phase 2a AD-1412 Pediatric OL. ABRO: abrocitinib, AIC: academic in confidence, BARI: baricitinib, CI: confidence interval, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, REF: reference, TCS: topical corticosteroids, TRA: tralokinumab, %: percent.

Table G1.36. Outcomes by subgroup: SCORAD, DLQI and CDLQI Stratified by Age (All available data were submitted by the manufacturer(s) as academic-in-confidence)[39,58,59]

Study Name	Arms	Category	SCORAD				DLQI				CDLQI				
			N	Change from baseline	SD	p value	N	Change from baseline	SD	p value	n	N	Change from baseline	SD	p value
Abrocitinib															
JADE MONO-2	**Week 12**														
	PBO	<18 years	NR	LSM: -14.4*	NR	NR	NA	NA	NA	NA	NR	NR	-0.9	NR	NR
	ABRO 100 mg		NR	LSM: -32.7*	NR	NR	NA	NA	NA	NA	NR	NR	-5.6	NR	NR
	ABRO 200 mg		NR	LSM: -51.3*	NR	NR	NA	NA	NA	NA	NR	NR	-9.9	NR	NR
	PBO	≥18 years	NR	LSM: -23.7*	NR	NR	NR	-3.8	NR	NR	NR	NR	NA	NR	NR
	ABRO 100 mg		NR	LSM: -47.4*	NR	NR	NR	-8.4	NR	NR	NR	NR	NA	NR	NR
	ABRO 200 mg		NR	LSM: -56.8*	NR	NR	NR	-9.6	NR	NR	NR	NR	NA	NR	NR
JADE MONO-1	PBO	<18 years	NR	LSM: -20.9*	NR	NR	NR	NR	NR	NR	NR	NR	-4.1	NR	NR
	ABRO 100 mg		NR	LSM: -45.1*	NR	NR	NR	NR	NR	NR	NR	NR	-5.9	NR	NR
	ABRO 200 mg		NR	LSM: -47.4*	NR	NR	NR	NR	NR	NR	NR	NR	-7.5	NR	NR
	PBO	≥18 years	NR	LSM: -21.8*	NR	NR	NR	-3.7	NR	NR	NR	NR	NA	NR	NR
	ABRO 100 mg		NR	LSM: -40.4*	NR	NR	NR	-7	NR	NR	NR	NR	NA	NR	NR
	ABRO 200 mg		NR	LSM: -57.2*	NR	NR	NR	-9.1	NR	NR	NR	NR	NA	NR	NR
Dupilumab															
Phase 2a AD-1412 Pediatric OL	**Week 12**														
	DUP 2 mg/kg	12-17 years	20	-47.7*	27.3	NR	NA	NA	NA	NA	NR	NR	NR	NR	NR
	DUP 4 mg/kg		20	-43.4*	25.4	NR	NA	NA	NA	NA	NR	NR	NR	NR	NR
	DUP 2 mg/kg	6-11 years	18	-57.5*	23.1	NR	NA	NA	NA	NA	NR	NR	NR	NR	NR
	DUP 4 mg/kg		19	-46.9*	24.3	NR	NA	NA	NA	NA	NR	NR	NR	NR	NR
LIBERTY AD PED-OLE (Children	Week 16														
	DUP 2 mg/kg	6-11 years	17	-61*	31	NR	NA	NA	NA	NA	NR	NR	NR	NR	NR
	DUP 4 mg/kg		15	-62*	18	NR	NA	NA	NA	NA	NR	NR	NR	NR	NR
	Week 52														

subgroup 1)	DUP 2 mg/kg	6-11 years	17	-79*	16	NR	NA	NA	NA	NA	NR	NR	NR	NR	NR
	DUP 4 mg/kg		16	-67*	19	NR	NA	NA	NA	NA	NR	NR	NR	NR	NR

Table G1.37. Outcomes by subgroup: SCORAD Stratified by Disease Severity[39,44,65]

Study Name	Arms	Category	SCORAD						
			N	Change from baseline	SD	p value	Diff from PBO	95% CI	p value
Abrocitinib									
JADE MONO-2	**Week 12**								
	PBO	Moderate (3)	NR	-24.2	NR	NR	NR	NR	NR
	ABRO 100 mg		NR	-46.2	NR	NR	NR	NR	NR
	ABRO 200 mg		NR	-58.7	NR	NR	NR	NR	NR
	PBO	Severe (4)	NR	-19.4	NR	NR	NR	NR	NR
	ABRO 100 mg		NR	-44.7	NR	NR	NR	NR	NR
	ABRO 200 mg		NR	-51.1	NR	NR	NR	NR	NR
JADE MONO-1	PBO	Moderate (3)	NR	-27.6	NR	NR	NR	NR	NR
	ABRO 100 mg		NR	-44.8	NR	NR	NR	NR	NR
	ABRO 200 mg		NR	-57.6	NR	NR	NR	NR	NR
	PBO	Severe (4)	NR	-13.1	NR	NR	NR	NR	NR
	ABRO 100 mg		NR	-35.9	NR	NR	NR	NR	NR
	ABRO 200 mg		NR	-51.3	NR	NR	NR	NR	NR
Tralokinumab									
ECZTRA 1	**Week 16**								
	PBO	Moderate (3)	56	-17.1	20.26	NR	REF	REF	REF
	TRA 300 mg		207	-29.3	18.95	NR	-13.75	-19 to -8.45	<0.001
	PBO	Severe (4)	40	-24	19.43	NR	REF	REF	REF
	TRA 300 mg		146	-30.8	18.58	NR	-5.91	-11.9 to 0.09	0.054
ECZTRA 2	PBO	Moderate (3)	57	-18.3	23.03	NR	REF	REF	REF

	TRA 300 mg		241	-28.6	19.2	NR	-11.97	-17.2 to -6.78	<0.001
	PBO	Severe (4)	41	-19.5	20.58	NR	REF	REF	REF
	TRA 300 mg		189	-34.6	20.72	NR	-16.69	-22.8 to -10.6	<0.001
ECZTRA 3	PBO + TCS	Moderate (3)	61	-32.5	19.97	NR	REF	REF	REF
	TRA 300 mg + TCS		122	-33.9	18.09	NR	-4.39	-9.88 to 1.1	0.116
	PBO + TCS	Severe (4)	46	-25.6	25	NR	REF	REF	REF
	TRA 300 mg + TCS		107	-43.6	18.6	NR	-19.4	-25.9 to -12.9	<0.001
Baricitinib									
BREEZE-AD5	**Week 16**								
	PBO	Moderate (3)	86	LSM: -17.31	SE: 3.878	NR	REF	REF	NR
	BARI 1 mg		NR	NR	NR	NR	NR	NR	NR
	BARI 2 mg		85	LSM: -27.99	SE: 2.912	NR	-10.68	-19.7, 1.65	NR
	PBO	Severe (4)	61	LSM: -11.75	6.212	NR	REF	REF	NR
	BARI 1 mg		NR	NR	NR	NR	NR	NR	NR
	BARI 2 mg		61	LSM: -26.02	3.911	NR	-14.26	-28.14, 0.38	NR

Data on SCORAD stratified by disease severity were not available in JADE COMPARE, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD7, Phase 2 Guttman-Yassky 2018, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL, Phase 2b AD-1021 Thaci 2016, LIBERTY AD PEDS, LIBERTY AD PED-OLE, and Phase 2a AD-1412 Pediatric OL. ABRO: abrocitinib, AIC: academic in confidence, BARI: baricitinib, CI: confidence interval, mg: milligram, N: total number, NR: not reported, PBO: placebo, REF: reference, SD: standard deviation, TCS: topical corticosteroids, TRA: tralokinumab.

Table G1.38. Outcomes by subgroup: DLQI and CDLQI Stratified by Disease Severity[39,44,65]

Study Name	Arms	Category	DLQI								CDLQI				
			n	N	Change from baseline	SD	p value	Diff from PBO	95% CI	p value	n	N	Change from baseline	SD	p value
Abrocitinib															
	Week 12														

JADE MONO-2	PBO	Moderate (3)	NR	NR	-3.9	NR	NR	NR	NR	NR	NR	8	0	NR	NR
	ABRO 100 mg		NR	NR	-8.1	NR	NR	NR	NR	NR	NR	16	-4.6	NR	NR
	ABRO 200 mg		NR	NR	-9.7	NR	NR	NR	NR	NR	NR	15	-8.8	NR	NR
	PBO	Severe (4)	NR	NR	-3.4	NR	NR	NR	NR	NR	NR	8	-0.5	NR	NR
	ABRO 100 mg		NR	NR	-9.3	NR	NR	NR	NR	NR	NR	16	-6.2	NR	NR
	ABRO 200 mg		NR	NR	-9.4	NR	NR	NR	NR	NR	NR	15	-12	NR	NR
JADE MONO-1	PBO	Moderate (3)	NR	NR	-2.8	NR	NR	NR	NR	NR	NR	15	-6.5	NR	NR
	ABRO 100 mg		NR	NR	-7.1	NR	NR	NR	NR	NR	NR	32	-6.1	NR	NR
	ABRO 200 mg		NR	NR	-7.8	NR	NR	NR	NR	NR	NR	32	-6.8	NR	NR
	PBO	Severe (4)	NR	NR	-5.4	NR	NR	NR	NR	NR	NR	15	-3.1	NR	NR
	ABRO 100 mg		NR	NR	-6.9	NR	NR	NR	NR	NR	NR	32	-5.8	NR	NR
	ABRO 200 mg		NR	NR	-11.4	NR	NR	NR	NR	NR	NR	32	-8	NR	NR
Tralokinumab															
ECZTRA 1	**Week 16**														
	PBO	Moderate (3)	NR	95	-4.7	6.42	NR	REF	REF	REF	NA	NA	NA	NA	NA
	TRA 300 mg		NR	296	-8.2	7.25	NR	-3.32	-5.02 to -1.61	<0.001	NA	NA	NA	NA	NA
	PBO	Severe (4)	NR	102	-8.1	6.63	NR	REF	REF	REF	NA	NA	NA	NA	NA
	TRA 300 mg		NR	305	-9.3	6.56	NR	-0.5	-2.54 to 1.54	0.628	NA	NA	NA	NA	NA
ECZTRA 2	PBO	Moderate (3)	NR	100	-4.8	7.93	NR	REF	REF	REF	NA	NA	NA	NA	NA
	TRA 300 mg		NR	305	-8.6	7.06	NR	-3.56	-5,26 to -1.86	<0.001	NA	NA	NA	NA	NA

	PBO	Severe (4)	NR	101	-7.1	7.71	NR	REF	REF	REF	NA	NA	NA	NA	NA
	TRA 300 mg		NR	286	-11	7.59	NR	-4.27	-6.38 to -2.16	<0.001	NA	NA	NA	NA	NA
ECZTRA 3	PBO + TCS	Moderate (3)	NR	66	-8.8	6.88	NR	REF	REF	REF	NA	NA	NA	NA	NA
	TRA 300 mg + TCS		NR	136	-10.8	7.38	NR	-18.1	-35.1 to -0.11	0.037	NA	NA	NA	NA	NA
	PBO + TCS	Severe (4)	NR	60	-9.1	7.38	NR	REF	REF	REF	NA	NA	NA	NA	NA
	TRA 300 mg + TCS		NR	116	-13.4	7.68	NR	-4.29	-6.37 to -2.2	<0.001	NA	NA	NA	NA	NA
Baricitinib															
BREEZE-AD5	**Week 16**														
	PBO	Moderate (3)	REF	86	LSM: -4.74	SE: 1.137	NR	REF	REF	REF	NA	NA	NA	NA	NA
	BARI 1 mg		REF	NR	NR	NR	NR	NR	NR	NR	NA	NA	NA	NA	NA
	BARI 2 mg		REF	85	LSM: -7.48	SE: 0.868	NR	-2.74	-5.56, 0.08	NR	NA	NA	NA	NA	NA
	PBO	Severe (4)	REF	61	LSM: -2.21	SE: 1.87	NR	REF	REF	REF	NA	NA	NA	NA	NA
	BARI 1 mg		REF	NR	NR	NR	NR	NR	NR	NR	NA	NA	NA	NA	NA
	BARI 2 mg		REF	61	LSM: -7.78	SE: 1.184	NR	-5.57	-9.90, -1.25	NR	NA	NA	NA	NA	NA

Data on DLQI and CDLQI stratified by disease severity were not available in JADE COMPARE, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD7, Phase 2 Guttman-Yassky 2018, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL, Phase 2b AD-1021 Thaci 2016, LIBERTY AD PEDS, LIBERTY AD PED-OLE, and Phase 2a AD-1412 Pediatric OL. ABRO: abrocitinib, AIC: academic in confidence, BARI: baricitinib, CI: confidence interval, mg: milligram, n: number, N: total number, NA: not applicable, NR: not reported, PBO: placebo, REF: reference, SD: standard deviation, TCS: topical corticosteroids, TRA: tralokinumab.

Table G1.39. Outcomes by subgroup: POEM Stratified by Age[39]

Study Name	Arms	Category	POEM				
			n	N	Change from baseline	SD	p value
Abrocitinib							
JADE MONO-2	**Week 12**						
	PBO	<18 years	NR	NR	-4.5	NR	NR
	ABRO 100 mg		NR	NR	-6.8	NR	NR
	ABRO 200 mg		NR	NR	-12.5	NR	NR
	PBO	≥18 years	NR	NR	-3	NR	NR
	ABRO 100 mg		NR	NR	-9.4	NR	NR
	ABRO 200 mg		NR	NR	-10.6	NR	NR
JADE MONO-1	PBO	<18 years	NR	NR	-4.2	NR	NR
	ABRO 100 mg		NR	NR	-7.3	NR	NR
	ABRO 200 mg		NR	NR	-9	NR	NR
	PBO	≥18 years	NR	NR	-3.6	NR	NR
	ABRO 100 mg		NR	NR	-6.5	NR	NR
	ABRO 200 mg		NR	NR	-11	NR	NR

Data on POEM stratified by age were not available in JADE COMPARE, ECZTRA 1, ECZTRA 2, ECZTRA 3, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD5, BREEZE-AD7, Phase 2 Guttman-Yassky 2018, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL, Phase 2b AD-1021 Thaci 2016, LIBERTY AD PEDS, LIBERTY AD PED-OLE, and Phase 2a AD-1412 Pediatric OL. ABRO: abrocitinib, AIC: academic in confidence, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, REF: reference, SD: standard deviation.

Table G1.40. Outcomes by subgroup: POEM Stratified by Disease Severity[39,44,65]

Study Name	Arms	Category	POEM							
			n	N	Change from baseline	SD	p value	Diff from PBO	95% CI	p value
Abrocitinib										
JADE MONO-2	**Week 12**									
	PBO	Moderate (3)	NR	NR	-3	NR	NR	NR	NR	NR
	ABRO 100 mg		NR	NR	-8.7	NR	NR	NR	NR	NR

	ABRO 200 mg		NR	NR	-10.7	NR	NR	NR	NR	NR
	PBO	Severe (4)	NR	NR	-2.7	NR	NR	NR	NR	NR
	ABRO 100 mg		NR	NR	-10	NR	NR	NR	NR	NR
	ABRO 200 mg		NR	NR	-11	NR	NR	NR	NR	NR
JADE MONO-1	PBO	Moderate (3)	NR	NR	-3.7	NR	NR	NR	NR	NR
	ABRO 100 mg		NR	NR	-6.6	NR	NR	NR	NR	NR
	ABRO 200 mg		NR	NR	-10.6	NR	NR	NR	NR	NR
	PBO	Severe (4)	NR	NR	-3.9	NR	NR	NR	NR	NR
	ABRO 100 mg		NR	NR	-6.8	NR	NR	NR	NR	NR
	ABRO 200 mg		NR	NR	-10.6	NR	NR	NR	NR	NR
Tralokinumab										
ECZTRA 1	**Week 16**									
	PBO	Moderate (3)	NR	54	-3.6	7.81	NR	REF	REF	REF
	TRA 300 mg		NR	196	-8.9	7.32	NR	-5.16	-7.09 to -3.24	<0.001
	PBO	Severe (4)	NR	39	-4.5	7.85	NR	REF	REF	REF
	TRA 300 mg		NR	138	-8.8	6.92	NR	-3.96	-6.24 to -1.68	<0.001
ECZTRA 2	PBO	Moderate (3)	NR	57	-4.3	8.46	NR	REF	REF	REF
	TRA 300 mg		NR	236	-9.4	7.68	NR	-4.63	-6.59 to -2.67	<0.001
	PBO	Severe (4)	NR	40	-4.2	6.72	NR	REF	REF	REF
	TRA 300 mg		NR	182	-10	7.76	NR	-5.58	-7.74 to -3.42	<0.001
ECZTRA 3	PBO + TCS	Moderate (3)	NR	56	-8.7	6.74	NR	REF	REF	REF
	TRA 300 mg + TCS		NR	120	-10.6	6.95	NR	-2.29	-4.34 to -0.25	0.028
	PBO + TCS	Severe (4)	NR	47	-8	8.12	NR	REF	REF	REF
	TRA 300 mg + TCS		NR	106	-13.4	7.36	NR	-5.98	-8.43 to -3.54	<0.001
Baricitinib										
BREEZE-AD5	**Week 16**									

	PBO	Moderate (3)	NR	86	LSM: -2.61	SE: 1.447	NR	REF	REF	NR
	BARI 1 mg		NR	NR	NR	NR	NR	NR	NR	NR
	BARI 2 mg		NR	85	LSM: -7.53	SE: 1.066	NR	-4.92	-8.43, -1.41	NR
	PBO	Severe (4)	NR	61	LSM: -3.27	SE: 2.307	NR	REF	REF	NR
	BARI 1 mg		NR	NR	NR	NR	NR	NR	NR	NR
	BARI 2 mg		NR	61	LSM: -7.16	SE: 1.455	NR	-3.89	-9.27, 1.50	NR

Data on POEM stratified by disease severity were not available in JADE COMPARE, AD-UP, MEASURE UP 1, MEASURE UP 2, Heads Up, Phase 2b Guttman-Yassky 2020, BREEZE-AD1, BREEZE-AD2, BREEZE-AD7, Phase 2 Guttman-Yassky 2018, SOLO 1, SOLO 2, LIBERTY AD CHRONOS, LIBERTY AD ADOL, Phase 2b AD-1021 Thaci 2016, LIBERTY AD PEDS, LIBERTY AD PED-OLE, and Phase 2a AD-1412 Pediatric OL. ABRO: abrocitinib, AIC: academic in confidence, BARI: baricitinib, CI: confidence interval, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, REF: reference, SD: standard deviation, TCS: topical corticosteroids, TRA: tralokinumab.

Table G1.41. Outcomes by subgroup: HADS Anxiety, HADS Depression and EQ-5D Stratified by Disease Severity[44]

Study Name		**BREEZE-AD5**					
Timepoint		**Week 16**					
Arms		**PBO**	**BARI 1 mg**	**BARI 2 mg**	**PBO**	**BARI 1 mg**	**BARI 2 mg**
Category		**Moderate (3)**			**Severe (4)**		
HADS Anxiety	N	NR	NR	NR	61	NR	61
	Change from baseline	LSM: -2.4	NR	LSM: -2.44	LSM: -0.61	NR	LSM: -2.71
	SD	SE: .519	NR	SE: .402	SE: 0.841	NR	SE: 0.539
	p value	NR	NR	NR	NR	NR	NR
	Diff from PBO	REF	NR	-0.04	REF	NR	-2.11
	95% CI	REF	NR	-1.33, 1.25	REF	NR	-4.08, -0.14
	p value	NR	NR	NR	NR	NR	NR
HADS Depression	N	86	NR	85	61	NR	61
	Change from baseline	LSM: -1.86	NR	LSM: -1.68	LSM: -0.12	NR	LSM: -1.86

	SD	SE: .421	NR	SE: .323	SE: 0.688	NR	SE: 0.439
	p value	NR	NR	NR	NR	NR	NR
	Diff from PBO	REF	NR	0.18	REF	NR	-1.98
	95% CI	REF	NR	-0.86, 1.23	REF	NR	-3.58, -0.37
	p value	NR	NR	NR	NR	NR	NR
EQ-5D	N	86	NR	85	NR	NR	NR
	Change from baseline	LSM: 0.05	NR	LSM: .08	LSM: 0.04	NR	LSM: 0.12
	SD	SE: 0.024	NR	SE: 0.018	SE: 0.04	NR	SE: 0.025
	p value	NR	NR	NR	NR	NR	NR
	Diff from PBO	REF	NR	0.03	REF	NR	0.08
	95% CI	REF	NR	-0.02, 0.09	REF	NR	-0.01, 0.17
	p value	REF	NR	NR	REF	NR	NR

Stratified data on HADS Anxiety, HADS Depression and EQ-5D were available only in BREEZE-AD5, and stratified data on total HADS were not available in any trials. AIC: academic in confidence, BARI: baricitinib, CI: confidence interval, mg: milligram, n: number, N: total number, PBO: placebo, REF: reference, SD: standard deviation.

Table G1.42. Short-Term Safety I[35-37,39,41-46,48,50-56,58-60,63-67,69,70,77,83]

Study Name	Arms	N	Timepoint	Any AE		TEAE		Study Drug-Related AEs		D/C due to AE		Serious AE		Serious TEAE	
				n	%	n	%	n	%	n	%	n	%	n	%
Abrocitinib															
JADE MONO-1	PBO	77	12 weeks	44	57	NR	NR	0*	0	7	9	3	4	NR	NR
	ABRO 100 mg	156		108	69	NR	NR	1*	1	9	6	5	3	NR	NR
	ABRO 200 mg	154		120	78	NR	NR	1*	1	9	6	5	3	NR	NR
JADE MONO-2	PBO	78	12 weeks	NR	NR	42	53.8	NR	NR	10	12.8	1	1.3	2	2.6
	ABRO 100 mg	158		NR	NR	99	62.7	NR	NR	6	3.8	5	3.2	2	1.3
	ABRO 200 mg	155		NR	NR	102	65.8	NR	NR	5	3.2	2	1.3	0	0
JADE TEEN	PBO	96	12 weeks	NR	NR	50	52.1	NR	NR	2	2.1	2	2.1	2	2.1
	ABRO 100 mg	95		NR	NR	54	56.8	NR	NR	1	1.1	0	0	0	0
	ABRO 200 mg	94		NR	NR	59	62.8	NR	NR	2	2.1	1	1.1	1	1.1
JADE COMPARE	PBO	131	16 weeks	70	53.4	NR	NR	NR	NR	5	3.8	5	3.8	NR	NR
	ABRO 100 mg	238		121	50.8	NR	NR	NR	NR	6	2.5	6	2.5	NR	NR
	ABRO 200 mg	226		140	61.9	NR	NR	NR	NR	10	4.4	2	0.9	NR	NR
	DUP 300 mg	242		121	50	NR	NR	NR	NR	8	3.3	2	0.8	NR	NR
Phase II Gooderham 2019	PBO	56	16 weeks	NR	NR	184	68.9	64	24	44	16.5	NR	NR	9	3.4
	ABRO 100 mg	56		NR	NR							NR	NR		
	ABRO 200 mg	55		NR	NR							NR	NR		
Baricitinib															
BREEZE-AD1	PBO	249	16 weeks	NR	NR	135	54.2	NR	NR	4	1.6	6	2.4	7†	2.8
	BARI 1 mg	127		NR	NR	69	54.3	NR	NR	2	1.6	1	0.8	5†	3.9
	BARI 2 mg	123		NR	NR	71	57.7	NR	NR	1	0.8	0	0	3†	2.4
	BARI 4 mg	125		NR	NR	73	58.4	NR	NR	1	0.8	2	1.6	2†	1.6
	PBO	244	16 weeks	NR	NR	137	56.1	NR	NR	2	0.8	9	3.7	9†	3.7

Study Name	Arms	N	Timepoint	Any AE		TEAE		Study Drug-Related AEs		D/C due to AE		Serious AE		Serious TEAE	
				n	%	n	%	n	%	n	%	n	%	n	%
BREEZE-AD2	BARI 1 mg	125		NR	NR	66	53.2	NR	NR	7	5.6	9	7.3	6[†]	4.8
	BARI 2 mg	123		NR	NR	71	57.7	NR	NR	3	2.4	3	2.4	5[†]	4.1
	BARI 4 mg	123		NR	NR	66	53.7	NR	NR	2	1.6	1	0.8	3[†]	2.4
BREEZE-AD5	PBO	146	16 weeks	NR	NR	72	49	NR	NR	4	2.7	3	2.1	6[†]	4
	BARI 1 mg	147		NR	NR	79	54	NR	NR	4	2.7	1	0.7	0[†]	0
	BARI 2 mg	145		NR	NR	74	51	NR	NR	4	2.8	2	1.4	1[†]	0.7
BREEZE-AD7	PBO + TCS	108	16 weeks	NR	NR	41	38	NR	NR	1	0.9	4	3.7	3[†]	2.8
	BARI 2 mg + TCS	109		NR	NR	61	56	NR	NR	0	0	2	1.8	6[†]	5.5
	BARI 4 mg + TCS	111		NR	NR	64	57.7	NR	NR	5	4.5	4	3.6	6[†]	5.4
Phase II Guttman-Yassky 2018	PBO + TCS	49	16 weeks	NR	NR	24	49	NR	NR	5[‡]	10.2	NR	NR	0	0
	BARI 2 mg + TCS	37		NR	NR	17	45.9	NR	NR	1[‡]	2.7	NR	NR	0	0
	BARI 4 mg + TCS	38		NR	NR	27	71.1	NR	NR	5[‡]	13.2	NR	NR	1	2.6
Tralokinumab															
ECZTRA 1	PBO	196	16 weeks	151	77	151	77	NR	NR	8	4.1	8	4.1	20	10.2
	TRA 300 mg	602		460	76.4	460	76.4	NR	NR	20	3.3	23	3.8	49	8.1
ECZTRA 2	PBO	200	16 weeks	132	66	132	66	NR	NR	3	1.5	5	2.5	17	8.5
	TRA 300 mg	592		364	61.5	364	61.5	NR	NR	9	1.5	10	1.7	25	4.2
ECZTRA 2 Subgroup[¶]	Placebo	91	16 weeks	57	62.6	26	28.6	NR	NR	0	0	0	0	NR	NR
	TRA 300 mg	270		151	55.9	52	19.3	NR	NR	4	1.5	4	1.5	NR	NR
ECZTRA 3	PBO + TCS	126	16 weeks	84	66.7	84	66.7	NR	NR	1	0.8	4	3.2	8	6.3
	TRA 300 mg + TCS	252		180	71.4	180	71.4	NR	NR	6	2.4	2	0.8	7	2.8
Upadacitinib															
MEASURE UP 1	PBO	281	16 weeks	NR	NR	166	59.1	NR	NR	12	4.3	8	2.8	NR	NR
	UPA 15 mg	281		NR	NR	176	62.6	NR	NR	4	1.4	6	2.1	NR	NR
	UPA 30 mg	285		NR	NR	209	73.3	NR	NR	11	3.9	8	2.8	NR	NR

Study Name	Arms	N	Timepoint	Any AE		TEAE		Study Drug-Related AEs		D/C due to AE		Serious AE		Serious TEAE	
				n	%	n	%	n	%	n	%	n	%	n	%
MEASURE UP 2	PBO	278	16 weeks	NR	NR	146	52.5	NR	NR	12	4.3	8	2.9	NR	NR
	UPA 15 mg	276		NR	NR	166	60.1	NR	NR	11	4	5	1.8	NR	NR
	UPA 30 mg	282		NR	NR	173	61.3	NR	NR	7	2.5	7	2.5	NR	NR
AD-UP	PBO + TCS	304	16 weeks	NR	NR	190	62.7	NR	NR	7	2.3	9	3	NR	NR
	UPA 15 mg + TCS	300		NR	NR	200	66.7	NR	NR	4	1.3	7	2.3	NR	NR
	UPA 30 mg + TCS	297		NR	NR	215	72.4	NR	NR	4	1.3	4	1.3	NR	NR
Heads Up	DUP 300 mg	344	16 weeks	216	62.8	NR	NR	122	35.3	4	1.2	4	1.2	NR	NR
	UPA 30 mg	348		249	71.6	NR	NR	153	44	7	2	10	2.9	NR	NR
Phase IIb Guttman-Yassky 2020	PBO	40	16 weeks	25	63	NR	NR	NR	NR	3	7.5	1	2.5	NR	NR
	UPA 7.5 mg	42		31	74	NR	NR	NR	NR	4	9.5	2	4.8	NR	NR
	UPA 15 mg	42		32	76	NR	NR	NR	NR	2	4.8	1	2.4	NR	NR
	UPA 30 mg	42		33	33	NR	NR	NR	NR	4	9.5	0	0	NR	NR
Dupilumab															
SOLO 1	PBO	224	16 weeks	145	65	NR	NR	NR	NR	2	1	11	5	NR	NR
	DUP 300 mg Q2W	224		167	73	NR	NR	NR	NR	4	2	7	3	NR	NR
	DUP 300 mg QW	223		150	69	NR	NR	NR	NR	4	2	2	1	NR	NR
SOLO 2	PBO	236	16 weeks	168	72	NR	NR	NR	NR	5	2	13	6	NR	NR
	DUP 300 mg Q2W	233		154	65	NR	NR	NR	NR	2	1	4	2	NR	NR
	DUP 300 mg QW	239		157	66	NR	NR	NR	NR	3	1	8	3	NR	NR
Phase IIb Thaci 2016	PBO QW	61	16 weeks	NR	NR	49	80	49	80	3‡	5	NR	NR	4	7
	DUP 200 mg Q2W	61		NR	NR	46	75	46	75	3‡	5	NR	NR	1	2
	DUP 300 mg Q2W	64		NR	NR	50	78	50	78	4‡	6	NR	NR	2	3
	DUP 300 mg Q4W	65		NR	NR	56	86	56	86	3‡	5	NR	NR	3	5

None of these short-term safety outcomes were available in LIBERTY AD CHRONOS. ABRO: abrocitinib, AE: adverse event, BARI: baricitinib, D/C: discontinuation, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, TCS: topical corticosteroids, TEAE: treatment-emergent adverse event, TRA: tralokinumab, UPA: upadacitinib, %: percent. *treatment-related serious AE, †severe TEAE, ‡discontinuation due to TEAE, ¶North American subgroup.

Table G1.43. Short-Term Safety II[35-37,41-43,45,46,48,51,56,63,64,66,67,69,83,84]

Study Name	Arms	N	Timepoint	Fatal TEAE		All-cause Mortality		Major Adverse Cardiovascular Event		Venous Thromboembolism	
				n	%	n	%	n	%	n	%
Abrocitinib											
JADE MONO-1	PBO	77	12 weeks	NR	NR	0	0	0	0	0	0
	ABRO 100 mg	156		NR	NR	0	0	0	0	0	0
	ABRO 200 mg	154		NR	NR	0	0	0	0	0	0
JADE MONO-2	PBO	78	12 weeks	NR	NR	0	0	0	0	0	0
	ABRO 100 mg	158		NR	NR	1	0.6	0	0	0	0
	ABRO 200 mg	155		NR	NR	0	0	0	0	0	0
JADE TEEN	PBO	96	12 weeks	NR	NR	0	0	NR	NR	NR	NR
	ABRO 100 mg	95		NR	NR	0	0	NR	NR	NR	NR
	ABRO 200 mg	94		NR	NR	0	0	NR	NR	NR	NR
JADE COMPARE	PBO	131	16 weeks	NR	NR	0	0	NR	NR	NR	NR
	ABRO 100 mg	238		NR	NR	0	0	NR	NR	NR	NR
	ABRO 200 mg	226		NR	NR	0	0	NR	NR	NR	NR
	DUP 300 mg	242		NR	NR	0	0	NR	NR	NR	NR
Phase II Gooderham 2019	PBO	56	16 weeks	0	0	0	0	NR	NR	0*	0
	ABRO 100 mg	56		0	0	0	0	NR	NR	0*	0
	ABRO 200 mg	55		0	0	0	0	NR	NR	1*	1.8
Baricitinib											

Study Name	Arms	N	Timepoint	Fatal TEAE		All-cause Mortality		Major Adverse Cardiovascular Event		Venous Thromboembolism	
				n	%	n	%	n	%	n	%
BREEZE-AD1	PBO	249	16 weeks	0	0	0	0	0	0	0	0
	BARI 1 mg	127		0	0	0	0	0	0	0	0
	BARI 2 mg	123		0	0	0	0	0	0	0	0
	BARI 4 mg	125		0	0	0	0	0	0	0	0
BREEZE-AD2	PBO	244	16 weeks	0	0	0	0	0	0	0	0
	BARI 1 mg	125		0	0	0	0	0	0	0	0
	BARI 2 mg	123		0	0	0	0	0	0	0	0
	BARI 4 mg	123		0	0	0	0	0	0	0	0
BREEZE-AD5	PBO	146	16 weeks	NR	NR	0	0	0	0	0	0
	BARI 1 mg	147		NR	NR	0	0	0	0	0	0
	BARI 2 mg	145		NR	NR	0	0	0	0	0	0
BREEZE-AD7	PBO + TCS	108	16 weeks	0	0	0	0	0	0	0	0[†]
	BARI 2 mg + TCS	109		0	0	0	0	0	0	0	0[†]
	BARI 4 mg + TCS	111		0	0	0	0	0	0	1	1[†]
Phase II Guttman-Yassky 2018	PBO + TCS	49	16 weeks	0	0	NR	NR	NR	NR	NR	NR
	BARI 2 mg + TCS	37		0	0	NR	NR	NR	NR	NR	NR
	BARI 4 mg + TCS	38		0	0	NR	NR	NR	NR	NR	NR
Upadacitinib											
MEASURE UP 1	PBO	281	16 weeks	NR	NR	0	0	0	0	0	0
	UPA 15 mg	281		NR	NR	0	0	0	0	0	0
	UPA 30 mg	285		NR	NR	0	0	0	0	0	0
MEASURE UP 2	PBO	278	16 weeks	NR	NR	0	0	0	0	1	0.4
	UPA 15 mg	276		NR	NR	0	0	0	0	0	0
	UPA 30 mg	282		NR	NR	0	0	0	0	0	0
AD-UP	PBO + TCS	304	16 weeks	NR	NR	0	0	0	0	0	0

Study Name	Arms	N	Timepoint	Fatal TEAE		All-cause Mortality		Major Adverse Cardiovascular Event		Venous Thromboembolism	
				n	%	n	%	n	%	n	%
	UPA 15 mg + TCS	300		NR	NR	0	0	0	0	0	0
	UPA 30 mg + TCS	297		NR	NR	0	0	0	0	0	0
Heads Up	DUP 300 mg	344	16 weeks	0	0	0	0	0	0	0	0
	UPA 30 mg	348		1	0.3	1	0.3	0	0	0	0
Phase IIb Guttman-Yassky 2020	PBO	40	16 weeks	NR	NR	0	0	0	0	0	0
	UPA 7.5 mg	42		NR	NR	0	0	0	0	0	0
	UPA 15 mg	42		NR	NR	0	0	0	0	0	0
	UPA 30 mg	42		NR	NR	0	0	0	0	0	0
Dupilumab											
SOLO 1	PBO	224	16 weeks	NR	NR	0	0	NR	NR	NR	NR
	DUP 300 mg Q2W	224		NR	NR	0	0	NR	NR	NR	NR
	DUP 300 mg QW	223		NR	NR	0	0	NR	NR	NR	NR
SOLO 2	PBO	236	16 weeks	NR	NR	0	0	NR	NR	NR	NR
	DUP 300 mg Q2W	233		NR	NR	1	<1	NR	NR	NR	NR
	DUP 300 mg QW	239		NR	NR	1	<1	NR	NR	NR	NR

None of these short-term safety outcomes were available in ECZTRA 1, ECZTRA 2, ECZTRA 3, LIBERTY AD CHRONOS, and Phase IIb Thaci 2016. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, TCS: topical corticosteroids, TEAE: treatment-emergent adverse event, UPA: upadacitinib, %: percent. *pulmonary embolism, †deep vein thrombosis and pulmonary embolism.

Table G1.44. Short-Term Safety III[35-37,41-43,45,46,48,51,53,56,63-66,69,70,79,83,84]

Study Name	Arms	N	Timepoint	Injection Site RXN		Skin Infection		Herpetic Infection		Serious Infection		Malignancy		Non-Melanocytic Skin Cancer		Conjunctivitis	
				n	%	n	%	n	%	n	%	n	%	n	%	n	%
Abrocitinib																	
JADE MONO-1	PBO	77	12 weeks	NR	NR	0	0	2*	2.6	NR	NR	0	0	NR	NR	0	0
	ABRO 100 mg	156		NR	NR	2	1	2*	1.3	NR	NR	0	0	NR	NR	1	1
	ABRO 200 mg	154		NR	NR	1	1	0*	0	NR	NR	0	0	NR	NR	1	1
JADE MONO-2	PBO	78	12 weeks	NR	NR	NR	NR	1*	1.3	1	1.3	0	0	NR	NR	0	0
	ABRO 100 mg	158		NR	NR	NR	NR	7*	4.4	3	1.9	0	0	NR	NR	4	3
	ABRO 200 mg	155		NR	NR	NR	NR	4*	2.6	0	0	0	0	NR	NR	4	3
JADE TEEN	PBO	96	12 weeks	NR	NR	NR	NR	0	0	NR	NR	NR	NR	NR	NR	NR	NR
	ABRO 100 mg	95		NR	NR	NR	NR	1	1.1	NR	NR	NR	NR	NR	NR	NR	NR
	ABRO 200 mg	94		NR	NR	NR	NR	2	2.1	NR	NR	NR	NR	NR	NR	NR	NR
JADE COMPARE	PBO	131	16 weeks	0†	0	1	0.8	0‡	0	NR	NR	NR	NR	NR	NR	3	2.3
	ABRO 100 mg	238		2†	0.01	1	0.4	2‡	0.8	NR	NR	NR	NR	NR	NR	2	0.8
	ABRO 200 mg	226		2†	0.01	1	0.4	4‡	1.8	NR	NR	NR	NR	NR	NR	3	1.3
	DUP 300 mg	242		3†	0.01	NR	NR	0‡	0	NR	NR	NR	NR	NR	NR	15	6.2
Phase II Gooderham 2019	PBO	56	16 weeks	NR	NR	NR	NR	2¶	3.6	NR	NR	0¥	0	NR	NR	NR	NR
	ABRO 100 mg	56		NR	NR	NR	NR	2¶	3.6	NR	NR	0¥	0	NR	NR	NR	NR
	ABRO 200 mg	55		NR	NR	NR	NR	0¶	0	NR	NR	0¥	0	NR	NR	NR	NR
Baricitinib																	
BREEZE-AD1	PBO	249	16 weeks	NA	NA	11§	4.4	3**	1.2	NR	NR	NR††	NR††	NR	NR	4‡‡	1.6
	BARI 1 mg	127		NA	NA	1§	0.8	7	5.5	NR	NR	0	0	NR	NR	1‡‡	0.8
	BARI 2 mg	123		NA	NA	6§	4.9	4	3.3	NR	NR	0	0	NR	NR	2‡‡	1.6
	BARI 4 mg	125		NA	NA	4§	3.2	9	7.2	NR	NR	0	0	NR	NR	1‡‡	0.8
BREEZE-AD2	PBO	244	16 weeks	NA	NA	19	7.8	11	4.5	NR	NR	NR††	NR††	NR	NR	2	0.8

Study Name	Arms	N	Timepoint	Injection Site RXN		Skin Infection		Herpetic Infection		Serious Infection		Malignancy		Non-Melanocytic Skin Cancer		Conjunctivitis	
				n	%	n	%	n	%	n	%	n	%	n	%	n	%
	BARI 1 mg	125		NA	NA	6	4.8	6	4.8	NR	NR	0	0	NR	NR	6	4.8
	BARI 2 mg	123		NA	NA	9	7.3	7	5.7	NR	NR	0	0	NR	NR	2	1.6
	BARI 4 mg	123		NA	NA	6	4.9	5	4.1	NR	NR	0	0	NR	NR	0	0
BREEZE-AD5	PBO	146	16 weeks	NR	NR	7¶¶	5	1¥¥	0.6	1	0.7	0	0	NR	NR	NR	NR
	BARI 1 mg	147		NR	NR	6¶¶	4	4¥¥	2.7	0	0	0	0	NR	NR	NR	NR
	BARI 2 mg	145		NR	NR	6¶¶	4	2¥¥	1.4	1	0.7	0	0	NR	NR	NR	NR
BREEZE-AD7	PBO + TCS	108	16 weeks	NA	NA	NR	NR	4##	3.7	2	1.9	0§§	0	NR	NR	NR	NR
	BARI 2 mg + TCS	109		NA	NA	NR	NR	7##	6.4	0	0	0§§	0	NR	NR	NR	NR
	BARI 4 mg + TCS	111		NA	NA	NR	NR	7##	6.3	0	0	0§§	0	NR	NR	NR	NR
Phase II Guttman-Yassky 2018	PBO + TCS	49	16 weeks	NA	NA	0	0	0**	0	NR	NR	NR	NR	NR	NR	1¥¥	2
	BARI 2 mg + TCS	37		NA	NA	0	0	0**	0	NR	NR	NR	NR	NR	NR	0¥¥	0
	BARI 4 mg + TCS	38		NA	NA	1	3	1**	3	NR	NR	NR	NR	NR	NR	0¥¥	0
Tralokinumab																	
ECZTRA 1	PBO	196	16 weeks	NR	NR	3	1.5	2	1	NR	NR	0#	0	NR	NR	4¥	2
	TRA 300 mg	602		24	4	6	1	3	0.5	NR	NR	0#	0	NR	NR	43¥	7.1
ECZTRA 2	PBO	200	16 weeks	NR	NR	11	5.5	5	2.5	NR	NR	0#	0	NR	NR	3¥	1.5
	TRA 300 mg	592		15	2.5	12	2	2	0.3	NR	NR	1#	0.2	NR	NR	18¥	3
ECZTRA 2 Subgroup¶¶¶	Placebo	91	16 weeks	NR	NR	8§	8.8	NR	NR	NR	NR	NR	NR	NR	NR	3	2.2
	TRA 300 mg	270		NR	NR	5§	1.9	1###	0.4	NR	NR	NR	NR	NR	NR	6	2.2
ECZTRA 3	PBO + TCS	126	16 weeks	0	0	7§	5.6	1	0.8	NR	NR	0#	0	NR	NR	4	3.2
	TRA 300 mg + TCS	252		17	6.7	4§	1.6	1	0.4	NR	NR	0#	0	NR	NR	28	11.1
Upadacitinib																	

Study Name	Arms	N	Timepoint	Injection Site RXN		Skin Infection		Herpetic Infection		Serious Infection		Malignancy		Non-Melanocytic Skin Cancer		Conjunctivitis	
				n	%	n	%	n	%	n	%	n	%	n	%	n	%
MEASURE UP 1	PBO	281	16 weeks	NR	NR	NR	NR	0	0	0	0	0	0	0	0	NR	NR
	UPA 15 mg	281		NR	NR	NR	NR	2	0.7	2	1	0	0	1	1	NR	NR
	UPA 30 mg	285		NR	NR	NR	NR	2	0.7	3	1	2	1	0	0	NR	NR
MEASURE UP 2	PBO	278	16 weeks	NR	NR	NR	NR	2	0.7	2	1	0	0	0	0	NR	NR
	UPA 15 mg	276		NR	NR	NR	NR	1	0.4	1	1	0	0	2	1	NR	NR
	UPA 30 mg	282		NR	NR	NR	NR	2	0.7	2	1	1	1	0	0	NR	NR
AD-UP	PBO + TCS	304	16 weeks	NR	NR	NR	NR	NR	NR	3	1	0	0	0	0	NR	NR
	UPA 15 mg + TCS	300		NR	NR	NR	NR	3	1	3	1	0	0	0	0	NR	NR
	UPA 30 mg + TCS	297		NR	NR	NR	NR	4	1.3	0	0	1	0.3	1	0.3	NR	NR
Heads Up	DUP 300 mg	344	16 weeks	NR	NR	NR	NR	3‡	0.9	2	0.6	0	0	1	0.3	29	8.4
	UPA 30 mg	348		NR	NR	NR	NR	7‡	2	4	1.1	0	0	0	0	5	1.4
Phase IIb Guttman-Yassky 2020	PBO	40	16 weeks	NR	NR	0	0	0‡	0	0	0	0	0	NR	NR	NR	NR
	UPA 7.5 mg	42		NR	NR	1	2.4	0‡	0	2	4.8	0	0	NR	NR	NR	NR
	UPA 15 mg	42		NR	NR	0	0	0‡	0	1	2.4	0	0	NR	NR	NR	NR
	UPA 30 mg	42		NR	NR	0	0	0‡	0	0	0	0	0	NR	NR	NR	NR
Dupilumab																	
SOLO 1	PBO	224	16 weeks	13	6	18	8	9***	4	NR	NR	NR	NR	NR	NR	2	0.9
	DUP 300 mg Q2W	224		19	8	13	6	15***	7	NR	NR	NR	NR	NR	NR	11	4.8
	DUP 300 mg QW	223		41	19	14	6	9***	4	NR	NR	NR	NR	NR	NR	7	3.2
SOLO 2	PBO	236	16 weeks	15	6	26	11	8	3	NR	NR	NR	NR	NR	NR	1	0.4
	DUP 300 mg Q2W	233		32	14	13	6	10	4	NR	NR	NR	NR	NR	NR	9	3.8
	DUP 300 mg QW	239		31	13	15	6	12	5	NR	NR	NR	NR	NR	NR	9	3.8

Study Name	Arms	N	Timepoint	Injection Site RXN		Skin Infection		Herpetic Infection		Serious Infection		Malignancy		Non-Melanocytic Skin Cancer		Conjunctivitis	
				n	%	n	%	n	%	n	%	n	%	n	%	n	%
Phase IIb Thaci 2016	PBO QW	61	16 weeks	2	3	NR	NR	1[†††]	2	NR	NR	NR	NR	NR	NR	2[‡‡‡]	3
	DUP 200 mg Q2W	61		4	7	NR	NR	6[†††]	10	NR	NR	NR	NR	NR	NR	6[‡‡‡]	10
	DUP 300 mg Q2W	64		3	5	NR	NR	5[†††]	8	NR	NR	NR	NR	NR	NR	3[‡‡‡]	5
	DUP 300 mg Q4W	65		5	8	NR	NR	4[†††]	6	NR	NR	NR	NR	NR	NR	4[‡‡‡]	6

None of these short-term safety outcomes were available in LIBERTY AD CHRONOS. ABRO: abrocitinib, BARI: baricitinib, DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NA: not applicable, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, RXN: reaction, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *herpes simplex, herpes zoster, oral herpes, and eczema herpeticum, [†]injection site erythema, oedema, pain, swelling, [‡]herpes zoster, [¶]herpes simplex, herpes zoster, and eczema herpecitum, [¥]malignant melanoma, [#]malignancies diagnosed after randomization, [§]skin infection requiring systemic treatment, [ɣ]conjunctivitis, conjunctivitis bacterial, conjunctivitis viral and conjunctivitis allergic, **herpes simplex, [††]2 malignancies were reported in patients on placebo, but publication doesn't distinguish which trial's patients experienced these (either BREEZE-AD1 or BREEZE-AD2), [‡‡]conjunctivitis/keratitis, [¶¶]skin infection requiring antibiotics, [¥¥]herpes zoster and herpes simplex, [##]oral herpes virus infection, herpes simplex virus infection, and herpes zoster virus infection, [§§]malignant tumors other than NMSC and NMSC, [ɣɣ]conjunctivitis viral, ***herpes viral infection include oral herpes, herpes simplex, eczema herpeticum, herpes virus infection, herpes zoster, ophthalmic herpes simplex, genital herpes, herpes ophthalmic, herpes simplex otitis externa, [†††]herpes viral infections include oral herpes, herpes simplex, eczema herpeticum, herpes virus infection, and herpes zoster, [‡‡‡]conjunctival infections, irritations, and inflammation, [¶¶¶]North American subgroup.

Table G1.45. Long-Term Safety I[50,53,54,60-64,67,76,78,83,107]

Study Name	Arms	N	Timepoint	Any AE		TEAE		Study Drug-Related AEs		D/C due to AE		Serious AE		Serious TEAE	
				n	%	n	%	n	%	n	%	n	%	n	%
Abrocitinib															
JADE EXTEND Subgroup 1‡	ABRO 100 mg	595	48 weeks	NR	NR	NR	NR	NR	NR	37	6.2	NR	NR	NR	NR
	ABRO 200 mg	521		NR	NR	NR	NR	NR	NR	45	8.6	NR	NR	NR	NR
JADE EXTEND Subgroup 2¶	ABRO 100 mg	130	32 weeks	NR	NR	54	41.5	NR	NR	1¥	0.8	NR	NR	3	2.3
	ABRO 200 mg	73		NR	NR	37	50.7	NR	NR	1¥	1.4	NR	NR	1	1.4
Tralokinumab															
ECZTRA 1	PBO	35	36 weeks	25	71.4	NR	NR	NR	NR	0	0	0	0	NR	NR
	TRA 300 mg Q2W	68		54	79.4	NR	NR	NR	NR	1	1.5	1	1.5	NR	NR
	TRA 300 mg Q4W	76		53	69.7	NR	NR	NR	NR	1	1.3	3	3.9	NR	NR
ECZTRA 2	PBO	46	36 weeks	32	69.6	NR	NR	NR	NR	0	0	0	0	NR	NR
	TRA 300 mg Q2W	91		62	68.1	NR	NR	NR	NR	2	2.2	0	0	NR	NR
	TRA 300 mg Q4W	89		56	62.9	NR	NR	NR	NR	1	1.1	3	3.4	NR	NR
ECZTRA 3	TRA 300 mg Q2W + TCS (PBO nonresponders)	79	16-32 weeks	55	69.6	NR	NR	NR	NR	2	2.5	0	0	NR	NR
	PBO Q2W + TCS (PBO responders)	41		26	63.4	NR	NR	NR	NR	1	2.4	1	2.4	NR	NR
	TRA 300 mg Q2W + TCS (TRA responders)	69		48	69.6	NR	NR	NR	NR	0	0	3	4.3	NR	NR
	TRA 300 mg Q4W + TCS (TRA responders)	69		41	59.4	NR	NR	NR	NR	1	1.4	0	0	NR	NR
	TRA 300 mg Q2W + TCS (TRA nonresponders)	95		62	65.3	NR	NR	NR	NR	1	1.1	2	2.1	NR	NR

Study Name	Arms	N	Timepoint	Any AE		TEAE		Study Drug-Related AEs		D/C due to AE		Serious AE		Serious TEAE	
				n	%	n	%	n	%	n	%	n	%	n	%
ECZTEND	TRA 300 mg Q2W	1174	56 weeks	844	71.9	NR	NR	NR	NR	19	1.6	55	4.7	NR	NR
Upadacitinib															
Heads Up	DUP 300 mg	344	24 weeks	230	66.9	NR	NR	129	37.5	4	1.2	7	2	NR	NR
	UPA 30 mg	348		270	77.6	NR	NR	170	48.9	11	3.2	14	4	NR	NR
Phase IIb Guttman-Yassky 2020	PBO→PBO	10	32 weeks	1	10.0	NR	NR	1*	10.0	0	0.0	0	0.0	NR	NR
	PBO→UPA 30 mg	10		7	70.0	NR	NR	5*	50.0	1	10.0	2	20.0	NR	NR
	UPA 7.5 mg→PBO	15		1	6.7	NR	NR	1*	6.7	0	0.0	0	0.0	NR	NR
	UPA 7.5 mg→UPA 7.5 mg	16		4	25.0	NR	NR	1*	6.3	0	0.0	0	0.0	NR	NR
	UPA 15 mg→PBO	19		5	26.3	NR	NR	3*	15.8	0	0.0	0	0.0	NR	NR
	UPA 15 mg→UPA 15 mg	18		5	27.8	NR	NR	3*	16.7	0	0.0	0	0.0	NR	NR
	UPA 30 mg→PBO	19		7	36.8	NR	NR	3*	15.8	0	0.0	0	0.0	NR	NR
	UPA 30 mg→UPA 30 mg	19		8	42.1	NR	NR	4*	21.1	1	5.3	0	0.0	NR	NR
Dupilumab															
LIBERTY AD CHRONOS	PBO + TCS	315	52 weeks	266	84	NR	NR	NR	NR	24	8	16	5	NR	NR
	DUP 300 mg + TCS Q2W	110		97	88	NR	NR	NR	NR	2	2	4	4	NR	NR
	DUP 300 mg + TCS QW	315		261	83	NR	NR	NR	NR	9	3	9	3	NR	NR
AD SOLO-CONTINUE	PBO	82	36 weeks	NR	NR	67	81.7	1†	1.2	3	3.7	NR	NR	NR	NR
	DUP 300 mg Q8W	84		NR	NR	63	75	3†	3.6	0	0	NR	NR	NR	NR
	DUP 300 mg Q4W	87		NR	NR	64	73.6	4†	4.6	2	2.3	NR	NR	NR	NR

Study Name	Arms	N	Timepoint	Any AE		TEAE		Study Drug-Related AEs		D/C due to AE		Serious AE		Serious TEAE	
				n	%	n	%	n	%	n	%	n	%	n	%
	DUP 300 mg QW/Q2W	167		NR	NR	118	70.7	6[†]	3.6	0	0	NR	NR	NR	NR

None of these long-term safety data were available in BREEZE-AD3 and BREEZE-AD6. AE: adverse event, D/C: discontinuation, DUP: dupilumab, kg: kilogram, LTE: long-term extension, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, RXN: reaction, TEAE: treatment-emergent adverse event, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent.*AE possibly related to drug, [†]treatment-emergent SAE, [‡]JADE MONO-1 & 2 and JADE COMPARE subgroup, [¶]JADE COMPARE dupilumab nonresponder subgroup, [¥]discontinuation due to TEAE.

Table G1.46. Long-Term Safety II[50,53,54,60,63,64,69,83,107]

Study Name	Arms	N	Timepoint	All-cause Mortality		Major Adverse Cardiovascular Event		Venous Thromboembolism		Nausea	
				n	%	n	%	n	%	n	%
Abrocitinib											
JADE EXTEND Subgroup 2*	ABRO 100 mg	130	32 weeks	NR	NR	NR	NR	NR	NR	0	0
	ABRO 200 mg	73		NR	NR	NR	NR	NR	NR	6	8.2
Tralokinumab											
ECZTRA 3	TRA 300 mg Q2W + TCS (PBO nonresponders)	79	16-32 weeks	NR	NR	NR	NR	NR	NR	1	1.3
	PBO 300 mg Q2W + TCS (PBO responders)	41		NR	NR	NR	NR	NR	NR	0	0
	TRA 300 mg Q2W + TCS (TRA responders)	69		NR	NR	NR	NR	NR	NR	3	4.3
	TRA 300 mg Q4W + TCS (TRA responders)	69		NR	NR	NR	NR	NR	NR	4	5.8
	TRA 300 mg Q2W + TCS (TRA nonresponders)	95		NR	NR	NR	NR	NR	NR	3	3.2
Upadacitinib											
Heads Up	DUP 300 mg	344	24 weeks	0	0	0	0	0	0	NR	NR
	UPA 30 mg	348		1	0.3	0	0	0	0	NR	NR
Phase IIb Guttman-Yassky 2020	PBO→PBO	10	32 weeks	NR	NR	0	0	0	0	NR	NR
	PBO→UPA 30 mg	10		NR	NR	0	0	0	0	NR	NR
	UPA 7.5 mg →PBO	15		NR	NR	0	0	0	0	NR	NR
	UPA 7.5 mg →UPA 7.5 mg	16		NR	NR	0	0	0	0	NR	NR
	UPA 15 mg→ PBO	19		NR	NR	0	0	0	0	NR	NR
	UPA 15 mg→ UPA 15 mg	18		NR	NR	0	0	0	0	NR	NR
	UPA 30 mg→ PBO	19		NR	NR	0	0	0	0	NR	NR
	UPA 30 mg→ UPA 30 mg	19		NR	NR	0	0	0	0	NR	NR
Dupilumab											

LIBERTY AD CHRONOS	PBO + TCS	315	56 weeks	0	0	NR	NR	NR	NR	NR	NR
	DUP 300 mg + TCS Q2W	110		0	0	NR	NR	NR	NR	NR	NR
	DUP 300 mg + TCS QW	315		1	<1	NR	NR	NR	NR	NR	NR
AD SOLO-CONTINUE	PBO	82	36 weeks	0	0	NR	NR	NR	NR	NR	NR
	DUP 300 mg Q8W	84		0	0	NR	NR	NR	NR	NR	NR
	DUP 300 mg Q4W	87		1	1.1	NR	NR	NR	NR	NR	NR
	DUP 300 mg QW/Q2W	167		0	0	NR	NR	NR	NR	NR	NR

None of these long-term safety data were available in BREEZE-AD3, BREEZE-AD6, ECZTRA 1, ECZTRA 2, and ECZTEND. There were no long-term data on Fatal TEAE's available. DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, TCS: topical corticosteroids, TEAE: treatment-emergent adverse event, TRA: tralokinumab, UPA: upadacitinib, %: percent. *JADE COMPARE dupilumab nonresponder subgroup.

Table G1.47. Long-Term Safety III[50,53-55,60-64,67,78,83]

Study Name	Arms	N	Timepoint	Injection Site RXN		Skin Infection		Herpetic Infection		Serious Infection		Malignancy		Non-Melanocytic Skin Cancer		Conjunctivitis	
				n	%	n	%	n	%	n	%	n	%	n	%	n	%
Tralokinumab																	
ECZTRA 1	PBO	35	36 weeks	1	2.9	0*	0	0†	0	NR	NR	0‡	0	NR	NR	2¶	5.7
	TRA 300 mg Q2W	68		5	7.4	2*	2.9	0†	0	NR	NR	0‡	0	NR	NR	6¶	8.8
	TRA 300 mg Q4W	76		7	9.2	2*	2.6	0†	0	NR	NR	0‡	0	NR	NR	5¶	6.6
ECZTRA 2	PBO	46	36 weeks	0	0	1*	2.2	0†	0	NR	NR	0‡	0	NR	NR	3¶	6.5
	TRA 300 mg Q2W	91		4	4.4	2*	2.2	1†	1.1	NR	NR	0‡	0	NR	NR	8¶	8.8
	TRA 300 mg Q4W	89		4	4.5	1*	1.1	0†	0	NR	NR	1‡	1.1	NR	NR	5¶	5.6
ECZTRA 3	TRA 300 mg Q2W + TCS (PBO non-responders)	79	16-32 weeks	2	2.5	2*	2.5	3¥	4	NR	NR	0‡	0	NR	NR	6#	7.6
	PBO Q2W + TCS (PBO responders)	41		0	0	0*	0	1¥	2	NR	NR	1‡	2.4	NR	NR	1#	2.4
	TRA 300 mg Q2W + TCS (TRA responders)	69		5	7.2	0*	0	3¥	4	NR	NR	0‡	0	NR	NR	3#	4.3
	TRA 300 mg Q4W + TCS (TRA responders)	69		4	5.8	0*	0	4¥	6	NR	NR	1‡	1.4	NR	NR	1#	1.4
	TRA 300 mg Q2W + TCS (TRA non-responders)	95		5	5.3	1*	1.1	5¥	5	NR	NR	0‡	0	NR	NR	4#	4.2
ECZTEND	TRA 300 mg Q2W	1174	Week 56	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	65¶	5.9
Upadacitinib																	
Heads Up	DUP 300 mg	344	24 weeks	NR	NR	NR	NR	4##	1.2	2	0.6	0	0	1	0.3	35	10.2
	UPA 30 mg	348		NR	NR	NR	NR	12##	3.4	4	1.1	1	0.3	0	0	5	1.4
Phase IIb	PBO→PBO	10	32 weeks	NR	NR	NR	NR	NR	NR	0	0	0	0	0§	0	NR	NR
	PBO→UPA 30 mg	10		NR	NR	NR	NR	NR	NR	1	10	1	10	1§	10	NR	NR

Study Name	Arms	N	Timepoint	Injection Site RXN		Skin Infection		Herpetic Infection		Serious Infection		Malignancy		Non-Melanocytic Skin Cancer		Conjunctivitis	
				n	%	n	%	n	%	n	%	n	%	n	%	n	%
Guttman-Yassky 2020	UPA 7.5 mg→ PBO	15		NR	NR	NR	NR	NR	NR	0	0	0	0	0[§]	0	NR	NR
	UPA 7.5 mg→ UPA 7.5 mg	16		NR	NR	NR	NR	NR	NR	0	0	0	0	0[§]	0	NR	NR
	UPA 15 mg→PBO	19		NR	NR	NR	NR	NR	NR	0	0	0	0	0[§]	0	NR	NR
	UPA 15 mg→ UPA 15 mg	18		NR	NR	NR	NR	NR	NR	0	0	0	0	0[§]	0	NR	NR
	UPA 30 mg→ PBO	19		NR	NR	NR	NR	NR	NR	0	0	0	0	0[§]	0	NR	NR
	UPA 30 mg→ UPA 30 mg	19		NR	NR	NR	NR	NR	NR	0	0	0	0	0[§]	0	NR	NR
Dupilumab																	
LIBERTY AD CHRONOS	PBO + TCS	315	52 weeks	24	8	56[¥]	18	25**	8	NR	NR	NR	NR	NR	NR	25[††]	8
	DUP 300 mg + TCS Q2W	110		16	15	12[¥]	11	8**	7	NR	NR	NR	NR	NR	NR	15[††]	14
	DUP 300 mg + TCS QW	315		60	19	26[¥]	8	22**	7	NR	NR	NR	NR	NR	NR	61[††]	19
AD SOLO-CONTINUE	PBO	82	36 weeks	7	8.5	8[¥]	9.8	5[‡‡]	6.1	NR	NR	0[¶¶]	0	0	0	4[¥¥]	4.9
	DUP 300 mg Q8W	84		6	7.1	5[¥]	6	10[‡‡]	11.9	NR	NR	2[¶¶]	2.4	2	2.4	3[¥¥]	3.6
	DUP 300 mg Q4W	87		6	6.9	1[¥]	1.1	3[‡‡]	3.4	NR	NR	1[¶¶]	1.1	1	1.1	4[¥¥]	4.6
	DUP 300 mg QW/Q2W	167		18	10.8	4[¥]	2.4	11[‡‡]	6.6	NR	NR	0[¶¶]	0	0	0	9[¥¥]	5.4
	DUP 4 mg/kg (Children)	19		2[##]	10.5	0[¥¥]	0	1[§§]	5.3	NR	NR	NR	NR	NR	NR	1***	5.3

None of these long-term safety data were available in JADE EXTEND, BREEZE-AD3, and BREEZE-AD6. DUP: dupilumab, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, QW: once weekly, Q2W: every two weeks, Q4W: every four weeks, Q8W: every eight weeks, RXN: reaction, TCS: topical corticosteroids, TRA: tralokinumab, UPA: upadacitinib, %: percent. *skin infection requiring systemic treatment, [†]eczema herpeticum, [‡]malignancies diagnosed after randomization, [¶]conjunctivitis, conjunctivitis bacterial, conjunctivitis viral, and conjunctivitis allergic, [¥]oral herpes and eczema herpeticum, [#]conjunctivitis, conjunctivitis allergic, and conjunctivitis viral, [§]non-melanoma skin cancer, [¥]non-herpetic skin infection, **oral herpes, herpes simplex, herpes virus infection, herpes zoster, eczema herpeticum, genital herpes, herpes ophthalmic, ophthalmic herpes simplex, and ophthalmic herpes

zoster, [††]conjunctivitis allergic, conjunctivitis bacterial, atopic keratoconjunctivitis, and conjunctivitis, [‡‡]herpes simplex virus infection, oral herpes infection, ophthalmic herpes infection, [¶¶]basal cell carcinoma, [¥¥]conjunctivitis, conjunctivitis bacterial, conjunctivitis viral, conjunctivitis allergic, and atopic keratoconjunctivitis, [##]herpes zoster.

Mild to Moderate Population

Table G1.48 Study Quality[92,95]

Trial	Comparable Groups	Non-differential Follow-up	Patient/ Investigator Blinding (Double-blind)	Clear Definition of Intervention	Clear Definition of Outcomes	Selective Outcome Reporting	Measurements Valid	Intention-to-treat Analysis	Approach to Missing Data	USPSTF Rating
Ruxolitinib Cream										
TRuE AD-1	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NRI	Good
TRuE AD-2	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NRI	Good
Crisaborole										
AD301/302	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Unclear	Good
CrisADe CARE 1	NA	Yes	NA	Yes	Yes	No	Yes	NA	NA	Fair

Includes on published phase II RCTs. NA: not applicable, NRI: non-responder imputation,

Table G1.49. Key Features

Trial	Patient Population	Interventions	Inclusion Criteria	Key Outcomes
Ruxolitinib Cream				
Phase III TRuE-AD1 (poster)[85,88,89] Papp, K. 2020	N~600 DB, PC, RCT Adolescents aged 12-17 and adults aged 18+ with mild-to-moderate AD	Applied twice daily for 8 weeks: • ruxolitinib cream 1.5% • ruxolitinib cream 0.75% • vehicle (placebo) cream Prohibited concomitant therapy: UV light therapy, JAK inhibitors (systemic/topical), bleach baths (diluted sodium hypochlorite) more than 2x/week	• Adolescents aged 12 to 17 years, inclusive, and adults aged ≥ 18 years. • Participants with AD for ≥ 2 years. • Participants with an IGA score of 2 to 3 at screening and 0 to 4 at Week 8 • Participants with % BSA (excluding scalp) of AD involvement of 3% to 20% at screening and 0% to 20% at Week 8 • Participants who agree to discontinue all agents used to treat AD during trial • Willingness to avoid pregnancy or fathering of children	Primary Endpoint at week 8: •IGA-TS response rate Secondary Endpoints at week 8: •EASI-75 response rate •Itch NRS 4-point improvement response rate •PROMIS Short Form-Sleep Disturbance 6-point improvement response rate •SCORAD, mean change from baseline
Phase III TRuE-AD2 (Poster)[85,88,89] Papp, K. 2020	N~600 DB, PC, RCT Adolescents aged 12-17 and adults aged 18+ with mild-to-moderate AD	Applied twice daily for 8 weeks: • ruxolitinib cream 1.5% • ruxolitinib cream 0.75% • vehicle (placebo) cream Prohibited concomitant therapy: UV light therapy, JKA inhibitors (systemic/topical), bleach baths (diluted sodium hypochlorite) more than 2x/week	• Adolescents aged 12 to 17 years, inclusive, and adults aged ≥ 18 years. • Participants with AD for ≥ 2 years. • Participants with an IGA score of 2 to 3 at screening and 0 to 4 at Week 8 • Participants with % BSA (excluding scalp) of AD involvement of 3% to 20% at screening and 0% to 20% at Week 8 • Participants who agree to discontinue all agents used to treat AD during trial • Willingness to avoid pregnancy or fathering of children	Primary Endpoint at week 8: •IGA-TS response rate Secondary Endpoints at week 8: •EASI-75 response rate •Itch NRS 4-point improvement response rate •PROMIS Short Form-Sleep Disturbance 6-point improvement response rate •SCORAD, mean change from baseline

Trial	Patient Population	Interventions	Inclusion Criteria	Key Outcomes
Phase II[86,87] Kim 2020, Kim 2019	N= 307 randomized, dose-ranging Adults 18 to 70 with active atopic dermatitis	Vehicle BID (n=52) Triamcinolone 0.1% BID (n=51) RUX 0.15% QD (n= 51) RUX 0.5% QD (n=51) RUX 1.5% QD (n=52) RUX 1.5 % BID (n=50) Prohibited concomitant therapy: systemic and topical treatments	• Patients aged 18–70 years with active atopic dermatitis • History of AD >2 years • IGA of 2 or 3 • BSA involvement of 3%–20%	Primary endpoint: mean percentage change from baseline EASI score at week 4 Secondary Endpoints: responder rates (IGA and EASI), itch NRS score, and safety
Crisaborole				
Phase III[95] AD 301	N=763 RCT, MC, DB, vehicle-controlled phase III studies Patients 2 and older with mild to moderate AD	Crisaborole or Vehicle cream Prohibited concomitant therapy: biologic or systemic therapy or TCS or TCI	Patients to be aged 2 years or older and have a clinical diagnosis of AD according to Hanifin and Rajka34 criteria, 5% or more treatable body surface area involvement, and a baseline Investigator's Static Global Assessment (ISGA) score of mild (2) or moderate (3) Patients were also allowed to use acceptable bland emollients to manage dry skin areas around, but not overlapping, the treatable AD-involved areas.	Primary Endpoint: success of ISGA score at 29 days Secondary endpoint: Proportion of patients with an ISGA score of clear or almost clear at 29 days, time to success in ISGA score, pruritus severity, signs of AD
Phase III[95] AD 302	N= 764 RCT, MC, DB, vehicle-controlled phase III studies Patients 2 and older with mild to moderate AD			
Phase III AD 303 Long-term safety study[90] Eichenfield 2017	Patients 2 and older with mild to moderate AD MC, OL, LTE safety study N= 517	Crisaborole Prohibited concomitant therapy: TCS or TCI	Patients eligible for AD-303 must have completed the pivotal study (AD-301, AD-302) without experiencing a crisaborole treatment-related AE or a serious AE (SAE) that precluded further treatment with crisaborole ointment; they could enroll in the extension study within 8 days of day 36 of the pivotal studies.	Safety

Trial	Patient Population	Interventions	Inclusion Criteria	Key Outcomes
Post Hoc Analyses of AD 301/302[91,93,94,96]	*Same as AD 301/302*	*Same as AD 301/302*	*Same as AD 301/302*	QoL
Phase IV CrisADe CARE 1[92] Schlessinger 2020	N= 137 MC, PK, OL, single arm Infants aged 3 <24 months with mild-to-moderate AD	Crisaborole	aged 3 to < 24 months with a diagnosis of AD per Hanifin and Rajka criteria [10], mild (2) or moderate (3) AD per ISGA [6], and a percentage of treatable body surface area (%BSA) ≥ 5, excluding the scalp.	Primary Endpoint: the incidence of TEAEs Secondary Endpoints: ISGA success, ISGA clear or almost clear at day 29, percent change in EASI, POEM

AD: atopic dermatitis, AE: adverse event, BID: twice daily, BSA: body surface area, DB: double-blind, LTE: long-term extension, MC: multicenter, N: total number, OL: open-label, PC: placebo-controlled, PK: pharmacokinetic, QD: once daily, RCT: randomized controlled trial, QoL: quality of life, RUX: ruxolitinib, SAE: serious adverse event, TCS: topical corticosteroid, TCI: topical corticoinhibitor, TEAE: treatment-emergent adverse event.

Table G1.50. Baseline Characteristics I[86-96]

Study Name	Arms	N	Age (years)		Male		White		Disease duration (years)	
			mean	SD	n	%	n	%	mean	SD
Ruxolitinib Cream										
TRuE AD 1	Vehicle cream	126	Median: 31.5	Range: 12 to 82	47	37.3	85	67.5	Median: 17.9	Range: 1.9 to 79.1
	RUX 0.75%	252	Median: 34.0	Range: 12 to 85	98	38.9	171	67.9	Median: 14.1	Range: 1.0 to 68.8
	RUX 1.5%	253	Median: 30.0	Range: 12 to 77	95	37.5	175	69.2	Median: 16.0	Range: 0 to 69.2
TRuE AD 2	Vehicle cream	124	Median: 37.5	Range: 12 to 82	44	35.5	84	67.7	Median: 15.9	Range: 0.8 to 70.7
	RUX 0.75%	248	Median: 33.0	Range: 12 to 81	98	39.5	174	70.2	Median: 15.9	Range: 0.1 to 68.6
	RUX 1.5%	246	Median: 32.0	Range: 12 to 85	96	39	178	72.4	Median: 16.6	Range: 0 to 68.8
Subgroup Analysis – Partial response	Vehicle cream	174	Median: 34.5	Range: 12 to 82	57	35.1	117	67.2	Median: 15.5	Range: 0.8 to 79.1
	RUX 0.75%	213	Median: 37.0	Range: 12 to 85	96	45.1	138	64.8	Median: 14.0	Range: 1.8 to 68.6
	RUX 1.5%	197	Median: 28.0	Range: 12 to 84	70	35.5	124	62.9	Median: 14.9	Range: 0.2 to 69.2
	Total	584	Median 33.0	Range: 12 to 85	227	38.9	379	64.9	Median: 14.9	Range: 0.2 to 79.1
Subgroup Analysis – BSA >10, EASI > 16	Vehicle cream	13	Median: 41.0	Range: 12 to 63	6	46.2	11	84.6	Median: 17.0	Range: 2.1 to 60.1
	RUX 0.75%	36	Median 45.5	Range: 12 to 75	12	33.3	27	75	Median: 18.2	Range: 1.9 to 55.8
	RUX 1.5%	32	Median: 26.5	Range: 13 to 85	15	46.9	27	84.4	Median: 18.1	Range: 1.9 to 60.1
	Total	81	Median: 34.0	Range: 12 to 85	33	40.7	65	80.2	Median: 17.0	Range: 2.1 to 60.1
Phase II Kim 2020	Vehicle cream	52	Median 31.5	Range: 18 to 69	20	38.5	27	51.9	Median: 19.5	Range: 2.2 to 65.3
	RUX 1.5%	50	Median: 35.5	Range: 18 to 70	24	52	33	66	Median: 21.2	Range: 0.1 to 64.8
	TAC 0.1%	51	Median: 35.0	Range: 18 to 69	23	45.1	28	54.9	Median: 24.8	Range: 2.3 to 62.2
	Total	307	Median: 35.0	Range: 18 to 70	139	45.3	172	56	Median: 20.8	Range: 0.1 to 66.1
Crisaborole										
AD 301	CRIS	503	12	NR	219	43.5	308	61.2	NR	NR
	Vehicle cream	256	12.4	NR	113	44.1	162	63.3	NR	NR
AD 302	CRIS	513	12.6	NR	231	45	309	60.2	NR	NR
	Vehicle cream	250	11.8	NR	112	44.8	144	57.6	NR	NR

Study Name	Arms	N	Age (years)		Male		White		Disease duration (years)	
			mean	SD	n	%	n	%	mean	SD
Post-Hoc AD 301/302	CRIS	1016	12.3	12.2	450	44.3	617	60.7	NR	NR
	Vehicle cream	506	12.1	11.7	225	44.5	306	60.5	NR	NR
AD 303	2-11 years	308	6.1	2.8	131	42.5	189	61.4	NR	NR
	12-17 years	146	14	1.5	61	41.8	94	64.4	NR	NR
	>18 years	63	34	13.4	19	30.2	32	50.8	NR	NR
	Total	517	11.7	10.4	211	40.8	315	60.9	NR	NR
CrisADe CARE 1	Non-PK	116	13.7	6.4	75	64.7	71	61.2	10.4	6.4
	PK	21	12.7	6.6	13	61.9	13	61.9	9.1	5.5
	Total	137	13.6	6.4	88	64.2	84	61.3	10.2	6.3

None of these baseline characteristics were available in the ruxolitinib pooled analysis. No trials reported on weight (kg) at baseline. CRIS: crisaborole, n: number, N: total number, NR: not reported, PK: pharmacokinetic, RUX: ruxolitinib, SD: standard deviation, TAC: triamcinolone acetonide cream, %: percent. *for these baseline data, N=250, †for these baseline data, N=500, ‡for these baseline data, N=499.

Table G1.51. Baseline Characteristics II[86-89,91-96,98-100,102]

Study Name	Arms	N	Disease Severity, n (%)						EASI score		% BSA affected	
			Mild		Moderate (3)		Severe (4)		mean	SD	mean	SD
			n	%	n	%	n	%				
Ruxolitinib Cream												
TRuE AD 1	Vehicle cream	126	31	24.6	95	75.4	NA	NA	7.4	4.3	9.2	5.1
	RUX 0.75%	252	61	24.2	191	75.8	NA	NA	8.2	4.8	9.9	5.4
	RUX 1.5%	253	60	23.7	193	76.3	NA	NA	7.9	4.6	9.3	5.2
TRuE AD 2	Vehicle cream	124	33	26.6	91	73.4	NA	NA	8.2	5.2	10.1	5.8
	RUX 0.75%	248	64	25.8	184	74.2	NA	NA	8.1	5.0	10.1	5.3
	RUX 1.5%	246	63	25.6	183	74.4	NA	NA	7.8	4.9	9.9	5.4
Subgroup analysis – Partial response	Vehicle cream	174	55	31.6	119	68.4	NA	NA	7.9	4.9	9.3	5.3
	RUX 0.75%	213	83	39	130	61	NA	NA	7.8	5.3	9.9	5.2
	RUX 1.5%	197	80	40.6	117	59.4	NA	NA	7.2	4.7	9.1	5.1
	Total	584	218	37.3	366	62.7	NA	NA	7.6	5	9.5	5.2
Subgroup analysis – BSA >10 EASI > 16	Vehicle cream	13	0	0	13	100	NA	NA	20.2	2.9	17.7	3.3
	RUX 0.75%	36	3	8.3	33	91.7	NA	NA	19.4	3.4	16.6	3
	RUX 1.5%	32	0	0	32	100	NA	NA	19.3	2.9	18	1.9
	Total	81	3	3.7	78	96.3	NA	NA	19.5	3.1	17.3	2.7
Phase II Kim 2020	Vehicle cream	52	15	28.8	36	69.2	NA	NA	8.6	5.1	9.5	5
	RUX 1.5%	50	14	28	36	72	NA	NA	8.4	4.7	10.5	5.2
	TAC 0.1%	51	18	35.3	33	64.7	NA	NA	8.4	4.7	9.9	5.5
	Total	307	95	30.9	210	68.4	NA	NA	8.4	4.7	9.6	5.4
Crisaborole												
AD 301	CRIS	503	196	39	307	61	NA	NA	NR	NR	18.8	Range: 5 to 95
	Vehicle cream	256	93	36.3	163	63.7	NA	NA	NR	NR	18.6	Range: 5 to 90
AD 302	CRIS	513	197	38.4	316	61.6	NA	NA	NR	NR	17.9	Range: 5 to 95

Study Name	Arms	N	Disease Severity, n (%)						EASI score		% BSA affected	
			Mild		Moderate (3)		Severe (4)		mean	SD	mean	SD
			n	%	n	%	n	%				
	Vehicle cream	250	100	40	150	60	NA	NA	NR	NR	17.7	Range: 5 to 90
Post-Hoc AD 301/302	CRIS	1016	393	38.7	623	61.3	NA	NA	NR	NR	18.3	18.0
	Vehicle cream	506	193	38.1	313	61.9	NA	NA	NR	NR	18.1	17.3
CrisADe CARE 1	Non-PK	116	52	44.8	64	55.2	0	0	10.4	8.2	23.5	20.1
	PK	21	0	0	20	95.2	1	4.8	19.8	4.4	53.5	12.6
	Total	137	52	38	84	61.3	1	0.7	11.8	8.4	28.1	22

None of these baseline characteristics were available in the ruxolitinib pooled analysis, Simpson 2021, and AD 303. BSA: body surface area, CRIS: crisaborole, n: number, N: total number, NA: not applicable, NR: not reported, PK: pharmacokinetic, RUX: ruxolitinib, SD: standard deviation, TAC: triamcinolone acetonide cream, %: percent. *for these baseline data, N=250, †for these baseline data, N=500, ‡for these baseline data, N=499.

Table G1.52. Baseline Characteristics III[86-96,98-100,102]

Study Name	Arms	N	Itch or PP-NRS		DLQI		POEM		CDLQI		Previous Treatments					
			mean	SD	mean	SD	mean	SD	mean	SD	Topical corticosteroids		Topical calcineurin inhibitors		Systemic steroids	
											n	%	n	%	n	%
Ruxolitinib Cream																
Week 8																
TRuE AD 1	Vehicle cream	126	5.1	2.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	RUX 0.75%	252	5.1	2.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	RUX 1.5%	253	5.2	2.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
TRuE AD 2	Vehicle cream	124	5.1	2.4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	RUX 0.75%	248	5.2	2.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	RUX 1.5%	246	4.9	2.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Simpson 2021	RUX pooled	1249	5.1	2.4	NR	NR	NR	NR	NR	NR	408*	32.7	269	21.5	218.6	17.5

Study Name	Arms	N	Itch or PP-NRS		DLQI		POEM		CDLQI		Previous Treatments					
			mean	SD	mean	SD	mean	SD	mean	SD	Topical corticosteroids		Topical calcineurin inhibitors		Systemic steroids	
											n	%	n	%	n	%
Weeks 4/8/12																
Phase II Kim 2020	Vehicle cream	52	6	2.1	NR	NR	NR	NR	NA	NA	NR	NR	NR	NR	NR	NR
	RUX 1.5%	50	5.9	2.3	NR	NR	NR	NR	NA	NA	NR	NR	NR	NR	NR	NR
	TAC 0.1%	51	5.2	2.2	NR	NR	NR	NR	NA	NA	NR	NR	NR	NR	NR	NR
	Total	307	6	2.1	NR	NR	NR	NR	NA	NA	NR	NR	NR	NR	NR	NR
Crisaborole																
Week 4/Day 29																
Post-Hoc AD 301/302	CRIS	1016	NR	NR	9.7[†¥]	6.3	NR	NR	9.3[‡§]	6.0	NR	NR	NR	NR	NR	NR
	Vehicle cream	506	NR	NR	9.3[†#]	6.6	NR	NR	9[‡**]	6.0	NR	NR	NR	NR	NR	NR
CrisADe CARE 1	Non-PK	116	NR	NR	NR	NR	13.9	5.9	NR	NR	63	54.3	2	1.7	NR	NR
	PK	21	NR	NR	NR	NR	19.7	5.2	NR	NR	9	49.2	0	0	NR	NR
	Total	137	NR	NR	NR	NR	14.8	6.1	NR	NR	72	52.6	2	1.5	NR	NR

None of these baseline characteristics were available in the ruxolitinib pooled analysis, AD 301, AD 302, and AD303. No trials reported on previous treatment use with antibiotics, crisaborole, topical agents alone, mycophenolate, cyclosporine, methotrexate, azathioprine, systemic agents, or dupilumab. Baseline data on SCORAD, PSSAD, total HADS, HADS anxiety, and HADS depression were not reported in any trials. CRIS: crisaborole, n: number, N: total number, NR: not reported, PK: pharmacokinetic, RUX: ruxolitinib, SD: standard deviation, TAC: triamcinolone acetonide cream, %: percent. *high potency topical corticosteroids, [†]population reported here is adolescents and adults ages ≥16 years, [‡]population reported here is children ages 2-15 years, [¥]N=201, [#]N=94, [§]N=815, **N=412, [††]for these baseline data, N=250, [‡‡]for these baseline data, N=500, [¥¥]for these baseline data, N=499.

Table G1.53. Efficacy Outcomes: IGA Response Rates[86-97]

Study Name	Arm	N	IGA response					
			N	n	%	Diff from PBO	95% CI	p value
Ruxolitinib Cream								
Week 8								
TRuE AD 1	Vehicle cream	126	126	20	15.1	REF	REF	REF
	RUX 0.75%	252	252	126	50.0	34.9	26.1 to 43.7	<0.0001
	RUX 1.5%	253	253	137	53.8	38.7	29.9 to 47.4	<0.0001
TRuE AD 2	Vehicle cream	124	124	10	7.6	REF	REF	REF
	RUX 0.75%	248	248	97	39.0	31.3	23.4 to 39.2	<0.0001
	RUX 1.5%	246	246	127	51.3	43.7	35.6 to 51.8	<0.0001
Subgroup analysis – partial response	Vehicle cream	174	174	75	43.1	NR	NR	REF
	RUX 0.75%	213	213	153	71.8	NR	NR	<0.0001
	RUX 1.5%	197	197	140	71.1	NR	NR	<0.0001
Subgroup analysis – BSA > 10, EASI > 16	Vehicle cream	13	13	0	0	NR	NR	NR
	RUX 0.75%	36	36	18	50	NR	NR	NR
	RUX 1.5%	32	32	19	59.4	NR	NR	NR
Week 4								
Phase II Kim 2020	Vehicle cream	52	52	4	7.7	NR	NR	REF
	TAC 0.1% BID	51	51	13	25.5	NR	NR	NS
	RUX 1.5% BID	50	50	20	38	NR	NR	<0.001
	Week 8							
	Vehicle cream	52	52	5	9.6	NR	NR	REF
	TAC 0.1% BID	40	40	8	20	NR	NR	NR
	RUX 1.5% BID	50	50	24	48	NR	NR	<0.0001
	Week 12							
	Vehicle cream	52	36	19	52.8	NR	NR	NR
	TAC 0.1% BID	39	39	26	66.7	NR	NR	NR
	RUX 1.5% BID	50	41	24	58.5	NR	NR	NR
Crisaborole								

Study Name	Arm	N	IGA response					
			N	n	%	Diff from PBO	95% CI	p value
Week 4/Day 29								
AD 301	CRIS	503	503	260	51.7	NR	NR	0.005
	Vehicle cream	256	256	104	40.6	NR	NR	REF
AD 302	CRIS	513	513	249	48.5	NR	NR	<0.001
	Vehicle cream	250	250	74	29.7	NR	NR	REF
CrisADe CARE 1	Overall population	137	129	61	47.3	NR	NR	NR

Data on IGA were not available in the Post-Hoc Analysis for AD 301/302. BID: twice daily, CI: confidence interval, CRIS: crisaborole, Diff: difference, n: number, N: total number, NR: not reported, NS: not significant, PBO: placebo, REF: reference, RUX: ruxolitinib cream, SE: standard error, TAC: triamcinolone acetonide cream, %: percent.

Table G1.54. Long term Efficacy Outcomes: IGA Response Rates[73,74]

Study Name	Arm	N	IGA response					
			N	n	%	Diff from PBO	95% CI	p value
Ruxolitinib Cream								
Week 52								
TRuE AD 1	Vehicle cream to 0.75% RUX	NR	38	29	76.3	NR	NR	NR
	Vehicle cream to 1.5% RUX	NR	38	28	73.7	NR	NR	NR
	RUX 0.75%	NR	173	133	76.9	NR	NR	NR
	RUX 1.5%	NR	171	129	75.4	NR	NR	NR
TRuE AD 2	Vehicle cream to 0.75% RUX	NR	34	27	79.4	NR	NR	NR
	Vehicle cream to 1.5% RUX	NR	43	32	74.4	NR	NR	NR
	RUX 0.75%	NR	150	115	76.7	NR	NR	NR
	RUX 1.5%	NR	171	137	80.1	NR	NR	NR
Subgroup Analysis—more severe	RUX 0.75%	39	30	20	66.7	NR	NR	NR
	RUX 1.5%	36	23	18	78.3	NR	NR	NR

There were no long-term data on IGA available in any of the crisaborole trials. CI: confidence interval, Diff: difference, n: number, N: total number, NR: not reported, PBO: placebo, REF: reference, RUX: ruxolitinib cream, %: percent.

Table G1.55. Efficacy Outcomes: EASI Response Rates[86-90,97,98,100,102]

Study Name	Arms	EASI 50		EASI 75					EASI 90	
		n/N	%	n/N	%	Diff from PBO	95% CI	p value	n/N	%
Ruxolitinib Cream										
Week 8										
TRuE AD 1	Vehicle cream	NR	NR	31/126	24.6	REF	REF	REF	12/126	9.5
	RUX 0.75%	NR	NR	142/252	56.0	31.4	21.7 to 41.1	<0.0001	96/252	38.1
	RUX 1.5%	NR	NR	158/253	62.1	37.5	27.8 to 47.1	<0.0001	112/253	44.3
TRuE AD 2	Vehicle cream	NR	NR	18/124	14.4	REF	REF	REF	5/118	4.2
	RUX 0.75%	NR	NR	128/248	51.5	37.1	28.1 to 46.2	<0.0001	81/231	35.1
	RUX 1.5%	NR	NR	153/246	61.8	47.4	38.5 to 56.4	<0.0001	99/228	43.4
Subgroup analysis – partial response	Vehicle cream	67/174	38.5	NR	NR	NR	NR	NR	NR	NR
	RUX 0.75%	136/213	63.8	NR	NR	NR	NR	NR	NR	NR
	RUX 1.5%	128/197	65	NR	NR	NR	NR	NR	NR	NR
Subgroup analysis – BSA > 10, EASI > 16	Vehicle cream	5/13	38.5	1/13	7.7	NR	NR	NR	1/13	7.7
	RUX 0.75%	29/36	80.6	27/36	75	NR	NR	NR	19/36	52.8
	RUX 1.5%	25/32	78.1	23/32	71.9	NR	NR	NR	15/32	46.9
Phase II Kim 2020	**Week 4**									
	Vehicle cream	41/52	78	9/52	17.3	NR	NR	REF	3/52	5.8
	TRI 0.1% BID	34/51	66.7	24/51	47.1	NR	NR	NR	7/51	13.7
	RUX 1.5% BID	12/50	23.1	28/50	56	48.6	NR	<0.001	13/50	26
	Week 12									
	Vehicle cream	NR	NR	NR	NR	NR	NR	NR	NR	NR
	TRI 0.1% BID	NR	NR	NR	NR	NR	NR	NR	NR	NR
	RUX 1.5% BID	37/39	95.1	22/30	73.2	NR	NR	NR	14/50	56.1

Data on EASI 50 and EASI 90 were not available in Phase II Kim 2020 at 8 weeks and crisaborole trials AD 301, AD 302, Post-Hoc AD 301/302, and CrisADe CARE 1. There were no Difference vs. placebo, 95% confidence intervals, or p-values available for EASI 50 and EASI 75 responses. BID: twice daily, CI: confidence

interval, CRIS: crisaborole, n: number, Diff: difference, N: total number, NR: not reported, NS: not significant, PBO: placebo, REF: reference, RUX: ruxolitinib, SE: standard error, TAC: Triamcinolone acetonide cream, %: percent.

Table G1.56. Efficacy Outcomes: PP-NRS Response Rates[86-89,97,100,102]

Study Name	Arms	N	Itch or PP-NRS (≥4-point improvement from baseline)					
			n/N	%	SD	Diff from PBO	95% CI	p value
Ruxolitinib Cream								
Week 8								
TRuE AD 1	Vehicle cream	126	20/126	15.4	SE: 4.1	REF	REF	REF
	RUX 0.75%	252	102/252	40.4	SE: 3.9	25	13.9 to 36.1	<0.001
	RUX 1.5%	253	133/253	52.2	SE: 3.9	36.8	25.7 to 47.9	<0.0001
TRuE AD 2	Vehicle cream	124	21/124	16.3	SE: 4.1	REF	REF	REF
	RUX 0.75%	248	106/248	42.7	SE: 4.0	26.4	15.2 to 37.6	<0.0001
	RUX 1.5%	246	125/246	50.7	SE: 4.1	34.4	23.0 to 45.9	<0.0001
Subgroup analysis – BSA > 10, EASI > 16	Vehicle cream	13	3/11	27.3	NR	NR	NR	NR
	RUX 0.75%	36	13/26	50	NR	NR	NR	NR
	RUX 1.5%	32	11/16	61.1	NR	NR	NR	NR
Phase II Kim 2020	**Week 4**							
	Vehicle cream	52	4/36	11.1*	NR	NR	NR	REF
	TAC 0.1% BID	51	6/31	19.4*	NR	NR	NR	NS
	RUX 1.5% BID	50	25/40	62.5*	NR	NR	NR	<0.001
	Week 8							
	Vehicle cream	52	5/35	14.3*	NR	NR	NR	REF
	TAC 0.1% BID	40	10/31	32.3*	NR	NR	NR	NS
	RUX 1.5% BID	50	22/38	57.9*	NR	NR	NR	<0.001

Data on PP-NRS were not available in the subgroup analysis on partial responders, Phase II Kim 2020 at 12 weeks and crisaborole trials AD 301, AD 302, Post-Hoc AD 301/302. BID: twice daily, CI: confidence interval, Diff: difference, n: number, N: total number, NR: not reported, NS: not significant, PBO: placebo, REF: reference, RUX: ruxolitinib, SD: standard deviation, SE: standard error, TAC: Triamcinolone acetonide cream, %: percent. *marked as clinically relevant improvements

Table G1.57. SCORAD[88,89]

Agent(s)		Ruxolitinib Cream		
Timepoint		Week 8		
Study Name		Pooled Analysis		
Arms		Vehicle cream	RUX 0.75%	RUX 1.5%
SCORAD	N	244	483	481
	Change from baseline	-30.4	-62.9	-67.3
	SD	NR	NR	NR
	Diff from PBO	NR	NR	NR
	95% CI	NR	NR	NR
	p value	REF	<0.0001	<0.0001

Data on SCORAD were available only in the ruxolitinib pooled analysis. CI: confidence interval, Diff: difference, N: total number, NR: not reported, PBO: placebo, REF: reference, RUX: ruxolitinib, SD: standard deviation.

Table G1.58. DLQI, CLDQI, POEM[91,92,94,96,98]

Agent(s)		Ruxolitinib Cream			Crisaborole		
Timepoint		Week 8			Week 4/Day 29		
Study Name		Pooled Analysis			Post-Hoc AD 301/302		CrisADe CARE 1
Arms		Vehicle cream	RUX 0.75%	RUX 1.5%	CRIS	Vehicle cream	Overall
DLQI	N	169	355	386	180	82	137
	Change from baseline	-3.1	-7.2	-7.1	-5.2	-3.5	NR
	SD	NR	NR	NR	NR	NR	NR
	p value	REF	<0.001	<0.001	0.015	REF	NR
CDLQI	N	27	66	53	750*	355*	NR
	Change from baseline	-2.3	-5.3	-6	-4.6	-3	NR
	SD	NR	NR	NR	NR	NR	NR
	p value	NR	NR	NR	<0.001	REF	NR
POEM	N	197	422	438	NR	NR	130
	Change from baseline	-4.2	-10.5	-11	NR	NR	-8.5
	SD	NR	NR	NR	NR	NR	0.51
	p value	REF	<0.001	<0.001	NR	NR	NR

Data on DLQI, CDLQI, and POEM were available on in Post-Hoc AD 301/302 and CrisADe CARE 1. No trials reported on HADS, HADS Anxiety or HADS Depression. CRIS: crisaborole, N: total number, NR: not reported, REF: reference, SD: standard deviation. *population reported here is children ages 2-15.

Table G1.59. Safety[85-96,98,102]

Trial	Arms	N	TEAE		Study Drug-Related AEs		D/C due to AE		Serious TEAE		Application Site Pain		Application Site Burning		Application Site Pruritus		Skin Infection	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
TRuE AD 1	**Week 8**																	
	Vehicle cream	126	44	34.9	16*	12.7	5†	4	2	1.6	NR	NR	2	1.6	2	1.6	NR	NR
	RUX 0.75%	252	74	29.4	15*	6.0	3†	1.2	1	0.4	NR	NR	0	0	2	0.8	NR	NR
	RUX 1.5%	253	73	28.9	14*	5.5	3†	1.2	2	0.8	NR	NR	2	0.8	0	0	NR	NR
TRuE AD 2	Vehicle cream	124	40	32.3	12*	9.7	3†	2.4	0	0	NR	NR	8	6.5	4	3.2	NR	NR
	RUX 0.75%	248	73	29.4	8*	3.2	1†	0.4	3	1.2	NR	NR	2	0.8	2	0.8	NR	NR
	RUX 1.5%	246	58	23.6	11*	4.5	0†	0	1	0.4	NR	NR	2	0.8	0	0	NR	NR
Subgroup – BSA > 10, EASI > 16	Vehicle cream	13	6	46.2	5	38.5	1†	7.7	1	7.7	2	15.4	NR	NR	NR	NR	NR	NR
	RUX 0.75%	36	14	38.9	1	2.8	0†	0	0	0	0	0	NR	NR	NR	NR	NR	NR
	RUX 1.5%	32	10	31.3	3	9.4	0†	0	0	0	0	0	NR	NR	NR	NR	NR	NR
Phase II Kim 2020	Vehicle cream	52	17	32.7	5*	9.6	1†	1.9	0	0	2	3.8	NR	NR	NR	NR	NR	NR
	TAC 0.1%	51	17	33.3	1*	2	1†	2	1	2	0	0	NR	NR	NR	NR	NR	NR
	RUX 1.5%	50	12	24	3*	6	0†	0	0	0	1	2	NR	NR	NR	NR	NR	NR
	Week 12																	
	Vehicle cream	41	5	12.2	0*	0	0†	0	0	0	NR	NR	NR	NR	NR	NR	NR	NR
	TAC 0.1%	40	11	227.5	0*	0	0†	0	0	0	NR	NR	NR	NR	NR	NR	NR	NR
	RUX 1.5%	43	17	39.5	0*	0	0†	0	0	0	NR	NR	NR	NR	NR	NR	NR	NR
Pooled AD 301/302	**Week 4**																	
	CRIS	1012	954	94.3	217	21.4	12	1.2	NR	NR	45	4.4	NR	NR	5	0.5	1‡	0.1
	Vehicle	499	484	96.9	79	15.8	6	1.2	NR	NR	6	1.2	NR	NR	6	1.2	5‡	1
AD 303	**Week 48**																	

Trial	Arms	N	TEAE		Study Drug-Related AEs		D/C due to AE		Serious TEAE		Application Site Pain		Application Site Burning		Application Site Pruritus		Skin Infection	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	2-11	308	NR	NR	53	10.3	9	1.7	NR	NR	6	1.9	NR	NR	1	0.3[¶]	12[¥]	3.9
	12-17	146							NR	NR	5	3.4	NR	NR	0	0[¶]	3[¥]	2.1
	>18	63							NR	NR	1	1.6	NR	NR	1	1.6[¶]	0[¥]	0
	Total	517							NR	NR	12	2.3	NR	NR	2	0.4[¶]	15	2.9
CrisADe CARE 1	**Week 8**																	
	Overall	137	88	64.2	22	16.1	4	2.9	NR	NR	5	3.6	4[#]	2.9	NR	NR	1[§]	0.7

None of these safety data were available in the ruxolitinib pooled analysis and Simpson 2021. No trials reported on safety data related to any AEs, Serious AE, MACE, venous thromboembolism, herpes infection, serious infection, malignancy, non-melanocytic skin cancer. AD301/302 and 303 reported no deaths across all arms. Only CrisADe CARE 1 reported conjunctivitis (3.6%). AE: adverse event, CRIS: crisaborole, D/C: discontinuation, n: number, N: total number, NR: not reported, RUX: ruxolitinib cream, TAC: Triamcinolone acetonide cream, TEAE: treatment-emergent adverse event, %: percent. *study drug-related TEAE, [†]discontinuation due to TEAE, [‡]staphylococcal skin infection, [¶]application site dermatitis, [¥]infections and infestations, [#]discomfort, [§]skin irritation.

Table G1.60. Long Term Safety[73,74]

Trial	Arms	N	TEAE		Study Drug-Related AEs		D/C due to AE		Serious TEAE		Application Site Pain		Application Site Burning		Application Site Pruritus	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%
Week 52																
TRuE AD 1	Vehicle cream to 0.75% RUX	101	54	53.5	2	2	0	0	5	5	NR	NR	101	54	53.5	2
	Vehicle cream to 1.5% RUX	99	57	57.6	6	6.1	0	0	1	1	NR	NR	99	57	57.6	6
	RUX 0.75%	426	256	60.1	20	4.7	9	2.1	10	2.3	NR	NR	426	256	60.1	20
	RUX 1.5%	446	240	53.8	13	2.9	0	0	6	1.3	NR	NR	446	240	53.8	13
TRuE AD 2	Vehicle cream to 0.75% RUX	39	28	71.8	6	15.4	0	0	1	2.6	1	2.6	39	28	71.8	6
	Vehicle cream to 1.5% RUX	36	24	66.7	6	16.7	0	0	1	2.8	2	5.6	36	24	66.7	6
	RUX 0.75%	101	54	53.5	2	2	0	0	5	5	NR	NR	101	54	53.5	2
	RUX 1.5%	99	57	57.6	6	6.1	0	0	1	1	NR	NR	99	57	57.6	6
	RUX 0.75%	426	256	60.1	20	4.7	9	2.1	10	2.3	NR	NR	426	256	60.1	20
Subgroup Analysis—more severe	RUX 0.75%	446	240	53.8	13	2.9	0	0	6	1.3	NR	NR	446	240	53.8	13
	RUX 1.5%	39	28	71.8	6	15.4	0	0	1	2.6	1	2.6	39	28	71.8	6

No trials reported on safety data related to any AEs, Serious AE, MACE, venous thromboembolism, herpes infection, serious infection, malignancy, non-melanocytic skin cancer. D/C: discontinuation, n: number, N: total number, NR: not reported, RUX: ruxolitinib cream, TEAE: treatment-emergent adverse event, %: percent

Table G1.61. Efficacy Outcomes by Subgroup: IGA[101,103]

Study	Arm	Category	N	IGA response					
				n	N	%	Diff from PBO	95% CI	p value
Ruxolitinib									
Pooled Analysis	Vehicle cream	Ages 12 to 17	250	6	43	14	NR	NR	NR
	RUX 0.75%		500	50	106	47.2	NR	NR	NR
	RUX 1.5%		499	44	87	50.6	NR	NR	NR
	Vehicle cream	Ages 18 to 64	250	18	175	10.3	NR	NR	NR
	RUX 0.75%		500	150	327	45.9	NR	NR	NR
	RUX 1.5%		499	186	356	52.2	NR	NR	NR
	Vehicle cream	>65	250	4	26	15.4	NR	NR	NR
	RUX 0.75%		500	16	50	32	NR	NR	NR
	RUX 1.5%		499	23	38	60.5	NR	NR	NR
	Vehicle cream	IGA 2	250	1	64	1.6	NR	NR	NR
	RUX 0.75%		500	24	125	19.2	NR	NR	NR
	RUX 1.5%		499	31	123	25.2	NR	NR	NR
	Vehicle cream	IGA 3	250	27	180	15	NR	NR	NR
	RUX 0.75%		500	192	358	53.6	NR	NR	NR
	RUX 1.5%		499	222	358	62	NR	NR	NR
Crisaborole									
Yosipovitch 2018	CRIS	Mild	1016	NR	NR	71.4	NR	NR	0.0024
		Moderate		NR	NR	36.7	NR	NR	<0.001
	Vehicle cream	Mild	506	NR	NR	56.7	NR	REF	NR
		Moderate		NR	NR	22.3	NR	REF	NR
	CRIS	2 to <7	506	NR	NR	30.5	NR	NR	0.064
		7 to <12	436	NR	NR	36.6	NR	NR	0.0037
		12 to <18	371	NR	NR	30.3	NR	NR	0.026
		18+	209	NR	NR	29.7	NR	NR	0.46
	Vehicle cream	2 to <7	506	NR	NR	21.8	NR	NR	REF
		2 to <12	436	NR	NR	22.9	NR	NR	REF
		12 to <18	371	NR	NR	19.4	NR	NR	REF
		18+	209	NR	NR	24.7	NR	NR	REF
Eichenfield 2020 (ages 2-17)	CRIS	Mild	874	NR	NR	72.3	NR	NR	<0.05
		Moderate		NR	NR	37.1	NR	NR	REF
	Vehicle cream	Mild	439	NR	NR	55.9	NR	NR	<0.0001
		Moderate		NR	NR	21.4	NR	NR	REF

CI: confidence interval, CRIS: crisaborole, Diff: difference, n: number, N: total number, NR: not reported, PBO: placebo, REF: reference, RUX: ruxolitinib, %: percent.

Table G1.62. Efficacy Outcomes by Subgroup: EASI 50[101,103]

Study	Arm	Category	N	EASI 50					
				n	N	%	Diff from PBO	95% CI	p value
Ruxolitinib									
Pooled Analysis	Vehicle cream	Ages 12 to 17	250	21	43	48.8	NR	NR	NR
	RUX 0.75%		500	79	106	74.5	NR	NR	NR
	RUX 1.5%		499	73	87	83.9	NR	NR	NR
	Vehicle cream	Ages 18 to 64	250	64	175	36.6	NR	NR	NR
	RUX 0.75%		500	239	327	73.1	NR	NR	NR
	RUX 1.5%		499	274	356	77	NR	NR	NR
	Vehicle cream	>65	250	10	26	38.5	NR	NR	NR
	RUX 0.75%		500	32	50	64	NR	NR	NR
	RUX 1.5%		499	32	38	84.2	NR	NR	NR
	Vehicle cream	IGA 2	250	27	64	42.2	NR	NR	NR
	RUX 0.75%		500	81	125	64.8	NR	NR	NR
	RUX 1.5%		499	88	123	71.5	NR	NR	NR
	Vehicle cream	IGA 3	250	68	180	37.8	NR	NR	NR
	RUX 0.75%		500	269	358	75.1	NR	NR	NR
	RUX 1.5%		499	291	358	81.3	NR	NR	NR

Subgroup data on this outcome were not available in any of the crisaborole trials. CI: confidence interval, Diff: difference, n: number, N: total number, NR: not reported, PBO: placebo, RUX: ruxolitinib, %: percent.

Table G1.63. Efficacy Outcomes by Subgroup: EASI 75 and EASI 90[101,103]

Study name	Arm	Category	N	EASI 75				EASI 90			
				n	N	%	p value	n	N	%	p value
Ruxolitinib											
Pooled Analysis	Vehicle cream	Ages 12 to 17	250	15	43	34.9	NR	3	43	7	NR
	RUX 0.75%		500	58	106	54.7	NR	44	106	41.5	NR
	RUX 1.5%		499	53	87	60.9	NR	34	87	39.1	NR
	Vehicle cream	Ages 18 to 64	250	29	175	16.6	NR	13	175	7.4	NR
	RUX 0.75%		500	180	327	55	NR	120	327	36.7	NR
	RUX 1.5%		499	217	356	61	NR	158	356	44.4	NR
	Vehicle cream	>65	250	4	26	15.4	NR	1	26	3.8	NR
	RUX 0.75%		500	22	50	44	NR	13	50	26	NR
	RUX 1.5%		499	28	38	73.7	NR	19	38	50	NR
	Vehicle cream	IGA 2	250	11	64	17.2	NR	7	64	10.9	NR
	RUX 0.75%		500	57	125	45.6	NR	36	125	28.8	NR
	RUX 1.5%		499	61	123	49.6	NR	41	123	33.3	NR
	Vehicle cream	IGA 3	250	37	180	20.6	NR	10	180	5.6	NR
	RUX 0.75%		500	203	358	56.7	NR	141	358	39.4	NR
	RUX 1.5%		499	237	358	66.2	NR	170	358	47.5	NR

Subgroup data on these outcomes were not available in any of the crisaborole trials. There were no Difference vs. placebo or 95% confidence intervals available for EASI 75 or EASI 90. n: number, N: total number, NR: not reported, RUX: ruxolitinib, %: percent.

Table G1.64. Efficacy Outcomes by Subgroup: PP-NRS ≥4[101,103]

Study	Arm	Category	N	Itch or PP-NRS (≥4-point improvement from baseline)					
				n	N	%	Change from baseline	SD	p value
Ruxolitinib									
Pooled Analysis	Vehicle cream	Ages 12 to 17	250	4	23	17.4	NR	NR	NR
	RUX 0.75%		500	24	58	41.4	NR	NR	NR
	RUX 1.5%		499	25	48	52.1	NR	NR	NR
	Vehicle cream	Ages 18 to 64	250	18	118	15.3	NR	NR	NR
	RUX 0.75%		500	93	219	42.5	NR	NR	NR
	RUX 1.5%		499	119	233	51.1	NR	NR	NR
	Vehicle cream	>65	250	3	17	17.6	NR	NR	NR
	RUX 0.75%		500	13	36	36.1	NR	NR	NR
	RUX 1.5%		499	14	26	53.8	NR	NR	NR
	Vehicle cream	IGA 2	250	4	38	10.5	NR	NR	NR
	RUX 0.75%		500	17	70	24.3	NR	NR	NR
	RUX 1.5%		499	32	75	42.7	NR	NR	NR
	Vehicle cream	IGA 3	250	21	120	17.5	NR	NR	NR
	RUX 0.75%		500	113	243	46.5	NR	NR	NR
	RUX 1.5%		499	126	232	54.3	NR	NR	NR
Crisaborole									
Yosipovitch 2018	CRIS	Mild	1016	NR	209	70.2	NR	NR	0.05
		Moderate		NR	385	53.8	NR	NR	0.01
	Vehicle cream	Mild	506	NR	105	58.1	NR	NR	REF
		Moderate		NR	188	39.1	NR	NR	REF

CRIS: crisaborole, n: number, N: total number, NR: not reported, RUX: ruxolitinib, SD: standard deviation, %: percent.

H. Public Comments

This section includes summaries of the public comments prepared for the New England CEPAC Public Meeting on July 23, 2021. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. One speaker did not submit a summary of their public comments.

A video recording of all comments can be found here. Conflict of interest disclosures are included at the bottom of each statement for each speaker.

Andrew J. Thorpe, PhD, Pfizer Inc.
Senior Medical Director, US Dermatology Team Leader
North America Medical Affairs, Inflammation, and Immunology

Pfizer would like to acknowledge the ICER staff and consultants, and the numerous stakeholders who have contributed to the review of "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis (AD)."

Pfizer is dedicated to the development of breakthrough therapies that change patients' lives, including those living with AD. Abrocitinib is an oral, once-daily, small molecule that selectively inhibits JAK 1 and is under investigation for the treatment of moderate-to-severe AD. Over the course of our work, we have heard directly from patients, families, advocacy groups and healthcare providers about the profound clinical, humanistic, and economic impact of AD. We have incorporated these perspectives into our activities, particularly in selecting trial outcomes that are meaningful to patients.

Pfizer has announced positive results from our phase 2 and 3 clinical trial program, where abrocitinib has demonstrated significant improvements in AD measures, including rapid itch relief (for example, within 2 days for some patients as seen in pooled monotherapy studies[1]), with a consistent safety and tolerability profile. In addition to the four trials included in ICER's network meta-analyses, we have also reported positive results from our adolescent phase 3 study (NCT03796676) and results from a responder-enriched, randomized withdrawal study (NCT03627767). We believe this body of evidence, inclusive of 20 distinct patient reported outcomes, coupled with longer-term safety data beyond 48 weeks, demonstrates the holistic value of abrocitinib and a favorable risk-benefit profile for patients who suffer from moderate-to-severe AD.

We appreciate that ICER has addressed many of the points Pfizer raised throughout the review process and highlight below elements of our recommended elevation of abrocitinib's Evidence Rating.

1. When considering the comparison of abrocitinib with standard of care, defined as "topical emollients," Pfizer recommends a change from "P/I" to B+, an "incremental or better" rating.

    - Our monotherapy studies[2-5] demonstrated abrocitinib's significant improvement across IGA, EASI, itch and additional validated patient-reported outcomes compared with placebo. The monotherapy trials permitted the use of topical non-medicated emollients.

    - Confirming ICER's network meta-analysis, a recently published and peer-reviewed network meta-analysis by Silverberg and colleagues[6] showed that abrocitinib was estimated to have a greater than 98% probability of superiority over placebo with respect to IGA and itch response.

2. When considering the Evidence Rating of abrocitinib compared with dupilumab, we recommend an elevation from "I" to B+, an "incremental or better" rating.
    - In the JADE (JAK1 Atopic Dermatitis Efficacy and Safety) COMPARE phase 3 clinical trial (NCT03720470)[7], when compared to dupilumab, statistical superiority of abrocitinib 200 mg, and numerically higher response of abrocitinib 100 mg was achieved on the key secondary itch response at week 2.
    - In addition to patient-centered trial endpoints, patient preference is an important consideration not traditionally captured in network meta-analyses or economic models. A recently published patient preference study of systemic AD treatment attributes among 320 moderate-to-severe AD patients found that patients significantly preferred an oral daily administration over a biweekly subcutaneous injection and also preferred treatments with rapid onset of itch relief.[8] We believe both of these characteristics of abrocitinib should be considered as part of the net health benefit rating compared with dupilumab.

3. ICER explained that a primary reason for not elevating abrocitinib's current Ratings centers around existing boxed warnings for oral JAK inhibitors for other indications. We fully recognize that safety is a critical consideration and component of a treatment's risk-benefit profile and ICER's Evidence Rating. The continuous assessment and reporting of the safety profile of our medicines is a priority and abrocitinib's long-term extension study, whose primary endpoint is safety, is ongoing. We are confident in the benefit-risk profile of abrocitinib as a treatment for moderate-to-severe atopic dermatitis.

In summary, Pfizer respectfully believes that the Evidence Rating of abrocitinib compared to standard of care and to dupilumab merits elevation as supported by the points highlighted here and in our prior Public Comments to ICER's Draft Evidence Report, posted on July 9, 2021.

Though we have some remaining concerns with the assessment, we acknowledge the efforts to seek and incorporate input from diverse stakeholders, especially considering a number of investigational agents are under active regulatory review. We believe that methods assessing the value of medicines

should continue improving, especially in their ability to capture patient-centered outcomes and preferences. Pfizer is dedicated to advancing such methodologies and is committed to working with stakeholders to identify solutions for creating a more effective, efficient, and equitable health care system for patients.

Dr. Thorpe is a full-time employee of Pfizer.

Meghan Feely, MD, FAAD, Eli Lilly
Senior Medical Advisor, U.S. Medical Affairs, Bio-Medicines

Today, most patients with moderate-to-severe AD live a life of compromise, where topical therapies are no longer able to manage their AD. In patients with moderate-to-severe AD, a review of existing treatment patterns indicate that the use of topical regimens is followed by an inadequate response, leading to the use of short-term systemic therapies to attempt to control patients' worsening symptoms, but without achieving good disease control. After completion of short courses of conventional immunosuppressants or systemic corticosteroids, topical regimens are then resumed. This cycle fails to provide appropriate management of symptoms, but still few patients advance in their care to using dupilumab. Dupilumab is presently the only novel systemic agent approved for the treatment moderate-to-severe AD.[1] There is a significant unmet need in AD for moderate-to-severe patients who are failing topical treatments, but who are not willing to commit to indefinite treatment with an injectable biologic.

At this time, baricitinib is not FDA approved for the treatment of moderate-to-severe atopic dermatitis, though discussions with the FDA are ongoing. Lilly believes that Olumiant (baricitinib) is uniquely placed to serve patients with moderate-to-severe AD where short-term systemics and topical regimens are inadequately controlling disease, adding an additional treatment option for patients suffering from moderate-to-severe atopic dermatitis.

The BREEZE-AD5 clinical trial of baricitinib 2 mg in moderate-to-severe atopic dermatitis is a North American study that best represents the US population of patients impacted by this disease.[2] In this trial, baricitinib 2 mg met the primary endpoint with 30% of patients with moderate-to-severe atopic dermatitis achieving at least a 75% or greater change from baseline in their Eczema Area and Severity Index (EASI) at week 16 compared to 8% of those taking placebo ($P < .001$ for 2 mg vs. placebo).[2] In addition, adults with moderate-to-severe atopic dermatitis receiving baricitinib 2 mg monotherapy experienced improvements in skin inflammation, skin pain, itch, sleep disturbance due to itch and quality of life versus placebo-treated patients.[2]

The safety profile in BREEZE-AD5 was consistent with the known safety findings of baricitinib in atopic dermatitis across the BREEZE-AD clinical trial program. The most common treatment-emergent adverse events included upper respiratory tract infections, nasopharyngitis, and diarrhea. No venous thromboembolic events or deaths were reported in the trial.[2] The drug was generally well tolerated with low rates of nausea (2.3%, adjusted percentage) and diarrhea (2.0%, adjusted percentage) reported in the 16-week placebo-controlled period across BREEZE-AD1 through BREEZE-AD6.[3] Lilly submitted data on the lowest efficacious dose of baricitinib in atopic dermatitis to the FDA at 2 mg.[2, 4-6]

We remain confident in the positive benefit-risk profile of Olumiant in this supplemental New Drug Application for the AD population and are committed to continuing to investigate its potential across the different indications being studied. There are more than 13,000 patient years and more than 8.4 years of exposure to Olumiant in rheumatoid arthritis clinical trials with no new safety concerns identified. We have ongoing Phase 3 programs in AD, alopecia areata, systemic lupus erythematosus and COVID-19 and have just recently published pooled safety data from eight clinical trials in AD collected for 2,531 patients who were given baricitinib for 2,247 patient-years (median duration 310 days). Lilly is committed to transparency about the clinical profile of baricitinib 2 mg in patients with moderate-to-severe AD, including its safety and tolerability.

Atopic Dermatitis is a heterogenous disease. As such, Dermatologists need more options available to connect the appropriate treatment to the appropriate patient. With so few treatments approved, there is room for more treatment options to help patients with a range of AD symptoms. ICER's assessment of potential novel treatment options for patients with moderate-to-severe AD has shed light on the variety of mechanisms and delivery systems that may soon be available with varying benefit and risk profiles. Lilly encourages ICER to acknowledge the need for treatment options for patients with atopic dermatitis in their final report for this disease state. Similarly, Lilly encourages ICER to recognize the clinical, economic, patient access, and equity implications of tactics such as non-evidence-based step therapy restrictions and rebate walls. It is essential for patients with atopic dermatitis to have access to a range of treatment options that best reflect the complex nature of their disease state, response to treatment, tolerance of side effects, and individual quality of life considerations.[7]

Dr. Feely is a full-time employee of Eli Lilly.

Kyle Hvidsten, MPH, Sanofi
Vice President, Head of Global Health Economics and Value Assessment

Good morning to our colleagues from ICER and members of the CEPAC. My name is Kyle Hvidsten and I am the Head of the Sanofi Genzyme Health Economics and Value Assessment Group. I am joined by my colleague Dr Ana Rossi who is a Dermatologist and a member of the Sanofi Genzyme Medical Organization. We are both pleased to participate in today's discussion.

We first engaged with ICER in 2017 during their review of dupilumab for moderate to severe atopic dermatitis (AD). At that time, ICER established a range of value-based prices. Independently of this process, Sanofi Genzyme, in collaboration with Regeneron, and taking into consideration patient needs, determined dupilumab's price according to Sanofi's Pricing Policy; the resulting price happened to fall within ICER's range.

I'd like to note that a company's pricing decision rarely aligns so well with ICER's recommendation. We feel that this demonstrates how we follow our stated principles for responsible pricing and our commitment to achieving affordable access for patients who need our medicines. Dupilumab's price was viewed by some analysts as "lower than it should have been" based on its transformative value.

Despite how well dupilumab's price aligned with ICER's recommendation, our discussions with payers have been dominated by rebates. This situation, which continues to exist, is based on a set of mixed incentives where companies are encouraged to set prices to enable substantial rebates. As stated in our Policy, we establish a clear rationale for our launch prices that includes a holistic assessment of our medicine's value and affordable access for patients.

Since dupilumab's launch we have only made modest and predictable price increases in line with our Policy. This is reflected in the fact that dupilumab, or any other Sanofi medicine, has never been included in ICER's annual list of products that have taken "unsubstantiated price increases."

ICER's 2017 review noted several important questions that could not be answered at that time. Recognizing that managing AD requires long-term treatment, we shared ICER's desire to learn more about this important medicine and initiated many studies to understand the difference it is making in the lives of patients. This included several independent registries and the largest pediatric registry in moderate to severe AD.

Our evaluation of long-term data has established that dupilumab is not an immunosuppressant. Pooled results of clinical trials including adults, adolescents and children have demonstrated that patients treated with dupilumab have lower rates of infections, serious infections, and herpetic infections compared to placebo. Dupilumab is also associated with reduced rates and duration of "all cause" and "AD-related" hospitalizations.

Additionally, a three-year open label extension study demonstrated dupilumab's favorable safety and sustained efficacy. Safety data from this study were consistent with one-year trials and the rate of infections at three years was even lower than at one year. Furthermore, the signs and symptoms of AD showed sustained improvements over three years.

As we all know, no medicine will help patients suffering from a chronic condition like AD if they do not take it consistently. Analyses of healthcare data have shown a very high rate of persistency with dupilumab over twelve months and an independent registry showed dupilumab's persistency to be over 80% after 2 years of treatment. We are encouraged by these findings as they suggest that patients who persist are probably receiving meaningful value from their treatment and thereby managing their chronic disease.

We appreciate that ICER has taken a holistic approach to its comparison of clinical effectiveness where all forms of evidence were considered. Dupilumab is the only systemic therapy with established long-term safety and effectiveness data. We appreciate how ICER acknowledged that unanswered questions from the 2017 review have been addressed with long-term evidence.

Thank you again for the opportunity to participate in today's meeting and in the important process that began last December. Both Dr Rossi and I look forward to answering your questions.

Kyle is a full-time employee of Sanofi.

Ahmad Naim, MD, Incyte
Vice President, Medical Affairs

As the manufacturer of ruxolitinib cream, Incyte Corporation appreciated the opportunity to provide oral comment at the public meeting held on July 23, 2021.

We are summarizing our oral statements and sharing our feedback on ICER's comparative clinical evaluation and assessment of ruxolitinib cream vs emollients in mild to moderate atopic dermatitis.

TrueAD 1 and 2 (Phase 3) studies of ruxolitinib cream were designed with input from clinical experts to reflect real world clinical management of AD patients. Over 90% of patients enrolled had prior experience with AD topical and/or systemic treatment and were inadequately controlled at the time of enrollment. Results from these Phase 3 studies have demonstrated superior clinical efficacy compared to vehicle (topical emollients):

- Significantly more patients treated with either ruxolitinib cream regimen achieved the primary endpoint of Investigator Global Assessment (IGA) treatment success at week 8 (44.7% and 52.6% for 0.75% and 1.5% ruxolitinib cream, respectively) versus vehicle (11.5%; all $p < 0.0001$).

- Eczema Area and Severity Index (EASI) 75 (75% improvement in EASI score from baseline) at week 8 was achieved by 53.8% and 62.0% of patients who applied 0.75% ruxolitinib cream and 1.5% ruxolitinib cream, respectively, versus 19.7% on vehicle (all $p < 0.0001$).

- Statistically significant itch reduction was observed within approximately 12 hours of first ruxolitinib cream application (mean change from baseline: –0.4 and –0.5 for 0.75% ruxolitinib and 1.5% ruxolitinib) versus vehicle (–0.1; all $p < 0.02$). At week 8, more patients who applied ruxolitinib cream achieved a four-point improvement from baseline on the Itch Numeric Rating Scale (Itch NRS4) (41.5% and 51.5% for 0.75% ruxolitinib cream and 1.5% ruxolitinib cream, respectively) versus vehicle (15.8%; all $p < 0.0001$).

- Ruxolitinib cream was well-tolerated as demonstrated with <1% of patients reporting application site burning and less than 5% reporting TEAEs.

- No adverse events indicative of systemic activity of ruxolitinib cream were observed and no ruxolitinib cream-related serious adverse events were reported.

Ruxolitinib cream was purposefully designed to be a topical JAK inhibitor from its inception, acting locally to reduce systemic absorption. Published pharmacokinetics of Phase 3 studies have shown that plasma ruxolitinib concentrations after treatment with topical ruxolitinib cream (mean bioavailability of 6.2-7.7%) is not expected to lead to systemic plasma concentrations that may be

associated with adverse effects commonly associated with oral JAK inhibitors. The AE profile observed in Phase 3 studies were consistent with negligible systemic absorption.

In June 2021, the Food and Drug Administration (FDA) extended its review of ruxolitinib cream to allow time to review additional analyses of previously submitted data. Ruxolitinib cream was well tolerated in clinical trials. Specifically, clinically meaningful trends in hematologic parameters were not observed.

Based on the aforementioned results and characteristics, we request ICER consider ruxolitinib cream as a novel topical JAK inhibitor and review it separately from oral JAK inhibitors.

We believe ruxolitinib cream provides a beneficial treatment option for patients suffering from mild to moderate atopic dermatitis. In closing, ruxolitinib cream has demonstrated superior evidence against topical emollients with high certainty of substantial net health benefit.

Dr. Naim is a full-time employee of Incyte.

I. Conflict of Interest Disclosures

Tables I1 through I3 contain conflict of interest (COI) disclosures for all participants at the July 23, 2021, Public meeting of the New England CEPAC.

Table I1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants	
Foluso Agboola, MBBS, MPH, Vice President of Research, ICER*	**Serina Herron-Smith**, BA, Senior Research Assistant, Evidence Synthesis, ICER*
Steven J. Atlas, MD, MPH, Associate Professor of Medicine, Harvard Medical School, Director, Practice Based Research & Quality Improvement, Division of General Internal Medicine, MGH*	**Maggie Houle**, BS, Program and Event Coordinator, ICER*
Elizabeth Brouwer, PhD, MPH, Research Scientist, The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute, Department of Pharmacy, University of Washington*	**Emily Nhan,** BA, Research Assistant, ICER*
Jon D. Campbell, PhD, MS, Senior Vice President for Health Economics, ICER*	**Steven D. Pearson,** MD, MSc, President, ICER*
Josh J. Carlson, PhD, MPH, Associate Professor, The CHOICE Institute, Department of Pharmacy, University of Washington*	**David M. Rind,** MD, MSc, Chief Medical Officer, ICER*
Yilin Chen, MPH, PhD Student, The CHOICE Institute, Department of Pharmacy, University of Washington*	**Liis Shea**, MA, Program Director, ICER*
Ryan N. Hansen, PharmD, PhD, Associate Professor, The CHOICE Institute, Department of Pharmacy, University of Washington*	

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Table I2. New England CEPAC Panel Member Participants and COI Disclosures

Participating Members of CEPAC	
Robert Aseltine, PhD, Professor and Chair, Division of Behavioral Sciences and Community Health, UCONN Health*	**Kimberly Lenz**, PharmD, FAMCP, Director of Clinical and Operational Pharmacy, University of Massachusetts Medical School*
Kelly Buckland, MS, Executive Director, National Council on Independent Living*	**Greg Low**, RPh, PhD, Director, MGPA Pharmacy Quality and Utilization Program, Massachusetts General Hospital*
Austin Frakt, PhD, Director, Partnered Evidence-Based Policy Resource Center, VA Boston Healthcare System*	**Eleftherios Mylonakis,** MD, PhD, FIDSA, Professor of Infectious Disease, Chief of Infectious Disease, Brown University*
Christopher Jones, PhD, MSc, Director, Ventures Investments, UVM Health Network*	**Leslie Ochs,** PharmD, PhD, MSPH, Associate Professor and Department Chair, University of New England School of Pharmacy*
Rebecca Kirch, JD, Executive Vice President of Policy and programs, National Patient Advocate Foundation*	**Jeanne Ryer,** MSc, EdD, Director, NH Citizens Health Initiative*
Stephen Kogut, PhD, MBA, RPh, Professor, University of Rhode Island College of Pharmacy*	**Jason L. Schwartz,** PhD, Associate Professor of Health Policy, Yale School of Public Health*
Donald M. Kreis, MS, JD, Consumer Advocate, New Hampshire Office of the Consumer Advocate*	**Jason Wasfy**, MD, MPhil, Medical Director, Mass General Physician's Organization[†]
Tara Lavelle, PhD, Assistant Professor, Tufts Medical Center*	**Albert Whitaker,** MA, MPH, Director of Community Impact, American Heart Association*

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

[†]Dr. Wasfy did not participate as a voting member of the New England CEPAC during this meeting.

Table I3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Samantha Bittner, Patient Ambassador, National Eczema Association	No financial conflicts to disclose.
Thomas Brownlie, MS, Senior Director, Pfizer Inc.	Thomas is a full-time employee of Pfizer Inc.
Jeffrey Casberg, MS, RPh, Vice President of Pharmacy, IPD Analytics	Jeffrey is a full-time employee of IPD Analytics.
Michele Guadalupe, MPH, Associate Director of Advocacy and Access, National Eczema Association	The National Eczema Association has received grants and sponsorship awards from a variety of industry partners, including Pfizer, AbbVie, Sanofi, Regeneron, Incyte, and LEO Pharma.
Catherine Herren, PharmD, MS, Advisor, Value Development, Eli Lilly, and Company	Dr. Catherine Herren is a full-time employee of Eli Lilly and Company.
Kyle Hvidsten, MPH, Vice President, Head of Global Health Economics and Value Assessment, Sanofi	Kyle is a full-time employee of Sanofi.
Erik Schindler, PharmD, Director, Emerging Therapeutics and Outcome-Based Contracting, UnitedHealthcare Pharmacy	Dr. Erik Schindler is a full-time employee of UnitedHealthcare Pharmacy.
Elaine Siegfried, MD, Professor of Pediatrics and Dermatology, Saint Louis University School of Medicine	Dr. Elaine Siegfried has received consulting fees and honoraria from industry partners, including Incyte, Regeneron, Sanofi, LEO Pharma, Pfizer, and AbbVie for participation in clinical trials as a PI. She also received funding from Pfizer to support a two-year fellowship position at Saint Louis University.
Jonathan Silverberg, MD, PhD, MPH, Associate Professor, George Washington University School of Medicine and Health Sciences	Dr. Jonathan Silverberg has received funding from industry partners, including AbbVie, Eli Lilly, Incyte, LEO Pharma, Regeneron, and Sanofi.

References

1. Sherry H Yu HA, Phyllis Zee, Jonathan I Silverberg. . Burden of Sleep and Fatigue in US Adults With Atopic Dermatitis. *Dermatitis.* 2016;27(2):50-58.
2. Ramirez FD CS, Langan SM, Prather AA, McCulloch CE, Kidd SA, Cabana MD, Chren MM, Abuabara K. Association of Atopic Dermatitis With Sleep Quality in Children. *JAMA Pediatr.* 2019;173(5)::e190025.
3. Silverberg J. Comorbidities and the impact of atopic dermatitis. *Ann Allergy Asthma Immunol.* 2019;123(2):144-151.
4. Holm JG AT, Clausen ML, Thomsen SF. Quality of life and disease severity in patients with atopic dermatitis. *J Eur Acad Dermatol Venereol.* 2016;30(10):1760-1767.
5. Eckert L GS, Amand C, Gadkari A, Mahajan P, Gelfand JM. Impact of atopic dermatitis on health-related quality of life and productivity in adults in the United States: An analysis using the National Health and Wellness Survey. *J Am Acad Dermatol.* 2017;77(2):274-279.
6. Ramirez FD CS, Langan SM, Prather AA, McCulloch CE, Kidd SA, Cabana MD, Chren MM, Abuabara K. Assessment of Sleep Disturbances and Exhaustion in Mothers of Children With Atopic Dermatitis. *JAMA Dermatol.* 2019;155(5):556-563.
7. Shaw TE CG, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermtol.* 2010;131(1):67-73.
8. McKenzie C SJ. The prevalence and persistence of atopic dermatitis in urban United States children. *Ann Allergy Asthma Immunol.* 2019;123(2):173-178.e171.
9. Silverberg JI HJ. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol.* 2013;132(5):1132-1138.
10. Silverberg JI GN, Paller AS, Fishbein AB, Zee PC. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. *J Invest Dermatol.* 2014;135(1):56-66.
11. D.R. Bickers HWL, D. Margolis, et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol.* 2006;55:490-500.
12. Drucker AM WA, Li WQ, Sevetson E, Block JK, Qureshi AA. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. *J Invest Dermatol.* 2017;137(1):26-30.
13. Brennan Z. Series of JAK inhibitor delays may signal an upcoming FDA adcomm. *Endpoints News.* 2021.
14. LeoPharma. Update on U.S. FDA review of LEO Pharma's Biologics License Application for tralokinumab for the treatment of adults with moderate-to-severe atopic dermatitis. 2021.
15. Incyte Announces U.S. FDA Has Extended the New Drug Application Review Period for Ruxolitinib Cream for the Treatment of Atopic Dermatitis [press release]. Business Wire2021.
16. Beck LT, D. Deleuran, M. Blauvelt, A. Bissonnette, R. de Bruin-Weller, M. Hide, M. Sher, L. Hussain, I. Chen, Z. Khokhar, FA. Beazley, B. Ruddy, M. Patel, N. Graham, NMH. Ardeleanu, M. Shumel. Dupilumab Provides Favorable Safety and Sustained Efficacy for up to 3 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. *American Journal of Clinical Dermatology* 2020.

17. Cheng B, Silverberg, JI. Association of pediatric atopic dermatitis and psoriasis with school absenteeism and parental work absenteeism: A cross-sectional United States population-based study. *Journal of the American Academy of Dermatology.* 2021.
18. Boguniewicz M LD. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. *Immunol Rev.* 2011;242(1):233-246.
19. Guttman-Yassky E WA, Ahluwalia J,Ong PY, Eichenfield LF. . Atopic dermatitis: pathogenesis. *Semin Cutan Med Surg.* 2017;36(3):100-103.
20. Silverberg JI SE. Associations of childhood eczema severity: a US population-based study. *Dermatitis.* 2014;25(3):107-114.
21. Mortz CG AK, Dellgren C, Barington T, Bindslev-Jensen C. Atopic dermatitis from adolescence to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. *Allergy.* 2015;70(7):836-845.
22. Silverberg JI MD, Boguniewicz M, Fonacier L, Grayson MH, Ong PY, Chiesa Fuxench ZC, Simpson EL, Gelfand JM. . Distribution of atopic dermatitis lesions in United States adults. *J Eur Acad Dermatol Venereol.* 2019;33(7):1341-1348.
23. Ballardini N KI, Söderhäll C, Lilja G, Wickman M, Wahlgren CF. Eczema severity in preadolescent children and its relation to sex, filaggrin mutations, asthma, rhinitis, aggravating factors and topical treatment: a report from the BAMSE birth cohort. *Br J Dermatol.* 2013;168(3):588-594.
24. Simpson EL ea. Association of Inadequately Controlled Disease and Disease Severity With Patient-Reported Disease Burden in Adults With Atopic Dermatitis. *JAMA Dermatol.* 2018.
25. Jr. ABF. Atopic dermatitis: the relationship to temperature and seasonality in the United States. *International Journal of Dermatology.* 2019.
26. Weidinger S, Novak N. Atopic dermatitis. *Lancet (London, England).* 2016;387(10023):1109-1122.
27. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol.* 2014;71(2):327-349.
28. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol.* 2014;71(1):116-132.
29. Gooderham MJ, Hong HC, Eshtiaghi P, Papp KA. Dupilumab: A review of its use in the treatment of atopic dermatitis. *J Am Acad Dermatol.* 2018;78(3 Suppl 1):S28-s36.
30. Moyle M, Cevikbas F, Harden JL, Guttman-Yassky E. Understanding the immune landscape in atopic dermatitis: The era of biologics and emerging therapeutic approaches. *Experimental dermatology.* 2019;28(7):756-768.
31. Ghamrawi R, Bell KA, Balogh EA, Strowd LC, Feldman SR. Current and emerging biologics for the treatment of pediatric atopic dermatitis. *Expert opinion on biological therapy.* 2020:1-11.
32. Hamann CR, Thyssen JP. Monoclonal antibodies against interleukin 13 and interleukin 31RA in development for atopic dermatitis. *J Am Acad Dermatol.* 2018;78(3 Suppl 1):S37-s42.
33. He H, Guttman-Yassky E. JAK Inhibitors for Atopic Dermatitis: An Update. *American journal of clinical dermatology.* 2019;20(2):181-192.
34. Allergy & Asthma Association AaAFoA, Global Parents for Eczema Research, International Topical Steroid Awareness Network, National Eczema Association. More Than Skin Deep Report. 2020.
35. Simpson EL, Sinclair R, Forman S, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-

blind, randomised, placebo-controlled, phase 3 trial. *Lancet (London, England).* 2020;396(10246):255-266.
36. Silverberg JI, Simpson EL, Thyssen JP, et al. Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. *JAMA Dermatology.* 2020;156(8):863-873.
37. Bieber T, Simpson EL, Silverberg JI, et al. Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis. *New England Journal of Medicine.* 2021;384(12):1101-1112.
38. Pfizer. Abrocitinib Data Request for ICER Assessment of "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis"2021.
39. Pfizer. Data on File2020.
40. Gooderham MJ, Forman SB, Bissonnette R, et al. Efficacy and Safety of Oral Janus Kinase 1 Inhibitor Abrocitinib for Patients With Atopic Dermatitis: a Phase 2 Randomized Clinical Trial. *JAMA dermatology.* 2019;155(12):1371-1379.
41. Eichenfield L, Flohr C, Sidbury R. Efficacy and Safety of Abrocitinib in Adolescent Patients With Moderate-to-Severe Atopic Dermatitis (AD): Results From the Phase 3 JADE TEEN study. Paper presented at: American Academy of Allergy Asthma & Immunology Virtual Annual Meeting2021.
42. Simpson EL, Lacour JP, Spelman L, et al. Baricitinib in Patients with Moderate-to-Severe Atopic Dermatitis and Inadequate Response to Topical Corticosteroids: results from Two Randomised Monotherapy Phase 3 Trials. *British journal of dermatology.* 2020.
43. EADV 2020: Lilly and Incyte Showcase New Data for Baricitinib for the Treatment of Moderate to Severe Atopic Dermatitis [press release]. 2020.
44. Lilly E. Data on File2021.
45. Simpson EL, Forman S, Silverberg JI, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis: Results from a randomized monotherapy phase 3 trial in the United States and Canada (BREEZE-AD5). *Journal of the American Academy of Dermatology.* 2021.
46. Reich K, Kabashima K, Peris K, et al. Efficacy and Safety of Baricitinib Combined With Topical Corticosteroids for Treatment of Moderate to Severe Atopic Dermatitis: a Randomized Clinical Trial. *JAMA dermatology.* 2020.
47. Clinicaltrials.gov. A Study of Baricitinib (LY3009104) in Combination With Topical Corticosteroids in Adults With Moderate to Severe Atopic Dermatitis (BREEZE-AD7). Published 2020. Accessed.
48. Guttman-Yassky E, Silverberg JI, Nemoto O, et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. *Journal of the American Academy of Dermatology.* 2019;80(4):913-921.e919.
49. Clinicaltrials.gov. A Study of Baricitinib (LY3009104) in Adult Participants With Moderate to Severe Atopic Dermatitis (BREEZE-AD5). Published 2021. Accessed.
50. Blauvelt A, e Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet (London, England).* 2017;389(10086):2287-2303.
51. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *New England Journal of Medicine.* 2016;375(24):2335-2348.
52. Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis: a Phase 3 Randomized Clinical Trial. *JAMA dermatology.* 2020;156(1):44-56.

53. Paller AS, Siegfried EC, Thaci D, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: a randomized, double-blinded, placebo-controlled phase 3 trial. *Journal of the American Academy of Dermatology.* 2020.
54. Worm M, Simpson EL, Thaci D, et al. Efficacy and Safety of Multiple Dupilumab Dose Regimens After Initial Successful Treatment in Patients With Atopic Dermatitis: a Randomized Clinical Trial. *JAMA dermatology.* 2020;156(2):131-143.
55. Sanofi-Regeneron. Sanofi-Regeneron Academic-in-Confidence Data Submission Table 2.1.2.1.2021.
56. Thaçi D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *The Lancet.* 2016;387(10013):40-52.
57. Simpson EL, Gadkari A, Worm M, et al. Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): A phase IIb, randomized, placebo-controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD). *Journal of the American Academy of Dermatology.* 2016;75(3):506-515.
58. Cork M, Thaçi D, Davis JD, et al. Pharmacokinetics, safety and efficacy of dupilumab in a pediatric population with moderate-to-severe atopic dermatitis: Results from an open-label phase 2A trial. *Pediatric Dermatology.* 2017;34:S32.
59. Clinicaltrials.gov. A Study to Determine the Safety and Tolerability of Dupilumab (REGN668/SAR231893) in Patients Aged ≥6 to <18 Years With Atopic Dermatitis (Eczema). Published 2020. Accessed.
60. Cork MJ, Thaci D, Eichenfield LF, et al. Dupilumab provides favourable long-term safety and efficacy in children aged >= 6 to < 12 years with uncontrolled severe atopic dermatitis: results from an open-label phase IIa study and subsequent phase III open-label extension study. *British journal of dermatology.* 2020.
61. Blauvelt A, Guttman-Yassky E, Paller A. Efficacy and Safety of Dupilumab for up to 1 Year in a Phase 3 Open-Label Extension (OLE) Trial (LIBERTY AD PED-OLE) in Adolescents With Moderate-to-Severe Atopic Dermatitis (AD). Paper presented at: American Academy of Dermatology Association Virtual Meeting Experience2021.
62. Cork M, Thaci D, Eichenfield L. Long-Term Efficacy and Safety Data for Dupilumab in a Phase 3, Open-Label Extension Trial (LIBERTY AD PED-OLE) in Patients Aged ≥ 6 to < 12 Years With Uncontrolled, Moderate-to-Severe Atopic Dermatitis (AD). Paper presented at: American Academy of Dermatology Association Virtual Meeting Experience2021.
63. Wollenberg A, Blauvelt A, Guttman-Yassky E, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). *British journal of dermatology.* 2020.
64. Silverberg JI, Toth D, Bieber T, et al. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. *British journal of dermatology.* 2020.
65. LeoPharma. Data on File2021.
66. LEO Pharma Presents Data for Tralokinumab on Pooled Safety, S. aureus Colonization Reduction and Impact on Vaccine Response Rates at the 29th Annual European Academy of Dermatology and Venereology (EADV) Virtual Congress [press release]. 2020.
67. Wiseman M, Armstrong AW, Soung J. Efficacy and safety of tralokinumab monotherapy in North American adult patients with moderate-to-severe atopic dermatitis: A subanalysis of the ECZTRA

2 trial. Paper presented at: American Academy of Dermatology Association Virtual Meeting Experience2021.
68. Blauvelt A, Wollenberg A, Pink A, Worm M. Assessing Long-term Maintenance of Efficacy With Tralokinumab Monotherapy in Patients With Moderate-to-severe Atopic Dermatitis: Combined Results From Two Phase 3, Randomized, Double-blind, Placebo-controlled Trials (ECZTRA 1 and 2). Paper presented at: American Academy of Dermatology Association Virtual Meeting Experience2021.
69. Guttman-Yassky E, Thaci D, Pangan AL, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. *Journal of allergy and clinical immunology.* 2020;145(3):877-884.
70. AbbVie. Data on File. 2021.
71. Simpson EL, Warren RB, Eichenfield LF. Rapid Skin Improvement With Upadacitinib With or Without Topical Corticosteroids (TCS) in Moderate-to-Severe Atopic Dermatitis (AD): Results From 3 Phase 3 Studies (Measure Up 1, Measure Up 2, and AD Up). Paper presented at: American Academy of Dermatology Association Virtual Meeting Experience2021.
72. Kristian Reich MdB-W, Mette Sondergaard Deleuran, Lisa Beck, Kim A. Papp,, Thomas Werfel NK, Saleem Farooqui, Pinaki Biswas, Ricardo Rojo, Marco Dibonaventura,, Claire Clibborn UK. Abrocitinib Efficacy and Safety as Monotherapy Over 48 Weeks: Results From a Long-Term Extension Study. Paper presented at: European Academy of Dermatology and Venereology Virtual Congress2020.
73. Papp J. Long-Term Safety and Disease Control With Ruxolitinib Cream in Atopic Dermatitis: Results From Two Phase 3 Studies. Revolutionizing Atopic Dermatitis (RAD) Virtual Conference; 2021.
74. EL S. Long-Term Safety and Disease Control With Ruxolitinib Cream in Patients With More Severe Atopic Dermatitis: Pooled Results From Two Phase 3 Studies. Revolutionizing Atopid Dermatitis (RAD) Virtual Conference; 2021.
75. Simpson EL. Efficacy and Safety of Abrocitinib in Adolescent Patients With Moderate-to-Severe Atopic Dermatitis: Stratified Analysis Across 3 Clinical Trials. Paper presented at: Revolutionizing Atopic Dermatitis (RAD) Virtual Conference2021.
76. Reich J. Long-Term Management of Moderate-to-Severe Atopic Dermatitis With Abrocitinib: A Phase 3 Extension Study (JADE EXTEND). Paper presented at: Revolutionizing Atopic Dermatitis (RAD) Virtual Conference2021.
77. Eichenfield L. Efficacy and Safety of Abrocitinib in Adolescents With Moderate-to-Severe Atopic Dermatitis From the JADE Clinical Trial Program. Paper presented at: Revolutionizing Atopic Dermatitis (RAD) Virtual Conference2021.
78. Blauvelt A. Long-term Improvements Observed in Tralokinumab-treated Patients With Moderate-to-severe Atopic Dermatitis: An ECZTEND Interim Analysis. Paper presented at: Revolutionizing Atopic Dermatitis (RAD) Virtual Conference2021.
79. Paller A. Efficacy and Safety of Upadacitinib in Adult and Adolescent Subgroups With Moderate-to-Severe Atopic Dermatitis: An Analysis of the Measure Up 1, Measure Up 2, and AD Up Phase 3 Clinical Trials. Paper presented at: Revolutionizing Atopic Dermatitis (RAD) Virtual Conference2021.
80. Guttman-Yassky E, Teixeira HD, Simpson EL, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *The Lancet (British edition).* 2021;397(10290):2151-2168.

81. Reich K, Teixeira HD, de Bruin-Weller M, et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet (British edition).* 2021;397(10290):2169-2181.
82. Simpson E. Long-term Efficacy of Baricitinib 2-mg for the Treatment of Atopic Dermatitis in North America. Paper presented at: Revolutionizing Atopic Dermatitis (RAD) Virtual Conference2021.
83. Blauvelt A, Teixeira HD, Simpson EL, et al. Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. *JAMA Dermatology.* 2021.
84. Clinicaltrials.gov. JAK1 Inhibitor With Medicated Topical Therapy in Adolescents With Atopic Dermatitis (JADE TEEN). Published 2021. Accessed2021.
85. Simpson E, Lee M, Brar K, et al. Disease Characteristics and Burden in Patients With Atopic Dermatitis: Insights From Two Phase 3 Studies of Ruxolitinib Cream. *Journal of allergy and clinical immunology.* 2021;147(2):AB35-AB35.
86. Kim BS, Sun K, Papp K, Venturanza M, Nasir A, Kuligowski ME. Effects of ruxolitinib cream on pruritus and quality of life in atopic dermatitis: Results from a phase 2, randomized, dose-ranging, vehicle- and active-controlled study. *Journal of the American Academy of Dermatology.* 2020;82(6):1305-1313.
87. Kim BS, Howell MD, Sun K, Papp K, Nasir A, Kuligowski ME. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. *Journal of allergy and clinical immunology.* 2020;145(2):572-582.
88. Papp K, Szepietowski JC. Efficacy and Safety of Ruxolitinib Cream for the Treatment of Atopic Dermatitis: Results From Two Phase 3, Randomized Double-Blind Studies. 2nd Annual Revolutionizing Atopic Dermatitis Conference; 2020; Chicago, IL.
89. Pooled Results from Incyte's TRuE-AD1 and TRuE-AD2 Atopic Dermatitis Studies of Ruxolitinib Cream Show Clinically Meaningful Improvements in Patient- Reported Quality of Life Assessments [press release]. Incyte.com: Incyte2020.
90. Eichenfield L, Call R, Forsha D, et al. Long-term safety of crisaborole ointment in children, adolescents, and adults with mild to moderate atopic dermatitis. *Pediatric dermatology Conference: 13th world congress of pediatric dermatology United states.* 2017;34:S32-S33.
91. Eichenfield LF, Yosipovitch G, Stein Gold LF, et al. Improvement in disease severity and pruritus outcomes with crisaborole ointment, 2%, by baseline atopic dermatitis severity in children and adolescents with mild-to-moderate atopic dermatitis. *Pediatric dermatology.* 2020.
92. Schlessinger J, Shepard JS, Gower R, et al. Safety, Effectiveness, and Pharmacokinetics of Crisaborole in Infants Aged 3 to < 24 Months with Mild-to-Moderate Atopic Dermatitis: A Phase IV Open-Label Study (CrisADe CARE 1). *American journal of clinical dermatology.* 2020;21(2):275-284.
93. Simpson EL, Paller AS, Boguniewicz M, et al. Crisaborole Ointment Improves Quality of Life of Patients with Mild to Moderate Atopic Dermatitis and Their Families. *Dermatology and therapy.* 2018;8(4):605-619.
94. Yosipovitch G, Gold LF, Lebwohl MG, Silverberg JI, Tallman AM, Zane LT. Early Relief of Pruritus in Atopic Dermatitis with Crisaborole Ointment, A Non-steroidal, Phosphodiesterase 4 Inhibitor. *Acta Derm Venereol.* 2018;98(5):484-489.
95. Paller ASMSMD, Tom WLMD, Lebwohl MGMD, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic

dermatitis (AD) in children and adults. *Journal of the American Academy of Dermatology.* 2016;75(3):494-503.e496.
96. Paller AS. Crisaborole ointment improves global atopic dermatitis severity: pooled results from two phase 3 clinical trials. *Journal of investigative dermatology.* 2018;Conference: 47th Annual Meeting of the European Society for Dermatological Research, ESDR 2017. Austria. 137(10 Supplement 2):S193.
97. Papp K, Szepietowski JC, Kircik L, et al. Efficacy and Safety of Ruxolitinib Cream for the Treatment of Atopic Dermatitis: Results From Two Phase 3, Randomized, Double-Blind Studies. *Journal of the American Academy of Dermatology.* 2021.
98. Blauvelt A, Eichenfield L. Efficacy of Ruxolitinib Cream Among Patients With Atopic Dermatitis Based on Previous Medication History: Pooled Results From Two Phase 3 Studies. Paper presented at: American Academy of Dermatology Virtual Meeting Experience2021.
99. EL. S, Augustin M, Thaçi D. Patient-Reported Outcomes of Ruxolitinib Cream for the Treatment of Atopic Dermatitis: Pooled Results From Two Phase 3 Studies. Paper presented at: American Academy of Dermatology Virtual Meeting Experience2021.
100. L SE, Kircik L, Blauvelt A. Efficacy of Ruxolitinib Cream in Patients With Atopic Dermatitis Who Demonstrated Partial Responses: Pooled Analysis From Two Randomized Phase 3 Studies. Paper presented at: American Academy of Dermatology Virtual Experience2021.
101. Papp K, Szepietowski JC. Efficacy of Ruxolitinib Cream for the Treatment of Atopic Dermatitis by Baseline Patient Demographics: Pooled Subgroup Analysis From Two Randomized Phase 3 Studies. American Academy of Dermatology Virtual Meeting Experience; 2021.
102. Simpson EL, Kircik L, Blauvelt A. Effects of Ruxolitinib Cream in Patients With Atopic Dermatitis With Baseline Body Surface Area ≥10% and Eczema Area and Severity Index Score ≥16: Pooled Results From Two Phase 3 Studies. Paper presented at: American Academy of Dermatology Virtual Meeting Experience2021.
103. Papp K, Szepietowski JC, Kircik L. Efficacy of Ruxolitinib Cream for the Treatment of Atopic Dermatitis by Baseline Clinical Characteristics: Pooled Subgroup Analysis From Two Randomized Phase 3 Studies. Paper presented at: American Academy of Dermatology Virtual Meeting Experience2021.
104. Basra MKA, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the Minimal Clinically Important Difference and Responsiveness of the Dermatology Life Quality Index (DLQI): Further Data. *Dermatology.* 2015;230(1):27-33.
105. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch Dermatol.* 2004;140(12):1513-1519.
106. Silverberg JI, Thyssen JP, Simpson EL, et al. Impact of Oral Abrocitinib Monotherapy on Patient-Reported Symptoms and Quality of Life in Adolescents and Adults with Moderate-to-Severe Atopic Dermatitis: A Pooled Analysis of Patient-Reported Outcomes. *American journal of clinical dermatology.* 2021;22(4):541-554.
107. Shi N. Abrocitinib in the Treatment of Moderate-to-Severe Atopic Dermatitis Refractory to Dupilumab Treatment: An Analysis of JADE-EXTEND, a Phase 3 Long-Term Extension Study. Paper presented at: REvolutionizing Atopic Dermatitis (RAD) Virtual Conference2021.
108. Clinicaltrials.gov. A Study of Baricitinib (LY3009104) in Patients With Moderate to Severe Atopic Dermatitis (BREEZE-AD1). U.S National Library of Medicine. Published 2018. Accessed.
109. Clinicaltrials.gov. Study of Baricitinib (LY3009104) in Patients With Moderate to Severe Atopic Dermatitis (BREEZE-AD2). Published 2018. Accessed.

110. Lilly E. Baricitinib Package Insert. 2018.
111. Abbvie. Upadacitinib Package Insert. 2019.
112. Beck LA, Thaçi D, Deleuran M, et al. Dupilumab Provides Favorable Safety and Sustained Efficacy for up to 3 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. *American journal of clinical dermatology.* 2020;21(4):567-577.
113. Fu T KE, Linos E, et al. Eczema and sensitization to common allergens in the United States: a multiethnic, population-based study. *Pediatric Dermatology.* 2014.
114. Ashcroft DM, Chen LC, Garside R, Stein K, Williams HC. Topical pimecrolimus for eczema. *Cochrane Database Syst Rev.* 2007(4):Cd005500.
115. Buysse DJ, Yu L, Moul DE, et al. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep.* 2010;33(6):781-792.
116. Zimmermann M, Rind D, Chapman R, Kumar V, Kahn S, Carlson J. Economic Evaluation of Dupilumab for Moderate-to-Severe Atopic Dermatitis: A Cost-Utility Analysis. *Journal of drugs in dermatology: JDD.* 2018;17(7):750-756.
117. Schmitt J, Langan S, Williams HC. What are the best outcome measurements for atopic eczema? A systematic review. *Journal of Allergy and Clinical Immunology.* 2007;120(6):1389-1398.
118. Arias E, Xu J. *United States life tables, 2018.* Hyattsville, MD: National Center for Health Statistics;2020.
119. National Economic Accounts. 2018. https://www.bea.gov/national/#gdp. Accessed August 10, 2018.
120. Hanifin JT, M. Omoto, M. Cherill, R. Tofte, SJ. Graeber, M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. 2001.
121. Futamura ML, YA. Thomas, KS. Nankervis, H. Williams, HC. Simpson, EL. . A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: many options, no standards. *Journal of the American Academy of Dermatology.*
122. Yosipovitch G, Reaney M, Mastey V, et al. Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. *British journal of dermatology (1951).* 2019;181(4):761-769.
123. Kunz BO, AP. Labrèze, L. Stalder, JF. Ring, J. Taïeb, A. . Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. 1997.
124. Barrett AH-P, J. Kragh, N. Evans, E. Gnanasakthy, A. . Patient-Reported Outcome Measures in Atopic Dermatitis and Chronic Hand Eczema in Adults. 2019.
125. Salek MJ, S. Brincat-Ruffini, LA. et al. . Clinical experience and psychometric properties of the Children's Dermatology Life Quality Index (CDLQI), 1995-2012. *The British journal of dermatology.* 2013.
126. Foley CT, N. Simpson, E. Teixeira, HD. Litcher-Kelly, L. Bodhani, A. . Development, and content validity of new patient-reported outcome questionnaires to assess the signs and symptoms and impact of atopic dermatitis: the Atopic Dermatitis Symptom Scale (ADerm-SS) and the Atopic Dermatitis Impact Scale (ADerm-IS). 2019.
127. Dodington SB, MK. Finlay, AY. Salek, MS. . The Dermatitis Family Impact questionnaire: a review of its measurement properties and clinical application. *The British journal of dermatology.* 2013.
128. Reilly MZ, AS. Dukes, EM. . The validity and reproducibility of a work productivity and activity impairment instrument. . *Pharmacoeconomics.* 1993.
129. Schneider LT, S. Lio, P. Boguniewicz, M. Beck, L. LeBovidge, J. Novak, N. Atopic dermatitis: A practice parameter update 2012. *American Academy of Allergy, Asthma & Immunology.* 2013.

130. Ting S, Elsada A, Hayre J, Powell J. *Dupilumab for treating moderate to severe atopic dermatitis : Technology appraisal guidance (TA534).* National Institute for Health and Care Excellence (NICE); 1 August 2018 2018.
131. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
132. Higgins JP. Cochrane Collaboration Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. 2008.
133. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg.* 2010;8(5):336-341.
134. Agency for Healthcare Research and Quality. U.S. Preventive Services Task Force Procedure Manual. Published 2008. Accessed.
135. Ollendorf D, Pearson, SD. ICER Evidence Rating Matrix: A User's Guide. https://icer-review.org/methodology/icers-methods/icer-evidence-ratingmatrix/. . Published 2020. Updated January 31, 2020. Accessed.
136. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE Decision Support Unit Technical Support Documents. In: *NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials.* London: National Institute for Health and Care Excellence (NICE) Copyright © 2014 National Institute for Health and Clinical Excellence, unless otherwise stated. All rights reserved.; 2014.
137. Cork MJ, Eckert L, Simpson EL, et al. Dupilumab improves patient-reported symptoms of atopic dermatitis, symptoms of anxiety and depression, and health-related quality of life in moderate-to-severe atopic dermatitis: analysis of pooled data from the randomized trials SOLO 1 and SOLO 2. *Journal of dermatological treatment.* 2020;31(6):606-614.
138. Silverberg JI, Thyssen JP, Fahrbach K, et al. Comparative efficacy and safety of systemic therapies used in moderate-to-severe atopic dermatitis: a systematic literature review and network meta-analysis. *Journal of the European Academy of Dermatology and Venereology.* 2021;n/a(n/a).
139. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama.* 2016;316(10):1093-1103.
140. Simpson EL, Sinclair R, Forman S, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet (London, England).* 2020;396(10246):255-266.
141. Silverberg JI, Simpson EL, Thyssen JP, et al. Efficacy and Safety of Abrocitinib in Patients with Moderate-to-Severe Atopic Dermatitis: a Randomized Clinical Trial. *JAMA dermatology.* 2020.
142. Thaçi D, Bieber T, Simpson EL, et al. A Phase 3 Study to Investigate the Efficacy and Safety of Abrocitinib and Dupilumab in Comparison With Placebo in Adults With Moderate-to-Severe Atopic Dermatitis.
143. Thaci D, L. Simpson E D, M K, et al. Efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: a pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2). *Journal of Dermatological Science.*94(2):266-275.
144. Wollenberg A, Boguniewicz M, Travers J, et al. Efficacy of Baricitinib in Patients with Atopic Dermatitis and Atopic Comorbidities: Results of Pooled Data from 2 Phase 3 Monotherapy Randomized, Double-Blind, Placebo-Controlled 16-week Trials (BREEZE-AD1 and BREEZE-AD2). *Journal of Allergy and Clinical Immunology.* 2020;145(2):AB190.

145. Simpson EL, Forman S, Silverberg JI, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis: Results from a randomized monotherapy Phase 3 trial in the United States and Canada (BREEZE-AD5). *Journal of the American Academy of Dermatology.* 2021.
146. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2019;22(8):931-941.
147. Measures of Central Tendency for Wage Data. In. United States Social Security Administration2019.
148. Health iW. Mometasone furoate: Average wholesale price. . *IBM Micromedex DRUGDEX* 2021.
149. Kuznik A, Bégo-Le-Bagousse G, Eckert L, et al. Economic evaluation of dupilumab for the treatment of moderate-to-severe atopic dermatitis in adults. *Dermatology and therapy.* 2017;7(4):493-505.
150. Costanzo A, Furneri G, Bitonti R, Pedone MP, Fanelli F, Di Turi R. Cost-effectiveness analysis of dupilumab for the treatment of severe atopic dermatitis in adults in Italy. *Global & Regional Health Technology Assessment.* 2020;7(1):57-65.
151. *Capital Markets Day: Epidemiology* 2019.
152. Dupixent® (dupilumab) Phase 3 data show significant improvement in severe atopic dermatitis for children aged 6 to 11 years [press release]. 2020.
153. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. https://icer-review.org/wp-content/uploads/2019/05/ICER_2020_2023_VAF_013120-4.pdf. Published 2020. Accessed.
154. Pearson SD. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2018;21(3):258-265.
155. Clinicaltrials.gov. Study to Evaluate Efficacy and Safety of PF-04965842 in Subjects Aged 12 Years And Older With Moderate to Severe Atopic Dermatitis (JADE Mono-1). Published 2019. Accessed.
156. Clinicaltrials.gov. Study Evaluating Efficacy and Safety of PF-04965842 in Subjects Aged 12 Years And Older With Moderate to Severe Atopic Dermatitis (JADE Mono-2). Clinical Trials. Published 2020. Accessed.
157. Clinicaltrials.gov. Study To Evaluate Pf-04965842 In Subjects With Moderate To Severe Atopic Dermatitis. Published 2019. Accessed2021.
158. Reich J. Treatment Withdrawal and Retreatment with Upadacitinib in Patients with Moderate-to-Severe Atopic Dermatitis from a Phase 2b, Randomized, Controlled Trial. Paper presented at: Revolutionizing Atopic Dermatitis (RAD) Virtual Conference2021.
159. Simpson E. Tralokinumab provides progressive improvements beyond week 16 in patients with atopic dermatitis with an initial partial response. Paper presented at: Revolutioniing Atopic Dermatitis (RAD) Virtual Conference2021.

Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks

Final Evidence Report

December 20, 2018

Prepared for

Authors:

ICER Staff/Consultants*	University of Colorado Skaggs School of Pharmacy Modeling Group†
Jeffrey A. Tice, MD Professor of Medicine University of California, San Francisco **Judith M. E. Walsh, MD, MPH** Professor of Medicine University of California, San Francisco **Patricia Synnott, MALD, MS** Senior Research Lead, Evidence Synthesis Institute for Clinical and Economic Review **Varun M. Kumar, MBBS, MPH, MSc** Health Economist Institute for Clinical and Economic Review **Ellie Adair, MPA** Program Manager Institute for Clinical and Economic Review **David Rind, MD, MSc** Chief Medical Officer Institute for Clinical and Economic Review **Steven D. Pearson, MD, MSc** President Institute for Clinical and Economic Review **None of the above authors have any conflicts of interest to disclose*	**Jonathan D. Campbell, PhD** Associate Professor Department of Clinical Pharmacy Center for Pharmaceutical Outcomes Research **Melanie D. Whittington, PhD** Research Instructor Department of Clinical Pharmacy **R. Brett McQueen, PhD** Assistant Professor Department of Clinical Pharmacy Center for Pharmaceutical Outcomes Research **Samuel McGuffin, MPH** Professional Research Assistant Department of Clinical Pharmacy **Sean Sullivan, PhD** Professor and Dean University of Washington School of Pharmacy †*The role of the University of Colorado Skaggs School of Pharmacy Modeling Group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of the UC. None of the above modelers have any conflicts of interest to disclose*

DATE OF PUBLICATION: December 20, 2018

Jeff Tice served as the lead author for this report, with assistance from Judith Walsh. Jeff Tice, Judith Walsh, and Patricia Synnott led the systematic review and authorship of the comparative clinical effectiveness section. Varun Kumar was responsible for oversight of the cost-effectiveness analyses and developing the budget impact model. The role of the University of Colorado Modeling Group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of the University of Colorado. Madeline O'Grady authored the section on coverage policies and clinical guidelines, with oversight from Ellie Adair. David Rind and Steven Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Aqsa Mugal, Ariel Jurmain, Milon Waththuhewa, Laura Cianciolo, and Madeline O'Grady for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Laura and John Arnold Foundation. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 20% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Life science companies relevant to this review who participate in this program include: AstraZeneca, Genentech, GlaxoSmithKline, Regeneron, and Sanofi. For a complete list of funders and for more information on ICER's support, please visit http://www.icer-review.org/about/support/.

About Midwest CEPAC

The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. Midwest CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The Midwest CEPAC is an independent committee of medical evidence experts from across the Midwest, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Council members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about Midwest CEPAC is available at https://icer-review.org/programs/midwest-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/asthma-stakeholder-list-2018/

Expert Reviewers

Kenneth Mendez
President and Chief Executive Officer
The Asthma and Allergy Foundation of America
Mr. Mendez personally owns stock in health care companies, but in an amount of less than $10,000. The AAFA receives greater than 25% of their funding to produce educational materials and for patient research through grants from pharmaceutical companies, including AstraZeneca, Genentech, GSK, Sanofi/Regeneron, and Teva.

Matt Stevenson, PhD
Professor of Health Technology Assessment
University of Sheffield
No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

David Stukus, MD
Associate Professor of Pediatrics
Nationwide Children's Hospital
The Ohio State University College of Medicine
No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table of Contents

Executive Summary ES1
1. Introduction 1
1.1 Background 1
1.2 Scope of the Assessment 4
1.3 Definitions 7
1.4 Insights Gained from Discussions with Patients and Patient Groups 9
1.5 Potential Cost-Saving Measures in Asthma 9
2. Summary of Coverage Policies and Clinical Guidelines 11
2.1 Coverage Policies 11
2.2 Clinical Guidelines 13
3. Comparative Clinical Effectiveness 18
3.1 Overview 18
3.2 Methods 18
3.3 Results 20
3.4 Summary and Comment 33
4. Long-Term Cost Effectiveness 38
4.1 Overview 38
4.2 Methods 38
4.3 Results 53
4.4 Summary and Comment 64
5. Potential Other Benefits and Contextual Considerations 66
5.1 Potential Other Benefits 66
5.2 Contextual Considerations 67
6. Value-Based Price Benchmarks 68
7. Potential Budget Impact 69
7.1 Overview 69
7.2 Methods 69
7.3 Results 70
7.4 Access and Affordability 71

8. Summary of the Votes and Considerations for Policy 72
8.1 About the Midwest CEPAC Process 72
8.2 Voting Results 74
8.3 Roundtable Discussion and Key Policy Implications 78
References 85
Appendix A. Search Strategies and Results 93
Appendix B. Previous Systematic Reviews and Technology Assessments 98
Appendix C. Ongoing Studies 103
Appendix D. Comparative Clinical Effectiveness Supplemental Information 109
Appendix E. Comparative Value Supplemental Information 138
Appendix F. Public Comments 143
Appendix G. Conflict of Interest Disclosures 149

List of Acronyms Used in this Report

ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AE	Adverse event
AQLQ	Asthma Quality of Life Questionnaire
BI	Budget impact
BSCA	Blue Shield of California
CDC	Centers for Disease Control and Prevention
CEA	Cost-effectiveness analysis
CI	Confidence interval
CMS	Centers for Medicare & Medicaid Services
DALY	Disability-adjusted life year
DHCS	Department of Health Care Services
ED	Emergency department
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GDP	Gross domestic product
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroids
ICU	Intensive care unit
IgE	Immunoglobulin E
IL-5	Interleukin 5
IV	Intravenous
LABA	Long-acting beta agonist
LCD	Local coverage determination
LTRA	Leukotriene receptor antagonist
MAC	Medicare Administrative Contractor
MART	Maintenance and reliever therapy
NCD	National coverage determination
NHE	National health expenditures
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OCS	Oral corticosteroids
PEF	Peak expiratory flow
PICOTS	Population(s), Intervention(s), Comparator(s), Outcome(s), Timing, and Setting(s)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial
SABA	Short-acting beta agonists
SAE	Serious adverse event
SC	Subcutaneous
SGRQ	St. George's Respiratory Questionnaire
SoC	Standard of care
UHC	UnitedHealthcare
URI	Upper respiratory infection
USD	United States Dollars
USPSTF	United States Preventive Services Task Force
WAC	Wholesale acquisition cost

Executive Summary

Background

The Centers for Disease Control and Prevention (CDC) estimates that 20.4 million Americans ages ≥18 years currently have asthma and an additional 6.1 million children have asthma.[1,2] There are approximately 14.2 million office visits, 1.8 million emergency room visits, and 440,000 hospitalizations due to asthma each year in the US.[2] The societal costs are estimated to be $82 billion including $50 billion in direct medical costs, $29 billion from asthma related mortality, and $3 billion from missed work and school.[2] Severe asthma comprises a small but important subset of all individuals with asthma. Those with severe asthma represent fewer than 5-10% of all individuals with asthma but account for approximately 50% of all costs. In addition to being treated with inhaled corticosteroids (ICS) and long-acting beta agonist (LABA) therapy, these patients are often treated with oral corticosteroids (OCS).[3]

Asthma has been divided into different phenotypes with some overlap. Allergic asthma, which is associated with allergic rhinitis, atopy, and elevated IgE levels, is characteristic of approximately half of all patients with asthma. About half of individuals with severe asthma exhibit the type 2 phenotype with increases in T helper 2 cells.[4] These cells secrete IL-4, IL-5, and IL-13, which increase the proliferation, survival and recruitment of eosinophils and increase IgE levels.[5,6] The medications evaluated in this review target specific components of these pathways and may be more effective in specific asthma patient subgroups.

There are five FDA approved monoclonal antibodies that affect the pathways involved in either the allergic or type 2 inflammatory phenotypes of asthma. The drugs, dosing, their mechanisms of action, and their FDA indications for asthma are summarized in Table ES1 below. Omalizumab is a monoclonal antibody to IgE, which is indicated for the treatment of patients with moderate to severe asthma with the allergic phenotype described above. Mepolizumab, reslizumab, and benralizumab target the IL-5 pathway either with monoclonal antibodies to IL-5 itself (mepolizumab, reslizumab) or to the IL-5 receptor (benralizumab). Dupilumab is a monoclonal antibody to the IL-4 receptor alpha, which modulates both the IL-4 and IL-13 pathways.

Table ES1. Monoclonal Antibody Therapies for Type 2 Inflammation in Asthma

Drug	Dosing	Mechanism	FDA Indication
Omalizumab (Xolair®, Genentech)	75-375 mg SC Q 2-4 weeks	Anti-IgE	Age ≥ 6 years with moderate to severe persistent asthma who test positive for year-round allergens[7]
Mepolizumab (Nucala®, GlaxoSmithKline)	100 mg SC Q 4 weeks	Anti-IL-5	Age ≥ 12 years with severe asthma and eosinophilic phenotype[8]
Reslizumab (Cinqair®, Teva)	3 mg/kg IV Q 4 weeks	Anti-IL-5	Age ≥ 18 years with severe asthma and eosinophilic phenotype[9]
Benralizumab (Fasenra™, AstraZeneca)	30 mg SC Q 4 weeks x 3, then Q 8 weeks	Anti-IL-5Rα	Age ≥ 12 years with severe asthma and eosinophilic phenotype[10]
Dupilumab (Dupixent®, Sanofi/Regeneron)	200 mg SC Q 2 weeks 300 mg SC Q 2 weeks	Anti-IL-4Rα	Age ≥ 12 years with moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma[11]

There are important differences in the indications for each of the drugs including age, severity of asthma, and asthma phenotype. These differences are reflected in the study populations enrolled in the pivotal trials for each drug and make comparisons between drugs challenging. In addition, dupilumab is the only drug approved for self-administration; the other four drugs must be administered by a health care professional.

Insights Gained from Discussions with Patients and Patient Groups

The most important insight gained from speaking with patients was their heartfelt desire to be able to perform their day to day tasks of living – to get back to their usual activities of daily living. Symptom relief, asthma control, and quality of life matter much more to them than a reduction in asthma exacerbations. The majority of patients with severe asthma report having symptoms more than once a day and being scared and burdened by their symptoms. They report that their asthma prevents them from living the life that they want to live. The patients report that it also impacts their loved ones: they report that their asthma is a burden to their family and that their caregivers are scared about the possible consequences of asthma. They also have learned to fear the side effects of corticosteroids and want to minimize the use of both systemic and inhaled corticosteroids as much as possible.

The Asthma and Allergy Foundation of America shared results from their survey of 805 Americans living with asthma including 185 with severe, uncontrolled asthma.[12] The two most important factors for choosing a therapy for both groups were effectiveness and then cost. However, effectiveness was the far more important factor for patients surveyed. An average of 82%

responded that effectiveness was a key criterion while an average of 52% cited cost as a key criterion.

Potential Cost-Saving Measures in Asthma

Stakeholders did not identify any potential cost-saving measures.

The Choosing Wisely statement from the **American Academy of Allergy, Asthma & Immunology** includes the following:

Don't diagnose or manage asthma without spirometry.

"Clinicians often rely solely upon symptoms when diagnosing and managing asthma, but these symptoms may be misleading and be from alternate causes. Therefore, spirometry is essential to confirm the diagnosis in those patients who can perform this procedure. Recent guidelines highlight spirometry's value in stratifying disease severity and monitoring control. History and physical exam alone may over- or under-estimate asthma control. Beyond the increased costs of care, repercussions of misdiagnosing asthma include delaying a correct diagnosis and treatment."[13]

Comparative Clinical Effectiveness

To inform our analysis of the comparative clinical effectiveness of the five biologics added to standard of care (SoC) versus SoC alone, we abstracted evidence from RCTs of individuals ages six years and older with moderate to severe allergic asthma or eosinophilic asthma. The comparator treatment for each intervention of interest included SoC treatment with ICS and at least one additional controller agent. Our review focused on clinical benefits (i.e., asthma exacerbations, ED visits, hospitalizations, quality of life (AQLQ, ACQ, SGRQ) as well as potential harms (severe adverse events, adverse events leading to discontinuation of therapy).

Clinical Benefits

Reduction in Exacerbation Rates Requiring Systemic Steroids

There were no head to head randomized or observational trials of the five monoclonal antibodies. The summary estimates from Cochrane meta-analyses[14,15] for each of the drugs are summarized in Table ES2 below in addition to the estimates for dupilumab from the pivotal trials.[16-18] As can be seen in the table, all five of the drugs reduced the annual exacerbation rate by about 50% with overlapping confidence intervals despite both the differences in the patient populations studied and the different mechanisms of action of the drugs. These estimates are specific to the populations in which each drug was studied and likely vary by patient characteristics. For instance, the relative rates have been shown to be consistently lower (greater efficacy) for each of the drugs

in populations with higher baseline eosinophil counts.[16-20] If the drugs were compared in identical patient populations the differences in rate ratios between each pair of the drugs might be larger or smaller than the ones observed in Table ES2.

Table ES2. Rate Ratio for Asthma Exacerbations Requiring Steroid Therapy

Treatment	Rate Ratio (95% CI)
Omalizumab	0.52 (0.37-0.73)
Mepolizumab	0.45 (0.36-0.55)
Reslizumab	0.43 (0.33-0.55)
Benralizumab	0.59 (0.51-0.68)
Dupilumab 200 mg	0.44 (0.34-0.58)
Dupilumab 300 mg	0.40 (0.31-0.53)

Measures of Health-Related Quality of Life and Asthma Control

The reduction in exacerbation rates is often the focus of the clinical trials, but patients only have one or two exacerbations per year (rate in the placebo group of the clinical trials). Their quality of life when they are not having exacerbations is more important to patients and to the long-term value of the therapy.

The AQLQ is a 32-item questionnaire covering four domains (symptoms, activity limitation, emotional function, and environmental stimuli). It is scored from one to seven with higher numbers representing better quality of life. The minimally important difference is 0.5 points. The average AQLQ score prior to therapy in the studies was close to four across all of the studies.

Table ES3. Mean Difference in AQLQ Between Treatment and Placebo

Treatment	Difference (95% CI)
Omalizumab	0.26 (0.05-0.47)
Mepolizumab	NR
Reslizumab	0.28 (0.17-0.39)
Benralizumab	0.23 (0.11-0.35)
Dupilumab 200 mg	0.29 (0.15-0.44)
Dupilumab 300 mg	0.26 (0.12-0.40)

AQLQ: Asthma Quality of Life Questionnaire, NR: not reported

As can be seen in Table ES3 above, the average improvement for four of the drugs compared with placebo is modest and none of them reach the minimally important difference, although all were statistically significant. The trials of mepolizumab using the FDA approved SC formulation did not report AQLQ outcomes data. As with the estimates for asthma exacerbations, the change in AQLQ estimates for each drug in Table ES3 come from different populations, so comparisons between drugs are uncertain due to potential selection bias.

The ACQ is a seven-item questionnaire that includes five questions on symptoms, FEV_1, and use of rescue inhalers. It is scored from zero to six with higher scores representing worse asthma control. The minimally important difference is 0.5 points. The average ACQ score prior to therapy in the studies was close to 2.5 across most of the studies (see Appendix Table D1).

Table ES4. Mean Difference in ACQ Between Treatment and Placebo

Treatment	Difference (95% CI)
Omalizumab	NR
Mepolizumab	-0.42 (-0.56 to -0.28)
Reslizumab	-0.27 (-0.36 to -0.19)
Benralizumab	-0.23 (-0.34 to -0.12)
Dupilumab 200 mg	-0.39 (-0.53 to -0.25)
Dupilumab 300 mg	-0.22 (-0.36 to -0.08)

ACQ: Asthma Control Questionnaire

As with the AQLQ, the improvements in the ACQ compared with placebo were clinically modest, but statistically significant for the four drugs that reported this outcome in randomized trials (Table ES4).

Some of the trials of mepolizumab also reported changes in the SGRQ. The SGRQ is a 50-item questionnaire focusing on overall health, daily life, and perceived well-being. It is scored from zero to 100 with higher numbers representing greater limitations. The minimally important difference is four points. The SGRQ has been used in COPD but has been extensively validated in patients with asthma.[21-25] The summary estimate for mepolizumab compared with placebo was -7.40 points (95% CI: -9.50 to -5.29). By this measure, the average patient treated with mepolizumab had a clinically meaningful improvement in quality of life, even though this was not observed with the ACQ in these trials.

Patients with Blood Eosinophils ≥ 300 cells/µL, ≥ 2 Exacerbations in the Prior Year, and ACQ ≥ 1.5

Four of the five biologic drugs considered in this review are indicated for eosinophilic asthma and the fifth drug has published data suggesting that there are greater relative reductions in exacerbation rates for patients with eosinophils ≥ 300 cells/µL compared with patients with lower eosinophil counts (see Table ES5 below).[16,19] We performed a network meta-analysis in the subgroup of patients with eosinophils ≥ 300 cells/µL, two or more exacerbations in the year prior to randomization, and an ACQ ≥ 1.5 because the benefits seemed greater in this population and because it may represent a more homogenous population.

Table ES5. Rate Ratio for Asthma Exacerbations by Eosinophil Level

Treatment	Eos < 300 (95% CI)	Eos ≥ 300 (95% CI)
Omalizumab	1.07 (0.45-2.53)	0.41 (0.20 -0.80)

Eos: blood eosinophils (cells/µL)

Table ES6 below shows the pairwise comparisons for all of the drugs as well as placebo.

Table ES6. NMA Results Comparing the Relative Rate of Asthma Exacerbations for Five Biologic Therapies

Dupilumab200						
1.00 (0.33, 3.00)	Dupilumab300					
0.78 (0.15, 4.09)	0.78 (0.15, 4.20)	Omalizumab				
0.75 (0.16, 3.70)	0.75 (0.16, 3.69)	0.97 (0.18, 5.20)	Reslizumab			
0.72 (0.18, 2.89)	0.72 (0.18, 2.87)	0.92 (0.21, 4.10)	0.95 (0.24, 3.86)	Mepolizumab		
0.44 (0.11, 1.74)	0.44 (0.11, 1.76)	0.57 (0.13, 2.41)	0.59 (0.15, 2.30)	0.62 (0.20, 1.89)	Benralizumab	
0.26 (0.08, 0.79)	**0.26 (0.08, 0.80)**	0.33 (0.10, 1.14)	0.34 (0.11, 1.03)	**0.36 (0.16, 0.81)**	0.59 (0.26, 1.29)	Placebo

Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

In Table ES6, only dupilumab (both doses) and mepolizumab were significantly better than placebo likely due to relatively small numbers of patients in this subgroup for omalizumab, mepolizumab and benralizumab. The point estimates for omalizumab, reslizumab, and mepolizumab were nearly identical. Dupilumab had the largest reduction in exacerbations and benralizumab the smallest, but none of the comparisons between drugs were statistically significant. The estimates for the RR for dupilumab, omalizumab, reslizumab, and mepolizumab are markedly better than those reported in the full trial, but the NMA estimate for benralizumab is nearly identical to its primary estimate, because it was studied in patients with severe asthma, an ACQ ≥ 1.5, at least two exacerbations in the prior year, and a baseline eosinophil count ≥ 300 cells/µL.

Harms

All five drugs were well tolerated. The risk for serious adverse events was lower in the active drug group than the placebo group for all five drugs. There were no differences in withdrawals due to adverse events except for an increase in drug discontinuation rates for the 300 mg dose of dupilumab. However, there was a significant reduction in discontinuation due to adverse events for dupilumab at the 200 mg dose, so this may be a chance finding. The only consistent adverse event that was more common in the drug arm of the randomized trials compared with the placebo arm was injection site reactions. They were about twice as common in the drug arm as in the placebo arm for most the drugs. Reslizumab was the exception, which may be due to the IV administration of the drug.

Controversies and Uncertainties

There are several important uncertainties. First, there is a lack of evidence on the long-term safety and effectiveness of these drugs, particularly in older patients, given that many of the patients taking the drugs are relatively young when they start and have 30 to 70-year life expectancies. The length of follow-up in some of the randomized trials was only 24 weeks and no trial was longer than 15 months. The long-term extension trials and real-world experience with omalizumab and mepolizumab are reassuring, but uncontrolled.

There is no clear definition for a response to therapy to help guide patients and clinicians in deciding when to stop one therapy for insufficient effect and consider switching to another. Similarly, apart from the allergic phenotype and eosinophilia, there are currently no biomarkers to help clinicians decide which of these drugs may be most appropriate for the individual patient confronting the decision to start one of these drugs.

While quality of life is an essential driver of the overall evaluation of the effectiveness of these therapies, there is no standard assessment of quality of life used across all studies. Ideally, there would be one measure, assessed at a standard time point, that could be used to compare quality of life across interventions.

Eosinophils are part of the immune response to parasitic infections. It is unknown if the therapies that decrease eosinophil counts will affect patients' ability to fight such infections. Current guidelines recommend that physicians treat patients for existing parasitic infections prior to initiating anti IL-5 therapy.

Finally, the current evidence base precludes reliable comparative effectiveness analyses between the five drugs as highlighted by Drs. Drazen and Harrington in their editorial accompanying the publication of the pivotal trials of dupilumab.[26] They assert that they regard the treatments targeting type 2 inflammation "as essentially equivalently effective treatments." They call for researchers to design and implement a large, pragmatic trial comparing all of the available drugs in order to clarify whether or not there are clinically important differences between the drugs and to facilitate studies of biomarkers that could identify subgroups of patients likely to benefit from one of the specific drugs.[26]

Summary and Comment

Results from our review of the drugs currently approved for uncontrolled moderate to severe asthma suggest that they are safe and effective. All five drugs reviewed reduced the number of asthma exacerbations compared with placebo, modestly improved day-to-day quality of life, and available data suggest few harms. None of the drugs prevented most exacerbations requiring systemic corticosteroids or improved average daily quality of life to a degree considered clinically

significant. Thus, the net health benefit for all five drugs is at best incremental. Omalizumab and mepolizumab have the longest follow-up in extension studies of the pivotal trials and the longest real-world data, so the uncertainty about long-term effectiveness and safety is lowest for these two drugs. Dupilumab is the only drug approved for self-administration, which is an important benefit for patients. Reslizumab must be administered IV, which may be important for some patients, but three of the other drugs also require administration by a health care professional, so it is not clear if this is important for patients as all require office visits. Given the requirement for office visits for administration, the every 8 week dosing of benralizumab may be important to some patients.

Because they have greater long-term follow-up and real-world data, we judged the net health benefit of both omalizumab and mepolizumab to be incremental compared with standard of care (B). There is greater uncertainty about the net health benefit of reslizumab, benralizumab, and dupilumab, so we judged their net health benefit to be comparable or better compared with standard of care (C+).

Long-Term Cost Effectiveness

We developed a cost-effectiveness model comparing five biologic agents (omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab), each to standard of care (SoC), for the treatment of moderate to severe uncontrolled asthma with evidence of type 2 inflammation in adults and in children six years and older. This analysis represents an update of our prior analysis on this topic.[27] The population for this updated review was designated with a broad intention to capture the existing or expected FDA indications for all the relevant biologics, though not all of the therapies are indicated for use in younger children or patients with moderate asthma (refer to Table 3.1 in the clinical section). Quality-adjusted survival and health care costs were estimated for each biologic and its relevant comparators using the health care sector perspective. Costs and outcomes were discounted at 3% per year, and were modeled over a lifetime time-horizon, with a model cycle length of two weeks. Incremental costs and outcomes were calculated comparing each intervention to its comparator.

The Markov model included three primary health states: 1) an asthma non-exacerbation state (i.e., day-to-day asthma symptoms), 2) an asthma exacerbation state (including three mutually exclusive subcategories: asthma-related event that requires an oral corticosteroid burst without emergency department (ED) or inpatient care, asthma-related ED visit, or asthma-related hospitalization), and 3) death (including asthma-related mortality and other cause mortality).

Key clinical inputs for the model, informed by the evidence review, included exacerbation rates (including oral steroid bursts, ED visits, and hospitalizations), chronic oral steroid use, asthma-related mortality, asthma control, asthma quality of life, biologic treatment response, and adverse events. Model outcomes for each intervention included total drug and non-drug health care costs,

life years (LY) gained, quality-adjusted life years (QALYs) gained, and annualized asthma exacerbations.

Key Model Characteristics and Assumptions

Presented below are the key model assumptions. The entire list of assumptions and accompanying rationale for each assumption is available in section 4 of the report.

- Base-case utility for the non-exacerbation health state was different for biologic plus SoC versus SoC alone due to potential improvements in day-to-day symptoms.
- Long-term biologic treatment only for treatment responders was included as a scenario analysis for all biologics.
- In order to eliminate differences across baseline characteristics, such as age, that may impact lifetime costs and outcomes, we averaged over baseline characteristics to estimate the same model cohort's baseline age, gender, weight, proportion of chronic oral steroid users, and SoC annualized exacerbation rates.

Model Inputs

Model inputs were estimated from the clinical review, as well as from published literature and information provided by stakeholders. The evidence suggested no differences in costs or disutility values associated with adverse events between biologics plus SoC versus SoC alone. Chronic oral steroid use and its associated long-run costs and disutility was included within this updated review. Asthma-related mortality and other cause mortality were modeled for all living health states (non-exacerbation and exacerbation).[28-31] Health state utilities were derived from publicly available literature and applied to the disease states. The non-exacerbation health state utility value was allowed to be different for the biologic plus SoC treatment arm versus SoC alone. Without known direct elicitation of utilities in trials comparing biologic plus SoC versus SoC alone, we relied on evidence of patient reported outcome instruments with known utility mappings. Disutilities associated with exacerbation events and chronic OCS use were included in the model with duration of disutility being two weeks for the exacerbation events.

Economic Inputs

The unit cost for each intervention is reported in Table ES7. Net price data that were submitted by the five manufacturers were used wherever calculations or reporting involves net price. Treatment-related costs (SoC and asthma biologics) were assigned by treatment scenario for all living health states (exacerbation and non-exacerbation states). Treatment-related administration and office-visits costs were included. We also included costs of lost productivity associated with treatment with asthma biologics and SoC for the modified societal perspective scenario. Threshold prices

were calculated at the three cost-effectiveness thresholds ($50,000, $100,000 and $150,000 per QALY gained).

Table ES7. Treatment Costs and Details

Characteristic	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Unit	150 mg vial	100 mg	100 mg/ml vial	30 mg	2 x 200mg or 2 x 300mg
Wholesale Acquisition Cost (WAC)	$1,084.66	$2,868.67	$878.80	$4,752.11	$2,931.54
Manufacturer Net Price (% of WAC)	$802.64* (74% of WAC)	$2,272† (79% of WAC)	$804.10‡ (91% of WAC)	$4,265¥ (90% of WAC)	$2,384.62^ (81% of WAC)

*Per manufacturer: "Net price per 150mg vial was calculated using the manufacturer-provided annual net cost. Omalizumab's average annual net cost per adult patient is $28,895. Average annual net cost of treatment for adults with allergic asthma only (as of July 2018) assuming three 150 mg vials per month. Net cost assumption is an average cost reflecting all price concessions given to customers, and inclusive of all statutory discounts and rebates. This calculation is an estimate for the purposes of financial modeling. Cost of treatment per patient varies as dosing depends on age, weight and IgE level and pricing differs by provider and payer (commercial insurance or government program)."
†Per manufacturer: "Average net sales price is inclusive of WAC rebates, allowances, and returns."
‡Per manufacturer: "This net price reflects a weighted average after applying statutory discounts."
¥Per manufacturer: "The net price for each 30mg/ml pre-filled syringe of Benralizumab is $4265. This price includes government statutory rebates, allowances, and returns." Benralizumab will have an additional cost of $6,302.30 for the first year of treatment due to the higher frequency of administration for the first three doses.
^Per the manufacturer: "The net price of $31,000 should be considered as inclusive of all discounts applied to dupilumab throughout the value chain and not just reflective of rebates alone." Dupilumab will have an additional cost of $1,192.31 for the first year of treatment due to the loading dose.

In addition to the base-case analyses, we conducted one-way and probabilistic analyses, as well as specific scenario analyses. Separate scenario analyses were conducted based on input and evidence provided by stakeholders, manufacturers, and informed by internal discussions. Four scenario analyses included within the Executive Summary are as follows: 1. Modified societal perspective; 2. Subpopulation of patients with baseline eosinophil counts ≥300 cells/µL and at least two exacerbations in the previous year; 3. Treatment responder scenario using evidence primarily from omalizumab studies and; 4. Collective best-case analyses using inputs that favor the lifetime value toward that of biologic therapy. A full list of scenario analyses is available in section 4 of the report.

Results

Base-case discounted incremental results are found in Table ES8 with all biologics falling in the $300,000 to $400,000 per QALY range.

Table ES8. Base-Case Incremental Cost-Effectiveness Ratio and Annual Price (side-by-side)

	Base-Case Incremental Cost-Effectiveness Ratio	Annual Price*
Omalizumab	$325,000	$28,900
Mepolizumab	$344,000	$29,500
Reslizumab	$391,000	$28,900
Benralizumab	$371,000	$27,800
Dupilumab	$351,000	$31,000

*Annual price excluding loading dose in year 1 of treatment and excluding administration costs.

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY. Key drivers of uncertainty for mepolizumab versus SoC included utility estimates for the biologic and SoC non-exacerbation health state, annual exacerbation rates for SoC, and cost of chronic oral steroid use (Figure 4.2). Other biologics had similar findings in terms of importance of inputs and relative impact on findings (See Appendix Figures E1- E4).

In probabilistic sensitivity analyses, no biologic achieved a greater than zero likelihood of meeting the $150,000/QALY or lower threshold (Table ES9).

Table ES9. Probabilistic Sensitivity Analysis Results: Biologic versus Standard of Care

	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY
Omalizumab	0%	0%	0%
Mepolizumab	0%	0%	0%
Reslizumab	0%	0%	0%
Benralizumab	0%	0%	0%
Dupilumab	0%	0%	0%

QALY: quality-adjusted life year

Only selected scenario analyses are presented herein. A modified societal perspective, differences in asthma study population characteristics and other features such as responder treatment strategies, and the subpopulation of chronic oral steroid users suggested a bounding of the value assessments toward generally favoring the biologic treatments.

The findings for the collective best-case scenarios that use SoC and relative signals that most favor the biologics suggest incremental cost-effectiveness ratios in the $200,000s and upper $100,000s per QALY. Scenario #1 suggests that when using the most severe of baseline characteristics and largest relative clinical signals and lowest biologic cost, the resulting incremental cost-effectiveness ratio decreases from the $300,000s per QALY to $226,000 per QALY. Further, when restricting the

treated population to only those who are on chronic oral corticosteroids, the resulting incremental cost-effectiveness ratio further decreases to approximately $174,000 per QALY. And when adding the responder scenario alongside assuming favorable clinical and cost inputs, the incremental lifetime findings are approximately $156,000 per QALY. We added the collective best-case scenarios due to public feedback from the draft evidence report. The feedback rightly pointed out differences in the asthma study populations across the assessed biologics.

Threshold Analyses

Table ES10 presents the annual price results for the five biologic agents in the review (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) at $50,000, $100,000, and $150,000 per QALY cost-effectiveness thresholds for within-trial and long-run variations.

Table ES10. Threshold Annual Price Results

Intervention	Annual Price at $50,000 per QALY	Annual Price at $100,000 per QALY	Annual Price at $150,000 per QALY
Omalizumab	$4,700	$9,000	$13,300
Mepolizumab	$5,100	$9,200	$13,400
Reslizumab	$2,900	$6,500	$10,400
Benralizumab	$4,700	$8,300	$11,900
Dupilumab	$6,000	$10,100	$14,300

QALY: quality-adjusted life year

Summary and Comment

The base-case findings from our analysis suggest that the use of asthma biologic agents in the studied populations provides clinical benefit in terms of gains in quality-adjusted survival over that of SoC alone. Due to high biologic treatment costs, the cost-effectiveness estimates did not meet commonly-cited cost-effectiveness thresholds. This interpretation of the incremental cost-effectiveness findings was robust to one-way and probabilistic sensitivity analyses for all biologic agents. Sensitivity analysis was also used to isolate the impact of the three main biologic agent benefits: non-exacerbation health state utility improvement alone, exacerbation reductions alone (with indirect mortality benefits), and chronic oral steroid reductions alone. The findings from this sensitivity analysis suggested that non-exacerbation health state utility improvements associated with biologic therapy are potentially the most influential benefit input on lifetime discounted cost-effectiveness, followed by exacerbation reductions and finally, the chronic oral steroid reductions. Scenario analyses suggested that the most influential scenarios were including the potential costs and benefits of biologic treatment responders (and non-responders) as well as reserving biologic treatment only in the chronic oral corticosteroid subgroup.

In conclusion, the findings of our analysis suggest that the biologic agents of focus for this review provide gains in quality-adjusted survival over standard of care alone. With the evidence available at this time, these biologic agents seem to be priced higher than the modeled benefits over a lifetime time horizon at commonly accepted cost-effectiveness thresholds. The findings were not sensitive to traditional sensitivity or scenario analyses but were most favorable in scenarios associated with long-term biologic treatment for responders or biologic initiation in the subgroup of chronic oral corticosteroid users. Comparative evidence is needed to support or refute these scenario value projections. Higher value care is more likely to be achieved through careful patient selection and continued biologic therapy for only treatment responders.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in table ES11 below.

Table ES11. Potential Other Benefits

Other Benefits	Description
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.	None
This intervention offers reduced complexity that will significantly improve patient outcomes.	None
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	None
This intervention will significantly reduce caregiver or broader family burden.	The five biologics are all parenteral, which may impact the acceptability and long-term adherence to therapy. Four are delivered subcutaneously and one (reslizumab) is given by IV infusion. Only dupilumab is approved for self-injection. All of the other drugs require an office visit for each dose for administration by a health care professional. The requirement for office visits is potentially burdensome. In addition, the dosing schedule varies between the drugs, which may also impact long-term adherence and acceptability to patients. Dupilumab is given every two weeks, omalizumab is given every two to four weeks, mepolizumab and reslizumab are given every four weeks, and after the first three doses, benralizumab is given every eight weeks, which some patients may prefer.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.	Dupilumab, in particular, offers a new mechanism of action. It is the first drug to target the IL-4 and IL-13 pathways in type 2 asthma.
This intervention will have a significant impact on improving return to work and/or overall productivity.	There is limited evidence in the studies to date, but patients with severe asthma often miss school or work due to their asthma and even if present, may be less alert due to poor sleep or ongoing shortness of breath. All five biologics have the potential to improve this aspect of a patient's life.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	None

Table ES12. Potential Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	These 5 drugs are primarily intended for severe asthma that is not controlled by available therapies. The disease is life threatening and has large impacts on quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	Asthma is a life-long disease and for children suffering from severe, poorly controlled asthma, the disease may impact the entire trajectory of their lives.
This intervention is the first to offer any improvement for patients with this condition.	None
Compared to "the comparator", there is significant uncertainty about the long-term risk of serious side effects of this intervention.	None
Compared to "the comparator", there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	All the biologic interventions manipulate the immune response of patients and the long-term implications of such manipulation remain unclear.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	None

Value-Based Benchmark Prices

Our value-based benchmark annual prices for the five asthma biologics are presented in Table ES13. The value-based benchmark price for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained. For all considered biologics, the discounts required to meet both threshold prices are greater than their current discount from WAC.

Table ES13. Value-Based Benchmark Prices of Asthma Biologics in the Treatment of Moderate to Severe Uncontrolled Asthma

Intervention	Annual WAC	Annual Price at $100,000 per QALY Threshold	Annual Price at $150,000 per QALY Threshold	Discount from WAC Required to Achieve Threshold prices
Omalizumab	$39,048	$9,000	$13,300	66% to 77%
Mepolizumab	$37,293	$9,200	$13,400	64% to 75%
Reslizumab	$31,637	$6,500	$10,400	67% to 80%
Benralizumab	$30,889*	$8,300	$11,900	62% to 73%
Dupilumab	$38,110‡	$10,100	$14,300	62% to 73%

*Assuming 6.5 doses per year, year-two onward since year-one has additional loading doses.

‡ Assuming 26 doses per year, year-two onward since year-one has an additional loading dose.

Potential Budget Impact

We used the cost-effectiveness model to estimate the potential total budgetary impact of dupilumab in its indicated population for asthma: adults and children twelve years of age and older with uncontrolled, moderate to severe asthma in the US. We used the WAC, net price, and the three threshold prices for dupilumab in our estimates of budget impact. We did not include omalizumab, mepolizumab, reslizumab or benralizumab in our calculations since they have all already been approved and have been in use in the US marketplace for close to a year, or more.

Table ES14 illustrates the per-patient budget impact calculations, based on WAC ($38,110 per year), net price ($31,000 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY for dupilumab ($14,300 per year, $10,140 per year, and $5,980 per year, respectively) compared to current treatment mix.

Table ES14. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon

	Average Annual Per Patient Budget Impact				
	WAC	Net Price	$150,000/QALY	$100,000/QALY	$50,000/QALY
Dupilumab	$46,059	$38,912	$22,127	$17,945	$13,764
Current Treatment Mix*	$44,651				
Difference (Dupilumab – Current Treatment Mix)	$1,408	($5,738)	($22,524)	($26,705)	($30,887)

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*27% of target population on biologics and 73% on standard of care. Market share among biologics: reslizumab – 1.8%, benralizumab – 5.2%, mepolizumab – 18.2%, and omalizumab – 74.9%

() – Cost-saving

The average potential budgetary impact when using the WAC was an additional per-patient cost of approximately $1,400 per year. Average potential budgetary impact at dupilumab's net price resulted in cost-savings of approximately $5,700 per patient annually. Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug were estimated to be cost saving, ranging from approximately $22,500 per patient in savings using the annual price to achieve $150,000 per QALY to approximately $30,900 per patient in savings using the annual price to achieve a $50,000 per QALY cost-effectiveness threshold. It is important to note that these findings are versus a population-level treatment mix of biologics and SoC. Against just SoC alone, using dupilumab will result in greater budget impact at both the per patient and the population level across the five price points (WAC, net price, prices to reach willingness-to-pay [WTP] thresholds of $50,000, $100,000 and $150,000 per QALY).

At dupilumab's WAC, 91% of the eligible population could be treated before the total budget impact exceeds the ICER annual budget impact threshold. At its net price and prices to reach the

cost-effectiveness thresholds between $50,000 and $150,000 per QALY, the total population budget impact resulted in cost-savings and the entire population could be treated.

Access and Affordability

As illustrated in the budget impact analysis, treating the entire patient population eligible for treatment with dupilumab at the net price and prices to reach commonly accepted WTP thresholds resulted in net savings. Additionally, at dupilumab's WAC, just over 90% of the entire eligible population could be treated each year without the total budget exceeding the ICER budget impact threshold. At the November 29, 2018 public meeting, the consensus among stakeholders was that uptake of dupilumab would likely not threaten access and affordability, given current market competition and dupilumab's anticipated net price for this indication. As such, ICER is not issuing an access and affordability alert at this time. However, all stakeholders should closely monitor the use of dupilumab for uptake exceeding expectations, along with any unprecedented net price increase.

Midwest CEPAC Votes

For patients ≥ 12 years with uncontrolled, moderate to severe asthma, and eosinophilic phenotype:

1. **Is the evidence adequate to demonstrate that the net health benefit of dupilumab is superior to that provided by standard of care (ICS plus at least one additional controller medication)?**

Yes: 12 votes	No: 3 votes

For patients ≥ 12 years with uncontrolled, severe asthma, and eosinophilic phenotype:

2. **Is the evidence adequate to distinguish the net health benefit *among* mepolizumab, reslizumab, and benralizumab?**

Yes: 1 vote	***No: 14 votes***

IF NO…

3. **Is the evidence adequate to distinguish the net health benefit *between* dupilumab and these three treatments?**

Yes: 0 votes	***No: 15 votes***

4. **Is the evidence adequate to distinguish the net health benefit *between* omalizumab and these three treatments?**

Yes: 0 votes	***No: 15 votes***

5. **In the treatment of patients ≥ 12 years with moderate to severe asthma, does dupilumab offer one or more of the following potential other benefits or disadvantages compared to best usual care without biologic treatment?**

Dupilumab offers reduced complexity that will significantly improve patient outcomes.	3/15
Dupilumab will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.	0/15
Dupilumab will significantly reduce caregiver or broader family burden.	6/15
Dupilumab offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	8/15
Dupilumab will have a significant impact on improving patients' ability to return to work and/or their overall productivity.	7/15
There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention	3/15

6. **Are any of the following contextual considerations important in assessing the long-term value for money of dupilumab versus best usual care without biologics?**

This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	11/15
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	12/15
This intervention is the first to offer any improvement for patients with this condition.	0/15
There is significant uncertainty about the long-term risk of serious side effects of this intervention.	8/15
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	11/15
There are additional contextual considerations that should have an important role in judgments of the value of this intervention:	3/15

7. **Are there important and distinctive other benefits or disadvantages, or unique contextual considerations that apply to any of the other biologic treatments for their labeled population?**

Council members noted that dupilumab can be self-administered at home by the patient, whereas the other biologics in the review required an office visit for administration. Conversely, one Council member commented that while self-administration presents an opportunity for increased access, it also risks causing a decrease in adherence. Lack of adherence is not only dangerous for patients but creates significant waste in health-care spending, particularly in this case due to the high cost of the drug. Many Council members acknowledged that self-administration presents a trade-off, but all agreed the increased ease of self-administration was a net-positive for patients.

Long-term Value for Money Votes

As described in ICER's recent update to its **value assessment framework**, questions on "long-term value for money" are subject to a value vote only when incremental cost-effectiveness ratios for the interventions of interest are between $50,000 and $175,000 per QALY in the primary "base case" analysis. As shown in the Evidence Report, the estimates for all five biologics exceed the higher end of the range and thus all interventions are deemed "low value" without a vote of the panel.

Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on asthma biologics to policy and practice. The policy roundtable members included two patient representatives, two clinical experts, one payer, one pharmacy benefits manager, and representatives from all five manufacturers of asthma biologics. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found in Section 8.3.

Manufacturers

- To provide fair value to patients and the health system, manufacturers should lower the prices of biologic therapies for asthma so that they align with the added value they bring to patients.

Plan Sponsors

- Plan sponsors should work with payers to develop insurance coverage that makes an explicit commitment to providing excellent access to all new biologic treatments for asthma if manufacturers will price their products in line with independent assessments of added value to patients.

Payers

- Given that, to date, manufacturers have not priced biologics for asthma at a value-based level, payers are likely to offer preferential formulary status in return for lower prices. For many patients the evidence is not adequate to determine which drug would be superior as a first option, therefore it is reasonable for payers to consider step therapy as a mechanism to achieve lower costs without harming patients.

- In addition to step therapy, payers will to develop prior authorization criteria to ensure that prescriptions are covered only for appropriate patients and that use of these expensive medications is prudent.
- The process for authorization of biologic therapies for asthma should be clear and efficient for providers.
- When patients change insurance, coverage for their biologic should be continued to avoid worsening of asthma control.
- Payers should not deny ongoing coverage of biologic therapy if patients are able to reduce the intensity of their ICS or other long-acting controller medications during treatment with the biologic.
- Manufacturers, insurers, and governments should work to remove barriers to indication-specific pricing.

Specialty Societies

- Specialty societies should develop a clear definition of response to biologic therapy.
- Because of pervasive cost issues, pulmonologists, allergists and their specialty societies should advocate for prices to be better tied to the clinical benefits that drugs bring to their patients.

Researchers

- Head to head comparisons of the biologic therapies for asthma are essential.
- Better instruments to measure quality of life need to be developed.

Regulators

- The FDA should update its guidance for the assessment of outcomes in asthma therapy to standardize the patient populations studied as well as the timing and instruments used to assess outcomes.
- Active comparators should be the standard in pivotal trials.

1. Introduction

1.1 Background

Background

The Centers for Disease Control and Prevention (CDC) estimates that 20.4 million Americans ages ≥ 18 years currently have asthma and an additional 6.1 million children have asthma.[1,2] Asthma causes the airways of the lungs to narrow or become blocked, making it hard to breathe. Many processes contribute to the narrowing, including tightening of the muscles around the airways, inflamed tissue lining the airways, and mucous plugging the airways. The disease follows a waxing and waning course with exacerbations initiated by allergens, cold weather, exercise, pollution, and other triggers. This leads to approximately 14.2 million office visits, 1.8 million emergency room visits, and 440,000 hospitalizations each year in the US.[2] The societal costs are estimated to be $82 billion including $50 billion in direct medical costs, $29 billion from asthma related mortality, and $3 billion from missed work and school.[2] There is a broad spectrum of asthma severity. Severe asthma comprises a small but important subset of all individuals with asthma. Those with severe asthma represent fewer than 5-10% of all individuals with asthma but account for approximately 50% of all costs. In addition to being treated with inhaled corticosteroids (ICS) and long-acting beta agonist (LABA) therapy, these patients are often treated with oral corticosteroids (OCS).[3]

Asthma severity is defined as intermittent or persistent, with persistent asthma subdivided into mild, moderate, and severe.[3] These categories are defined by the frequency of symptoms, lung function, and frequency of exacerbations requiring OCS. Severe asthma is defined as asthma that requires either OCS for >50% of the year or the combination of high dose ICS and a LABA or other medication (leukotriene inhibitor/theophylline) to maintain control.[32] Patients with severe asthma commonly have daily symptoms, awaken at night due to symptoms, have significant limitations in normal activities and an FEV_1 <60% of the normal predicted volume. When asthma is well-controlled, patients have symptoms ≤2 times per week, nocturnal awakening ≤2 times per month, no interference with normal activity, and an FEV_1 >80% of predicted.[3]

Asthma prevalence and severity is greater in Black Americans and in low income, urban populations leading to more hospitalizations and death from asthma.[33-35] Evidence suggests that most of the disparities are due to social determinants of health (education, environmental exposures, psychosocial stressors, access to health care) rather than biologic factors.[36-40]

There are a number of treatments available for asthma, and a stepped care approach is recommended.[3] Short-acting beta agonists (SABAs), such as albuterol, are the primary treatment for mild intermittent asthma. ICS are usually added for persistent asthma. More severe asthma is

treated with the combination of ICS and LABAs. OCS are used for short-term therapy to control asthma exacerbations and chronically for severe asthma that cannot be controlled without OCS. Physicians try to avoid frequent or chronic OCS therapy because it is associated with many long-term complications including growth suppression in children, osteoporosis, Cushing's syndrome, adrenal insufficiency, muscle weakness, diabetes, cataracts, joint necrosis, and an increased risk for infections.[41] Additional therapies for severe asthma include leukotriene inhibitors, theophylline, omalizumab, mepolizumab, reslizumab and benralizumab. Treatment is progressive from Step 1 (SABA as needed), Step 2 (addition of controlled medication, typically low does ICS) to Step 3 (low dose ICS + LABA) Step 4 (medium dose ICS +LABA) to Step 5 (high dose ICS + LABA with consideration of OCS, omalizumab in the subgroup of patients with allergic asthma, or one of the three drugs targeting the IL-5 pathway (mepolizumab, reslizumab and benralizumab) in patients with eosinophilic asthma).[42]

Asthma has been divided into different phenotypes with some overlap. Allergic asthma, which is associated with allergic rhinitis, atopy, and elevated IgE levels, is characteristic of approximately half of all patients with asthma. About half of individuals with severe asthma exhibit the type 2 phenotype with increases in T helper 2 cells.[4] These cells secrete IL-4, IL-5, and IL-13, which increase the proliferation, survival and recruitment of eosinophils and increase IgE levels.[5,6] Activated eosinophils can increase airway smooth muscle contraction and mucous secretion, which are hallmarks of asthma.[43,44]. The medications evaluated in this review target specific components of these pathways and may be more effective in specific asthma patient subgroups.

Monoclonal antibody therapies

This assessment will consider 5 monoclonal antibodies that affect the pathways involved in either the allergic or type 2 inflammatory phenotypes of asthma. The drugs, dosing, their mechanism of action, and their FDA indications for asthma are summarized in Table 1.1 below. Omalizumab is a monoclonal antibody to IgE, which is indicated for the treatment of patients with moderate to severe asthma with the allergic phenotype described above. Mepolizumab, reslizumab, and benralizumab target the IL-5 pathway either with monoclonal antibodies to IL-5 itself (mepolizumab, reslizumab) or to the IL-5 receptor (benralizumab). Dupilumab is a monoclonal antibody to the IL-4 receptor alpha, which modulates both the IL-4 and IL-13 pathways.

Table 1.1. Monoclonal Antibody Therapies for Type 2 Inflammation in Asthma

Drug	Dosing	Mechanism	FDA Indication
Omalizumab (Xolair®, Genentech)	75-375 mg SC Q 2-4 weeks	Anti-IgE	Age ≥ 6 years with moderate to severe persistent asthma who test positive for year-round allergens[7]
Mepolizumab (Nucala®, GlaxoSmithKline)	100 mg SC Q 4 weeks	Anti-IL-5	Age ≥ 12 years with severe asthma and eosinophilic phenotype[8]
Reslizumab (Cinqair®, Teva)	3 mg/kg IV Q 4 weeks	Anti-IL-5	Age ≥ 18 years with severe asthma and eosinophilic phenotype[9]
Benralizumab (Fasenra™, AstraZeneca)	30 mg SC Q 4 weeks x 3, then Q 8 weeks	Anti-IL-5Rα	Age ≥ 12 years with severe asthma and eosinophilic phenotype[10]
Dupilumab (Dupixent®, Sanofi/Regeneron)	200 mg SC Q 2 weeks 300 mg SC Q 2 weeks	Anti-IL-4Rα	Age ≥ 12 years with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma[11]

There are important differences in the indications for each of the drugs even though each drug targets some part of the type 2 inflammatory phenotype (Table 1.1). The covered ages in the pediatric population varies across the five agents from ≥ 6 years for omalizumab, to ≥ 12 years for mepolizumab, benralizumab and dupilumab, to ≥ 18 years for reslizumab. Omalizumab is the only drug approved for the allergic asthma, while the other four drugs are approved for asthma with the eosinophilic phenotype. Finally, two of the drugs are approved for moderate to severe asthma (omalizumab, dupilumab), while the other three are approved for severe asthma only (mepolizumab, reslizumab, benralizumab). It is also worth noting that dupilumab is the only one of the five biologics that is approved for self-administration. The other four require administration by a health professional.

There may be additional benefits for patients suffering from other conditions linked to type 2 inflammation. Three of the 5 agents carry FDA indications for conditions other than asthma. Omalizumab is indicated for chronic idiopathic urticaria. Mepolizumab is indicated for eosinophilic granulomatosis with polyangiitis, and dupilumab is indicated for moderate to severe atopic dermatitis.

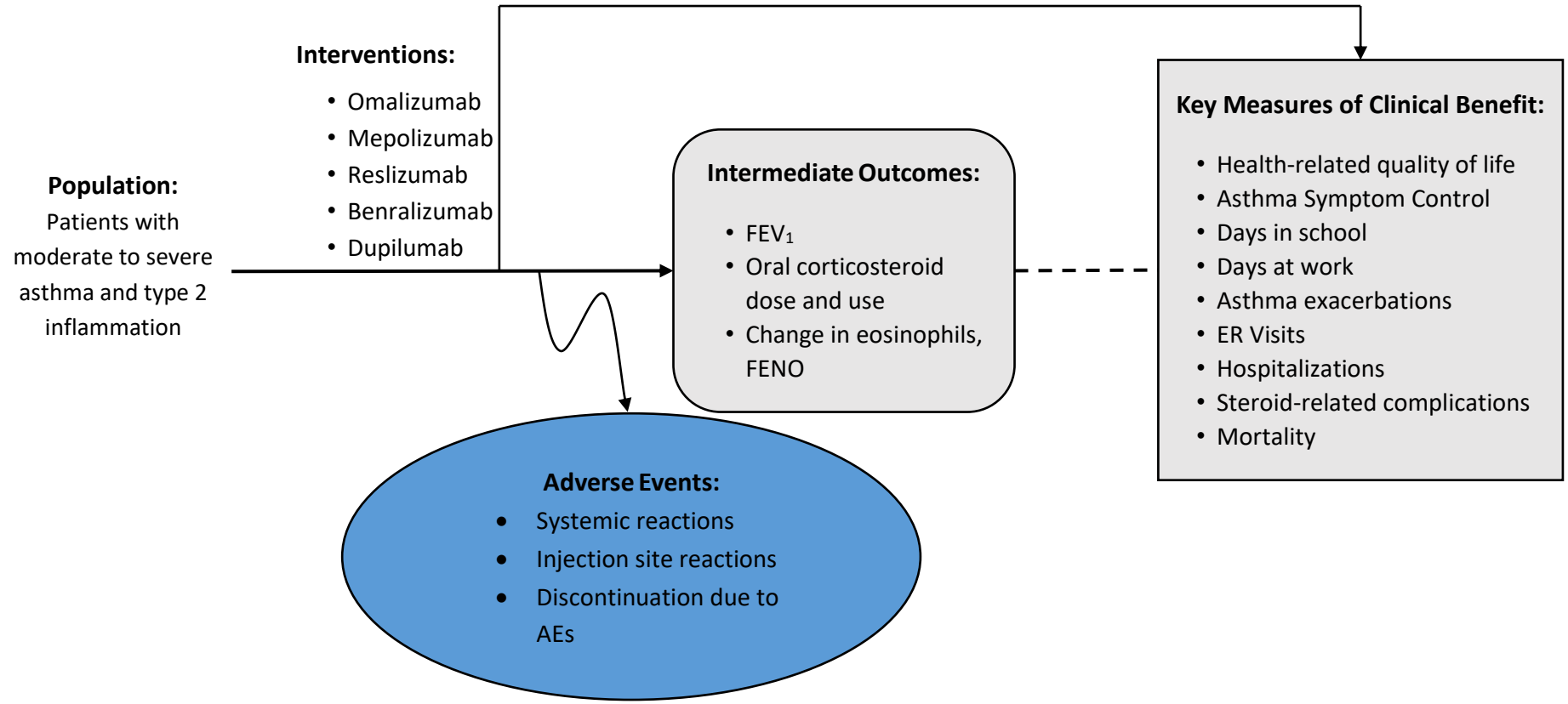
1.2 Scope of the Assessment

The scope for this assessment is described below using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was abstracted from randomized controlled trials as well as high-quality systematic reviews and high-quality cohort studies. Our evidence review included input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/). Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis are available in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.1 on the following page.

Figure 1.1. Analytic Framework: Asthma Management with Biologic Therapies



Note: AEs: adverse effects; FENO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in one second; SAEs: severe adverse effects

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., Oral corticosteroid dose), and those within the squared-off boxes are key measures of benefit (e.g., Health-related quality of life). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.[45]

Populations

The population of focus for the review is adults and children ages six years and older with moderate to severe, uncontrolled asthma and evidence of type 2 inflammation and/or allergic asthma. The population is intentionally broad to capture the indicated populations for all of the biologics, though not all of the therapies are indicated for younger children or patients with moderate asthma. However, for each biologic, we focus primarily on the evidence in its labeled indication. Severe asthma is typically defined as asthma that requires either oral corticosteroids for >50% of the year or the combination of high-dose inhaled corticosteroids and a long-acting beta-agonist or other controller medication (leukotriene inhibitor/theophylline) to maintain control.[32] We recognize that the definitions of both moderate and severe asthma have evolved over time and differ slightly in the most recent GINA and ERS/ATS guidelines.[32,42] Uncontrolled asthma is typically defined by at least one of the following: frequent exacerbations (2+ bursts of oral steroid therapy lasting at least 4 days in the past year); at least one serious exacerbation (hospitalization, ICU stay or mechanical ventilation) in the past year; airflow limitation (FEV_1 <80% predicted); or poor symptom control (Asthma Control Questionnaire >1.5; Asthma Control Test < 20).[32] Similarly, we recognize that the definition of an asthma exacerbation varies across the trials. All individuals should be treated with high-dose inhaled corticosteroid therapy and at least one additional controller medication (e.g., long-acting beta-agonists, long-acting muscarinic agents, leukotriene agonists, theophylline, oral corticosteroids).

Many of the trials excluded participants who were on long-term OCS, although some of the trials allowed maintenance OCS use. Finally, some of the trials included only individuals who were dependent on long-term oral corticosteroids for asthma control, which is a subgroup of individuals with more severe asthma. In addition to looking at overall outcomes, we also summarized data for the subgroup of patients who require long-term oral corticosteroid therapy to maintain control of their asthma.

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The interventions of interest will be one of the following added to daily inhaled corticosteroid therapy plus at least one additional controller therapy:

- Omalizumab 75-375 mg by subcutaneous injection once every two or four weeks
- Mepolizumab 100 mg by subcutaneous injection once every four weeks
- Reslizumab 3 mg/kg by intravenous infusion once every four weeks
- Benralizumab 30 mg by subcutaneous injection once every four weeks for three doses; then every eight weeks
- Dupilumab 200 mg or 300 mg by subcutaneous injection once every two weeks

Comparators

The comparator of interest is standard of care (daily inhaled corticosteroids plus at least one additional controller therapy).

Outcomes

This review will examine clinical and health care utilization outcomes related to asthma. Listed below are the outcomes of interest:

- Symptom scale/quality of life including nocturnal symptoms and impact on daily activities such as the Asthma Quality of Life Questionnaire (AQLQ)
- Asthma control assessed by standard questionnaires: Asthma Control Questionnaire or Asthma Control Test (ACQ or ACT)
- Clinically significant asthma exacerbations (3+ days of systemic corticosteroids with or without ER visit or hospitalization)
- Asthma-related hospitalizations and emergency room visits
- Mortality (Asthma-specific and total)
- Use of oral steroids including a reduction in dose for those on chronic oral steroids
- Forced expiratory volume in one second (FEV_1)
- Absence from school
- Absence from work
- Adherence
- Harms (serious adverse events, injection site reactions, infections)

Timing

Evidence on intervention effectiveness and harms were derived from studies of at least 24 weeks duration.

Settings

All relevant settings were considered, including inpatient, clinic, and outpatient settings, but the focus will be outpatient use of the five therapies.

1.3 Definitions

Severe asthma is defined as asthma that requires either OCS for >50% of the year or the combination of high dose ICS and a LABA or other controller medication (leukotriene inhibitor/theophylline) to maintain control.[32]

Moderate asthma is defined as asthma that is controlled with low dose ICS plus LABA.[42]

Uncontrolled asthma is defined by at least one of the following:

- Frequent exacerbations (two or more bursts of oral corticosteroid therapy lasting at least four days)
- Serious exacerbations (hospitalization, ICU stay or mechanical ventilation)
- Airflow limitation (FEV_1 <80% predicted)
- Poor symptom control (Asthma Control Questionnaire >1.5; Asthma Control Test <20)[32]

Eosinophilic inflammation is typically defined as a blood eosinophil level ≥150 cells/µL at initiation of therapy or ≥300(cells/µL in the prior 12 months, though sometimes as blood eosinophil level ≥400 cells/µL.

Asthma Control Questionnaire (ACQ) scores range from zero to six with higher scores indicating worse control and a change of 0.5 points being the minimal clinically important difference. The ACQ is a seven-item questionnaire that includes five questions on symptoms, FEV_1, and use of rescue inhalers. It is scored from zero to six with higher scores representing worse asthma control. The minimally important difference is 0.5 points.

St George's Respiratory Questionnaire (SGRQ) scores range from zero to 100 with higher scores indicating worse function and a change of four points being the minimal clinically important difference.

Asthma Quality of Life Questionnaire (AQLQ): The AQLQ is a 32-item questionnaire covering four domains (symptoms, activity limitation, emotional function, and environmental stimuli). It is scored from one to seven with higher numbers representing better quality of life. The minimally important difference is 0.5 points.

FEV_1: The FEV_1 is the maximal volume of air that a person is able to blow out in one second. It is a measure of airflow obstruction in the lungs with lower values representing greater obstruction.

1.4 Insights Gained from Discussions with Patients and Patient Groups

The most important insight gained from speaking with patients was their heartfelt desire to be able to perform their day to day tasks of living – to get back to their usual activities of daily living. They want to be back at work and back at school without limitations. Symptom relief, asthma control, and quality of life matter much more to them than a reduction in asthma exacerbations. These include the ability to exercise and the ability to get a good night's sleep, uninterrupted by asthma symptoms. The majority of patients with severe asthma report having symptoms more than once a day and being scared and burdened by their symptoms. They report that their asthma prevents them from living the life that they want to live. The patients report that it also impacts their loved ones: they report that their asthma is a burden to their family and that their caregivers are scared about the possible consequences of asthma. They also have learned to fear the side effects of corticosteroids and want to minimize the use of both systemic and inhaled corticosteroids as much as possible.

The Asthma and Allergy Foundation of America shared results from their survey of 805 Americans living with asthma including 185 with severe, uncontrolled asthma.[12] The two most important factors for choosing a therapy for both groups were effectiveness and then cost. However, effectiveness was the far more important factor for patients surveyed. An average of 82% responded that effectiveness was a key criterion while an average of 52% cited cost as a key criterion.

Adherence with therapy was also raised as an issue. The top three reasons for non-adherence were related to cost: inability to afford treatment, treatment too expensive, and lack of insurance coverage for treatment.[12]

In addition, the Asthma and Allergy Foundation of America's survey showed that patients had limited knowledge about biologic treatments. An average of only 10% of those surveyed were knowledgeable about biologic treatments. This suggests that biologics are not widely discussed nor prescribed by clinicians.[12]

1.5 Potential Cost-Saving Measures in Asthma

As described in its Final Value Assessment Framework for 2017-2019, ICER now includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by biologic therapy for moderate to severe asthma (e.g., reduction in exacerbations, ER visits, and hospitalizations), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of asthma beyond the potential offsets that arise from a new intervention.

ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

Stakeholders have not identified any such services to date.

The Choosing Wisely statement from the **American Academy of Allergy, Asthma & Immunology** includes the following:

Don't diagnose or manage asthma without spirometry.

"Clinicians often rely solely upon symptoms when diagnosing and managing asthma, but these symptoms may be misleading and be from alternate causes. Therefore, spirometry is essential to confirm the diagnosis in those patients who can perform this procedure. Recent guidelines highlight spirometry's value in stratifying disease severity and monitoring control. History and physical exam alone may over- or under-estimate asthma control. Beyond the increased costs of care, repercussions of misdiagnosing asthma include delaying a correct diagnosis and treatment." [13]

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

To understand the insurance landscape for biologic therapies for treatment of asthma associated with type two inflammation, we reviewed publicly available 2018 coverage policies and formularies for Midwestern state Medicaid programs (Missouri and Illinois), regional commercial plans (Blue Cross Blue Shield Kansas City, WellCare IL, and Aetna Better Health IL), and major national commercial plans, including Aetna and Cigna. We surveyed each plan's coverage policies for the five biologics in this review: omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab. No coverage policies were found for dupilumab as a treatment for asthma, because at the time of this publication it has only just been approved by the FDA as an asthma treatment.

Across most of these policies, coverage of these drugs required one to three severe exacerbations in a three to twelve-month period, despite the continued use of a moderate to high-dose inhaled cortical steroid (ICS) and another controller therapy such as a long-acting beta agonist (LABA) or leukotriene receptor antagonist (LTRA). Most policies defined a "severe exacerbation" as one that required multiple days of systemic corticosteroids use (either oral, intravenous, or subcutaneous) and/or an ER visit, hospitalization, or mechanical ventilation.

More specifically, for the four biologics approved by the FDA, all had a non-preferred status in both MO and IL Medicaid programs. Missouri requires the first dose for all four biologics be prescribed by a specialist and the patient have symptoms uncontrolled with continued use of an ICS and another controller therapy. The state also requires that the patient visited the ER for an asthma exacerbation in the past 45 days.[46] Specific criteria for Illinois' Medicaid program could not be found.

Among the three regional commercial plans surveyed, none covered any of these biologics except for WellPoint IL, which covered omalizumab.[47] No specific formulary information could be found.

On the national level, Aetna and Cigna each covered all four of the FDA approved biologics in this review—both payers requiring step therapies and previous exacerbations necessitating an ER or urgent care visit, hospital admission, or high dose injectable or oral cortical steroids. Coverage specifics for these national plans are detailed below in Table 2.1.

Table 2.1. Representative National Private Payer Policies for Omalizumab, Mepolizumab, Reslizumab, and Benralizumab[48-53]

	Aetna	Cigna
Omalizumab		
Tier	4	3
Prior Authorization	Yes	Yes
Step Therapy	Yes	Yes
Eligibility Requirements	≥ 3 exacerbations in the past 3 months despite use of ICS	Uncontrolled symptoms despite use of ICS and controller therapy
Reauthorization Required	Yes, after 3 months	Yes, after 12 months
Mepolizumab		
Tier	5	4
Prior Authorization	Yes	Yes
Step Therapy	Yes	Yes
Eligibility Requirements	≥ 2 exacerbations in past 12 months despite use of high-dose ICS and additional controller therapy	≥ 2 exacerbations or 1 hospitalization in the past 12 months despite use of high-dose ICS and an additional controller therapy OR inadequate control with daily oral corticosteroids in the last 12 months
Reauthorization Required	Yes	Yes, after 12 months
Reslizumab		
Tier	3	
Prior Authorization	Yes	Yes
Step Therapy	Yes	Yes
Eligibility Criteria	≥ 1 exacerbation in past 12 months despite use of high-dose ICS and oral corticosteroids	≥ 2 exacerbations in the past 12 months OR ≥ 1 exacerbation requiring hospitalization in the past 12 months, despite use of high-dose ICS and an additional controller therapy
Reauthorization Required	Yes	Yes, after 12 months
Benralizumab		
Tier	3	
Prior Authorization	Yes	N/S
Step Therapy	Yes	N/S
Eligibility Criteria	≥ 2 exacerbations requiring systemic corticosteroid treatment in the past 12 months, despite use of high-dose ICS and an additional controller therapy	N/S
Reauthorization Required	Yes	N/S

2.2 Clinical Guidelines

The U.S. Department of Health and Human Services, National Institutes of Health, and National Heart, Lung, and Blood Institute

The U.S. Department of Health and Human Services (HHS), National Institutes of Health (NIH), and National Heart, Lung, and Blood Institute (NHLBI) jointly released clinical guidelines for the diagnosis and treatment of asthma. The most updated guidelines, released in 2007, specify four components to care after diagnosis: assessment and monitoring, education, controlling environmental factors and comorbid conditions, and medications. These four components, as well as diagnostic criteria, are summarized below.[54]

Diagnosis: Clinicians must evaluate symptoms of recurrent airflow obstructions, ruling out other possible causes, such as a heart condition. Common symptoms of asthma include: wheezing, coughing, and difficulty breathing, with symptoms potentially worsening at night, during one's menstrual cycle, and/or with exercise, presence of allergens, changes in weather or strong emotional expression. The presence of multiple symptoms may suggest that asthma is probable, but clinicians must use spirometry in patients at or above the age of five to establish an asthma diagnosis. Spirometry can demonstrate whether the airway is obstructed and if the obstruction is at least partially reversible.

Four Components to Care

I. **Assessment and Monitoring:** Clinicians are instructed to use the severity classification chart to determine initial treatment, keeping in mind multiple measures of impairment and risk. Asthma manifests in different ways and these measures may or may not correlate to each other and may respond differently to the same treatments. The guidelines warn that asthma is highly variable over time and requires consistent periodic monitoring, recommending that doctors see patients at two to six-week intervals while gaining control of symptoms, at least every six months to evaluate care management, and every three months if a step-down therapy is being considered.
II. **Education:** Guidelines emphasize teaching patients how to self-assess their symptoms and avoid environmental factors that exacerbate the condition. Clinicians are advised to work with patients to create a "written asthma action plan" so patients can agree on treatment goals and understand treatment protocol. Moreover, the guidelines state that clinicians should take special care to review the differences between long-term control and quick-relief medication and what medications and/or interventions each involves. Clinicians also must ensure that patients understand how to correctly use their inhalers and/or devices.
III. **Control Environmental Factors and Comorbid Conditions:** Clinicians must evaluate patients for environmental sensitivities and symptom triggers and advise patients on how to avoid common irritants. The guidelines recommend using skin or in vitro testing to assess

sensitivity to indoor allergens, in patients with persistent asthma; and when there is clear evidence of a relationship between exposure to a particular allergen and exacerbated symptoms, allergen immunotherapy should be considered. The guidelines also stress the necessity of treating comorbid conditions that could exacerbate symptoms, highlighting—allergic bronchopulmonary aspergillosis; gastroesophageal reflux, obesity, obstructive sleep apnea, rhinitis and sinusitis, and stress or depression—noting that asthma control may improve by treating these conditions.

IV. **Medications:** The last component to care is medication. The guidelines divide asthma medications into long-term control medications and quick-relief medications. Patients with persistent asthma require long-term control medication in addition to quick-relief medications for acute exacerbations. These clinical guidelines outline a stepwise approach (Step 1 being the minimum medication protocol and Step 5 being the heaviest medication protocol) to identifying appropriate medications for asthma patients.
    a. **Quick relief medications:** These medications should be used to treat acute exacerbations.
        i. **Short-acting beta agonists (SABAs):** Step 1 treatment involves administering SABAs, such as albuterol, for relief of mild intermittent asthma. If SABAs are used more than twice a week for symptom relief, this indicates uncontrolled asthma and additional therapies should be considered.
        ii. **Anticholinergics** can be used as an alternative to SABAs if SABAs are not tolerated by the patient.
    b. **Long-Term Control Medications:** Patients suffering persistent symptoms, despite the use of SABAs or anticholinergics, should consider daily long-term control medications. The guidelines outline the most common medications and broad step-therapy guidance, which is listed below:
        i. **Corticosteroids**, most often as an Inhaled Corticosteroids (ICS), are the most consistently effective treatment for patients with persistent asthma at Steps 2 and above. Clinicians are advised to begin long-term therapy with ICS and then reevaluate control. Oral corticosteroids (OCS) are used as a Step 6 treatment for patients with severe persistent asthma.
        ii. **Cromolyn sodium and nedocromil** are an alternative to corticosteroids for patients requiring Step 2 care but should only be used if corticosteroids do not provide control.
        iii. **LABAs** (salmeterol and formoterol) are used in combination with ICS for long-term control of moderate to severe persistent asthma in patients ages five and above requiring Step 3 care or higher, and patients under the age of five requiring Step 4 care or higher. Of all the available controller medications, the guidelines highlight LABAs as the preferred adjunctive therapy for patients at or over the age of 12.

iv. **Leukotriene modifiers** include LTRAs (montelukast and zafirlukast) and a 5-lipoxygenase inhibitor (zileuton). LTRAs are alternative therapies for patients with mild persistent asthma requiring Step 2 care, often used in conjunction with ICS. However, if the patient is at or over the age of 12, LABAs should be considered as an alternative treatment first. Zileuton is another alternative therapy for adults with mild, persistent asthma, but is not preferred.

v. **Immunomodulators** are used as additional therapy for patients at or over the age of 12 with moderate to severe, persistent asthma requiring Step 5 or 6 care, who also have sensitivities to applicable allergens. These guidelines specifically name omalizumab as one of these treatments.

vi. **Methylxanthines** (including theophylline) are an alternative, but not preferred, adjunctive controller therapy for patients requiring Step 2 care at or above the age of five.

c. The guidelines advise that clinicians consistently monitor level of asthma control and adjust as needed. If asthma is well-controlled for three months, a step-down therapy should be considered. As therapies are being stepped up or down, clinicians should see patients every one to six weeks.

National Institute for Health and Care Excellence (NICE)

We also reviewed clinical guidelines from the National Institute for Health and Care Excellence (NICE). Recommendations were similar to those discussed above, aside from the following key differences:

- **Anticholinergics** are not advised for mild intermittent asthma. A long-acting muscarinic receptor antagonist may be used as an additional therapy for patients at or above the age of 17 if asthma remains uncontrolled on ICS with a LABA, with or without an LTRA.
- **LTRAs and LABAs:** If asthma is uncontrolled with first-line maintenance therapy on ICS, NICE recommends offering a LTRA in addition to ICS and reevaluating treatment after four to eight weeks. If asthma remains uncontrolled, patients may be offered a LABA in combination with ICS, and LTRA treatment may be continued or discontinued depending on the response to treatment.
- **Maintenance and reliever therapy (MART)**, involving the combination of low maintenance ICS dose and a LABA with a fast-acting component in a single inhaler, may be used if asthma is uncontrolled on ICS with a LABA, with or without an LTRA.[55]

These guidelines make clear that the biologics evaluated in this report are one piece of a comprehensive treatment plan that includes close clinician monitoring and assessment, control of patient's environment and comorbidities, and patient engagement and adherence to his/her full treatment plan.

American Thoracic Society (ATS) and European Respiratory Society (ERS)

In 2013, a task force supported by the American Thoracic Society (ATS) and European Respiratory Society (ERS) produced clinical guidelines on the diagnosis and treatment of severe asthma in children and adults. These guidelines, summarized below, outline a stepwise treatment plan that is similar to that recommended by the HHS, NIH, and NHLBI.

Diagnosis: The ATS-ERS task force recommends diagnosis in children by clinical criteria along. In adults, sputum eosinophil counts should be evaluated in addition to clinical criteria only in centers experienced in using this technique. Exhaled nitric oxide should not be used to guide therapy.

Treatment: Severe asthma should be controlled with a combination of high dose inhaled corticosteroids, beta-agonists, leukotriene receptor antagonists, and/or other controller medications.

- **Oral and inhaled corticosteroids:** Because severe asthma necessarily involves corticosteroid insensitivity, OCS are often required in addition to ICS to maintain control of asthma symptoms. Higher than average doses of ICSs may be used in patients with moderate to severe asthma. However, it is noted that systemic corticosteroid use can lead to serious long-term adverse effects.
- **Beta-agonists:** Step-wise increases in the dose of ICS together with a LABA are recommended if asthma is not controlled with an ICS alone. Patients with severe asthma may also receive a LABA in combination with an as-needed SABA.
- **Leukotriene pathway modifiers:** Adding a leukotriene receptor antagonist or synthesis inhibitor to ICS has been shown to improve lung function in adults with moderate to severe asthma. However, montelukast has been shown to be less effective than LABAs when added to ICS.
- **Other therapies:** A therapeutic trial of omalizumab is recommended in adults and children with severe allergic asthma. In moderate asthma, theophylline may be added to an ICS to improve asthma control. Tiotropium bromide, a long-acting muscarinic antagonist, has also been shown to improve lung function in adults whose asthma was not controlled on moderate- to high-dose ICS with or without a LABA.

Global Initiative for Asthma

The Global Initiative for Asthma (GINA) Science Committee meets biannually alongside the ATS and ERS international conferences to conduct a systematic review of the asthma literature and produce revised clinical guidelines for evaluation and treatment of asthma. Recommendations from the most recent version of the report, updated in 2018, are summarized below. The GINA guidelines outline a continuous asthma management cycle emphasizing assessment, pharmacological and non-pharmacological treatment, and review.

Assessment: Patients with asthma will present with respiratory symptoms such as wheezing, shortness of breath, cough, and chest tightness, that are often worse at night or in the early morning and may be triggered by environmental factors, exercise, or viral infections. The presence of these symptoms suggest that a patient may have asthma, but a diagnosis should be confirmed by a detailed history and examination for asthma and spirometry. Asthma control should then be assessed by symptom control, treatment issues, and comorbidities.

Treatment: A step-wise approach is recommended to control asthma symptoms and minimize future risk. Step 1 treatment should be initiated with an as-needed SABA and low dose ICS may be considered as a controller. If asthma remains uncontrolled on step 1 treatment, low dose ICS should be administered. An LTRA or low dose theophylline may be used as an additional controller. Allergen immunotherapy may also be considered if is there is a clear relationship between exacerbations and exposure to a specific allergen. Step 3 treatment involves addition of an LABA to low dose ICS. ICS dosage may be increased at this point, if needed, and formoterol may be considered as an alternative reliever medication. Medium or high dose ICS in addition to a LABA is recommended for step 4 treatment, and tiotropium may be considered as a controller option. If severe asthma remains uncontrolled on step 4 therapy, the patient should be referred for add-on treatment, such as an anti-IgE or anti-IL5 biologic. Low dose OCS may also be added as a controller.

Review: Before stepping up treatment, clinicians should check for issues such as improper use of an inhaler, poor adherence to medication, or environmental factors, and confirm that the diagnosis is correct. Clinicians may consider stepping down treatment if symptoms remain controlled for three months and there is low risk for exacerbations. However, stopping ICS treatment is not recommended.

3. Comparative Clinical Effectiveness

3.1 Overview

To inform our analysis of the comparative clinical effectiveness of the five biologics added to standard of care (SoC) versus SoC alone, we abstracted evidence from RCTs of individuals ages six years and older with moderate to severe allergic asthma or eosinophilic asthma. The comparator treatment for each intervention of interest included SoC treatment with ICS and at least one additional controller agent. Our review focused on clinical benefits (i.e., asthma exacerbations, ED visits, hospitalizations, quality of life (AQLQ, ACQ, SGRQ) as well as potential harms (severe adverse events, adverse events leading to discontinuation of therapy). We also summarized intermediate markers of interest including change in FEV_1 and blood eosinophil levels.

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab for moderate to severe asthma follow established best methods.[56,57] The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[58,59] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Eligibility criteria described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Appendix Tables A2 and A3.

To supplement the database searches, we performed a manual check of the reference lists of included trials and reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection was accomplished through two levels of screening, at the abstract and full-text level. Two reviewers independently screened the titles and abstracts of all publications using DistillerSR (Evidence Partners, Ottawa, Canada) and resolved any issues of disagreement through consensus. No study was excluded at abstract level screening due to insufficient information. For example, an abstract that did not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening were retrieved in full text for review. Reasons for exclusion were categorized according to the PICOTS elements during full-text review.

Data Extraction Strategy

Data were extracted into evidence tables (Appendix Tables D1-D6).

Data extraction was performed in the following steps:

1. Two reviewers extracted information from the full articles.
2. Extracted data was reviewed for logic, and data were validated by a third investigator for additional quality assurance.

We used criteria employed by the US Preventive Services Task Force ([USPSTF] see Appendix D) to assess the quality of clinical trials, using the categories "good," "fair," or "poor."[60]

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include "omalizumab," "mepolizumab," "reslizumab," "benralizumab," and "dupilumab." We selected studies which would have met our inclusion criteria, and for which no findings have been published. We provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Summary of Evidence Base

The studies are summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. Evidence tables are presented in Appendix Tables D1-D6. Relevant data include those listed in the data extraction section. Important differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality are noted in the text of the report.

Synthesis of Results

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. We used the estimates from two Cochrane systematic reviews and meta-analyses for omalizumab, mepolizumab, reslizumab and benralizumab.[14,15] We identified only one relevant trial for dupilumab for each of the outcomes (reduction in exacerbations, improvements in quality of life, reduction in oral corticosteroid dose), so no meta-analysis needed to be performed. We performed our own meta-analysis for outcomes that were not assessed in the Cochrane reviews (discontinuation due to AEs for omalizumab; injection site reactions for mepolizumab, reslizumab, and Benralizumab).

We defined a population that was similar enough in baseline characteristics to conduct a network meta-analysis: patients with baseline eosinophil counts ≥ 300, at least 2 exacerbations in the prior year, and a baseline ACQ score ≥ 1.5. We appreciate the cooperation of the manufacturers who shared data for this subgroup to inform our report. The inputs and methods used for the analysis are reported in Appendix D.

3.3 Results

The results are organized by outcome and then by drug within outcome in the order of FDA approval. For each drug, we only included trials that randomized patients to the FDA approved dose and formulation of the drug with at least 24 weeks follow-up. For example, trials of the IV formulation of mepolizumab are not included because the FDA approved formulation is SC. For summary estimates, we used the 2014 Cochrane Review for omalizumab[14] and the 2017 Cochrane Review for mepolizumab, reslizumab, and benralizumab.[15] For mepolizumab, reslizumab, and benralizumab we only used the results for patients with eosinophilic asthma to match the FDA indications for those three drugs.[8-10]

There is significant heterogeneity in the FDA indications for the five drugs: allergic versus eosinophilic asthma and starting ages of 6, 12, or 18 years. This is reflected in the differences in the inclusion criteria for the trials (Table 3.1 below and Appendix Table D2), although not always in the characteristics of the patients in the clinical trials (Appendix Table D1). For example, across the clinical trials, approximately 60% of the participants were female and their baseline AQLQ score was approximately 4.1. Among the trials that enrolled both patients using and not using OCS, the proportion on OCS was approximately 17%. However, the patients in the omalizumab trials were somewhat younger (approximately 42 years vs. 48 for the other trials), which reflects the epidemiology of allergic asthma, which tends to be in patients younger than those with severe eosinophilic asthma. In addition, the annualized exacerbation rates in the placebo groups of the trials of mepolizumab and reslizumab (~2.1 per person year) were higher than those observed in the placebo groups of the trials of the other 3 drugs (~1.1 per person year).

Table 3.1. Inclusion Criteria Heterogeneity Among the Clinical Trials

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Asthma Severity	Moderate to severe	Severe	Moderate to severe	Severe	Moderate to severe
Exacerbation History (past 12 months)	-	≥2	≥1	≥2	≥1
Allergy Required	+	-	-	-	-
IgE level	30-700 IU/mL	-	-	-	-
Eosinophil Level (cells/µl)	-	≥150 at initiation or ≥300 in past 12 months	≥400	Any (stratified < vs. ≥300 at enrolment)	Any (690/1638 patients with ≥300)
Standard of Care Therapy	Medium to high dose ICS Secondary controllers allowed but not required	High dose ICS With a secondary controller medication	Medium to high dose ICS With or without another controller drug	Medium to high dose ICS With LABA	Medium to high dose ICS With LABA
Use of maintenance OCS allowed	Yes	Yes	Yes	Yes	No

ICS: inhaled corticosteroids, LABA: long-acting beta2-adrenergic agonist, OCS: oral corticosteroids, SoC: standard of care, - : not required

Another important difference seen in row 2 of Table 3.1 is that the trials of both omalizumab and dupilumab enrolled patients with both moderate and severe asthma, while the trials of the 3 IL-5 drugs (mepolizumab, reslizumab, and benralizumab) restricted their studies to patients with severe asthma. This is mirrored in the FDA indications for the 5 drugs.

In addition, the definition of an exacerbation differed between studies (Table 3.2) in part due to changes in the guidelines used to design the pivotal trials for asthma biologics. The 1997 National Heart, Blood and Lung Institute (NHLBI) Asthma guideline, which focused on level of asthma severity, was used to inform the design of the Xolair pivotal trials.[61] However, other asthma biologics, all of which were approved after 2015, based their pivotal trials on the more recent 2007 NHLBI Asthma and Global Initiative for Asthma (GINA) guidelines which focus on asthma control.[42,54]

Table 3.2. Differences in the Definition of an Asthma Exacerbation Among the Clinical Trials

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab[62,6352,5351,5249,50]	Dupilumab
Exacerbation defined by: Doubling ICS dose	+	-	+	-	-
OCS use	+	+	+	+	+
ED visit or hospitalization	-	+	+	+	+

ED: emergency department, ICS: inhaled corticosteroids, + : met definition, - : not required, OCS: oral corticosteroids

Because of these differences, we did not think it was appropriate to perform an NMA across the trials as our primary analysis. We did perform an exploratory NMA in the subgroup of patients with high eosinophil counts and at least two exacerbations in the prior year, because this group was more homogeneous and several trials reported that their biologic therapy was more effective in patients with eosinophil counts ≥ 300 cells/µL.[16,19,64]

Study Selection

Details of the search criteria are described above. The PRISMA flow diagram is Appendix Figure A1.

Quality of Individual Studies

Appendix Table D3 summarizes the quality of the included randomized trials. We judged that the trials met all criteria and were thus judged to be of good quality. Comparable groups were assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and an intention to treat analysis was used as the primary analysis.

Clinical Benefits

Reduction in Exacerbation Rates Requiring Systemic Steroids

As noted above, there were no head to head randomized or observational trials of the five monoclonal antibodies. The summary estimates from the Cochrane meta-analyses[14,15] for each of the drugs are summarized in Table 3.3 below in addition to the estimates for dupilumab from the pivotal trial.[16-18] As can be seen in the Table, all five of the drugs reduced the annual exacerbation rate by about 50% with overlapping confidence intervals despite both the differences in the patient populations studied and the different mechanisms of action of the drugs. These estimates are specific to the populations in which each drug was studied and likely vary by patient characteristics.

For instance, the relative rates have been shown to be consistently lower (greater efficacy) for each of the drugs in populations with higher baseline eosinophil counts.[16-20] If the drugs were compared in identical patient populations the differences in rate ratios between each pair of the drugs might be larger or smaller than the ones observed in Table 3.3.

Table 3.3. Rate Ratio for Asthma Exacerbations Requiring Steroid Therapy

Treatment	Rate Ratio (95% CI)
Omalizumab	0.52 (0.37-0.73)
Mepolizumab	0.45 (0.36-0.55)
Reslizumab	0.43 (0.33-0.55)
Benralizumab	0.59 (0.51-0.68)
Dupilumab 200 mg	0.44 (0.34-0.58)
Dupilumab 300 mg	0.40 (0.31-0.53)

Measures of Health-Related Quality of Life and Asthma Control

The reduction in exacerbation rates is often the focus of the clinical trials, but patients only have one or two exacerbations per year (rate in the placebo group of the clinical trials). Their quality of life when they are not having exacerbations is even more important to patients. They want to be able to go to work and school, exercise, and sleep through the night. The measures below attempt to quantify patients' quality of life.

The AQLQ is a 32-item questionnaire covering four domains (symptoms, activity limitation, emotional function, and environmental stimuli). It is scored from one to seven with higher numbers representing better quality of life. The minimally important difference is 0.5 points. The average AQLQ score prior to therapy in the studies was close to four in across all of the studies.

Table 3.4. Mean Difference in AQLQ Between Treatment and Placebo

Treatment	Difference (95% CI)
Omalizumab	0.26 (0.05-0.47)
Mepolizumab	NR
Reslizumab	0.28 (0.17-0.39)
Benralizumab	0.23 (0.11-0.35)
Dupilumab 200 mg	0.29 (0.15-0.44)
Dupilumab 300 mg	0.26 (0.12-0.40)

AQLQ: Asthma Quality of Life Questionnaire, NR: not reported

As can be seen in Table 3.4 above, the average improvement for four of the drugs compared with placebo is modest and none of them reach the minimally important difference, although all were statistically significant. The trials of mepolizumab using the FDA approved SC formulation did not report AQLQ outcomes data, though they did report it for the IV formulation. The AQLQ scores in Table 3.4 are average changes across all participants, some of whom had large improvements, and

some had no improvement at none at all. As with the estimates for asthma exacerbations, the change in AQLQ estimates for each drug in Table 3.4 come from different populations, so comparisons between drugs are highly uncertain due to potential selection bias. This caveat applies to all of the Tables 3.3 through 3.10 but will not be repeated for each outcome.

The ACQ is a 7-item questionnaire that includes five questions on symptoms, FEV_1, and use of rescue inhalers. It is scored from zero to six with higher scores representing worse asthma control. The minimally important difference is 0.5 points. The average ACQ score prior to therapy in the studies was close to 2.5 in across all of the studies (see Appendix Table D1) except for the INNOVATE study of omalizumab (mean ACQ 3.9)[65] and the DREAM study of mepolizumab (mean ACQ 4.2).[66]

Table 3.5. Mean Difference in ACQ Between Treatment and Placebo

Treatment	Difference (95% CI)
Omalizumab	NR
Mepolizumab	-0.42 (-0.56 to -0.28)
Reslizumab	-0.27 (-0.36 to -0.19)
Benralizumab	-0.23 (-0.34 to -0.12)
Dupilumab 200 mg	-0.39 (-0.53 to -0.25)
Dupilumab 300 mg	-0.22 (-0.36 to -0.08)

ACQ: Asthma Control Questionnaire

As with the AQLQ, the improvements in the ACQ compared with placebo were clinically modest, but statistically significant for the four drugs that reported this outcome in randomized trials (Table 3.5).

Some of the trials of mepolizumab also reported changes in the SGRQ. The SGRQ is a 50-item questionnaire focusing on overall health, daily life, and perceived well-being. It is scored from 0 to 100 with higher numbers representing greater limitations. The minimally important difference is the four points. The SGRQ has been used in COPD but has been extensively validated in patients with asthma.[21-25] The summary estimate for mepolizumab compared with placebo was -7.40 points (95% CI: -9.50 to -5.29). By this measure, the average patient treated with mepolizumab had a clinically meaningful improvement in quality of life, even though this was not observed with the ACQ or AQLQ in these trials.

Surrogate markers of response

Several surrogate markers were reported in the majority of trials.

Pre-Bronchodilator FEV_1: The forced expiratory volume in one second (FEV_1) is a measure of obstruction to the flow of air in the lungs. When asthma is under poor control, the FEV_1 is lower than when it is under good control. All of the drugs significantly improved FEV_1 compared with

placebo (Table 3.6 below), although the magnitude of the improvement appeared to be somewhat smaller for omalizumab compared to the other four biologics. This may represent differences in the patient populations studied, particularly given that omalizumab is indicated for allergic asthma, while the other drugs are indicated for eosinophilic asthma.

Table 3.6. Mean Difference in Pre-Bronchodilator FEV_1 Between Treatment and Placebo

Treatment	Difference, L (95% CI)
Omalizumab	0.06 (0.02-0.10)
Mepolizumab	0.10 (0.01-0.18)
Reslizumab	0.12 (0.08-0.16)
Benralizumab	0.13 (0.08-0.19)
Dupilumab 200 mg	0.14 (0.08-0.19)
Dupilumab 300 mg	0.13 (0.08-0.18)

FEV_1: forced expiratory volume in one second

Blood Eosinophil Levels: Blood eosinophil levels are a marker of type 2 inflammation and are explicitly targeted by three of the drugs (mepolizumab, reslizumab, and benralizumab). The changes in blood eosinophils were not reported for omalizumab and were markedly greater for reslizumab than for the other three drugs reporting changes in eosinophil levels (Table 3.7 below). Despite having the greatest reductions in blood eosinophils, reslizumab did not have the greatest improvements in quality of life measure or improvements in FEV_1, though it did have the greatest reduction in asthma exacerbations. The inclusion criteria for the trials of reslizumab required an eosinophil count ≥ 400 cells/µL, which led to an average starting eosinophil count for the reslizumab trials (655 cells/µL) that was much higher than that for the other trials (300-500 cells/µL). This may explain in part the larger absolute decrease in eosinophil counts with reslizumab, but this does not appear to predict greater improvements in quality of life nor markedly greater reductions in asthma exacerbations.

Table 3.7. Mean Difference in Blood Eosinophil Levels Between Treatment and Placebo

Treatment	Difference, cells/µL (95% CI)
Omalizumab	NR
Mepolizumab	-170 (-228 to -110)*
Reslizumab	-477 (-499 to -454)
Benralizumab	-105 (-116 to -93)
Dupilumab 200 mg	-129 (-192 to -66)
Dupilumab 300 mg	-129 (-193 to -65)

* This is for IV dosing. Not reported for SC dosing.

Harms

All five drugs were well tolerated. As can be seen in Table 3.8 below, the risk for serious adverse events was lower in the active drug group than the placebo group for all five drugs, with the

exception of the 300 mg dose of dupilumab. The reductions were statistically significant for both omalizumab and mepolizumab. This likely reflects a reduction in asthma-related events.

Table 3.8. Risk Ratio for Serious Adverse Events

Treatment	Risk Ratio (95% CI)
Omalizumab	0.72 (0.57-0.91)
Mepolizumab	0.63 (0.41-0.97)
Reslizumab	0.79 (0.51-1.22)
Benralizumab	0.80 (0.60-1.06)
Dupilumab 200 mg	0.93 (0.59-1.47)
Dupilumab 300 mg	1.03 (0.67-1.61)

There were no differences in withdrawals due to adverse events with omalizumab compared with placebo. There were trends towards greater drug discontinuation rates due to adverse events for benralizumab (Table 3.9 below) and a significant increase in drug discontinuation rates for the 300 mg dose of dupilumab. However, there was a significant reduction in discontinuation due to adverse events for dupilumab at the 200 mg dose. Either these are chance findings, or the 300 mg dose causes more adverse events that are bothersome to patients than the 200 mg dose. For the other two drugs (mepolizumab, reslizumab), there were non-significant trends towards a lower rate of drug discontinuation due to adverse events.

Table 3.9. Risk Ratio for Adverse Events Leading to Drug Discontinuation

Treatment	Risk Ratio (95% CI)
Omalizumab	*
Mepolizumab	0.45 (0.11-1.80)
Reslizumab	0.67 (0.37-1.20)
Benralizumab	2.70 (0.86-8.49)
Dupilumab 200 mg	0.50 (0.27-0.92)
Dupilumab 300 mg	2.23 (1.14-4.38)

*The Cochrane review reported qualitatively that there were no differences in drug discontinuation due to adverse events compared with placebo.[14]

The only consistent adverse event that was more common in the drug arm of the randomized trials compared with the placebo arm was injection site reactions. They were about twice as common in the drug arm as in the placebo arm for most the drugs. Reslizumab was the exception, which may be due to the IV administration of the drug. However, the confidence interval for reslizumab was wide (Table 3.10).

Table 3.10. Risk Ratio for Injection Site Reactions

Treatment	Risk Ratio (95% CI)
Omalizumab	1.72 (1.33-2.24)
Mepolizumab	1.98 (1.06-3.72)
Reslizumab	0.62 (0.20-1.89)
Benralizumab	1.43 (0.81-2.52)
Dupilumab 200 mg	2.80 (1.70-4.61)
Dupilumab 300 mg	1.79 (1.24-4.38)

Other Harms

Both omalizumab and reslizumab carry a black box warning for anaphylaxis, which can occur with the first dose or shortly after doses given more than a year on therapy. Patients must be taught the signs and symptoms of anaphylaxis and clinicians need to be prepared to manage anaphylaxis. The estimated rate of anaphylaxis for omalizumab is 0.1%.[8] The estimated rate of anaphylaxis for reslizumab is 0.3%.[9]

The most common side effects of omalizumab are myalgias, fatigue and injection site reactions. During the five-year follow-up of omalizumab mandated by the FDA, there was a suggestion of an excess of transient ischemic attacks, myocardial infarctions, and pulmonary hypertension, but this was not confirmed in a review of 25 randomized, placebo controlled clinical trials.

The most common side effects of mepolizumab are headache, fatigue, nasopharyngitis and injection site reactions. Hypersensitivity reactions have been reported after receiving mepolizumab. There may also be a small risk of herpes zoster. However, in the initial clinical trials, only three subjects receiving mepolizumab developed herpes zoster compared to two subjects who received placebo, which may be a chance finding.

The most common side effect of reslizumab is oropharyngeal pain.

The most common side effects with benralizumab are headache, pharyngitis and pyrexia. Hypersensitivity reactions have been reported rarely with benralizumab. Benralizumab binds to the Fc receptor on natural killer cells which markedly lowers eosinophils by inducing apoptosis. It is unclear if this has any important clinical implications at this time.

In the trials of dupilumab for atopic dermatitis, injection site reaction, nasopharyngitis, and headache were the most common side effects and there appeared to be increased rates of conjunctivitis. In the trials for asthma, only injection site reactions were more common in the dupilumab group (9% vs. 4%). Among the other common AEs in the asthma trials, the risk was lower or similar with dupilumab compared with placebo (viral upper respiratory infections 9% vs. 18%; bronchitis 7% vs. 6%; sinusitis 7% vs. 4%; and influenza 3% vs. 6%)

Subgroup Analyses

Pediatric Patients

The pivotal trials for several of the drugs enrolled patients with ages younger than 18 years, but the number of participants were small. Two randomized trials of omalizumab specifically enrolled pediatric patients.[67,68] The first randomized 334 children ages 6-12 to omalizumab or placebo. Follow-up was 24 weeks, but only 16 weeks at stable dose ICS followed by eight weeks of ICS dose reduction. Patients on omalizumab had fewer exacerbations (18.2% vs. 38.5%, p<0.001) during the dose reduction phase and more patients on omalizumab were able to completely stop ICS (55% vs. 39%, p=0.004).[68] It is noteworthy that 39% of patients in the placebo group were able to stop ICS use, which suggests overtreatment in a substantial proportion of pediatric patients. It may be reasonable to attempt steroid down-titration prior to initiating biologic therapy.

The second trial randomized 419 children ages six to twenty years (mean 11 years) to omalizumab or placebo and followed them for 60 weeks.[67] Patients on omalizumab had fewer exacerbations (30.3% vs. 48.8%, p<0.001), fewer days with asthma symptoms (1.48 vs. 1.96 days per two weeks, p<0.001), and fewer days missed from school (0.16 vs. 0.25 per 2 weeks, p=0.038). Similarly, there were fewer hospitalizations for asthma among the participants randomized to omalizumab (1.5% vs. 6.3%, p=0.02). These benefits were seen despite greater reductions in the dose of inhaled corticosteroids (p<0.001) and LABA (p=0.003) for patients in the omalizumab group.

Omalizumab is the only biologic with studies dedicated to the pediatric population. The two studies consistently demonstrated a reduction in asthma exacerbations with fewer hospitalization and days missed from school in the larger, longer study. The studies demonstrated these benefits while also demonstrating a reduction in the need for ICS and LABA therapies.

Patients on Oral Corticosteroids

There are published studies for omalizumab,[69] mepolizumab,[70] benralizumab,[71] and dupilumab[17] that specifically evaluated the reduction in OCS use in patients requiring chronic OCS for asthma. We did not identify any studies of reslizumab for patients on chronic OCS.

A subgroup of 82 patients in the open label EXALT study were using OCS at baseline.[69] By week 32, patients randomized to omalizumab had greater reductions in their dose of OCS (-45% vs. +18.3%, p=0.002) and there was a trend towards a greater proportion who were able to completely stop OCS use (32.2% vs. 13%, p=0.08).

The SIRIUS study randomized 135 patients with severe eosinophil asthma on OCS to either mepolizumab or placebo.[70] The median reduction in OCS dose was 50% in the mepolizumab group versus 0% in the placebo group (p=0.007). A greater proportion of patients in the mepolizumab group were able to reduce OCS to ≤ 5 mg per day of prednisone (54% vs. 32%, p=0.02), though the

proportions able to stop OCS were not different (14% vs. 8%, p=0.41). Despite the greater reduction in OCS, patients in the mepolizumab group had lower rates of exacerbations (1.44 vs. 2.12, p=0.04) and a greater reduction in symptoms on the ACQ (difference=0.52, p=0.004).

The ZONDA study randomized 220 patients with severe eosinophilic asthma on OCS to either benralizumab 30 mg every four or eight weeks or to placebo every four weeks.[71] The median reduction in OCS dose was 75% in the two benralizumab groups versus 25% in the placebo group (p<0.001). More patients receiving benralizumab were able to stop OCS use (56% every 4 weeks; 52% every eight weeks; 19% placebo, p<0.001 and p=0.002 respectively). The final dose was ≤ 5 mg per day prednisone for 61% of patients in the four-week benralizumab group, 59% in the eight-week group compared with 33% in the placebo group (p<0.001 and p=0.002 respectively). Even with greater reductions in OCS use, the benralizumab groups had lower rates of asthma exacerbations (rate ratio 0.30, 95% CI 0.17-0.53, p<0.001 for the eight-week group).

The LIBERTY ASTHMA VENTURE study randomized 210 patients with severe asthma on OCS to dupilumab 300 mg SC every two weeks for 24 weeks.[17] The mean reduction in OCS dose was 70% in the benralizumab group versus 42% in the placebo group (p<0.001) and the median reduction was 100% versus 50% (p<0.001). More patients receiving dupilumab were able to stop OCS use (52% vs. 29%, p=0.002). The final dose was <5 mg per day prednisone for 72% of patients in the dupilumab group compared with 37% in the placebo group (p<0.001). Even with greater reductions in OCS use, the benralizumab groups had significantly lower rates of asthma exacerbations (0.65 vs. 1.60, p<0.05).

Across the studies of these four drugs (omalizumab, mepolizumab, benralizumab, and dupilumab), the initial daily dose of OCS was between 10 and 15 mg of prednisone. Despite heterogeneity in the patient populations and study designs, the benefits were similar across the trials: between 20% and 30% more patients compared with placebo were able to reduce their dose of prednisone to <5 mg per day or to completely stop their prednisone. It is unknown if patients treated with reslizumab would achieve similar reductions in OCS. As with ICS in the pediatric population, a remarkable proportion of patients in the placebo group of these studies were able to stop OCS use (8%, 13%, 19%, and 29% of patients in the four studies). A trial of OCS dose down-titration may be useful prior to starting biologic therapy.

Patients with Blood Eosinophils ≥ 300 cells/µL, ≥ 2 Exacerbations in the Prior Year, and ACQ ≥ 1.5

Four of the five biologic drugs considered in this review are indicated for eosinophilic asthma and the fifth drug has published data suggesting that there are greater relative reductions in exacerbation rates for patients with eosinophils ≥ 300 cells/µL compared with patients with lower eosinophil counts (see Table 3.11 below).[16,19] Because the benefits seemed greater in this population and because it may represent a more homogenous population, we performed a network meta-analysis (NMA) in this subgroup. In addition, to further limit the analysis to patients with

similar characteristics, we requested data from manufacturers in the subgroup of patients with eosinophils ≥ 300 cells/µL, two or more exacerbations in the year prior to randomization, and an ACQ ≥ 1.5. We received data in confidence from three manufacturers to support this analysis and data were available for the remaining drugs in a similar subgroup. Data informing the analysis as well as details about our methods are reported in Appendix D.

Table 3.11. Rate Ratio for Asthma Exacerbations by Eosinophil Level

Treatment	Eos < 300 (95% CI)	Eos ≥ 300 (95% CI)
Omalizumab	1.07 (0.45-2.53)	0.41 (0.20 -0.80)

Eos: blood eosinophils (cells/µL)

The network diagram (Figure 3.1) shows that all of the biologics connect through the placebo group, but there are no head to head trials (other than the two doses of dupilumab) to assess whether our indirect estimates are consistent with direct estimates.

Figure 3.1. Network Diagram for NMA of Asthma Biologic Therapies in Patients with Eosinophil Counts ≥ 300 cells/µL, ≥ 2 exacerbations in the prior year, and ACQ ≥ 1.5

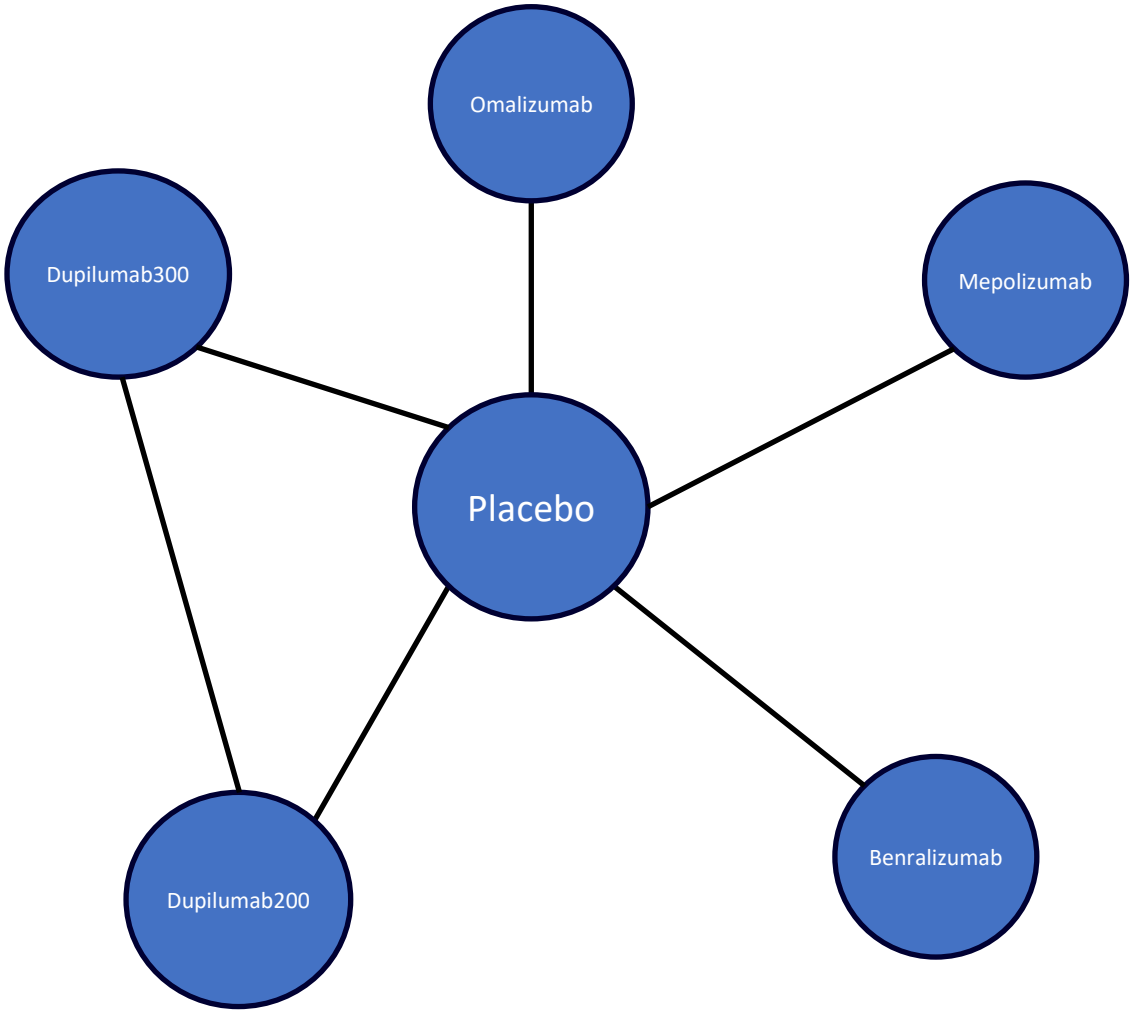


Table 3.12 below shows the pairwise comparisons for all of the drugs as well as placebo.

Table 3.12. NMA Results Comparing the Relative Rate of Asthma Exacerbations for Five Biologic Therapies

Dupilumab200						
1.00 (0.33, 3.00)	**Dupilumab300**					
0.78 (0.15, 4.09)	0.78 (0.15, 4.20)	**Omalizumab**				
0.75 (0.16, 3.70)	0.75 (0.16, 3.69)	0.97 (0.18, 5.20)	**Reslizumab**			
0.72 (0.18, 2.89)	0.72 (0.18, 2.87)	0.92 (0.21, 4.10)	0.95 (0.24, 3.86)	**Mepolizumab**		
0.44 (0.11, 1.74)	0.44 (0.11, 1.76)	0.57 (0.13, 2.41)	0.59 (0.15, 2.30)	0.62 (0.20, 1.89)	**Benralizumab**	
0.26 (0.08, 0.79)	**0.26 (0.08, 0.80)**	0.33 (0.10, 1.14)	0.34 (0.11, 1.03)	**0.36 (0.16, 0.81)**	0.59 (0.26, 1.29)	**Placebo**

Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

In Table 3.12, only dupilumab (both doses) and mepolizumab were significantly better than placebo due to relatively small numbers of patients in this subgroup for omalizumab, mepolizumab and benralizumab. The point estimates for omalizumab, reslizumab, and mepolizumab were nearly identical. Dupilumab had the largest reduction in exacerbations and benralizumab the smallest, but none of the comparisons between drugs were statistically significant. The estimates for the RR for dupilumab, omalizumab, reslizumab, and mepolizumab are markedly better than those reported in the full trial, but the NMA estimate for benralizumab is nearly identical to its primary estimate, because it was studied in patients with severe asthma, an ACQ≥1.5, at least 2 exacerbations in the prior year, and a baseline eosinophil count ≥ 300 cells/µL. These results are more robust than those presented in the draft report because of additional data provided by manufacturers. They demonstrate that the relative and absolute benefits of all of the drugs are greatest in patients with high eosinophil counts (≥ 300 cells/µL) and more exacerbations in the prior year (≥2).

Controversies and Uncertainties

There are several important uncertainties. First, there is a lack of evidence on the long-term safety and effectiveness of these drugs, particularly in older patients, given that many of the patients taking the drugs are relatively young when they start and have 30 to 70-year life expectancies. The potential cardiovascular harms identified in the 5-year follow-up of omalizumab highlight the importance of carefully evaluating these therapies over the long-term. The length of follow-up in some of the randomized trials was only 24 weeks and no trial was longer than 15 months. The long-term extension trials and real-world experience with omalizumab and mepolizumab are reassuring, but uncontrolled.

There is no clear definition for a response to therapy to help guide patients and clinicians in deciding when to stop one therapy and consider switching to another. Similarly, apart from the allergic phenotype and eosinophilia, there are currently no biomarkers to help clinicians decide

which of these drugs may be most appropriate for the individual patient confronting the decision to start one of these drugs.

A related question is defining the optimal length for biologic therapy. Studies of omalizumab and mepolizumab report worsening asthma when treatment is stopped. To date, it does not appear that biologic therapy results in long-term remission of asthma. However, some experts expressed hope that these therapies could impact long-term remodeling of the airways, which could lead to greater benefits than were observed in the clinical trials.

While quality of life is an essential driver of the overall evaluation of the effectiveness of these therapies, there is no standard assessment of quality of life used across all studies. Ideally, there would be one measure, assessed at a standard time point, that could be used to compare quality of life across interventions.

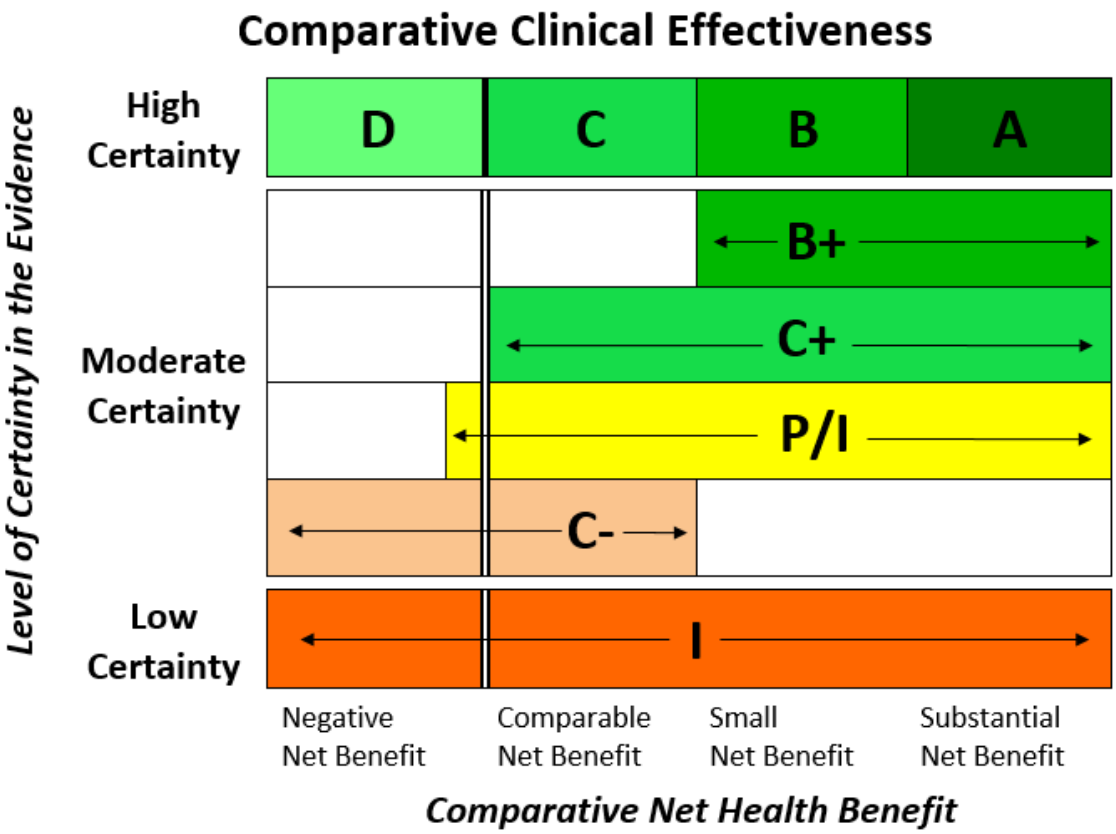
Eosinophils are part of the immune response to parasitic infections. It is unknown if the therapies that decrease eosinophil counts will affect patients' ability to fight such infections. Current guidelines recommend that physicians treat patients for existing parasitic infections prior to initiating anti IL-5 therapy.

Finally, the current evidence base precludes reliable comparative effectiveness analyses between the five drugs as highlighted by Drs. Drazen and Harrington in their editorial accompanying the publication of the pivotal trials of dupilumab.[26] They assert that they regard the treatments targeting type 2 inflammation "as essentially equivalently effective treatments." They call for researchers to design and implement a large, pragmatic trial comparing all of the available drugs in order to clarify whether or not there are clinically important differences between the drugs and to facilitate studies of biomarkers that could identify subgroups of patients likely to benefit from one of the specific drugs.[26]

3.4 Summary and Comment

Using the ICER Evidence Matrix (Figure 3.2), we assigned evidence ratings to each of the biologics relative to standard of care (Table 3.13). As noted previously, the lack of head-to-head data as well as our inability to indirectly compare the regimens through network meta-analysis precluded assessment of the comparative net health benefit of these regimens relative to each other.

Figure 3.2. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D = "Negative"- High certainty of an inferior net health benefit
B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

Omalizumab

For patients ages 12 years and older with moderate to severe persistent asthma who have a positive skin or blood test to year-round airborne allergens and whose symptoms are not well-controlled by inhaled corticosteroids, we judge there to be high certainty of a small net benefit for omalizumab 75 to 375 mg SC every two to four weeks as add-on maintenance treatment compared with standard of care including high dose ICS plus LABA or additional controller medications. Omalizumab carries a black box warning for anaphylaxis and requires administration by a health care professional. In addition to trials in adults, there are randomized trials supporting comparable

benefits in the pediatric population, trial extension studies confirming ongoing benefits from therapy up to nine years, and real-world observational studies reporting similar benefits to those observed in the randomized trials. There remains some uncertainty about the long-term durability of the benefits of the therapy when used for many years and about the potential harms from modulation of the immune system, but these have decreased with the additional data. In addition, there are suggestions of cardiovascular adverse events that may be more important in patients older than those studies in the randomized trials. The benefits in terms of the reductions in exacerbations and improvement in quality of life are modest, rather than substantial and the harms are small. Therefore, we judge the current body of evidence on omalizumab to be "incremental" compared with standard of care ("B").

Mepolizumab

For patients ages six years and older with severe eosinophilic asthma, we judge there to be high certainty of a small net benefit for mepolizumab 100 mg SC every four weeks as add-on maintenance treatment compared with standard of care including high dose ICS plus LABA or additional controller medications. Mepolizumab requires administration by a health care professional. Since the prior ICER review of mepolizumab (C+ rating, comparable or better), there are trial extension studies confirming ongoing benefits from therapy beyond one year of therapy and some real-world observational data supporting similar benefits to those observed in the randomized trials. In addition to trials in adults, there are randomized trials supporting comparable benefits in the pediatric population, trial extension studies confirming ongoing benefits from therapy up to five years, and real-world observational studies reporting similar benefits to those observed in the randomized trials. There remains some uncertainty about the long-term durability of the benefits of the therapy when used for many years and about the potential harms from modulation of the immune system, but these have decreased with the additional evidence. The benefits in terms of the reductions in exacerbations and improvement in quality of life are modest, rather than substantial and the overall harms are small. Therefore, we judge the current body of evidence on mepolizumab to be "incremental" compared with standard of care ("B").

Reslizumab

For adult patients 18 years and older with severe eosinophilic asthma, we judge there to be moderate certainty of a comparable or better net benefit for reslizumab 3 mg/kg IV every four weeks as add-on maintenance treatment compared with standard of care including high dose ICS, LABA, and additional controller medications. Reslizumab carries a black box warning for anaphylaxis and requires administration by a health care professional. There is moderate certainty because the randomized trials demonstrating efficacy were relatively small studies of short duration given the lifetime time horizon for potential use of reslizumab. There remains uncertainty about the long-term durability of the benefits of the therapy and about the potential harms from modulation of the immune system. The consistent benefits and minimal harms observed with the

two other asthma biologics targeting the IL-5 pathway, reduces the uncertainty somewhat. Ongoing post-marketing trials and extension studies evaluating reslizumab may demonstrate a wide variety of outcomes, from substantial net health benefit to a comparable net benefit given the potential harms associated with the monoclonal antibody (opportunist infections, anaphylaxis). Therefore, we judge the current body of evidence on reslizumab to be "comparable or better" compared with standard of care ("C+").

Benralizumab

For patients ages 12 years and older with severe eosinophilic asthma, we judge there to be moderate certainty of a comparable or better net benefit for benralizumab 30 mg SC every four weeks for twelve weeks, then every eight weeks as add-on maintenance treatment compared with standard of care including high dose ICS, LABA, and additional controller medications. Benralizumab requires administration by a health care professional. There is moderate certainty because the randomized trials demonstrating efficacy were relatively small studies of short duration given the lifetime time horizon for potential use of benralizumab. There remains uncertainty about the long-term durability of the benefits of the therapy and about the potential harms from modulation of the immune system. The consistent benefits and minimal harms observed with the two other asthma biologics targeting the IL-5 pathway, reduces the uncertainty somewhat, but it targets the receptor rather than IL-5 itself and causes greater depletion in eosinophils. Ongoing post-marketing trials and extension studies evaluating benralizumab may demonstrate a wide variety of outcomes, from substantial net health benefit to a comparable net benefit given the potential harms associated with the monoclonal antibody (opportunist infections, anaphylaxis). Therefore, we judge the current body of evidence on benralizumab to be "comparable or better" compared with standard of care ("C+").

Dupilumab

For patients ages 12 years and older with moderate to severe asthma with at least one exacerbation in the prior year, we judge there to be moderate certainty of a comparable or better net benefit for dupilumab 200 mg or 300 mg SC every two weeks as add-on maintenance treatment compared with standard of care including high dose ICS, LABA, and an additional controller medication. There is moderate certainty because the two trials were relatively small studies of short duration. There remains uncertainty about the long-term durability of the benefits of the therapy and about the potential harms from modulation of the immune system. A unique benefit of dupilumab that matters to patients is that it may be self-administered at home, while the other biologics require administration by a health professional. The common AEs reported in studies of dupilumab for atopic dermatitis were not replicated in the trials for asthma. Ongoing post-marketing trials and extension studies evaluating dupilumab may demonstrate a wide variety of outcomes, from substantial net health benefit to a comparable net benefit given the potential harms associated with the monoclonal antibody (opportunistic infections, anaphylaxis). Therefore,

we judge the current body of evidence on dupilumab to be "comparable or better" compared with standard of care ("C+").

Comparisons Between Biologic Therapies for Asthma

There are no head to head trials and the heterogeneity in the populations studied in the randomized trials precluded performing a network meta-analysis. When comparing the effect sizes from the meta-analyses of the individual drugs compared with placebo, the improvements in exacerbation rates and quality of life appear qualitatively similar, but this may be misleading. We attempted to perform a network meta-analysis in the population of patients with severe asthma with baseline eosinophil counts ≥ 300 cells/µL, but there remained significant heterogeneity in the populations. In addition, the results did not differ substantially from the estimates from the original trials, which was unexpected as analyses for several of the trials found substantially greater relative risk reductions for exacerbations in the subgroup of patients with high baseline eosinophil counts. Therefore, there is low certainty in the comparative clinical effectiveness of the agents: an I rating or insufficient.

Table 3.13. ICER Ratings for Biologic Therapies for the Treatment of Asthma

Treatment	ICER Evidence Rating
Omalizumab	B: Incremental
Mepolizumab	B: Incremental
Reslizumab	C+: Comparable or better
Benralizumab	C+: Comparable or better
Dupilumab 200 mg	C+: Comparable or better
Dupilumab 300 mg	C+: Comparable or better
Between drugs	I: Insufficient

4. Long-Term Cost Effectiveness

4.1 Overview

The primary aim of this analysis was to estimate the cost-effectiveness of five biologic agents (omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab) for the treatment of moderate to severe uncontrolled asthma with evidence of type 2 inflammation in adults and in children six years and older. This analysis represents an update of our prior analysis on this topic.[27] The population for this updated review was designated with a broad intention to capture the existing or expected FDA indications for all the relevant biologics, though not all of the therapies are indicated for use in younger children or patients with moderate asthma (refer to Table 3.1 in the clinical section). Quality-adjusted survival and health care costs were estimated for each biologic and its relevant comparators using the health care sector perspective. Costs and outcomes were discounted at 3% per year. Incremental costs and outcomes were calculated comparing each intervention to its comparator. The model was developed in Microsoft Excel 2016 (Redmond, WA) and followed the general structure of the Institute for Clinical and Economic Review (ICER) 2016 mepolizumab review with updates to accommodate best-available evidence and the additional agents.[27] The model framework and assumptions are described in detail below.

4.2 Methods

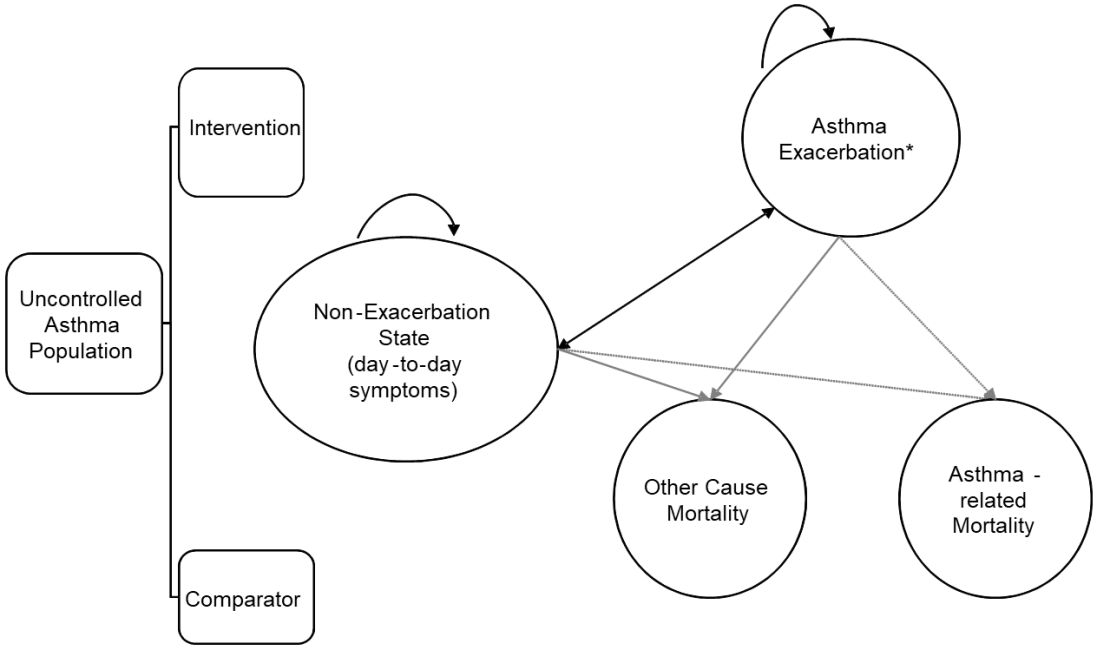
Model Structure

The decision analytic model structure was informed by the primary aim, previous modeling evidence, the evidence review, and stakeholder input. The model structure was based on formerly developed models assessing the cost-effectiveness of asthma biologics including mepolizumab and omalizumab.[72,73]

The Markov model included three primary health states: 1) an asthma non-exacerbation state (i.e., day-to-day asthma symptoms), 2) an asthma exacerbation state (including three mutually exclusive subcategories: asthma-related event that requires an oral corticosteroid burst without emergency department (ED) or inpatient care, asthma-related ED visit, or asthma-related hospitalization), and 3) death (including asthma-related mortality and other cause mortality) (Figure 4.1). The model structure was similar to other published asthma cost-effectiveness analysis (CEA) models, including ICER's 2016 report on mepolizumab and related peer-reviewed manuscript[27,73] and the omalizumab model for patients with severe uncontrolled asthma described in the National Institute for Health and Care Excellence (NICE) appraisal determination in 2013 and elsewhere.[72,74-78] Compared to ICER's 2016 initial report on mepolizumab, this updated model structure allowed for one evaluation of treatment responders (where patients who respond to therapy remain on that therapy, and

those who do not have the therapy discontinued) and a separate set of inputs for those who were defined as treatment responders. Treatment responders versus non-responders and their corresponding treatment duration were modeled as a scenario analysis due to heterogeneous and limited responder evidence across the biologic agents.

Figure 4.1. Model Framework



*Exacerbations are defined as three mutually exclusive and exhaustive subcategories:

1. Asthma related event that requires an oral steroid burst (but not emergency department or hospitalization)
2. Asthma related event that requires admittance to the emergency department (but not a hospitalization)
3. Asthma related event that requires a hospitalization

A lifetime horizon was assumed in the base-case, consistent with the ICER Value Framework and other asthma cost-effectiveness models.[74,79,80] The discount rate for all future costs and outcomes was 3% per year.

We used a cycle length of two weeks to reflect the average length of time for an asthma exacerbation and to be consistent with prior published cost-effectiveness analyses[72,76] and asthma guidelines that suggest new exacerbation events should only be considered after at least a 7-day period from a prior event.[81]

Key clinical inputs for the model, informed by the evidence review, included exacerbation rates (including oral steroid bursts, ED visits, and hospitalizations), chronic oral steroid use, asthma-related mortality, asthma control, biologic treatment response, and adverse events.

Model outcomes for each intervention included total drug and non-drug health care costs, life years (LY) gained, quality-adjusted life years (QALYs) gained, and annualized asthma exacerbations.

Separate scenario analyses were conducted based on input and evidence provided by stakeholders, manufacturers, and informed by internal discussions. First, a modified societal perspective was completed to account for costs of lost productivity and work due to asthma. Second, a scenario that evaluated the possible costs and outcomes associated with long-term biologic treatment only for treatment responders was modeled with noted evidence gaps. In this scenario, biologic non-responders were assumed to revert to standard of care after failing to respond to the biologic treatment; non-responders were assigned standard of care average costs and outcomes. Finally, we completed a scenario analysis based on the ≥ 300 eosinophil count population stratification, using trial results across biologics in patients with elevated eosinophil counts.

Target Population

Adults and children ages six years and older with moderate to severe, uncontrolled asthma and evidence of type 2 inflammation characterized the population of focus for this updated review. The population was designed to be intentionally broad to capture the indicated populations for all identified biologics, though not all of the therapies are indicated for younger children or patients with moderate asthma.

Table 4.1 presents the base-case model cohort characteristics for the five interventions of interest in this review (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab). Best-available evidence for Table 4.1 was derived from the clinical review averaged across the included clinical review studies and biologics. Plausible ranges including a lower and upper value for listed characteristics were tested in one-way sensitivity and scenario analyses. Only characteristics that were used within the economic model are displayed in Table 4.1. See the clinical review for further description of patient cohort characteristics.

Table 4.1. Base-Case Model Cohort Characteristics

Characteristic	Across All Biologic Agents*
Mean (SD) age in years	46 (42-50)
Mean (SD) weight (kg)	85 (75-95)[82]
Percent female	62% (60%-64%)
Percent Chronic OCS Users†	17% (13%-28%)

*Values displayed are derived from the clinical review unless otherwise specified, averaged over trials; plausible ranges include the minimum and maximum values from an individual trial evidence, where available.
†Chronic oral steroid (OCS) definitions differ by evidence source but can be interpreted as the proportion of the biologic eligible cohort that use > 5 mg per day of prednisone or equivalent with high levels of adherence.

Treatments

Interventions

The list of included interventions was developed with input from patient organizations, clinicians, manufacturers, and payers. Each intervention of interest, represented in the list of asthma biologics below, was added on to a standard of care (SoC) comparator.

- Omalizumab 75-375 mg by subcutaneous injection once every two or four weeks
- Mepolizumab 100 mg by subcutaneous injection once every four weeks
- Reslizumab 3 mg/kg by intravenous infusion once every four weeks
- Benralizumab 30 mg by subcutaneous injection once every four weeks for three doses; then every eight weeks
- Dupilumab 200mg or 300 mg by subcutaneous injection once every two weeks

Dupilumab dosing for asthma includes the 200mg and 300mg strength per the Food and Drug Administration. Given that both doses have the same price per administration and comparable efficacy and safety signals, the long-term cost-effectiveness section of the report considered the doses to be interchangeable.

Comparators

The comparators of interest were SoC, typically defined as daily inhaled corticosteroids plus at least one additional controller therapy.

Key Model Characteristics and Assumptions

The base-case analysis took a health care sector perspective, focusing on direct medical care and drug costs. Cycle length is two weeks. Costs and outcomes were discounted at 3% per year. Model assumptions are described in Table 4.2.

Table 4.2. Key Model Assumptions

Assumption	Rationale
Base-case utility for the non-exacerbation health state was different for biologic plus SoC vs. SoC alone due to potential improvements in day-to-day symptoms.	Without direct elicitation of utilities in trials comparing biologic plus SoC vs. SoC alone, we relied on evidence of patient reported outcome (PRO) instruments with known utility mappings. From the prior review, mepolizumab utility estimates were used through the Saint George's Respiratory Questionnaire mapping algorithm.[83] A manufacturer submission to NICE used a similar approach.[28] Although other utility relationships are known for the Asthma Quality of Life Questionnaire,[84] using such a mapping produced less favorable results for all biologics.
Long-term biologic treatment only for treatment responders was included as a scenario analysis for all biologics.	The ability to evaluate treatment responders within this updated review was consistent with recent asthma biologic health technology assessments.[28] However, given heterogeneity across treatment responder definitions, stakeholder comments, limited comparative outcomes evidence tied to treatment responders vs. non-responders, and limited understanding of how such responder definitions would be implemented in US practice settings, the inclusion of the potential impact of treatment responders was reserved as a scenario analysis.
Exacerbations requiring only an oral steroid burst were assumed to not impact mortality over and above the severe asthma-related mortality rate for all living health states in the model.	Increased mortality rates were included for exacerbations requiring emergency care (hospitalizations or ED visits), consistent with United Kingdom evidence. No added mortality was included for oral steroid burst exacerbations given that the risk of death found in the United Kingdom evidence was similar to the annual US risk of severe asthma-related mortality conditioned on age, a parameter that was already incorporated into the model.[28,29]
Reduction in daily chronic oral glucocorticoid dose to a level of 5 mg or less was not harmful in terms of adverse events or disutility.	5 mg per day was a typical literature cutoff, with chronic doses above 5 mg considered harmful and associated with both costs and disutilities.[85]
Disutility values for hospitalizations, ED visits, and oral steroid bursts were assumed to be for two weeks.	Disutility was comparable to the NICE omalizumab and mepolizumab reference-case.[28,74]
In order to eliminate differences across baseline characteristics, such as age, that may impact lifetime costs and outcomes, we averaged over baseline characteristics to estimate the same model cohort's baseline age, gender, weight, proportion of chronic oral steroid users, and SoC annualized exacerbation rates.	The comparative clinical evidence was allowed to be unique for each biologic plus SoC vs. SoC alone; differences in SoC cohort characteristics across evidence sources were normed as we did not expect such characteristics to have a significant effect on the incremental lifetime findings. The normed plausible characteristic ranges were tested using sensitivity and scenario analyses.

ED: emergency department, SoC: standard of care

Model Inputs

Model inputs were estimated from the clinical review, as well as from published literature and information provided by stakeholders. The inputs that informed the model are described below.

Clinical Inputs

Treatment Regimen

Table 4.3 indicates the inputs corresponding to the regimen for the specified interventions. Further, Table 4.3 includes the findings for each regimen as compared to SoC alone on the proportion of patients who are on oral corticosteroids at the end of study, generally from oral steroid sparing studies. Consistent with NICE reports, we assumed 100% compliance and adherence for those who respond to biologic add-on therapy.[28,74]

Table 4.3. Treatment Regimen

Characteristic	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Treatment Dose	75-375 mg every 2 to 4 weeks (assumed 36 vials per year with wastage)[72]	100 mg every 4 weeks	3.0 mg/kg every 4 weeks (assumed 2 to 3 single-use 100mg/ml vials per administration or 36 per year with wastage)	30 mg every 4 weeks (first 3 doses) then every 8 weeks[62]	200mg or 300 mg every 2 weeks[16]
Route of Administration	Subcutaneous injection	Subcutaneous injection	Intravenous infusion	Subcutaneous injection	Subcutaneous injection
Relative Reduction in Chronic Oral Corticosteroid Use Post Trial (% biologic vs. % SoC with chronic use > 5mg per day)	0.78 (67.8% vs. 87.0%)[69]	0.68 (46% vs. 68%)[70]	1.0 (No comparative evidence reported)*	0.61 (41% vs. 67%)[71]	0.46 (31% vs. 67%)[17]

*For evidence "Not reported," no difference was assumed (i.e., relative reduction of 1.0) between biologic plus SoC vs. SoC alone.

Exacerbation-Related Inputs

Inputs related to exacerbations are detailed in Tables 4.4 and 4.5, consistent with the clinical review.

Table 4.4. Exacerbation-Related Inputs: Rate Ratios for Intervention versus SoC

Characteristic	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab†
Rate Ratio for Exacerbations Resulting in Steroid Burst (without ED visit or hospitalization)	0.52 (0.37-0.73)[14]	0.45 (0.36- 0.55)[15]	0.43 (0.33-0.55)[15]	0.59 (0.51- 0.68)[15]	Not reported; assumed 0.40 (0.31- 0.53)[16-18]
Rate Ratio for Exacerbations Resulting in ED visit (without hospitalization)	0.40 (0.19- 0.82)[86]*	0.36 (0.20- 0.66)[15]	0.67 (0.39- 1.17)[15]	0.68 (0.47- 0.98)[15]	Not reported; assumed 0.40 (0.31- 0.53)[16-18]
Rate Ratio for Exacerbations Resulting in Hospitalization	0.16 (0.06- 0.42)[14]	0.31 (0.13- 0.73)[15]	0.67 (0.39- 1.17)[15]	0.68 (0.47- 0.98)[15]	Not reported; assumed 0.40 (0.31- 0.53)[16-18]

*Evidence source was not reported within the clinical review but was included in a prior meta-analysis
†Rate ratio for dupilumab for each subcategory of exacerbation was assumed the same as the overall exacerbation rate ratio that most closely reflected the Food and Drug Administration labeled population.

Table 4.5. Exacerbation Related Inputs: SoC

Characteristic	Standard of Care Across All Biologics
Annualized Exacerbation Rate Per Person Year, End of Study (95% CI)*	1.30 PPY (plausible range: 0.9- 2.3)
Proportion of Exacerbations Resulting in Steroid Burst (without ED visit or hospitalization)†	90%[86-88]
Proportion of Exacerbations Resulting in ED visit (without hospitalization) †	5%[86-88]
Proportion of Exacerbations Resulting in Hospitalization**	5%[86-88]

PPY: per person year
*Values displayed are derived from the clinical review unless otherwise specified, averaged over trials; plausible ranges include the minimum and maximum values from an individual trial evidence, where available.
†Assumed based off of values from Ortega et al. 2014, Bousquet et al. 2005, and Castro et al. 2015.

Adverse Events

The evidence suggested no differences in costs or disutility values associated with adverse events between biologics plus SoC versus SoC alone. Chronic oral steroid use and its associated long-run costs and disutility was included within this updated review.

Asthma-Related Mortality

Asthma-related mortality and other cause mortality were modeled for all living health states (non-exacerbation and exacerbation).[28-31] Watson and colleagues, who analyzed a United Kingdom database including 250,043 asthma-related hospital admissions to determine the mortality rate following hospitalizations, described a risk of death linked with asthma-related hospitalizations (2.48%).[30] For the asthma-related hospitalization exacerbation subcategory, the relationship of increased death, consistent with Watson et al., was added to the background of severe asthma-related mortality and other cause mortality. Further, the NICE mepolizumab technology appraisal suggested there may be an increased risk of death for other exacerbation-related subcategories.[28] The National Review of Asthma Deaths report was the largest worldwide study on asthma deaths to date and the first United Kingdom-wide investigation into the topic.[31] They used "death by location" to show indications for death at home, on the way to the hospital, and in the hospital. Due to this evidence, the NICE mepolizumab appraisal suggested that the risk of death for those over age 45 years was 1.79% for those who experienced an asthma-related ED visit. We added the 1.79% risk of death for asthma-related ED visits to the background of severe asthma-related mortality and other cause mortality. The NICE mepolizumab appraisal also suggested the risk of death for those over age 45 years was 0.38% for those who experienced an asthma-related oral steroid burst exacerbation. Given the annual risk of death for those with severe asthma from de Vries et al. was 0.4% per year and due to potential differences in death rates in the US,[29] we assumed no increased risk of death over that of severe asthma-related mortality for the oral steroid burst asthma exacerbation sub category (see assumptions Table 4.2).

Utility Inputs

Model Health States

To adjust for potential quality of life differences, utilities were applied for each model health state. Health state utilities were derived from publicly available literature and applied to the disease states. The utilities for the non-exacerbation health state are presented in Table 4.6. The disutility values for other health states or events are displayed in Table 4.7.

The non-exacerbation health state utility value was allowed to be different for the biologic plus SoC treatment arm versus SoC alone. For the non-exacerbation health state, the clinical evidence from Ortega et al.[87] and Chupp et al.[89] reported on the St George's Respiratory Questionnaire (SGRQ) for mepolizumab plus SoC versus SoC alone.[15] We identified a published mapping between mean total SGRQ scores and the EQ-5D. The mean total SGRQ score of 38.9 for SoC[87] and 31.5 for

mepolizumab plus SoC based on the pooled study mean difference[15] provided the required inputs for the aggregate mapping algorithm (EQ-5D utility = 0.9617 - 0.0013*SGRQ score - 0.0001*(SGRQ score)^2 + 0.0231* male).[83]

Without known direct elicitation of utilities in trials comparing biologic plus SoC versus SoC alone, we relied on evidence of patient reported outcome instruments with known utility mappings. From the prior review, mepolizumab utility estimates were used through the SGRQ mapping algorithm.[83] The improvement in utility based on the SGRQ mapping algorithm suggests mepolizumab is associated with 0.062 higher utility in the non-exacerbation health state compared to SoC alone (See Table 4.6).

Utility relationships are published for the Asthma Quality of Life Questionnaire (AQLQ) with the most applicable utility mapping suggesting a one-unit improvement in AQLQ is associated with an improvement of 0.12 in utility.[84] More sophisticated AQLQ mapping algorithms are published but require sub-domain scores or other more granular-level of AQLQ evidence. Based on the clinical review across all five biologics' mean change differences versus SoC for AQLQ, the corresponding mapped improvement in non-exacerbation health state utility would be between 0.028 and 0.042 as compared to SoC. Because AQLQ improvements were in the same range across all biologics, we assumed the higher SGRQ mapped utility for all biologic treatments in terms of the non-exacerbation health state utility. The decision to use the SGRQ-mapped utility for all biologic treatments was strengthened by prior patient-level research suggesting an omalizumab AQLQ-mapped utility improvement of 0.063 compared to SoC.[65,72] If the AQLQ signals from this report were mapped into utilities (instead of assuming the SGRQ-mapped utility applied to all biologics), lower incremental QALYs would be observed across all biologics versus SoC and less favorable cost-effectiveness estimates would have been produced (see scenario results section for the incremental cost-effectiveness ratio finding for the biologic with the most favorable AQLQ improvement according to the clinical review). Given this utility assumption is more uncertain for biologics other than mepolizumab, we doubled the standard error for all non-mepolizumab biologic-treated non-exacerbation health state utilities.

Table 4.6 shows the associated asthma patient-reported outcome responses for each respective biologic, the mean change difference in AQLQ according to the clinical review and the non-exacerbation mean health state utility for biologic plus SoC versus SoC alone.

Table 4.6. Asthma Patient-Reported Outcome Response and Corresponding Non-Exacerbation Utility

Characteristic	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Asthma Patient-Reported Outcome Measure	AQLQ	AQLQ SGRQ	AQLQ	AQLQ	AQLQ
Asthma Patient-Reported Outcome Mean Change Difference vs. SoC (95% CI)	0.26 (0.05-0.47)[14]	AQLQ: 0.35 (0.08-0.62)[90] SGRQ: -7.4 (-9.5 to -5.3)[15]	0.28 (0.17-0.39)[15]	0.23 (0.11-0.35)[15]	0.26 (0.12-0.40)[16]
Non-Exacerbation Mean Health State Utility for biologic plus SoC vs. SoC alone (SE)*	0.830 (0.020) vs. 0.768 (0.015)	0.830 (0.010) vs. 0.768 (0.015)	0.830 (0.020) vs. 0.768 (0.015)	0.830 (0.020) vs. 0.768 (0.015)	0.830 (0.020) vs. 0.768 (0.015)

AQLQ: Asthma Quality of Life Questionnaire, SGRQ: St. George's Respiratory Questionnaire, SE: standard error, SoC: standard of care

*Utility mapping based on mepolizumab plus SoC vs. SoC alone for the St. George's Respiratory Questionnaire; mepolizumab utility values for the non-exacerbation health state were assumed the same for the other biologics plus SoC, but with double the standard error.

Treatment Disutility Values

Disutility values for the exacerbation health states were assumed to be the same across treatment strategies (i.e., the same for biologic plus SoC vs. SoC alone).[91] Given a dearth of data on the utility associated with an asthma-related ED visit, we assumed the mid-point between the values for hospitalization and oral steroid burst events. We assigned the pre-post decrement in utilities observed in Lloyd et al.[91] for exacerbation-related events. A two-week duration was assumed for all exacerbation health states, consistent with the model cycle. Although an oral steroid burst or ED visit does not typically last two weeks, the stress and anxiety related to these events may remain over a two-week period.

Severe asthma flare-ups are commonly treated through prescribed bursts of oral corticosteroids (OCS), ranging in intensive treatment periods from five days to two weeks. While consistent use of OCS is associated with a greater likelihood of side effects, a time-limited steroid burst is distinct from chronic OCS.[92]

The disutility of chronic OCS for the proportion of patients using >5 mg daily (-0.023)[75] was assumed to be equivalent to the disability-adjusted life years (DALYs) that were weighted by the proportion of chronic oral corticosteroid users who developed the following adverse events: type 2 diabetes,

myocardial infarction, glaucoma, cataracts, ulcer, osteoporosis, and stroke. Table 4.7 displays the disutility values present in the model.

Table 4.7. Disutility Values

Characteristic	Disutility	Source
Exacerbation Requiring Steroid Burst*	-0.1	Lloyd et al. 2007[91]
Exacerbation Requiring ED Visit*	-0.15	Lloyd et al. 2007[91] and assumption
Exacerbation Requiring Hospitalization*	-0.20	Lloyd et al. 2007[91]
Chronic Oral Corticosteroid Use†	-0.023	Norman et al. 2013[75]

*Two-week duration, †Lifetime duration

Treatment Responders

In order to build in a one-time evaluation to identify possible treatment responders for the purposes of modeling long-term biologic treatment, evidence needs include the definition of treatment response and its corresponding time post biologic initiation, proportion who respond, and the associated costs and outcomes within the subgroup who respond. The primary clinical outcomes for the subgroup of responders, all compared to SoC alone, include exacerbation rate ratios, changes in chronic oral steroid use, and changes in non-exacerbation health state utilities. Given the lack of publicly available evidence on treatment response definitions, proportions who respond, and the corresponding comparative outcomes for the reviewed biologics, we included a *what if* scenario on the potential impact that treatment responders may have on lifetime incremental costs and QALYs.

Economic Inputs

Treatment Costs and Details

The unit cost for each intervention is reported in Table 4.8. Net price data that were submitted by the five manufacturers were used wherever calculations or reporting involves net price.

Threshold prices were calculated at the three cost-effectiveness thresholds ($50,000, $100,000 and $150,000 per QALY gained).

Treatment-related costs (SoC and asthma biologics) were assigned by treatment scenario for all living health states (exacerbation and non-exacerbation states).

Table 4.8. Treatment Costs and Details

Characteristic	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Unit	150 mg vial	100 mg	100 mg/ml vial	30 mg	2 x 200mg or 2 x 300mg
Wholesale Acquisition Cost (WAC)	$1,084.66	$2,868.67	$878.80	$4,752.11	$2,931.54
Manufacturer Net Price (% of WAC)	$802.64* (74% of WAC)	$2,272† (79% of WAC)	$804.10‡ (91% of WAC)	$4,265¥ (90% of WAC)	$2,384.62^ (81% of WAC)

*Per manufacturer: "Net price per 150mg vial was calculated using the manufacturer-provided annual net cost. Omalizumab's average annual net cost per adult patient is $28,895. Average annual net cost of treatment for adults with allergic asthma only (as of July 2018) assuming three 150 mg vials per month. Net cost assumption is an average cost reflecting all price concessions given to customers, and inclusive of all statutory discounts and rebates. This calculation is an estimate for the purposes of financial modeling. Cost of treatment per patient varies as dosing depends on age, weight and IgE level and pricing differs by provider and payer (commercial insurance or government program)."
†Per manufacturer: "Average net sales price is inclusive of WAC rebates, allowances, and returns."
‡Per manufacturer: "This net price reflects a weighted average after applying statutory discounts."
¥Per manufacturer: "The net price for each 30mg/ml pre-filled syringe of Benralizumab is $4265. This price includes government statutory rebates, allowances, and returns." Benralizumab will have an additional cost of $6,302.30 for the first year of treatment due to the higher frequency of administration for the first three doses.
^Per the manufacturer: "The net price of $31,000 should be considered as inclusive of all discounts applied to dupilumab throughout the value chain and not just reflective of rebates alone." Dupilumab will have an additional cost of $1,192.31 for the first year of treatment due to the loading dose.

Health Care Utilization Inputs

Health Care Utilization Costs

Table 4.9 details the health care utilization unit costs that will be used in the model. Unit costs for health care utilization were the same across different treatments and populations.

Unit costs for asthma-related hospital stays, emergency department (ED) visits, and exacerbations requiring an OCS burst were estimated using a cohort of 222,817 US patients with asthma from the Clinformatics DataMart Multiplan dataset. Costs were estimated for 30-day periods after an exacerbation and were summarized as mean health care cost per exacerbation and inflated to 2018 US Dollars.[93] All costs were inflated to 2018 levels using the health care component of the personal consumption expenditure index,[94] in accordance with the ICER Reference Case.[95]

There are likely standard of care (SoC) treatment differences within and across biologic therapies. Given that the biologic interventions were indicated as add-on therapies to SoC, the annual cost of SoC in an incremental analysis compared to SoC alone will approximate an incremental difference of $0. We assumed the same annualized cost of SoC from the prior mepolizumab ICER review and consistent with Whittington et al. 2018.[73]

The chronic use of oral corticosteroids likely results in adverse clinical events and their associated costs. We assumed that doses of daily oral corticosteroids above 5 mg were potentially harmful to the patient in terms of adverse events and could impact day-to-day living. Annual US costs associated with an individual using oral corticosteroids chronically above the 5 mg dose level was $7983.[85] This annual estimate compared chronic oral steroid users to asthma patients who did not use oral steroids.

Costs associated with biologic administration are also displayed in Table 4.9. We assumed that four office visits each year would be associated with standard of care. Therefore, administration costs were assigned to the listed therapies in Table 4.9 for each administration in a year above four. Dupilumab was assumed to be self-administered after training, as described within the Food and Drug Administration label.

Table 4.9. Health Care Utilization Cost Inputs

Health Care Unit Costs	Unit Cost (2018 USD)	Source
Exacerbation-Related Steroid Burst (SD)	$1,538 ($2,626)	Suruki et al. 2017[93]
Exacerbation-Related ED Visit (SD)	$2,072 ($2,751)	Suruki et al. 2017[93]
Exacerbation-Related Hospitalization (SD)	$9,053 ($7,257)	Suruki et al. 2017[93]
Annual Cost for SoC (95% interval)	$6,227 ($5079, $7505)	Whittington et al. 2018[73]
Annual Cost of Long-Term Oral Corticosteroid Use with Adverse Events (SD assumed)	$7983 ($7983)	Lefebvre et al. 2017[85]
Intravenous Treatment Administration (1st Hour) for Reslizumab	$144.72 per administration	Physicians' Fee and Coding Guide, 2018 (HCPCS code 96413)[96] Physicians' Fee and Coding Guide, 2018 (HCPCS code 96413)[96]
Office Visit Treatment Administration for Subcutaneous Office-Administered Biologics for Omalizumab, Mepolizumab, and Benralizumab (Dupilumab assumed to be self-administered after loading dose)	$74.16 per administration	Physicians' Fee and Coding Guide, 2018 (HCPCS code 99213)[96]

ED: emergency department, SD: standard deviation, SoC: standard of care, USD: US dollar

Productivity Costs

In order to estimate a modified societal perspective as a scenario analysis, we included lost productivity costs associated with biologic treated populations versus SoC. The Asthma and Allergy Foundation of America notes that the value of additional days lost attributable to asthma is $93 for students and $301 for adults in the work force.[97] For the purposes of calculations in the model due

to limited evidence on the proportion in the work force or otherwise, we used an average hourly wage of $24.68 per hour ($197.44 per day), reported by the Bureau of Labor Statistics, and multiplied this hourly wage by the average number of hours missed from work based on evidence from omalizumab (1.46 hours per week missed) versus SoC (3.09 hours per week missed).[98,99] We assumed this same level of productivity lost applied across all biologic agents.

Table 4.10 details the additional costs included in the modified societal perspective.

Table 4.10: Productivity Costs

Input	Variable	Source*
Average Hourly Wage	$24.68 per hour	Bureau of Labor Statistics, 2018[98]
Hours missed per week (Asthma Biologic)	1.46	Data on file (Genentech)[99]
Hours missed per week (Standard of Care)	3.09	Data on file (Genentech)[99]

Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses were performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. Additionally, we conducted a threshold analysis by systematically altering the price of the acquisition cost for each treatment option to estimate the maximum prices that would correspond to given willingness to pay (WTP) thresholds between $50,000 and $150,000 per QALY gained. Finally, for the three main biologic treatment benefits: non-exacerbation utility improvement, exacerbation reductions, and chronic oral steroid reductions, we computed the incremental cost-effectiveness ratio for one biologic treatment for only assigning a benefit based on non-exacerbation utility improvement, based on only exacerbation reductions, and finally based on only the benefit of chronic oral steroid reductions to demonstrate the impact that each benefit has on the base-case finding.

Scenario Analyses

In addition to the modified societal perspective, we also ran three other scenario analyses for the Evidence Report: 1. Subpopulation of patients with baseline eosinophil counts ≥300 cells/µL and at least two exacerbations in the previous year; 2. Treatment responder scenario using evidence primarily from omalizumab studies and; 3. Collective best-case analyses using inputs that favor the lifetime value toward that of biologic therapy.

The modified societal perspective includes productivity-related costs as specified in Table 4.10 and all other base-case inputs.

For the subpopulation of high eosinophil ≥300 cells/µL, the clinical review conducted a network meta-analysis of exacerbation rate ratios and yielded the following rate ratios for overall exacerbations for each biologic versus SoC: 0.33 for omalizumab versus SoC; 0.36 for mepolizumab versus SoC; 0.34 for reslizumab versus SoC; 0.59 for benralizumab versus SoC; and 0.26 for dupilumab 300 mg versus SoC. No evidence was produced related to the rate ratios or proportion of exacerbation sub-types. Therefore, the same proportions were assumed as in the base-case SoC (90% oral steroid burst, 5% ED visit, and 5% hospitalization). The pooled annualized SoC exacerbation rate per person year was estimated as 1.23 in this subpopulation. No other base-case estimates changed for this scenario analysis.

For the treatment responder scenario, we recognize that biologic agents with longer post-approval clinical experience are more likely to have evidence on response and its consequences. A *what if* responder scenario was generated using evidence from omalizumab studies and assumptions consistent with the following: evaluate response after 16 weeks of treatment, assume 60.5% of biologic-treated population respond, assume the rate ratio for exacerbations in responders to be 0.25 for all subcategories of exacerbation, and assume the utility improvement in the non-exacerbation health state compared to SoC can be fully assigned to those who are identified as responders (0.1025 increase in utility for responders vs. SoC and no increase in utility for non-responders vs. SoC).[75]

For the collective best-case analyses, we used inputs across all assessed biologics that would favor the lifetime value toward the biologics (i.e. lower incremental cost-effectiveness finding) in order to produce three incremental cost-effectiveness findings versus SoC alone: 1. used most favorable exacerbation and chronic oral steroid inputs and the lowest annualized price; 2. #1 and assumed a subpopulation of only those on chronic oral corticosteroids as a part of SoC and; 3. #1 and assumed the responder scenario as previously described. The input values that changed for #1 included the following: average age = 45 years old; % female = 60%; % chronic OCS users on SoC = 28%; SoC exacerbation rate = 2.3 per person year; exacerbation relative rate used most favorable from Table 4.4; chronic OCS relative risk = 0.46; and an annualized cost of $27,800. The input values changed for #2 that were not identified in #1 was only to assume that 100% of the modeled cohort were chronic OCS users on SoC. Finally, the input values changed for #3 that were not identified in #1 are those identified in the *what if* responder scenario text.

We added the collective best-case scenarios to the Evidence Report due to public feedback from the draft evidence report. The feedback rightly pointed out differences in the asthma study populations across the assessed biologics. Differences in asthma study population characteristics and other features such as responder treatment strategies and the subpopulation of chronic oral steroid users suggested a bounding of the value assessments toward favoring the biologic treatments.

Model Validation

We used several approaches to validate the model. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model, as needed. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using reviewers. Finally, we compared results to other cost-effectiveness models in this therapy area.

4.3 Results

Base-Case Results

Base-case discounted costs and outcomes from the model are found in Tables 4.11-4.15 for all five biologic agents. The total lifetime discounted QALYs across biologics are in a narrow range from 16.32 for omalizumab to 16.00 for benralizumab. The total lifetime discounted costs were also in a narrow range from $715,000 for benralizumab and $771,000 for reslizumab. The domains included within the health care sector base-case results as well as those included within the modified societal perspective are listed in the impact inventory (Appendix Table E1).

Table 4.11. Base-Case Discounted Costs and Outcomes from Model: Omalizumab

	Intervention Costs	Non-Intervention Costs	Total Costs	QALYs
Omalizumab¶	$715,000	$41,500	$757,000	16.32
SoC	$120,000	$73,300	$193,000	14.59

QALYs: quality-adjusted life years, SoC: standard of care

¶ Price = $802.64* (150 mg vial)

*Per manufacturer: "Net price per 150mg vial was calculated using the manufacturer-provided annual net cost. Omalizumab's average annual net cost per adult patient is $28,895. Average annual net cost of treatment for adults with allergic asthma only (as of July 2018) assuming three 150 mg vials per month. Net cost assumption is an average cost reflecting all price concessions given to customers, and inclusive of all statutory discounts and rebates. This calculation is an estimate for the purposes of financial modeling. Cost of treatment per patient varies as dosing depends on age, weight and IgE level and pricing differs by provider and payer (commercial insurance or government program)".

Table 4.12. Base-Case Discounted Costs and Outcomes from Model: Mepolizumab

	Intervention Costs	Non-Intervention Costs	Total Costs	QALYs
Mepolizumab¶	$717,000	$38,400	$756,000	16.22
SoC	$120,000	$73,300	$193,000	14.59

QALYs: quality-adjusted life years, SoC: standard of care

Table 4.13. Base-Case Discounted Costs and Outcomes from Model: Reslizumab

	Intervention Costs	Non-Intervention Costs	Total Costs	QALYs
Reslizumab¶	$721,000	$50,000	$771,000	16.06
SoC	$120,000	$73,300	$193,000	14.59

QALYs: quality-adjusted life years, SoC: standard of care

Table 4.14. Base-Case Discounted Costs and Outcomes from Model: Benralizumab

	Intervention Costs	Non-Intervention Costs	Total Costs	QALYs
Benralizumab¶	$669,000	$45,800	$715,000	16.00
SoC	$120,000	$73,300	$193,000	14.59

QALYs: quality-adjusted life years, SoC: standard of care

Table 4.15. Base-Case Discounted Costs and Outcomes from Model: Dupilumab

	Intervention Costs	Non-Intervention Costs	Total Costs	QALYs
Dupilumab¶	$732,000	$31,900	$764,000	16.21
SoC	$120,000	$73,300	$193,000	14.59

QALYs: quality-adjusted life years, SoC: standard of care

Base-Case Incremental Results

Base-case discounted incremental results are found in Table 4.16 with all biologics falling in the $300,000 to $400,000 per QALY range. The comparison of base-case discounted incremental results alongside the corresponding biologic treatment's annual price are found in Table 4.17.

Table 4.16. Base-Case Discounted Incremental Results

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Cost per QALY Gained (vs. SoC)	$325,000 / QALY	$344,000 / QALY	$391,000 / QALY	$371,000 / QALY	$351,000 / QALY

QALYs: quality-adjusted life years, SoC: standard of care

Table 4.17. Base-Case Incremental Cost-Effectiveness Ratio and Annual Price (side-by-side)

	Base-Case Incremental Cost-Effectiveness Ratio	Annual Price*
Omalizumab	$325,000	$28,900
Mepolizumab	$344,000	$29,500
Reslizumab	$391,000	$28,900
Benralizumab	$371,000	$27,800
Dupilumab	$351,000	$31,000

*Annual price excluding loading dose in year 1 of treatment, and excluding administration costs

Lifetime Annualized Clinical Outcomes

Appendix Tables E2- E6 indicate the average annual lifetime clinical outcomes for all five biologic agents. This analysis investigated the average events per person year for exacerbations resulting in oral corticosteroid burst, ED visit, hospitalization, and death (all cause). The exacerbation rate ratios drive these incremental findings.

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY. Key drivers of uncertainty for mepolizumab versus SoC included utility estimates for the biologic and SoC non-exacerbation health state, annual exacerbation rates for SoC, and cost of chronic oral steroid use (Figure 4.2 and Table 4.18). Other biologics had similar findings in terms of importance of inputs and relative impact on findings (See Appendix Figures E1- E4).

No biologic achieved a greater than zero likelihood of meeting the $150,000/QALY or lower threshold (Table 4.19).

Similar to the intent of one-way sensitivity analyses, we conducted additional analyses that isolated each of the three main measures of biologic treatment benefit in order to understand how each benefit component alone impacted the discounted incremental lifetime results. We computed the discounted incremental results for mepolizumab treatment by only assigning a benefit based on non-exacerbation utility improvement (nulling out the exacerbation reduction benefit and chronic oral steroid reduction benefit). The discounted incremental result was $514,000/QALY. Nulling out the non-exacerbation utility improvement and the chronic oral steroid reduction benefit, the exacerbation reductions associated with mepolizumab yielded a discounted incremental result of $1,355,000/QALY. Finally, nulling out the non-exacerbation utility improvement and the exacerbation reduction benefit, the chronic oral steroid reductions associated with mepolizumab yielded a discounted incremental result of $23,792,000/QALY. Similar levels of impact were observed across all other biologic treatments.

Figure 4.2. Tornado Diagram(s) for One-Way Sensitivity Analyses of Mepolizumab versus Standard of Care

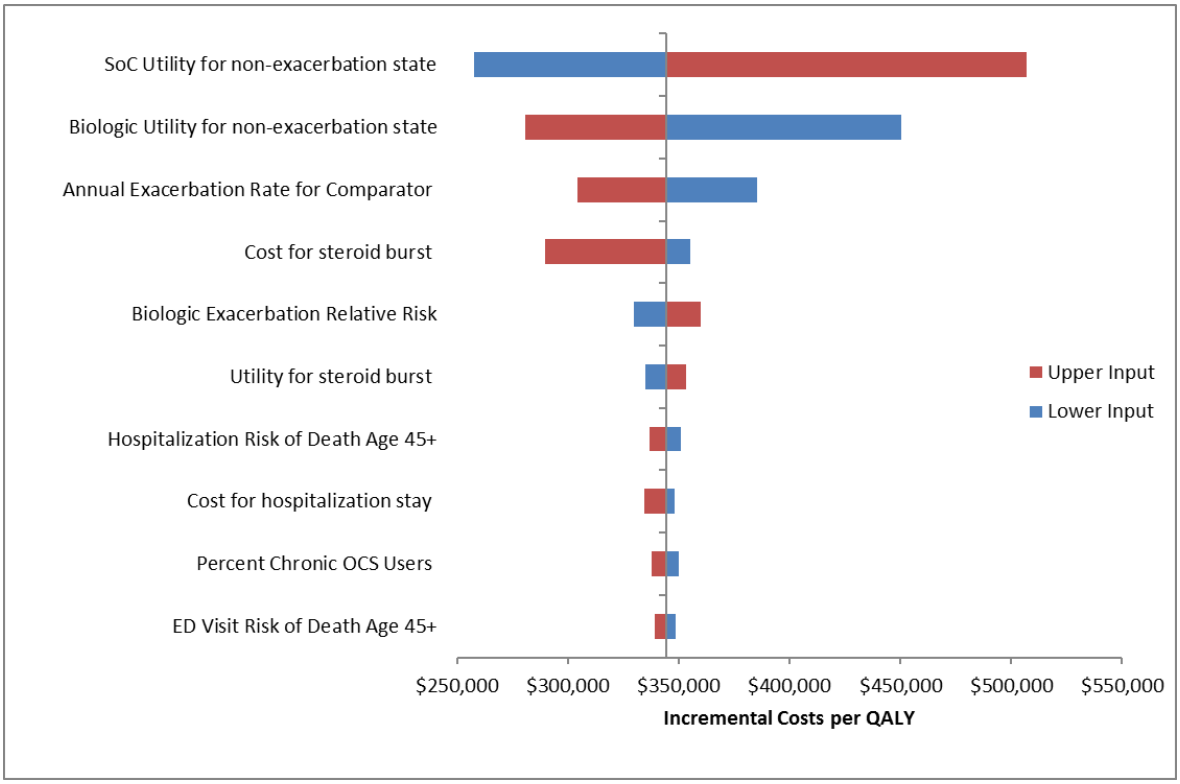


Table 4.18. Tornado Diagram Inputs and Results for Mepolizumab versus Standard of Care

Input Name	Lower Incremental Cost-Effectiveness Ratio	Upper Incremental Cost-Effectiveness Ratio	Lower Input*	Upper Input*
SoC Utility for Non-Exacerbation State	$258,000	$507,000	0.74	0.80
Biologic Utility for Non-Exacerbation State	$451,000	$281,000	0.81	0.85
Annual Exacerbation Rate for Comparator	$385,000	$304,000	0.78	1.95
Cost for Exacerbation-Related Steroid Burst	$355,000	$290,000	$0	$9,172
Biologic Overall Exacerbation Relative Risk	$330,000	$360,000	0.34	0.54
Utility for Exacerbation-Related Steroid Burst	$335,000	$353,000	0.57	0.76
Hospitalization Risk of Death Age 45+ Years	$351,000	$337,000	0.021	0.029
Cost for Hospitalization Stay	$348,000	$335,000	$702	$27,798
SoC Percent Chronic OCS Users	$350,000	$338,000	10.9%	24.2%
ED Visit Risk of Death Age 45+	$349,000	$339,000	0.015	0.021

ED: emergency department, SoC: standard of care

*Note lower input may reflect either upper or lower incremental cost-effectiveness ratio value depending on the direction that the input has on the incremental cost-effectiveness ratio output.

Table 4.19. Probabilistic Sensitivity Analysis Results: Biologic versus Standard of Care

	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY
Omalizumab	0%	0%	0%
Mepolizumab	0%	0%	0%
Reslizumab	0%	0%	0%
Benralizumab	0%	0%	0%
Dupilumab	0%	0%	0%

QALY: quality-adjusted life year

Scenario Analyses Results

Results from a modified societal perspective that considers lost work and productivity are presented in Table 4.20. To address concerns about using the SGRQ mapping algorithm to estimate non-exacerbation health state utilities for biologic treated patients, we estimated the incremental cost-effectiveness ratio for the biologic that produced the largest AQLQ improvement according to the clinical review (mepolizumab). If we used the AQLQ mapping algorithm instead of the SGRQ mapping algorithm, the incremental cost-effectiveness ratio for mepolizumab was $448,000/QALY (instead of $344,000/QALY in the base-case). Given the even weaker AQLQ improvements observed for the other biologics, the corresponding incremental cost-effectiveness ratios based on the AQLQ mappings would be even higher than $448,000/QALY. Although the evidence is weak or missing for including aspects of treatment responders within the base-case, we conducted a *what if* scenario including costs and outcomes of treatment responders using a uniform set of inputs and assumptions across all biologics (Table 4.21). Such findings may be interpreted as a best-case scenario related to how these biologics may be used in clinical practice, given the best available comparative evidence. Because several of the drugs had trials with data pertaining to the ≥300 count eosinophil category, we designed and implemented a scenario analysis in this subgroup (Table 4.22). Given that only the exacerbation rates changed within the ≥300 eosinophil count subpopulation and did not change substantially from the base-case inputs, the findings for this scenario are similar to that of the base-case. Finally, the findings for the collective best-case scenarios that use SoC and relative signals that most favor the biologics suggest incremental cost-effectiveness ratios in the $200,000s and upper $100,000s per QALY (Table 4.23). Scenario #1 suggests that when using the most severe of baseline characteristics and largest relative clinical signals and lowest biologic cost, the resulting incremental cost-effectiveness moves from the $300,000s per QALY to $224,000 per QALY. Further, when restricting the treated population to only those who are on chronic oral corticosteroids, the finding becomes $173,000 per QALY. And when adding the responder scenario alongside assuming favorable clinical and cost inputs moves to the incremental lifetime findings to $156,000 per QALY.

Table 4.20. Incremental Results for Modified Societal Perspective versus Standard of Care

	Incremental Costs	Incremental QALYs	Incremental Cost-Effectiveness Ratio per QALY
Omalizumab	$524,000	1.73	$303,000 / QALY
Mepolizumab	$524,000	1.63	$320,000 / QALY
Reslizumab	$538,000	1.48	$364,000 / QALY
Benralizumab	$482,000	1.41	$342,000 / QALY
Dupilumab	$532,000	1.63	$327,000 / QALY

QALY: quality-adjusted life year, SoC: standard of care

Table 4.21. Treatment Responder Scenario Incremental Cost-Effectiveness Ratio

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Cost per QALY Gained (vs. SoC)	$ 213,000/ QALY	$ 214,000/ QALY	$222,000 / QALY	$199,000 / QALY	$218,000 / QALY

QALY: quality-adjusted life year, SoC: standard of care

Table 4.22. Eosinophils ≥ 300 Count Incremental Cost-Effectiveness Ratio with ≥ 2 Exacerbations in the Prior Year and Baseline ACQ ≥ 1.5

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Cost per QALY Gained (vs. SoC)	$330,000 / QALY	$346,000 / QALY	$346,000 / QALY	$360,000 / QALY	$332,000 / QALY

QALY: quality-adjusted life year, SoC: standard of care

Table 4.23. Collective Best-Case Scenarios

	#1 (favorable base-case inputs)	#2 (#1 and assume 100% chronic OCS users)	#3 (#1 and responder scenario)
Cost per QALY Gained (vs. SoC)	$224,000 / QALY	$173,000 / QALY	$156,000 / QALY

QALY: quality-adjusted life year, SoC: standard of care

Threshold Analyses Results

Tables 4.24 and 4.25 present the threshold monthly price results for the five biologic agents in the review (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) at $50,000, $100,000, and $150,000 per QALY for within-trial and long-run variations.

Table 4.24. Threshold Annual Price Results

Intervention	Annual Price at $50,000 per QALY	Annual Price at $100,000 per QALY	Annual Price at $150,000 per QALY
Omalizumab	$4,700	$9,000	$13,300
Mepolizumab	$5,100	$9,200	$13,400
Reslizumab	$2,900	$6,500	$10,400
Benralizumab	$4,700	$8,300	$11,900
Dupilumab	$6,000	$10,100	$14,300

QALY: quality-adjusted life year

Table 4.25. Threshold Unit Price Results

Intervention	Unit	WAC per Unit	Manufacturer Net Price	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY
Omalizumab	150 mg vial	$1,084.66	$802.64*	$130	$250	$370
Mepolizumab	100 mg	$2,868.67	$2,272†	$390	$710	$1,030
Reslizumab	100 mg/ml vial	$878.80	$804.10‡	$80	$180	$290
Benralizumab	30 mg	$4,752.11	$4,265¥	$720	$1,270	$1,820
Dupilumab	2 x 200 or 300 mg	$2,931.54	$2,384.62^	$460	$780	$1,100

*Per manufacturer: "Net price per 150mg vial was calculated using the manufacturer-provided annual net cost. Omalizumab's average annual net cost per adult patient is $28,895. Average annual net cost of treatment for adults with allergic asthma only (as of July 2018) assuming three 150 mg vials per month. Net cost assumption is an average cost reflecting all price concessions given to customers, and inclusive of all statutory discounts and rebates. This calculation is an estimate for the purposes of financial modeling. Cost of treatment per patient varies as dosing depends on age, weight and IgE level and pricing differs by provider and payer (commercial insurance or government program)."
†Per manufacturer: "Average net sales price is inclusive of WAC rebates, allowances, and returns."
‡Per manufacturer: "This net price reflects a weighted average after applying statutory discounts."
¥Per manufacturer: "The net price for each 30mg/ml pre-filled syringe of Benralizumab is $4265. This price includes government statutory rebates, allowances, and returns."
^Per the manufacturer: "The net price of $31,000 should be considered as inclusive of all discounts applied to dupilumab throughout the value chain and not just reflective of rebates alone."

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

The current ICER model's structure is based on prior asthma model structures including ones developed by Campbell et al., Kim et al., McQueen et al. and the prior ICER report on mepolizumab.[27,72,100,101] The model by Campbell et al. estimated the cost-effectiveness of omalizumab plus SoC versus SoC in patients with moderate to severe persistent asthma. In Campbell et al.'s model, omalizumab treatment had a stopping rule of five years after which patients where shifted to usual care while omalizumab's treatment was over a lifetime in the ICER

model. The rate ratios of OCS burst and asthma exacerbation-related hospitalizations in the ICER model are higher than those used by Campbell et al., while the asthma exacerbation-related ED visits are the same between both models. Difference in non-exacerbation state utilities for biologic treatment versus standard of care treated populations in the ICER model where derived from the SGRQ-EQ-5D mapping algorithm and yielded a biologic-treated improvement of 0.062 in utility while in Campbell et al.'s model utility differences were derived using patient-level data and an AQLQ-EQ-5D mapping algorithm but yielded a comparable utility improvement of 0.063 for omalizumab treated patients versus standard of care alone. The omalizumab price used in both models differ, with omalizumab's net price in the ICER model being approximately 1.4 times the 2008 list price of omalizumab. While exacerbation-related steroid bursts costs and ED costs are substantially higher in the ICER model ($1,538 vs. $120 and $2,072 vs. $548, respectively), exacerbation-related hospitalizations cost are similar between the two models (ICER: $9,053 vs. $9,132). The treatment duration, coupled with higher baseline utilities resulted in higher lifetime discounted QALYs in the ICER model (16.32 vs. 14.19), with the longer treatment duration and higher drug and other costs contributing to higher total costs ($757,000 vs. $174,500) in the omalizumab arm in the ICER model. Comparing incremental results, the ICER model resulted in an incremental cost per QALY of $325,000 while Campbell et al.'s model reported an incremental result of approximately $287,000 per QALY.

A model developed by NICE's Evidence Review Group evaluated the cost-effectiveness of omalizumab as an add-on to SoC versus SoC alone from a UK NHS perspective in patients aged six years and older, with uncontrolled persistent severe asthma.[102] The model structure was similar to what the manufacturer submission was, with health states including day-to-day asthma symptoms (non-exacerbation states), exacerbations states being categorized into clinically significant non-severe (CSNS) and severe (CSS), and asthma and all-cause-related mortality. The CSNS state corresponds to the asthma-exacerbation sub-state requiring only oral-steroid burst without ED visit or hospitalization, while the CSS state corresponds to the ED visit or hospitalization sub-states in the ICER model. Patients subgroups modeling severity categorized by number of hospitalizations, maintenance OCS and number of exacerbations in the NICE model while the ICER model categorized severity by high eosinophil ≥300 cells/µL in a scenario analysis. Baseline exacerbations in the NICE model were derived from the INNOVATE SoC arm for adults and adolescent for both CSNS and CSS, and from IA-05 EUP for children aged 6-11 years. The ICER model uses rate ratios for omalizumab from a Cochrane review (summarized in Comparative Clinical Review Section 3) for the exacerbation-related oral-steroid burst and hospitalization sub-categories. The SoC exacerbation rates were averaged across trials for the five treatments included in the ICER review. Both models apply similar rate ratios of exacerbations for the intervention(s) relative to SoC. The ICER model derived utility estimates for the non-exacerbation health state using mapping algorithms between the SGRQ and EQ-5D while the NICE model used the same findings reported in Campbell et al. However, the NICE model used the utility improvement associated with only omalizumab treatment responders (0.11 vs. SoC) rather than the utility improvement associated with all those who

received omalizumab (0.063 vs. SoC). Exacerbation-related disutility values in both models were derived from the same source, Lloyd et al., which was conducted in the UK.[91] The NICE model used a three-month cycle length while the ICER model uses a two-week cycle length. While the modeled time horizon is 40 years for the NICE model, treatment duration with omalizumab was ten years. The ICER model uses a lifetime time-horizon with treatment duration not being limited to ten years. The ICER model uses a 3% discount rate while the NICE model used a higher 3.5% discount rate. Since the two models cater to different health systems, we do not draw comparisons on treatment-related cost inputs or outcomes. However, comparing QALYs, both intervention and SoC in the ICER model had higher QALYs relative to those in the NICE model in the ≥12-year age group. The higher lifetime discounted QALYs in the ICER model is possibly due to higher ongoing treatment with omalizumab with no stopping rule as seen in the NICE model.

In 2016, ICER conducted a review of mepolizumab plus ICS versus SoC in adults with severe uncontrolled asthma with evidence of eosinophilic inflammation.[27] Model structure for this review followed the same structure as seen in Campbell et al.'s 2010 publication.[72] Compared to the 2016 report on mepolizumab, this updated model structure in the current review allowed for one treatment responder evaluation (where patients who respond to therapy remain on that therapy, and those who do not discontinue therapy) and a separate set of inputs for treatment responders. Comparison of baseline SoC exacerbation rates between the two reviews showed that the 2016 review had a higher rate of 1.74 per year versus 1.3 per year in the current review due to a pooling across biologic therapies in the current review. Proportion of baseline SoC hospitalizations, ED visits and OCS bursts were similar between the two reviews, but mepolizumab-related hospitalization, ED visits and OCS bursts were lower in the current review compared to the 2016 review. Baseline SoC and mepolizumab utilities and exacerbation-related disutility values in both reviews were similar. Like in the 2016 mepolizumab review, the current review did not include an added mortality risk in the exacerbation-related OCS burst subcategory. However additional mortality risk was included for the exacerbation-related hospitalization and ED visit subcategories, with an increased mortality risk for ED visits being applied to the current review. While all treatment related costs in the current review are higher, note that in the 2016 review we used the WAC instead of a net price estimate for mepolizumab, which resulted in higher unit cost of the biologic relative to the current review. Comparing results, the current review versus the 2016 review generated more lifetime discounted QALYs in both the mepolizumab (16.22 vs. 15.12) and SoC (14.59 vs. 13.59) arms, as well as higher costs. The lifetime discounted QALY within treatment increases are driven mainly by the difference in starting age (46 years in current review and 50 years old in 2016 review) but are not thought to significantly impact the incremental findings; higher costs are driven by the higher health care unit costs in the current review. Comparing incremental cost-effectiveness results, the current review resulted in a cost per QALY of approximately $344,000 while the 2016 review resulted in a cost per QALY of approximately $386,000 over a lifetime time horizon, with differences in results driven by differences in mepolizumab treatment cost and other updates such as unit costs and exacerbation rates. The

model by Whittington et al. closely resembles the 2016 ICER review in interventions, target population, methods and results and is hence not described here.[73]

One model submitted to NICE by the manufacturers of mepolizumab compared mepolizumab to SoC in three distinct populations, namely, "modified intention-to-treat (ITT)", a "proposed population" and a "restricted population", and mepolizumab to omalizumab in the "modified ITT" population.[28] The manufacturer "proposed population" comprised patients with blood eosinophil count of ≥150 cells/µL when starting treatment and on systemic corticosteroids. The model used a lifetime horizon and a four-week cycle length, unlike the ICER model's two-week cycle length. Health states in the manufacturer-submitted model included treatment responder evaluation (after one year for mepolizumab and after 12 weeks for omalizumab). If no increase in exacerbation was found at time of assessment, patients could continue on biologic treatment, whereas if an increase in exacerbations was found, patients moved to SoC. The model assumed an attrition of 10% annually, unlike the ICER model which did not assume any treatment-related attrition. The model also assumed a stopping rule of 10-years as time on treatment for biologics, while no such assumption was employed in the ICER model. Treatment effect of mepolizumab was based on the MENSA trial in the manufacturer submitted model. Both models included mortality associated with exacerbation-related hospitalizations, but we found no information on mortality estimates for exacerbation-related ED visits or OCS bursts in the manufacturer submitted model. Utility and disutility estimates in both models are similar. Owing to the difference in setting, we do not compare costs in the two models. We are unable to compare lifetime discounted QALYs between the two models since there no published QALY results, only incremental cost-effectiveness ratios.

4.4 Summary and Comment

The base-case findings from our analysis suggest that the use of asthma biologic agents in the studied populations provides clinical benefit in terms of gains in quality-adjusted survival over that of SoC alone. Due to increased biologic treatment costs, the cost-effectiveness estimates did not meet commonly-cited cost-effectiveness thresholds. This interpretation of the incremental cost-effectiveness findings was robust to one-way and probabilistic sensitivity analyses for all biologic agents. Sensitivity analysis was also used to isolate the impact of the three main biologic agent benefits: non-exacerbation health state utility improvement alone, exacerbation reductions alone (with indirect mortality benefits), and chronic oral steroid reductions alone. The findings from this sensitivity analysis suggested that non-exacerbation health state utility improvements associated with biologic therapy are potentially the most influential benefit input on lifetime discounted cost-effectiveness, followed by exacerbation reductions and finally, the chronic oral steroid reductions. Scenario analyses suggested that the most influential scenarios were including the potential costs and benefits of biologic treatment responders (and non-responders) as well as reserving biologic treatment only in the chronic oral corticosteroid subgroup. In what might be interpreted as an optimistic responder scenario based on best-available comparative evidence, we found incremental cost-effectiveness findings that ranged from $199,000/QALY to $222,000/QALY for the various biologics. The uncertainty in the responder scenario findings is lowest for omalizumab given more available evidence; this uncertainty was not characterized given that the responder scenario is outside of the base-case analysis. When looking at the collective best-case analyses that chose biologically favorable clinical signals and standard of care characteristics, the scenario that included potential costs and outcomes of responders or the scenario that restricted the treatment population to only the chronic oral corticosteroid group resulted in incremental cost-effectiveness findings of $156,000 and $173,000 per QALY, respectively. The modified societal perspective findings reduced the base-case incremental findings by approximately five to ten percent. The ≥ 300 eosinophil subpopulation scenario did not change the results substantially from the base-case.

Limitations

The model analysis was limited by several factors. Long-run clinical evidence on biologic treatment responders as well as discontinuation was not available and, with respect to that limitation, we assumed constant treatment benefits and long-run (lifetime) treatment duration. As the collective best-case treatment responder scenario and chronic oral corticosteroid subpopulation yielded the lowest incremental cost-effectiveness findings, further research is suggested to either refute or support these findings that we cautiously interpret as best case.

Health utility for the day-to-day non-exacerbation health state was identified as the most influential input of biologic benefit with significant uncertainty. Therefore, this is another important area for research.

Mortality was assigned an indirect impact in the model through reduced asthma-related hospitalizations and ED visits. Differences in mortality were not observed in the clinical evidence review.

We identified a need for more biologic-attributable evidence specifically around subpopulations and aspects of treatment responders that are conducted in the United States. While NICE has conducted extensive research on asthma biologics, such as mepolizumab and reslizumab,[28,103] the patient populations in their reports are based on the United Kingdom, not the United States, which limits the potential adaptability of our model.

We did not evaluate subpopulations such as those with income or ethnic disparities due to a lack of clinical evidence in these subgroups.

Finally, this analysis focused on estimating the long-term cost effectiveness of biologics within the asthma target population included in this review. Comorbidities associated with asthma were indirectly included within the asthma populations studied, and thus are included in the cost-effectiveness findings. However, specific subpopulations that included one or more comorbidities were not pre-specified for additional cost-effectiveness scenarios due to a lack of available evidence.

Conclusions

In conclusion, the findings of our analysis suggest that the biologic agents of focus for this review provide gains in quality-adjusted survival over standard of care alone. With the evidence available at this time, these biologic agents seem to be priced higher than the modeled benefits over a lifetime time horizon at commonly accepted cost-effectiveness thresholds. The findings were not sensitive to traditional sensitivity or scenario analyses but were most favorable in scenarios associated with long-term biologic treatment for responders or biologic initiation in the subgroup of chronic oral corticosteroid users. Evidence is needed to support or refute these scenario value projections. Higher value care is more likely to be achieved through careful patient selection and continued biologic therapy for only treatment responders.

5. Potential Other Benefits and Contextual Considerations

Table 5.1. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to standard therapy with high dose ICS and LABA there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to standard therapy with high dose ICS and LABA there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

5.1 Potential Other Benefits

The five biologics are all parenteral, which may impact the acceptability and long-term adherence to therapy. Four are delivered subcutaneously and one (reslizumab) is given by IV infusion. Only dupilumab is approved for self-injection. All of the other drugs require a visit to a medical center for each dose for administration by a health care professional.

In addition, the dosing schedule varies between the drugs, which may also impact acceptability to patients and long-term adherence. Dupilumab is given every two weeks, omalizumab is given every two to four weeks, mepolizumab and reslizumab are given every four weeks, and after the first three doses, benralizumab is given every eight weeks.

Dupilumab, in particular, offers a new mechanism of action. It is the first drug to target the IL-4 and IL-13 pathways in type 2 asthma.

There is limited evidence in the studies to date, but patients with severe asthma often miss school or work due to their asthma and even if present, may be less alert due to poor sleep or ongoing shortness of breath. All five biologics have the potential to improve this aspect of a patient's life.

5.2 Contextual Considerations

Asthma is a life-long disease and for children suffering from severe, poorly controlled asthma, the disease may impact the entire trajectory of their lives.

All the biologic interventions manipulate the immune response of patients and the long-term implications of such manipulation remain unclear.

6. Value-Based Price Benchmarks

Our value-based benchmark annual prices for the five asthma biologics are presented in Table 6.1. The value-based benchmark price for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained. For all considered biologics, the discounts required to meet both threshold prices are greater than their current discount from WAC.

Table 6.1 Value-Based Benchmark Prices of Asthma Biologics in the Treatment of Moderate to Severe Uncontrolled Asthma

Intervention	Annual WAC	Annual Price at $100,000 per QALY Threshold	Annual Price at $150,000 per QALY Threshold	Discount from WAC Required to Achieve Threshold prices
Omalizumab	$39,048	$9,000	$13,300	66% to 77%
Mepolizumab	$37,293	$9,200	$13,400	64% to 75%
Reslizumab	$31,637	$6,500	$10,400	67% to 80%
Benralizumab	$30,889*	$8,300	$11,900	62% to 73%
Dupilumab	$38,110‡	$10,100	$14,300	62% to 73%

*Assuming 6.5 doses per year, year-two onward since year-one has additional loading doses.

‡Assuming 26 doses per year, year-two onward since year-one has an additional loading dose.

7. Potential Budget Impact

7.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impact of dupilumab in its indicated population for asthma: adults and children twelve years of age and older with uncontrolled, moderate to severe asthma in the US. We used the WAC, net price, and the three threshold prices for dupilumab in our estimates of budget impact. We did not include omalizumab, mepolizumab, reslizumab or benralizumab in our calculations since they have all already been approved and have been in use in the US marketplace for close to a year, or more.

7.2 Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total net cost of using dupilumab rather than relevant existing therapy (SoC and other biologics) for the treated population, calculated as health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

As stated previously, the potential budget impact analysis included adults and children six years of age and older with persistent moderate to severe uncontrolled asthma in the US. We applied the CDC-reported asthma prevalence (8.3% among all US adults and children in 2016) to the 2018-2022 projected US population 12 years and older, to find the average number of patients with asthma.[104,105] We then applied the prevalence of persistent asthma, 64.8% in adults and 60.3% in children, to further narrow the population to reflect our target population.[106,107] While there exist estimates for severe asthma among those with persistent asthma, there aren't any robust published estimates on the percentage of population with moderate to severe asthma among those with persistent disease. We thus assumed that those on medications for long-term control comprised the moderate to severe group and hence applied these CDC reported estimates (39% in adults and 40.2% in children) to the persistent asthma population to derive the population with moderate to severe asthma.[108] In their review of asthma prevalence, disease burden and treatment options, Peters et al. reported that 20% of patients with severe asthma had uncontrolled asthma.[109] We applied this estimate more broadly to the moderate to severe asthma population, to arrive at an estimate of approximately 1.2 million patients over five years, or approximately 237,000 patients each year.

ICER's methods for estimating potential budget impact are described in detail elsewhere[110] and have been recently updated. The intent of our revised approach to budgetary impact is to

document the percentage of patients who could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. For 2018-19, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $991 million per year for new drugs.

To estimate potential budget impact, we evaluate a new drug that would take market share from one or more drugs and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that dupilumab would take market share from other biologics and non-biologic SoC. We found recent estimates on market share among biologics in asthma treatment (reslizumab – 1.8%, benralizumab – 5.2%, mepolizumab – 18.2% and omalizumab – 74.9%)[a], as well as the proportion of patients with moderate to severe asthma on biologics (27%) based on a manufacturer-sponsored survey in that patient group.[111,112] As the uptake of dupilumab among the incident target population or among patients currently on treatment for uncontrolled moderate to severe asthma remains unknown, we estimated the percentage of patients on the current treatment mix that could be displaced to dupilumab before the budget impact threshold is reached. Of course, this percentage need not reflect real-world uptake, especially in the presence of existing and established biologics in the asthma treatment paradigm.

7.3 Results

Table 7.1 illustrates the per-patient budget impact calculations, based on WAC ($38,110 per year), net price ($31,000 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY for dupilumab ($14,300 per year, $10,140 per year, and $5,980 per year, respectively) compared to current treatment mix.

Table 7.1. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon

	Average Annual Per Patient Budget Impact				
	WAC	Net Price	$150,000/QALY	$100,000/QALY	$50,000/QALY
Dupilumab	$46,059	$38,912	$22,127	$17,945	$13,764
Current Treatment Mix*	$44,651				
Difference (Dupilumab – Current Treatment Mix)	$1,408	($5,738)	($22,524)	($26,705)	($30,887)

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*27% of target population on biologics and 73% on standard of care. Market share among biologics: reslizumab – 1.8%, benralizumab – 5.2%, mepolizumab – 18.2%, and omalizumab – 74.9%

() – Cost-saving

[a] Note: This information is an estimate derived from the use of information under license from the following IQVIA information service: IQVIA US Defined Daily Doses (DDD) data for the period July 2018. IQVIA expressly reserves all rights, including rights of copying, distribution and republication.

The average potential budgetary impact when using the WAC was an additional per-patient cost of approximately $1,400 per year. Average potential budgetary impact at dupilumab's net price resulted in cost-savings of approximately $5,700 per patient annually. Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug were estimated to be cost saving, ranging from approximately $22,500 per patient in savings using the annual price to achieve $150,000 per QALY to approximately $30,900 per patient in savings using the annual price to achieve a $50,000 per QALY cost-effectiveness threshold. It is important to note that these findings are versus a population-level treatment mix of biologics and SoC. Against just SoC alone, using dupilumab will result in greater budget impact at both the per patient and the population level across the five price points (WAC, discounted WAC, prices to reach willingness-to-pay [WTP] thresholds of $50,000, $100,000 and $150,000 per QALY).

At dupilumab's WAC, 91% of the eligible population could be treated before the total budget impact exceeds the ICER annual budget impact threshold. At its net price and prices to reach the cost-effectiveness thresholds between $50,000 and $150,000 per QALY, the total population budget impact resulted in cost-savings and the entire population could be treated.

7.4 Access and Affordability

As illustrated in the budget impact analysis, treating the entire patient population eligible for treatment with dupilumab at the net price and prices to reach commonly accepted WTP thresholds resulted in net savings. Additionally, at dupilumab's WAC, just over 90% of the entire eligible population could be treated each year without the total budget exceeding the ICER budget impact threshold. At the November 29, 2018 public meeting, the consensus among stakeholders was that uptake of dupilumab would likely not threaten access and affordability, given current market competition and dupilumab's anticipated net price for this indication. As such, ICER is not issuing an access and affordability alert at this time. However, all stakeholders should closely monitor the use of dupilumab for uptake exceeding expectations, along with any unprecedented net price increase.

8. Summary of the Votes and Considerations for Policy

8.1 About the Midwest CEPAC Process

During Midwest CEPAC public meetings, the Midwest CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to Midwest CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Midwest CEPAC Panel during their deliberation and help to shape recommendations on ways the evidence can apply to policy and practice.

After the Midwest CEPAC Panel votes, a policy roundtable discussion is held with the Midwest CEPAC Panel, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the November 29, 2018 meeting, the Midwest CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of biologic therapies for the treatment of asthma. Following the evidence presentation and public comments (public comments from the meeting can be accessed here, starting at minute 6:06), the Midwest CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and potential other benefits and contextual considerations related to biologic treatments for asthma. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by Midwest CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the Midwest CEPAC Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 8.1 below):

1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. Midwest CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

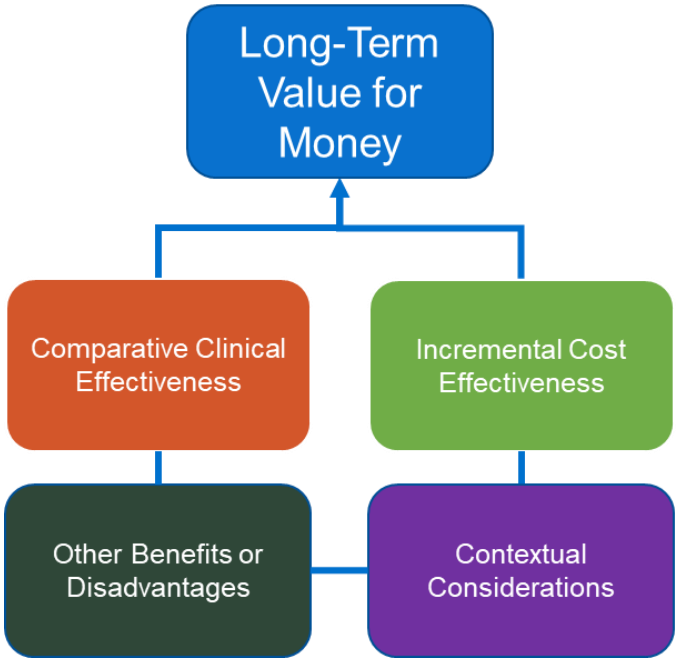
2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the Midwest CEPAC voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

3. Potential other benefits refer to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of potential other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether potential other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for potential other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the

condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 8.1. Conceptual Structure of Long-term Value for Money



8.2 Voting Results

For patients ≥ 12 years with uncontrolled, moderate to severe asthma, and eosinophilic phenotype:

1. **Is the evidence adequate to demonstrate that the net health benefit of dupilumab is superior to that provided by standard of care (ICS plus at least one additional controller medication)?**

Yes: 12 votes	No: 3 votes

A majority of the CEPAC Council voted that the evidence was adequate to demonstrate that the net health benefit of dupilumab is superior to that provided by standard of care. Council members who voted in the affirmative stated that quality of life improvements weighed heavily on their votes. Additionally, Council members considered reduction in the use of OCS for patients treated with dupilumab as an important clinical outcome of benefit to patients given the significant side effects of long-term steroid use. Finally, the relative risk reduction in exacerbation events was substantially larger for patients treated with dupilumab as compared to those receiving standard of care and Council members cited this absolute reduction as a clear indication of positive net health benefit.

For patients ≥ 12 years with uncontrolled, severe asthma, and eosinophilic phenotype:

2. Is the evidence adequate to distinguish the net health benefit *among* mepolizumab, reslizumab, and benralizumab?

Yes: 1 vote	***No: 14 votes***

A majority of the Council determined that the evidence was inadequate to distinguish the net health benefit among mepolizumab, reslizumab, and benralizumab. One Council member who voted in the negative emphasized that the lack of head-to-head trials and heterogeneity in trial populations precluded their ability to distinguish between agents. Another Council member noted that four out of five network meta-analyses conducted on these three biologics (including the one performed by ICER) did not find statistically-significant differences among them and agreed with the point made by the clinical experts present at the meeting that the biologics are essentially interchangeable in clinical practice.

IF NO…

3. Is the evidence adequate to distinguish the net health benefit *between* dupilumab and these three treatments?

Yes: 0 votes	***No: 15 votes***

The Council unanimously judged that the evidence was inadequate to distinguish the net health benefit between dupilumab and the three agents listed above. Several Council members cited the lack of head-to-head trials, and the heterogeneity between trial populations.

4. Is the evidence adequate to distinguish the net health benefit *between* omalizumab and these three treatments?

Yes: 0 votes	***No: 15 votes***

The Council voted unanimously that the evidence was inadequate to distinguish the net health benefit between omalizumab and mepolizumab, reslizumab, and benralizumab. Once again, the lack of head-to-head trials made distinguishing between treatments difficult. One Council member asked why there didn't seem to be a correlation between time on the market, and the amount and quality of evidence for these biologics? Dr. Jeff Tice generally agreed that time on the market did not correlate with better evidence but stipulated that a drug's safety profile was the expectation. The clinical experts agreed and confirmed that the risk for unexpected harms from omalizumab or mepolizumab was low given the longevity of each. Even so, Council members were unconvinced that this one piece of evidence was enough to distinguish these biologics and voted the evidence was inadequate to distinguish.

5. In the treatment of patients ≥ 12 years with moderate to severe asthma, does dupilumab offer one or more of the following potential other benefits or disadvantages compared to best usual care without biologic treatment?

Dupilumab offers reduced complexity that will significantly improve patient outcomes.	3/15
Dupilumab will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.	0/15
Dupilumab will significantly reduce caregiver or broader family burden.	6/15
Dupilumab offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	8/15
Dupilumab will have a significant impact on improving patients' ability to return to work and/or their overall productivity.	7/15
There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention	3/15

Three Council members judged that dupilumab offers reduced complexity, noting that if treatment leads to reduced OCS use, a patient's treatment regimen will be simplified. Those who did not vote for this option argued that adding a biologic to standard of care inherently increases the complexity of treatment. Council members also discussed adherence as another important benefit. Clinical experts present at the meeting noted that adherence rates have been shown to be very high with biologics but under 60% with standard of care. Both the ability to reduce OCS use and the potential for high adherence led Council members to vote dupilumab would decrease caregiver burden and improve patients' ability to return to work and/or their overall productivity. Council members also acknowledged that dupilumab has a different mechanism of action from the other biologics, so it could allow for the successful treatment of many patients for whom other treatments have failed. No Council members voted that this drug would reduce health disparities, noting that this disease disproportionately impacts people of color and families with low socioeconomic status and those individuals are also the least likely to seek treatment.

6. Are any of the following contextual considerations important in assessing the long-term value for money of dupilumab versus best usual care without biologics?

This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	11/15
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	12/15
This intervention is the first to offer any improvement for patients with this condition.	0/15
There is significant uncertainty about the long-term risk of serious side effects of this intervention.	8/15
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	11/15
There are additional contextual considerations that should have an important role in judgments of the value of this intervention:	3/15

Council members acknowledged the high burden of disease asthma presents to patients with severe asthma. They thanked the patients who delivered public comments for sharing their stories and painting a picture of what it's like to live with what can be a debilitating and life-threatening condition. The majority voted that dupilumab is intended to care for patients with a condition of high severity and a high lifetime burden of illness. Due to the availability of multiple treatments available for patients with severe asthma, no Council members voted that dupilumab was the first to offer improvements to this patient population. A majority of the Council members felt that there is uncertainty about the long-term benefits of dupilumab, citing the lack of long-term trial evidence. Similarly, eight out of the 15 Council members voted that there was uncertainty about the long-term risk of side effects, again noting the lack of evidence.

7. Are there important and distinctive other benefits or disadvantages, or unique contextual considerations that apply to any of the other biologic treatments for their labeled population?

Council members noted that dupilumab can be self-administered at home by the patient, whereas the other biologics in the review required an office visit for administration. Conversely, one Council member commented that while self-administration presents an opportunity for increased access, it also risks causing a decrease in adherence. Lack of adherence is not only dangerous for patients but creates significant waste in health-care spending, particularly in this case due to the high cost of the drug. Many Council members acknowledged that self-administration presents a trade-off, but all agreed the increased ease of self-administration was a net-positive for patients.

Long-term Value for Money Votes

As described in ICER's recent update to its **value assessment framework**, questions on "long-term value for money" are subject to a value vote only when incremental cost-effectiveness ratios for the interventions of interest are between $50,000 and $175,000 per QALY in the primary "base case"

analysis. As shown in the Evidence Report, the estimates for all five biologics exceed the higher end of the range and thus all interventions are deemed "low value" without a vote of the panel.

8.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on biologics for treatment of asthma to policy and practice. The policy roundtable members included two patient representatives, two clinical experts, two payers, and five representatives from pharmaceutical manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix G.

Table 8.1. Policy Roundtable Members

Name	Title and Affiliation
Mario Castro, MD, MPH	Professor of Medicine, Pediatrics, and Radiology, Washington University School of Medicine
David Evan	Senior Director, Strategic Brand Marketing, Teva
Marsha Fisher, MD, FACOG	Medical Operations Director, Anthem BCBS of Missouri
Mark S. Forshag, MD, MHA	US Medical Expert – Respiratory, GlaxoSmithKline
Jeremy Fredell, PharmD, BCPS	Director, Trend Solutions - Drug Trend & Formulary, Express Scripts
Benjamin Kramer, MD	Vice President, Immunology and Ophthalmology, US Medical Affairs, Genentech
Andreas Kuznik, PhD	Senior Director, Health Economics and Outcomes Research, Regeneron
Donna J. Matlach, DMin, MM, CDA	Patient Advocate; Board Member, Allergy and Asthma Network
Kenny Mendez, MBA	President and CEO, Asthma and Allergy Foundation of America
Kaharu Sumino, MD, MPH	Staff physician, Saint Louis VA Medical Center; Associate Professor of Medicine, Washington University School of Medicine
Frank Trudo, MD, MBA	Vice President, US Medical Affairs, Respiratory, AstraZeneca

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Manufacturers

To provide fair value to patients and the health system, manufacturers should lower the prices of biologic therapies for asthma so that they align with the added value they bring to patients.

The price increases observed for omalizumab and the launch prices of more recent biologics do not align with usual standards for value that reflect a price proportionate to the added benefits

experienced by patients. There is no a priori reason why monoclonal antibody therapy for asthma should command exceptional pricing. There has been extensive experience with the development and manufacturing of monoclonal antibody therapies for many indications over the past two decades. Indeed, some monoclonal antibodies are sold for less than $3,000 a year (denosumab) and maintain profitability for their manufacturers.

Given the high clinical burden borne by patients with uncontrolled, severe asthma, high prices for these effective drugs impose an unfair burden on patients and are likely to trigger greater constraints by insurers on access. Manufacturers should bring lower prices to the negotiating table with insurers in return for broader access for patients who can benefit from these important treatments.

Plan Sponsors

Plan sponsors should work with payers to develop insurance coverage that makes an explicit commitment to providing excellent access to all new biologic treatments for asthma if manufacturers will price their products in line with independent assessments of added value to patients.

Current approaches to insurance coverage often rely on negotiations for preferential formulary status in return for lower net prices. This approach is one of the few tools that plan sponsors have to seek any leverage in controlling costs, but it can create complexity and burdens for clinicians and patients. Plan sponsors should work with payers to develop benefit design and negotiation platforms that can provide a clear pathway for drugs that are priced fairly to be covered with minimum prior authorization controls. In addition, fair pricing as established in comparison to external, independent assessment, should be matched with low out-of-pocket requirements for patients.

Payers

Given that, to date, manufacturers have not priced biologics for asthma at a value-based level, payers are likely to offer preferential formulary status in return for lower prices. For many patients the evidence is not adequate to determine which drug would be superior as a first option, therefore it is reasonable for payers to consider step therapy as a mechanism to achieve lower costs without harming patients.

Until recently, patients and clinicians had limited options when background inhaler therapy was not able to provide adequate control for patients with severe eosinophilic asthma. Now, in addition to omalizumab, there are four options, not all of which have identical indications, but which have similar mechanisms of action and therefore offer options for many patients. Clinical experts involved in the ICER review expressed the opinion that it was reasonable for payers to establish step therapy policies as long as patients who did not respond on a first-step option would not face

significant barriers in switching to another option. The four biologics currently available for uncontrolled, moderate to severe, eosinophilic asthma appear to offer similar improvements in asthma exacerbations and quality of life. There are no head to head clinical trials of the agents and indirect treatment comparisons have not identified significant differences between the biologics. Given the lack of biomarkers that indicate that one agent is more likely than the others to benefit an individual patient, step therapy is a reasonable option. However, even at the first step, there should be an easy pathway for appeal for alternative agents. For example, weight-based dosing, which is only used with reslizumab, may be appropriate for obese patients who fail initial therapy.

In addition to step therapy, payers will develop prior authorization criteria to ensure that prescriptions are covered only for appropriate patients and that use of these expensive medications is prudent. Potential considerations regarding elements of prior authorization criteria for the biologics other than omalizumab are shown below:

Patient eligibility

Patients who meet the FDA indications for mepolizumab, reslizumab, benralizumab, and dupilumab (other than in patients on chronic OCS) have uncontrolled, moderate to severe eosinophilic asthma.

1. *Diagnosis of asthma*: Clinical experts suggested that as many as 30% of patients referred to specialty asthma providers are found not to have asthma. Therefore, a confirmation of asthma is reasonable. Clinical guidelines suggest that the diagnosis of asthma should be confirmed with spirometry: a pre-bronchodilator FEV1 < 80% predicted and FEV1 reversibility of at least 12%.
2. *Uncontrolled*: The definition of uncontrolled can be left to the discretion of the clinician but many payers will establish some empirical threshold. This criterion could be set at a number of exacerbations in the past 12 months, but it may ideally reflect both the number and severity of asthma exacerbations. For example, uncontrolled asthma could be defined as at least two exacerbations requiring oral corticosteroids or at least one hospitalization due to an asthma exacerbation. In Europe, the criteria for use of some of these biologics requires at least four exacerbations in the prior year, reflecting greater relative and absolute benefits in the population of patients with greater numbers of exacerbations.
3. *Severe*: Looking to authoritative guidelines, payers may consider requiring that patients meet the criteria for Global Initiative for Asthma (GINA) step 5: treatment with high dose ICS and another controller agent for at least six months. Ensuring that patients have been receiving excellent background care prior to consideration of biologics will ensure that patients are not started on biologics unnecessarily.
4. *Eosinophilic phenotype*: Eosinophilia could be defined as eosinophil levels ≥ 150, 300, or 400 cells/µl with greater relative and absolute benefits for higher eosinophil levels. Given the high costs and low value of the biologics, some clinical experts felt that it would be reasonable to require levels of at least 300 eosinophils/µl within the prior year. Note, when the FDA indicated these drugs for eosinophilia, an exact cut-point was not defined.

Continuation criteria

Given that the effectiveness of the biologics is usually apparent within six months of use, payers should work with clinicians to assess treatment response after six months of therapy.

Clinical experts indicated that 6 months of treatment was sufficient to assess response. Measures commonly used by asthma experts to assess response include an improvement in the ACT of at least three points or an improvement in FEV1 of at least 100 ml.

Combination therapy

Combination therapy with two or more biologics should not be covered except under exceptional circumstances. There is no evidence that combinations of any of the five biologic therapies improve outcomes.

Provider criteria

It would be reasonable for payers to require that biologic therapy prescribing be restricted to specialists (pulmonary specialist/allergy and immunology specialist) or by primary care physicians only after consultation with a specialist.

Since biologic therapies for asthma are expensive and as many as 30% of patients referred to specialist with severe asthma do not have asthma as the underlying diagnosis, payers may wish to consider requiring diagnosis by an asthma specialist to confirm the diagnosis of asthma and to ensure the optimal delivery of non-biologic therapies. However, consideration should be given to access to care in geographic regions where specialists are not readily accessible. In that case, specialist consultation may suffice for coverage of therapy.

The process for authorization of biologic therapies for asthma should be clear and efficient for providers.

Patients and providers reported delays of several months in obtaining authorization decisions for biologic therapies. Specialists in asthma spoke of the need for a full-time employee primarily to assist with authorization and continuation therapy for biologic therapies for asthma. They also reported that some specialists refer patients to severe asthma clinics solely for assistance with obtaining authorization. Insurers should implement streamlined processes that are evidence-based and timely to ensure that patients for whom biologic therapy is appropriate are able to begin treatment in a timely manner.

When patients change insurance, coverage for their biologic should be continued to avoid worsening of asthma control.

Patients should not be denied effective therapy because of a change of insurance. However, it would be reasonable to require documentation of the effectiveness of therapy for continuation of the biologic after six months.

Payers should not deny ongoing coverage of biologic therapy if patients are able to reduce the intensity of their ICS or other long-acting controller medications during treatment with the biologic.

One of the benefits of biologic therapy for asthma is improved control, which may allow for de-intensification of therapy. A reduction in the use of oral corticosteroids, high dose inhaled corticosteroids, and rescue medications are markers of the effectiveness of the biologic and should not be viewed as a reason to stop therapy. To date, there is no evidence supporting ongoing efficacy once a biologic therapy is withdrawn.

Manufacturers, insurers, and governments should work to remove barriers to indication-specific pricing.

Indication-specific pricing would be an important innovation for drugs that offer dissimilar value for different indications. Many of the biologics have FDA approval for other indications. Some, such as dupilumab, meet typical willingness to pay thresholds for one indication (atopic dermatitis), but not for asthma. The "Medicaid best price" provision may limit innovation in pricing that separately reflects the value in multiple indications, formularies may not be set up in a way that allows for differential tiering based on indication, insurers may have difficulty tracking indication-specific pricing without separate drug codes and/or brand names by indication, and anti-kickback laws may limit the rebates that manufacturers are able to include in these arrangements [ICER ISP White Paper, 2016]. Alternative approaches to fair pricing need to be developed to facilitate better alignment of prices with patient benefit across indications. As an example, if utilization tracking is relatively straightforward, insurers could negotiate a "weighted" rebate across indications based on the value-based price in each indication adjusted by expected or actual utilization in each indication. As a final option, manufacturers may consider rebranding treatments by indication to facilitate indication-specific prices.

Specialty Societies

Specialty societies should develop a clear definition of response to biologic therapy.

Clinical guidelines should include both the time frame for assessing response to biologic therapies for asthma and the criteria for response. Suggested criteria that could serve as a starting point include an evaluation after six months of therapy and an improvement of three points or more on

the Asthma Control Test (ACT) or an improvement of FEV1 at least 100 ml for an adequate response. Non-responders should not continue the biologic but could be considered for another biologic.

Because of pervasive cost issues, pulmonologists, allergists and their specialty societies should advocate for prices to be better tied to the clinical benefits that drugs bring to their patients.

Specialists recognize the financial impact that these expensive drugs have on their patients. They need to include cost as part of shared decision-making with patients and advocate for lower prices on behalf of their patients.

Researchers

Head to head comparisons of the biologic therapies for asthma are essential.

Ideally, an organization, such as PCORI, should support a pragmatic comparative clinical trial for the four biologics with an indication for uncontrolled eosinophilic asthma. Given the low likelihood of that happening in the short term, there should be support for a large, prospective observational study capturing data on patients eligible for these biologics that would allow for state-of-the-art methods, such as propensity score adjusted analysis, to compare the clinical effectiveness of the five biologic therapies.

Better instruments to measure quality of life need to be developed.

Under the leadership of the FDA, companies should develop and validate a novel quality of life measure that captures benefits that matter to patients and maps to standard measures of utility such as the EQ5D.

Regulators

The FDA should update its guidance for the assessment of outcomes in asthma therapy to standardize the patient populations studied as well as the timing and instruments used to assess outcomes.

The heterogeneity across the trials of asthma biologics both in the instruments used to assess asthma exacerbations and quality of life and the timing of their assessment preclude high quality comparative effectiveness studies between biologics. The FDA should work with specialty societies and manufacturers to update the guidance for asthma trials to facilitate comparisons between active therapies.

Active comparators should be the standard in pivotal trials.

Given the large body of evidence that that treatment of uncontrolled, severe asthma with biologic agents decreases asthma exacerbations and increases quality of life, it is unethical to continue to perform placebo-controlled trials in high-risk patients. Requiring an active comparator in clinical trials would also improve patient and clinician understanding of the relative benefits and risks of available treatment options.

****

This is the second ICER review of asthma treatments.

References

1. Centers for Disease Control and Prevention. National Center For Health Statistics Faststats. 2017; https://www.cdc.gov/nchs/fastats/asthma.htm. Accessed 05/15, 2018.
2. Centers for Disease Control and Prevention. ASTHMA FACTS - CDC's National Asthma Control Program Grantees. 2013; https://www.cdc.gov/asthma/pdfs/asthma_facts_program_grantees.pdf. Accessed 05/15, 2018.
3. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *The Journal of allergy and clinical immunology.* 2007;120(5 Suppl):S94-138.
4. Schatz M, Rosenwasser L. The allergic asthma phenotype. *J Allergy Clin Immunol Pract.* 2014;2(6):645-648; quiz 649.
5. Fahy JV. Type 2 inflammation in asthma--present in most, absent in many. *Nat Rev Immunol.* 2015;15(1):57-65.
6. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *American journal of respiratory and critical care medicine.* 2010;181(4):315-323.
7. Food and Drug Administration (FDA). Xolair Label. 2007; https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103976s5102lbl.pdf. Accessed 05/15, 2018.
8. Food and Drug Administration (FDA). Nucala Label. 2015; https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125526Orig1s000Lbl.pdf. Accessed 05/15, 2018.
9. Food and Drug Administration (FDA). Cinquair Label. 2016; https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761033lbl.pdf. Accessed 05/15, 2018.
10. Food and Drug Administration (FDA). Fasenra Label. 2017; https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761070s000lbl.pdf. Accessed 05/15, 2018.
11. Food and Drug Administration (FDA). Dupixent Label. 2018; https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761055s007lbl.pdf. Accessed 11/01/2018, 2018.
12. Asthma and Allergy Foundation of America. My Life With Asthma: Survey Overview. 2017. www.aafa.org/media/my-life-with-asthma-in-2017-survey-findings-report.pdf.
13. American Academy of Allergy Asthma & Immunology. Choosing Wisely. 2012; http://www.choosingwisely.org/clinician-lists/american-academy-allergy-asthma-immunology-spirometry-for-asthma-diagnosis-and-management/. Accessed September 24, 2018.
14. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev.* 2014(1):CD003559.
15. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev.* 2017;9:CD010834.
16. Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *The New England journal of medicine.* 2018;378(26):2486-2496.
17. Rabe KF, Nair P, Brusselle G, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. *The New England journal of medicine.* 2018;378(26):2475-2485.

18. Regeneron Pharmaceuticals Inc. and Sanofi. Statement at Midwest CEPAC Public Meeting. In:November 29, 2018.
19. Busse W, Spector S, Rosen K, Wang Y, Alpan O. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. *The Journal of allergy and clinical immunology.* 2013;132(2):485-486.
20. Busse W, Chupp G, Nagase H, et al. Anti-IL5 treatments in severe asthma by blood eosinophil thresholds: indirect treatment comparison. *The Journal of allergy and clinical immunology.* 2018.
21. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med.* 1991;85 Suppl B:25-31; discussion 33-27.
22. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *The American review of respiratory disease.* 1992;145(6):1321-1327.
23. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *The European respiratory journal.* 2002;19(3):398-404.
24. Bae YJ, Kim YS, Park CS, et al. Reliability and validity of the St George's Respiratory Questionnaire for asthma. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease.* 2011;15(7):966-971.
25. Nelsen LM, Vernon M, Ortega H, et al. Evaluation of the psychometric properties of the St George's Respiratory Questionnaire in patients with severe asthma. *Respir Med.* 2017;128:42-49.
26. Drazen JM, Harrington D. New Biologics for Asthma. *The New England journal of medicine.* 2018;378(26):2533-2534.
27. ICER. Mepolizumab (Nucala®, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value, and ValueBased Price Benchmarks. *Institute for Clinical and Economic Review.* 2016.
28. National Institute for Health and Care Excellence. Mepolizumab for treating severe refractory eosinophilic asthma. Technical appraisal guidance TA431. In: NICE, ed. London2017.
29. de Vries F, Setakis E Fau - Zhang B, Zhang B Fau - van Staa TP, van Staa TP. Long-acting {beta}2-agonists in adult asthma and the pattern of risk of death and severe asthma outcomes: a study using the GPRD. *The European respiratory journal.* 2010;36(3):494-502.
30. Watson L, Turk F, James P, Holgate ST. Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. *Respiratory medicine.* 2007;101(8):1659-1664.
31. Levy M, Andrews R, Buckinghma R, et al. Why asthma still kills: The national review of asthma deaths (NRAD). In: Physicians RCo, ed. London: Royal College of Physicians; 2014.
32. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *The European respiratory journal.* 2014;43(2):343-373.
33. Anarella JP, Wagner VL, McCauley SG, Mane JB, Waniewski PA. Eliminating Disparities in Asthma Care: Identifying Broad Challenges in Quality Improvement. *American journal of medical quality : the official journal of the American College of Medical Quality.* 2017;32(6):598-604.
34. Mitchell SJ, Bilderback AL, Okelo SO. Racial Disparities in Asthma Morbidity Among Pediatric Patients Seeking Asthma Specialist Care. *Academic pediatrics.* 2016;16(1):64-67.
35. Zhang Q, Lamichhane R, Diggs LA. Disparities in emergency department visits in American children with asthma: 2006-2010. *J Asthma.* 2017;54(7):679-686.
36. Beck AF, Huang B, Auger KA, Ryan PH, Chen C, Kahn RS. Explaining Racial Disparities in Child Asthma Readmission Using a Causal Inference Approach. *JAMA pediatrics.* 2016;170(7):695-703.

37. Cazzola M, Calzetta L, Matera MG, Hanania NA, Rogliani P. How does race/ethnicity influence pharmacological response to asthma therapies? *Expert opinion on drug metabolism & toxicology.* 2018;14(4):435-446.
38. DePriest K, Butz A. Neighborhood-Level Factors Related to Asthma in Children Living in Urban Areas. *The Journal of school nursing : the official publication of the National Association of School Nurses.* 2017;33(1):8-17.
39. Hughes HK, Matsui EC, Tschudy MM, Pollack CE, Keet CA. Pediatric Asthma Health Disparities: Race, Hardship, Housing, and Asthma in a National Survey. *Academic pediatrics.* 2017;17(2):127-134.
40. Louisias M, Phipatanakul W. Managing Asthma in Low-Income, Underrepresented Minority, and Other Disadvantaged Pediatric Populations: Closing the Gap. *Current allergy and asthma reports.* 2017;17(10):68.
41. Buchman AL. Side effects of corticosteroid therapy. *J Clin Gastroenterol.* 2001;33(4):289-294.
42. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2018; https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed 06/11, 2018.
43. Bousquet J, Chanez P, Lacoste JY, et al. Eosinophilic inflammation in asthma. *The New England journal of medicine.* 1990;323(15):1033-1039.
44. Wardlaw AJ, Brightling CE, Green R, Woltmann G, Bradding P, Pavord ID. New insights into the relationship between airway inflammation and asthma. *Clin Sci (Lond).* 2002;103(2):201-211.
45. Woolf S. *An organized analytic framework for practice guideline development: using the analytic logic as a guide for reviewing evidence, developing recommendations, and explaining the rationale.*: Agency for Health Care Policy and Research;1994.
46. Net MH. Clinical Edit Criteria. 2017; https://dss.mo.gov/mhd/cs/pharmacy/pdf/Respiratory-Monoclonal-Antibodies-Clinical.pdf.
47. Wellcare I. Perscription Drug Plans. 2018; https://wellcare.destinationrx.com/PlanCompare/Consumer/Type1/2018/Compare/ComparePlans. Accessed August 27 2018.
48. Aetna. Mepolizumab (Nucala). 2018; http://www.aetna.com/cpb/medical/data/800_899/0897.html. Accessed Aug 27, 2018.
49. Aetna. Reslizumab (Cinqair). 2018; http://www.aetna.com/cpb/medical/data/900_999/0907.html. Accessed Aug 28, 2018.
50. Aetna. Benralizumab (Fasenra). 2018; http://www.aetna.com/cpb/medical/data/900_999/0925.html. Accessed Aug 27, 2018.
51. Cigna. Cigna Drug and Biologic Coverage Policy: Interleukin (IL)-5 Antagonists: Mepolizumab and Reslizumab. 2017; https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/pharmacy/ph_1608_pharmacycoverageposition_IL5_antagonists.pdf. Accessed Aug 27, 2018.
52. Cigna. Cigna Drug and Biologic Coverage Policy: Omalizumab. 2018; https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/pharmacy/ph_4026_pharmacycoverageposition_xolair.pdf. Accessed Aug 27, 2018.
53. Aetna. Specialty Pharmacy Clinical Policy Bulletins Aetna Non-Medicare Perscription Drug Plan. 2017; http://www.aetna.com/products/rxnonmedicare/data/2017/RESP/Xolair.html. Accessed August 27, 2018.
54. US Department of Health and Human Services NIoH, National Heart, Lungs, and Blood Institute, . *Guidelines for the Diagnosis and Management of Asthma.* October 2007 2007.
55. National Institute for Health and Care Excellence. Asthma: diagnosis, monitoring and chronic asthma management. In:2017.

56. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Annals of internal medicine.* 1997;126(5):376-380.
57. Higgins JPG, S. *Cochrane Collaboration Handbook for Systematic Reviews of Interventions* Version 5.1.0 ed: The Cochrane Collaboration; 2008.
58. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Bmj.* 2009;339:b2700.
59. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International journal of surgery (London, England).* 2010;8(5):336-341.
60. Agency for Healthcare Research and Quality (AHRQ). U.S. Preventive Services Task Force Procedure Manual. 2008; https://www.uspreventiveservicestaskforce.org/Home/GetFile/6/7/procmanual/pdf.
61. National Asthma Education and Prevention Program. Expert Panel Report 2 (EPR-2): Guidelines for the Diagnosis and Management of Asthma. *NIH Publication No 97-4051.* 1997.
62. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet (London, England).* 2016;388(10056):2115-2127.
63. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet (London, England).* 2016;388(10056):2128-2141.
64. Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *The Lancet Respiratory medicine.* 2016;4(7):549-556.
65. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy.* 2005;60(3):309-316.
66. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet (London, England).* 2012;380(9842):651-659.
67. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *The New England journal of medicine.* 2011;364(11):1005-1015.
68. Milgrom H, Berger W, Nayak A, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics.* 2001;108(2):E36.
69. Siergiejko Z, Swiebocka E, Smith N, et al. Oral corticosteroid sparing with omalizumab in severe allergic (IgE-mediated) asthma patients. *Current Medical Research and Opinion.* 2011;27(11).
70. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *The New England journal of medicine.* 2014;371(13):1189-1197.
71. Nair P, Wenzel S, Rabe KF, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. *The New England journal of medicine.* 2017;376(25):2448-2458.
72. Campbell JD, Spackman DE, Sullivan SD. The costs and consequences of omalizumab in uncontrolled asthma from a USA payer perspective. *Allergy.* 2010;65(9):1141-1148.
73. Whittington MD, McQueen RB, Ollendorf DA, et al. Assessing the value of mepolizumab for severe eosinophilic asthma: a cost-effectiveness analysis. *Annals of Allergy, Asthma & Immunology.* 2018;118(2):220-225 (Print).

74. National Institute for Health and Care Excellence. *Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201).* 04/2013 2013.
75. Norman G, Faria R, Paton F, et al. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. *Health Techonlogy Assessment.* 2013;17(52).
76. Sullivan SD, Turk F. An evaluation of the cost-effectiveness of omalizumab for the treatment of severe allergic asthma. *Allergy.* 2008;63(6):670-684.
77. Campbell JD, B. MR, Briggs A. The "e" in cost-effectiveness analyses. A case study of omalizumab efficacy and effectiveness for cost-effectiveness analysis evidence. *Annals of the American Thoracic Society.* 2014(2325-6621 (Electronic)).
78. Faria R, McKenna C, Palmer S. Optimizing the position and use of omalizumab for severe persistent allergic asthma using cost-effectiveness analysis. *Value in Health.* 2014;17(8):772-782.
79. Campbell JD, Spackman DE, Sullivan SD. Health economics of asthma: assessing the value of asthma interventions. *Allergy.* 2008;63(12):1581-1592.
80. Einarson TR, Bereza BG, Nielsen TA, Van Laer J, Hemels ME. Systematic review of models used in economic analyses in moderate-to-severe asthma and COPD. *Journal of Medical Economics.* 2016;19(4):319-355.
81. Reddel H, Taylor D, Bateman E, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *American journal of respiratory and critical care medicine.* 2009;180(1):59-99.
82. Chipps BE, Zeiger RS, Luskin AT, et al. Baseline asthma burden, comorbidities, and biomarkers in omalizumab-treated patients in PROSPERO. 2017(1534-4436 (Electronic)).
83. Starkie H, Briggs A, Chambers M, Jones P. Predicting EQ-5D values using the SGRQ. *Value in Health.* 2011;14(2):354-360.
84. Tsuchiya A, Brazier J, McColl E. Deriving preference-based single indices from non-preference based condition-specific instruments: Converting AQLQ into EQ5D indices. *White Rose Research Online.* 2002.
85. Lefebvre P, Duh MS, Lafeuille MH, et al. Burden of systemic glucocorticoid-related complications in severe asthma. *Current medical research and opinion.* 2017;33(1):57-65.
86. Bousquet J, Cabrera P Fau - Berkman N, Berkman N Fau - Buhl R, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy.* 2005(0105-4538 (Print)).
87. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *The New England journal of medicine.* 2014;371(13):1198-1207.
88. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *The Lancet Respiratory medicine.* 2015;3(5):355-366.
89. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *The Lancet Respiratory medicine.* 2017;5(5):390-400.
90. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *The New England journal of medicine.* 2009;360(10):973-984.
91. Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. *Primary care respiratory journal: journal of the General Practice Airways Group.* 2007;16(1):22-27.

92. Sutter Health Palo Alto Medical Foundation. Oral Corticosteroids. Accessed 06/15/2018, 2018.
93. Suruki RY, Daugherty JB, Boudiaf N, Albers FC. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. *BMC Pulmonary Medicine.* 2017;17(1):74.
94. Bureau of Labor Statistics. Consumer Price Index Historical Table, U.S. City Average, All items, 1982-84=100. https://www.bls.gov/regions/midwest/data/consumerpriceindexhistorical_us_table.pdf. Accessed 08/28/2018, 2018.
95. ICER. *ICER's Reference Case for Economic Evaluations: Principles and Rationale.* 07/26/2018 2018.
96. Centers for Medicare and Medicaid Services. Physician Fee Schedule Search. 2017; https://www.cms.gov/apps/physician-fee-schedule/license-agreement.aspx.
97. Asthma and Allergy Foundation of America (AAFA). Cost of Asthma on Society. 2018; http://www.aafa.org/page/cost-of-asthma-on-society.aspx. Accessed 08/24/18, 2018.
98. Bureau of Labor Statistics. Average hourly and weekly earnings of all employees on private nonfarm payrolls by industry sector, seasonally adjusted. 2017; https://www.bls.gov/news.release/empsit.t19.htm. Accessed 08/22/18, 2018.
99. Genentech. Data on File.
100. Kim CH, Dilokthornsakul P, Campbell JD, van Boven JFM. Asthma Cost-Effectiveness Analyses: Are We Using the Recommended Outcomes in Estimating Value? *J Allergy Clin Immunol Pract.* 2018;6(2):619-632.
101. McQueen RB, Sheehan DN, Whittington MD, van Boven JFM, Campbell JD. Cost-Effectiveness of Biological Asthma Treatments: A Systematic Review and Recommendations for Future Economic Evaluations. *PharmacoEconomics.* 2018.
102. National Institute for Health and Care Excellence. *Omalizumab for treating severe persistent allergic asthma. Technical appraisal guidance (TA278).* London, UK2013.
103. National Institute for Health and Care Excellence. Reslizumab for treating severe eosinophilic asthma. Technical appraisal guidance TA479. In: NICE, ed. London2017.
104. Most Recent Asthma Data. 2018. https://www.cdc.gov/asthma/most_recent_data.htm. Accessed Septemebr 15, 2018.
105. 2017 National Population Projections Datasets. 2018. Accessed September 15, 2018.
106. Asthma Severity among Adults with Current Asthma. 2015. https://www.cdc.gov/asthma/asthma_stats/severity_adult.htm. Accessed September 15, 2018.
107. Asthma Severity among Children with Current Asthma. 2015. https://www.cdc.gov/asthma/asthma_stats/severity_child.htm. Accessed September 15, 2018.
108. Use of long-term control medication among persons with active asthma. 2014. https://www.cdc.gov/asthma/asthma_stats/longterm_medication.htm. Accessed September 15, 2018.
109. Peters SP, Ferguson G, Deniz Y, Reisner C. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. *Respir Med.* 2006;100(7):1139-1151.
110. Pearson SD. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2018;21(3):258-265.
111. Teva Pharmaceuticals. *IQVIA Data on File.* 2018.
112. Genentech. *Living with Moderate-to-Severe Persistent Asthma: Perspectives from Patients and Caregivers.* South San Francisco, CA: Genentech;2018.
113. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.

114. Vignola AM, Humbert M, Bousquet J, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy.* 2004;59(7):709-717.
115. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Annals of internal medicine.* 2011;154(9):573-582.
116. Bardelas J, Figliomeni M, Kianifard F, Meng X. A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma. *J Asthma.* 2012;49(2):144-152.
117. Li J, Kang J, Wang C, et al. Omalizumab Improves Quality of Life and Asthma Control in Chinese Patients With Moderate to Severe Asthma: A Randomized Phase III Study. *Allergy, asthma & immunology research.* 2016;8(4):319-328.
118. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting beta2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet (London, England).* 2016;388(10039):31-44.
119. van Valkenhoef G, Kuiper J. gemtc: Network Meta-Analysis Using Bayesian Methods. R package version 0.8-2. 2016; https://CRAN.R-project.org/package=gemtc.
120. Casale TB, Chipps BE, Rosen K, et al. Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. *Allergy.* 2018;73(2):490-497.

APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

	#	Checklist item
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

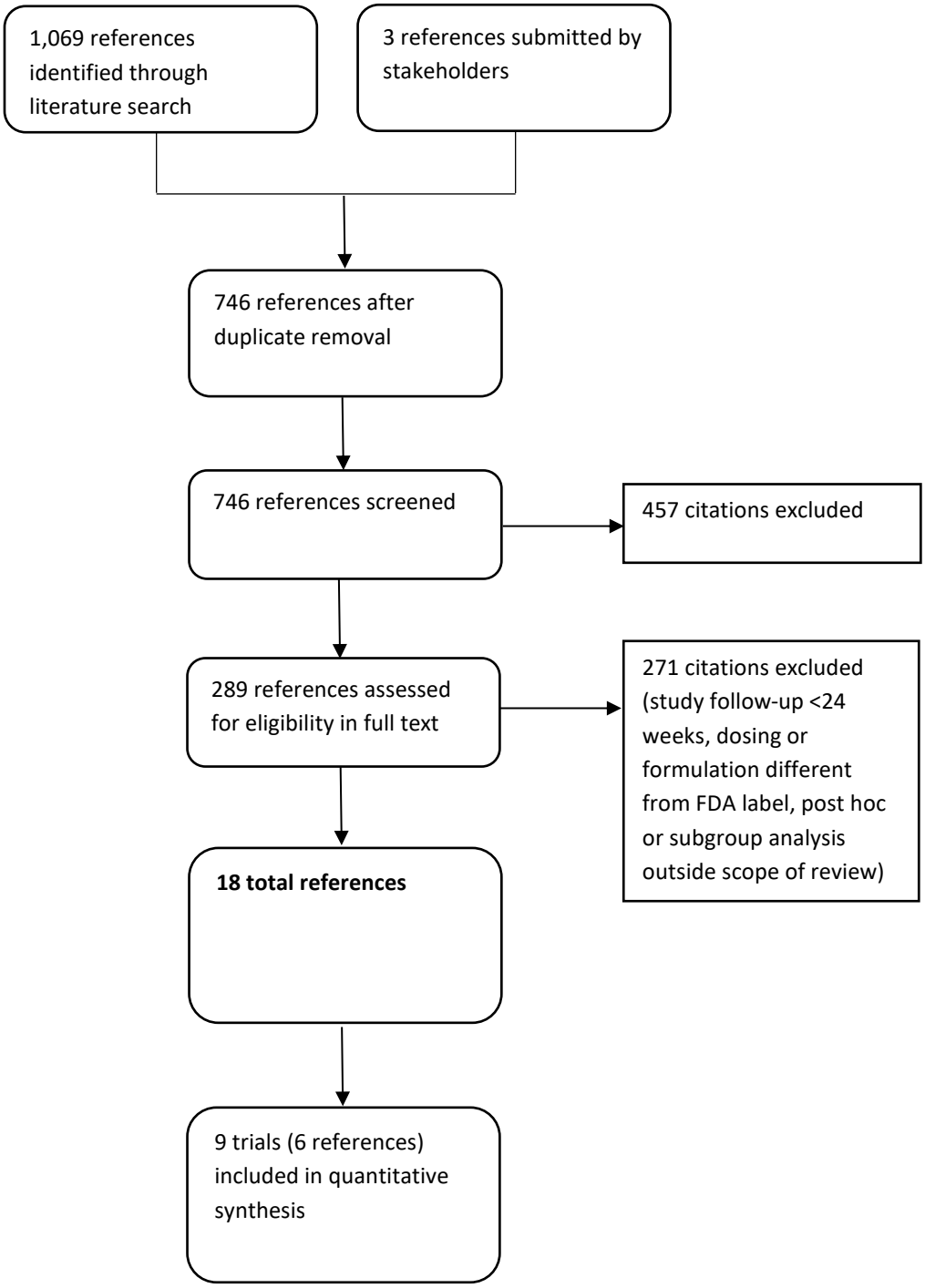
Table A2. Search Strategy of Medline and Cochrane Central Register of Controlled trials (via Ovid)

1	exp asthma/
2	asthma$.mp.
3	exp bronchial spasm/
4	bronchospas$.mp.
5	(bronch$ adj3 spasm$).mp.
6	exp bronchoconstriction/
7	bronchoconstrict$.mp.
8	(bronch$ adj3 constrict$).mp.
9	bronchial hyperreactivity/
10	respiratory hypersensitivity/
11	((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyper-sensitiv$ or hyperreactiv$ or hyper-reactiv$ or allerg$ or insufficien$ or hyperresponsive$ or hyper-responsive$)).mp.
12	or/1-11
13	omalizumab/
14	omalizumab.ti,ab.
15	(rhuMAB-E25* or Xolair*).ti,ab.
16	mepolizumab.ti,ab.
17	(nucala* or bosatria or sb-240563 or sb240563 or 90Z2UFOE52).ti,ab.
18	(reslizumab or cinqair or cinqaero or cinquil or DCP835 or DCP-835 or CEP38072 or CEP-38072 or SCH55700 or SCH-55700).ti,ab.
19	(benralizumab or fasenra or medi563 or medi-563).ti,ab.
20	(dupilumab or dupixent or regn 668 or regn668 or sar 231893 or sar231893).ti,ab.
21	or/13-20
22	12 and 21
23	(animals not (humans and animals)).sh.
24	22 not 23
25	limit 24 to english language
26	'clinical trial'.ti,ab.
27	'randomized controlled trial'.ti,ab.
28	'randomised controlled trial'.ti,ab.
29	randomi$ation.ti,ab.
30	'single blind'.ti,ab.
31	(double adj2 blind$).ti,ab.
32	placebo.ti,ab.
33	rct.ti,ab.
34	'random allocation'.ti,ab.
35	'randomly allocated'.ti,ab.
36	'allocated randomly'.ti,ab.
37	(allocated adj2 random$).mp.
38	or/26-37
39	((case adj2 study) or (case adj2 studies) or (case adj2 series) or (case adj2 report)).ti,ab.
40	38 not 39
41	40 and 25
Date of search: June 4, 2018	

Table A3. Search Strategy of EMBASE

#1	'asthma'/exp
#2	'asthm*'
#3	'bronchospasm'/exp
#4	'bronchospas*'
#5	bronch* NEAR/3 spasm*
#6	'bronchoconstriction'/exp
#7	bronchoconstrict*
#8	'bronchus hyperreactivity'/exp
#9	'respiratory tract allergy'/exp
#10	(bronch* OR respiratory OR airway$ OR lung$) NEAR/3 (hypersensitiv* OR hyperreactiv* OR allerg* OR insufficien* OR hyperresponsiv)
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	'omalizumab'/exp
#13	'omalizumab':ti,ab
#14	'rhumab e25*':ti,ab OR xolair*:ti,ab
#15	'mepolizumab'/exp
#16	'mepolizumab':ti,ab
#17	nucala*:ti,ab OR bosatria:ti,ab OR sb240563:ti,ab OR 90z2ufoe52:ti,ab
#18	'reslizumab'/exp
#19	reslizumab:ti,ab OR cinqair:ti,ab OR cinqaero:ti,ab OR cinquil:ti,ab OR dcp835:ti,ab OR cep38072:ti,ab OR sch55700:ti,ab
#20	'benralizumab'/exp
#21	benralizumab:ti,ab OR fasenra:ti,ab OR medi563:ti,ab
#22	'dupilumab'/exp
#23	dupilumab:ti,ab OR dupixent:ti,ab OR regn668:ti,ab OR sar231893:ti,ab
#24	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#25	#11 AND #24
#26	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#27	'human'/exp
#28	#26 AND #27
#29	#26 NOT #28
#30	#25 NOT #29
#31	#30 AND [english]/lim
#32	#31 AND [medline]/lim
#33	#31 NOT #32
#34	'clinical trial':ti,ab
#35	'randomized controlled trial'
#36	'randomized controlled trial':ti,ab
#37	'randomised controlled trial':ti,ab
#38	'randomi$ation':ti,ab
#39	'single blind procedure'
#40	(single NEAR/2 blind*):ti,ab
#41	(double NEAR/2 blind*):ti,ab
#42	'double blind procedure'
#43	placebo:ti,ab
#44	rct:ti,ab
#45	(random* NEAR/3 allocat*):ti,ab
#46	random*:ti,ab
#47	#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46
#48	((case NEAR/2 stud*):ti,ab) OR ((case NEAR/2 report):ti,ab)
#49	#47 NOT #48
#50	#49 AND #33
#51	#50 AND ('editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#52	#50 NOT #51
Date of search: June 4, 2018	

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Biologic Therapies for Asthma



Appendix B. Previous Systematic Reviews and Technology Assessments

Prior Systematic Reviews, Meta-analyses, and Network Meta-analyses

There are numerous systematic reviews addressing one or more of the five biologics for asthma, though only one of the reviews compared dupilumab to other therapies. We summarize the most recent and prominent reviews below. The conclusions include evidence that mepolizumab is better, benralizumab is better, both reslizumab and dupilumab are better, or that there are no clear differences between the therapies. They vary in their inclusion criteria and the subgroup analyses performed. None of the NMAs included the recently published phase 3 trials of dupilumab. We summarize the most recent and prominent reviews below by year of publication.

Bourdin A, Husereau D, Molinari N, et al. Matching-Adjusted Indirect Comparison of Benralizumab versus Interleukin-5 Inhibitors: Systematic Review. *The European respiratory journal.* 2018.

The investigators performed an indirect comparison between benralizumab, reslizumab, and mepolizumab, which adjusts for differences in patient characteristics across trials. Benralizumab and reslizumab patient populations were too dissimilar to perform the analysis. The benefits of benralizumab and mepolizumab compared to placebo were nearly identical after adjustment.

Busse W, Chupp G, Nagase H, et al. Anti-IL5 treatments in severe asthma by blood eosinophil thresholds: indirect treatment comparison. *The Journal of allergy and clinical immunology.* 2018.

The investigators performed a network meta-analysis (NMA) based on the results of the Cochrane review of the three anti-IL-5 therapies, which is summarized below (Farne et al., 2017), with an updated search that identified two subgroup analyses and a pooled analysis not included in the Cochrane review. The NMA included 11 randomized trials with 3,723 patients who received the FDA indicated doses of the three drugs or matching placebo. The investigators performed subgroup analyses based on baseline eosinophil level and exacerbation history. They found that all treatments significantly reduced clinically significant asthma exacerbations and improved asthma control compared with placebo. Mepolizumab significantly reduced exacerbations and asthma control compared with both reslizumab and benralizumab. For example, in the subgroup of patients with baseline eosinophils ≥ 400 cells/µL, the rate ratio for mepolizumab versus reslizumab was 0.55 (95% CI 0.36 to 0.85) and the rate ratio for mepolizumab versus benralizumab was 0.55 (95% CI 0.35 to 0.87). They conclude that at the same baseline level of eosinophils, mepolizumab is superior to reslizumab and benralizumab.

Casale TB, Pacou M, Mesana L, Farge G, Sun SX, Castro M. Reslizumab Compared with Benralizumab in Patients with Eosinophilic Asthma: A Systematic Literature Review and Network Meta-Analysis. *J Allergy Clin Immunol Pract.* 2018.

The investigators identified 11 studies, but only 4 had clinically relevant doses and outcomes at similar timepoints. They limited their analysis for reslizumab to patients with severe asthma and ≥2 exacerbations in the prior year with eosinophils ≥400 cells/µl and the analysis for benralizumab to patients with eosinophils ≥300 cells/µl. In their NMA, reslizumab had significantly greater improvements on the ACQ and AQLQ than benralizumab and a trend towards superiority of reslizumab for FEV1 and clinically significant asthma exacerbations. The investigators conclude that reslizumab may be more efficacious than benralizumab in patients with severe eosinophil asthma.

He LL, Zhang L, Jiang L, Xu F, Fei DS. Efficacy and safety of anti-interleukin-5 therapy in patients with asthma: A pairwise and Bayesian network meta-analysis. *International immunopharmacology.* 2018;64:223-231.

The investigators identified 21 placebo controlled randomized trials of mepolizumab (n=8), reslizumab (n=5) and benralizumab (n=7) for asthma. In their NMA there all 3 drugs significantly improved FEV1 and the AQLQ, but not exacerbations. There were no significant differences between the 3 drugs for any of the outcomes.

Iftikhar IH, Schimmel M, Bender W, Swenson C, Amrol D. Comparative Efficacy of Anti IL-4, IL-5 and IL-13 Drugs for Treatment of Eosinophilic Asthma: A Network Meta-analysis. *Lung.* 2018;196(5):517-530.

The investigators used the frequentist NMA method to combine data from seven studies of mepolizumab, four of reslizumab, seven of benralizumab, two of dupilumab along with 6 studies of two drugs not included in our review (tralokinumab and lebrikizumab). The studies of dupilumab were short, phase 2 trials not included in the ICER review. The investigators found that all of the drugs except tralokinumab significantly improved FEV1, ACQ, and AQLQ, but only reslizumab and dupilumab had significant reductions in asthma exacerbation rates. There were no significant differences between drugs for any of the outcomes.

Cabon Y, Molinari N, Marin G, et al. Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo-controlled trials. *Clinical & Experimental Allergy.* 2017;47(1):129-138.

The investigators identified 10 placebo controlled randomized trials (n=3421) of mepolizumab (n=4), reslizumab (n=4) and benralizumab (n=5) for asthma. They performed subgroup and sensitivity analyses by baseline eosinophil levels. They found that all 3 agents reduced asthma exacerbation rates by about 40% with slightly greater reductions when restricted to patients with eosinophil levels > 300 cells/µl. They found improvements in the ACQ that were significant, but

below the MCID as well as significant improvements in FEV1. The concluded that all 3 agents were effective, but that there was no clear superiority of one agent compared with another.

Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev.* 2017;9:CD010834.

The investigators identified 13 placebo controlled randomized trials (n=6000) of mepolizumab (n=4), reslizumab (n=4) and benralizumab (n=5) for asthma. They rated the randomized trials all to be low risk of bias and the evidence for all comparisons to be high quality. They found that all three therapies reduced clinically significant asthma exacerbations by about half in participants with severe eosinophilic asthma with modest improvements in health-related quality of life scores that did not reach the minimum clinically important difference for either the ACQ or the AQLQ. They found no excess in serious adverse events. Thus, they concluded that the evidence supports the use of any of the 3 agents in addition to standard of care in patients with severe eosinophilic asthma and poor control.

Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev.* 2014(1):CD003559.

The investigators identified 25 trials including 6382 individuals randomized to omalizumab or placebo for moderate to severe allergic asthma. Omalizumab significantly reduced asthma exacerbations (RR 0.52, 95% CI 0.37-0.73)) as well as hospitalizations for asthma. Omalizumab patients were more likely to withdraw ICS completely (OR 2.50, 95% CI 2.0-3.1) and to have improvements in FEV1 (56.4 ml, 95% CI 16.8-96.0). Overall, there were fewer SAEs, but an increase in injection site reactions (OR 1.72, 95% CI 1.33-2.24). The authors concluded that omalizumab was effective at reducing asthma exacerbations and hospitalizations.

Selected Technology Assessments

National Institute for Health and Care Excellence (NICE)

NICE evaluated omalizumab for treating severe persistent allergic asthma in 2013. They recommend it as an option for treating severe persistent allergic IgE mediated asthma as an add-on to optimized standard therapy in people aged 6 and older who need continuous or frequent treatment with oral steroids (4 or more courses in the previous year). Optimized standard therapy includes inhaled high-dose corticosteroids, long-acting beta agonists leukotriene receptor antagonists, theophylline, oral corticosteroids and smoking cessation.

NICE evaluated mepolizumab for treating severe refractory eosinophilic asthma in 2017. It is recommended as an add on to optimized standard therapy for treating severe refractory eosinophilic asthma in adults. It is recommended in adults who have eosinophil count >300/µL in the previous 12 months and have had 4 or more asthma exacerbations requiring systemic

corticosteroids in the previous 6 months. An adequate response is defined as at least 50% fewer asthma exacerbations requiring steroids in the previous 12 months or a significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control.

NICE evaluated reslizumab as an add on therapy for severe eosinophilic asthma in 2017. They recommend it as an option for the treatment of severe eosinophilic asthma that is not adequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids plus another drug in individuals who have an eosinophil count of 400 cells/µL or greater and have had 3 or more severe exacerbations in the past year. They recommend assessing response annually. And adequate response is a reduction in exacerbations and or a reduction in oral corticosteroid use while maintaining control.

The NICE final assessment for benralizumab is expected in December 2018. The preliminary recommendation is that benralizumab is not recommended for treating severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy that includes high dose ICS and LABAs.

CADTH Canadian Agency for Drugs and Technologies in Health

CADTH conducted a review of omalizumab treatment for adults and children with allergic asthma in 2015. They published a summary with a critical appraisal. They concluded that omalizumab decreases the risk of asthma exacerbations in patients with moderate to severe allergic asthma inadequately controlled by standard therapies. They acknowledged that one evidence-based guideline recommended its use for the treatment of individuals aged 6 and older who had severe persistent confirmed allergic IgE mediated asthma as an add on to optimized standard therapy for those who need frequent treatment with oral corticosteroids.

CADTH evaluated mepolizumab in 2015. They recommended it to be used as add-on maintenance treatment of adults with severe eosinophilic asthma who are inadequately controlled with high dose inhaled corticosteroids and one or more additional controllers and have a blood eosinophil count of 150 cells/microL or greater at initiation or ≥300 cells/microL in the past 12 months. Eligible patients must have experienced two or more clinically significant exacerbations in the past 12 months and show reversibility (at least 12% and 200 mL) on pulmonary function tests OR be on daily oral corticosteroids.

CADTH evaluated reslizumab in 2016. They recommended that reslizumab be used as add-on maintenance treatment of adult patients with severe eosinophilic asthma who are inadequately controlled with a medium to high dose inhaled corticosteroid and an additional controller, and who have a blood eosinophil count of ≥400 cells/microL, if they have had one or more clinically significant asthma exacerbations in the past 12 months and have an Asthma Control Questionnaire

7 score ≥1.5 points and show some reversibility (at least 12% and 200 ml) on pulmonary function tests.

CADTH evaluated benralizumab in 2018. They recommended that benralizumab be reimbursed as an add on maintenance treatment for adult patients with severe eosinophilic asthma. Patients eligible for treatment include those inadequately controlled with high dose inhaled corticosteroids and one or more additional asthma controllers if either 1) the blood eosinophil count is ≥300 mcg/L and patient has experienced two or more clinically significant asthma exacerbations in the past 12 months or 2) eosinophil count of ≥150 mcg/L and treated chronically with oral corticosteroids.

Appendix C. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Head-to-Head Studies					
Study of Magnitude and Prediction of Response to Omalizumab and Mepolizumab in Adult Severe Asthma (PREDICTUMAB) **NCT03476109** **Sponsor: Cliniques universitaires Saint-Luc- Université Catholique de Louvain**	Phase 4 Factorial assignment Single Blind (outcome assessor) RCT Estimated enrollment: 100	•Omalizumab (non-responders to be switched to mepolizumab) •Mepolizumab (non-responders to be switched to omalizumab)	Inclusion Criteria: •Age ≥18 years •Documented physician-diagnosed asthma •Severe disease and eligible for omalizumab and mepolizumab who have not yet received these therapies Exclusion Criteria: •History of evidence of drug/substance abuse that would pose a risk to patient safety, interfere with the conduct of study, have an impact on the study results, or affect the patient's ability to participate in the study •Treatment with an investigational therapy with 6 months or 5 drug half-lives prior to enrolment •Sensitivity to any of the active substances or their excipients to be administered during the study.	Primary Outcomes: •Asthma symptoms (Asthma Control Test) •Lung function (FEV1) •Number of severe exacerbations Secondary Outcomes: •Predictive factors of therapeutic response	December 31, 2020

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Omalizumab					
Preventing Asthma in High Risk Kids (PARK) **NCT02570984** **Sponsor: Wanda Phipatanakul**	Phase 2 Parallel assignment Quadruple masked RCT Estimated enrollment: 250	•Omalizumab •Placebo	Inclusion Criteria: •Age 24-47 months •Positive allergy to aeroallergen •2-4 wheezing episodes in past year •First degree relative with history or current diagnosis of asthma or allergy Exclusion Criteria: •>4 episodes of wheezing in the past year •Inhaled steroids with/without LABAs for respiratory symptoms within 4 weeks prior to screening •Systemic corticosteroids or hospitalization for respiratory symptoms within 4 weeks prior to screening •≥3 courses of systemic corticosteroids for wheezing in the last year •≥4 days of wheezing, tightness in the chest or cough in past 2 weeks that limit activity •≥4 days of albuterol for symptoms in past 2 weeks •Prematurity •≥5 days of oxygen during neonatal period •History of intubation or mechanical ventilation for respiratory illness •Prior aeroallergen immunotherapy, biologics, IVIG, systemic immunosuppressant •History of hypoxic seizures during wheezing episode •IgE outside omalizumab dosing range	Primary Outcomes: •Active asthma diagnosis •Asthma severity Secondary Outcomes: •Number of positive new allergic sensitization •Decrease in number of wheezing episodes	September 2023

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Mepolizumab					
A Safety and Efficacy Study of Mepolizumab in Subjects with Severe Asthma **NCT03562195** **Sponsor: GlaxoSmithKline**	Phase 3 Parallel assignment Double blind RCT Estimated enrollment: 300	•Mepolizumab (100mg) + Salbutamol •Placebo + Salbutamol	Inclusion Criteria: •Age ≥12 years •Weight ≥40kgs •Persistent airflow obstruction •Eosinophilic asthma •Regular high dose ICS in prior 12 months •Current treatment with additional controller medication for ≥3 months •History of ≥2 exacerbations requiring systemic corticosteroid in 12 months prior to Visit 1 Exclusion Criteria: •Current or former smoker •Bronchial thermoplasty and radiotherapy •Clinically significant cardiovascular disease, respiratory, endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, hematological, or any other system abnormalities or conditions uncontrolled with standard treatment •Alcohol misuse or substance abuse •QT interval corrected by Fridericia's formula (QTc[F]) >450 milliseconds (msec) or QTc(F) >480 msec for subjects with Bundle Branch Block at Visit 1 •Other conditions that could lead to elevated eosinophils •Previous mepolizumab study participation, previous omalizumab or other monoclonal antibodies	Primary Outcome: •Clinically significant exacerbations Secondary Outcomes: •Time to first clinically significant exacerbation •Mean change from baseline in St. George's Respiratory Questionnaire •Exacerbations requiring hospitalization or ED visits •Exacerbations requiring hospitalization •Mean change from baseline in clinic prebronchodilator FEV1 •Number of subjects with adverse events including systemic and injection site reactions •Number of subjects with abnormal hematology, clinical chemistry, blood pressure, pulse rate, ECG parameters •Number of subjects with anti-mepolizumab antibody positive results •Change from baseline in blood eosinophil ratio	March 31, 2021

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Benralizumab					
Efficacy and Safety Study of Benralizumab in Patients with Uncontrolled Asthma on Medium to High Dose Inhaled Corticosteroid Plus LABA (MIRACLE) **NCT03186209** **Sponsor: AstraZeneca**	Phase 3 Parallel assignment Triple blind RCT Estimated enrollment: 666	•Benralizumab •Placebo	Inclusion Criteria: •Age 12-75 years •Physician-diagnosed asthma requiring treatment with medium-to-high dose ICS and a LABA for ≥6 months prior to Visit 1 •Additional maintenance controller medications •≥2 documented asthma exacerbations in previous 12 months with ≥1 exacerbation occurring during treatment of medium-to-high dose ICS-LABA •Post-bronchodilator (post-BD) reversibility in FEV1 of >12% and >200 mL in FEV1 within 12 months prior to Visit 1 •>2 days with symptoms score >1 or SABA use >2 days or ≥1 nocturnal awakening due to asthma Exclusion Criteria: •Clinically important pulmonary disease other than asthma or any systemic disease associated with elevated peripheral eosinophil counts •Any disorder or abnormal findings that could influence safety, participation, or study findings •Acute upper or lower respiratory infections requiring antibiotics or antiviral medication •Current or former smokers	Primary Outcome: •Annual asthma exacerbation rate Secondary Outcomes: Change from baseline: •Pre-bronchodilator FEV1 • Asthma Symptom Score • ACQ6 •SGRQ •Time to First Asthma Exacerbation •Patients with ≥1 asthma exacerbation •Annual asthma exacerbation rate associated with an ED/urgent care visit or hospitalization •Participants that utilized Health Care resources •Mean PK concentrations •Immunogenicity •Blood eosinophil levels •Change in asthma rescue medication •Morning and evening PEF •Night awakening due to asthma	February 26, 2021

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
A Study of the Safety and Effectiveness of Benralizumab to Treat Patients with Severe Uncontrolled Asthma (ANDHI) **NCT03170271** **Sponsor: AstraZeneca**	Phase 3 Parallel assignment Double blind RCT Estimated enrollment: 630	•Benralizumab •Placebo	Inclusion Criteria: •Age 18-75 years •High daily doses of ICS plus ≥1 other asthma controller for ≥3 months prior to Visit 1 •≥2 asthma exacerbations while on ICS plus another asthma controller that required treatment with systemic corticosteroids in 12 months prior to Visit 1 •ACQ6 ≥1.5 •Pre-bronchodilator FEV1 <80% predicted at Visit 2 •Excessive variability in lung function •Peripheral blood eosinophil count of 300 cells/µ or 150-300 cells/µ if using maintenance OCS, history of nasal polyposis, age of asthma onset ≥18 years, ≥3 exacerbations in previous 12 months, or pre-bronchodilator forced vital capacity <65% of predicted Exclusion Criteria: •Other clinically important pulmonary disease •Acute upper or lower respiratory infections within 30 days •Helminth parasitic infection within 24 weeks •Drug or alcohol abuse within 12 months •Smokers or former smokers •History of known immunodeficiency disorder •Previous benralizumab, investigational medication (within 5 half-lives), immunoglobulin or blood products (within 30 days), live attenuated vaccines (within 30 days)	Primary Outcome: •Annualized rate of asthma exacerbations Secondary Outcome: •Change from baseline in SGRQ	August 13, 2020

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Dupilumab					
Evaluation of Dupilumab in Children with Uncontrolled Asthma (VOYAGE) **NCT02948959** Sponsor(s): Sanofi, Regeneron Pharmaceuticals	Phase 3 Parallel assignment Triple masked RCT Estimated enrollment: 294	•Dupilumab •Placebo •Asthma controller therapies (including prednisone/ prednisolone) •Asthma reliever therapies	Inclusion criteria •Age 6 to <12 years of age with a physician diagnosis of persistent asthma for ≥12 months prior to Screening, based on clinical history and examination, pulmonary function parameters according to GINA 2015 Guidelines and the following criteria: •Existing background therapy of medium-dose ICS with second controller medication or high-dose ICS with or without second controller, for at least 3 months •Pre-bronchodilator FEV1≤95% of predicted normal or pre-bronchodilator FEV1/FVC ratio <0.85 at Screening and Baseline visits. •Reversibility of at least 10% in FEV1 after the administration of albuterol/salbutamol or levalbuterol/levosalbutamol reliever medication •Treatment with a systemic corticosteroid for worsening asthma at least once in previous year, or hospitalization or emergency room visit for worsening asthma in previous year •Evidence of uncontrolled asthma	Primary Outcome: •Annualized rate of severe exacerbation events Secondary Outcomes: Change from baseline in: •Pre-bronchodilator % predicted FEV1 • Other lung function measurements •Morning and evening asthma symptom scores •Time to first severe exacerbation event •Time to first loss of asthma control event •Number of nocturnal awakenings due to asthma symptoms requiring the use of reliever medication •Use of reliever medication	July 22, 2021

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table D3)[60] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

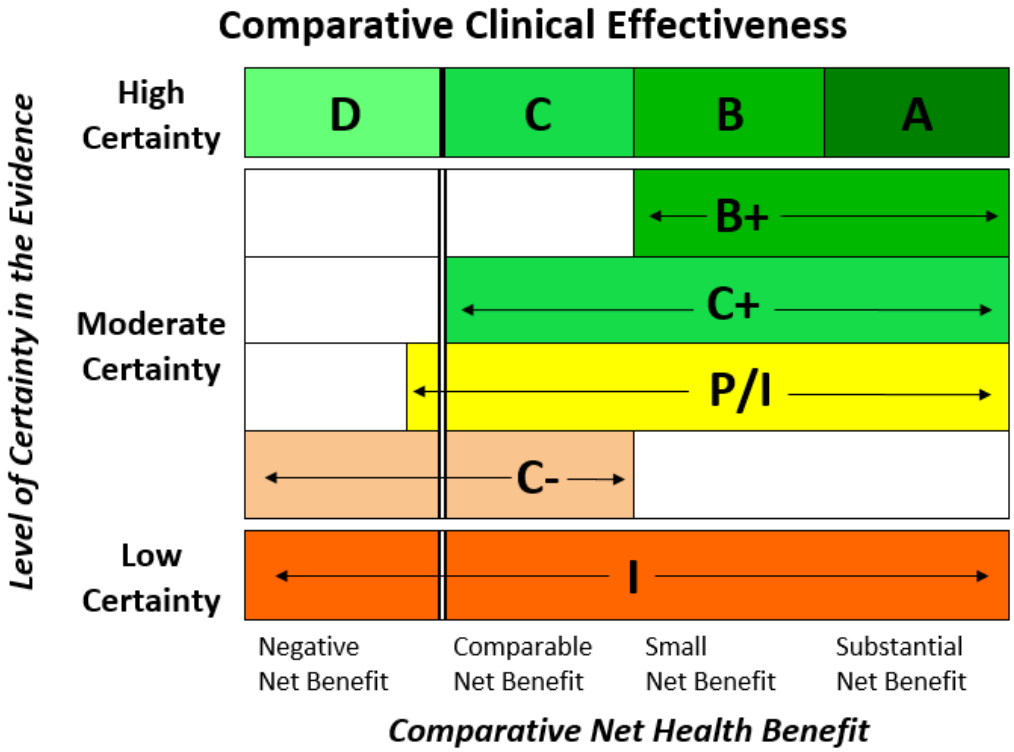
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[113]

Figure D1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable" *- High certainty of a comparable net health benefit*
D = "Negative" *- High certainty of an inferior net health benefit*
B+ = "Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C- = "Comparable or Inferior" *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
I = "Insufficient" *- Any situation in which the level of certainty in the evidence is low*

Table D1. Overview of Studies

Reference & Study Name	Phase	FU, weeks	Interventions	Population	Age, years	Sex, %F	Asthma duration, years	FEV1, % predicted	Reversibility, %	ACQ score	OCS use, %	Eosinophil count	Exacerbations in prior year
Omalizumab													
Allergic asthma / asthma with elevated Ige													
Vignola 2004[114] **SOLAR (N=405)**		28	Omalizumab 0.016 mg/kg sc every 2-4 weeks Placebo	Moderate to severe persistent allergic asthma	38.4	55	20	78	18	NR	0	N/A	2.1
Humbert 2005[65] **INNOVATE (n=419)**	3	28	Omalizumab 0.016 mg/kg sc every 2-4 weeks Placebo	Severe persistent allergic asthma with recurrent exacerbations	43.3	43	23	61	27	3.9	22	N/A	2.1
Busse 2011[67] **ICATA (n=419)**	3	60	Omalizumab 0.016 mg/kg sc every 2-4 weeks Placebo	Severe persistent allergic asthma with recurrent exacerbations	10.8	42	7.3	92	NR	NR	0	N/A	NR
Hanania 2011[115] (n=850)	3	48	Omalizumab 0.016 mg/kg sc every 2-4 weeks Placebo	Severe persistent allergic asthma with recurrent exacerbations	44.5	66	23.7	64.9	NR	NR	17	N/A	2

Reference & Study Name	Phase	FU, weeks	Interventions	Population	Age, years	Sex, %F	Asthma duration, years	FEV1, % predicted	Reversibility, %	ACQ score	OCS use, %	Eosinophil count	Exacerbations in prior year
Bardelas 2012[116] (n=271)	3	24	Omalizumab 0.016 mg/kg sc every 2-4 weeks Placebo	Severe persistent allergic asthma with recurrent exacerbations	41.5	66	NR	76	NR	NR	0	N/A	NR
Busse 2013[19] (n=328)	3	24	Omalizumab 0.016 mg/kg sc every 2-4 weeks Placebo	Moderate to severe persistent allergic asthma	36	69	NR	86%	NR	NR	NR	N/A	NR
Li 2016[117] **China omalizumab (n=616)**	3	24	Omalizumab 0.016 mg/kg sc every 2-4 weeks Placebo	Moderate to severe persistent allergic asthma	46.5	54	14.7	62.50%	27%	NR	NR	N/A	NR
Mepolizumab													
Severe eosinophilic asthma													
Pavord 2012[66] **DREAM (n=616)**	3	52	Mepolizumab 75 mg, 250 mg, or 750 mg IV q4 weeks Placebo	Recurrent exacerbations	49	63	19	60	28	4.2	31	250	3.6

Reference & Study Name	Phase	FU, weeks	Interventions	Population	Age, years	Sex, %F	Asthma duration, years	FEV1, % predicted	Reversibility, %	ACQ score	OCS use, %	Eosinophil count	Exacerbations in prior year
Ortega 2014[87] **MENSA (n=576)**	3	32	Mepolizumab 75 mg IV or 100 mg SC q4 weeks Placebo	Recurrent exacerbations	50	57	20	61	27	2.3	25	290	3.6
Chupp 2017[89] **MUSCA (n=551)**	3	24	Mepolizumab 100 mg SC q 4 weeks Placebo	Severe eosinophilic asthma	51	59	19.5	55	21	2.2	24	325	2.8
OCS-dependent eosinophilic asthma													
Bel 2014[70] **SIRIUS (n=135)**	3	24	Mepolizumab 100 mg SC q4 weeks Placebo	Chronic OCS use	50	55	19	59	26	2.2	100	240	3.1
Reslizumab													
Severe eosinophilic asthma													
Castro 2015[88] (n=953)	3	64	Reslizumab 3.0 mg/kg q 4 weeks Placebo	Poorly controlled eosinophilic asthma	48	61	14	66	18	2.7	17	655	2
Benralizumab													
Bleecker 2016[62] **SIROCCO (n=1205)**	3	48	Benralizumab 30 mg q 4 weeks or q 8 weeks Placebo	Asthma on medium or high dose ICS and at least 2 exacerbations	48	66	14	57	20	2.87	NR	370	3.1

Reference & Study Name	Phase	FU, weeks	Interventions	Population	Age, years	Sex, %F	Asthma duration, years	FEV1, % predicted	Reversibility, %	ACQ score	OCS use, %	Eosinophil count	Exacerbations in prior year
Fitzgerald 2016[63] **CALIMA (n=1306)**	3	56	Benralizumab 30 mg q 4 weeks or q 8 weeks Placebo	Poorly controlled eosinophilic asthma	49	62	16	58	20	2.7	NR	380	2.7
OCS-dependent severe eosinophilic asthma													
Nair 2017[71] **ZONDA (n=220)**	3	28	Benralizumab 30 mg q 4 weeks or q 8 weeks Placebo	Eosinophilic asthma requiring OCS for control	51.4	64	13.4	60.5	19.5	2.6	NR	486	2.8
Dupilumab													
Moderate to severe uncontrolled asthma													
Wenzel 2016[118] (n=769)	2b	24	Dupilumab 200 or 300 mg every 2 or 4 weeks Placebo	Uncontrolled persistent asthma on ICS	49	63	22	61	NR	2.74	0	347	2.17
Castro 2018[16] **LIBERTY ASTHMA QUEST (n=1902)**	3	52	Dupilumab 200 mg or 300 mg SQ every two weeks Placebo	Moderate to severe uncontrolled asthma	47.9	63	NR	1.78	26	2.76	0	360	2.09
OCS-dependent severe asthma													

Reference & Study Name	Phase	FU, weeks	Interventions	Population	Age, years	Sex, %F	Asthma duration, years	FEV1, % predicted	Reversibility, %	ACQ score	OCS use, %	Eosinophil count	Exacerbations in prior year
Rabe 2018[17] LIBERTY ASTHMA VENTURE (n=210)	3	24	Dupilumab 300 mg SQ ever 2 weeks Placebo	Chronic OCS use	51.3	60	NR	52	18	2.5	100	347	2.09

ACQ: Asthma Control Questionnaire; FEV1: forced expiratory volume in one second, FU: follow-up, N/A: not applicable, NR: not reported, OCS; oral corticosteroids

Table D2. Key Inclusion Criteria

Reference & Study Name	N	Age	Asthma Severity	FEV1 criteria	FEV1 reversibility	Exacerbations	ICS Criteria	OCS criteria	Eosinophil Criteria	Sputum Eosinophils	Serum IGE	ACQ Score
Omalizumab												
Allergic asthma/asthma with elevated IgE												
Vignola 2004[114] SOLAR	405	12-75	Moderate to severe	N/A	≥12%	≥2	High dose ICS	Excluded if OCS	N/A	N/A	≥30 to ≤1300 IU/ml	-
Humbert 2005[65] INNOVATE	419	12-75	Severe	≥40 to ≤80% predicted	≥12%	≥2	High dose ICS and another controller	Maintenance permitted if at least one exacerbation occurred on OCS	NR	NR	>30 to <700 IU/ml	-
Busse 2011[67] ICATA	419	6-20	Severe	N/A	N/A	≥1	High dose ICS and another controller	No	N/A	N/A	>30 to <1300 IU/ml	-
Hanania 2011[115]	850	12-75	Severe	≥40 to ≤80% predicted	NR	≥1	High dose ICS and another controller	Maintenance permitted	NR	NR	>30 to <700 IU/ml	-
Bardelas 2012[116]	271	≥12	Severe	≤80% predicted	NR	dx ≥12m	Medium dose ICS and another controller	No	N/A	N/A	>30 to <700 IU/ml	-

Reference & Study Name	N	Age	Asthma Severity	FEV1 criteria	FEV1 reversibility	Exacerbations	ICS Criteria	OCS criteria	Eosinophil Criteria	Sputum Eosinophils	Serum IGE	ACQ Score
Busse 2013[19]	328	12-75	Severe	>80% predicted	N/A	≥1	High dose ICS and another controller	No	N/A	N/A	>30 to <1300 IU/ml	-
Li 2016[117]	616	18-75	Moderate to severe	≥40 to ≤80% predicted	≥12%	≥2	Medium dose ICS and another controller	No	N/A	N/A	NR	-
Mepolizumab												
Severe eosinophilic asthma												
Pavord 2012[66] DREAM	616	12-74	Severe		Improvement >12% with inhaled salmeterol or variability of more than 20% between clinic visits	≥2	≥880 mcg fluticasone with or without OCS	No	>300	3% or more	NR	NR
Ortega 2014[87] MENSA	576	12-82	Severe	<80% predicted for adults or <90% predicted for adolescents	>12%	≥2	≥880 mcg fluticasone and another controller	No	>150 at screening or >300 in previous year	NR	NR	NR
Chupp 2017[89]	551	≥12	Severe	<80% predicted for adults or	NR	≥2	High does ICS and	If on OCS, exacerbations	>150 at screening or >300 in	NR	NR	NR

Reference & Study Name	N	Age	Asthma Severity	FEV1 criteria	FEV1 reversibility	Exacerbations	ICS Criteria	OCS criteria	Eosinophil Criteria	Sputum Eosinophils	Serum IGE	ACQ Score
MUSCA				<90% predicted for adolescents			another controller	requiring doubling	previous year			
OCS-dependent severe eosinophilic asthma												
Bel 2014[70] SIRIUS	135	≥12	Severe	NR	NR	NR	≥880 mcg fluticasone and another controller	≥6 months OCS; ≥40 mcg for age 12-17	>300 during 12 months before or <150 during optimi-zation	NR	NR	NR
Reslizumab												
Castro 2015[88]	953	12-75	Moderate to severe	NR	≥12%	≥1	≥440 mcg fluticasone with or without another controller including OCS	Allowed	≥400	NR	NR	≥1.5
Benralizumab												
Bleecker 2016[62] SIROCCO	1205	12-75	Severe	<80% predicted for adults or	≥12%	≥2	high dose ICS; med	No	NR	NR	NR	>1.5

Reference & Study Name	N	Age	Asthma Severity	FEV1 criteria	FEV1 reversibility	Exacerbations	ICS Criteria	OCS criteria	Eosinophil Criteria	Sputum Eosinophils	Serum IGE	ACQ Score
				<90% predicted for adolescents			or high for age 12-17					
Fitzgerald 2016[63] CALIMA	1306	12-75	Severe	<80% predicted for adults or <90% predicted for adolescents	≥12%	≥2	Med. (≥250 mcg) to high dose ICS (≥500 mcg) fluticasone with another controller	No	>300	NR	NR	NR
OCS-dependent severe eosinophilic asthma												
Nair 2017[71] ZONDA	220	Adults	OCS for at least 6 months	NR	NR	NR	NR	NR	≥150	NR	NR	NR
Dupilumab												
Wenzel 2016[118]	769	≥18	Moderate to severe	≥40 to ≤80% predicted	≥12%	≥1	≥500 mcg fluticasone and at least one other controller	NR	NR	NR	NR	≥1.5
Castro 2018[16] LIBERTY ASTHMA QUEST	1902	≥12	Moderate to severe	<80% predicted for adults or <90% predicted for adolescents	≥12%	≥1	≥500 mcg fluticasone and up to two other controllers	NR	No minimum	No minimum	NR	NR

Reference & Study Name	N	Age	Asthma Severity	FEV1 criteria	FEV1 reversibility	Exacerbations	ICS Criteria	OCS criteria	Eosinophil Criteria	Sputum Eosinophils	Serum IGE	ACQ Score
OCS-dependent severe asthma												
Rabe 2018[17] LIBERTY ASTHMA VENTURE	210	≥12	Severe	<80% predicted for adults or <90% predicted for adolescents	≥12%	NR	≥500 mcg fluticasone ad up to two other controllers	On OCS	No minimum	No min-imum	N/A	NR

ACQ: Asthma Control Questionnaire, ICS: inhaled corticosteroids, FEV1: forced expiratory volume in one second, N/A: not applicable, NR: not reported, OCS: oral corticosteroids

Table D3. Study Quality Metrics

Reference & Study Name	Adequate randomization	Allocation concealment	Patient blinding	Staff blinding	Outcome adjudication blinding	Completeness of follow-up	Intention to treat analysis	Incomplete data addressed	Selective outcome reporting	Industry funding	Free from other bias	Overall quality
Omalizumab												
Vignola 2004[114] SOLAR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Humbert 2005[65] INNOVATE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Busse 2011[67] ICATA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Hanania 2011[115]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Bardelas 2012[116]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Busse 2013[19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Li 2016[117] Chinese Omalizumab	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Mepolizumab												
Severe eosinophilic asthma												
Pavord 2012[66] DREAM	Yes	Yes	Yes	Yes	Yes	16% withdrew	Yes	Yes	No	Yes	Yes	Good
Ortega 2014[87] MENSA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good

Reference & Study Name	Adequate randomization	Allocation concealment	Patient blinding	Staff blinding	Outcome adjudication blinding	Completeness of follow-up	Intention to treat analysis	Incomplete data addressed	Selective outcome reporting	Industry funding	Free from other bias	Overall quality
Chupp 2017[89] MUSCA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
OCS-dependent												
Bel 2014[70] SIRIUS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Reslizumab												
Severe eosinophilic asthma												
Castro 2015[88]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Benralizumab												
Bleecker 2016[62] SIROCCO	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Fitzgerald 2016[63] CALIMA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
OCS-dependent												
Nair 2017[71] ZONDA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Dupilumab												
Moderate to severe uncontrolled asthma												
Wenzel 2016[118]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Castro 2018[16] LIBERTY ASTHMA QUEST	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good

Reference & Study Name	Adequate randomization	Allocation concealment	Patient blinding	Staff blinding	Outcome adjudication blinding	Completeness of follow-up	Intention to treat analysis	Incomplete data addressed	Selective outcome reporting	Industry funding	Free from other bias	Overall quality
OCS-dependent												
Rabe 2018[17] LIBERTY ASTHMA VENTURE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good

OCS: oral corticosteroids

Table D4. Key Outcomes: Exacerbations and Changes in FEV1

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	Annual rate of exacerbations	Annual Rate ER or hospitalization	Annual rate of hospitalization	Change in FEV1 from baseline pre-bronchodilator	Change in FEV1 from baseline post-bronchodilator
Omalizumab							
Asthma with elevated IgE							
Vignola 2004[114] SOLAR	Omalizumab 0.016 mg/kg per IU/ml of IGE	209	NR	NR	NR	NR	NR
	Placebo	196	NR	NR	NR	NR	NR
Humbert 2005[65] INNOVATE	Omalizumab 0.016 mg/kg per IU/ml of IGE	209	0.68	0.24	0.06	190	
	Placebo	210	0.91	0.43	0.12	96	
	Rate Ratio		0.738 (0.552-0.998)	0.56 (0.33-0.97)	0.54 (0.25-1.1.7)	NR	NR
Busse 2011[67] ICATA	Omalizumab 0.016 mg/kg per IU/ml of IGE	208	NR	NR	NR	NR	NR
	Placebo	211	NR	NR	NR	NR	NR
Hanania 2011[115]	Omalizumab 0.016 mg/kg per IU/ml of IGE	427	0.66	NR	NR	NR	NR
	Placebo	423	0.88	NR	NR	NR	NR
	Rate ratio	NR	0.75 (0.61-0.92)	NR	NR	NR	NR
Bardelas 2012[116]	Omalizumab 0.016 mg/kg per IU/ml of IGE	136	NR	NR	NR	NR	NR
	Placebo	135	NR	NR	NR	NR	NR

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	Annual rate of exacerbations	Annual Rate ER or hospitalization	Annual rate of hospitalization	Change in FEV1 from baseline pre-bronchodilator	Change in FEV1 from baseline post-bronchodilator
Busse 2013[19]	Omalizumab 0.016 mg/kg per IU/ml of IGE	51	0.25	NR	NR	NR	NR
	Placebo	40	0.59	NR	NR	NR	NR
	Rate ratio		0.41 (0.20-0.82)	NR	NR	NR	NR
Li 2016[117] China Omalizumab	Omalizumab 0.016 mg/kg per IU/ml of IGE	310	NR	NR	NR	NR	NR
	Placebo	299	NR	NR	NR	NR	NR
	Rate ratio	NR	0.61	NR	NR	NR	NR
Mepolizumab							
Severe eosinophilic asthma							
Pavord 2012[66] DREAM	Mepolizumab 75 mg IV	153	1.24	0.17	0.1	NR	NR
	Mepolizumab 250 mg IV	152	1.46	0.25	0.1	NR	NR
	Mepolizumab 750 mg IV	156	1.15	0.22	0.07	NR	NR
	Placebo	155	2.4	0.43	0.2	NR	NR
Ortega 2014[87] MENSA	Mepolizumab 75 mg IV	191	0.93	0.14	0.06	186	176
	Mepolizumab 100 mg SC	194	0.83	0.08	0.03	183	167
	Placebo	191	1.74	0.2	0.1	68	30
	Difference SC vs. Placebo		53% (36%-65%)	61% (17%-82%)	69% (9%-89%)	NR	NR

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	Annual rate of exacerbations	Annual Rate ER or hospitalization	Annual rate of hospitalization	Change in FEV1 from baseline pre-bronchodilator	Change in FEV1 from baseline post-bronchodilator
Chupp 2017[89] MUSCA	Mepolizumab 100 SQ	274	0.51	0.03	0.02	176	NR
	Placebo	277	1.21	0.1	0.07	56	NR
	Difference	NR	0.42* (0.31-0.56)	0.32 (0.12-0.90)	0.31 (0.0-1.24)	120 (47-192)	NR
OCS-dependent							
Bel 2014[70] SIRIUS	Mepolizumab 100 mg SC	69	1.44	NR	0	NR	NR
	Placebo	66	2.12	NR	NR	NR	NR
	Rate ratio	NR	0.68 (0.47-0.99)	NR	NR	NR	NR
Reslizumab							
Poorly controlled eosinophilic asthma							
Castro 2015[88]	Reslizumab 3.0 mb/kg q 4 weeks	477	NR	0.077	NR	220	NR
	Placebo	476	NR	0.12	NR	120	NR
	Rate Ratio	NR	NR	0.66 (0.38-1.16)	NR	0.11 (0.067-0.15)	NR
Benralizumab							
Bleecker 2016[62] SIROCCO	Benralizumab 30 mg q 4 weeks	399 (275)	0.73	NR	NR	345	NR
	Benralizumab 30 mg q 8 weeks	398 (267)	0.65	NR	NR	398	NR
	Placebo	407 (261)	1.33	NR	NR	239	NR

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	Annual rate of exacerbations	Annual Rate ER or hospitalization	Annual rate of hospitalization	Change in FEV1 from baseline pre-bronchodilator	Change in FEV1 from baseline post-bronchodilator
	Rate Ratio for 30 q 4	NR	0.55 (0.42-0.71)	NR	NR	NR	NR
	Rate Ratio for 30 q 8	NR	0.49 (0.37-0.64)	NR	NR	NR	NR
Fitzgerald 2016[63] CALIMA	Benralizumab 30 mg q 4 weeks	425 (241)	0.6	NR	NR	340	NR
	Benralizumab 30 mg q 8 weeks	441 (239)	0.66	NR	NR	330	NR
	Placebo	440 (248)	0.93	NR	NR	215	NR
	Rate Ratio for 30 q 4	NR	0.64 (0.49-0.85)	0.93 (0.48-1.92)	NR	NR	NR
	Rate Ratio for 30 q 8	NR	0.72 (0.54-0.95	1.23 (0.64-2.35)	NR	NR	NR
OCS-dependent							
Nair 2017[71] ZONDA	Benralizumab 30 mg q 4 weeks	72	0.83	0.14	NR	NR	NR
	Benralizumab 30 mg q 8 weeks	73	0.54	0.02	NR	NR	NR
	Placebo	75	1.83	0.32	NR	NR	NR
	Rate Ratio for 30 q 4	NR	0.45 (0.27-0.76)	0.44 (0.13-1.49)	Difference q 4	256	NR
	Rate Ratio for 30 q 8	NR	0.30 (0.17-0.53)	0.07 (0.01-0.63)	Difference q 8	222	NR
Dupilumab							

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	Annual rate of exacerbations	Annual Rate ER or hospitalization	Annual rate of hospitalization	Change in FEV1 from baseline pre-bronchodilator	Change in FEV1 from baseline post-bronchodilator
Moderate to severe uncontrolled asthma							
Wenzel 2016[118]	Dupilumab 200 mg SC q 2 weeks	154	0.42	NR	NR	0.26	NR
	Dupilumab 20 mg q 4 weeks	157	0.599	NR	NR	0.23	NR
	Dupilumab 300 mg q 2 weeks	150	0.269	NR	NR	0.26	NR
	Dupilumab 300 mg q 4 weeks	157	0.265	NR	NR	0.29	NR
	Placebo	158	0.897	NR	NR	0.28	NR
Castro 2018[16] LIBERTY ASTHMA QUEST	Dupilumab 200 mg SC q 2 weeks	621	0.46 (0.39-0.53)	NR	NR	0.32	NR
	Placebo 200 mg	317	0.87 (0.72-1.05)	NR	NR	0.18	NR
	Dupilumab 300 mg SC q 2 weeks	633	0.52 (0.45-0.61)	NR	NR	0.34	NR
	Placebo 300 mg	321	0.97 (0.81-1.16)	NR	NR	0.21	NR
	Rate Ratio 200 mg vs. Placebo	NR	0.52 (0.41 to 0.66)	NR	NR	NR	NR
	Rate Ratio 300 mg vs. Placebo	NR	0.54 (0.43 to 0.68)	NR	NR	NR	NR
Glucocorticoid dependent Severe asthma							

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	Annual rate of exacerbations	Annual Rate ER or hospitalization	Annual rate of hospitalization	Change in FEV1 from baseline pre-bronchodilator	Change in FEV1 from baseline post-bronchodilator
Rabe 2018[17] LIBERTY ASTHMA VENTURE	Dupilumab 300 mg	103	0.7	NR	NR	0.21	NR
	Placebo	107	1.6	NR	NR	0.01	NR
	Rate Ratio vs Placebo	NR	0.59	NR	NR	NR	NR

ER: emergency room, FEV1: forced expiratory volume in one second, IV: intravenous, N/A: not applicable, NR: not reported, OCS: oral corticosteroids, SC: subcutaneous

Table D5. Key Outcomes: Quality of Life and Reductions in OCS Dose

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	Change in ACQ (95% CI)	Change in AQLQ (95% CI)	Change in SGRQ (95% CI)	90-100% reduction in OCS dose (%)	≥50% reduction in OCS dose (%)	No reduction in OCS dose (%)
Omalizumab								
Asthma with elevated IgE								
Vignola 2004[114] SOLAR	Omalizumab 0.016 mg/kg per IU/ml of IGE	209	NR	NR	NR	NR	NR	NR
	Placebo	196	NR	NR	NR	NR	NR	NR
Humbert 2005[65] INNOVATE	Omalizumab 0.016 mg/kg per IU/ml of IGE	209	NR	NR	NR	NR	NR	NR
	Placebo	210	NR	NR	NR	NR	NR	NR
	Rate Ratio	NR	NR	NR	NR	NR	NR	NR
Busse 2011[67] ICATA	Omalizumab 0.016 mg/kg per IU/ml of IGE	208	NR	NR	NR	N/A	N/A	N/A
	Placebo	211	NR	NR	NR	NR	NR	NR
Hanania 2011[115]	Omalizumab 0.016 mg/kg per IU/ml of IGE	NR	NR	0.29	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR	NR	NR
Bardelas 2012[116]	Omalizumab 0.016 mg/kg per IU/ml of IGE	136	NR	NR	NR	N/A	N/A	N/A
	Placebo	135	NR	NR	NR	NR	NR	NR

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	Change in ACQ (95% CI)	Change in AQLQ (95% CI)	Change in SGRQ (95% CI)	90-100% reduction in OCS dose (%)	≥50% reduction in OCS dose (%)	No reduction in OCS dose (%)
Busse 2013[19]	Omalizumab 0.016 mg/kg per IU/ml of IGE	51	NR	NR	NR	NR	NR	NR
	Placebo	40	NR	NR	NR	NR	NR	NR
Li 2016[117] China Omalizumab	Omalizumab 0.016 mg/kg per IU/ml of IGE	310	NR	NR	NR	N/A	N/A	N/A
	Placebo	299	NR	NR	NR	NR	NR	NR
Mepolizumab								
Severe eosinophilic asthma								
Pavord 2012[66] DREAM	Mepolizumab 75 mg IV	153	-0.75	NR	NR	NR	NR	NR
	Mepolizumab 250 mg IV	152	-0.87	NR	NR	NR	NR	NR
	Mepolizumab 750 mg IV	156	-0.8	NR	NR	NR	NR	NR
	Placebo	155	-0.59	NR	NR	NR	NR	NR
Ortega 2014[87] MENSA	Mepolizumab 75 mg IV	191	-0.92	NR	-15.4	NR	NR	NR
	Mepolizumab 100 mg SC	194	-0.94	NR	-16	NR	NR	NR
	Placebo	191	-0.5	NR	-9	NR	NR	NR
	Difference SC vs. Placebo	NR	-0.44 (-0.63 to -0.25)	NR	-7 (-10.2 to -3.8)	NR	NR	NR
Chupp 2017[89] MUSCA	Mepolizumab 100 SQ	274	-0.8	NR	-15.6	NR	NR	NR
	Placebo	277	-0.4	NR	-7.9	NR	NR	NR
	Difference	NR	-0.4	NR	-7.7	NR	NR	NR

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	Change in ACQ (95% CI)	Change in AQLQ (95% CI)	Change in SGRQ (95% CI)	90-100% reduction in OCS dose (%)	≥50% reduction in OCS dose (%)	No reduction in OCS dose (%)
			(-0.6 to -0.2)					
OCS-dependent								
Bel 2014[70] SIRIUS	Mepolizumab 100 mg SC	69	NR	NR	NR	23%	54%	36%
	Placebo	66	NR	NR	NR	11%	33%	56%
	Difference	NR	-0.52 (-0.87 to -0.17)	NR	-5.8 (-10.1 to -1.0)	NR	NR	NR
Reslizumab								
Poorly controlled eosinophilic asthma								
Castro 2015[88]	Reslizumab 3.0 mb/kg q 4 weeks	477	-1.02	NR	NR	NR	NR	NR
	Placebo	476	-0.77	NR	NR	NR	NR	NR
	Rate Ratio	NR	-0.25	NR	NR	NR	NR	NR
Benralizumab								
Bleecker 2016[62] SIROCCO	Benralizumab 30 mg q 4 weeks	399 (275)	-1.12	NR	NR	NR	NR	NR
	Benralizumab 30 mg q 8 weeks	398 (267)	-1.3	NR	NR	NR	NR	NR
	Placebo	407 (261)	-1.04	NR	NR	NR	NR	NR
Fitzgerald 2016[63] CALIMA	Benralizumab 30 mg q 4 weeks	425 (241)	-1.4	NR	NR	NR	NR	NR
	Benralizumab 30 mg q 8 weeks	441 (239)	NR	NR	NR	NR	NR	NR
	Placebo	440 (248)	-1.16	NR	NR	NR	NR	NR
OCS-dependent								
Nair 2017[71] ZONDA	Benralizumab 30 mg q 4 weeks	72	NR	NR	NR	33%	67%	NR

Reference & Study Name	Intervention	N, Overall (eosinophils ≥300/) μ L	Change in ACQ (95% CI)	Change in AQLQ (95% CI)	Change in SGRQ (95% CI)	90-100% reduction in OCS dose (%)	≥50% reduction in OCS dose (%)	No reduction in OCS dose (%)
	Benralizumab 30 mg q 8 weeks	73	NR	NR	NR	37%	66%	NR
	Placebo	75	NR	NR	NR	12%	37%	NR
Dupilumab								
Moderate to severe uncontrolled asthma								
Wenzel 2016[118]	Dupilumab 200 mg SC q 2 weeks	154	-1.32	NR	NR	NR	NR	NR
	Dupilumab 20 mg q 4 weeks	157	-1.34	NR	NR	NR	NR	NR
	Dupilumab 300 mg q 2 weeks	150	-1.49	NR	NR	NR	NR	NR
	Dupilumab 300 mg q 4 weeks	157	-1.45	NR	NR	NR	NR	NR
	Placebo	158	-1.14	NR	NR	NR	NR	NR
Castro 2018[16] LIBERTY ASTHMA QUEST	Dupilumab 200 mg SC q 2 weeks	631	-1.44	128	NR	NR	NR	NR
	Placebo 200 mg	317	-1.10	0.99	NR	NR	NR	NR
	Dupilumab 300 mg SC q 2 weeks	633	-1.40	1.29	NR	NR	NR	NR
	Placebo 300 mg	321	-1.21	1.03	NR	NR	NR	NR
Glucocorticoid dependent Severe asthma								
Rabe 2018[17] LIBERTY ASTHMA VENTURE	Dupilumab 300 mg	103	NR	NR	NR	NR	80%	NR
	Placebo	107	NR	NR	NR	NR	50%	NR

ACQ: Asthma Control Questionnaire, ER: emergency Room, FEV1: forced expiratory volume in one second, IV: intravenous, N/A: not applicable, NR: not reported, OCS: oral corticosteroid, SGRQ: St. George's Respiratory Questionnaire, SC: subcutaneous

Table D6. Harms

Reference & Study Name	Intervention	N	Any AE	SAE	Death	Drug related	Discontinue due to AE	Hyper-sensitivity	Injection reaction	Headache	URI	Sinusitis
Omalizumab												
Vignola 2004[114]	Omalizumab	209	78%	6.2%	0	NR	0	NR	7.70%	NR	NR	NR
	Placebo	196	69%	9.2%	0	NR	0	NR	4.60%	NR	NR	NR
Humbert 2005[65]	Omalizumab	419	72%	12%	0	12%	NR	NR	5%	7%	5%	6%
	Placebo	NR	76%	16%	0	9%	NR	NR	5%	9%	6%	8%
Busse 2011[67]	Omalizumab	NR	39%	6%	0	NR	NR	NR	4%	NR	NR	NR
	Placebo	NR	47%	14%	0	NR	NR	NR	3%	NR	NR	NR
Hanania 2011[115]	Omalizumab	NR	80	NR	0	NR	3.7	1.6	1.2	NR	NR	NR
	Placebo	NR	80	NR	1	NR	2.4	2.9	3.1	NR	NR	NR
Bardelas 2012[116]	Omalizumab	136	66	NR	NR	8%	NR	NR	NR	5%	11%	10%
	Placebo	135	69	NR	NR	3%	NR	NR	NR	7%	13%	7%
Busse 2013[19]	Omalizumab	157	59	2.50%	0	NR	2%	1.30%	1.30%	NR	9.60%	7.00%
	Placebo	171	63	3.50%	0	NR	1%	2.30%	0.60%	NR	9.90%	9.40%
Li 2016[117]	Omalizumab	310	39%	1.90%	0	NR	NR	NR	NR	1.00%	12.90%	NR
	Placebo	299	40%	3%	0	NR	NR	NR	NR	1.30%	13%	NR
Mepolizumab												
Severe eosinophilic asthma												
Pavord 2012[66] DREAM	Mepolizumab 75 mg IV	153	NR	13%	0 (0%)	NR	3%	NR	NR	NR	NR	NR
	Mepolizumab 250 mg IV	152	NR	16%	2 (1%)	NR	5%	NR	NR	NR	NR	NR
	Mepolizumab 750 mg IV	156	NR	12%	1 (1%)	NR	6%	NR	NR	NR	NR	NR
	Placebo	155	NR	16%	0 (0%)	NR	4%	NR	NR	NR	NR	NR
Ortega 2014[87]	Mepolizumab 75 mg IV	191	84%	7%	0 (0%)	17%	0%	NR	3%	24%	12%	6%

Reference & Study Name	Intervention	N	Any AE	SAE	Death	Drug related	Discontinue due to AE	Hyper-sensitivity	Injection reaction	Headache	URI	Sinusitis
MENSA	Mepolizumab 100 mg SC	194	78%	8%	0 (0%)	20%	1%	NR	9%	20%	12%	9%
	Placebo	191	83%	14%	1 (1%)	16%	2%	NR	3%	17%	14%	9%
Chupp 2017[89] **MUSCA**	Mepolizumab 100 SQ	274	70%	5%	0%	11%	1%	NR	3%	16%	6%	NR
	Placebo	277	74%	8%	0%	9%	1%	NR	2%	21%	5%	NR
OCS-dependent												
Bel 2014[70] **SIRIUS**	Mepolizumab 100 mg SC	69	83%	1%	0 (0%)	30%	5%	NR	6%	20%	4%	10%
	Placebo	66	92%	18%	1 (2%)	18%	4%	NR	3%	21%	8%	9%
Reslizumab 3 mg/kg IV												
Severe eosinophilic asthma												
Castro 2015[88]	Reslizumab 3.0 mb/kg q 4 weeks	477	78%	9%	0	NR	3%	NR	NR	11%	10%	7%
	Placebo	476	86%	12%	0	NR	4%	NR	NR	11%	10%	8%
Benralizumab												
Bleecker 2016[62]	Benralizumab 30 mg q 4 weeks	293	73%	12%	<1%	NR	2%	3%	4%	7%	11%	4%
	Benralizumab 30 mg q 8 weeks	281	71%	13%	<1%	NR	2%	3%	2%	9%	8%	6%
	Placebo	311	76%	14%	1%	NR	<1%	3%	2%	5%	9%	7%
Fitzgerald 2016[63] **CALIMA**	Benralizumab 30 mg q 4 weeks	425	74%	10%	<1%	12%	2%	3%	3%	8%	7%	5%
	Benralizumab 30 mg q 8 weeks	441	75%	9%	<1%	13%	2%	3%	3%	8%	8%	5%
	Placebo	440	78%	14%	0	8%	<1%	4%	2%	8%	9%	8%
OCS-dependent												

Reference & Study Name	Intervention	N	Any AE	SAE	Death	Drug related	Discontinue due to AE	Hyper-sensitivity	Injection reaction	Headache	URI	Sinusitis
Nair 2017[71] ZONDA	Benralizumab 30 mg q 4 weeks	72	68%	10%	0%	NR	0%	1%	3%	7%	6%	7%
	Benralizumab 30 mg q 8 weeks	73	75%	10%	3%	NR	4%	3%	0%	8%	7%	5%
	Placebo	75	83%	19%	0%	NR	3%	1%	3%	5%	7%	11%
Dupilumab												
Wenzel 2016[118]	Dupilumab 200 mg every 4 weeks	154	75%	4%	0	NR	5%	NR	9%	6%	15%	NR
	Dupilumab 300 mg every 4 weeks	157	83%	10%	1%	NR	6%	NR	8%	12%	12%	NR
	Dupilumab 200 mg every 4 weeks	150	80%	8%	0	NR	4%	NR	14%	11%	15%	NR
	Dupilumab 300 mg every 4 weeks	157	78%	7%	0	NR	3%	NR	21%	11%	13%	NR
	Placebo	158	75%	6%	0	NR	3%	NR	8%	13%	18%	NR
Castro 2018[16] LIBERTY ASTHMA QUEST	Dupilumab 200 mg or 300 mg	1263	81%	8.20%	0.40%	NR	5%	NR	16.80%	6.80%	11.60%	4.90%
	Placebo	634	83%	8.40%	0.50%	NR	4.60%	NR	7.90%	8.00%	13.60%	8.80%
OCS-dependent												
Rabe 2018[17] LIBERTY ASTHMA VENTURE	Dupilumab 300 mg	103	62%	9.00%	0.00%	NR	1.00%	NR	9.00%	NR	9.00%	7.00%
	Placebo	107	64%	6.00%	0.00%	NR	4.00%	NR	4.00%	NR	18.00%	4.00%

AE: adverse event, NR: not reported, SAE: severe adverse event, URI: upper respiratory infection

Network Meta-Analysis Supplemental Information

As described in the report, we conducted an exploratory network meta-analysis (NMA) of asthma exacerbations in the subgroup of patients with high baseline eosinophils (≥300 cells/L) and ≥2 exacerbations in the previous year. An NMA extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator[s]). The NMA was conducted in a Bayesian framework with random effects on the treatment parameter using the gemtc package in R.[119] The log exacerbation rates were analyzed using a normal likelihood and identity link. Inputs used for the analysis are reported in Appendix Table D7. Tabular results are presented for the treatment effects (rate ratio) of each intervention versus placebo along with 95% credible intervals (95% CrI) in Section 3 of the report.

Table D7. Network Meta-Analysis Inputs: Asthma Exacerbations in Patients with ≥300 eosinophils/µL and ≥2 Exacerbations in Previous Year

Study	Intervention(s)	Exacerbation Rate (95% CI)	Rate ratio vs. Placebo (95% CI)
Casale 2018[120]	Placebo	NR	0.33 (0.16, 0.64)
	Omalizumab	NR	
MENSA[87]	Placebo	2.04 (1.78, 2.30)	0.34 (0.21, 0.54)
	Mepolizumab	0.70 (0.31, 1.09)	
MUSCA[89]	Placebo	1.62 (1.37, 1.87)	0.38 (0.25, 0.58)
	Mepolizumab	0.62 (0.26, 0.98)	
Study 3082 &3083 (Castro 2015)[88]	Placebo	NR	0.34 (0.25, 0.47)
	Reslizumab	NR	
Study 3083 (Castro 2015)[88]	Placebo	NR	0.34 (0.25, 0.47)
	Reslizumab	NR	
CALIMA[63]	Placebo	0.93 (0.77, 1.12)	0.72 (0.54, 0.95)
	Benralizumab	0.66 (0.54, 0.82)	
SIROCCO[62]	Placebo	1.33 (1.12, 1.58)	0.49 (0.37, 0.64)
	Benralizumab	0.65 (0.53, 0.80)	
LIBERTY ASTHMA QUEST[16]	Placebo	NR	0.26 (0.19, 0.36)
	Dupilumab 200mg	NR	
	Placebo	NR	0.26 (0.19, 0.35)
	Dupilumab 300mg	NR	
Wenzel 2016[118]	Placebo	NR	0.26 (0.19, 0.36)
	Dupilumab 200mg	NR	
	Dupilumab 300mg	NR	0.26 (0.19, 0.35)

NR: not reported

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	Only included chronic oral steroid use changes
Medical costs	Paid by third-party payers	X	X	Included within unit cost estimates
	Paid by patients out-of-pocket	X	X	Included within unit cost estimates to the extent possible
	Future related medical costs	X	X	Included future asthma event and treatment costs
	Future unrelated medical costs	☐	☐	Non-asthma costs were not directly included
Informal Health Care Sector				
Health-related costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	X	Included in modified societal perspective
	Cost of unpaid lost productivity due to illness	NA	X	Included in modified societal perspective
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	

Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: Not applicable

Adapted from Sanders et al.[120]

Lifetime Annualized Clinical Outcomes

Tables E2 -E6 indicate the long-run clinical outcomes for all five biologic agents. This analysis investigated the average events per person year for oral corticosteroid burst, ED visit, hospitalization, and death (all cause). The exacerbation rate ratios drive these incremental findings.

Table E2. Long-Run Clinical Outcomes: Omalizumab

Omalizumab: Average Events per Person Year			
Average Events per Person Year	**Omalizumab**	**SoC**	**Incremental**
Steroid Burst	0.601	1.141	-0.540
ED Visit	0.026	0.063	-0.038
Hospitalization	0.010	0.063	-0.053
Death (all cause)	0.030	0.031	-0.001

SoC: Standard of Care

Table E3. Long-Run Clinical Outcomes: Mepolizumab

Mepolizumab: Average Events per Person Year			
Average Events per Person Year	**Mepolizumab**	**SoC**	**Incremental**
Steroid Burst	0.521	1.141	-0.620
ED Visit	0.023	0.063	-0.040
Hospitalization	0.020	0.063	-0.043
Death (all cause)	0.030	0.031	-0.001

SoC: Standard of Care

Table E4. Long-Run Clinical Outcomes: Reslizumab

Reslizumab: Average Events per Person Year			
Average Events per Person Year	**Reslizumab**	**SoC**	**Incremental**
Steroid Burst	0.497	1.141	-0.644
ED Visit	0.043	0.063	-0.020
Hospitalization	0.043	0.063	-0.020
Death (all cause)	0.030	0.031	-0.001

SoC: Standard of Care

Table E5. Long-Run Clinical Outcomes: Benralizumab

Benralizumab: Average Events per Person Year			
Average Events per Person Year	**Benralizumab**	**SoC**	**Incremental**
Steroid Burst	0.680	1.141	-0.461
ED Visit	0.044	0.063	-0.020
Hospitalization	0.044	0.063	-0.020
Death (all cause)	0.030	0.031	-0.001

SoC: Standard of Care

Table E6. Long-Run Clinical Outcomes: Dupilumab

Dupilumab: Average Events per Person Year			
Average Events per Person Year	**Dupilumab**	**SoC**	**Incremental**
Steroid Burst	0.463	1.141	-0.678
ED Visit	0.026	0.063	-0.038
Hospitalization	0.026	0.063	-0.038
Death (all cause)	0.030	0.031	-0.001

SoC: Standard of Care

Sensitivity Analysis Results

Figure E1. Omalizumab Tornado Diagram

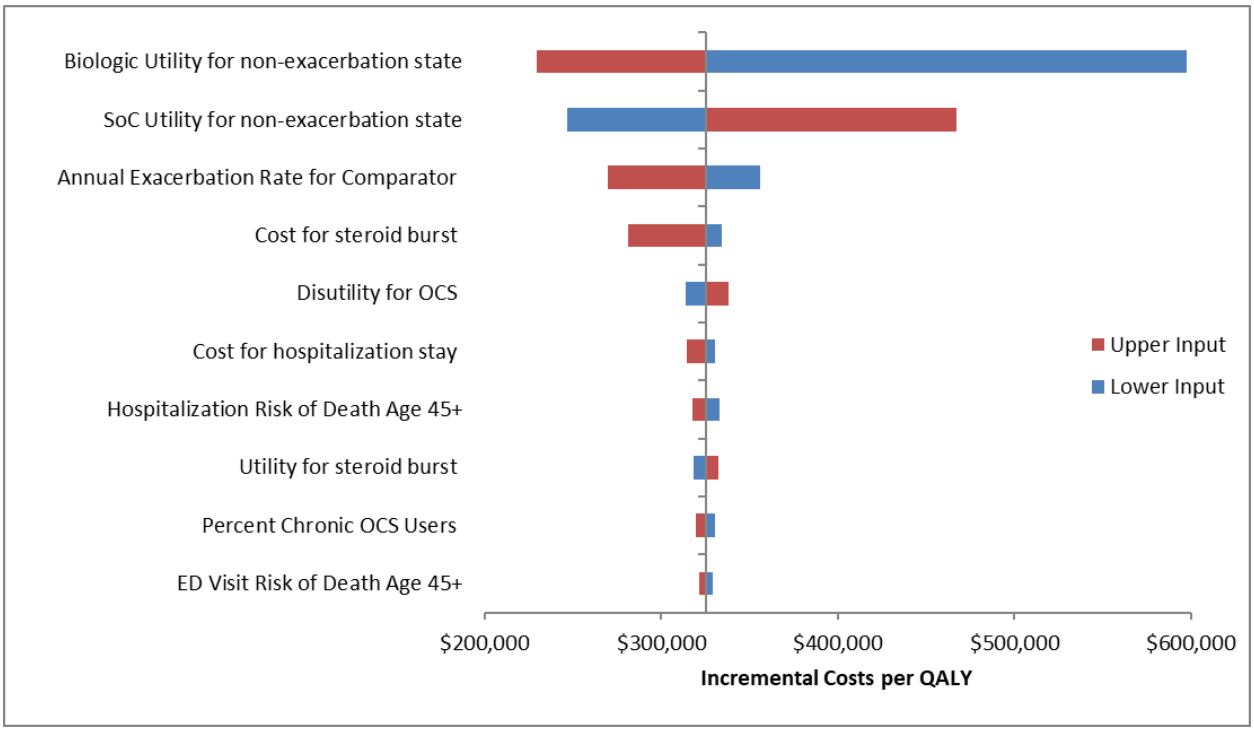


Figure E2. Reslizumab Tornado Diagram

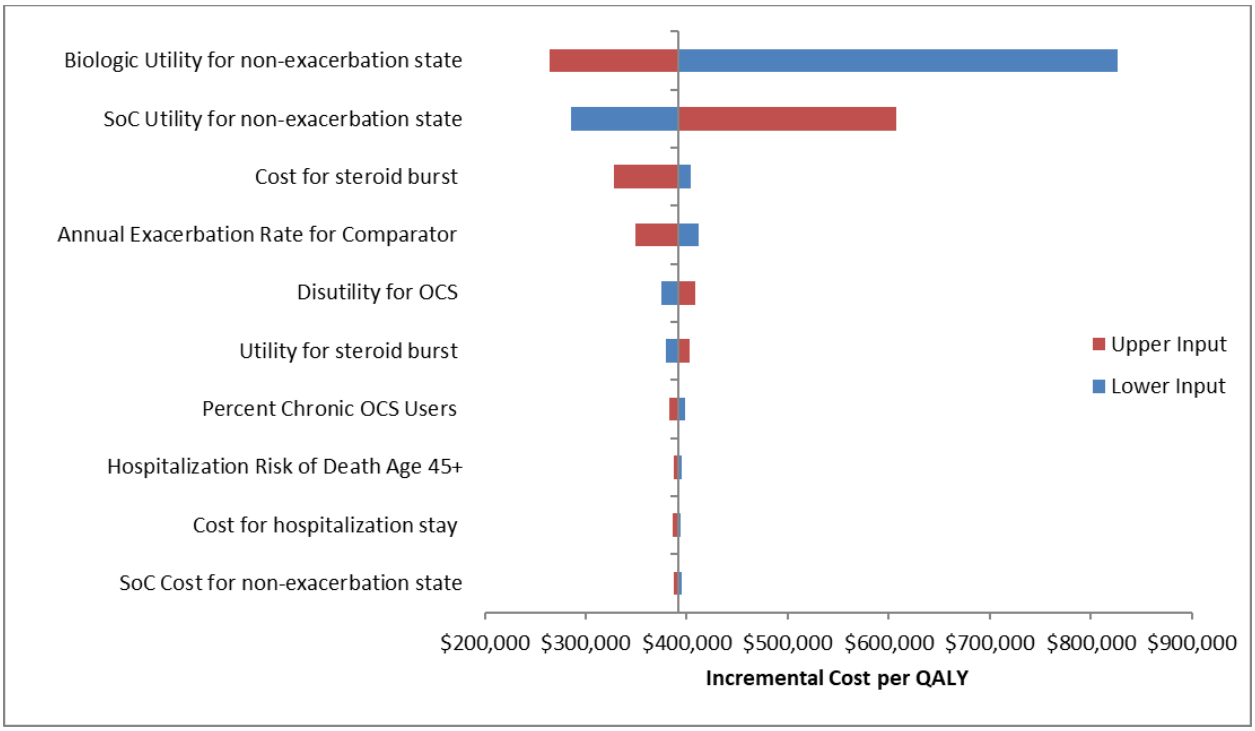


Figure E3. Benralizumab Tornado Diagram

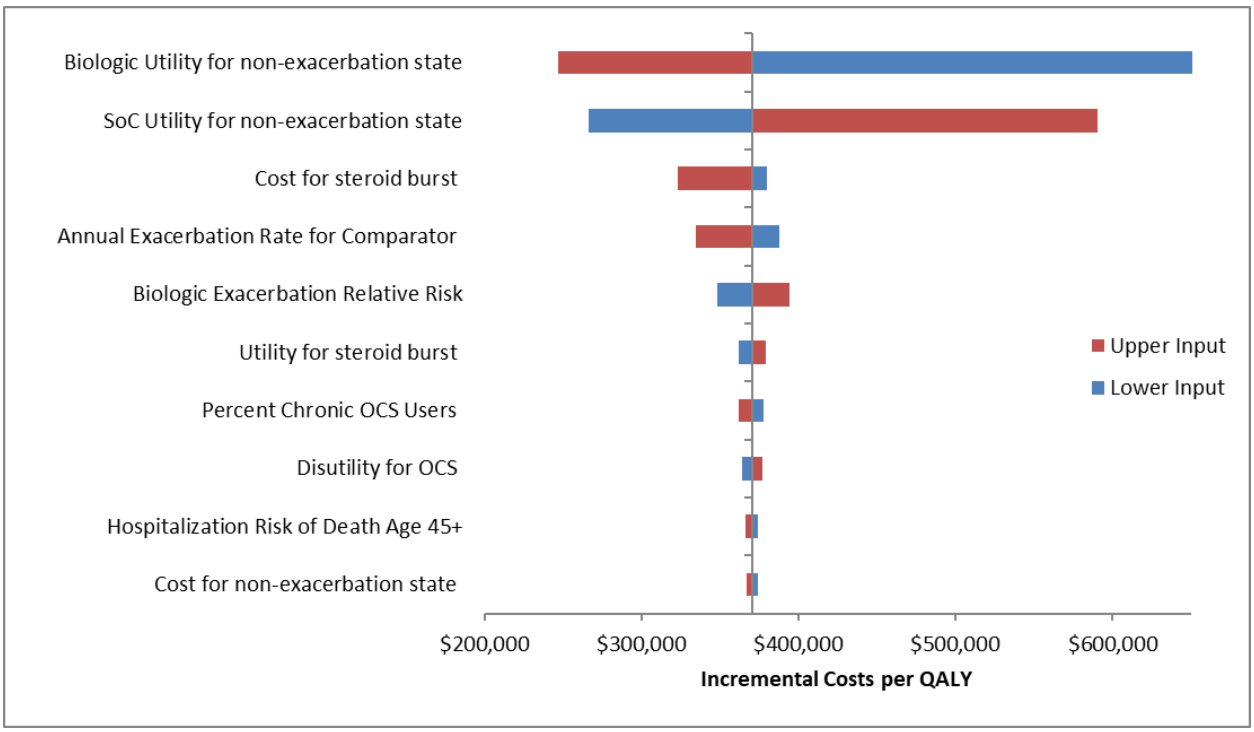
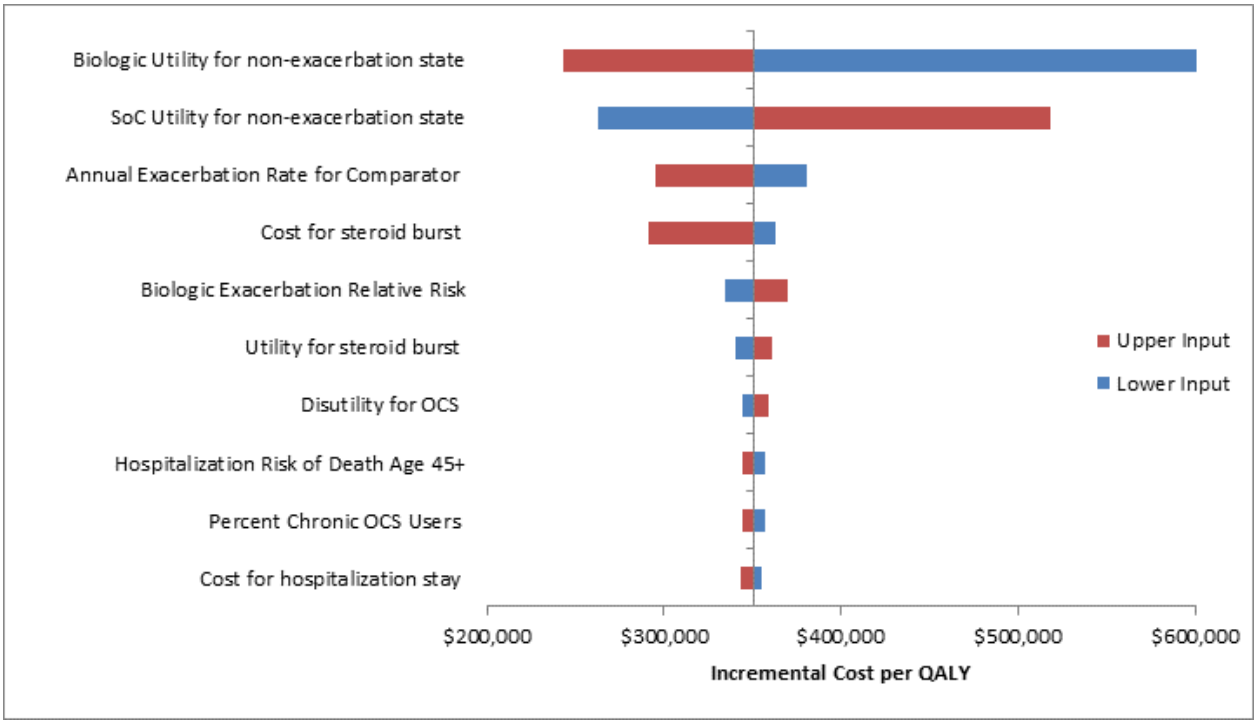


Figure E4. Dupilumab Tornado Diagram



Appendix F. Public Comments

This section includes summaries of the public comments prepared for the Midwest CEPAC Public Meeting on November 29, 2018 in St. Louis, MO. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Two speakers did not submit summaries of their public comments.

A video recording of all comments can be found here, beginning at minute 1:23:05. Conflict of interest disclosures are included at the bottom of each statement for each speaker.

Mark S. Forshag, MD, MHA
US Medical Expert – Respiratory, GlaxoSmithKline

Conflicts of Interest: Mark Forshag is a full-time employee of GlaxoSmithKline.

NUCALA remains the only IL-5 with up to 4.5 years of evidence that demonstrates positive clinical and humanistic outcomes. Accordingly, ICER's evidence rating for NUCALA was "high certainty of incremental net health benefit" and exploratory network meta-analysis demonstrated a significant clinical benefit for NUCALA versus placebo in a sub-set of clinically appropriate patients. This finding is consistent with GSK's clinical evidence package and FDA-approved product label for NUCALA for severe eosinophilic asthma.

GSK has identified several important limitations. First, the report assumes a payer's perspective, narrowing the analyses to potential offsets for existing healthcare costs, while limiting new costs. Thus, ICER's review omits critical considerations, including prescriber/patient experience and non-healthcare related patient/family impact.

Secondly, there is increased uncertainty in using model inputs from heterogenous patient populations and clinical metrics, and over-reliance on expert opinion. GSK reiterates our recommendations to: (1) report model outcomes as ranges and (2) release the complete model methodology to support stakeholder decision-making.

The third limitation is ICER's use of a model that applies common assumptions across five drugs as if representing a single class, whereas they represent four different mechanisms of action. A related issue extends to their unsupported market uptake assumptions for a new biologic with existing biologics approved. Assessment of the new therapy's budget impact is dependent on the degree it will replace existing biologics, versus being added to standard of care in biologic-naive patients.

GSK urges ICER to include transparent discussions of these limitations in the summary and body of their final report.

Margaret Garin, MD, MSCR
Director, Clinical Development, Global Research and Development, Teva

Conflicts of Interest: Margaret Garin is a full-time employee of Teva.

Teva strongly believes in patient-centered care, prescriber choice, and shared decision-making. Evidence suggests patients with asthma have individual qualities that may impact the value of one therapy over another for different patients. It is therefore imperative that prescribers have choices for personalizing therapy including intravenous (IV) reslizumab, the only biologic with weight-based dosing and consistent serum exposures across all body weights. Our trial evidence demonstrated early, consistent, and meaningful reductions in exacerbations, and improvements in FEV_1, asthma control, and quality of life, with sustained results up to 3 years. A real-world analysis showed similar OCS reductions for reslizumab as mepolizumab and benralizumab, and thus should be valued as such in cost-effectiveness evaluations.

Appropriate patient selection is paramount to optimize therapeutic value. Reslizumab's indication is in patients with severe asthma, a more restricted population than our clinical trials. ICER must prioritize the efficacy data for the subpopulation of patients that were severe and exacerbation-prone to understand the benefit and value in the indicated population. We agree that only responders should continue therapy, consistent with ICER's best-case scenario where the value of biologics neared commonly accepted cost-effectiveness thresholds; recent evidence demonstrates feasibility of assessment at 16 weeks after the first dose.[b]

Finally, patients with severe asthma may change their daily lives to avoid asthma triggers and may worry daily about when the next asthma exacerbation will occur. These are meaningful aspects of asthma that are not captured in trials for which reslizumab use can add significant value for patients.

Benjamin Kramer, MD
Vice President, Immunology and Ophthalmology, U.S. Medical Affairs, Genentech*

Conflicts of Interest: Benjamin Kramer is a full-time employee of Genentech.

We fundamentally believe in the value of Xolair and supporting patients' access to all innovative therapies. Xolair is uniquely distinguished from other asthma biologics. It is the first and only

[b] Bateman ED, Djukanović R, Castro M, Canvin J, Germinaro M, Noble R, Garin M, Buhl R. Predicting responders to reslizumab after 16 weeks of treatment using an algorithm derived from clinical studies of severe eosinophilic asthma patients. *Am J Respir Crit Care Med*. Published online: October 22, 2018 (doi:10.1164/rccm.201708-1668OC).

biologic indicated for the treatment of moderate-to-severe persistent allergic asthma in adults and children six years of age and older.

Xolair's extensive evidence base. There are >15 years of post-marketing experience with Xolair, culminating in >860,000 treated patient-years. There are >25 high-quality randomized controlled trials demonstrating Xolair's efficacy in reducing asthma exacerbations. These findings are supported by >25 observational studies that reflect long-term safety and real-world clinical and patient-reported outcomes. This body of evidence suggests a reduction of up to 80% in asthma exacerbation rates and up to 96% in hospitalization rates. Xolair's benefit has been demonstrated across a broad array of healthcare settings and patient sub-groups. Therefore, Xolair's clinical evidence rating should be higher than a B.

Limited comparability of asthma biologics. The understanding of asthma complexity and heterogeneity has evolved, with a recognition of allergic and eosinophilic phenotypes. Xolair's development program was different from more recently approved therapies. As a result, important patient characteristics that are highly related to trial endpoints, such as baseline lung function and exacerbation history, differed. This limits comparisons between biologics.

Importance of maintaining treatment options. Approximately 60-80% of asthma is allergic. Without Xolair, many allergic moderate-to-severe persistent asthma patients would have no biologic option after failing standard of care therapy.

We thank the asthma community for providing their perspectives on this important topic.

* In the U.S., Genentech and Novartis Pharmaceuticals Corporation work together to develop and co-promote Xolair.

Andreas Kuznik, PhD
Senior Director, Health Economics and Outcomes Research, Regeneron Pharmaceuticals
Representing Sanofi Genzyme/Regeneron

Conflicts of Interest: Andreas Kuznik is a full-time employee of Regeneron Pharmaceuticals.

1. ICER has used inappropriate clinical data for dupilumab in the base case of the model. Dupilumab was recently approved in the US as an add-on maintenance treatment in patients with moderate-to-severe asthma aged ≥12 years with an eosinophilic phenotype or with OCS-dependent asthma. The annualized exacerbation rate ratios corresponding to the labeled populations are 0.44, 0.40, and 0.41 for the 200mg and 300mg doses in QUEST and the 300mg dose for OCS-dependent patients in the VENTURE study, whereas ICER used a single rate ratio of 0.52 in the model and presented rate ratios of 0.52 and 0.54 for the 200mg and 300mg doses, respectively, in Table ES2.

2. We reiterate the methodological importance of incorporating a response rule in the base case model. We believe that patients, physicians, and payers will observe response to treatment and discontinue therapy upon non-response. Response rules have been consistently used by ICER and NICE in their models across different symptomatic diseases. We recommend again that ICER use a response rule in their base case.
3. Finally, ICER assumes that patients in the standard of care (SOC) arm experience an annual exacerbation rate of 1.3, and this rate is assumed to be constant over a patient's lifetime. However, what is observed in the real world is a gradual increase in exacerbation risk among biologic-eligible patients on SOC that peaks well over 2 exacerbations annually prior to biologic initiation. We recommend that ICER apply more realistic exacerbation rates to the SOC arm over time.

Frank Trudo, MD, MBA
Vice President, Medical Affairs Respiratory, AstraZeneca

Conflicts of Interest: Frank Trudo is a full-time employee of AstraZeneca.

Severe asthma is a heterogeneous disease and a one-size-fits-all treatment approach is not effective. This has resulted in an over-reliance on systemic corticosteroids and for many, inadequate asthma control. Cumulative exposure to systemic corticosteroids is associated with an increased risk of related co-morbidities like diabetes, osteoporosis and other diseases. These risks increase based on the total exposure of systemic corticosteroids over time. Innovative treatments for severe asthma more precisely target key effector inflammatory cells, like the eosinophil, and have shown in clinical trials to reduce the rate of asthma exacerbations and reduce or eliminate chronic daily steroid use.

It is difficult to interpret the results of an analysis which assumes that every individual patient will achieve the same mean treatment response reported from clinical trials and then continue that very same medication indefinitely. In the real world, every patient is different, with most patients achieving clinical responses different than the mean. Through a shared decision-making process with patients, providers determine at each clinical encounter the best treatment plan based on clinical effectiveness and acceptable tolerability. This informs a medication continuation decision.

The output from this review will impact the lives of patients living with severe uncontrolled asthma. Providers should have therapeutic optionality and patients with severe uncontrolled asthma should have access to the treatments they need.

Bradley Becker, MD
Professor, Allergy and Immunology
St. Louis University School of Medicine, Departments of Pediatrics and Internal Medicine

Conflicts of Interest: None disclosed.

Children with asthma are a subpopulation which benefit from biologic therapies when used for the treatment of severe asthma with Type 2 inflammation. Eighty-five percent of children with asthma have allergic triggers or an eosinophilic phenotype.

In the Severe Asthma Research Program of the NIH, 30% of children reported a history of intubation for near-fatal respiratory failure.

The use of biologics for moderate to severe asthma is associated with significant decreases in morbidity and mortality.

The death of a child has a devastating lifelong impact on his family and caregivers. According to the CDC, about 200 kids died from asthma per year in the US.

Children with severe asthma, compared with adults, are more atopic, and have higher serum IgE and eosinophil levels.

In SARP: children had declines in lung function, greatest in those with aeroallergen sensitization. Studies suggest a subset of children with severe asthma have increased risk of developing COPD. Biologics for asthma decrease exacerbations which are felt to be major drivers for decreases in lung function.

ICER's analysis does not look at subpopulations such as pediatrics. It is likely QALY would improve if the analysis is limited to subgroups such as children.

I suggest the ICER Midwest CEPAC, consider these factors in reimbursement for biologic therapies for the treatment of type-2 asthma in children.

Tonya Winders
President and CEO, Allergy & Asthma Network

Conflicts of Interest: Allergy & Asthma Network has received funding for unbranded disease education & awareness in excess of $5,000 from AstraZeneca, Genentech, GSK, Sanofi Genzyme, and Teva.

Tonya Winders, CEO of Allergy & Asthma Network, presented the voice of the 1-2M patients living with severe asthma by highlighting four emotional patient stories. From ER visits, hospitalizations, disability, etc. to oral steroid side effects, relational and financial toil, the patient journeys shared

allowed the panel to hear how this disease is limiting so many lives beyond what the ICER value framework currently accounts.

Winders implored ICER to reconsider its value assessment by recognizing more patient-reported outcomes vs QALY's and to better account for the heterogeneity and complexity of the disease rather than relying on clinical trial data which was never intended for cost effectiveness analysis. Moreover, she challenged ICER to move away from solely a healthcare sector perspective to a patient-centered perspective.

In a time of unprecedented scientific advancements and personalized medicine in asthma, the ICER report is likely to unnecessarily limit access to innovation based on minimal "exploratory" data. It is imperative for all community stakeholders (Policymakers, Manufacturers, Healthcare Providers, & Patients) to collaborate to ensure the most appropriate treatment to the most appropriate patient at the most appropriate time and at the most affordable cost to the system. This will certainly take compromise by all parties and can only be accomplished by placing patients at the center of the conversation. The "small net benefit" noted by ICER's evaluation of the asthma biologics is inconsistent with testimonials of lives changed due to these treatments and should not be used to undermine the patient/physician shared decision-making process.

Appendix G. Conflict of Interest Disclosures

Tables G1 through G3 contain conflict of interest (COI) disclosures for all participants at the November 29, 2018 public meeting of the Midwest CEPAC.

Table G1. ICER Staff and Consultant COI Disclosures

Name	Organization	Disclosures
Ellie Adair, MPA	ICER	None
Jonathan D. Campbell, PhD	University of Colorado Skaggs School of Pharmacy	None
Maggie O'Grady, BS	ICER	None
Steve Pearson MD, MSc	ICER	None
David Rind, MD, MSc	ICER	None
Jeffrey A. Tice, MD	University of California, San Francisco	None

Table G2. Midwest CEPAC Panel Member COI Disclosures

Name	Organization	Disclosures
Eric Armbrecht, PhD	St. Louis University	*
Ryan Barker, MSW, MPPA	Missouri Foundation for Health	*
Aaron Carroll, MD, MS	Indiana University School of Medicine	*
Don Casey, MD, MPH, MBA	IPO4Health, Medecision	*
Rena Conti, PhD	University of Chicago	She and family members have been treated or likely are candidates for treatment with these biologics.
Gregory Curfman, MD	Journal of the American Medical Association (JAMA)	*
Stacie Dusetzina, PhD	Vanderbilt University School of Medicine	*
Elbert Huang, MD, MPH	University of Chicago	*
Jill Johnson, PharmD	University of Arkansas for Medical Sciences	*
Timothy McBride, PhD	Washington University in St. Louis	*
Scott Micek, PharmD	St. Louis College of Pharmacy	*
Harold Pollack, PhD	University of Chicago	*
Rachel Sachs, JD, MPH	Washington University in St. Louis	*
Timothy Wilt, MD, MPH	Minneapolis VA Center for Chronic Disease Outcomes Research	*
Stuart Winston, DO	St. Joseph Mercy Health System	*

* No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table G3. Policy Roundtable Participant COI Disclosures

Name	Organization	Disclosures
Mario Castro, MD, MPH	Washington University School of Medicine	Receives grant funding from AstraZeneca, GSK, and Sanofi-Aventis. Consultant for Genentech, Teva, and Sanofi-Aventis. Speaker for AstraZeneca, Genentech, Regeneron, Sanofi, and Teva.
David Evan	Teva	Full-time employee of Teva.
Marsha Fisher, MD, FACOG	Anthem BCBS of Missouri	Full-time employee of Anthem BCBS of Missouri.
Mark S. Forshag, MD, MHA	GlaxoSmithKline	Full-time employee of GlaxoSmithKline.
Jeremy Fredell, PharmD, BCPS	Express Scripts	Full-time employee of Express Scripts.
Benjamin Kramer, MD	Genentech	Full-time employee of Genentech.
Andreas Kuznik, PhD	Regeneron	Full-time employee of Regeneron.
Donna J. Matlach, DMin, MM, CDA	Allergy and Asthma Network	AAN receives funding from AstraZeneca, Genentech, GSK, Sanofi Genzyme, and Teva.
Kenny Mendez, MBA	Asthma and Allergy Foundation of America	AAFA receives funding from AstraZeneca, Genentech, GSK, Sanofi/Regeneron, and Teva.
Kaharu Sumino, MD, MPH	Saint Louis VA Medical Center; Washington University School of Medicine	None.
Frank Trudo, MD, MBA	AstraZeneca	Full-time employee of AstraZeneca.

Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value

Condition Update

Final Evidence Report

August 03, 2018

Prepared for:

Important note: Per ICER's data in-confidence policy, this report was updated in October 2018 to unredact data that were previously submitted in confidence and have subsequently been published. We also updated the language regarding a preliminary vote taken during public deliberation in July 2018 that was contingent on the publication of the confidential data in a peer-reviewed journal.

ICER Staff/Consultants	University of Washington School of Pharmacy Modeling Group*
Reiner Banken, MD, MSc Senior Fellow Institute for Clinical and Economic Review **Foluso Agboola, MBBS, MPH** Director, Evidence Synthesis Institute for Clinical and Economic Review **Alexandra Ellis, MSc, AM** Senior Scientist, HTA and Economic Evaluation Institute for Clinical and Economic Review **Rick Chapman, PhD, MS** Director of Health Economics Institute for Clinical and Economic Review **Celia Segel, MPP** Director of CER Policy Development Institute for Clinical and Economic Review **Katherine Fazioli, BS** Research Assistant Institute for Clinical and Economic Review **Daniel A. Ollendorf, PhD** Chief Scientific Officer Institute for Clinical and Economic Review **Steven D. Pearson, MD, MSc** President Institute for Clinical and Economic Review	**David L. Veenstra, PharmD, PhD** Professor and Associate Director Pharmaceutical Outcomes Research and Policy Program The Comparative Health, Outcomes, Policy, and Economics Institute **Nathaniel Hendrix, PharmD** Pharmaceutical Outcomes Research and Policy Program The Comparative Health, Outcomes, Policy, and Economics Institute *The role of the University of Washington School of Pharmacy Modeling Group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of UW.

DATE OF PUBLICATION: August 03, 2018

Reiner Banken served as the lead author for the report. Foluso Agboola led the systematic review, network meta-analysis and authorship of the comparative clinical effectiveness section. Katherine Fazioli assisted with the systematic review and network meta-analysis. Rick Chapman was responsible for oversight of the cost-effectiveness analyses and developed the budget impact model. Celia Segel authored the section on coverage policies and clinical guidelines. Alexandra Ellis, Daniel Ollendorf, and Steven Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Varun Kumar, Erin Lawler and Matt Seidner for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Laura and John Arnold Foundation. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 15% of its overall revenue from these health industry organizations to run a separate Policy Forum program, with funding approximately equally split between insurers/PBMs and life science companies. For a complete list of funders and for more information on ICER's support, please visit http://www.icer-review.org/about/support/

Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org

About New England CEPAC

The New England Comparative Effectiveness Public Advisory Council (New England CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. New England CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The New England CEPAC is an independent committee of medical evidence experts from across New England, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Council members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about New England CEPAC is available at http://icer-review.org/programs/new-england-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results.

This is an ICER update. The first report was issued in December 2016 and can be found here: https://icer-review.org/material/pso-final-report/.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/psoriasis-stakeholder-list/

Expert Reviewers

Alexa B. Kimball, MD
Harvard Medical Faculty Physicians
Beth Israel Deaconess Medical Center

Conflict of Interest Declaration: *Alexa B. Kimball is a consultant for Novartis, AbbVie, UCB, Lilly, Janssen. Investigator to AbbVie, and UCB. Fellowship funding from Janssen and AbbVie. President of the International Psoriasis Council.*

Joseph F. Merola, MD MMSc
Assistant Professor, Director of the Center for Skin and Related Musculoskeletal Disease
Dept of Dermatology and Medicine Division of Rheumatology
Harvard Medical School, Brigham and Women's Hospital

Conflict of Interest Declaration: *J. F. Merola is a consultant and/or investigator for the following relevant companies: AbbVie, Amgen, Eli Lilly, Novartis, Pfizer, Janssen, UCB, Celgene.*

Leah McCormick Howard, J.D.
Chief Operating Officer
National Psoriasis Foundation

Conflict of Interest Declaration: *The National Psoriasis Foundation works with all the manufacturers that have a therapy in the psoriatic disease space, including AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, Merck, Novartis, Ortho Dermatologics, Pfizer, Sandoz, Sun Pharma, and UCB. A full list of their funders can be found in their Annual Report.*

Bram Ramaekers, PhD
Senior Researcher Health Economics
Department of Clinical Epidemiology and Medical Technology Assessment (KEMTA)
Maastricht University Medical Center

Conflict of Interest Declaration: *Bram Ramaekers did consulting for Janssen, but the consulting fee was <$5,000.*

Table of Contents

Condition Update vii
Executive Summary ES1
1. Introduction 1
1.1 Background 1
1.2 Scope of the Assessment 7
1.3 Definitions 10
1.4 Insights Gained from Discussions with Patients and Patient Groups 13
1.5. Potential Cost-Saving Measures in Psoriasis 15
2. Summary of Coverage Policies and Clinical Guidelines 16
2.1 Coverage Policies 16
2.2 Clinical Guidelines & Statements on Managing Care 19
3. Comparative Clinical Effectiveness 21
3.1 Overview 21
3.2 Methods 21
3.3 Results 25
3.4 Summary and Comment 42
4. Long-Term Cost Effectiveness 46
4.1 Overview 46
4.2 Methods 46
4.3 Results 61
4.4 Summary and Comment 69
5. Additional Considerations 72
6. Value-Based Price Benchmarks 74
7. Potential Budget Impact 75
7.1 Overview 75
7.2 Methods 75
7.3 Results 77
8. Summary of the Votes and Considerations for Policy 81

8.1 About the New England CEPAC Process....81
8.2 Voting Results....84
8.3 Key Policy Implications....89
References....96
Appendices....112
Appendix A. Evidence Review Methods and Results....113
Appendix B. Evidence Summary Tables....119
Appendix C. Previous Systematic Reviews and Technology Assessments....210
Appendix D. Ongoing Trials....216
Appendix E. Comparative Clinical Effectiveness Supplemental Information....238
Additional Comparative Clinical Effectiveness Results....242
Subgroup Analyses....245
Appendix F. Network Meta-Analysis Supplemental Information....248
Supplemental NMA Results....249
Appendix G. Comparative Value Supplemental Information....258
Appendix H. Coverage Policies in New England....260
Appendix I. Public Comments....265
Appendix J. Conflict of Interest Disclosures....268

List of Acronyms Used in this Report

AAD	American Academy of Dermatology
AE	Adverse Event
BI	Budget impact
BSA	Body Surface Area
CMS	Centers for Medicare and Medicaid Services
CUA	Cost utility analysis
DC	Discontinuation
DIC	Deviance information criterion
DLQI	Dermatology Life Quality Index
dPGA	Dynamic Physician Global Assessment
EADV	European Association for Dermatology and Venereology
ERG	Evidence Review Group
EQ-5D	EuroQol five-dimension questionnaire
GDP	Gross domestic product
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IGA	Investigator's Global Assessment
IPC	International Psoriasis Council
LY	Life year
MACE	Major adverse cardiac events
MCS	Mental component score
NHE	National Health Expenditures
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMSC	Non-melanoma skin cancer
PASI	Psoriasis Area and Severity Index
PCS	Physical component score
PDI	Psoriasis Disability Index
PGA	Physician Global Assessment
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSD	Psoriasis Symptom Diary
PSI	Psoriasis Symptom Inventory
PSOLAR	Psoriasis Longitudinal Assessment and Registry
PUVA	Psoralen and ultraviolet A radiation
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
Resdev	Residual deviance
SF-36	Short Form-36
sPGA	Static Physician Global Assessment
TB	Tuberculosis
TNF	Tumor necrosis factor
USPSTF	U.S. Preventative Services Task Force
UVB	Ultraviolet B
VAS	Visual Analog Scale
WAC	Wholesale acquisition cost
WLQ	Work Limitations Questionnaire
WPAI	Work Productivity and Activity Impairment
WPI	Worker Productivity Index

Condition Update

In November 2016, the New England CEPAC Panel deliberated on the available evidence to help patients, clinicians, and payers address important questions related to the use of targeted immunomodulators for the treatment of patients with moderate-to-severe chronic plaque psoriasis. Following the evidence presentation and public comments, the New England CEPAC Panel voted on key questions concerning the comparative clinical effectiveness and comparative value of these agents. The final 2016 report can be found here.

Since the publication of the report in 2016, four new drugs have been approved, and one drug is under FDA review for this condition. One of the drugs, brodalumab, was included in our 2016 review, but was not yet approved at the time of our deliberations. The other two drugs, guselkumab and tildrakizumab, were not included and specifically target IL-23, which represents a novel method of action. Certolizumab pegol, a TNFα inhibitor already approved by the FDA for other autoimmune conditions, is now approved for plaque psoriasis. Finally, risankizumab, another novel IL-23 inhibitor, was filed with the FDA for review on April 25, 2018.

ICER has therefore decided to revisit its 2016 report in a "Condition Update" for adults with moderate-to-severe plaque psoriasis. In our Condition Update, we have performed a full systematic review of new treatments that have emerged since our 2016 report and have identified new evidence that has emerged on the treatments already included in the original assessment. In the following report, we integrate these new data in updated syntheses of the clinical evidence as well as our evaluations of long-term cost-effectiveness and budgetary impact.

Executive Summary

Background

Psoriasis is a cell-mediated autoimmune and inflammatory disease[1,2] that affects about 3% of the population.[3,4] Plaque psoriasis accounts for about 80% to 90% of all patients with psoriasis[5-7] and manifests itself through itchy pruritic, red, scaly, raised lesions on the skin.[8] Up to 30% of patients with plaque psoriasis have at least some manifestations of psoriatic arthritis,[9-11] Psoriasis is associated with systemic diseases, including other autoimmune diseases (e.g., inflammatory bowel disease), metabolic syndrome, and cardiovascular disease.[12,13] Psoriasis itself is not a direct cause of increased mortality, but patients with severe psoriasis have increased mortality due to cardiovascular disease and infection.[10,14] Patients are considered to have a "moderate-to-severe" degree of plaque psoriasis when the disease affects more than 5% to 10% of a patient's body surface; produces lesions that have significant redness, thickness, and scale; or significantly reduces quality of life (e.g., lesions on the face, palm, or soles of the feet).[15,16]

Roughly 70% to 80% of patients with plaque psoriasis have mild disease that can be adequately managed with topical therapy, including emollients; topical corticosteroids, vitamin D analogs, coal tar products, topical retinoids and topical calcineurin inhibitors, or managed with phototherapy, most commonly narrow-band ultraviolet B light (NBUVB). Before the advent of targeted immunomodulators that are assessed in the current report, patients whose psoriasis was inadequately controlled with topical therapy or phototherapy had little choice but to take older systemic therapies, such as cyclosporine and methotrexate, that can have important side effects.

Targeted immunomodulators include monoclonal antibodies that reduce the level of pathogenic cytokines, specifically tumor necrosis factor-α (TNF-α) and interleukin (IL)-23 and IL-17, and the PDE4 inhibitor apremilast that reduces the production of proinflammatory mediators.[2] Monoclonal antibodies are part of the class of drugs called biological products or biologics: large, complex molecules that are produced through biotechnology in a living system, such as a microorganism.[17] The FDA now refers to the first approved specific biologic product as the "Reference Product," (often simply called a "Biologic"), and subsequent versions are known as "Biosimilars". When approving a biosimilar, the FDA determines that there are no clinically meaningful differences from an existing FDA-approved reference product.[17]

The 2016 report estimated the monthly drug acquisition costs for targeted immunomodulators to be about 3-4 times more expensive than for non-targeted therapy.[18] Considering the effectiveness of these therapies, the cost of treatment was found to be within generally accepted thresholds of cost-effectiveness. This update attempts to capture not only evidence on the comparative clinical effectiveness and value of new treatments for plaque psoriasis, but also an updated view on existing agents given the availability of new evidence and changes in price.

Table ES1 provides an overview of the targeted immunomodulators approved or under review by the FDA for the treatment of moderate-to-severe plaque psoriasis. Of note, several of these agents are newly available or under FDA review since ICER's 2016 report, including three agents in a new class of selective IL-23 inhibitors (guselkumab, tildrakizumab, and risankizumab), as well an IL-17 inhibitor (brodalumab), a TNFα inhibitor (certolizumab pegol), and a second biosimilar for the TNFα inhibitor infliximab.

Table ES1. Targeted Immunomodulators for Moderate-to-Severe Plaque Psoriasis[1]

Mechanism of Action	Name and Company	FDA approval for plaque psoriasis	Market availability	FDA recommended dosing
TNFα	adalimumab / Humira® AbbVie	Reference Biologic 2008/01/18	Available	80mg subcutaneously, then 40mg every other week starting 1 week after initial dose
	etanercept / Enbrel® Amgen	Reference Biologic 2004/04/30	Available	50mg subcutaneously 2x/week for 3 months, then 50mg 1x/week
	infliximab (dyyb/abda) Remicade® | Janssen Inflectra® | Pfizer Renflexis® | Merck	Reference Biologic: 2006/09/26 Biosimilars: 2016/04/05 2017/04/24	Available	5mg/kg intravenously at weeks 0, 2, and 6, then every 8 weeks
	certolizumab pegol / Cimzia® UCB	Reference Biologic, 2018/05/28	Available	400mg subcutaneously at weeks 0, 2, and 4, then either 400mg every 2 weeks or for some patients (with body weight ≤ 90 kg) 200mg every 2 weeks
IL 12/23	ustekinumab / Stelara® Janssen	Reference Biologic 2009/09/25	Available	Patients ≤100kg/>100kg: 45mg/90mg subcutaneously at week 0 and 4, then every 12 weeks
IL 23	guselkumab/ Tremfya® Janssen	Reference Biologic 2017/07/13	Available	100mg subcutaneously at weeks 0, week 4, then every 8 weeks
	tildrakizumab-asmn / Ilumya® Sun/Merck	Reference Biologic 2018/03/20	Not yet launched	100 mg subcutaneously at weeks 0, 4, then every twelve weeks
	risankizumab AbbVie	Submitted to the FDA on April 25, 2018	n/a	n/a
IL 17	secukinumab / Cosentyx® Novartis	Reference Biologic 2015/01/21	Available	300mg subcutaneously at weeks 0, 1, 2, 3, 4 then 300mg every 4 weeks
	ixekizumab / Taltz® Eli Lilly	Reference Biologic, 2016/03/22	Available	160mg subcutaneously at week 0, then 80mg at weeks 2, 4, 6, 8, 10, 12, then 80mg every 4 weeks
	brodalumab / Siliq® Valeant	Reference Biologic 2017/02/15	Available	210mg subcutaneously at weeks 0, 1 and 2, then every 2 weeks*
PDE-4	Apremilast / Otezla® Celgene	Reference Biologic 2014/09/23	Available	5-day titration then 30mg orally 2x/day thereafter

[1] This table includes all reference biologics approved or submitted for approval, but only the 2 biosimilars that are currently available. Four other biosimilars have been FDA approved, but are not available mainly due to patent litigation.[19,20]

For many of these agents, there is some suggestion of waning effectiveness with continued use, known as biologic fatigue.[21] To maintain effectiveness, physicians often prescribe increasing doses of targeted immunomodulators. On the other hand, physicians occasionally prescribe *lower* doses of effective medications to decrease out-of-pocket costs. Patients switching from one biologic to another may have a slightly lower response rate, however this has not been consistently demonstrated.[22]

General safety concerns for targeted immunomodulators primarily relate to effects on the immune system: a range of infections, including tuberculosis, and malignancies, especially skin cancer and lymphoma. Specifically, the use of TNFα agents is associated with increased risk of reactivation of latent tuberculosis infections. But overall, registry studies have shown that increased risks of major adverse cardiovascular events and cancer, especially lymphoma and nonmelanoma skin cancer, initially attributed to biologic therapy, are most likely related to psoriasis itself and not to its treatment.[23,24] Evidence on the safety of specific agents will be further discussed in Section 3.

Insights Gained from Discussions with Patients and Patient Groups

In the development of the 2016 report,[25] ICER had conversations with and received input from patient advocacy groups, including the National Psoriasis Foundation, and individual patients.[26] These conversations highlighted the shortcomings associated with clinical trial outcomes in many studies of psoriasis therapies, frustrations with the healthcare system, as well as the social, emotional, and financial impact of psoriasis. These issues were presented by the National Psoriasis Foundation at the ICER public meeting on the topic.[27,25] A discussion of the shortcomings associated with clinical trial outcomes in many studies of psoriasis therapies can be found in section 1.4 of this report.

Stigma of disease

- People seeing the lesions conclude the patient has a communicable disease.
- Choices of clothing to hide psoriatic skin.
- Avoidance of certain activities such as swimming.
- Children with psoriasis, especially teens, face teasing, bullying, and shunning.
- Psoriasis is associated with a higher likelihood of having depression, anxiety, and suicidal ideation.

Difficulties with treatments

- Time from onset to diagnosis averages two years, even more in patients with darker skin tones.

- Difficult to apply topical therapies, especially when the affected area involves the scalp or covers a large part of the body.
- Multiple injections on a daily or weekly basis, especially initially, during induction.
- Time and travel for administration of phototherapy and infused therapy.

Problems with coverage

- Requirements for "step therapy" forcing patients to start treatment with less efficacious medications.
- Lack of clarity in the exception process and timing for physicians and patients.
- Patients have to "start over" with "step therapy" of previously-tried medications after switching insurance.
- High out of pocket costs hindering treatment or leading to undertreatment.

Potential Cost-Saving Measures in Psoriasis

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for people with psoriasis that could be reduced, eliminated, or made more efficient.

We did not receive any suggestions in response to the final scoping document or draft report. We also did not identify recommendations specific to the management of plaque psoriasis from professional organizations such as Choosing Wisely, the American Academy of Dermatology, or the US Preventive Services Task Force.

Comparative Clinical Effectiveness

To inform our analysis of the comparative clinical effectiveness of targeted immunomodulators for moderate-to-severe psoriasis, we abstracted evidence from available clinical studies. We included all articles from our 2016 review. We updated our previous search strategy to include new evidence on the drugs in the 2016 review; and added in the four new drugs (guselkumab, tildrakizumab, risankizumab and certolizumab pegol). Our updated literature search identified 17 RCTs. In addition, we included all 36 individual RCTs from the previous review, to make a total of 53 RCTs.

Trials were rated to be of good or fair quality using criteria from U.S. Preventive Services Task Force (USPSTF).[28] We did not assign a quality rating to two trials that were available only in the grey

literature (one placebo controlled trial of risankizumab and one head-to-head trial between secukinumab and ustekinumab). Characteristics of the trials for the new agent are presented in Table ES2 (See full report for characteristics of all Phase III trials).

Trial populations included patients with moderate-to-severe plaque psoriasis despite generally having used topical treatments, older systemic treatments, phototherapy, or other targeted immunomodulators. Trials required washout of prior therapies and participants not to use non-trial treatments. Use of other treatments was prohibited in the interest of directly evaluating the comparative effectiveness of targeted immunomodulators to placebo or to one another.

The primary outcome for all RCTs of targeted immunomodulator therapy was assessed at the end of the induction period (between 10 and 16 weeks after initiation, depending on agent), after which treatment crossover was typically allowed. Because of this, we could only confidently compare the comparative efficacy of targeted immunomodulators at the end of the induction period. Long-term effectiveness and safety data were variably reported by individual drug.

Table ES2. Certolizumab Pegol, Guselkumab, Tildrakizumab and Risankizumab Phase III Trials

Drug	Trials	Total patients	Induction period (weeks)	PASI, (mean)	Age (years)	Psoriasis duration (years)	Previous biologics, %	PsA, %
Certolizumab Pegol [29,30]	CIMPASI 1 CIMPASI 2 CIMPACT†	1,020	16/12	20	46	18	30	18
Guselkumab[31,32]	VOYAGE 1† VOYAGE 2†	1,829	16	22	44	18	21	19
Tildrakizumab[33]	RESURFACE 1† RESURFACE 2†	1, 862	12	20	46	NR	17	NR
Risankizumab [34 35]	UltIMMA 1† UltIMMA 2† IMMhance*	1,504	16	20	48	NR	42	NR

*Only available in the grey literature as of September 2018; †Placebo controlled trials with active comparators (others are placebo controlled); See Table 3.1 in main report for complete list of all Phase III trials

Clinical Benefits

Psoriasis Area and Severity Index (PASI)

The Psoriasis Area and Severity Index (PASI) was reported as the primary measure of clinical benefit in all trials. PASI is a measure of the percent body surface area with psoriatic lesions in each of four regions (head, trunk, arms, and legs) as well as the degree of erythema, induration, and scale of the lesions in each area. The primary endpoint for most trials was the proportion of patients achieving PASI 75 (a 75% reduction in the PASI score) at the end of the induction period. However, five new trials relating to guselkumab (VOYAGE 1 &2) and risankizumab (ULTIMMA 1 & 2, IMMHANCE); one head-to-head trial between ixekizumab and ustekinumab (IXORA-S), and two head-to-head trials

between secukinumab and ustekinumab [CLEAR and CLARITY] specified PASI 90 as their primary endpoint.

All targeted immunomodulators showed statistically-significantly higher PASI 75, PASI 90 and PASI 100 response rates in comparison to placebo at the end of induction. In individual placebo-controlled RCTs, the incremental proportion of patients achieving PASI 75 above placebo within trials was 61% to 69% for certolizumab pegol (three trials); [36,37] 78% to 85% for guselkumab (two trials);[31,32] 56% to 60% for tildrakizumab (two trials);[33] and 80% to 85% for risankizumab (three trials).[35,38] In direct comparative trials of the new agents, guselkumab was superior to adalimumab; tildrakizumab and 400mg certolizumab pegol was superior to etanercept; and risankizumab was superior to ustekinumab (see Table ES3). However, 200mg certolizumab pegol was not significantly different from etanercept (see Table ES3).

Direct comparative trials of the older agents showed that ustekinumab, secukinumab, ixekizumab and infliximab were superior to etanercept; secukinumab, ixekizumab, and brodalumab were superior to ustekinumab (see report for details).

Given the paucity of head-to-head data comparing treatments, we performed indirect comparisons of PASI response using Bayesian network meta-analyses (NMAs). Further details on these methods are available in the full report. On relative effectiveness of the PASI measures (measured as relative risk (RR) of achieving PASI 75 or 90 responses during induction), the result showed that two of the IL-23 agents (risankizumab and guselkumab), all three IL-17 agents (ixekizumab, brodalumab and secukinumab), and infliximab all had similar effectiveness on PASI response. These agents did not differ statistically, as the likelihood of achieving PASI 75 or PASI 90 response included 1.0 (no difference) in the 95% credible intervals (see Table ES4). These agents were statistically significantly more effective in terms of PASI 75 and PASI 90 outcomes than adalimumab, ustekinumab 45/90 mg, certolizumab pegol 200/400mg, tildrakizumab, etanercept and apremilast. Adalimumab, ustekinumab 45/90 mg, certolizumab 200mg/400mg, and tildrakizumab did not differ significantly, and all were significantly better than etanercept and apremilast.

Table ES3. Comparative Trials: PASI Responses

Trial	Treatment	PASI 75	p-value	PASI 90	p-value	PASI 100	p-value
New Drugs							
VOYAGE 1	Adalimumab	73	<0.001	50	<0.001	21	<0.001
	Guselkumab	91		73		37	
VOYAGE 2	Adalimumab	69	<0.001	47	<0.001	17	<0.001
	Guselkumab	86		70		34	
CIMPACT	Etanercept	53		27.1		NR	
	Certolizumab 200mg	61	NS	31.2	NR	NR	NR
	Certolizumab 400mg	67	0.02	34		NR	
RESURFACE 2	Etanercept	48	<0.001	21	<0.001	5	<0.001
	Tildrakizumab	61		39		12	
ULTIMMA 1	Ustekinumab	76	0.003	42	<0.001	12	<0.001
	Risankizumab	89		75		36	
ULTIMMA 2	Ustekinumab	70	<0.0001	48	<0.001	24	<0.001
	Risankizumab	91		75		51	
New Evidence on Old Drugs							
PIECE	Etanercept	22	0.0	0	0.05	0	NS
	Infliximab	76		20		4	
CLARITY*	Ustekinumab	74	<0.0001	48	<0.0001	20	<0.0001
	Secukinumab	88		67		38	

NR- not reported; See Appendix E for other comparative trials

Table ES4. Base Case NMA: League Table of PASI 75 Response

Risankizumab											
1.00 (0.96, 1.05)	**Ixekizumab**										
1.02 (0.96, 1.08)	1.01 (0.96, 1.07)	**Guselkumab**									
1.03 (0.98, 1.09)	1.03 (0.98, 1.08)	1.02 (0.96, 1.07)	**Brodalumab**								
1.07 (1.02, 1.14)	**1.07 (1.02, 1.13)**	1.06 (0.99, 1.13)	1.04 (0.99, 1.1)	**Secukinumab**							
1.12 (1.04, 1.22)	**1.11 (1.05, 1.21)**	**1.1 (1.02, 1.2)**	**1.09 (1.02, 1.18)**	1.04 (0.97, 1.12)	**Infliximab**						
1.26 (1.17, 1.38)	**1.25 (1.16, 1.38)**	**1.24 (1.15, 1.35)**	**1.22 (1.13, 1.34)**	**1.17 (1.08, 1.28)**	**1.12 (1.03, 1.24)**	**Adalimumab**					
1.26 (1.18, 1.37)	**1.26 (1.18, 1.36)**	**1.24 (1.16, 1.35)**	**1.23 (1.15, 1.32)**	**1.18 (1.11, 1.26)**	**1.13 (1.05, 1.22)**	1.01 (0.93, 1.08)	**Ustekinumab†**				
1.3 (1.18, 1.47)	**1.29 (1.18, 1.46)**	**1.28 (1.17, 1.44)**	**1.26 (1.15, 1.41)**	**1.21 (1.1, 1.35)**	**1.16 (1.05, 1.3)**	1.03 (0.94, 1.15)	1.03 (0.94, 1.14)	**Certolizumab‡**			
1.42 (1.26, 1.66)	**1.42 (1.26, 1.66)**	**1.4 (1.24, 1.64)**	**1.38 (1.23, 1.6)**	**1.32 (1.17, 1.54)**	**1.27 (1.12, 1.47)**	1.13 (1, 1.31)	1.13 (1, 1.29)	1.1 (0.95, 1.27)	**Tildrakizumab**		
1.74 (1.54, 1.98)	**1.74 (1.55, 1.98)**	**1.71 (1.52, 1.95)**	**1.69 (1.51, 1.92)**	**1.62 (1.45, 1.82)**	**1.55 (1.4, 1.73)**	**1.38 (1.25, 1.54)**	**1.37 (1.27, 1.5)**	**1.34 (1.2, 1.5)**	**1.22 (1.07, 1.38)**	**Etanercept**	
2.44 (1.98, 3.12)	**2.43 (1.97, 3.11)**	**2.4 (1.95, 3.03)**	**2.37 (1.92, 3)**	**2.28 (1.85, 2.87)**	**2.18 (1.78, 2.75)**	**1.94 (1.61, 2.4)**	**1.93 (1.6, 2.38)**	**1.88 (1.54, 2.34)**	**1.71 (1.39, 2.14)**	**1.4 (1.17, 1.71)**	**Apremilast**
16.54 (12, 23.47)	**16.53 (11.94, 23.32)**	**16.27 (11.76, 22.9)**	**16.05 (11.63, 22.59)**	**15.43 (11.33, 21.42)**	**14.81 (10.97, 20.31)**	**13.12 (9.91, 17.67)**	**13.08 (9.93, 17.48)**	**12.74 (9.5, 17.03)**	**11.6 (8.84, 15.5)**	**9.51 (7.6, 12.09)**	**6.74 (5.3, 8.68)**

Legend: The interventions are arranged from most effective (top left) to least effective (bottom right). Each box represents the estimated relative risk and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

†dosing by weight;

‡200 mg and 400 mg combined

PBO: placebo

Other Outcome Measures

Physician Global Assessment (PGA) or Investigators Global Assessment (IGA) were generally consistent with the PASI results. All immunomodulators showed statistically significantly higher PGA or IGA of 'clear/almost clear' than placebo at the primary endpoint of each trial. In head-to-head trials of the new drugs, guselkumab was superior to adalimumab (85% vs. 66% in VOYAGE 1 and 84% vs. 64% in VOYAGE 2; p<0.001); [31,32] and risankizumab was superior to ustekinumab (63% vs. 88% in ULTIMMA 1 and 62% vs. 84% in ULLTIMMA 2). [34,35] Tildrakizumab was not significantly different from etanercept, and no inferential statistical comparison was conducted between certolizumab and etanercept on PGA scores.

Dermatology Life Quality Index (DLQI) results were also generally consistent with the PASI results. All targeted immunomodulators statistically significantly improved quality of life relative to placebo. In the head-to-head comparisons of the new drugs, guselkumab achieved a statistically significantly greater improvement on DLQI than adalimumab at 16 weeks in two trials (Mean DLQI change: 11.2 to 11.3 for guselkumab vs. 9.3 to 9.7 for adalimumab; p<0.001).[31,32] In addition, significantly greater proportion of patients on guselkumab achieved DLQI 0/1 (indicating very little to no effect on quality of life) compared to adalimumab (52% to 56% vs. 39%; p<0.001).[31,32] Similarly, significantly greater proportion of patients on risankizumab achieved DLQI 0/1 following induction period compared to patients on ustekinumab (66% vs. 43% in two trials; p<0.001).[34,35] However, there was no significant difference between tildrakizumab and etanercept at 12 weeks.[33] We found no head-to-head DLQI evidence reported between certolizumab pegol and etanercept in CIMPACT.

Measures of symptom control were inconsistently reported across trials and used a variety of instruments. For example, based on the Psoriasis Symptom and Sign Diary (PSSD), guselkumab demonstrated a statistically significant benefit over placebo [31,32] but this measure was not presented in any of the other new trials we identified.

Harms

Most adverse events were mild or moderate during the induction phase of treatment (See Table 3.7 in main report). Severe or serious adverse events, death, and AEs leading to discontinuation were rare and generally comparable between the treatment and placebo groups. The most common AEs in the clinical trials included mild infections (e.g. nasopharyngitis, upper respiratory tract infections, etc.), injection site reactions for subcutaneously administered drugs, headache, and nausea. There was no evidence of increased risk of serious infections or malignancies in the placebo-controlled trials. Incident rates of candidiasis and other opportunistic infections were reported to be low and comparable between groups in all trials. There were no reports of tuberculosis, demyelinating disease, or lymphoma in the clinical trials. We also did not find differences in the risk of major adverse cardiac events (MACE). Of note, five of the agents included in our review have boxed warnings included in their FDA label: All TNF-α therapies (adalimumab, etanercept, infliximab, and certolizumab pegol) have boxed warning for serious infections and malignancy based on findings from rheumatoid arthritis trials, while brodalumab has a boxed warning for suicidal ideation and behavior based on finding from a psoriasis clinical trial.[39]

The types and patterns of AEs reported for these agents at longer timepoints (48-52 weeks) were similar to those reported during the placebo-controlled periods. In addition, comparative trials reported generally similar rates and types of AEs. As expected, there is currently no long-term safety observational data for any of the newer agents.

Controversies and Uncertainties

Across the 48 key trials identified for this review, 16 were based on head-to-head comparisons of the drugs of interest. Our network meta-analyses of PASI response are largely driven by indirect evidence; however, our findings are consistent with the results of head-to-head studies as well as with our assessment of relative differences in PASI response in comparison to placebo. Our NMA findings are also comparable to other recent assessments of the evidence.[40,41] Although PASI 75 or PASI 90 was reported as the primary endpoint in nearly all studies, other clinical outcomes (such as PGA, IGA, DLQI, measures of symptom control) were inconsistently reported across trials making cross-drug comparisons difficult. For example, DLQI was evaluated in just about half of the included trials, and not all trials used the same standard of measurement, and other scales were not uniformly employed. Additionally, many of the tools developed to measure outcomes were not developed in a patient-centered perspective, and psoriasis-specific instruments are limited.

Longer-term data on both drug effectiveness and harms were also variable across trials; many studies reassigned patients to different groups (mostly cross-over to the intervention) and evaluated outcomes at different time periods. As such, we could only confidently compare the comparative efficacy of targeted immunomodulators at the end of the induction period.

Finally, subgroup data were primarily reported in conference abstracts, and the interventions were only compared statistically to placebo, thereby limiting our understanding of how outcomes may differ across population types (e.g., patients with psoriatic arthritis or prior biologic experience). Concerning the choice of the appropriate first-line biologic therapy, there are current evidence-based recommendations available for some comorbid conditions in clinical practice. For example, in the presence of severe psoriatic arthritis, TNFα inhibitors are recommended to be the preferred options, while they are to be avoided for patients with comorbid multiple sclerosis.[42] Expert opinion, clinical judgment and patient preferences will often determine the choice of the most appropriate therapeutic option for many comorbidities.[42] Future studies should be pragmatic in nature, including patients with these type of comorbid conditions encountered in routine clinical practice.

Summary and Comment

Using the ICER evidence rating matrix, our evidence ratings for the comparisons of interest are provided in Table ES5; ratings are presented for the targeted immunomodulator listed in each row relative to the comparator listed in each column. Note that comparisons to placebo are not included in the table. As described previously, findings from placebo-controlled trials indicated substantial improvements in clinical measures for all agents. The safety of any new therapy is an important consideration. Severe or serious adverse events were rare during short-term trials and extension studies on these agents. So, all targeted immunomodulator receive a letter grade of "A" (i.e., high certainty of substantial net health benefit) relative to placebo.

The presence of some direct comparisons allowed us to be reasonably confident about the relative net health benefit for these comparisons. However, because of the lack of many head-to-head comparisons, we relied on a network meta-analysis to estimate the comparative clinical effectiveness between many targeted immunomodulators (see Appendix F). Ratings based on a combination of direct and indirect evidence are highlighted in green in the table along with the number of head-to-head studies that informed the rating.

ICER Ratings

There were two head-to-head trials comparing guselkumab and adalimumab (VOYAGE 1 &2), both of which showed incremental benefit for guselkumab over adalimumab in the percentage of patients achieving various PASI thresholds, PGA/IGA response, and DLQI outcome. In addition, there was a similar magnitude of benefit when indirect evidence was included. We felt that the consistency of results across the two trials represented *high certainty* of a small net benefit for guselkumab ("B") and an inferior net health benefit ("D") for adalimumab in this comparison.

Similarly, evidence from two trials (ULTIMMA 1 & 2) comparing risankizumab to ustekinumab consistently showed greater benefit for risankizumab on various PASI thresholds, PGA/IGA response

and DLQI outcome. The magnitude of benefit when the indirect PASI evidence was included, gave us a *high certainty* of a small net benefit for risankizumab ("B") when compared to ustekinumab.

In the one head-to-head comparisons between tildrakizumab and etanercept (RESURFACE 2), tildrakizumab resulted in a modestly better PASI outcome (supported by network meta-analysis), and no difference on PGA and DLQI outcome, so we judged the evidence of tildrakizumab versus etanercept to represent a comparable or better net health benefit ("C+"), and "C-" (comparable or inferior) for etanercept in this comparison.

The one head-to-head trial comparing certolizumab pegol and etanercept (CIMPACT) was a single-blind study which found no statistically significant difference between the two agents on PASI outcomes when using 200mg certolizumab pegol, but significantly better response when using 400mg certolizumab pegol. Inclusion of indirect evidence combining both the 200mg and 400mg arms yielded a significant improved outcome for certolizumab over etanercept. However, we have very limited evidence on the PGA and DLQI outcomes from this study. As such, we rated the evidence "C+" (comparable or better) for certolizumab pegol and "C-" (comparable or inferior) for etanercept in this comparison.

Ratings based on indirect evidence alone are highlighted in blue in the table. For these ratings, results of the network meta-analyses represented the only guide with which to judge the evidence. Drugs with evidence of net health benefit were judged "B+" or "C+" based on the observed magnitude of benefit, and their comparators received an "C-"rating (moderate certainty of comparable or inferior net health benefit). In situations where the credible interval (the Bayesian equivalent of the confidence interval) crossed 1.0, the evidence was rated I (insufficient) for both directions of the comparison.

We also considered the 'second-order' effect in our evidence ratings. For example, since we have *moderate certainty* of an incremental or better net health benefit of risankizumab over ustekinumab, and moderate certainty that ustekinumab provides an incremental or better benefit over etanercept and apremilast, we conclude that there is moderate certainty that risankizumab would also provide an incremental benefit over etanercept or apremilast.

ICER Rating on the Drugs Included in the 2016 Review

Our ratings on the existing drugs evaluated in the 2016 review remain unchanged, except in three instances. The first is the rating of secukinumab versus adalimumab, which we originally rated as "I" based on indirect evidence. We have now changed the rating to "C+" based on the result of the updated NMA that shows evidence of net health benefit. The second is the rating of secukinumab versus ustekinumab. This has now changed from C+ to B based on the addition of a second trial and the results of the NMA. The third is a comparison of infliximab versus etanercept. In this instance, the rating between the two drugs did not change from a B+, however, it is now highlighted in green in the table because we found data from one head-to-head trial which provides additional direct evidence.

Table ES5. ICER Evidence Ratings for Available Head-to-Head Comparisons (New ratings based on the current review are in bold fonts)

Treatment	Comparator								New comparators			
	Adalimumab	Apremilast	Brodalumab	Etanercept	Infliximab	Ixekizumab	Secukinumab 300	Ustekinumab 45/90	**Certolizumab pegol**	**Guselkumab**	**Risankizumab**	**Tildrakizumab**
Adalimumab	-	B+	C-	C+	C-	C-	**C-***	I	**I**	**D (2)**	**C-**	**I**
Apremilast	C-	-	D	I	C-	C-	C-	C-	**C-**	**C-**	**C-**	**C-**
Brodalumab	C+	B	-	B	I	I	I	B (2)	**C+**	**I**	**I**	**C+**
Etanercept	C-	C+	D	-	**C- (1)†**	D (2)	C- (1)	C- (1)	**C- (1)**	**C-**	**C-**	**C-(1)**
Infliximab	C+	B+	I	**B+ (1)†**	-	I	I	C+	**C+**	**I**	**I**	**C+**
Ixekizumab	C+	B+	I	A (2)	I	-	C+	B+ (1)	**C+**	**I**	**I**	**C+**
Secukinumab 300	**C+***	B+	I	B+ (1)	I	C-	-	**B (2)**	**C+**	**I**	**I**	**C+**
Ustekinumab 45/90	I	B+	D (2)	B+ (1)	C-	C- (1)	**D (2)**	-	**I**	**C-**	**D (2¥)**	**I**
New agents												
Certolizumab pegol	**C-**	**B+**	**C-**	**C+ (1)**	**C-**	**C-**	**C-**	**I**	-	**C-**	**C-**	**I**
Guselkumab	**B (2)**	**B+**	**I**	**C+**	**I**	**I**	**I**	**C+**	**C+**	-	**I**	**C+**
Risankizumab	**C+**	**B**	**I**	**B**	**I**	**I**	**I**	**B (2¥)**	**C+**	**I**	-	**C+**
Tildrakizumab	**I**	**B+**	**C-**	**C+ (1)**	**C-**	**C-**	**C-**	**I**	**I**	**C-**	**C-**	-

Note: The table should be read row-to-column. For example, there is moderate certainty that adalimumab has a small net benefit compared to apremilast (B+). Conversely, there is moderate certainty that the point estimate for comparative net health benefit of apremilast is either comparable or inferior to adalimumab (C-).

Table key: green=direct + indirect evidence; blue=indirect evidence only

Number of head-to-head studies in parentheses

*Rating of secukinumab vs. adalimumab changed from the previous review from I to C+ based on the result of the updated NMA;

†Rating of infliximab vs. etanercept did not change from previous report, however the rating is now highlighted in green in the table because we found evidence on 1 head-to-head trial;

Long-Term Cost Effectiveness

We estimated the cost-effectiveness of treatments for patients with moderate to severe plaque psoriasis who have failed topical treatment, methotrexate, and phototherapy. Our base case analysis was conducted from a health sector perspective. All treatments included in the NMA were included in the primary analysis of the cost-effectiveness model, except for risankizumab and tildrakizumab, for which pricing data were not available at time of the analysis; threshold prices were calculated for all drugs.

As in our 2016 report on targeted immunomodulators, we developed a decision-analytic model based on the York psoriasis cost-effectiveness model. Our model used monthly cycle lengths and was run over ten-year and lifetime time horizons, both using a 3% annual discount rate for costs and outcomes. In the model, each month patients can move between health states defined by PASI response and the treatment they are receiving. After the initiation period of first-line targeted therapy (typically 12-16 weeks), patients were categorized into one of four health states based on their percent improvement in PASI score over baseline: PASI 90 and higher, PASI 75-89, PASI 50-74, and PASI <50.

Patients with a PASI improvement of at least 75% after the initiation periods continued on first-line therapy after the initiation period. We applied a drug-specific discontinuation rate to each initial targeted drug that accounted for discontinuation due to all causes (e.g., loss of efficacy, development of adverse effects) after the end of the initiation period; these rates differed between the first and subsequent years of treatment. After discontinuing first-line treatment, patients transitioned to either second line targeted therapy or non-targeted therapy.

Efficacy estimates for first-line targeted therapy were derived from the network meta-analysis. Second-line targeted therapy estimates were derived from available literature data, as were drug discontinuation rates. Utility (quality of life) estimates were based on correlations between PASI response and the EQ-5D instrument in multiple randomized controlled trials.

Drugs used for second-line targeted therapy varied based on first-line targeted treatment: those patients taking an IL-17 drug switched to guselkumab; patients using guselkumab switched to a market basket representing the average of all IL-17 drugs; all other patients switched to a market basket of all IL-17 drugs plus guselkumab. Risankizumab and tildrakizumab were not included in the market basket because drug prices were not available at the time of the report.

We made the following key model assumptions:

- Patients do not transition between effectiveness (PASI improvement) levels in the base case.
- Probability of discontinuing first-line therapy is drug-specific as supported by available data.

- All discontinuation in the first year is due to lack of effectiveness at the end of the initiation period, except for infliximab.
- Probability of discontinuing newer drugs (brodalumab, certolizumab pegol, guselkumab, ixekizumab, tildrakizumab) is the same as ustekinumab in years 2+.
- Seventy-five percent of patients discontinuing first line targeted drug therapy receive second-line targeted drug and the remainder receive non-targeted drug.
- Second-line targeted treatment was assumed to vary by first-line treatment as follows: patients receiving an IL-17 drug first-line receive guselkumab second-line; patients receiving guselkumab first-line receive a market basket equivalent to the average of all IL-17 drugs second-line; patients receiving any other first-line drug receive a market basket equivalent to the average of all IL-17 drugs plus guselkumab.
- Second-line targeted treatments have a 10% lower probability of achieving PASI 75-100 (i.e., 5% lower probability of PASI 75-89, 5% lower probability of PASI 90-100, 5% higher probability of PASI 50-74, and 5% higher probability of PASI < 50).
- Mortality in the model was not disease-specific and was age based.
- Patients remain on first-line therapy during the trial period.
- Subcutaneous drugs are administered in-clinic during the initiation dose and by the patient themselves during the maintenance period.
- Drug cost discount was applied on a drug-by-drug (rather than class) basis. Guselkumab received the average discount of all drugs included in this report (33%).
- No additional months in PASI states > 0% improvement, on average, are attributable to non-targeted treatment.

A comprehensive list of model assumptions along with rationales for each assumption are available in section 4.2 of the main report.

With the exception of infliximab, net pricing estimates for all reviewed drugs were derived from SSR Health, LLC, which combines data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs to derive a net price. The derived net price is at the unit level and across all payer types.[43] Infliximab, which, because it is administered in-office or clinic, is priced based on Average Sales Price (ASP) plus a mark-up of 9.5%.[44] We used drug-specific rebates, in contrast to our 2016 report that used drug class-based rebates, because rebates varied within classes – likely due to variability in list pricing strategies and product profiles.

We used initiation and maintenance dosing from drug labels, averaged to a daily dose and multiplied by 30.44 (average number of days per month) to calculate expected doses per cycle. We assumed an average patient weight of 90kg based on patients enrolled in clinical trials for weight-based regimens; we estimated thirty percent of patients received a higher dose of ustekinumab;

one-half of certolizumab patients based on our assumed average weight and labeled dosing guidelines received a higher dose; and that infliximab patients used five full vials for each dose. Targeted drug costs are presented below in Table ES6. Drug administration and monitoring costs were also included in the model; prices for administration and monitoring were obtained from the CMS Medicare Physician Fee Schedule for Year 2017.[45] Detailed explanations of model inputs are presented in section 4 of the report.

Table ES6. Drug Cost Inputs

Intervention	Unit	WAC per Unit/Dose*	Discount %	Net price per Unit	Cost of first year	Annual cost of year 2+
Adalimumab	40 mg	$2,436.02	31%	$1,674.64	$46,751.16	$43,693.75
Apremilast	30 mg	$54.72	22%	$42.46	$30,807.28	$31,019.58
Brodalumab	210 mg	$1,750.00	20%	$1,400.00	$37,684.00	$36,528.00
Certolizumab pegol	400 mg (see above for dosing note)	$4,044.32	36%	$2,583.70	$54,097.14	$50,559.32
Etanercept	50 mg	$1,218.00	31%	$837.69	$54,641.32	$43,713.06
Guselkumab	100 mg	$10,158.52	33%	$6,806.21	$50,609.02	$44,395.93
Infliximab	450 mg	$1,167.82	22%**	$911.99	$38,466.44	$29,743.90
Ixekizumab	80 mg	$5,161.60	44%	$2,888.74	$51,374.18	$37,685.68
Secukinumab	300 mg	$4,712.38	38%	$2,926.22	$49,624.51	$38,174.63
Ustekinumab	45 / 90 mg (see above)	$10,292.15 / $20,584.30	27%	$7,532.84 / $15,063.47	$58,620.92	$42,584.22

Patient preferences for psoriasis treatment outcomes were included by assigning utilities to the health states (PASI response) in the model. The relationships between PASI response categories and utility values have been estimated in analyses of RCTs of targeted drugs (although the relationship between treatment arm and utility was not assessed). In contrast to our 2016 report, rather than estimating utilities derived from a single study, we averaged utilities from five studies (see Table 4.4 in main report) to account for variability across trials and utilize all available evidence.

Model outputs include quality-adjusted life years (QALY) gained, life years (LYs), and total costs for intervention and comparators, as well as incremental costs per additional QALY gained and per additional LY gained for the intervention relative to nontargeted care. We also evaluated cost per month in PASI States 90 and 75.

Base-Case Results

Our results suggest that initiating treatment with the IL-17 drugs or guselkumab leads to the greatest improvement in QALYs, while initiation with apremilast, etanercept, or infliximab is the least effective. Perhaps not surprisingly, initiation with the IL-17 drugs or guselkumab generally leads to the highest total cost, while initiation with apremilast, etanercept, or infliximab leads to lower total costs.

Table ES7. Results for the Base Case for Targeted Treatments Over 10 years

First-line Treatment	Total Cost	Total QALYs	Months spent in PASI 90+*	Months spent in PASI 75+*
Non-targeted treatment	$67,800	5.70	0.0	0.0
Adalimumab	$308,000	7.17	52.0	74.1
Apremilast	$215,000	6.79	32.6	53.5
Brodalumab	$289,000	7.39	67.8	84.9
Certolizumab pegol	$341,000	7.16	50.5	73.5
Etanercept	$272,000	6.88	37.7	57.9
Guselkumab	$342,000	7.40	69.0	85.3
Infliximab	$238,000	6.98	47.8	62.5
Ixekizumab	$311,000	7.42	70.9	86.1
Secukinumab	$305,000	7.34	63.5	82.4
Ustekinumab	$315,000	7.17	51.1	74.1

* Time spent in PASI health states is discounted at the same rate at costs and other outcomes.

Note that the results above should not be interpreted as treatments with a single targeted drug, but as sequences of targeted drugs (including 'step therapy'). For example, treatment beginning with guselkumab continues to IL-17 and/or non-targeted drugs upon discontinuation, and treatments beginning with IL-17 drugs continue to guselkumab and/or non-targeted drugs upon discontinuation. All other drugs are followed by a market basket of IL-17 drugs and guselkumab upon discontinuation from the first-line targeted treatment.

The incremental cost-effectiveness ratios compared to non-targeted treatment are shown below.

Table ES8. Incremental Cost-Effectiveness Ratios (ICERs) for the Base Case, Compared to Non-Targeted Treatment

First-line Treatment	Cost / QALY	Cost / month in PASI 90+	Cost / month in PASI 75+
Adalimumab	$164,000	$4,600	$3,200
Apremilast	$135,000	$4,500	$2,800
Brodalumab	$131,000	$3,300	$2,600
Certolizumab pegol	$188,000	$5,400	$3,700
Etanercept	$175,000	$5,400	$3,500
Guselkumab	$161,000	$4,000	$3,200
Infliximab	$134,000	$3,600	$2,700
Ixekizumab	$142,000	$3,400	$2,800
Secukinumab	$145,000	$3,700	$2,900
Ustekinumab	$169,000	$4,800	$3,300

ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year

Sensitivity Analyses

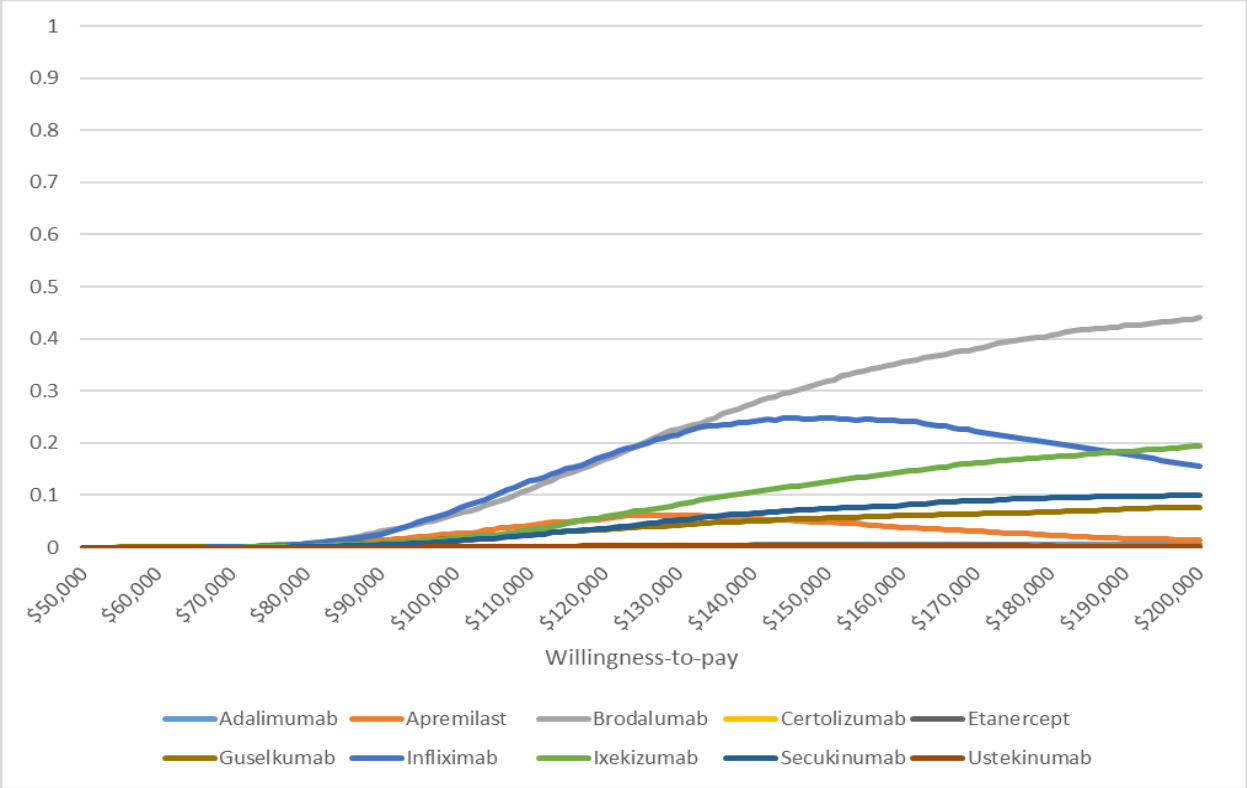
To demonstrate effects of model parameter uncertainty on incremental cost per QALY gained, we varied input parameters based on standard errors or reasonable ranges for two examples: ixekizumab versus non-targeted treatment and ixekizumab versus etanercept. These examples were selected because ixekizumab is one of the most effective drugs and has some long-term data, and because etanercept represents one of the more commonly used original targeted agents. Furthermore, some health care plans require patients to utilize a less effective and less expensive targeted agent as a step therapy.

In the base-case, ixekizumab has an ICER of $142,000 per QALY compared to non-targeted, and an ICER of $72,000 per QALY compared to etanercept.

In the comparison to non-targeted treatment, uncertainty in utility scores and drug costs are the primary sources of uncertainty; the ICER exceeds $150,000 per QALY gained with reasonable, albeit less likely, values for each of these parameters.

In the comparison to etanercept, uncertainty in model results is again dominated by uncertainty in drug costs, but also drug discontinuation rates, utility for PASI response states, and drug effectiveness. Despite varying these parameters, initiation with ixekizumab compared to initiation with etanercept is below the $150K/QALY threshold in almost all cases.

Figure ES1. Cost-Effectiveness Acceptability Curve



This graph shows the probabilities (y-axis) that initiation with each targeted drug is the most cost effective strategy at various willingness-to-pay thresholds (x-axis), comparing all targeted drugs to each other and to non-targeted treatment. (Note: non-targeted treatment not shown for clarity).

We also conducted a probabilistic sensitivity analysis (PSA) to more comprehensively evaluate the impact of uncertainty in all model parameters when comparing all interventions (targeted drugs and non-targeted therapy) with each another. The cost effectiveness acceptability curves shown in the Figure above indicate the probabilities (y-axis) that initiation with each drug is the most cost-effective approach at various willingness to pay thresholds (x-axis).

These results indicate that at a $50K/QALY threshold, no targeted drugs offer good value; at a $100K/QALY threshold, initiation with brodalumab or infliximab each have a 10% probability of being optimal value, and probabilities for the other targeted agents are all near zero; and at a $150K/QALY threshold there is more separation, as initiation with brodalumab or infliximab is most likely to be cost effective, while the other IL-17s and guselkumab have somewhat lower probabilities of being most cost effective. Apremilast has a modest probability of being cost effective across the $100K-$150K/QALY range, while initiation with adalimumab, etanercept, ustekinumab, and certolizumab have essentially no probability of being the most cost-effective strategies across all thresholds.

Scenario Analyses

In order to understand the effects of various assumptions, we ran a variety of scenario analyses, including:

- Patients in the PASI 50-74 group continued therapy, with small improvement in PASI over time and higher discontinuation; costs increased by 0.9% to 3.3%, while QALYs changed by 0.2% to 0.4%.
- Used 2016 drug prices; total costs of treatment increased by 0.2% to 11.5% from using 2018 versus 2016 drug prices.
- Included suicide as a potential adverse outcome with brodalumab; negligible effect on overall outcomes, with a loss of QALYs equivalent to less than 0.1% of the total.
- Assessed effect of timing of onset of response using secukinumab as an illustrative example; impact on ICER was less than 1%.
- Assumed second-line targeted treatment was an average of all 10 targeted drugs; changed costs and QALYs by no more than 1%.
- Including productivity offsets led to 10-13% decreases in total costs, and ICER's compared to non-targeted that were notably lower than in the base case (i.e., $109-166K/QALY rather than $133-$188K/QALY).
- Using only the lower doses for certolizumab pegol and ustekinumab, we find that cost per QALY versus non-targeted decreases from $188,000 to $129,000 and $169,000 to $130,000, respectively.

Threshold Analyses

To estimate the maximum prices that would correspond to given willingness to pay thresholds, we systematically altered the price of each drug in the base case scenario in order to match that threshold. Prices for each drug that would achieve cost-effectiveness thresholds ranging from $50,000 to $150,000 per QALY gained are shown below.

Table ES9. Threshold Analysis Results (Prices indicate annual maintenance price)

Intervention	Annual price of maintenance therapy	Price needed for $50k/QALY	Price needed for $100k/QALY	Price needed for $150k/QALY
Adalimumab	$43,700	$11,600	$25,700	$39,800
Apremilast	$31,000	< $0*	$17,500	$36,600
Brodalumab	$36,500	$14,900	$28,200	$41,500
Certolizumab pegol	$50,600	$11,300	$25,500	$39,700
Etanercept	$43,700	$1,700	$18,500	$35,400
Guselkumab	$44,400	$15,400	$28,400	$41,500
Infliximab	$29,700	$2,600	$18,800	$35,000
Ixekizumab	$37,700	$14,500	$27,100	$39,700
Secukinumab	$38,200	$13,600	$25,500	$39,400
Ustekinumab	$42,600	$12,600	$25,200	$37,800

*Threshold price of apremilast needed to be below zero to offset cost of second-line targeted drug therapy

Risankizumab threshold analysis

No WAC will be announced for this product for some time, and the approved dosing is not certain. Assuming discontinuation parameters identical to guselkumab, induction dosing as in risankizumab's phase III trials, and no laboratory monitoring, we have calculated the following value-based annual maintenance prices: $50,000 per QALY: $14,700; $100,000 per QALY: $27,300; $150,000 per QALY: $39,800.

Tildrakizumab threshold analysis

Tildrakizumab was approved to be dosed at 100 mg every 12 weeks, following initiation doses of 100 mg at weeks zero and four. Using this dosing information and an assumption of no lab monitoring, we have calculated annual maintenance prices for tildrakizumab as follows: $50,000 per QALY: $9,200; $100,000 per QALY: $23,000; $150,000 per QALY: $36,800.

Summary and Comment

In our analysis of cost-effectiveness of targeted drugs for moderate to severe plaque psoriasis, we found that the most effective treatment strategies were initiation with the IL-17 agents or guselkumab. The least effective strategies were initiation with apremilast, infliximab, or etanercept. Analogously, the most expensive treatment strategies were initiation with the IL-17 agents or guselkumab, and the least expensive strategies were initiation with apremilast, infliximab, or etanercept.

Approximately half of the treatment strategies were cost effective compared to non-targeted therapy at a $150K/QALY threshold; the value of tildrakizumab and risankizumab will be dependent on their final list price and discounts provided in the marketplace.

In our 2016 analysis, we concluded that initiation with IL-17 drugs is a reasonable strategy due to their high efficacy and reasonable economic value – even in comparison to step therapy using a less effective and less expensive targeted drug first line. This conclusion remains valid in our current analysis. Among the IL-17's, initiation with brodalumab appears to be the most cost-effective strategy due to drug pricing. Of note, the IL-17 drug prices have increased, leading to less favorable value than in our 2016 report.

Conclusions

Targeted drug treatment for moderate to severe plaque psoriasis can provide reasonable economic value. Our analysis indicates first-line treatment with infliximab or the IL-17 drugs is cost effective at higher willingness to pay thresholds, and infliximab and brodalumab are most likely to be cost effective. Guselkumab may be cost effective depending on drug discounts, and apremilast, while the least effective drug, may be cost effective at moderate willingness to pay thresholds. Initiation with other targeted drugs was not found to be cost effective.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Table ES10. Potential Other Benefits

Potential Other Benefits	Description
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.	The use of targeted immunomodulators offers patients better treatment potential in regard to greater skin clearance and overall improved quality of life.
This intervention offers reduced complexity that will significantly improve patient outcomes.	All the targeted immunomodulators are administered subcutaneously except for apremilast (oral) and infliximab (intravenous). Subcutaneous route of administration is less burdensome and has reduced complexity, which is likely to improve adherence as well as the ability for some patients with limited mobility to self-administer prophylaxis; intravenous administration used for infliximab has been identified as a barrier for patients. Patients may also favor the convenience of an oral drug like apremilast.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	N/A
This intervention will significantly reduce caregiver or broader family burden.	For individuals with moderate to severe psoriasis and with associated emotional and psychological issues, the use of targeted immunomodulators may decrease caregiver/family burden, but there are currently no data on this.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.	Targeted immunomodulators have dramatically revolutionized the treatment of psoriasis. However, not all patients respond well to their first agent. Therefore, the introduction of a new class of targeted immunomodulator drugs that selectively targets interleukin 23 (anti-IL-23 agents) is likely to benefit patients who did not achieve adequate control with the other agents.
This intervention will have a significant impact on improving return to work and/or overall productivity.	We found limited data on the impact of these drugs on productivity. However, there is reason to believe that controlling plaque psoriasis with targeted immunomodulators will have significant impact on improving the psychological and emotional health of patients, which may in turn affect productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	N/A

Contextual Considerations

Table ES11. Potential Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	Psoriasis is rarely life threatening, however, it has substantial impact on the overall health-related quality of life of patients, particularly if lesions are in areas that can affect daily functioning (e.g., the hands or soles of the feet) or social functioning (e.g., the face).
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	Patients with psoriasis have a high lifetime burden of illness
This intervention is the first to offer any improvement for patients with this condition.	N/A
Compared to systemic therapies, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	Serious side effects appear to be minimal in the short-term trials on these agents. However, psoriasis is chronic condition requiring long term treatment. Observation data on the drugs that have been around for longer periods (TNFα inhibitors) have been generally reassuring. However, long term data are not yet available on the newer class of drugs (IL-17s and IL-23s).
Compared to systemic therapies, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	Longer term data on targeted immunomodulators have shown that loss of effect over time is a very common problem with these drugs. In fact, switching treatment is generally expected among patients. However, the magnitude and durability of the benefit of the new class of agents (IL-23) has not yet been reliably quantified at this time.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	N/A

Value-Based Benchmark Prices

Value-based benchmark prices for all drugs are presented in Table ES12. Annual prices and discounts required to reach the $100,000 per QALY threshold ranged from 38% to 71% and to reach the $150,000 per QALY threshold ranged from 8% to 44%. Since no WAC is available for risankizumab or tildrakizumab, we calculated only the price to reach the cost-effectiveness thresholds.

Table ES12. Value-Based Benchmark Prices for Targeted Therapies

	Annual WAC	Annual Estimated Net Price	Annual Price to Achieve $100,000 per QALY Threshold	Annual Price to Achieve $150,000 per QALY Threshold	Discount from WAC required to Reach Threshold Prices
Adalimumab	$63,600	$43,700	$25,700	$39,800	37% to 60%
Apremilast	$40,000	$31,000	$17,500	$36,600	8% to 56%
Brodalumab	$45,700	$36,500	$28,200	$41,500	9% to 38%
Certolizumab pegol*	$79,100	$50,600	$25,500	$39,700	43% to 63%
Etanercept	$63,600	$43,700	$18,500	$35,400	44% to 71%
Guselkumab	$66,300	$44,400	$28,400	$41,500	37% to 57%
Infliximab	$38,100	$29,700	$18,800	$35,000	8% to 51%
Ixekizumab	$67,300	$37,700	$27,100	$39,700	41% to 60%
Secukinumab	$61,500	$38,200	$25,500	$39,400	36% to 59%
Ustekinumab	$58,200	$42,600	$25,200	$37,800	35% to 57%
Risankizumab†	-	-	$27,300	$39,800	-
Tildrakizumab†	-	-	$23,000	$36,800	-

QALY: Quality-adjusted life year

All annual prices do not include loading dose administered at initiation in year-one, and represent only maintenance dose-related prices from year-two onward

All prices rounded to the nearest $100

*Assumed that 50% of treated patients had body weight >90kg and were hence administered the higher maintenance dose of 400mg once every two weeks

†No WAC or estimated net price currently available

Potential Budget Impact

We used the results from the cost-effectiveness model to estimate the potential total budgetary impact of certolizumab pegol and guselkumab in place of non-targeted therapy. We used the WAC, the same estimated net price for each drug as in the cost-effectiveness analyses, and the three threshold prices in our estimates of potential budget impact. All costs were undiscounted and estimated over a five-year time horizon.

The candidate populations eligible for treatment with certolizumab pegol or guselkumab included adults with moderate to severe plaque psoriasis who are eligible for biologic therapy and are biologic naïve. To estimate the size of the potential candidate populations for treatment, we first estimated the size of the US adult population by gender for years 2018 to 2022 using population projection data published by the US Census Bureau.[46] As in our 2016 report, we used incidence (78.9 cases per 100,000 persons) rather than prevalence because we were interested only in patients who were taking a biologic for the first time.[5] Applying estimates of 79% with plaque psoriasis among those with psoriasis and 18.2% among this sub-population with moderate-to-severe disease to our projected US population resulted in 146,710 incident cases over five years, or 29,342 cases each year.[4,5] This was assumed to be the candidate population for treatment with these novel agents.

For certolizumab pegol, the per-patient annual budget impact ranged from approximately $58,500 at its WAC ($79,100 per year) to approximately $38,200 at its net price ($50,600 per year). The per patient annual budget impact at the threshold prices ranged from approximately $30,400 at the price ($39,700 per year) to reach the $150,000 per QALY threshold to approximately $4,700 at the price ($11,300 per year) to reach $50,000 per QALY threshold (Table ES13).

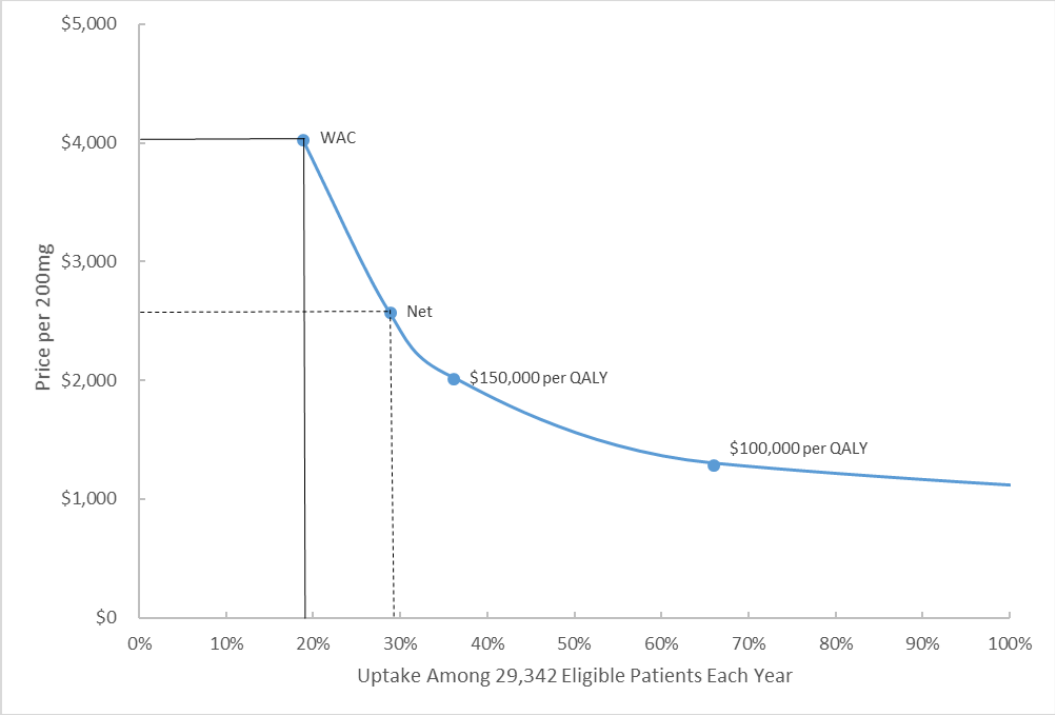
Table ES13. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon for Certolizumab Pegol in Adults with Moderate to Severe Plaque Psoriasis

	Average Annual Per Patient Budget Impact				
	WAC	Discounted WAC	$150,000/ QALY	$100,000/ QALY	$50,000/ QALY
Certolizumab pegol	$66,109	$45,761	$38,019	$24,266	$12,274
Non-targeted therapy	$7,589				
Difference	$58,520	$38,172	$30,430	$16,677	$4,685

WAC: wholesale acquisition cost; QALY: quality adjusted life year

At all prices except the price to reach the $50,000 per QALY threshold, the annual potential budgetary impact for the entire eligible population exceeded the ICER annual budget impact threshold of $915 million. At certolizumab pegol's current WAC and estimated net price, only 19% and 29% of the entire eligible population could be treated per year without the budget exceeding the $915 million threshold (Figure ES2).

Figure ES2. Potential Budget Impact Scenarios at Different Prices for Certolizumab Pegol in Adults with Moderate to Severe Plaque Psoriasis*



*Graph shows the relation between price per 200mg and proportion of patients eligible for treatment with certolizumab pegol who could be treated over five years without crossing $915-million budget impact threshold.

For guselkumab, the per-patient annual budget impact ranged from approximately $58,900 at its WAC ($66,300 per year) to approximately $37,200 at its net price ($44,400 per year). The per patient annual budget impact at the threshold prices ranged from approximately $34,700 at the price ($41,500 per year) to reach the $150,000 per QALY threshold to approximately $8,500 at the price ($15,400 per year) to reach $50,000 per QALY threshold (Table ES14).

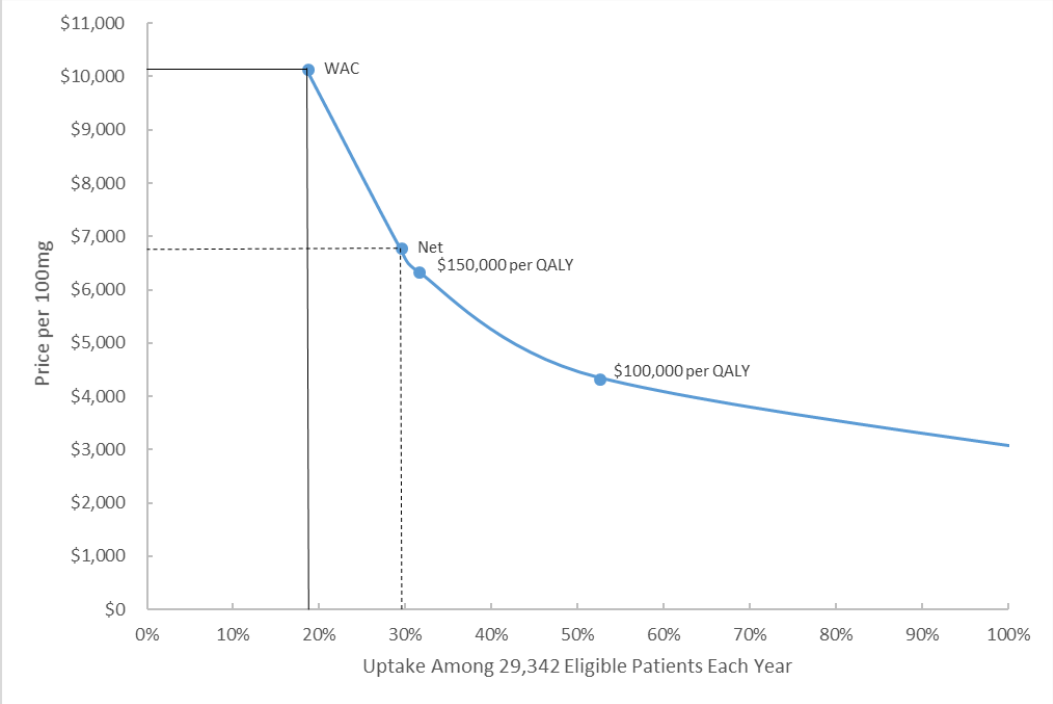
Table ES14. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon for Guselkumab in Adults with Moderate to Severe Plaque Psoriasis

	Average Annual Per Patient Budget Impact				
	WAC	Discounted WAC	$150,000/ QALY	$100,000/ QALY	$50,000/ QALY
Guselkumab	$66,488	$44,797	$42,261	$28,478	$16,048
Non-targeted therapy	$7,589				
Difference	$58,900	$37,208	$34,672	$20,889	$8,459

WAC: wholesale acquisition cost; QALY: quality-adjusted life year

At all prices except the price to reach the $50,000 per QALY threshold, the annual potential budgetary impact for the entire eligible population exceeded the ICER annual budget impact threshold of $915 million. At guselkumab's current WAC and estimated net price, only 18% and 29% of the entire eligible population could be treated per year without the budget exceeding the $915 million threshold (Figure ES3).

Figure ES3. Potential Budget Impact Scenarios at Different Prices for Guselkumab in Adults with Moderate to Severe Plaque Psoriasis*



*Graph shows the relation between price per 100mg and proportion of patients eligible for treatment with guselkumab who could be treated over five years without crossing $915-million budget impact threshold.

Detailed budget impact results for both drugs are available in section 7.3 of this report.

Voting Results

At the July 12, 2018 meeting, the New England CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis. Following the evidence presentation and public comments, the New England CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and potential other benefits and contextual considerations related to targeted immunomodulators. The voting results are presented below, and a full summary of the discussion is described in Chapter 8 of the full report.

Patient Population for all questions: Patients with moderate-to-severe plaque psoriasis for whom treatment with topical therapies, older systemic therapies, and/or phototherapy has been ineffective, contraindicated, or not tolerated.

1) Is the evidence adequate to demonstrate that the net health benefit of certolizumab pegol is superior to that provided by the other subcutaneous TNFα inhibitors (adalimumab and etanercept)?

Yes: 2 votes	**No: 9 votes**

2) Is the evidence adequate to demonstrate that the net health benefit of guselkumab is superior to that provided by all subcutaneous TNFα inhibitors (adalimumab, etanercept, and certolizumab pegol)?

Yes: 10 votes	No: 1 vote

3) Is the evidence adequate to demonstrate that the net health benefit of risankizumab is superior to that provided by all subcutaneous TNFα inhibitors (adalimumab, etanercept, and certolizumab pegol)?

Yes: 10 votes	No: 1 vote

4) Is the evidence adequate to demonstrate that the net health benefit of tildrakizumab is superior to that provided by all subcutaneous TNFα inhibitors (adalimumab, etanercept, and certolizumab pegol)?

Yes: 0 votes	**No: 11 votes**

5) When compared to non-targeted therapy, do newer treatments for moderate-severe plaque psoriasis offer one or more of the following "potential other benefits"?

# of Votes	Other Benefits
10/11	This intervention offers reduced complexity that will significantly improve patient outcomes.
0/11	This intervention will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.
7/11	This intervention will significantly reduce caregiver or broader family burden.
8/11	This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.
8/11	This intervention will have a significant impact on improving patient's ability to return to work and/or their overall productivity.
6/11	Other important benefits.

6) Are any of the following contextual consideration important in assessing long-term value for money for the newer targeted immunomodulators?

# of Votes	Contextual Considerations
10/11	This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
8/11	This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
1/11	This intervention is the first to offer any improvement for patients with this condition.
7/11	Compared to no treatment, there is significant uncertainty about longterm risk of serious side effects.
7/11	Compared to no treatment, there is significant uncertainty about the magnitude or durability of long-term benefits.
2/11	Other important contextual considerations

7) Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of guselkumab compared with non-targeted therapy?

Low: 2 votes	**Intermediate: 8 votes**	High: 1 vote

8) Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of certolizumab pegol compared with non-targeted therapy?

Low: 7 votes	Intermediate: 4 votes	High: 0 votes

Key Policy Implications

As the present assessment constitutes a condition update from 2016, the discussion of the evidence on new and established therapies did not include a formal Policy Roundtable. Instead, the 2016 policy recommendations were updated in a moderated discussion of the New England CEPAC that followed the panel vote on Clinical Effectiveness and Value. This discussion was supported by input from a clinical expert and a representative from a patient advocacy organization. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

Recommendations marked with an asterisk (*) are updated based on the 2018 Condition Update. All other recommendations remain unchanged from 2016, but are nevertheless included full report for completeness. Highlighted recommendations are listed below.

- **Manufacturers**: Foster transparency in the rationale for price increases*
- **Payers**: Consider limiting or abolishing "step therapy" approaches to coverage*
- **Specialty Societies**: Update treatment guidelines for patients with moderate-to-severe chronic plaque psoriasis in a form that is easy to understand and easy-to-use by payers, clinicians, and patients*
- **Researchers and Manufacturers**: Generate additional information on the durability of clinical benefit seen with IL-17 and IL-23 agents*

More details on all policy recommendations are described in Section 8.3 of the full report.

1. Introduction

1.1 Background

Psoriasis

Plaque psoriasis is a common, chronic disease that manifests itself by itchy pruritic, red, scaly, raised lesions on the skin, most commonly on the scalp, elbows, knees, scalp, and back extensor extremities and trunk.[8] Psoriasis affects about 3% of the population and generally occurs before age 35.[3,4] In this T cell-mediated autoimmune and inflammatory disease genetic predispositions play a major role.[1,2] The pathogenesis is driven by multiple cytokine-mediated pathways, including tumor necrosis factor-α (TNF-α) and interleukin (IL)-23 and IL-17 cytokines.[2] It is associated with systemic diseases including other autoimmune diseases (e.g., inflammatory bowel disease), metabolic syndrome, and cardiovascular disease.[12,13] In addition, up to 30% of patients with plaque psoriasis have at least some manifestations of psoriatic arthritis,[9-11] and may reach up to 40% among patients treated with biologics.[9,47]

Plaque psoriasis accounts for about 80% to 90% of all patients with psoriasis.[5-7] Other types of cutaneous psoriasis include inverse psoriasis (affecting the skin folds, particularly the genital area), guttate psoriasis (small spots all over the body), palmar-plantar psoriasis (on the hands and feet), nail psoriasis, erythrodermic psoriasis (where the entire body may turn red), and pustular psoriasis (sterile pustules).[1,8,48]. These other types of cutaneous psoriasis, accompanying plaque psoriasis in up to 40% of patients, are often hard to treat and have an important impact on their quality of life[49].

Roughly 70% to 80% of patients with plaque psoriasis have mild disease that can be adequately managed with topical therapy. Definitions of "moderate-to-severe" plaque psoriasis vary, but generally consist of psoriasis that affects at least 5% to 10% of a patient's body surface; produces lesions that have significant redness, thickness, and scale; or significantly reduces quality of life (e.g., lesions on the face, palm, or soles of the feet).[15,16]

Plaque psoriasis significantly decreases health-related quality of life, particularly if lesions are in areas that can affect daily functioning (e.g., the hands or soles of the feet), social functioning (e.g., the face) or sexual activities (genital areas).[50-52] Psoriasis itself is not a direct cause of increased mortality, but patients with severe psoriasis have increased mortality due to cardiovascular disease and infection.[10,14]

The direct annual medical costs of psoriasis, excluding the cost of co-morbidities, have been estimated to cost the United States $52 billion to $63 billion and indirect costs of lost work productivity have been estimated to range between $24 billion and $35 billion.[53]

Treatments

Treatments for psoriasis can be grouped within four broad categories:

1. Topical therapies such as steroids, vitamin D analogs, retinoids, and calcineurin inhibitors;
2. Older systemic therapies, such as acitretin, cyclosporine, and methotrexate;
3. Phototherapy, most commonly narrow-band ultraviolet B light (NBUVB); and
4. "Targeted immunomodulators" including biologics and apremilast

Topical Treatments include emollients; topical corticosteroids of varying strength; vitamin D analogs (e.g., calcipotriene, calcitriol); coal tar products which are usually available without a prescription; topical retinoids (tazarotene); topical calcineurin inhibitors (e.g., tacrolimus or pimecrolimus), which can be useful for treatment of the face and intertriginous areas; and anthralin. Topical treatments are usually in the forms of creams, ointments, or lotions, but can also be gels, foams, sprays, and shampoos. Topical treatment can be impractical for patients with psoriasis that affects a large area or for patients who have significant scalp or nail involvement. Higher potency topical corticosteroids can cause skin atrophy if used on non-psoriatic skin, particularly on areas of thinner skin, such as the face. Topical calcineurin inhibitors may be associated with skin cancer.

Older Systemic Therapy includes methotrexate, cyclosporine, and acitretin.

- *Methotrexate* is a folic acid inhibitor. It is effective but is associated with hepatotoxicity, requires close, potentially invasive (i.e., liver biopsy) monitoring, cannot be used in patients with liver disease or kidney disease, and is an abortifacient. Drug interactions are common; bone marrow suppression is a possibility. Methotrexate is generally given weekly and many patients describe a post-dose fatigue that can last for several days ("methotrexate fog"). Patients often get stomatitis, nausea, and vomiting and, more rarely, can have lung complications. Methotrexate can be combined with TNF-α inhibitors.
- *Cyclosporine* is a T cell inhibitor. It works rapidly but causes hypertension and may be associated with lymphoma and skin cancer (especially when combined with psoralen and ultraviolet A radiation [PUVA]). Cyclosporine is also associated with nephrotoxicity, liver disease, hypertrichosis, gingival changes, GI symptoms, and neurologic symptoms. Drug interactions are common and there are many contraindications. Current US guidelines limit the continuous use of cyclosporine to one-year; European guidelines to two years.[54] Cyclosporine cannot be combined with other systemic treatments (other than phototherapy).
- *Acitretin,* a retinoid, vitamin A analogue is highly teratogenic, associated with dry eyes and dry mouth, hair loss, as well as elevated triglycerides and musculoskeletal problems. Acitretin can be combined with phototherapy and, unlike many other psoriasis treatments, is not immunosuppressive.

Phototherapy includes sun exposure, broadband ultraviolet B (UVB), narrowband UVB, and psoralen with ultraviolet A (PUVA) treatment. Narrowband UVB is more effective than broadband UVB; both can be delivered at home. Psoralen, a photosensitizing drug, can be used orally or topically, as a bath, to the affected areas. Psoralen is associated with nausea, and PUVA is associated with increased squamous cell cancer and possibly melanoma; as such, UVB by far the most common form of phototherapy delivered in current clinical practice. A final form of phototherapy involves the use of excimer lasers for focused UVB light therapy.

Targeted immunomodulators

Targeted immunomodulators include the monoclonal antibodies reducing the level of the pathogenic cytokines, specifically TNF-α and interleukin (IL)-23 and IL-17 cytokines, and the PDE4 inhibitor apremilast reducing the production of proinflammatory mediators.[2]

Monoclonal antibodies are part of the class of drugs called biological products or biologics, large, complex molecules that are produced through biotechnology in a living system, such as a microorganism.[17] The FDA calls the first approved specific biologic product the Reference Product, often simply called Biologic, and the subsequent product the Biosimilar Product or simply Biosimilar. When approving a biosimilar, the FDA determines that there are no clinically meaningful differences from an existing FDA-approved reference product.[17] Since 2015, the FDA has added four-letter meaningless suffixes at the end of all non-proprietary names of biosimilars. Starting in November 2017, these suffixes are also added to all newly approved reference biologics' nonproprietary names.[55] In this report, we will be using the nonproprietary names as used by the FDA for reference biologics and biosimilars.

Table 1.1 provides an overview of the targeted immunomodulators approved or under review by the FDA for the treatment of moderate-to-severe plaque psoriasis. Of note, several of these agents are newly available or under FDA review since ICER's 2016 review, including three agents in a new class of selective IL-23 inhibitors (guselkumab, tildrakizumab, and risankizumab), as well an IL 17 inhibitor (brodalumab), a TNFα inhibitor (certolizumab pegol) and a second biosimilar for infliximab.

Table 1.1. Targeted Immunomodulators for Moderate-to-Severe Plaque Psoriasis[1]

Mechanism of Action	Name and Company	FDA approval for plaque psoriasis	Market availability	FDA recommended dosing
TNFα	adalimumab / Humira® AbbVie	Reference Biologic 2008/01/18	Available	80mg subcutaneously, then 40mg every other week starting 1 week after initial dose
	etanercept / Enbrel® Amgen	Reference Biologic 2004/04/30	Available	50mg subcutaneously 2x/week for 3 months, then 50mg 1x/week
	infliximab (dyyb/abda) Remicade® | Janssen Inflectra® | Pfizer Renflexis® | Merck	Reference Biologic: 2006/09/26 Biosimilars: 2016/04/05 2017/04/24	Available	5mg/kg intravenously at weeks 0, 2, and 6, then every 8 weeks
	certolizumab pegol / Cimzia® UCB	Reference Biologic, 2018/05/28	Available	400mg subcutaneously at weeks 0, 2, and 4, then either 400mg every 2 weeks or for some patients (with body weight ≤ 90 kg) 200mg every 2 weeks
IL 12/23	ustekinumab / Stelara® Janssen	Reference Biologic 2009/09/25	Available	Patients ≤100kg/>100kg: 45mg/90mg subcutaneously at week 0 and 4, then every 12 weeks
IL 23	guselkumab/ Tremfya® Janssen	Reference Biologic 2017/07/13	Available	100mg subcutaneously at weeks 0, week 4, then every 8 weeks
	tildrakizumab-asmn / Ilumya® Sun/Merck	Reference Biologic 2018/03/20	Not yet launched	100 mg subcutaneously at weeks 0, 4, then every twelve weeks
	risankizumab AbbVie	Submitted to the FDA on April 25, 2018	n/a	n/a
IL 17	secukinumab / Cosentyx® Novartis	Reference Biologic 2015/01/21	Available	300mg subcutaneously at weeks 0, 1, 2, 3, 4 then 300mg every 4 weeks
	ixekizumab / Taltz® Eli Lilly	Reference Biologic, 2016/03/22	Available	160mg subcutaneously at week 0, then 80mg at weeks 2, 4, 6, 8, 10, 12, then 80mg every 4 weeks
	brodalumab / Siliq® Valeant	Reference Biologic 2017/02/15	Available	210mg subcutaneously at weeks 0, 1 and 2, then every 2 weeks*
PDE-4	Apremilast / Otezla® Celgene	Reference Biologic 2014/09/23	Available	5-day titration then 30mg orally 2x/day thereafter

[1] This table include all reference biologics approved or submitted for approval, but only biosimilars that are currently available.

Aspects of Treatment

Non-Standard Dosing: For many of these agents, there is some suggestion of waning effectiveness with continued use, known as biologic fatigue.[21] To maintain effectiveness, physicians often prescribe increasing doses of targeted immunomodulators. On the other hand, physicians occasionally physicians prescribe *lower* doses of effective medications to decrease out-of-pocket costs. A US commercial database that evaluated claims from 2007 to 2012 found that in the 12 months after the dose titration period, there were dose escalation rates with etanercept, adalimumab, and ustekinumab of 41%, 37%, and 36%;[56] dose reductions of 49%, 54%, and 37%; and discontinuation rates of 15%, 10%, and 5%, respectively. Within the same 12 months, many patients discontinued, restarted, and switched biologic treatments. This may be due to a lack of efficacy, to coverage changes or other reasons. In an examination of infliximab use, 26% of treatment courses involved use of a greater-than-initially-recommended dose.[57]

A more recent study also evaluated claims over 12 months for 7,527 patients receiving adalimumab, etanercept, or ustekinumab. The study found rates of dose escalation with adalimumab, etanercept, and ustekinumab of 8%, 31%, and 18%; discontinuations of 53%, 56%, and 39%; restarts of the same medication following discontinuation of 18%, 23%, and 9%; and switching to a different medication of 21%, 22%, and 15%, respectively. Among patients who continued receiving ustekinumab, only 0.5% decreased their dose (from 90 mg to 45 mg) during the study period.[58]

Combination Therapy: The role of combination therapy – for example, the use of topical therapies with targeted immunomodulators or use of methotrexate as an adjunctive systemic therapy – has not been rigorously evaluated, but such use might provide enhanced effectiveness and is typical in clinical practice.[59] Combination therapy seems likely to be discussed in a forthcoming guideline from the American Academy of Dermatology and the National Psoriasis Foundation.

Previous Biologic Therapy Exposure: Generally, patients receiving a second TNFα inhibitor after not having responded to another TNFα inhibitor have a lower effectiveness of this second drug compared to patients who never received an agent from this class of drugs before.[22,60] Patients switching from one biologic to another may have a slightly lower response rate, however this has not been consistently demonstrated.[22]

Biosimilars

As of April 2018, the FDA has approved six biosimilars for use in plaque psoriasis, [61] but only two have been launched. The delays for launching biosimilars despite FDA approval are mainly due to patent litigation.[19,20] When approving a biosimilar, the FDA determines that there are no clinically meaningful differences from an existing FDA-approved reference product.[17] Head to head studies

and registry studies for TNF-α therapy have shown that biosimilars can replace the reference biologic without losing effectiveness.[62-66] Switching studies have confirmed that TNF-α biosimilars do not trigger immune responses that could diminish the long-term effectiveness of biologic therapy for psoriasis.[2] However, for biosimilars to be substituted for the reference product without the involvement of the prescriber, additional requirements have to be fulfilled.[17,67] Currently none of the FDA approved biosimilars has been recognized as an interchangeable product.[68]

Safety aspects of treatment with biologics

The targeted immunomodulator treatments that are the subject of the present assessment act on specific pathways in the immune system, multiple cytokine-mediated pathways, including tumor necrosis factor-α (TNF-α) and IL-23 and IL-17 cytokines.[2] Safety concerns for these agents are primarily relate to effects on the immune system: a range of infections, including tuberculosis, and malignancies, especially skin cancer and lymphoma. Such safety concerns are studied using registries that provide real world evidence in large patient cohorts; such evidence is of course not yet available for the newer agents.

It is known that the use of TNF-α agents is associated with increased risk of reactivation of latent tuberculosis infections, leading in most cases to disseminated or extrapulmonary disease, and tuberculosis screening has become mandatory prior to treatment with biologics. Cohort studies have shown however that the risk of tuberculosis reactivation in patients receiving biologics not targeting TNF is almost negligible.[2] TNFα inhibitor treatment can also induce new autoimmune diseases, such as lupus erythematosus.[69]

IL-23 and IL-17 are required for optimal skin host defense against Candida albicans.[70] Not surprisingly, Candida infections are more common with the use of IL-17 agents (secukinumab and ixekizumab), but they are superficial, not systemic.[2,71] The use of brodalumab, the third IL-17 agent, carries an increased risk of suicide[72] and a Risk Evaluation and Mitigation Strategy (REMS) has been requested by the FDA before the approval.[73]

Registry studies have shown that increased risks of major adverse cardiovascular events and cancer, especially lymphoma and nonmelanoma skin cancer, initially attributed to biologic therapy, are most likely related to psoriasis itself and not to the treatment.[23,24]

Apremilast, an anti-phosphodiesterase-4 agent, is the only available oral targeted immunotherapy. Apremilast is associated with diarrhea, especially at initiation, that is lessened by titrating up the dose gradually. For elderly patients the diarrhea and weight loss can be of particular concern. Other adverse effects include mood disorders, upper respiratory tract infection and nasopharyngitis.[74]

Emerging therapies

As mentioned in the 2016 report,[25] tofacitinib and baricitinib are oral first-generation Janus kinase (JAK) inhibitors that have been shown to be effective for moderate-to-severe plaque psoriasis in randomized controlled trials.[75,76] They are part of a large number of novel therapies for immune-mediated inflammatory diseases targeting different pathways such as type I and II interferons, cellular adhesion processes, B-cells, regulatory T-cells and bispecific antibodies.[77]

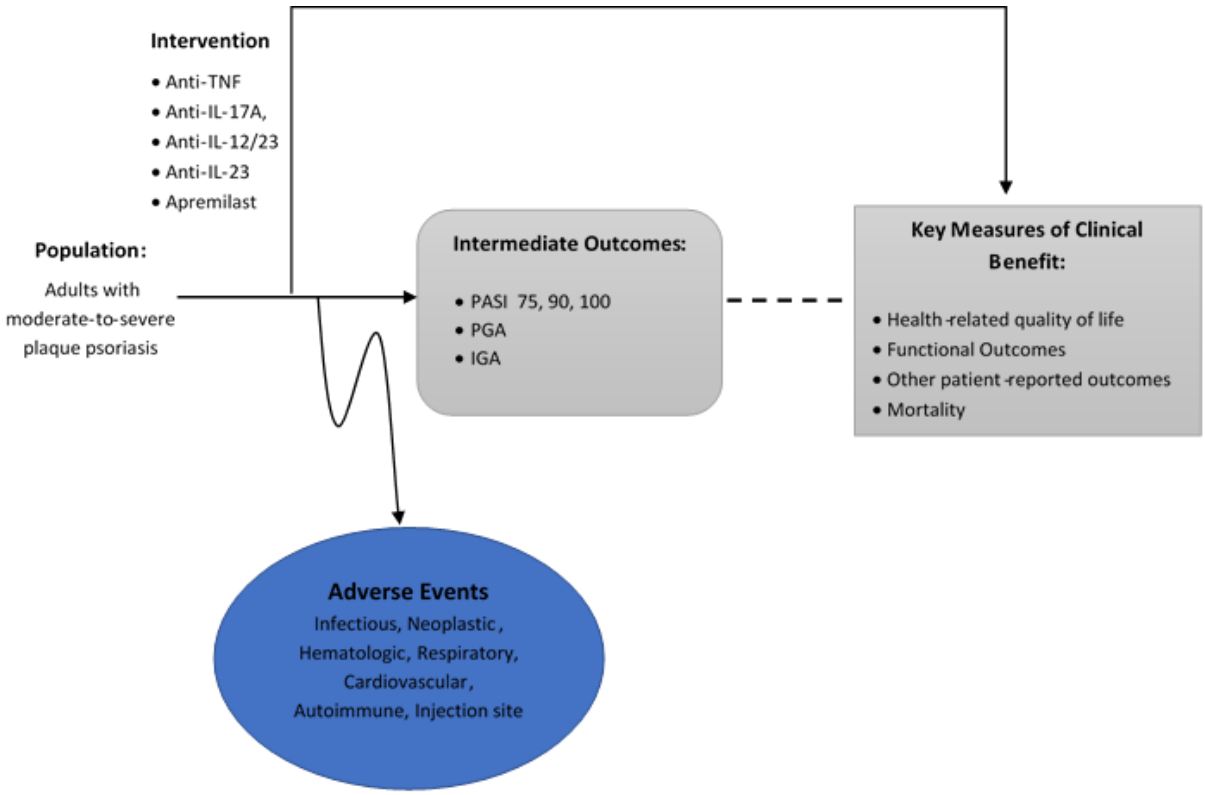
1.2 Scope of the Assessment

The scope for this update followed the approach used in 2016 and is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was collected from available randomized controlled trials as well as high-quality systematic reviews; higher-quality comparative cohort studies will also be evaluated as necessary. We did not restrict studies according to study duration or study setting; however, we limited our review to those that captured the key outcomes of interest. We supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Analytic Framework

The analytic framework for assessment of anti-plaque psoriasis medications is depicted in Figure 1.1 below.

Figure 1.1. Analytic Framework: Management of Moderate-to-Severe Chronic Plaque Psoriasis



PASI = psoriasis area severity index; PGA = physician global assessment; IGA = Investigator Global Assessment

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., PASI 75, 90, and 100), and those within the squared-off boxes are key measures of benefit (e.g., health-related quality of life). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipsis.[78]

Populations

The population of focus for this review included adults with moderate-to-severe chronic plaque psoriasis. Although not a focus of the review, we did not exclude patient populations with other concomitant psoriasis types or psoriatic arthritis and evaluated psoriasis outcomes in these subgroups if data were available. Additionally, we attempted to distinguish outcomes for patients who have and have not been previously treated with a targeted immunomodulator.

Subgroup analyses conducted in the 2016 report were updated: patients with concomitant psoriatic arthritis, patients who had previous used biologic therapy, and results from Asian studies.

Interventions

The interventions of interest were the targeted immunomodulators (biologics and apremilast) approved, expected to be approved or submitted to the FDA for approval, by July 2018 for the treatment of moderate-to-severe plaque psoriasis:

- **TNF-α inhibitors**: adalimumab, etanercept, infliximab, certolizumab pegol
- **IL-17 agents**: secukinumab, ixekizumab, brodalumab
- **IL-12/23 agent**: ustekinumab
- **IL-23 agents**: guselkumab (approved in 2017), tildrakizumab (approved in March 2018), risankizumab (submitted to the FDA on April 25, 2018)
- **Anti-PDE-4 agent**: apremilast

Comparators

We compared to placebo, and wherever possible, we evaluated head-to-head trials of these interventions.

Outcomes

This review examined key clinical outcomes, including outcomes common to plaque psoriasis trials (a list of outcomes is included on the next page). We examined available data for evidence about the comparative effectiveness of targeted immunomodulators in affecting domains such as itch, scaling, pain, quality of life, work productivity, and satisfaction with treatment.

Clinical Trial and Study Outcomes

- Psoriasis Area and Severity Index (PASI): 50, 75, 90, 100
- Physician Global Assessment (PGA)
- Investigator Global Assessment (IGA)
- Treatment-related adverse events

Patient-Reported Outcomes

- Dermatology Life Quality Index (DLQI)
- Other measures of health-related quality of life (e.g., Psoriasis Symptoms and Signs Diary)
- Psoriasis Symptom Inventory (PSI)
- Symptom control
- Treatment tolerability

We updated the evidence tables with data from the newly selected studies and results were summarized in a qualitative fashion. As in the 2016 review, network meta-analyses to combine direct and indirect evidence on PASI 50, PASI 75 and PASI 90 scores were conducted, and were updated based on new direct and indirect evidence.

Timing

Evidence on intervention effectiveness and harms were derived from studies of any duration. Because psoriasis is a chronic condition with no cure, we were particularly interested in evidence of durability of response to medications, as well as long-term safety.

Settings

Plaque psoriasis is generally treated in outpatient and/or clinic settings, which was the focus of our review.

1.3 Definitions

Psoriasis Area and Severity Index (PASI)

The PASI is a measure of the percent body surface area with psoriatic lesions in each of four regions (head, trunk, arms, and legs) as well as the degree of erythema, induration, and scale of the lesions in each area. PASI scores range from 0 to 72. Higher numbers indicate more surface involvement and severity of lesions. The PASI is generally reported as the percentage reduction in the PASI score from baseline to follow-up. The most consistently reported result in clinical trials is PASI 75, i.e., a 75% reduction in the PASI score. For these outcomes, higher numbers indicate a greater percentage improvement: PASI 90 is a 90% improvement in the PASI score; PASI 100 indicates full disease clearance, or a follow-up PASI score of zero.

Physician Global Assessment (PGA) and Investigator's Global Assessment (IGA)

The Static Physician Global Assessment (sPGA) and the Investigator's Global Assessment (IGA) are similar, being scored by the treating or evaluating physician and only considers the time of evaluation. Scores usually range from 0 to 7 with higher scores indicating worse severity, but 5-point, 6-point and 7-point scales have all been used. A good response in clinical trials in treatment generally requires sPGA scores of 0 ("clear") or 1 ("almost clear"). The Dynamic Physician Global Assessment (dPGA), also scored from 0 to 7, considers a patient's change from their baseline status, and is used less frequently. Unless otherwise noted, "PGA" in this report refers to the Static Physician Global Assessment.

The IGA is a modified version of the PGA, and it is based on a 5-point rather than a 6- or 7-point scale; the proportion of patients achieving a score of 0 or 1 ("clear/almost clear") are often considered "responders" in clinical trials.

Dermatology Life Quality Index (DLQI)

The DLQI was the first dermatology-specific health-related quality-of-life (HRQoL) instrument introduced in 1994.[79] It comprises 10 questions relating to symptoms, feelings, daily activities, leisure, work, school, social interactions, clothing choice, sexual difficulties, and treatment problems. DLQI scores range from 0 to 30 with lower scores representing better quality of life. A DLQI change of 5-points is the minimal amount of change needed to establish meaningful clinical significance in health-related quality of life (HRQL).

EuroQol Five Dimensions (EQ-5D)

The EQ-5D is a standardized, self-reported questionnaire for evaluating a patient's health status across disease states, and is based on five dimensions: self-care, pain/discomfort, anxiety/depression, mobility, and usual care activities. It is often used to compute a quality-adjusted life year.

Short Form-36 (SF-36)

The SF-36 is a 36-item quality of life instrument that captures eight domains and is reported as a score from 0 to 100 with higher scores indicating better functioning. The SF-36 also has summary component scores for physical functioning (physical component score, or PCS) and mental functioning (mental component score or MCS). Scores can be standardized to a population reference, such that the population mean score is 50 with a standard deviation of 10.

Psoriasis Disability Index (PDI)

The Psoriasis Disability Index is a 15-question instrument that assesses five domains of health-related quality of life: daily activities; work or school performance; personal relationships; leisure; and treatment.[80] Each question is scored from 0 to 3 and the individual items are summed to a total score of 0 to 45 with higher scores indicating greater impairment. The PDI can also be expressed as a proportion of total possible score.

Visual Analog Scale (VAS)-skin pain

VAS is a commonly used measure of pain, which is also used to assess the skin pain associated with scaly plaques in psoriatic patients, which can have a serious impact on quality of life. This modified version of the VAS is based on a score of 0 (no skin pain) to 100 (severe skin pain).

Visual Analog Scale (VAS)-itch

The VAS is also used to as a measure of pruritus assessment. Patients are asked to rate the severity of their itching on a five-point scale, from no pruritus (0 points) to severe pruritus (5 points).

Psoriasis Symptom Inventory (PSI)

The PSI is an 8-item measurement in which patients rate the severity of signs and symptoms of psoriasis from the past 24 hours. Each item is scored 0 to 4. Individual scores are summed, and a total score can range from 0 to 32 with higher scores indicating worse symptoms.

Psoriasis Symptom Diary (PSD)

The PSD measures the impact of psoriasis treatments on daily activities. Patients report disease severity on a scale of 0 to 10 on 20 psoriasis-specific signs and symptoms, including itching, pain, scaling, flaking, and changes in skin appearance.

Psoriasis Symptom and Sign Diary (PSSD)

The PSSD is a patient-reported instrument that assesses severity of six psoriasis symptoms (itch, skin tightness, burning, stinging, and pain,) and five signs (dryness, cracking, scaling, shedding/flaking, redness, and bleeding) with a summary score between 0 and 100.

Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14-item scale that scores anxiety and depression. Seven items are related to anxiety and seven are related to depression. Each item is scored 0 to three to generate anxiety or depression scores of 0 to 21, with higher scores indicting more anxiety or depression. A score above eight is a generally-used cutoff indicating a possible diagnosis of anxiety or depression. The HADS is used for screening only and does not represent a clinical diagnosis.

Work Productivity and Activity Impairment (WPAI)

The WPAI consists of six questions about current employment and, in the past seven days, hours missed due to health problems, hours missed for other reasons, hours worked, productivity impairment at work ("presenteeism"), and productivity impairment in unpaid activities. Results are reported on a percentage scale from 0 to 100 in four domains: percent work time missed due to health; percent impairment while working; percent overall work impairment; and percent impairment due to health.

Worker Productivity Index (WPI)

The WPI combines an objective absenteeism measure and a subjective presenteeism (i.e., attending work while ill) measure into a measure of "total lost hours per week."

Work Limitations Questionnaire (WLQ)

The WLQ is a self-administered instrument of 25 items, which measures four domains of work limitations, including physical, time management, mental-interpersonal, and output demands.[81]

Visual Analog Scale-productivity

Although more frequently used in arthritis patients, the VAS-productivity scale can also be used to measure work productivity in psoriasis. VAS-productivity is measured on a 0-10 scale, indicating no impact to severe impact on productivity at school, home, or work.

1.4 Insights Gained from Discussions with Patients and Patient Groups

In the development of the 2016 report,[25] ICER had conversations with and received input from patient advocacy groups, including the National Psoriasis Foundation, and individual patients.[26] These conversations highlighted the shortcomings associated with clinical trial outcomes in many studies of psoriasis therapies, frustrations with the healthcare system, as well as the social, emotional, and financial impact of psoriasis. These issues were presented by the National Psoriasis Foundation at the ICER public meeting on the topic.[27,25]

Certain aspects of research into psoriasis are not patient-centered. Many of the tools developed to measure outcomes were not developed in patient-centered perspective, and psoriasis-specific patient-centered outcome measures are limited (although the Psoriasis Symptom Inventory [PSI] and the Psoriasis Disability Index [PDI] are being used; see below). At an FDA meeting in 2017 on Patient-Focused Drug Development for Psoriasis, patients rated flaking/scaling and itching as a having a more significant impact on their quality of life than the rash itself.[82] Simple body surface area (BSA) measurements of psoriasis involvement do not consider the greater effect that lesions in particular areas –such as the nails, genitals, scalp, face, flexural areas, palms, and soles of the feet—have on an individual's quality of life. Patients also pointed out that average treatment responses described in clinical trials may not capture individual patient variability.

Up to half of patients are dissatisfied with their psoriasis treatment.[51,83] Dissatisfaction may be due to the unpredictable effectiveness of many agents to treat psoriasis, poor tolerability, lack of durable response, and lack of access to medications because of coverage restrictions or costs.[51] Patients also expressed frustration with misdiagnoses and delayed diagnoses. The time from onset to diagnosis for plaque psoriasis averages two years. A psoriasis diagnosis may be delayed even further in those with darker skin tones.

In addition to delayed diagnosis, racial and ethnic minorities appear to have a higher prevalence of psoriasis, more severe disease, more common misdiagnosis, and more frequent non-treatment; they are less likely to be included in clinical trials. Furthermore, in a Medicare population, black

patients were 70% less likely to have received biologics for their psoriasis compared to white patients.[84]

For all patients, treatments for plaque psoriasis may be challenging. It can be difficult to apply topical therapies, especially when the affected area involves the scalp or covers a large part of the body. Therapies can also be inconvenient to use; some require multiple injections on a daily or weekly basis, especially initially, during induction. Patients need to consider time and travel for administration of phototherapy and infused therapy. Psoriasis is a chronic disease that requires management over a lifetime, potentially during the treatment of other chronic conditions, including cancer.

Psoriasis affects social functioning. Patients with psoriasis often feel the need to make different clothing choices to hide psoriatic skin. Patients with psoriasis may moderate choices of activities, such as swimming. Because of different clothing choices, the manifestations and difficulties faced by people with psoriasis may not be visible to others. Children with psoriasis, especially teens, face teasing, bullying, and shunning because of the visible effect of the disease. Many find that some people seeing the lesions conclude the patient has a communicable disease.

Plaque psoriasis has both psychological and emotional effects. The psychological impact of severe psoriasis is comparable to that of diabetes or depression.[85] Psoriasis is associated with a higher likelihood of having depression, anxiety, and suicidal ideation.[52,86] Some patients reported somatic manifestations of psychiatric disease or emotional difficulties, including GI symptoms and hypertension.

Patients are concerned about lack of access to treatment because of inadequate insurance coverage, out of pocket costs, and future availability of drugs to treat their disease. About half of patients with psoriasis are either undertreated or not treated,[83] and one of the main reasons is the cost of therapy. Patients are frustrated that they are being forced to start treatment with less efficacious medications due to insurance requirements for "step therapy" that mandates use of "preferred medications" first. Patients are also frustrated by a lack of clarity in the exception process and timing in many plans, reporting that their physicians are not always sure how to get through a step therapy process even when that patient is an appropriate candidate to move on to a more advanced treatment. In addition, switching insurance or within-plan coverage changes might require movement to another step therapy approach, which often requires patients to "start over" with previously-tried medications. Patients are anxious that individual drugs will stop working for them and want access to alternatives. Another source of frustration is that coverage decisions for biologics often seem to be dictated by other autoimmune conditions, like rheumatoid arthritis, which is a listed indication for many of the drugs of interest for this review.

1.5. Potential Cost-Saving Measures in Psoriasis

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for people with psoriasis that could be reduced, eliminated, or made more efficient.

We did not receive any suggestions in response to the final scoping document or draft report. We also did not identify recommendations specific to the management of plaque psoriasis from professional organizations such as Choosing Wisely, the American Academy of Dermatology, or the US Preventive Services Task Force.

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

We analyzed insurance coverage for treatment options for patients with moderate-to-severe plaque psoriasis in six New England state Medicaid programs, and 13 silver-tiered insurance plans on individual marketplaces across New England. Formularies and prior authorization criteria were obtained from documentation on plan sites as reference documents for the specific marketplace plans under review. This plan survey does not necessarily present a weighted representation of drug availability for members on individual market plans in New England. Rather, the survey presents differences in big and small regional plans and how they may design their formularies differently based on their size. A complete listing of plans surveyed, and key formulary designs, are included as tables in Appendix H.

Across all plans, we analyzed formulary exclusions, preferred agents, benefit design, and step protocols. All plans required an initial trial or contraindication to systemic therapy such methotrexate or phototherapy. After the trial with systemic therapy, all plans covered at least one TNFα inhibitor as a preferred agent; nearly half of plans covered an IL-17 as preferred; and over two-thirds of plans covered either an IL-17 or an IL-12/23 therapy as a preferred therapy. Preferred therapies still required prior authorization and required a trial of systemic therapy but had lower cost-sharing than their non-preferred counterparts. Certain non-preferred therapies, such as ixekizumab, guselkumab or apremilast, often required trials of systemic therapy, followed by one, two, or three other specialty medications, before gaining access to the drug therapy. Some non-preferred therapies required up to five trials with other drug therapies for treating moderate-severe psoriasis. Our analysis of formulary designs is summarized in Table 2.1 below.

Importantly, it appears that a marked shift in coverage policy has occurred since our 2016 review. At that time, TNFα inhibitors were the only preferred agents in nearly all plans, and most insurers required patients to step through adalimumab and/or etanercept before attempting treatment with an agent from another class. In fact, in our 2016 analysis, only two plans offered secukinumab and ustekinumab as preferred drug therapies for treatment. In 2018, the landscape has shifted so that nearly two-thirds of plans surveyed offer at least one other preferred agent outside the TNFα inhibitor class.

Still, newer agents, such as brodalumab and guselkumab, remain unlikely to be covered; and apremilast and ixekizumab are most likely to see several step requirements. Table 2.1 presents key findings from our survey of commercial plans.

Medicaid

A few New England Medicaid programs have also evolved in their coverage policies since our analysis in 2016. Five of the six states continue to prefer adalimumab and etanercept on their drug list. However, two states – Vermont and Maine – added secukinumab to their list of preferred drugs after treatment failure with adalimumab. Coverage policies for New England state Medicaid programs are summarized in Appendix H in Table H2.

Formulary Survey commissioned by National Psoriasis Foundation

A survey conducted by Avalere for the National Psoriasis Foundation found that formulary coverage for targeted immunomodulators fell between 2015-2017, with increased utilization management and cost sharing.[87] The analysis evaluated formularies for both public and private payers. For employer sponsored plans, coverage fell slightly from 88% in 2015 to 84% in 2017; however, in general, therapies were placed on specialty tiers with higher cost sharing and had more restrictions on use. According to the study, coverage for targeted immunomodulators on Medicare plans fell more drastically from 60% in 2015 to 40% in 2017. On the exchange market, coverage fell, and co-insurance for therapies averaged 37%, representing the growing out-of-pocket burden on patients. On Medicaid formularies, drug therapies were more likely to be listed as non-preferred. These figures may be informed by the availability of more therapeutic options in each class, contributing to more within class competition that allow for exclusions; it may also reflect a general shift by insurance companies to employ more utilization management and more cost-sharing burdens for patients who need branded drugs. Still, it is clear from the survey that patients are feeling more of a cost burden when seeking treatment for psoriasis.

Table 2.1. Benefit Design for Treating Moderate-Severe Plaque Psoriasis across New England Commercial Payers**

			# of Step edits				
	% of Plans Excluding Drug from Coverage	% of Plans Covering Drug under Medical Benefit	0	1	2	3+	% of Plans Covering as Preferred Agents
TNFα inhibitors							
etanercept	0%	0%	92%	8%	0%	0%	92%
infliximab	0%	54%	23%	8%	15%	0%	38%
adalimumab	0%	0%	100%	0%	0%	0%	100%
certolizumab pegol	*Approved for psoriasis in May 2018; Not included on formularies for treating psoriasis at the time of survey.*						
IL-17							
secukinumab	0%	0%	46%	23%	31%	0%	38%
ixekizumab	38%	0%	0%	38%	38%	13%	13%
brodalumab*	54%	0%	0%	0%	33%	0%	0%
IL-12/23							
ustekinumab	15%	23%	55%	27%	0%	0%	73%
IL-23							
guselkumab*	69%	0%	0%	25%	25%	0%	25%
risankizumab	*Investigational; Submitted to the FDA in April 2018*						
tildrakizumab	*Tildrakizumab was approved in March 2018; formulary status currently unknown*						
PDE-4							
Apremilast*	31%	0%	22%	44%	11%	0%	33%
**** brodalumab, guselkumab, and apremilast had incomplete information on step criteria.*** ***** Survey was conducted in March 2018***							

2.2 Clinical Guidelines & Statements on Managing Care

From the Medical Board of the National Psoriasis Foundation: Treatment Targets for Plaque Psoriasis
http://www.jaad.org/article/S0190-9622(16)30909-4/pdf

In February 2017, the National Psoriasis Foundation published a paper in the Journal of the American Academy of Dermatology (JAAD) encouraging clinicians to establish treatment targets for their patients with plaque psoriasis in order to monitor disease progression and evaluate patient response to drug interventions. Based on consensus among dermatologists, and patient focus groups, they recommend that dermatologists measure body surface area (BSA) as the most practical outcome for monitoring response to treatment. The panel of experts defined an acceptable treatment response to a medical intervention within three months as BSA of 3% or less; or 75% improvement from baseline. Over maintenance therapy every six months, they suggested a treatment target of BSA 1% or less. In their discussion, the authors recognized the barriers to care in a real world setting and encouraged payers to improve accessibility to therapeutic options in order to help patients achieve treatment success. They do not suggest any specific drugs or sequencing of drug therapies as that is not the intended purpose of these treatment goals. Rather the purpose is to encourage a paradigm shift in care strategy to improve health outcomes.

American Academy of Dermatology
https://www.aad.org/practice-tools/quality-care/clinical-guidelines/psoriasis

The American Academy of Dermatology (AAD) were published in 2011 and precede FDA approval of secukinumab, ixekizumab, and apremilast.

The AAD guidelines recommend that patients with limited disease be treated with topicals and/or targeted phototherapy. They do not recommend treating patients with limited disease with systemic therapies that have higher levels of risk. Methotrexate, for instance, carries the risk of hepatotoxicity, is contraindicated for several conditions, and can have drug interactions. For extensive disease, the guidelines recommend treatment with topical treatments, phototherapy, systemic therapies, and biologics, but do not prioritize among the targeted immunomodulators (biologics) available at the time they were written. The AAD is preparing an update to their guideline specific to combination therapy for 2018.

NICE Guidelines
https://www.nice.org.uk/guidance/cg153?unlid=389990376201651723735

The UK National Institute for Health and Care Excellence (NICE) reviewed therapies and offered guidance for treatment. The guidelines were most recently updated in September 2017. NICE

recommends progression from topical (mostly steroid) to systemic non-biologic therapy such as phototherapy, methotrexate or cyclosporine before moving on to treatment with a targeted immunomodulator. After failure of non-biological treatment, they recommend a trial period of etanercept, ixekizumab, or secukinumab for 12 weeks; or adalimumab or ustekinumab for 16 weeks. Treatment response is considered a 75% improvement from baseline in the PASI. NICE also recommends secukinumab if a discount is available from the company. Infliximab is recommended after failure of first-line treatment for those patients with very severe psoriasis, which they define as a PASI >20 and a DLQI of more than 18. In October 2016, NICE released a new determination recommending apremilast for severe disease if systemic therapy fails to achieve treatment response and apremilast is provided at a discount.

European Guideline on Systemic Treatment of Psoriasis Vulgaris, 2017 Update
http://www.euroderm.org/edf/index.php/edf-guidelines/category/5-guidelines-miscellaneous?download=79:psoriasis-update-2017-incl-grade-tables

An expert European panel updated their 2015 guidelines with an addendum in September 2017. They stated that systemic treatments have many unwanted side effects and toxicity but should be first-line therapy. If phototherapy and older systemic agents are ineffective, contraindicated, or not tolerated, they recommended treatment with TNF-α inhibitors or secukinumab. Ustekinumab and apremilast were recommended as second-line therapy. Ixekizumab, brodalumab, and guselkumab were not included in the review.

British Association of Dermatologists Guidelines for Biologic Therapy for Psoriasis 2017
https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjd.15665

In their 2017 guidelines, the British Association of Dermatologists updated treatment guidelines for biologics, recommending first line treatment with systemic therapy, unless not well tolerated or contraindicated; or moving directly to biologic treatment if the patient has either a BSA or PASI score of >10 or has severe localized psoriasis associated with functional impairment. As first line biologic treatment, they recommend ustekinumab, adalimumab (especially for patients with psoriatic arthropathy), and secukinumab. For second line treatment, they do not recommend a particular treatment. However, they suggest reserving treatment with infliximab for patients with severe disease when other biologics are ineffective. When biologic therapy fails, they suggest supplementing treatment with lifestyle interventions, systemic therapy, alternative biologic therapy, or alternative methods of administration of therapy. The guidelines also make recommendations for when to escalate dosage based on inadequate response and how to transition between biologic therapy.

3. Comparative Clinical Effectiveness

3.1 Overview

To inform our analysis of the comparative clinical effectiveness of targeted immunomodulators for moderate-to-severe chronic plaque psoriasis, we abstracted evidence from available clinical studies, whether in published, unpublished, or abstract form. The drugs and regimens of interest are included in Table 1.1.

We included evidence from placebo-controlled trials, but concentrated on evidence about the comparative clinical effectiveness of these treatments compared to each other. Our review focused on key clinical outcomes common to plaque psoriasis trials, as well as symptoms and burdens of psoriasis that are not well-captured by standard trial outcomes.

- Clinical Benefits
  - Trial Outcomes
    - Psoriasis Area and Severity Index (PASI): 50, 75, 90, 100
    - Physician Global Assessment (PGA) or Investigator's Global Assessment (IGA)
  - Patient-Reported Outcomes
    - Dermatology Life Quality Index (DLQI)
    - Other measures of health-related quality of life (e.g., Short Form [SF]-36)
    - Symptom control (e.g., Visual Analog Scale [VAS], Psoriasis Symptom Inventory [PSI])
- Harms
    - Treatment-related adverse events (e.g., rate of infections)
    - Treatment tolerability (i.e., discontinuation due to adverse events)

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on targeted immunomodulators for moderate-to-severe plaque psoriasis followed established best methods used in systematic review research.[88] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[89] The PRISMA guidelines include a checklist of 27 items, further details of which is available in Appendix Table A1.

Since this was an update of the review conducted in 2016, we searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for relevant studies from the date of the last search (June 28th, 2016) to January 2, 2018 to update the evidence on the drugs included in the 2016

review (Appendix A). For the four new drugs added to the current review (guselkumab, tildrakizumab, risankizumab and certolizumab pegol), our search of the electronic databases spanned from January 1996 to January 2, 2018 (Appendix A). We limited each search to English language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent relevant reviews and meta-analyses. Other grey literature sources included submissions from manufacturers of psoriasis therapies that were not otherwise publicly available, as well as data recently presented during the American Academy of Dermatology conference from February 16-20, 2018.

Study Selection

We included evidence from randomized controlled trials (RCTs), comparative observational studies, and high-quality systematic reviews where available. We excluded single-arm studies and studies from an early clinical development phase (i.e., Phase I). We included phase II studies only if they evaluated unique subpopulations or outcomes not otherwise available in Phase III data. Finally, we did not include studies that evaluated targeted immunomodulators as part of combination treatment.

In recognition of the evolving evidence base for psoriasis, we supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature that met ICER standards for review (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/). We excluded abstracts which reported duplicative data available in published articles or reported results from observational studies since it would be difficult, if not impossible, to evaluate the methodological quality of these studies. We also did not include any outcomes from conference proceedings or regulatory documents on the TNF-α therapies given that these treatments have been available for at least a decade and primarily have peer-reviewed data available.

Data Synthesis and Statistical Analyses

Data were abstracted and summarized into evidence tables for all outcomes (see Appendix B, Tables B1-B3) and are synthesized in the text below. In addition, because the treatments of interest have usually not been directly compared, we developed quantitative, indirect comparisons among all agents using a Bayesian network meta-analysis (NMA) for the PASI outcome. Consistent with prior published methods,[90] PASI 50,75 and 90 response outcomes from clinical trials were tabulated to create numbers of patients in mutually exclusive categories (i.e., <50, <75, 50-74,75-89, ≥90); these data were analyzed using a random-effects, multinomial likelihood model to generate proportions of patients in each category. An adjusted model was specified with a covariate for

placebo response rate which was assumed to be common across all treatments and provided a control for known and unknown differences between study populations.

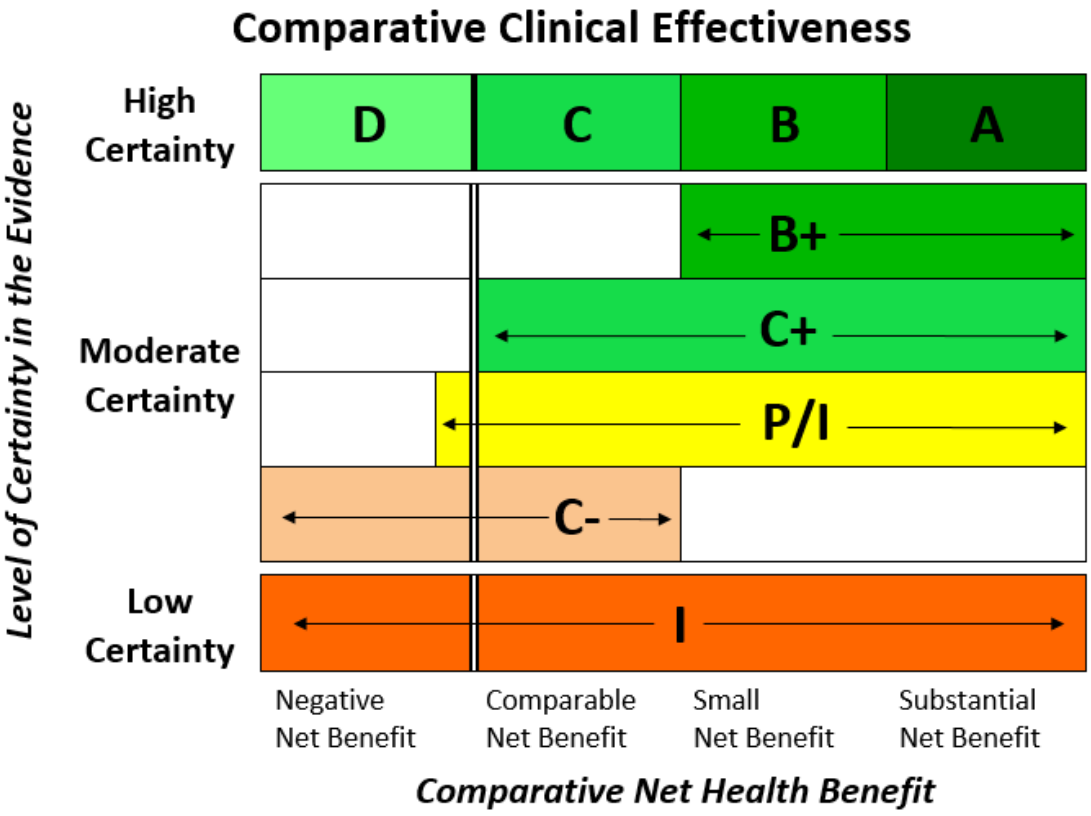
The NMA was conducted using JAGS software (version 4.3.0) via R using the R2jags package.[91] Criteria for trial selection, statistical methods and R code are detailed in Appendix F.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 3.1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[92]

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D = "Negative"- High certainty of an inferior net health benefit
B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

3.3 Results

Study Selection

Our updated literature search identified 1,781 potentially relevant references (see Appendix A), of which 45 references, relating to 17 RCTs and two observational studies (32 publications and 12 abstracts/conference presentations) met our inclusion criteria. In addition, we included all 80 references relating to 36 individual RCTs and eleven observational study from the previous review.[25] In total, we included 125 references of 53 RCTs and 13 observational studies. Primary reasons for study exclusion included the evaluation of study populations or outcomes related specifically to patients with psoriatic arthritis, other types of psoriasis (e.g., erythrodermic), or psoriasis specific to a location (e.g. genital psoriasis, nail psoriasis) and non-comparative study design. Ustekinumab and the TNF-α therapies were the only treatments for which we found comparative observational data that met our inclusion criteria. Additional details of the included references are described in Appendix B, and the key studies are summarized in Table 3.1.

Quality of Individual Studies

As noted in the previous review, all the identified trials were rated to be of good or fair quality using criteria from U.S. Preventive Services Task Force (USPSTF).[28] We rated 15 of the newly identified trials, of which 12 were Phase III, to be of good or fair quality using the same criteria. Trials of good quality had study arms that were comparable at baseline, the authors used valid instruments to evaluate outcomes, and no differential attrition was observed. Fair quality studies typically used modified intention-to-treat (mITT) as the primary method of analysis. We did not assign a quality rating to two trials that were available only in the grey literature (one placebo controlled trial of risankizumab and one head-to-head trial between secukinumab and ustekinumab).

Included Studies

Of the 53 individual RCTs, we identified 48 key trials (47 Phase III trials and one investigator-initiated trial), while the remaining five were Phase II trials that presented data on subpopulations of interest. Fourteen of the of the 48 key trials are newly identified trials, of which 10 relate to the four new drugs of interest (three on certolizumab pegol; three on risankizumab; two on guselkumab; and two on tildrakizumab), and the remaining four relates to new studies on five drugs in the 2016 review (adalimumab, infliximab, head-to-head between infliximab and etanercept and head-to-head between secukinumab and ustekinumab).

We identified six head-to-head trials on the new drugs: etanercept versus (certolizumab pegol [CIMPACT] and tildrakizumab [RESURFACE 2]); ustekinumab versus risankizumab [ULTIMMA 1 & 2]; and adalimumab versus guselkumab [VOYAGE 1 and 2]. All six studies included a placebo-controlled arm.

In addition, we included ten head to head trials on the previously reviewed drugs: etanercept versus (ustekinumab [ACCEPT], secukinumab [FIXTURE], ixekizumab [UNCOVER 2 and 3], and infliximab [PIECE]); ustekinumab versus (brodalumab [AMAGINE 2 and 3], secukinumab [CLEAR], secukinumab [CLARITY] and ixekizumab [IXORA-S]). Five of these studies (ACCEPT, CLEAR, CLARITY, IXORA-S, and PIECE) did not include a placebo arm.

All the key trials were Phase III, multicenter, double-blind, RCTs, except for the PIECE trial (etanercept versus infliximab) and the active comparator arms of the CIMPACT trial (etanercept versus certolizumab pegol). PIECE was an investigator initiated multicenter single-blind study, while the CIMPACT was a Phase III, multicenter, double-blind RCTs with a single-blinded active comparator arms. Many of the trials removed blinding following the induction period, and some also re-randomized patients to different treatment groups and measured outcomes at various timepoints, making it difficult to evaluate the comparative durability of effect and harms across therapies beyond the induction phase. Most studies required washout of prior therapies and prohibited concurrent use of these treatments throughout the trials. Study populations had similar inclusion criteria (≥18 years old, BSA ≥10%, PASI score ≥12, ±PGA/IGA ≥ 3, ≥6 months of plaque psoriasis diagnosis, and were candidates for phototherapy or systemic therapy.

Studies were comparable with respect to age (range of means: 39-50 years, median: 45) and duration of psoriasis (range of means: 11-22 years, median: 18). Across all studies, an average of 21% of patients (range of means: 3% to 37%) had psoriatic arthritis at baseline and an average of 16.5% (range of means: 0% to 57%) of patients received prior biologic therapy. Of note, fewer patients were generally biologic-experienced in the studies of the older TNF-α drugs relative to the newer therapies (Median 0% vs 16.5%). Baseline PASI scores across trials ranged from 15 to 33 (median: 20). Given potential between-trial heterogeneity, we adjusted for the placebo response rate in our network meta-analysis which, to some degree, accounts for baseline patient differences between studies as well as possible unknown confounders. In addition, we also conducted a subgroup scenario analysis in our network meta-analysis adjusting for other baseline variations such as prior biologic exposure; the details and results of this analysis are discussed in Appendix F.

Subgroups

In the 2016 report, several populations were identified as being of special interest to stakeholders as described in the subgroups section of this report. [25] We have updated the analyses for these subgroups for the present report (see Appendix E). The characteristics of these subgroups are as follows:

Asian Studies: We separately considered and described the outcomes in seven trials (five phase III and two phase II) that were conducted exclusively in Asia (i.e., Japan, Korea, China, and Taiwan), plus a subgroup analysis of the ERASURE study. These trials were generally smaller (with the exception of LOTUS, n=322)[93] with patients who had a briefer duration of psoriasis (Median: 15

years vs. 18 years from other studies), higher PASI score (Median: 28 vs. 20 in the other studies), less prior experience with biologic therapy (proportion of previous biologics, median: 0% vs. 21% in other studies) and lower BMI. We considered the Asian trials as a subgroup because of the generally smaller study size and differences in patient characteristics from the worldwide studies.

Patients with Previous Biologic Therapy Exposure: We also examined subgroups of patients who had and had not been previously treated with a targeted immunomodulator. As noted above, fewer patients were biologic-experienced in the studies of the older TNF-α drugs relative to the newer therapies. Patients who previously used biologic therapy might be less likely to respond to a subsequent targeted immunomodulator. Thus, we describe the results of 10 trials reporting this subgroup analysis below.

Patients with Psoriatic Arthritis: Because up to a third of patients with psoriasis develop psoriatic arthritis, we evaluated subgroup analysis of psoriasis patients with and without psoriatic arthritis. Patients with concomitant psoriatic arthritis might have more severe skin disease and might respond better or worse to targeted immunomodulators than patients without psoriatic arthritis.

Table 3.1. All Phase III Studies (New Studies are Bolded)

Drug	Trials	Total patients	Induction period (weeks)	PASI, (mean)	Age (years)	Psoriasis duration (years)	Previous biologics, %	PsA, %
Placebo Controlled Studies with or without Active Comparators								
Adalimumab [94-97]	REVEAL CHAMPION Asahina, 2010† **Cai, 2017†¥**	2,077	16/12	24	44	16	2	20
Etanercept [98-104]	Papp, 2005 Leonardi, 2003 Tyring, 2006 Strober, 2011 Gottlieb, 2011 Bagel, 2012 Bachelez, 2015	3,775	12	20	44	17	6	25
Infliximab[105-108]	EXPRESS I & II Yang, 2012† **Torii, 2010†¥**	1,396	10	23	43	17	8	25
Certolizumab Pegol[¥ 29,30]	**CIMPASI 1 & 2** **CIMPACT‡**	1,020	16/12	20	46	18	30	18
Ustekinumab [93,109-112]	PHOENIX 1‡ & 2‡ Igarashi, 2012† PEARL† LOTUS†	2,566	12	23	44	17	25	21
Secukinumab[113-115]	FEATURE JUNCTURE ERASURE FIXTURE	2,403	12	22	45	18	26	20
Ixekizumab[116,117]	UNCOVER 1, 2‡ & 3‡	3,866	12	24	46	19	27	NR
Brodalumab[118,119]	AMAGINE 1, 2‡ & 3‡	4,373	12	23	45	19	33	22
Apremilast [120,121]	ESTEEM 1 & 2 LIBERATE	1,505	16	19	46	19	31	NR
Guselkumab[¥ 31,32]	**VOYAGE 1‡ & 2‡**	1,829	16	22	44	18	21	19
Tildrakizumab[¥ 33]	**RESURFACE 1 & 2‡**	1, 862	12	20	46	NR	17	NR
Risankizumab[¥ 34 35]	**UltIMMA-1 & 2‡, IMMhance***	1,504	16	20	48	NR	42	NR
Head-to Head Studies								
Etanercept/ Infliximab[¥122]	**PIECE**	48	12	17	44	20	15	11
Etanercept/Ustekinumab[123]	ACCEPT	903	12	20	45	19	11	28
Ustekinumab/ Secukinumab[124]	CLEAR	679	12	22	45	18	14	19
Ustekinumab/ Ixekizumab[125]	IXORA-S	302	12	20	44	18	14	NR
Ustekinumab/ Secukinumab	CLARITY*	1,102	12	21	45	17	22	NR

*Only available in the grey literature as of September 2018.; †Asian population only; ¥New drugs/studies (not in 2016 review); ‡Placebo controlled trials with active comparators.

Clinical Benefits

As in the 2016 review, the primary endpoint for most trials was the proportion of patients achieving PASI 75 at the end of the induction period. However, five new trials relating to guselkumab (VOYAGE 1 &2) and risankizumab (ULTIMMA 1 & 2, IMMHANCE); and one head-to-head trial between ixekizumab and ustekinumab (IXORA-S), and two head-to-head trials between secukinumab and ustekinumab [CLEAR and CLARITY] specified PASI 90 as their primary endpoint. The duration of the induction period varied by agent: week 10 for infliximab; week 12 for etanercept, ustekinumab, secukinumab, ixekizumab, brodalumab, and tildrakizumab; week 16 for apremilast, guselkumab, and risankizumab; week 12 or 16 for adalimumab and certolizumab pegol. Other clinical outcomes included the proportion of patients meeting additional PASI thresholds (e.g., 50, 100), or achieving a score of 0 or 1 ("cleared or minimal") on the Physician Global Assessment (PGA) or Investigator's Global Assessment (IGA), although these were not consistently reported. Patient-reported outcomes, including quality of life, were primarily based on mean change or proportion of patients achieving a score of 0 or 1 on the DLQI (indicating very little to no disease effect on quality of life); other quality of life instruments, such as the SF-36, were not commonly used. Measures of symptom control, such as VAS scales for itch or skin pain, as well as a recently validated tool for assessing symptom control in psoriasis patients (Psoriasis Symptom Inventory [PSI]), were infrequently employed.

All data used in the NMA are based on the FDA-approved or proposed dosing at the end of the induction period for each drug with the three exceptions. First, for secukinumab, while the drug label indicates that 150mg may be appropriate for some patients, we included just the 300mg dose in our NMA. Second, although FDA-approved dosing for ustekinumab is weight-based, neither the placebo-controlled trials nor the ACCEPT study randomized participants based on weight; other direct comparison trials (i.e., IXORA-S, AMAGINE 2 and 3, and CLEAR) assigned patients their appropriate weight-based dose. So, we present the data separately for the ustekinumab doses in the description of the placebo-controlled trials and pooled all arms into one for the network meta-analysis. Third, the FDA-approved dosing for certolizumab pegol is also weight-based (although, the dosing in the trials were random and not weight based). However, similar to ustekinumab, we presented the data separately for the two different doses in the description of the trials and pooled all arms into one for the network meta-analysis.

In addition, although the LIBERATE trial included the approved dose of apremilast, patients in the etanercept arm received a maintenance dose (i.e., 50 mg once weekly); the study was also not statistically powered to detect differences between the agents. As such, the PASI outcomes from the etanercept arm were not included in the NMA, and only comparison of apremilast to placebo are described in the sections that follow.

Psoriasis Area Severity Index (PASI)

PASI

- ***All targeted immunomodulators showed statistically-significantly higher PASI 75, PASI 90 and PASI 100 response rates in comparison to placebo at the end of induction (10 to 16 weeks, depending on agent).***
- ***In direct comparative trials of the new agents, guselkumab was superior to adalimumab; tildrakizumab and 400mg certolizumab pegol were superior to etanercept; and risankizumab was superior to ustekinumab. 200mg certolizumab pegol was not significantly different from etanercept.***
- ***Direct comparative trials of the older agents showed that ustekinumab, secukinumab, ixekizumab and infliximab were superior to etanercept; secukinumab, ixekizumab, and brodalumab were superior to ustekinumab.***

The percentages of patients achieving PASI 75, PASI 90 and PASI 100 response rates at the end of the induction period was statistically-significantly greater for all immunomodulators compared to placebo. The range of PASI responses in the intervention and placebo groups across trials for the new drugs (guselkumab, tildrakizumab, risankizumab and certolizumab pegol) are shown in Table 3.2. None of the new agents reported PASI 50. In individual placebo-controlled RCTs, the incremental proportion of patients achieving PASI 75 above placebo within trials was 61% to 69% for certolizumab pegol (three trials); [36,37] 78% to 85% for guselkumab (two trials);[31,32] 56% to 60% for tildrakizumab (two trials);[33] and 80% to 85% for risankizumab (three trials).[35,38] The incremental proportion of patients achieving PASI 75 for the other drugs compared to placebo did not change from what was previously reported in the 2016 report (see Appendix E, Table E2 for PASI responses on all drugs).

Table 3.2. Placebo-Controlled Trials on New Drugs: Ranges of PASI Response Rates across Trials

Treatment	PASI 50		PASI 75		PASI 90		PASI 100	
	Tx	Placebo	Tx	Placebo	Tx	Placebo	Tx	Placebo
Certolizumab 200mg	NR	NR	67-81	4-12	36-53	0-5	NR	NR
Certolizumab 400mg	NR	NR	75-83	4-12	43-55	0-5	NR	NR
Guselkumab	NR	NR	86-91	6-8	70-73	2-3	34-37	1
Tildrakizumab	NR	NR	62-66	6	35-39	1-3	12-14	0-1
Risankizumab	NR	NR	89-91	6-9	73-75	2-5	47	1

We identified six head-to-head RCTs on the new drugs, and five of the trials showed statistically-significant differences between treatments in PASI 75 responses after the induction period (Table 3.3) Guselkumab was superior to adalimumab in two trials (70% & 73% vs. 47% & 50%, p<0.001);[31,32] tildrakizumab was superior to etanercept in one trial (61% vs. 48%; p<0.001); and risankizumab was superioir to ustekinumab in two trials (89% & 91% vs. 76% & 70%; p<0.005)[{Gordon, 2018, 898}.[33]

In the CIMPACT trial, although a higher proportion of patients on 200mg certolizumab achieved PASI 75 compared to etanercept at 12 weeks (61% vs. 53%), there was no statistically significant difference between the two agents.[30] However, the 400mg dose of certolizumab pegol was significantly better than etanercept in achieving PASI 75 (67% vs. 53%; p=0.02).[30]

Longer term results available on three trials on the new agents showed that guselkumab remained superior to adalimumab at week 48 (PASI 90: 76% vs. 48%; p<0.001) in one trial,[31] and risankizumab remained superior to ustekinumab at week 52 in two trials (PASI 90: 82% & 81% vs. 44% & 51%, respectively; p<0.001).[35]

As noted above, four of the head-to-head trials on the new drugs relating to guselkumab (two trials: guselkumab vs. adalimumab) and risankizumab (two trials: risankizumab vs. ustekinumab) specified the PASI 90 response as their primary endpoint. All four showed statistically-significant differences between treatments in PASI 90 responses in favor of the new agents (see Table 3.3). In addition, tildrakizumab was also shown to be superior to etanercept. However, inferential statistical comparisons of certolizumab pegol and etanercept was not conducted on PASI 90 response in the CIMPACT trial.

In addition to the above trials, we identified two head-to head trials on the old drugs. One is an investigator initiated head-to-head trial between infliximab and etanercept. Infliximab was found to be significantly different to etanercept in achieving PASI 75 response (76% vs. 22%, p<0.0001),[122] but there was no statistical significant difference between both agents in achieving PASI 90 (see Table 3.3). The other study is a head-to-head trial between secukinumab and ustekinumab [CLARITY]. Secukinumab was found to be superior to ustekinumab on both PASI 75 (88% vs. 74%; p<0.0001) and PASI 90 (67% vs. 48%; p<0.0001) responses at week 12.[126] Findings on the eight other head-to-head trials on the other agents included in the 2016 review showed that ustekinumab, secukinumab, and ixekizumab were superior to etanercept; and secukinumab, ixekizumab, and brodalumab were superior to ustekinumab (see Appendix E, Table E3).

Table 3.3. Comparative Trials: PASI Responses

Trial	Treatment	PASI 75	p-value	PASI 90	p-value	PASI 100	p-value
New Drugs							
VOYAGE 1	Adalimumab	73	<0.001	50	<0.001	21	<0.001
	Guselkumab	91		73		37	
VOYAGE 2	Adalimumab	69	<0.001	47	<0.001	17	<0.001
	Guselkumab	86		70		34	
CIMPACT	Etanercept	53		27.1		NR	
	Certolizumab 200mg	61	NS	31.2	NR	NR	NR
	Certolizumab 400mg	67	0.02	34		NR	
RESURFACE 2	Etanercept	48	<0.001	21	<0.001	5	<0.001
	Tildrakizumab	61		39		12	
ULTIMMA 1	Ustekinumab	76	0.003	42	<0.001	12	<0.001
	Risankizumab	89		75		36	
ULTIMMA 2	Ustekinumab	70	<0.0001	48	<0.001	24	<0.001
	Risankizumab	91		75		51	
New Evidence on Old Drugs							
PIECE	Etanercept	22	0.0	0	0.05	0	NS
	Infliximab	76		20		4	
CLARITY*	Ustekinumab	74	<0.0001	48	<0.0001	20	<0.0001
	Secukinumab	88		67		38	

NR- not reported; See Appendix E for other comparative trials;

Network Meta-Analysis of PASI Results

Given the paucity of head-to-head data comparing treatments, we performed indirect comparisons of PASI response using Bayesian network meta-analyses (NMAs). An NMA was felt to be appropriate, as the populations of the individual trials were sufficiently similar. We included all identified Phase III trials, including the studies conducted in exclusively Asian populations in the NMA. Further details on our methods, including data input tables, network diagrams, league tables of results, and sensitivity analysis can be found in Appendix F. Briefly, we used a random-effects approach. For the primary analysis, we also adjusted for the placebo response rate in each study to account for baseline patient differences between studies (for example, given the baseline severity and the proportion of study subjects who previously used a biologic treatment) as well as possible unknown confounders.

Our base case network meta-analysis confirmed our descriptive findings, namely that all immunomodulators were significantly more likely to achieve PASI 50, PASI 75, PASI 90 and PASI 100 responses compared to placebo (see Table 3.4). All biologics were approximately 9-17 times more

likely to achieve PASI 75 or better response when compared to placebo, while apremilast was about seven times more likely to achieve PASI 75 or better.

Results of the head-to-head comparisons were consistent with the direct evidence from the head-to-head trials, showing that guselkumab was statistically significantly better than adalimumab; ixekizumab, secukinumab, infliximab, ustekinumab, certolizumab pegol and tildrakizumab were statistically significantly better than etanercept; and risankizumab, ixekizumab, brodalumab, and secukinumab were statistically significantly better than ustekinumab (see Tables 3.5).

On relative effectiveness of the PASI measures (measured as relative risk (RR) of achieving PASI 75 or 90 responses during induction), two of the anti-IL-23 agents (risankizumab and guselkumab), all three IL-17 agents (ixekizumab, brodalumab and secukinumab), and infliximab all had similar effectiveness on PASI response. These agents did not differ statistically, as the likelihood of achieving PASI 75 or PASI 90 response included 1.0 (no difference) in the 95% credible intervals (see Tables 3.5). These agents were statistically significantly more effective in terms of PASI 75 and PASI 90 outcome than adalimumab, ustekinumab 45/90 mg, certolizumab pegol 200/400mg, tildrakizumab, etanercept and apremilast. Adalimumab, ustekinumab 45/90 mg, certolizumab 200mg/400mg, and tildrakizumab did not differ significantly, and all were significantly better than etanercept and apremilast.

We also conducted two subgroup analyses: 1) we assessed multi-national studies separately, by excluding all seven Asian studies; and 2) we assessed the biologic experienced studies separately, by excluding studies 11 studies that had only biologic naïve patients or had previous biologic exposure in less than 5% of their patient population. The results of the two subgroup analyses were generally similar to our base case NMA (see Appendix F), and the relative ranking of the agents were preserved, demonstrating that these characteristics did not meaningfully impact our analyses.

Table 3.4. Relative Risks and Credible Intervals of Treatments Compared to Placebo

Treatments	PASI 50			PASI75			PASI90		
	RR	95% CrI		RR	95% CrI		RR	95% CrI	
Risankizumab¥	6.22	4.84	8.14	16.54	12.00	23.47	55.87	37.90	83.87
Ixekizumab	6.21	4.84	8.18	16.53	11.94	23.32	55.62	37.95	82.83
Guselkumab¥	6.18	4.82	8.08	16.27	11.76	22.90	54.01	36.80	80.71
Brodalumab	6.15	4.79	8.05	16.05	11.63	22.59	52.50	35.51	77.94
Secukinumab	6.05	4.74	7.87	15.43	11.33	21.42	48.37	33.56	70.40
Infliximab	5.94	4.70	7.65	14.81	10.97	20.31	44.59	31.37	64.62
Adalimumab	5.61	4.49	7.17	13.12	9.91	17.67	36.10	26.04	50.76
Ustekinumab	5.61	4.47	7.13	13.08	9.93	17.48	35.81	26.01	49.70
Certolizumab¥	5.54	4.42	7.03	12.74	9.50	17.03	34.28	24.14	48.26
Tildrakizumab¥	5.27	4.25	6.66	11.60	8.84	15.50	29.32	21.01	41.40
Etanercept	4.72	3.92	5.77	9.51	7.60	12.09	21.34	16.54	28.02
Apremilast	3.83	3.20	4.67	6.74	5.30	8.68	12.79	9.32	17.63

¥New drugs; CrI: credible interval

Table 3.5. Base Case NMA: League Table of PASI 75 Response

Risankizumab											
1 (0.96, 1.05)	**Ixekizumab**										
1.02 (0.96, 1.08)	1.01 (0.96, 1.07)	**Guselkumab**									
1.03 (0.98, 1.09)	1.03 (0.98, 1.08)	1.02 (0.96, 1.07)	**Brodalumab**								
1.07 (1.02, 1.14)	**1.07 (1.02, 1.13)**	1.06 (0.99, 1.13)	1.04 (0.99, 1.1)	**Secukinumab**							
1.12 (1.04, 1.22)	**1.11 (1.05, 1.21)**	**1.1 (1.02, 1.2)**	**1.09 (1.02, 1.18)**	1.04 (0.97, 1.12)	**Infliximab**						
1.26 (1.17, 1.38)	**1.25 (1.16, 1.38)**	**1.24 (1.15, 1.35)**	**1.22 (1.13, 1.34)**	**1.17 (1.08, 1.28)**	**1.12 (1.03, 1.24)**	**Adalimumab**					
1.26 (1.18, 1.37)	**1.26 (1.18, 1.36)**	**1.24 (1.16, 1.35)**	**1.23 (1.15, 1.32)**	**1.18 (1.11, 1.26)**	**1.13 (1.05, 1.22)**	1.01 (0.93, 1.08)	**Ustekinumab†**				
1.3 (1.18, 1.47)	**1.29 (1.18, 1.46)**	**1.28 (1.17, 1.44)**	**1.26 (1.15, 1.41)**	**1.21 (1.1, 1.35)**	**1.16 (1.05, 1.3)**	1.03 (0.94, 1.15)	1.03 (0.94, 1.14)	**Certolizumab‡**			
1.42 (1.26, 1.66)	**1.42 (1.26, 1.66)**	**1.4 (1.24, 1.64)**	**1.38 (1.23, 1.6)**	**1.32 (1.17, 1.54)**	**1.27 (1.12, 1.47)**	1.13 (1, 1.31)	1.13 (1, 1.29)	1.1 (0.95, 1.27)	**Tildrakizumab**		
1.74 (1.54, 1.98)	**1.74 (1.55, 1.98)**	**1.71 (1.52, 1.95)**	**1.69 (1.51, 1.92)**	**1.62 (1.45, 1.82)**	**1.55 (1.4, 1.73)**	**1.38 (1.25, 1.54)**	**1.37 (1.27, 1.5)**	**1.34 (1.2, 1.5)**	**1.22 (1.07, 1.38)**	**Etanercept**	
2.44 (1.98, 3.12)	**2.43 (1.97, 3.11)**	**2.4 (1.95, 3.03)**	**2.37 (1.92, 3)**	**2.28 (1.85, 2.87)**	**2.18 (1.78, 2.75)**	**1.94 (1.61, 2.4)**	**1.93 (1.6, 2.38)**	**1.88 (1.54, 2.34)**	**1.71 (1.39, 2.14)**	**1.4 (1.17, 1.71)**	**Apremilast**
16.54 (12, 23.47)	**16.53 (11.94, 23.32)**	**16.27 (11.76, 22.9)**	**16.05 (11.63, 22.59)**	**15.43 (11.33, 21.42)**	**14.81 (10.97, 20.31)**	**13.12 (9.91, 17.67)**	**13.08 (9.93, 17.48)**	**12.74 (9.5, 17.03)**	**11.6 (8.84, 15.5)**	**9.51 (7.6, 12.09)**	**6.74 (5.3, 8.68)**	**PBO**

Legend: The interventions are arranged from most effective (top left) to least effective (bottom right). Each box represents the estimated relative risk and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.
†dosing by weight;
‡200 mg and 400 mg combined
PBO: placebo;

Physician Global Assessment or Investigator Global Assessment "Clear/Almost Clear"

Physician Global Assessment (PGA) or Investigators Global Assessment (IGA) were generally consistent with the PASI results. All immunomodulators showed statistically significantly higher PGA or IGA of 'clear/almost clear' than placebo at the primary endpoint of each trial. In head-to-head trials of the new drugs, guselkumab was superior to adalimumab; and risankizumab was superior to ustekinumab. Tildrakizumab was not significantly different from etanercept.

Head-to-head trials of the older agents showed that ustekinumab, secukinumab, and ixekizumab were superior to etanercept; secukinumab, ixekizumab, and brodalumab were superior to ustekinumab.

All immunomodulators showed statistically significantly higher efficacy on PGA/IGA compared to placebo. Across the trials on the new drugs, the ranges of PGA/IGA response rates were 1% to 9% for placebo, 84% to 85% for guselkumab,[31,32] 55% to 58% for tildrakizumab,[33] 84% to 88% for risankizumab,[34,35] and 48% to 72% for 200mg and 400mg certolizumab pegol.[29,30]

All six head-to-head RCTs on the new drugs reported IGA or PGA response, of which four found statistically significant differences between treatments following the induction period. The pattern of response rates and differences between treatments were similar to those of PASI response. Guselkumab had a higher proportion of patients achieve IGA scores of 0/1 than adalimumab in two trials (85% vs. 66% in VOYAGE 1 and 84% vs. 64% in VOYAGE 2; p<0.001), [31,32] and risankizumab had a higher proportion of patients achieving static PGA (sPGA) in two trials (63% vs. 88% in ULTIMMA 1 and 62% vs. 84% in ULLTIMMA 2).[35] There was no statistical significant difference between tildrakizumab and etanercept on the proportion of patients achieving PGA scores of 0/1 at 12 weeks (55% vs. 48%; p=0.07).[33] The sixth head-to-head trial (CIMPACT) did not report inferential statistical comparisons of certolizumab pegol and etanercept on the proportion of patients achieving PGA scores of 0/1 at 12 weeks, however, compared to the etanercept arm, the result was numerically the same for 200mg certolizumab pegol (39% vs. 39%), and numerically higher for 400mg certolizumab pegol (39% vs. 50%).[30]

Longer term results showed that guselkumab remained superior to adalimumab at week 48 (IGA 0/1: 81% vs. 55%; p<0.001) in one trial,[31] and risankizumab remained superior to ustekinumab at week 52 in two trials (sPGA 0/1: 86% & 83% vs. 54% & 56%, respectively; p<0.001).[35]

Findings from the new head-to head trial between infliximab and etanercept (PIECE) showed that infliximab had a higher proportion of patients achieving IGA score of 0/1 compared to etanercept (68% vs. 9%; p<0.001).[122] In addition, the new head-to-head trial between secukinumab and ustekinumab showed that a higher proportion of patients on secukinumab achieved IGA score 0/1 compared to ustekinumab at week 12 (72% vs. 55%; p<0.0001).[126]

As previously reported, evidence on all the other drugs were similar to the PASI responses, and showed that ustekinumab, secukinumab, and ixekizumab were superior to etanercept; and secukinumab, ixekizumab, and brodalumab were superior to ustekinumab.[25]

Dermatology Life Quality Index (DLQI)

DLQI results were generally consistent with PASI results. All targeted immunomodulators statistically significantly improved quality of life relative to placebo. In head-to-head trials of new agents, guselkumab was superior to adalimumab; and risankizumab was superior to ustekinumab.

Head-to-head trials of the older agents showed that secukinumab and ixekizumab were superior to both etanercept and ustekinumab.

Quality of life was measured in the majority of studies we identified in our search, primarily using the DLQI instrument. As noted in previous report, all targeted immunomodulators statistically significantly improved quality of life relative to placebo.[25] Some studies evaluated the mean DLQI change (MCID: defined as at least a 5-point reduction), others evaluated the proportion of patients achieving a DLQI score of 0 or 1 (indicating very little to no effect on quality of life), and some evaluated both measures.

The mean DLQI change was reported on two of the new drugs (certolizumab and guselkumab). The mean absolute difference between these interventions and the placebo group were as follows: 200mg certolizumab pegol (-5.6 to -8.2; p<0.01),[29], 400mg certolizumab pegol (-6.3 to -7.1), [29], guselkumab (-8.7 to -10.6; p<0.01).[31,32]

We did not identify any data on mean change in DLQI change for tildrakizumab and risankizumab. However, we found data on the proportion of patients achieving a DLQI score of 0/1 for these drugs in 5 trials. All trials resulted in a statistically significant greater proportion in favor of the intervention compared to placebo. The absolute differences between these agents and placebo were as follows: tildrakizumab (32% to 37%; p<0.001);[33] risankizumab (58% to 63%; p<0.001).[34,35] In addition, the proportion of patients with a score of 0/1 was reported in the guselkumab trials. There was also a significant difference in favor of guselkumab compared to placebo (absolute difference: 49% to 52%; p<0.001).

In the head-to-head comparisons, guselkumab achieved a statistically significantly greater improvement on DLQI than adalimumab at 16 weeks in two trials; and significantly greater proportion of patients on risankizumab achieved DLQI 0/1 compared to ustekinumab (Table 3.6). There was no significant difference between tildrakizumab and etanercept at 12 weeks, and no head-to-head DLQI evidence was reported between certolizumab pegol and etanercept in CIMPACT.

As previously reported, head-to-head evidence on the old drugs showed that secukinumab and ixekizumab were superior to both etanercept and ustekinumab. See Appendix E, Table E3 for results of the other head-to-head comparisons.

Table 3.6. DLQI Outcomes Across Direct Comparative Trials

Trial	Drug	Mean change	p-value	DLQI 0/1 (%)	p-value
VOYAGE 1	Adalimumab	-9.3	P<0.001	39	P<0.01
	Guselkumab	-11.2		56	
VOYAGE 2	Adalimumab	-9.7		39	P<0.01
	Guselkumab	-11.3	P<0.001	52	
RESURFACE 2	Etanercept	NR	NR	36	NS
	Tildrakizumab	NR		40	
ULTIMMA 1*	Ustekinumab	NR	NR	43	P<0.001
	Risankizumab	NR		66	
ULTIMMA 2*	Ustekinumab	NR	NR	43	P<0.001
	Risankizumab	NR		66	

See Appendix E for other comparative trials

Symptom Control

Measures of symptom control were inconsistently reported across trials and used a variety of instruments. Guselkumab demonstrated a statistically significant benefit over placebo using PSSD measure.

As noted in our previous report, measures of symptom control were inconsistently reported across trials. In addition, a variety of instruments which includes a single symptom or a group of symptoms, were used to assess symptom control. These instruments include: Psoriasis Symptom Inventory (PSI), Psoriasis Symptom Diary (PSD), Psoriasis Symptom and Sign Diary (PSSD), pruritus VAS, Pain VAS, scaling etc.

We identified the two new placebo-controlled trials on guselkumab (VOYAGE 1 &2), assessing the improvement from baseline in psoriasis symptom and sign diary (PSSD) score. Guselkumab resulted in significantly greater improvement on PSSD score, compared to placebo at 16 weeks (symptoms mean change -41.9 vs -3.0; signs mean change: 44.6 vs. 4.1;all p<0.001),[31,127] and significantly greater compared to adalimumab at 24 weeks (symptoms mean change: -44 vs. -36; signs mean change: -47.2 vs. -40.1; all p<0.001).[127]

In addition, new data on one head-to head trial (IXORA-S), showed that mean changes from baseline in itch NRS and skin pain VAS, were not significantly different between ixekizumab and ustekinumab. However, ixekizumab-treated patients reported faster improvements than ustekinumab-treated patients in itch and skin pain.[125]

Data previously reported on the old agents showed that brodalumab, secukinumab and apremilast all demonstrated an improvement in symptom control using one or more of the instrument listed above when compared to placebo.[25] In addition, head-to-head comparisons showed secukinumab to be better than ustekinumab (on itching, pain and scaling relief), and ixekizumab to be better than over etanercept VAS-skin pain.[25]

Worker Productivity

Positive effects on productivity were seen in the few studies that measured it. We found no data on productivity on any of the new drugs.

Very few studies measured worker productivity. Instruments used to measure productivity in the few trials that measured it include: Work Productivity and Activity Impairment (WPAI), Worker Productivity Index (WPI), Work Limitations Questionnaire (WLQ). See the Definitions section of the report for details about the productivity instruments.

We found no data on productivity for any of the new drugs.

In the previous report, data was found on four agents (adalimumab, infliximab, ustekinumab and apremilast), and all showed significant improvements compared to placebo using different measures of productivity.[25] In addition, findings from head-to-head trials showed that ixekizumab demonstrated a statistically significant improvement over etanercept using WPAI and work productivity loss; and secukinumab was statistically significantly better than ustekinumab in reducing presenteeism, work productivity loss and activity impairment on the WPAI.

Sexual Function

Very few studies reported sexual function as an outcome. We found no data on sexual function on any of the new drugs.

We identified no data on sexual function for any of the new drugs.

In the previous review we identified two abstracts of head to head studies that included data showing superiority of ixekizumab over etanercept and secukinumab over ustekinumab; [128,129] and one published pooled analysis showed superiority of secukinumab over etanercept. [130]

Subgroup Analyses

Limitations in the evidence base preclude determining whether there are meaningful differences in effectiveness within the subgroups of interest. Outcomes were statistically significantly in favor for all the agents available for review relative to placebo across subgroups.

As previously mentioned, three subgroups were identified as being of particular interest to stakeholders: patients with psoriatic arthritis; patients who have or have not previously received biologic agents; and studies that were conducted in Asia. Detailed discussions of these analyses are available in the Appendix E.

Harms

Severe or serious adverse events were rare during treatment. Nasopharyngitis, upper respiratory tract infections, and headaches were the most common side effects noted during the trials of guselkumab, tildrakizumab, tildrakizumab and certolizumab pegol. There was no indication of increased rates of serious infections, malignancies, and major cardiovascular events for any of the agents.

Adverse Events During Induction

Common adverse events (AEs) that occurred in ≥5% of patients as well as specific AEs of interest in the guselkumab, tildrakizumab, risankizumab, and certolizumab trials are shown as trial-weighted averages in Table 3.7 (see Appendix E, Table E5 for all agents). We had limited data on the AEs occurring in the unpublished risankizumab trials.

Most adverse events were mild or moderate. Severe or serious adverse events, death, and AEs leading to discontinuation were rare and generally comparable between the treatment and placebo groups. The most common AEs noted during clinical trials included mild infections (e.g. nasopharyngitis, upper respiratory tract infections, etc.); injection site reactions for subcutaneously administered drugs, headache; and nausea. There was no evidence of increased risk of serious infections or malignancies in the placebo-controlled trials. Incident rates of candidiasis and other opportunistic infections were reported to be low and comparable between groups in all trials. There were no reports of tuberculosis, demyelinating disease, or lymphoma in these trials. We also did not find differences in risk of major adverse cardiac events (MACE). Of note, five of the agents included in our review have boxed warnings included in their FDA label: All TNF-α therapies (adalimumab, etanercept, infliximab, and certolizumab pegol) have boxed warning for serious infections and malignancy based on findings from rheumatoid arthritis trials, while brodalumab has a boxed warning for suicidal ideation and behavior based on finding from psoriasis clinical trials (AMAGINE 1 & 2).[39]

The types and patterns of AEs reported for these agents at longer timepoints (48-52 weeks) were similar to those reported during the placebo-controlled periods. In addition, comparative trials reported generally similar rates and types of AEs. At 48 weeks in VOYAGE 1, proportion of patients with AEs (74% vs. 75%), AEs leading to discontinuation (3% vs. 4%) and serious AEs (5% vs. 5%) were similar in the guselkumab and adalimumab group.[31] Similar pattern was observed between

risankizumab and ustekinumab in ULTIMMA 1 & 2 at 52 weeks,[35] and between tildrakizumab and etanercept in a pooled analysis of RESURFACE 1 & 2 over 52 to 64 weeks.[131]

Table 3.7. Adverse Events During the Placebo-Controlled Period

	Guselkumab	Tildrakizumab	Risankizumab	Certolizumab 200	Certolizumab 400	Placebo
Number of Patients	823	616	1005	350	342	1189
Week	16	12	16	12-16	12-16	12-16
Any AE, (%)	49	46	47	53	58	50
Tx-related death	0	0.1	0	0	0	0
D/C due to AEs	1.3	0.5	0.5	1.1	1.1	1.3
Serious AEs	1.9	1.5	2.1	1.4	3.8	2.5
≥Grade 3 AEs	NR	NR	NR	NR	NR	NR
Common AEs occurring in ≥5% in one or more agent						
Any Infections	23	NR	22	29	32	21
Nasopharyngitis	8	10	NR	11	11	7.9
Upper respiratory tract infection	5	1.5	4.7	4.8	6	4
Headache	4.5	NR	NR	NR	NR	3.3
AEs of Interest						
Malignancy excluding NMSC	0	NR	0.2	0	0.3	0
NMSC	0.1	0.1	0.3	0	0	0.1
MACE	0.1	0.2	0	NR	NR	0.1
Serious Infections	0.1	0.2	0.4	0	0.6	0.3

Long-term Adverse Events from observational studies

As expected, there is currently no long-term safety observational data on any of the new agents. We previously reported long-term safety data from PSOLAR (Psoriasis Longitudinal Assessment and Registry) in our 2016 report.[25] Data from the identified studies suggest an increased rate of serious infections for infliximab and other biologic agents relative to nonbiologic therapy, although not for ustekinumab.[132,133] There were no material differences on other safety concerns among the biologic agents or in comparison with nonbiologic therapy. In addition, we identified one study that

assessed drug survival, which is defined as the time from initiation of a biologic to discontinuation.[134] Result of the analysis showed that infliximab (Hazard ratio[HR]: 2.73;P = 0.0014); adalimumab [HR: 4.16; P < 0.0001]; and etanercept [HR: 4.91; P < 0.0001] have statistically significantly shorter times to discontinuation in first-time biologic users, when compared with ustekinumab.[134]

Table 3.8: Incidence of Adverse Events from the PSOLAR Registry[133]

Adverse Event	Ustekinumab	Infliximab	Other biologics	Nonbiologics
	Per 100 person-years			
All-Cause Mortality	0.36	0.45	0.42	0.70
MACE	0.34	0.38	0.33	0.45
Malignancy	0.51	0.64	0.74	0.81
Serious infections	0.95	2.78	1.80	1.26

MACE = major adverse cardiovascular events

Controversies and Uncertainties

Across the 48 key trials (47 Phase III and one investigator initiated) identified for this review, only sixteen were based on head-to-head comparisons of the drugs of interest. As such, our network meta-analyses of PASI response are largely driven by indirect evidence; however, our findings are consistent with the results of head-to-head studies as well as with our assessment of relative differences in PASI response in comparison to placebo, and our NMA findings are also comparable to other recent assessments of the evidence.[40,41] Although PASI 75 or PASI 90 was reported as the primary endpoint in nearly all studies, other clinical outcomes (such as PGA/IGA, measures of symptom control) were inconsistently reported across trials making cross-drug comparisons difficult. For example, DLQI was evaluated in just about half of the included trials, and not all trials used the same standard of measurement, and other scales were not uniformly employed. Additionally, many of the tools developed to measure outcomes were not developed in a patient-centered perspective, and psoriasis-specific instruments are limited.

Longer-term data on both drug effectiveness and harms were also variable; many studies reassigned patients to different groups (mostly cross-over to the intervention) and evaluated outcomes at different time periods. As such, we could only confidently compare the comparative efficacy of targeted immunomodulators at the end of the induction period. Observational data were only available for ustekinumab, secukinumab, and the TNF-α therapies, which limited our understanding of real-world effectiveness and durability of benefit for many of these therapies.

Trials required washout of non-study treatments prior to initiating targeted immunomodulators and prohibited non-study treatments during the trials. Prohibition of non-trial treatments permits direct comparative evaluation of targeted immunomodulators with placebo or one another, but it does not represent actual practice in which combination therapy (e.g., topical use during targeted immunomodulator treatment) is common.

Assessments of real-world effectiveness also are limited by lack of comparative data on non-standard dosing, whether increased (to preserve effectiveness) or decreased (to reduce costs). Treatment durability and cost are both important factors in choosing a treatment for psoriasis. This uncertainty hinders our understanding of the relative effectiveness of these agents.

We also did not identify any studies evaluating the potential association between early aggressive treatment and cardiovascular risk. There is some data suggesting that diminishing the psoriasis-related inflammation in the skin also decreases the risk of cardiovascular disease,[2,135,136] while other studies have suggested an associated between targeted immunomodulators and increased risk of major adverse cardiovascular events.[137] This is a controversial topic, however, and larger and more long term studies are needed to better understand the impact of biologic therapies on cardiovascular outcomes in patients with moderate to severe psoriasis.[138,139]

Finally, subgroup data were primarily reported in conference abstracts and the interventions were only compared statistically to placebo, thereby limiting our understanding of how outcomes may differ across population types (e.g., patients with psoriatic arthritis or prior biologic experience). Concerning the choice of the appropriate first-line biologic therapy, there are current evidence-based recommendations available for some comorbid conditions in clinical practice. For example, in the presence of severe psoriatic arthritis, TNF-α inhibitors are recommended to be the preferred options, while they are to be avoided for patients with multiple sclerosis.[42] Expert opinion, clinical judgment and patient preferences will often determine the choice of the most appropriate therapeutic option for many comorbidities.[42] Future studies should be pragmatic in nature, including patients with these type of comorbid conditions encountered in routine clinical practice.

3.4 Summary and Comment

Using the ICER evidence rating matrix, our evidence ratings for the comparisons of interest are provided in Table 3.9; ratings are presented for the targeted immunomodulator listed in each row relative to the comparator listed in each column. Note that comparisons to placebo are not included in the table. As described previously, findings from placebo-controlled trials indicated substantial improvements in clinical measures for all agents. The safety of any new therapy is an important consideration. Severe or serious adverse events were rare during short-term trials and extension studies on these agents. So, all targeted immunomodulator receive a letter grade of "A" (i.e., high certainty of substantial net health benefit) relative to placebo.

The presence of some direct comparisons allowed us to be reasonably confident about the relative net health benefit for these comparisons. However, because of the lack of many head-to-head comparisons, we relied on a network meta-analysis to estimate the comparative clinical effectiveness between many targeted immunomodulators (see Appendix F). Ratings based on a combination of direct and indirect evidence are highlighted in green in the table along with the number of head-to-head studies that informed the rating.

ICER Ratings

There were two head-to-head trials comparing guselkumab and adalimumab (VOYAGE 1 &2), both of which showed incremental benefit for guselkumab over adalimumab in the percentage of patients achieving various PASI thresholds, PGA/IGA response, and DLQI outcome. In addition, there was a similar magnitude of benefit when indirect evidence was included. We felt that the consistency of results across the two trials represented *high certainty* of a small net benefit for guselkumab ("B") and an inferior net health benefit ("D") for adalimumab in this comparison.

Similarly, evidence from two trials (ULTIMMA 1 & 2) comparing risankizumab to ustekinumab consistently showed greater benefit for risankizumab on various PASI thresholds, PGA/IGA response and DLQI outcome. The magnitude of benefit when the indirect PASI evidence was included, gave us a *high certainty* of a small net benefit for risankizumab ("B") when compared to ustekinumab.

In the one head-to-head comparisons between tildrakizumab and etanercept (RESURFACE 2), tildrakizumab resulted in a modestly better PASI outcome (supported by network meta-analysis), and no difference on PGA and DLQI outcome, so we judged the evidence of tildrakizumab versus etanercept to represent a comparable or better net health benefit ("C+"), and "C-" (comparable or inferior) for etanercept in this comparison.

The one head-to-head trial comparing certolizumab pegol and etanercept (CIMPACT) was a single blind study which found no statistically significant difference between the two agents on PASI outcome when using 200mg certolizumab pegol, but significantly better response when using 400mg certolizumab pegol. Inclusion of indirect evidence combining both the 200mg and 400mg arms yielded a significant improved outcome for certolizumab over etanercept. However, we have very limited evidence on the PGA and DLQI outcomes. As such, we rated the evidence "C+" (comparable or better) for certolizumab and "C" (comparable or inferior) for etanercept in this comparison.

Ratings based on indirect evidence alone are highlighted in blue in the table. For these ratings, results of the network meta-analyses represented the only guide with which to judge the evidence. Drugs with evidence of net health benefit were judged "B+" or "C+" based on the observed magnitude of benefit, and their comparators received an "C-"rating (moderate certainty of comparable or inferior net health benefit). In situations where the credible interval (the Bayesian

equivalent of the confidence interval) crossed 1.0, the evidence was rated I (insufficient) for both directions of the comparison.

We also considered the 'second-order' effect in our evidence ratings. For example, since we have *moderate certainty* of an incremental or better net health benefit of risankizumab over ustekinumab, and moderate certainty that ustekinumab provides an incremental or better benefit over etanercept and apremilast, we conclude that there is moderate certainty that risankizumab would also provide an incremental benefit over etanercept or apremilast.

ICER Rating on the Drugs Included in the 2016 Review

Our ratings on the old drugs in the 2016 review remain mostly unchanged, except in three instances. The first is the rating of secukinumab versus adalimumab which we rated as "I" based on indirect evidence. We have now changed the rating to "C+" based on the result of the updated NMA which shows evidence of net health benefit. The second is the rating of secukinumab versus ustekinumab. This has now changed from C+ to B based on the addition of a second trial and the result of the NMA. The third is a comparison of infliximab versus etanercept. In this instance, the rating between the two drugs did not change, however, it is now highlighted in green in the table because we found data from one head-to-head trial which provides additional direct evidence.

Table 3.9. ICER Evidence Ratings for Head-to-Head Comparisons (New ratings based on the current review are in bold fonts)

Treatment	Comparator								New comparators			
	Adalimumab	Apremilast	Brodalumab	Etanercept	Infliximab	Ixekizumab	Secukinumab 300	Ustekinumab 45/90	**Certolizumab pegol**	**Guselkumab**	**Risankizumab**	**Tildrakizumab**
Adalimumab	-	B+	C-	C+	C-	C-	**C-***	I	**I**	**D (2)**	**C-**	**I**
Apremilast	C-	-	D	I	C-	C-	C-	C-	**C-**	**C-**	**C-**	**C-**
Brodalumab	C+	B	-	B	I	I	I	B (2)	**C+**	**I**	**I**	**C+**
Etanercept	C-	C+	D	-	**C- (1)†**	D (2)	C- (1)	C- (1)	**C- (1)**	**C-**	**C-**	**C-(1)**
Infliximab	C+	B+	I	**B+ (1)†**	-	I	I	C+	**C+**	**I**	**I**	**C+**
Ixekizumab	C+	B+	I	A (2)	I	-	C+	B+ (1)	**C+**	**I**	**I**	**C+**
Secukinumab 300	**C+***	B+	I	B+ (1)	I	C-	-	B (2)	**C+**	**I**	**I**	**C+**
Ustekinumab 45/90	I	B+	D (2)	B+ (1)	C-	C- (1)	D (2)	-	**I**	**C-**	**D (2¥)**	**I**
New agents												
Certolizumab pegol	**C-**	**B+**	**C-**	**C+ (1)**	**C-**	**C-**	**C-**	**I**	-	**C-**	**C-**	**I**
Guselkumab	**B (2)**	**B+**	**I**	**C+**	**I**	**I**	**I**	**C+**	**C+**	-	**I**	**C+**
Risankizumab	**C+**	**B**	**I**	**B**	**I**	**I**	**I**	**B (2¥)**	**C+**	**I**	-	**C+**
Tildrakizumab	**I**	**B+**	**C-**	**C+ (1)**	**C-**	**C-**	**C-**	**I**	**I**	**C-**	**C-**	-

Note: The table should be read row-to-column. For example, there is moderate certainty that adalimumab has a small net benefit compared to apremilast (B+). Conversely, there is moderate certainty that the point estimate for comparative net health benefit of apremilast is either comparable or inferior to adalimumab (C-).

Table key: green=direct + indirect evidence; blue=indirect evidence only

Number of head-to-head studies in parentheses

*Rating of secukinumab vs. adalimumab changed from the previous review from I to C+ based on the result of the updated NMA;

†Rating of infliximab vs. etanercept did not change from previous report, however the rating is now highlighted in green in the table because we found evidence on 1 head-to-head trial

4. Long-Term Cost Effectiveness

4.1 Overview

The aim of this analysis was to estimate the cost-effectiveness of treatments for patients with moderate to severe plaque psoriasis who have failed topical treatment and phototherapy. All treatments included in the NMA, except for risankizumab and tildrakizumab (which do not yet have publicly-available prices), are included in the cost-effectiveness model. We developed a decision-analytic model, based originally on the structure of the York psoriasis cost-effectiveness model,[140] to assess the clinical and economic outcomes of the treatments of interest. Model parameters were estimated from the NMA described earlier in this report and the published literature. The analysis uses a health sector perspective with ten-year and lifetime time horizons, both using a 3% annual discount rate for costs and outcomes. The outcomes of the model include total costs, quality-adjusted life years (QALYs), months spent in health states of PASI improvement greater than or equal to 75% and 90%, and incremental cost-effectiveness ratios. Uncertainty in the data inputs and assumptions were evaluated using sensitivity and scenario analyses.

Since our prior report on targeted treatments for plaque psoriasis, we have made the following changes to the model:

- Updated discontinuation rates based on new data.
- Modeled treatment sequences in which second-line targeted treatment depends on the choice of first-line targeted treatment.
- Updated all costs.
- Updated the rate of switching to a second-line targeted treatment (vs. non-targeted) from 50% to 75% upon discontinuation from the first-line targeted treatment.
- In light of increasingly different discounts and pricing strategies, we have switched from using class-based discounts from WAC to drug-specific discounts to estimate net prices.
- Switched to using average selling price (ASP) plus mark-up for infliximab to more closely reflect the way that office- or clinic-administered products are reimbursed.

4.2 Methods

Model Structure

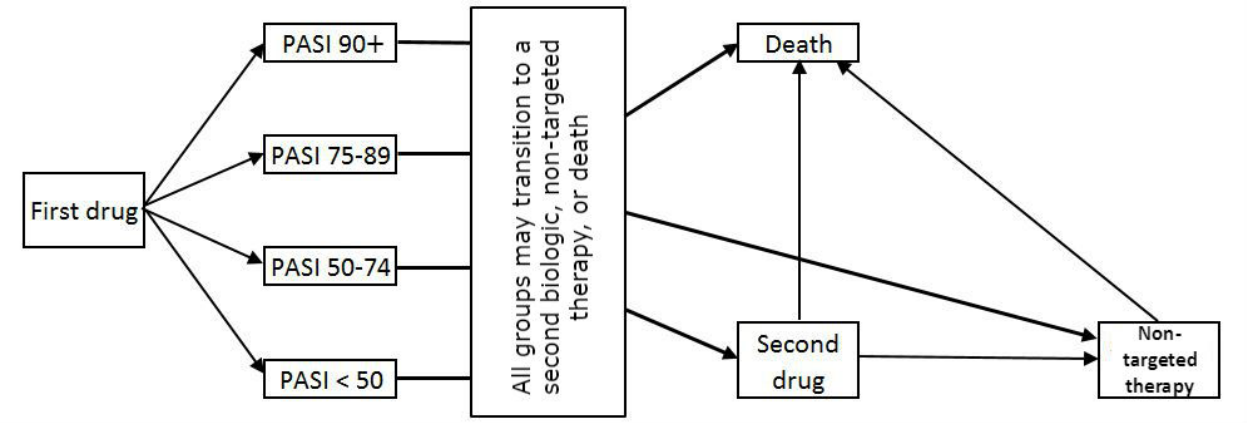
The model structure is unchanged since our prior report.

We developed a Markov model in Excel with eight health states, as shown in Figure X; patients could transition between states every month. After the initiation period of the first-line targeted therapy, defined as the point in time at which the primary trial outcome was measured, typically 12-16 weeks, patients were categorized into one of four health states based on their percent improvement in PASI score over baseline: PASI 90 and higher, PASI 75-89, PASI 50-74, and PASI <50. In the base-case analysis, no transition between PASI improvement states was allowed in the model, but drug switching and discontinuation over time could occur.

Patients with response below 75% improvement after the initiation period (16 weeks for adalimumab, apremilast, and guselkumab, 10 weeks for infliximab, and 12 weeks for all other drugs) were assumed to discontinue the first-line therapy in the base-case (this assumption was evaluated in a scenario analysis, described below). A proportion of these patients then began second-line targeted therapy and the remainder received non-targeted therapy (i.e., topical therapy, other systemic therapy, and phototherapy). Second-line therapy varied based on first-line targeted treatment: those patients taking an IL-17 drug switched to guselkumab; patients using guselkumab switched to a market basket representing the average of all IL-17 drugs; all other patients switched to a market basket of all IL-17 drugs plus guselkumab.

Patients with a PASI improvement of at least 75% after the initiation periods continued on first-line therapy after the initiation period. However, we applied a drug-specific discontinuation rate to each initial targeted drug which determines the rate of discontinuation due to all causes (e.g., loss of efficacy, development of adverse effects) after the end of the initiation period. This rate differed between the first and subsequent years of treatment. After discontinuing their first-line treatment, these patients transition to either second line targeted therapy or non-targeted therapy in the same proportion as those patients who did not have an adequate initial response to their first-line drug. All health states were assumed to have an equal risk of death, which is treated as a function of age alone (i.e., neither change in psoriasis disease state nor treatment alters mortality rate).

Figure 4.1. Model Framework



Target Population

The population of focus for this review was adult patients with moderate to severe plaque psoriasis who failed topical treatment and phototherapy. Consistent with the patient populations in the key clinical trials, the mean age of patients in the base case is 45 years and mean weight is 90 kg.

Treatment Strategies

The interventions included for review are those assessed in the evidence review and NMA, except for risankizumab and tildrakizumab, for which there was no pricing information at the time of the report.

We modeled sequential targeted treatments and targeted treatment discontinuation as described above.

The administration schedules for included drugs are listed below. Each of these therapies includes an initial period with dosing that differs from the maintenance dose. Regimens are based on labeled dosing recommendations for all currently marketed drugs.

Table 4.1. Medication Dosing Schedules

Drug	Initial dosing	Maintenance dosing
Adalimumab	80 mg once	40 mg every other week, starting one week after initial dose
Apremilast	Day 1: 10 mg in morning; Day 2: 10 mg in morning and 10 mg in evening; Day 3: 10 mg in morning and 20 mg in evening; Day 4: 20 mg in morning and 20 mg in evening; Day 5: 20 mg in morning and 30 mg in evening	30 mg twice daily
Brodalumab	210 mg at weeks 0, 1, and 2	210 mg every two weeks
Certolizumab pegol	400 mg at weeks 0, 2, and 4	400 mg once every two weeks (200 mg for patients < 90 kg)
Etanercept	50 mg twice weekly for three months	50 mg once weekly
Guselkumab	100 mg at weeks 0 and 4	100 mg every eight weeks
Infliximab	5 mg/kg at weeks 0, 2, and 6	5 mg/kg every eight weeks
Ixekizumab	160 mg at week 0, then 80 mg at weeks 2, 4, 6, 8, 10, and 12	80 mg every four weeks
Secukinumab	300 mg at weeks 0, 1, 2, 3, and 4	300 mg every 4 weeks
Ustekinumab	45 mg at weeks 0 and 4 (90 mg for weight > 100 kg)	45 mg every 12 weeks (90 mg for weight > 100 kg)

Key Model Characteristics and Assumptions

Table 4.2. Key model characteristics and assumptions

Assumption	Rationale
A patient cannot transition between effectiveness (PASI improvement) levels.	There is only modest improvement in effectiveness beyond the trial period, and discontinuation rate accounts for decline in effectiveness over time.
Probability of discontinuing first-line therapy is drug-specific as supported by available data	Empirical evidence indicates discontinuation rates beyond the initiation period are higher for infliximab and etanercept and differs in year 1 vs. years 2+. (See section *Drug discontinuation and switching* section below for details.)
All discontinuation in the first year is due to lack of effectiveness at the end of the initiation period, except for infliximab	Our assumption in the base-case is that patients who receive benefit of less than PASI 75 from initial targeted treatment will discontinue that treatment at the end of the initiation period. The one exception to this is infliximab, which has a greater discontinuation in year one than indicated by drug response alone. This assumption was evaluated in a scenario analysis.
Probability of discontinuing newer drugs (brodalumab, certolizumab pegol, guselkumab, ixekizumab, tildrakizumab) is the same as ustekinumab in years 2+	There are limited to no data on discontinuation rates for the newer agents. This assumption was evaluated in a sensitivity analyses.
Seventy-five percent of patients discontinuing first line targeted drug therapy receive second line targeted drug and remainder receive non-targeted drug.	Recently published data[22] and expert clinical opinion suggest that, among those patients who discontinue their first-line targeted drug, approximately 75% begin a different targeted drug.
Second-line targeted treatment was assumed vary by first-line treatment as follows: patients receiving an IL-17 drug first-line receive guselkumab second-line; patients receiving guselkumab first-line receive a market basket equivalent to the average of all IL-17 drugs second-line; patients receiving any other first-line drug receive a market basket equivalent to the average of all IL-17 drugs plus guselkumab.	Clinical experts indicated that second-line treatment is likely to vary according to the choice of first-line agent and suggested this allocation of treatments. Different second-line targeted drug baskets were assessed in scenario analyses.
Second-line targeted treatments have a 10% lower probability of achieving PASI 75-100 (i.e., 5% lower probability of PASI 75-89, 5% lower probability of PASI 90-100, 5% higher probability of PASI 50-74, and 5% higher probability of PASI < 50).	There are no RCTs of second line targeted therapy and limited data on second line targeted therapy response in general.
Risk of death is based on age alone.	There is no clear evidence supporting an improvement in survival with targeted treatments for psoriasis.

Patients remain on first-line therapy during the trial period.	A full trial period (16 weeks for adalimumab and apremilast, 12 weeks for all others) is needed to determine whether the drug will produce an adequate response.
Subcutaneous drugs are administered in-clinic during the initiation dose and by the patient themselves during the maintenance period.	Allows for patient instruction while acknowledging that patients will self-administer the vast majority of their doses.
Drug cost discount was applied on a drug-by-drug (rather than class) basis. Guselkumab received the average discount of all drugs included in this report (33%).	There is significant heterogeneity in the amount that each drug is discounted within classes. Therefore, we have chosen to calculate each drug's net price using drug-specific discounts. Guselkumab had insufficient data to collect actual discount percentages and was therefore assumed to have the average discount of all other drugs in this analysis.
No additional months in PASI states > 0% improvement, on average, are attributable to non-targeted treatment	The population for this model has already not seen adequate improvement with non-targeted treatment alone and thus is eligible for targeted treatment. While some individuals who continue on non-targeted treatment may temporarily improve in PASI status, some will get worse. We therefore did not attribute any change in average PASI status to continued use of non-targeted drugs.

Model Inputs

Clinical Inputs

Clinical Probabilities/Response to Treatment

First-line targeted drug response

First-line targeted drug effectiveness is taken from the results of the NMA described earlier in the report, in section 3.

Table 4.3. Probability of PASI Response as First-Line Targeted Treatment

Drug	PASI < 50	PASI 50-74	PASI 75-89	PASI 90-100
Adalimumab	0.13	0.17	0.23	0.47
Apremilast	0.40	0.23	0.20	0.17
Brodalumab	0.04	0.09	0.18	0.69
Certolizumab pegol	0.14	0.17	0.24	0.45
Etanercept	0.27	0.22	0.23	0.28
Guselkumab	0.04	0.08	0.17	0.71
Infliximab	0.08	0.13	0.21	0.58
Ixekizumab	0.03	0.08	0.16	0.73
Secukinumab	0.06	0.11	0.20	0.63
Ustekinumab	0.13	0.17	0.24	0.47

Second-line targeted treatment effectiveness

No randomized controlled clinical trials have been conducted in an exclusively second-line patient population. Warren et al[141] recently studied secukinumab 150 and 300mg in a second-line (first-line non-responder) population (no placebo group). The 16-week PASI 75 response for 300mg (N=118) was 71% for patients with one previous non-response, and 48% in patients who had failed more than one TNFα inhibitor; in contrast, the first-line PASI 75 response was 83% in the NMA. Griffiths et al[142] evaluated outcomes with guselkumab among adalimumab PASI 90 non-responders, and found approximately 60% of patients achieved PASI 90 after 16 weeks of treatment; in contrast, 83% of all patients initiated on guselkumab achieved PASI 90 in the NMA. Similarly, results from the NAVIGATE study[143] indicate that response to guselkumab is likely lower (48% PASI 90 at 12 weeks vs. 70-73% PASI 90 at 16 weeks in the VOYAGER studies) in patients who fail a targeted therapy. Papp et al[144] studied the effect of previous targeted drug use on brodalumab and ustekinumab outcomes; 27% and 26% of patients had previously received a targeted agent, respectively, and 12% and 10% had previously failed targeted agent. For brodalumab, PASI 100 was achieved in 41.7% and 32.0% of patients in whom prior targeted therapy had been successful or failed; the corresponding results for ustekinumab were 21.1% and 11.3%.

These findings indicate that prior experience, and in particular prior failure, with targeted drugs is associated with a lower response rate. We assumed the PASI 75 response for second-line therapy was 10% lower than for findings in the NMA, which included studies primarily enrolling patients who were naïve to targeted drugs and were adjusted for placebo group differences.

Drug discontinuation and switching

The three main data sources for drug discontinuation and switching are 1) patient registries, 2) long-term trial follow-up, and 3) claims data. Some of the most exhaustive data come from Denmark, where all treated psoriasis patients in the country are enrolled in a long-term patient registry, known as Dermbio. Egeberg et al[145] reported real-world drug discontinuation based on a total of 3,495 treatment series (adalimumab: 1,332; etanercept: 579; infliximab: 333; ustekinumab: 1,055 and secukinumab: 196). Targeted treatment-naïve patients had lower discontinuation rates than non-naïve patients. Infliximab and etanercept had the highest discontinuation rates (etanercept primarily due to lack of effectiveness; infliximab primarily due to causes other than lack of effectiveness) and ustekinumab had the lowest rate. Secukinumab, for which there were limited data, had a discontinuation rate similar to infliximab and etanercept. However, interpretation of these findings is complicated by dose increases for etanercept (29% patients were >50% higher than label) and ustekinumab (33% patients were >50% higher than label for patients <=100kg) compared to almost none for adalimumab and secukinumab, use of secukinumab primarily in patients who had previous exposure to targeted agents, and different definitions of treatment gaps due to dosing schedules. In contrast, Iskandar et al,[22] in a UK-based patient registry (BADBIR) of 2,980 patients (adalimumab: 1,675; etanercept: 996; ustekinumab: 309), found that ustekinumab and adalimumab had similar discontinuation rates. This finding may be explained by similar treatment gap definitions and lack of ustekinumab dose increases due to UK coverage policies. Of note, approximately 77% of patients with a treatment gap switched to another targeted therapy.

Long-term trial follow-up studies generally have found low rates of drug discontinuation. Interpretation of findings from these studies and comparison to real-world patient registry data is complicated by controlled trial settings, and these data are primarily useful for assessing the discontinuation rates of newer agents in relation to older agents across similar study designs. Langley et al[146] reported a ustekinumab discontinuation rate of 30% (363 of 1,212 patients) over 4.7 years, with approximately half of patients receiving dose adjustments. Mrowietz et al[147] reported a 4% dropout during secukinumab induction, and 8% dropout for PASI 75 responders during remainder of year 1; Bissonnette et al[148] reported a secukinumab discontinuation rate from end of year 1 to end of year 3 of 19% (32 of 168 patients). Leonardi et al[149] reported 22% of (84/385) ixekizumab patients discontinued therapy or were lost to follow-up after three years (27% had dose adjustments). Blauvelt et al[31] reported a guselkumab discontinuation rate of 8.5% (28 of 329) after 48 weeks in the VOYAGER 1 RCT; Gordon et al[150] unfortunately did not report discontinuation rates at 100 weeks. While not definitive, results from these clinical trials suggest discontinuation rates for ustekinumab, secukinumab, and ixekizumab are generally similar.

Several studies have been conducted in the U.S. using claims data. These studies suggest etanercept and infliximab have the highest discontinuation rates, and that secukinumab discontinuation is similar to ustekinumab. Cao et al ,[151] in a study of 1,000 ustekinumab treated patients (60% targeted treatment experienced), using a treatment gap period of 130 days, found 81% persistence with a mean follow-up ~6 mos. Feldman et al[152] in a study of 1,504 secukinumab patients (mean follow-up ~6 months; 68% targeted treatment experienced) reported an 87% persistence. Bagel et al[153] evaluated discontinuation and persistence among targeted drug-naïve (N=3,584) and targeted drug-experienced patients (N=1,185) who initiated secukinumab, adalimumab, or etanercept. Mean follow-up ranged from 529-615 days across drugs. Discontinuation rates at one year for the three drugs were 35%, 42%, 47% for treatment-naïve and 32%, 41%, and 54% for treatment-experience patients, respectively. Adherence ranking at one year was analogous. These studies suggest ustekinumab and secukinumab discontinuation over the first 6 mos. are similar, secukinumab discontinuation in year one is lower than for adalimumab and etanercept, and discontinuation is higher for targeted drug experienced patients.

Mortality

There is no clear evidence that the modification of the psoriasis-related health state through treatment alters mortality risk. As such, mortality depends upon age alone.

Utilities

Our base case uses considers the utility of each level of PASI improvement to be represented by the estimated mean utility weight as derived by co-administration of the generic quality of life instrument, the EQ-5D, with the PASI in five clinical trials; trial findings are listed below and the average used in the model is presented on the last line of the table.[154]

Table 4.4. Health State Utilities Using Targeted Therapies

	Non-targeted treatment	PASI < 50	PASI 50-74	PASI 75-89	PASI 90-100
Adalimumab	0.660	0.723	0.838	0.838	0.968
Apremilast	0.660	0.710	0.830	0.850	0.870
Ixekizumab	0.660	0.689	0.785	0.826	0.844
Secukinumab	0.660	0.769	0.853	0.886	0.924
Ustekinumab	0.660	0.700	0.830	0.880	0.910
EQ-5D average (Pickard, 2016)	*0.660*	*0.718*	*0.827*	*0.856*	*0.903*

Adverse Events

As serious adverse event frequencies are similar across all drugs, most previously published cost-effectiveness analyses in plaque psoriasis have not included adverse events, and our previous analysis indicated inclusion of serious infection had little effect on results, they are hence not included in the base case scenario. We have included an analysis of the hypothetical impact of suicidality associated with brodalumab in a scenario analysis.

Economic Inputs

Drug Acquisition Costs

The below table refers to drug acquisition cost alone, not including administration costs or the cost of required laboratory tests. Two drugs – infliximab and ustekinumab – are dosed by weight. Infliximab is dosed at 5 mg/kg. We assumed that vials are not shared and that an average of five vials will be used per patient. The dose of ustekinumab is doubled from its baseline of 45 mg for patients weighing over 100 kg. Based on the clinical trials, we assumed that 30% of patients would receive the 90 mg dose. Likewise, the standard dose of certolizumab pegol is 400 mg every two weeks, but the label indicates that a 200 mg dose may be considered for patients under 90 kg. Our base-case assumes that 50% of patients receive this lower dose.

Additionally, there is some evidence to support that dose escalation occurs, particularly for etanercept. However, existing evidence does not clearly support that *average* doses are higher

than labeled dosing. The Egeberg study[145] in Denmark found the mean etanercept dose over the first 24 weeks was similar to U.S. labeled dosing, the Feldman JMCP 2015[155] study in the US found similar proportions of patients getting dose increases and dose decreases, and the Feldman JMCP 2017[156] study evaluated dose increases but failed to account for dose decreases or report mean doses.

In order to reflect differential discount and pricing strategies, we used net price in the cost-effectiveness model. With the exception of infliximab, net pricing estimates for all modeled drugs were derived from SSR Health, LLC, which combines data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs, to derive a net price. The derived net price is at the unit level and across all payer types. We estimated net prices by comparing the four-quarter averages (i.e., first quarter of 2017 through fourth quarter of 2017) of both net prices and WAC per unit to arrive at a mean discount from current WAC for the drug.[43] In contrast to the 2016 report, when we used discounts based on drug class, we used drug-specific discounts in this model. This is due to heterogeneity that has arisen within classes. For example, brodalumab combines a smaller discount with a lower WAC to arrive at an overall annual maintenance cost that is only slightly lower than other members of the IL-17 class. Guselkumab had insufficient data on discounts and therefore was assumed to have the average discount of all other drugs in this analysis (33%).

Infliximab is a unique drug within this set, as it is the only drug administered intravenously. Because the drug is not being dispensed directly to the patient, we used average selling price (ASP) plus a 9.5% markup representing the mean markup by physicians' offices and hospital outpatient units.[44]

Non-targeted cost includes the cost of topical medications such as corticosteroids, non-targeted oral medications such as methotrexate, and hospitalization. The cost of $626.74 was determined from a claims analysis published in 2009 with its results recalculated to 2017 US dollars using the medical inflation rate.[157]

Table 4.5. Drug Cost Inputs

Intervention	Unit	WAC per Unit/Dose*	Discount %	Net price per Unit	Cost of first year	Annual cost of year 2+
Adalimumab	40 mg	$2,436.02	31%	$1,674.64	$46,751.16	$43,693.75
Apremilast	30 mg	$54.72	22%	$42.46	$30,807.28	$31,019.58
Brodalumab	210 mg	$1,750.00	20%	$1,400.00	$37,684.00	$36,528.00
Certolizumab pegol	400 mg (see above for dosing note)	$4,044.32	36%	$2,583.70	$54,097.14	$50,559.32
Etanercept	50 mg	$1,218.00	31%	$837.69	$54,641.32	$43,713.06
Guselkumab	100 mg	$10,158.52	33%	$6,806.21	$50,609.02	$44,395.93
Infliximab	450 mg	$1,167.82	22%**	$911.99	$38,466.44	$29,743.90
Ixekizumab	80 mg	$5,161.60	44%	$2,888.74	$51,374.18	$37,685.68
Secukinumab	300 mg	$4,712.38	38%	$2,926.22	$49,624.51	$38,174.63
Ustekinumab	45 / 90 mg (see above)	$10,292.15 / $20,584.30	27%	$7,532.84 / $15,063.47	$58,620.92	$42,584.22

Administration and Monitoring Costs

All drugs except for apremilast and infliximab are administered subcutaneously. Apremilast is an oral medication, and infliximab is intravenously administered over a two-hour period.

As stated above, our assumption is that only the first administration of a subcutaneously-administered drug is performed in a clinic. The 2017 national payment for a subcutaneously administration (CPT code 96372) is $25.84. Intravenous administration over two hours is represented by two CPT codes – 96413 for the first hour and 96415 for the second hour – and costs a total of $183.89.

Health Care Utilization Costs

Psoriasis patients receiving certain targeted drugs require monitoring for potential infection. Some drugs also require testing of physiologic systems, such as hepatic function. The costs for each of the laboratory tests required by one or more targeted psoriasis therapies and the schedule of laboratory tests indicated for each drug are provided below. When possible, the indicated

laboratory tests were obtained from the drug's labeling; otherwise, they were gathered by examination of the therapeutic protocol in the pivotal trials. In addition to these laboratory tests, each patient was assumed to receive four physician visits (CPT code 99213, $80.77) per year related to the disease.

Costs for the laboratory tests are:

- Latent TB screen (CPT 71010): $25.08
- Active TB screen (CPT 86580): $9.02
- Complete blood count (CPT 85025): $14.41
- Hepatitis B test (CPT 86317): $27.79
- Renal function test (CPT 80069): $16.10

Table 4.6. Laboratory Test Schedule

Intervention	Latent TB	Active TB	CBC	HBV	Renal function
Adalimumab	Annually		Quarterly	Once	
Apremilast					Annually
Brodalumab	Once				
Certolizumab pegol	Annually		Quarterly		
Etanercept	Annually		Quarterly	Once	
Guselkumab	Annually				
Infliximab	Once	Annually		Once	
Ixekizumab		Annually			
Secukinumab		Annually			
Ustekinumab	Annually		Quarterly		

Test abbreviations: TB = tuberculosis, CBC = complete blood count, HBV = hepatitis B virus

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using reasonable ranges for each input described in the model inputs section above. We chose to compare ixekizumab to non-targeted treatment in order to focus on the comparison between a highly effective therapy and the least effective. We also included a comparison of ixekizumab versus etanercept, as it compares a more effective to a less effective but commonly used targeted drug.

Scenario Analyses

We conducted a variety of scenario analysis to assess the assumptions in our base-case analysis.

1. *Continuation of treatment in PASI 50-74 group:* In this scenario, we allowed 2% of individuals in the PASI 50-74 group to improve to PASI 75-89 per month in the first year after the initiation period. In this group, 10% of patients discontinued their first-line treatment per month as well. All patient in this PASI category discontinue targeted treatment by the end of year one
2. *Effect of net price increases:* We used net prices from the 2016 report in this model in order to isolate the effect of price increases since that time. To allow for comparability, we used drug-specific rebates derived from 2016 data as applied to prices from the same time period. This is in contrast to the class-based rebates we had applied in the previous report.
3. *Completed suicides with brodalumab:* Four participants among the 4,464 (0.09%) in the brodalumab arm of that drug's trials completed suicide, compared to zero completed suicides in the control arm. In acknowledgment of the severity of this event, we conducted a scenario analysis that, pessimistically, assumes completed suicide takes place immediately after the first month of brodalumab.
4. *Time to onset:* We included one scenario where we varied the onset of drug response in order to test its effect on overall outcomes. Using secukinumab as a test case, we examined the effects of holding all patients in the PASI < 50 state until month 1, 2, or 3.
5. *Second-line market baskets:* We assessed the effect of including all non-first-line drugs in the second-line basket; that is, we averaged the costs and effectiveness of all eleven drugs (with the second-line penalty mentioned in the assumptions) and use this as the second-line market basket for all drugs.
6. *Modified Societal Perspective:* It is well known that psoriasis affects productivity. We evaluated a scenario using a limited societal perspective in which productivity benefits of psoriasis treatment and the productivity loss associated with intravenous administration of a drug are accounted for. Productivity cost offsets were derived from work productivity impact measures in RCTs of adalimumab and ixekizumab.[158,159] We estimated that patients achieving a PASI 75 improvement who were employed had a 15% improvement in total work productivity (primarily presenteeism vs. absenteeism). We also estimated that 60% of patients were employed full-time and 15% half-time based on baseline characteristics of study participants. We used an average 2017 US income of $50,620.[160] We assumed presenteeism improvements were valued equally to absenteeism improvements, and that presenteeism effects were not already captured

by quality of life (EQ-5D) measurements. The cost offset per year for a patient achieving a PASI 75 improvement was thus $5,100.

7. *Lower doses with certolizumab pegol and ustekinumab*: Both certolizumab pegol and ustekinumab have lower doses that can be used on patients with lower body weight (under 90 kg for certolizumab pegol and under 100 kg for ustekinumab). We tested a scenario in which only those patients who are eligible are treated with these drugs.
8. Additionally, we performed a threshold analysis by systematically altering the price of all drugs to estimate the maximum prices that would correspond to given willingness to pay (WTP) thresholds. Risankizumab, an IL-23 drug expected to be approved by the FDA in 2018, and tildrakizumab, another IL-23 drug that was recently approved but does not have an official price, have been included in this threshold analysis.

Model Validation

We used several approaches to validate the model. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model. Second, we varied model input parameters to evaluate face validity of changes in results. We developed a simple back-of-the-envelope model using only drug costs and trial drug response data and compared to our full model results. We compared results to other cost-effectiveness models in this therapy area. Finally, an external health economist with expertise in psoriasis assessed the modeling approach and draft results.

4.3 Results

Base Case Results

Our results suggest that, while quality-of-life improvements are similar across the targeted agents, initiating treatment with the IL-17 drugs or guselkumab leads to the greatest improvement in QALYs, while initiation with apremilast, etanercept, or infliximab is the least effective. In contrast, initiation with the IL-17 drugs, guselkumab, or certolizumab pegol generally leads to the highest total cost, while initiation with apremilast, etanercept, or infliximab leads to lower total costs.

Table 4.7. Results for the Base Case for Targeted Treatments Over 10 years

First-line Treatment	Total Cost	Total QALYs	Months spent in PASI 90+*	Months spent in PASI 75+*
Non-targeted treatment	$67,800	5.70	0.0	0.0
Adalimumab	$308,000	7.17	52.0	74.1
Apremilast	$215,000	6.79	32.6	53.5
Brodalumab	$289,000	7.39	67.8	84.9
Certolizumab pegol	$341,000	7.16	50.5	73.5
Etanercept	$272,000	6.88	37.7	57.9
Guselkumab	$342,000	7.40	69.0	85.3
Infliximab	$238,000	6.98	47.8	62.5
Ixekizumab	$311,000	7.42	70.9	86.1
Secukinumab	$305,000	7.34	63.5	82.4
Ustekinumab	$315,000	7.17	51.1	74.1

* Time spent in PASI health states is discounted at the same rate at costs and other outcomes.

Note that the results above should not be interpreted as treatments with a single targeted drug, but as sequences of targeted drugs (including 'step therapy'). For example, treatment beginning with guselkumab continues to IL-17 and/or non-targeted drugs upon discontinuation, and treatments beginning with IL-17 drugs continue to guselkumab and/or non-targeted drugs upon discontinuation. All other drugs are followed by a market basket of IL-17 drugs and guselkumab upon discontinuation from the first-line targeted treatment.

The incremental cost-effectiveness ratios compared to non-targeted treatment are shown below.

Table 4.8. Incremental Cost-Effectiveness Ratios (ICERs) for the Base Case, Compared to Non-Targeted Treatment

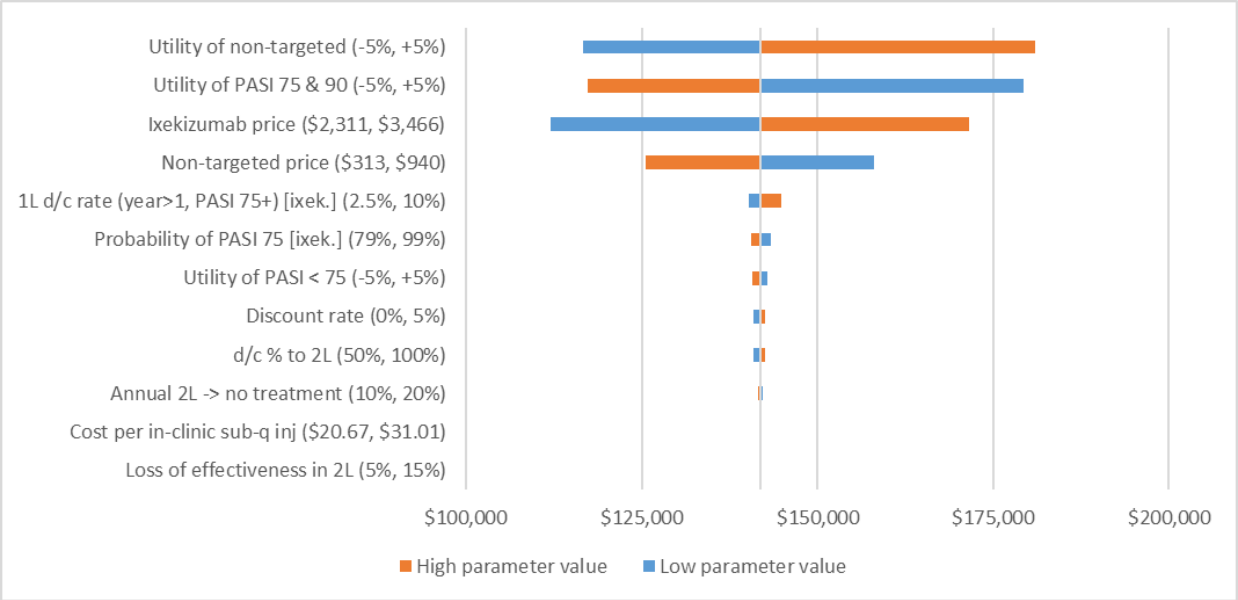
First-line Treatment	Cost / QALY	Cost / month in PASI 90+	Cost / month in PASI 75+
Adalimumab	$164,000	$4,600	$3,200
Apremilast	$135,000	$4,500	$2,800
Brodalumab	$131,000	$3,300	$2,600
Certolizumab pegol	$188,000	$5,400	$3,700
Etanercept	$175,000	$5,400	$3,500
Guselkumab	$161,000	$4,000	$3,200
Infliximab	$134,000	$3,600	$2,700
Ixekizumab	$142,000	$3,400	$2,800
Secukinumab	$145,000	$3,700	$2,900
Ustekinumab	$169,000	$4,800	$3,300

Sensitivity Analysis Results

To demonstrate effects of model parameter uncertainty on incremental cost per QALY gained, we varied input parameters based on standard errors or reasonable ranges for two examples: ixekizumab versus non-targeted treatment and ixekizumab versus etanercept. These examples were selected because ixekizumab is one of the most effective drugs and has some long-term data, and because etanercept represents one of the more commonly used original targeted agents. Furthermore, some health care plans require patients to utilize a less effective and less expensive targeted agent as a step therapy.

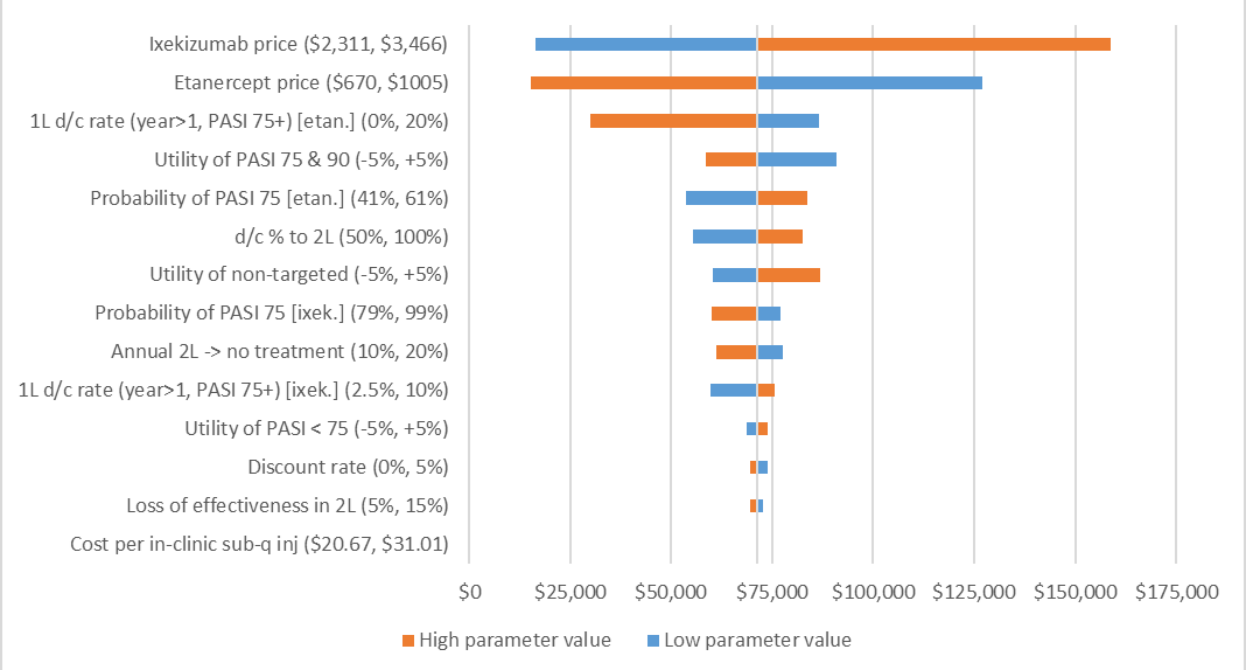
In the base-case, ixekizumab has an ICER of $142,000 per QALY compared to non-targeted, and an ICER of $72,000 per QALY compared to etanercept.

Figure 4.2. One-Way Sensitivity Analyses of ICER for Ixekizumab Versus Non-Targeted



In the comparison to non-targeted treatment, uncertainty in utility scores and drug costs are the primary sources of uncertainty; the ICER exceeds $150,000 per QALY gained with reasonable, albeit less likely, values for each of these parameters.

Figure 4.3. One-Way Sensitivity Analyses of ICER for Ixekizumab Versus Etanercept

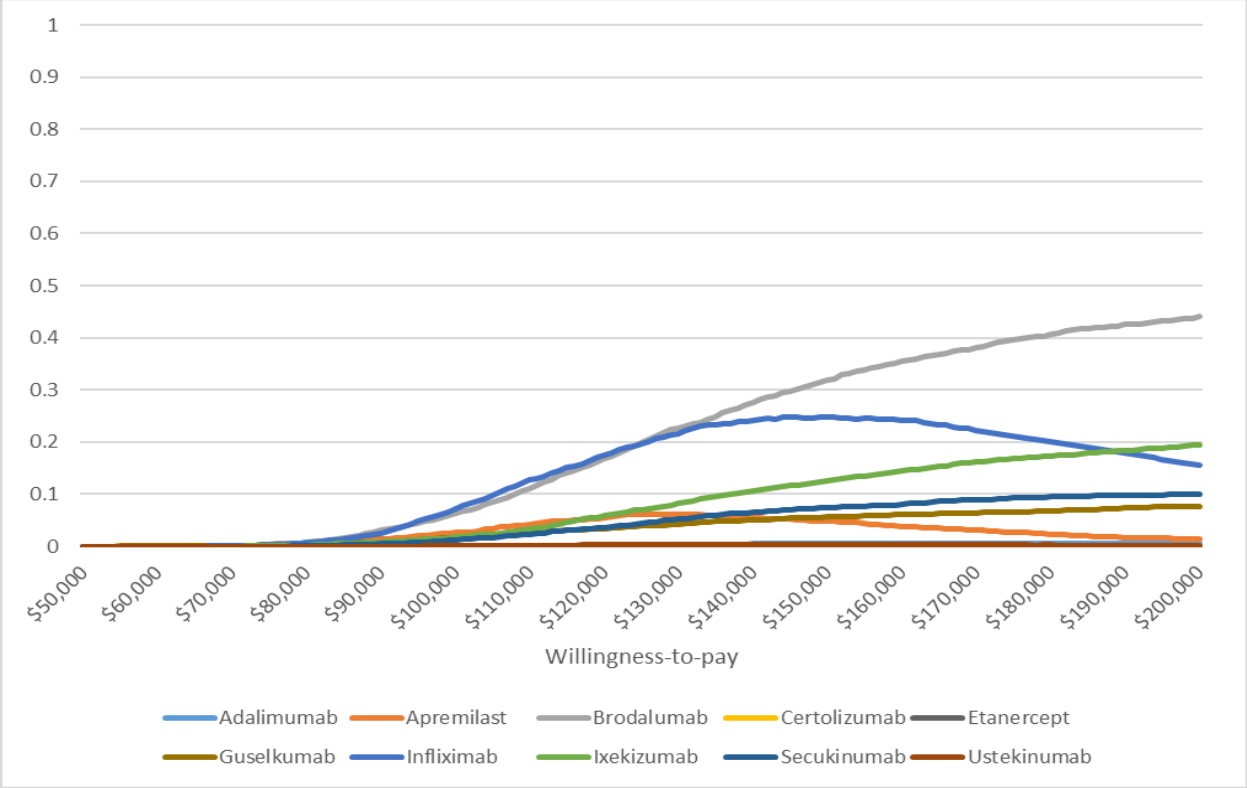


(Note: Ixekizumab Dominates Etanercept at a Price of $2,311 Per Unit)

In the comparison to etanercept, uncertainty in model results is again driven by uncertainty in drug costs, but also drug discontinuation rates, utility for PASI response states, and drug effectiveness. Despite varying these parameters, initiation with ixekizumab compared to initiation with etanercept is below the $150K/QALY threshold in almost all cases.

We also conducted a probabilistic sensitivity analysis (PSA) to more comprehensively evaluate the impact of uncertainty in all model parameters when comparing all interventions (targeted drugs and non-targeted therapy) with each another. The cost effectiveness acceptability curves indicate the probabilities (y-axis) that initiation with each drug is the most cost-effective approach at various willingness to pay thresholds (x-axis).

Figure 4.4. Cost-Effectiveness Acceptability Curves



This graph shows the probabilities (y-axis) that initiation with each targeted drug is the most cost effective strategy at various willingness-to-pay thresholds (x-axis), comparing all targeted drugs to each other and to non-targeted treatment. (Note: non-targeted treatment not shown for clarity).

These results indicate that at a $50K/QALY threshold, no targeted drugs offer good value; at a $100K/QALY threshold, initiation with brodalumab or infliximab each have a 10% probability of being optimal value, and probabilities for the other targeted agents are all near zero; and at a $150K/QALY threshold there is more separation, as initiation with brodalumab or infliximab is most

likely to be cost effective, while the other IL-17s and guselkumab have somewhat lower probabilities of being most cost effective. Apremilast has a modest probability of being cost effective across the $100K-$150K/QALY range, while initiation with adalimumab, etanercept, ustekinumab, and certolizumab have essentially no probability of being the most cost-effective strategies across all thresholds.

Scenario Analyses Results

Continuation of treatment in PASI 50-74 group

When we assumed patients in the PASI 50-74 group continued therapy with small improvement and relatively higher discontinuation, the results for costs increased by small amounts (0.9% to 3.3%, depending on the drug), while QALYs changed by 0.2% to 0.4%. The conclusions were unchanged.

Table 4.9. Results of maintaining first-line targeted treatment in patients with PASI 50-74

	Cost (% change)	QALYs (% change)
Adalimumab	$315,000 (2.1%)	7.194 (0.3%)
Apremilast	$220,000 (2.4%)	6.822 (0.4%)
Brodalumab	$292,000 (1.2%)	7.401 (0.2%)
Certolizumab	$350,000 (2.6%)	7.178 (0.3%)
Etanercept	$281,000 (3.3%)	6.903 (0.4%)
Guselkumab	$345,000 (0.9%)	7.412 (0.1%)
Infliximab	$241,000 (1.2%)	6.992 (0.2%)
Ixekizumab	$314,000 (1.0%)	7.430 (0.2%)
Secukinumab	$309,000 (1.4%)	7.350 (0.2%)
Ustekinumab	$322,000 (2.3%)	7.190 (0.3%)

Effect of Net Price Changes

This scenario analysis is intended to isolate the effect of net price changes from other changes that have been made to the model since the 2016 report. Only drugs that were included in the 2016 analysis have been included here. The brodalumab price was estimated in 2016 and has not been

included. To ensure comparability, we applied drug-specific discounts as available in both 2016 and 2018 for this analysis.

The total effect of drug price increases since 2016 accounts for an increase in costs of between 0.2% and 11.3%. Note that, while the calculated net price of ustekinumab was higher in 2016 than 2018, the effect of lower prices for second-line targeted treatments means that its overall cost using 2016 prices was lower.

Table 4.10. Results (% Change in Results) Over 10 Years of this Year's Base Case Versus When Prices from the 2016 Report are Substituted

Treatment	Total Cost	Net price per unit (rebate %), 2016	Net price per unit (rebate %), 2018
Adalimumab	$273,000 (-11.5%)	$1,433.98(30%)	$1,674.64 (31%)
Apremilast	$195,000 (-9.4%)	$34.91 (19%)	$42.46 (22%)
Etanercept	$259,000 (-4.8%)	$788.82 (23%)	$837.69 (31%)
Infliximab	$211,000 (-11.3%)	$734.71 (34%)	$911.99*
Ixekizumab	$277,000 (-11.0%)	$2,502.64 (44%)	$2,888.74 (44%)
Secukinumab	$278,000 (-8.8%)	$2,601.33 (36%)	$2,926.22 (38%)
Ustekinumab	$313,000 (-0.2%)	$7,602.59 (14%)	$7,532.84 (27%)

* Net price for infliximab was previously estimated by a discounted WAC; however, we have changed to estimating it by ASP plus a mark-up, as this better replicates how intravenously administered drugs are reimbursed. WACs were accurate as of June 1, 2018.

Completed suicides with brodalumab

In this scenario, completed suicides would be expected to reduce the number of QALYs gained with brodalumab use over 10 years from 7.388 to 7.382, or a decrease of 0.1%.

Time to onset

While our base case assumption was that drug response is immediate with the first administration of the drug, we examined onset of response at months two and three for secukinumab as an illustrative example. ICERs compared to non-targeted did not change appreciably:

- Onset at month 1: $145,000
- Onset at month 2: $145,000
- Onset at month 3: $146,000

Second-line market baskets

Changing the second-line targeted treatment to a market basket represented by an average of all 10 targeted drugs changed total costs by 0.7% to -0.4%, and decreased QALYs by up to 0.7%.

Table 4.11. Scenario Analysis: Changing Second Line Market Basket to Average of All Drugs

	Cost (% change)	QALYs (% change)
Adalimumab	$308,000 (-0.1%)	7.141 (-0.4%)
Apremilast	$215,000 (-0.1%)	6.744 (-0.7%)
Brodalumab	$288,000 (-0.4%)	7.388 (-0.0%)
Certolizumab	$341,000 (-0.0%)	7.123 (-0.4%)
Etanercept	$272,000 (-0.1%)	6.828 (-0.7%)
Guselkumab	$344,000 (0.7%)	7.381 (-0.3%)
Infliximab	$238,000 (-0.1%)	6.933 (-0.6%)
Ixekizumab	$310,000 (-0.4%)	7.419 (-0.0%)
Secukinumab	$303,000 (-0.4%)	7.335 (-0.0%)
Ustekinumab	$314,000 (-0.1%)	7.135 (-0.0%)

Modified Societal Perspective

Including productivity offsets led to 10-13% decreases in total costs, and ICERs compared to non-targeted that were notably lower than in the base case (i.e., $109,000 to 166,000 per QALY rather than $133,000 to $188,000 per QALY in the base case range).

Table 4.12. Inclusion of Productivity Offsets

First-line treatment	Total Cost	Cost per QALY, compared to non-targeted
Adalimumab	$275,000 (-11%)	$141,000 (-14%)
Apremilast	$188,000 (-12%)	$111,000 (-18%)
Brodalumab	$251,000 (-13%)	$109,000 (-17%)
Certolizumab pegol	$308,000 (-10%)	$165,000 (-12%)
Etanercept	$244,000 (-10%)	$151,000 (-14%)
Guselkumab	$304,000 (-11%)	$139,000 (-14%)
Infliximab	$209,000 (-12%)	$111,000 (-17%)
Ixekizumab	$273,000 (-12%)	$120,000 (-16%)
Secukinumab	$268,000 (-12%)	$123,000 (-15%)
Ustekinumab	$281,000 (-11%)	$146,000 (-14%)

Lower dose with certolizumab pegol and ustekinumab

Using only the lower doses for certolizumab pegol and ustekinumab compared to the mix of lower and higher doses used in the base case, we found that cost per QALY versus non-targeted changed from $188,000 to $129,000 and $169,000 to $130,000, respectively. These findings suggest certolizumab pegol and ustekinumab may be reasonable choices for patients who are eligible for the lower doses of each.

Threshold analysis results

To estimate the maximum prices that would correspond to given willingness to pay thresholds, we systematically altered the price of each drug in the base case scenario in order to match that threshold. Prices (calculated as annual prices for maintenance treatment after the induction period) for each drug that would achieve cost-effectiveness thresholds ranging from $50,000 to $150,000 per QALY gained are shown below.

Table 4.13. Threshold Analysis Results (Prices indicate annual maintenance price)

Intervention	Annual net price of maintenance therapy	Price needed for $50k/QALY	Price needed for $100k/QALY	Price needed for $150k/QALY
Adalimumab	$43,700	$11,600	$25,700	$39,800
Apremilast	$31,000	< $0*	$17,500	$36,600
Brodalumab	$36,500	$14,900	$28,200	$41,500
Certolizumab pegol	$50,600	$11,300	$25,500	$39,700
Etanercept	$43,700	$1,700	$18,500	$35,400
Guselkumab	$44,400	$15,400	$28,400	$41,500
Infliximab	$29,700	$2,600	$18,800	$35,000
Ixekizumab	$37,700	$14,500	$27,100	$39,700
Secukinumab	$38,200	$13,600	$25,500	$39,400
Ustekinumab	$42,600	$12,600	$25,200	$37,800

*Threshold price of apremilast needed to be below zero to offset cost of second-line targeted drug therapy

In all cases, discounts from WAC would be required to achieve cost-effectiveness thresholds of $50,000, $100,000, or $150,000 per QALY, while premiums over net price could be charged for some drugs and remain below $150,000 per QALY. For apremilast, there was no positive price that could be charged to achieve a level of cost-effectiveness of $50,000/QALY. This occurs primarily

because most patients who initiate treatment with apremilast quickly move on to second-line treatment which is more expensive, making it impossible to achieve a cost-effectiveness threshold of $50,000/QALY unless second-line treatment were discounted as well. Second-line treatment is more influential for apremilast than for the other drugs because approximately 70% of patients discontinue after the apremilast initiation period.

Risankizumab threshold analysis

No WAC will be announced for this product for some time, and the approved dosing is not certain. Assuming discontinuation parameters identical to guselkumab, induction dosing as in risankizumab's phase III trials, and no laboratory monitoring, we have calculated the following value-based annual maintenance prices: $50,000 per QALY: $14,700; $100,000 per QALY: $27,300; $150,000 per QALY: $39,800.

Tildrakizumab threshold analysis

Tildrakizumab was approved to be dosed at 100 mg every 12 weeks, following initiation doses of 100 mg at weeks zero and four. Using this dosing information and an assumption of no lab monitoring, we have calculated annual maintenance prices for tildrakizumab as follows: $50,000 per QALY: $9,200; $100,000 per QALY: $23,000; $150,000 per QALY: $36,800.

4.4 Summary and Comment

The most effective treatment strategies were initiation with the IL-17 agents or guselkumab. The least effective strategies were initiation with apremilast, infliximab, or etanercept. Analogously, the most expensive treatment strategies were initiation with the IL-17 agents or guselkumab, and the least expensive strategies were initiation with apremilast, infliximab, or etanercept. Of note, the drug cost discount used for guselkumab was estimated based on observed discounts for other agents.

Approximately half of the treatment strategies were cost effective compared to non-targeted therapy at a $150K/QALY threshold; the value of tildrakizumab and risankizumab will be dependent on their final list price and discounts provided in the marketplace.

In our 2016 analysis, we concluded that initiation with IL-17 drugs is a reasonable strategy due to their high efficacy and reasonable economic value – even in comparison to step therapy using a less effective and less expensive targeted drug in the first line. This conclusion remains valid – for example, in the base case, ixekizumab has an ICER of $71,199 per QALY compared to etanercept.

Among the IL-17s, initiation with brodalumab appears to be the most cost-effective strategy due to drug pricing. Of note, the prices for the other IL-17 drugs have increased, leading to less favorable value than in our 2016 report.

Our current analysis also indicates 1) initiation with infliximab provides good economic value given its high initial response and lower pricing, despite the high discontinuation rate, 2) initiation with guselkumab may be cost effective at a $150K/QALY threshold, depending on the drug discount, 3) initiation with apremilast, while the least effective, may be cost effective within the $100K/QALY to $150K/QALY threshold range because of its relatively lower pricing, and lastly 4) initiation with etanercept or adalimumab does not appear to provide good long-term value for money because of drug costs in relation to effectiveness, and initiation with ustekinumab or certolizumab is also challenged because of the cost of using significantly higher doses in a notable proportion of patients based on labeled dosing.

Limitations

We currently lack robust data on treatment patterns and discontinuation rates in the U.S. setting for all of the drugs studied. While we have some data from psoriasis registries in other countries, the choice of what drug to switch to is largely determined by policies unique to each locale. This issue becomes even more complicated when there is the possibility of increasing the dosage of the first-line targeted drug to titrate the treatment to be more effective. The model is fairly sensitive to these parameters, although the fundamental conclusions are not changed.

Next, while we have evidence that suggests a 10% decrease in effectiveness for second-line targeted treatments is approximately correct, data are limited and generally from non-randomized studies.

We also estimated net prices based on data provided to us on net U.S. dollar and unit sales. However, these data are net of multiple concessions made by the manufacturer, some of which happen outside of negotiated agreements with payers (e.g., discounts to wholesalers, patient assistance programs). As such, we may overestimate the discounts actually received by the payer in some circumstances. Nevertheless, our threshold price analysis gives a good indication of the discounts payers may wish to seek to achieve certain cost-effectiveness thresholds.

Perhaps most importantly, we were limited by the existing data on the utility of response to treatment. Our model, like the clinical trials for each of these drugs, used the percent change in PASI from baseline, but this approach is problematic. One issue is that there is likely to be poorly characterized heterogeneity in the participants between these studies. Another is that, even within a given level of PASI response, there may be different distributions of response. For example, two

drugs may have the same percentage responding with PASI 75-90, although the average response within that grouping may be closer to 75% improvement for one drug and closer to 90% for the other. The ideal solution to this issue would be to collect directly-elicited utility data from a generic or psoriasis-specific instrument before and after treatment with each drug.

Conclusions

Targeted drug treatment for moderate to severe plaque psoriasis can provide reasonable economic value. Our analysis indicates first-line treatment with infliximab or the IL-17 drugs provides good value at higher willingness to pay thresholds, and infliximab and brodalumab are the most likely to fall within the upper bound of commonly cited cost-effectiveness thresholds. Guselkumab may provide good value depending on drug discounts, and apremilast, while the least effective drug, may also provide value at moderate willingness to pay thresholds. Initiation with other targeted drugs was found to exceed cost-effectiveness thresholds.

5. Additional Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparison of targeted immunomodulators to each other.

Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to systemic therapies, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to systemic therapies, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

As described in Section 1.4, many aspects of patients' lives are affected by plaque psoriasis. For example, many psoriasis patients reported difficulties in finding and/or maintaining a job and socialization with family members and friends. In addition, many patients with psoriasis have serious emotional and psychological issues. Psoriasis is associated with a higher likelihood of having depression, anxiety, and suicidal ideation. Data from clinical effectiveness shows that the use of targeted immunomodulators offers patients better treatment potential in regard to greater skin

clearance and overall improved quality of life. Although we have very limited data on the evaluating the effect of these drugs on patients' quality of life, there is reason to believe that for some patients with psoriasis, targeted immunomodulators may make many aspects of day-to-day living easier.

All of the targeted immunomodulators are administered subcutaneously except for apremilast (oral) and infliximab (intravenous). Subcutaneous route of administration is less burdensome and has reduced complexity, which is likely to improve adherence as well as the ability for some patients with limited mobility to self-administer prophylaxis. Further, patients may favor the convenience of an oral drug like apremilast. Although infliximab has a relatively better efficacy in our evidence review, patients might be disinclined to use an intravenous medication that is associated with administration time and discomfort.

In addition, patients could favor agents that need to be taken less frequently. The frequency of administration during maintenance is greatest for apremilast (twice a day). Other targeted immunomodulators are taken weekly (adalimumab, etanercept), every two weeks (brodalumab), every four weeks (secukinumab and ixekizumab), every 8 weeks (infliximab, guselkumab), and every 12 weeks (ustekinumab, tildrakizumab, risankizumab).

Psoriasis is chronic condition requiring long term treatment. Therefore, there is a need to understand the potential risks for serious events or events with long-latency periods that may be associated with the use of targeted immunomodulators. Observation data on the drugs that have been around for longer periods (TNFα inhibitors) have been generally reassuring. The long-term risks of the newer agents (IL-17s and IL-23s) will only become apparent with ongoing use in a large number of treated individuals. Current data from the short-term trials, and extension studies on these agents have generally been positive, however, it will be important to follow the safety profile of these drugs in post-marketing registries to ensure their long-term safety.

Finally, longer term data have shown that that loss of effect over time is a very common problem with these drugs. In fact, switching treatment is generally expected among patients. However, due to limited guidance in clinical practice, there is some uncertainty about the best choice of second-line biologic agent needed to achieve optimal outcomes.

6. Value-Based Price Benchmarks

Value-based benchmark prices for all drugs are presented in Table 6.1. Annual prices and discounts required to reach the $100,000 per QALY threshold ranged from 38% to 71% and to reach the $150,000 per QALY threshold ranged from 8% to 44%. Since no WAC is available for risankizumab or tildrakizumab, we calculated only the price to reach the cost-effectiveness thresholds.

Table 6.1. Value-Based Benchmark Prices for Targeted Therapies

	Annual WAC	Annual Estimated Net Price	Annual Price to Achieve $100,000 per QALY Threshold	Annual Price to Achieve $150,000 per QALY Threshold	Discount from WAC required to Reach Threshold Prices
Adalimumab	$63,600	$43,700	$25,700	$39,800	37% to 60%
Apremilast	$40,000	$31,000	$17,500	$36,600	8% to 56%
Brodalumab	$45,700	$36,500	$28,200	$41,500	9% to 38%
Certolizumab pegol*	$79,100	$50,600	$25,500	$39,700	43% to 63%
Etanercept	$63,600	$43,700	$18,500	$35,400	44% to 71%
Guselkumab	$66,300	$44,400	$28,400	$41,500	37% to 57%
Infliximab	$38,100	$29,700	$18,800	$35,000	8% to 51%
Ixekizumab	$67,300	$37,700	$27,100	$39,700	41% to 60%
Secukinumab	$61,500	$38,200	$25,500	$39,400	36% to 59%
Ustekinumab	$58,200	$42,600	$25,200	$37,800	35% to 57%
Risankizumab†	-	-	$27,300	$39,800	-
Tildrakizumab†	-	-	$23,000	$36,800	-

QALY: Quality-adjusted life year; All annual prices do not include loading dose administered at initiation in year-one, and represent only maintenance dose-related prices from year-two onward; All prices rounded to the nearest $100; *Assumed that 50% of treated patients had body weight >90kg and were hence administered the higher maintenance dose of 400mg once every two weeks; †No WAC or estimated net price currently available

7. Potential Budget Impact

7.1 Overview

We used results from the same model employed for the cost-effectiveness analyses to estimate the total potential budgetary impact of the two novel treatments for psoriasis patients: certolizumab pegol (approved in May 2018) and guselkumab (approved in July 2017). We used the WAC for each drug, an estimate of discounted WAC, and the cost-effectiveness threshold prices at $50,000, $100,000, and $150,000 per QALY in our estimates of budget impact. We did not include the other therapies modeled above in this potential budget impact analysis, given their established presence on the market.

7.2 Methods

Potential budget impact was defined as the total incremental cost of using the new therapies rather than non-targeted therapy for the treated population, calculated as incremental health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapies.

The potential budget impact analysis included the entire candidate population for treatment, which included adults with moderate to severe plaque psoriasis who are taking a biologic agent for psoriasis for the first time. To estimate the size of the potential candidate population for treatment with certolizumab pegol or guselkumab, we first determined the estimated incidence of psoriasis in the U.S. We did not include brodalumab in our analysis given its presence on the market for nearly two years, and we could not estimate budget impact for tildrakizumab or risankizumab in the absence of an established price.

As in our 2016 report, we used incidence rather than prevalence because we were interested only in patients who were taking a biologic for the first time. Psoriasis incidence in the United States has been estimated at 78.9 cases per 100,000 persons.[5] The proportion of psoriasis patients with plaque psoriasis has been estimated to be 79%.[5] Helmick found that 18.2% of psoriasis patients have moderate-to-severe disease, defined as involving greater than 3% of body surface area.[4] Applying these proportions to the projected 2018-2022 U.S. adult population results in an average estimate of 29,342 incident cases of moderate-severe plaque psoriasis in the US per year, or approximately 146,710 incident cases over five years, assuming equal incidence rates for each of

the five years in our analysis. This was assumed to be the candidate population for treatment with these novel agents.

ICER's methods for estimating potential budget impact are described in detail here. The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. Briefly, we evaluate a new drug that would take market share from one or more drugs and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. For this analysis, we assumed that certolizumab pegol or guselkumab would replace non-targeted therapy as additional first-line targeted immunomodulator options for the eligible patients being treated.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (http://icer-review.org/wp-content/uploads/2018/03/ICER-value-assessment-framework-update-FINAL-062217.pdf), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 7.1.

For 2017-18, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $915 million per year for new drugs.

Table 7.1. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2017 (est.) +1%	3.20%	World Bank, 2016
2	Total health care spending, 2016 ($)	$2.71 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	17.7%	CMS National Health Expenditures (NHE), 2016; Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$479 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.3 billion	Calculation
6	Average annual number of new molecular entity approvals, 2015-2016	33.5	FDA, 2017
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$457.5 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$915 million	Calculation

7.3 Results

Table 7.2 illustrates the per-patient budget impact calculations for certolizumab pegol in adults with moderate to severe plaque psoriasis, compared to non-targeted therapy. Potential budget impact is presented based on WAC ($79,100 per year), discounted WAC ($50,600 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY in this population ($39,700, $25,500 and $11,300 per year, respectively).

Table 7.2. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon for Certolizumab Pegol in Adults with Moderate to Severe Plaque Psoriasis

	Average Annual Per Patient Budget Impact				
	WAC	Discounted WAC	$150,000/ QALY	$100,000/ QALY	$50,000/ QALY
Certolizumab pegol	$66,109	$45,761	$38,019	$24,266	$12,274
Non-targeted therapy	$7,589				
Difference	$58,520	$38,172	$30,430	$16,677	$4,685

WAC: wholesale acquisition cost; QALY: quality adjusted life year

The average potential budgetary impact when using the WAC was an additional per-patient cost of approximately $58,500 and approximately $38,200 using the discounted WAC. At the three cost-

effectiveness threshold prices (at $50,000, $100,000 and $150,000 per QALY), the average annual budget impact ranged from approximately $30,400 per patient using the price to achieve $150,000 per QALY to approximately $4,700 using the price to achieve a $50,000 per QALY cost-effectiveness threshold.

Table 7.3 illustrates the per-patient budget impact calculations for guselkumab in adults with moderate to severe plaque psoriasis, compared to non-targeted therapy. We present the potential budget impact results based on WAC ($66,300 per year), assumed discounted WAC ($44,400 per year), and the prices for guselkumab to reach $150,000, $100,000, and $50,000 per QALY ($41,500, $28,400, and $15,400 per year, respectively). We present the potential budget impact results based on WAC ($66,300 per year), assumed discounted WAC ($44,400 per year), and the prices for guselkumab to reach $150,000, $100,000, and $50,000 per QALY ($41,500, $28,400, and $15,400 per year, respectively).

Table 7.3. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon for Guselkumab in Adults with Moderate to Severe Plaque Psoriasis

	Average Annual Per Patient Budget Impact				
	WAC	Discounted WAC	$150,000/ QALY	$100,000/ QALY	$50,000/ QALY
Guselkumab	$66,488	$44,797	$42,261	$28,478	$16,048
Non-targeted therapy	$7,589				
Difference	$58,900	$37,208	$34,672	$20,889	$8,459

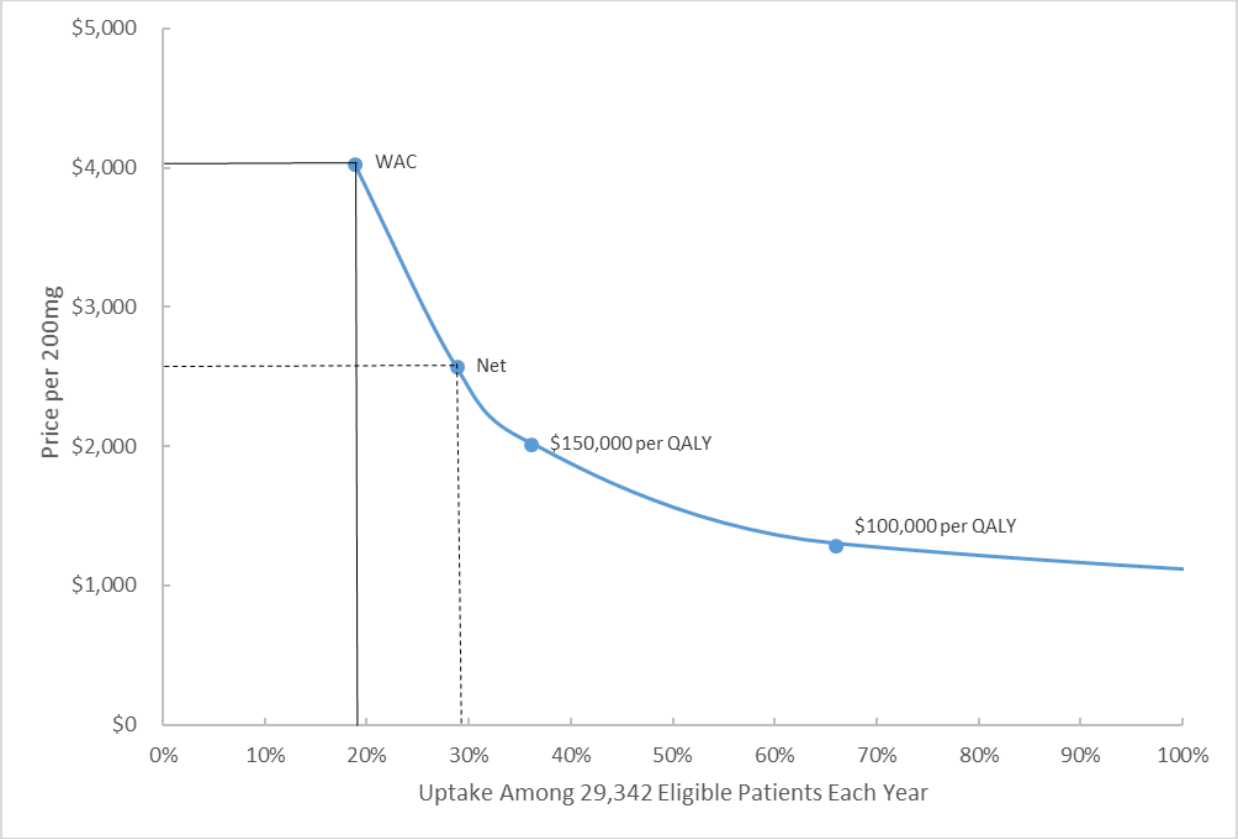
WAC: wholesale acquisition cost; QALY: quality-adjusted life year

The average potential budgetary impact when using the WAC was an additional per-patient cost of approximately $58,900 and approximately $37,200 using the assumed discount from WAC. At the three cost-effectiveness threshold prices (at $50,000, $100,000 and $150,000 per QALY), the average annual budget impact ranged from approximately $34,700 per patient using the price to achieve $150,000 per QALY to approximately $8,500 using the price to achieve a $50,000 per QALY cost-effectiveness threshold.

For certolizumab pegol, as shown in Figure 7.1, approximately 19% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $915 million at total treatment costs using WAC, and approximately 29% using the discounted WAC. Approximately 36% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY threshold price, while 66% of the population could be treated without crossing the threshold at the $100,000 per QALY threshold price. At the $50,000 per QALY threshold price,

the entire eligible cohort could be treated without exceeding the $915 million threshold, with a budget impact that comprises approximately 42% of the threshold.

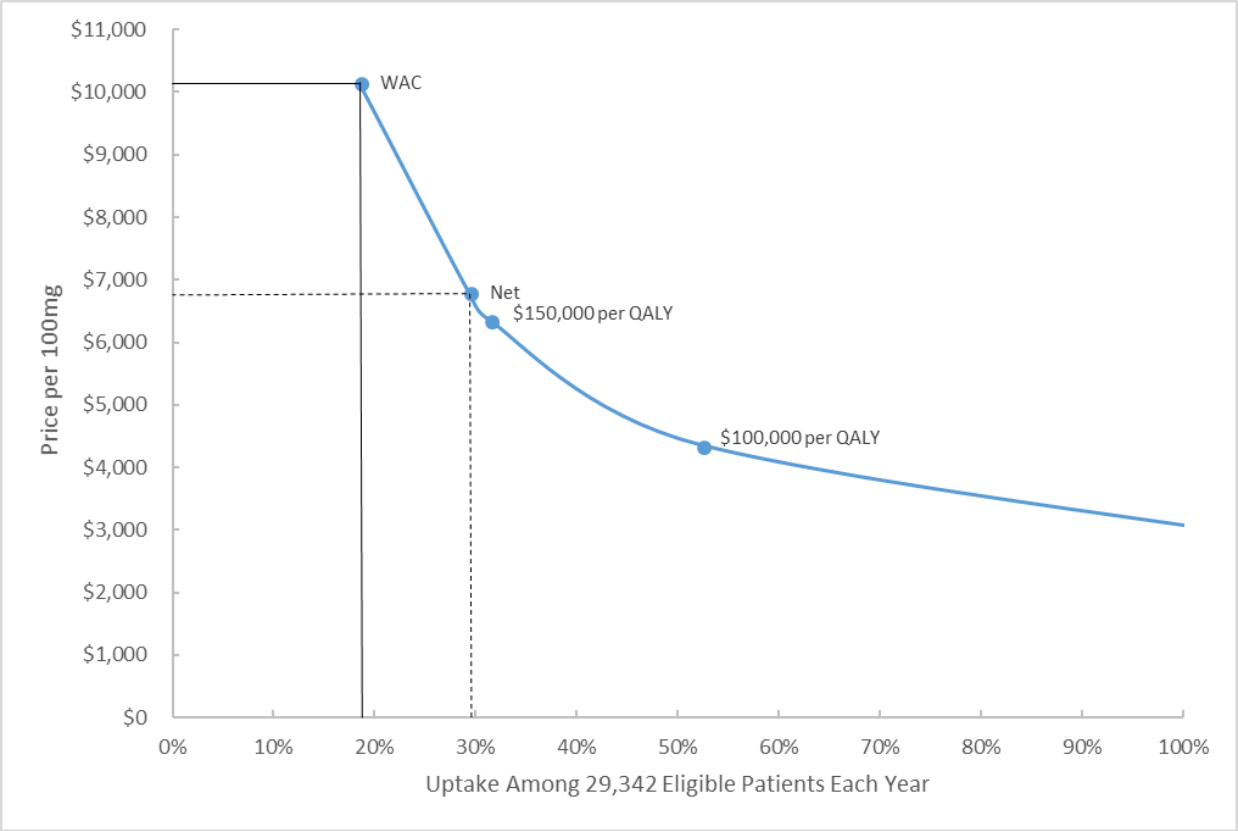
Figure 7.1. Potential Budget Impact Scenarios at Different Prices for Certolizumab Pegol in Adults with Moderate to Severe Plaque Psoriasis*



*Graph shows the relation between price per 200mg and proportion of patients eligible for treatment with certolizumab pegol who could be treated over five years without crossing $915-million budget impact threshold.

For guselkumab (Figure 7.2), approximately 18% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $915 million at total treatment costs using WAC ($10,159 per 100mg), and approximately 29% using the assumed discounted WAC. Approximately 31% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY threshold price ($6,355), while 52% of the population could be treated without crossing the threshold at the $100,000 per QALY threshold price ($4,747). At the $50,000 per QALY threshold price ($4,360), the entire eligible cohort could be treated without exceeding the $915 million threshold, with a budget impact that comprises approximately 77% of the threshold.

Figure 7.2. Potential Budget Impact Scenarios at Different Prices for Guselkumab in Adults with Moderate to Severe Plaque Psoriasis*



*Graph shows the relation between price per 100mg and proportion of patients eligible for treatment with guselkumab who could be treated over five years without crossing $915-million budget impact threshold.

In summary, the annual budget impact over a five-year time-horizon for treating eligible patients with moderate to severe plaque psoriasis with certolizumab pegol rather than non-targeted therapy was estimated to be approximately $38,200 per patient using net price, and approximately $37,200 per patient using net price for guselkumab. For both drugs, the total annual potential budget impact is estimated to exceed ICER's annual $915 million budget impact threshold using WAC, discounted WAC, and prices to achieve cost-effectiveness thresholds from $100,000 to $150,000 per QALY gained. At the price to achieve a cost-effectiveness threshold of $50,000 per QALY, the total annual budget would not exceed ICER's $915 million annual budget impact threshold for either certolizumab pegol or guselkumab.

8. Summary of the Votes and Considerations for Policy

8.1 About the New England CEPAC Process

During New England CEPAC public meetings, the New England CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to New England CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the New England CEPAC Panel during their deliberation, and help to shape recommendations on ways the evidence can apply to policy and practice.

At the July 12, 2018 meeting, the New England CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis. Following the evidence presentation and public comments (public comments from the meeting can be accessed here, starting at minute 1:12:50, the New England CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and potential other benefits and contextual considerations related to targeted immunomodulators. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by New England CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the New England CEPAC Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 8.1 below):

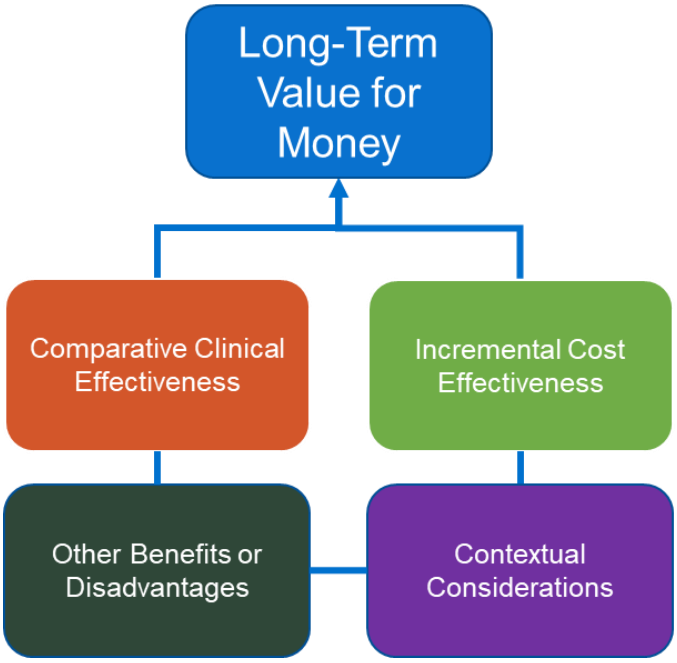
1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. The New England CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the New England CEPAC voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

3. Potential other benefits refer to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of potential other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether potential other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for potential other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 8.1. Conceptual Structure of Long-term Value for Money



8.2 Voting Results

Patient Population for all questions: Patients with moderate-to-severe plaque psoriasis for whom treatment with topical therapies, older systemic therapies, and/or phototherapy has been ineffective, contraindicated, or not tolerated.

1) Is the evidence adequate to demonstrate that the net health benefit of certolizumab pegol is superior to that provided by the other subcutaneous TNFα inhibitors (adalimumab and etanercept)?

Yes: 2 votes	**No: 9 votes**

Comments: A majority of the panel voted that the available evidence was inadequate to demonstrate that the net health benefit of certolizumab pegol is superior to that provided by the other subcutaneous TNFα inhibitors (adalimumab and etanercept). The panelists in the majority emphasized the overall lack of direct evidence among the three treatments and the absence of head-to-head trials comparing certolizumab pegol and adalimumab. Panelists noted that certolizumab pegol's efficacy in a direct comparison to etanercept was dependent on its dosing; although a higher dose of certolizumab pegol was superior to etanercept, a lower dose was not, and both doses have been approved by the FDA for use in this patient population.

2) Is the evidence adequate to demonstrate that the net health benefit of guselkumab is superior to that provided by all subcutaneous TNFα inhibitors (adalimumab, etanercept, and certolizumab pegol)?

Yes: 10 votes	No: 1 vote

Comments: A majority of the panel judged that the evidence was adequate to demonstrate that the net health benefit of guselkumab is superior to that provided by all subcutaneous TNFα inhibitors (adalimumab, etanercept, and certolizumab pegol). Panelists in the majority noted that the results from the network meta-analysis and the direct comparison between guselkumab and etanercept were compelling. Specifically, the panelists emphasized that guselkumab received favorable scores when directly compared to etanercept on the Psoriasis Area Severity Index (PASI), the Investigator's Global Assessment (IGA) scale, and the Dermatology Quality of Life Index (DLQI).

3) Is the evidence adequate to demonstrate that the net health benefit of risankizumab is superior to that provided by all subcutaneous TNFα inhibitors (adalimumab, etanercept, and certolizumab pegol)?*

Yes: 10 votes	No: 1 vote

Comments: A majority of the panel determined that the evidence was adequate to demonstrate that the net health benefit of risankizumab is superior to that provided by all subcutaneous TNFα inhibitors (adalimumab, etanercept, and certolizumab pegol). The majority ultimately voted that given the comparative magnitude of effect in the indirect comparisons as shown in the network meta-analysis, the evidence was sufficient to show substantial benefits of risankizumab in comparison to the subcutaneous TNFα inhibitors.

The panelist who voted no exhibited caution about the uncertainty around any potential adverse events not presented in the grey literature; and the potential for unpublished data to only promote the benefits of the drug, without presenting the harms.

**The description of this vote was updated in October 2018. The previous version noted that, at the time of the July 2018 meeting, data pertaining to risankizumab were only available as grey literature or as in-confidence submissions from the manufacturer. As such, the New England CEPAC considered their vote to be provisional until the results were published. After these data were published, the New England CEPAC voted to confirm their provisional vote, a decision now reflected in the above text.*

4) Is the evidence adequate to demonstrate that the net health benefit of tildrakizumab is superior to that provided by all subcutaneous TNFα inhibitors (adalimumab, etanercept, and certolizumab pegol)?

Yes: 0 votes	**No: 11 votes**

Comments: The panel unanimously judged that the evidence was inadequate to demonstrate that the net health benefit of tildrakizumab is superior to that provided by all subcutaneous TNFα inhibitors (adalimumab, etanercept, and certolizumab pegol). The panel emphasized that the available head-to-head evidence between tildrakizumab and etanercept was inconsistent; while it supported PASI improvement, there was no statistically significant benefit on DLQI or PGA. Furthermore, indirect comparisons in the network meta-analysis did not find significant differences between tildrakizumab and adalimumab, etanercept, and certolizumab pegol respectively.

5) When compared to non-targeted therapy, do newer treatments for moderate-severe plaque psoriasis offer one or more of the following "potential other benefits"?

# of Votes	Other Benefits
10/11	This intervention offers reduced complexity that will significantly improve patient outcomes.
0/11	This intervention will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.
7/11	This intervention will significantly reduce caregiver or broader family burden.
8/11	This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.
8/11	This intervention will have a significant impact on improving patient's ability to return to work and/or their overall productivity.
6/11	Other important benefits.

Comments: The majority of the panel voted that newer treatments for moderate-to-severe plaque psoriasis offer reduced complexity; reduced caregiver or family burden; represent a novel mechanism of action; and have a positive impact on the likelihood of returning to work and productivity. The panelists in the majority emphasized that the newer treatments have the potential to improve relationships, presenteeism, social engagement, the general wellbeing and happiness of loved ones, and the ability to fulfill family, workplace, and social obligations. Panelists also offered additional other benefits associated with newer therapies, including improved mental health (including reduction in feelings of anxiety, frustration, and helplessness) and self-image; a reduction in the stigma felt by many persons with psoriasis; and the ability to choose from among multiple treatment options.

6) Are any of the following contextual consideration important in assessing long-term value for money for the newer targeted immunomodulators?

# of Votes	Contextual Considerations
10/11	This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
8/11	This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
1/11	This intervention is the first to offer any improvement for patients with this condition.
7/11	Compared to no treatment, there is significant uncertainty about longterm risk of serious side effects.
7/11	Compared to no treatment, there is significant uncertainty about the magnitude or durability of long-term benefits.
2/11	Other important contextual considerations

Comments: A vast majority of the panel voted that persons with psoriasis have a condition of particularly high severity, and an overwhelming majority also judged that persons with the condition have a high lifetime burden of illness. These panel members emphasized that psoriasis can negatively impact a person's level of social engagement and productivity, which can lead to the loss of family and social opportunities and fewer job prospects throughout a person's life. Overall, the panel emphasized the lack of data on the long-term risk of serious side effects and the substantial uncertainty regarding the long-term benefits of treatment with these new therapies. Relatedly, one panelist noted that many patients that are treated with other TNFα inhibitors are at risk for developing lymphoma and melanoma, and another panelist expressed concern that potential adverse effects of newer treatments may not have been detected yet. One panelist offered an additional contextual consideration and questioned whether the results are generalizable to patients with comorbidities, and remarked that patients with comorbidities may gain more QALYs relative to those without these conditions.

7) Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of guselkumab compared with non-targeted therapy?

Low: 2 votes	Intermediate: 8 votes	High: 1 vote

Comments: A majority of the panel judged the long-term value for money to be "intermediate" for treatment with guselkumab compared with non-targeted therapy. The

panelists in the majority emphasized the superior clinical effectiveness of guselkumab, including the compelling evidence and favorable PASI scores associated with the treatment.

8) Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of certolizumab pegol compared with non-targeted therapy?

Low: 7 votes	Intermediate: 4 votes	High: 0 votes

Comments: A majority of the panel determined the long-term value for money to be "low" for treatment with certolizumab pegol compared with non-targeted therapy. The panelists in the majority emphasized that certolizumab pegol is more expensive and with no evidence to suggest it is better than other therapies within the same class. Furthermore, they noted certolizumab pegol's high cost per QALY of $188,000, which is above commonly cited thresholds for cost effectiveness. One panelist who selected "intermediate" explained that the evidence to support the clinical effectiveness of certolizumab pegol in comparison to non-targeted therapy was substantial and underscored that, unlike other targeted immunomodulators, the treatment has been shown to be safe for pregnant women, which factored heavily into her vote.

8.3 Key Policy Implications

As the present assessment constitutes a condition update from 2016, the discussion of the evidence on new and established therapies did not include a formal Policy Roundtable. Instead, the 2016 policy recommendations were updated in a moderated discussion of the New England CEPAC that followed the Panel vote on Clinical Effectiveness and Value. This discussion was supported by input from a clinical expert and a representative from a patient advocacy organization. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the experts are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix J.

Table 8.1 Psoriasis experts in moderated discussion

Name	Title and Affiliation
Alexa B. Kimball, MD	Harvard Medical Faculty Physicians Beth Israel Deaconess Medical Center
Leah McCormick Howard, JD	Chief Operating Officer National Psoriasis Foundation

The discussion was facilitated by Dan Ollendorf, PhD, Chief Scientific Officer of ICER. Participants in the discussion agreed that the policy recommendations from the prior report needed only minor adjustments, as they remain relevant today. The main themes and recommendations from the discussion are organized by audience and summarized below.

Recommendations marked with an asterisk (*) are updated based on the 2018 Condition Update. All other recommendations remain unchanged from 2016.

Manufacturers

Foster transparency in the rationale for price increases*

In 2016, our report noted that some of the classes of psoriasis drugs had seen significant price increases on a year-over-year basis. Since 2016, price increases have continued and cost-effectiveness ratios for many of the treatments are now near the high end of or exceed traditionally accepted thresholds for cost-effectiveness. Manufacturers should seek to keep prices at a level that reflect the added benefit to patients; be mindful of the overall impact on health care costs of the growing use of targeted immunomodulators; and recognize the potential for lower prices to be linked to greater access for all patients. In addition, manufacturers should be transparent about the rationale for future price increases, including new clinical evidence, improvements in therapy delivery or tolerability, and/or other considerations.

Release treatment-specific quality-of-life data

Health economists are often frustrated by a lack of available data on disease-specific quality of life. When evaluated, information is often provided at the condition level, without data on the effect of treatment on quality of life measures. As an example, data from the commonly-used EuroQol (EQ)-5D was available for the psoriasis model, but was not stratified by treatment group. Quality-of-life assumptions were therefore driven primarily by model structure rather than actual, trial-based data on treatment effect. To address this concern, manufacturers should release both summarized and treatment-stratified quality-of-life information.

Payers

Consider limiting or abolishing "step therapy" approaches to coverage*

In 2016, all targeted immunomodulators represented reasonable long-term value for money compared to non-targeted treatment for patients with moderate-to-severe plaque psoriasis, based on the comparative value evaluation. Given their reasonable cost effectiveness, ICER recommended that payers consider eliminating most step therapy requirements for patients with moderate-to-severe psoriasis, especially for those patients who demonstrate the need for intensive, ongoing regimens.

In 2018, step therapy continues to be the dominant approach among most insurers, and a formulary survey commissioned by National Psoriasis Foundation showed that levels of coverage

for targeted immunomodulators fell between 2015 and 2017, with increased utilization management and cost sharing.

Patients and clinicians continue to reiterate that step therapy protocols can seriously delay improvements to patients' quality of life. Patients are often required to continue with less effective drugs for months or years prior to being allowed access to more effective, well-tolerated treatments. Patient representatives said that step therapy can discourage patients from being treated at all, especially when clinicians do not have the resources to vigorously advocate on behalf of patients with payers.

Policy discussants agreed that step therapy and access to medications are the primary challenges in managing patients with severe plaque psoriasis. Clinicians are concerned about patients dropping out of treatment because of frustrations with non-response and the administrative burdens of step therapy, burdens that are frequently repeated with every change of insurer. It was argued that excellent clinical care requires access to all targeted immunomodulators because of the unique benefits or disadvantages of some targeted immunomodulators for certain clinical scenarios (e.g., treatment of a patient with concomitant uveitis or axial arthritis); and availability of multiple routes of administration and dosing schedules that allow tailored regimens for patients who must travel, live far from home, or have other relevant considerations.

According to industry experts, there are some best practices that have emerged since 2016. For example, leaders at Express Scripts say they have sought to renegotiate contracts with the manufacturers of all targeted immunomodulators with a psoriasis indication, the goal being to eliminate all step therapy for treatment of a psoriasis diagnosis, and establish a formulary with an equal co-payment structure for all drugs for treating psoriasis (see more details here). Negotiations have been successful for most targeted psoriasis drugs, and have included provisions to refund payers the cost of treatment for patients who discontinue their chosen therapy early. For those psoriasis therapies that have not been brought into this contract approach, however, step therapy requirements and higher cost-sharing structures remain. It is unclear how successful Express Scripts has been in selling this product to payers, and this initiative appears to be the exception rather than the rule.

As noted above, both list and net prices have continued to increase, and cost-effectiveness ratios for many of the treatments now reach or exceed the high end of traditionally accepted thresholds for cost effectiveness. While these trends bear watching, it remains the case that current, rebate-driven step therapy protocols are not serving patients, so payers should consider limiting or abolishing step therapy for any targeted immunomodulator that represents good value for money. Further, potential other benefits and contextual considerations should be considered when payers contemplate ways to manage therapies.

Given that many targeted immunomodulators have good value relative to non-targeted treatment, payers should strongly consider eliminating most step therapy requirements for patients with moderate-to-severe psoriasis, especially for those patients who demonstrate the need for intensive, ongoing regimens.

If step therapy will be used:

> ***Allow individuals switching insurers to bypass step therapy if they are already on an effective treatment***
>
> Psoriasis is a chronic disease that patients manage for decades. It is important that patients maintain continuity of care, despite switching employers or insurers. Individuals switching insurer for any reason should be able to bypass step therapy protocols if current treatment is working, especially if they have used prior steps in the past. Some insurers, such as Blue Cross Blue Shield of Massachusetts, allow new members, with eligibility less than 90 days, to bypass step therapy to avoid interruption of therapy and treatment.
>
> ***Remove requirements for patients to have higher out-of-pocket expenses for "later step" treatments***
>
> For patients who follow a step therapy protocol and end up on a higher tier or "later step" medication, efforts should be taken to design the formulary so that patients are not required to pay a substantially higher co-payment or switch from co-payment to co-insurance. One patient advocate commented that when out-of-pocket costs go over $100 per month, adherence tends to drop. The general principle in formulary design should be that patients who are "good soldiers" and have tried but failed the first drug in a step therapy protocol should not be required to pay substantially more out of pocket for a subsequent treatment.

As alternative mechanisms to manage costs, consider developing indication-specific formulary designs and outcome-based payment contracts*

Payers should explore the use of mechanisms other than step therapy to help manage the outcomes and costs of care. Chief among the options to be considered are indication-specific formulary designs and outcome-based payment contracts. Indication-specific formulary design would allow payers to benefit from competition within each clinical indication for targeted immunomodulators. The general pattern has been for certain drugs with broad indications to gain formulary preference since most payers have not developed practical ways to link the use of these drugs to specific diagnoses. Payers should consider following the lead of the Express Scripts

program described above, which has developed an indication-specific formulary design for the auto-immune conditions, allowing "niche" drugs to gain preference even if they could not compete across multiple indications. Further details on the Express Scripts program can be found here.

A second option is to consider some form of outcome-based payment, in which rebates or refunds are linked to outcomes. As part of the Express Scripts program, plan sponsors will receive a refund of up to $6,000 if patients discontinue a preferred auto-immune medication within the first 90 days. As part of any refund program of this type it should be explored whether refunds to patients for their out-of-pocket payments can also be included.

Co-payment and/or co-insurance for therapies should be based on prices net of discounts and rebates instead of list price

Higher out-of-pocket costs put patients at high risk of coverage loss, bankruptcy, and inability to access effective treatment necessary to control a chronic disease. As shown in our report, rebates and discounts are substantial for most psoriasis drugs. However, patient out-of-pocket payments are based on the list price for these medications. Insurers should seek ways to calculate patient contributions based on the negotiated price, allowing patients to share in savings from cost-effective treatment pathways, especially if part of a step therapy protocol.

Patient Advocacy Organizations

Lead research efforts to evaluate heritability of psoriasis and the impact of managing plaque psoriasis on caregivers and families

Patients groups describe the quality-of-life impacts of plaque psoriasis as extending well beyond the challenges and stigma faced by individual patients—there are substantial effects on family members and caregivers. Patients expressed concern about genetic factors associated with psoriasis onset and the likelihood of "passing the disease on" to future generations. Research on the impact of psoriasis on caregivers, family members, and the heritability of psoriasis would help broaden the understanding of the impact of psoriasis and capture the value of new treatments.

Specialty Societies

Update treatment guidelines for patients with moderate-to-severe chronic plaque psoriasis in a form that is easy to understand and easy-to-use by payers, clinicians, and patients*

Payers base their coverage decisions and integration of utilization tools to a great extent on clinical guidelines. In 2016, Payers on the policy roundtable expressed frustration with difficult-to-interpret, out-of-date clinical guidelines that precede the introduction of IL-17 agents. They expressed the need for updated guidelines from clinical societies with detailed guidance and understanding of clinical nuance that would allow for creation of meaningful step therapy approaches with "edits" that would represent reasonable clinical exceptions—for example, use of an agent that can address both psoriasis and psoriatic arthritis, or avoidance of an agent with suboptimal performance in patients with a certain comorbidity profile.

The need for revised treatment guidelines is now even more urgent considering the availability of the IL-23 agents, and the approval of certolizumab pegol for use during pregnancy. The National Psoriasis Foundation and American Academy of Dermatology are collaborating to update clinical practice guidelines for psoriasis with a release anticipated within the coming year.

Patient Advocacy Groups, Clinicians, and Researchers

Patients and patient organizations should take a leadership role in the design of clinical trials and all stakeholders should advocate for rigorous study in diverse populations evaluating real-world comparative treatments.

Given the evolution of new therapies for moderate-severe plaque psoriasis, patients and clinicians often lack information on comparative clinical effectiveness of different treatment options that is necessary to help them tailor care for the individual patient. Clinical experts noted, for example, that patients who have not yet taken a targeted immunomodulator are under-represented in many US-based clinical trials; furthermore, it is not always clear what the best second treatment option is for a patient, since the effectiveness of second-line treatment is not well studied. Patient groups can help by encouraging patients to participate in clinical trials and by taking a leadership role in identifying treatment strategies and outcome measures that matter most to patients. Clinicians should also encourage patients to consider participating in research, and should develop the practice infrastructure needed to make that participation as seamless as possible. Researchers should work directly with patient groups and clinicians to ensure that trial design and implementation present the lowest barriers possible to participation.

Researchers and Manufacturers

Converge on a single metrics for patient reported psoriasis specific outcomes for trials

The Psoriasis Area and Severity Index (PASI), which is the standard outcome measure used in trials for plaque psoriasis treatments, does not measure patient relevant outcomes, particularly itch, pain and scaling. The Dermatology Life Quality Index (DLQI) is the most frequently used outcome measure in psoriasis research, but it is not specific for psoriasis. Different psoriasis-specific patient reported outcomes measures are used inconsistently in trials. To address this important concern, researchers and manufacturers, with the collaboration of patient advocacy groups should converge on a single metric for patient reported psoriasis specific outcomes.

Conduct research that directly compares real-world treatment options and sequential treatment effectiveness for both naïve and treatment-experienced patients

There is little information on how each targeted immunomodulator performs in early- versus later-line use. Patients, clinicians, and payers would benefit from real-world data comparing multiple treatment options, sequences, and combinations. For example, first-line use of targeted immunomodulators could be compared to other systemic therapies like methotrexate to evaluate their effectiveness and durability of benefit. In addition, within-class comparisons could be performed to identify advantages for particular agents. Finally, use of specific sequences of targeted immunomodulator therapy should be evaluated to identify the optimal treatment strategy for specific groups of patients, and to assess the possible decreased benefit for medications in early- versus later-line use.

Generate additional information on the durability of clinical benefit seen with IL-17 and IL-23 agents*

Since IL-17 and IL-23 inhibitors are very new classes of drugs for plaque psoriasis, data on clinical benefits and potential harm are relatively short-term. It is therefore important that manufacturers and researchers begin research on the longer-term effects of the IL-17 and IL-23 inhibitors, including benefits, harms, and durability of response.

****

This is an ICER update evaluating targeted immunomodulators for treating moderate-to-severe plaque psoriasis. This is ICER's first update of the topic, which was originally reviewed in 2016.

References

1. Menter A. *An Overview of Psoriasis, Chapter 1 in Koo, John Y. M. editor Moderate to severe psoriasis.* Fourth edition ed: CRC Press; 2014.
2. Conrad C, Gilliet M. Psoriasis: from Pathogenesis to Targeted Therapies. *Clinical reviews in allergy & immunology.* 2018;54(1):102-113.
3. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol.* 2014;70(3):512-516.
4. Helmick CG, Lee-Han H, Hirsch SC, Baird TL, Bartlett CL. Prevalence of psoriasis among adults in the U.S.: 2003-2006 and 2009-2010 National Health and Nutrition Examination Surveys. *Am J Prev Med.* 2014;47(1):37-45.
5. Icen M, Crowson CS, McEvoy MT, Dann FJ, Gabriel SE, Maradit Kremers H. Trends in incidence of adult-onset psoriasis over three decades: a population-based study. *J Am Acad Dermatol.* 2009;60(3):394-401.
6. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol.* 2008;58(5):826-850.
7. Gottlieb A, Korman NJ, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. *J Am Acad Dermatol.* 2008;58(5):851-864.
8. Bergstrom KG, Kimball AB. *100 questions & answers about psoriasis.* 2nd ed. Sudbury, Mass.: Jones and Bartlett; 2011.
9. Ibrahim G, Waxman R, Helliwell PS. The prevalence of psoriatic arthritis in people with psoriasis. *Arthritis Rheum.* 2009;61(10):1373-1378.
10. Abuabara K, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K. *The British journal of dermatology.* 2010;163(3):586-592.
11. Mease P. Non-anti-TNF biologics in PSA. *Annals of the Rheumatic Disease.* 2013;71.
12. Boehncke WH, Schon MP. Psoriasis. *Lancet.* 2015;386(9997):983-994.
13. Lockshin B, Balagula Y, Merola JF. Interleukin-17, Inflammation, and Cardiovascular Risk in Patients With Psoriasis. *J Am Acad Dermatol.* 2018.
14. Reich K. The concept of psoriasis as a systemic inflammation: implications for disease management. *J Eur Acad Dermatol Venereol.* 2012;26 Suppl 2:3-11.
15. Mrowietz U, Kragballe K, Reich K, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res.* 2011;303(1):1-10.
16. Nast A, Jacobs A, Rosumeck S, Werner RN. Efficacy and Safety of Systemic Long-Term Treatments for Moderate-to-Severe Psoriasis: A Systematic Review and Meta-Analysis. *J Invest Dermatol.* 2015;135(11):2641-2648.
17. FDA. Biological Product Definitions. In: U.S. Department of Health & Human Services; 2018: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM581282.pdf. Accessed 2018-03-11.
18. Institute for Clinical and Economic Review. Table 17: Drug acquisition costs, page 60 in Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness

and Value. 2016; https://icer-review.org/wp-content/uploads/2016/11/NE_CEPAC_Psoriasis_Evidence_Report_FINAL_012317.pdf#page=95.
19. Brennan Z. Top-Selling Drugs in 2018: Biosimilar Competition is FDA Approved but Not Marketed. *Regulatory Focus* 2018; https://www.raps.org/news-and-articles/news-articles/2018/2/top-selling-drugs-in-2018-biosimilar-competition. Accessed March 11, 2018.
20. Sagonowsky E. AbbVie's Humira gets biosim reprieve—and Amgen wins copycat advantage—in patent deal with Samsung Bioepis. 2018; https://www.fiercepharma.com/legal/abbvie-biogen-agree-2023-date-for-u-s-humira-biosim-launch. Accessed April 6, 2018.
21. Levin EC, Koo JY. *Biologic Fatigue, Chapter 15 in Koo, John Y. M. editor Moderate to severe psoriasis.* Fourth edition ed: CRC Press; 2014.
22. Iskandar IYK, Warren RB, Lunt M, et al. Differential Drug Survival of Second-Line Biologic Therapies in Patients with Psoriasis: Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *J Invest Dermatol.* 2018;138(4):775-784.
23. Bissonnette R, Kerdel F, Naldi L, et al. Evaluation of Risk of Major Adverse Cardiovascular Events With Biologic Therapy in Patients With Psoriasis. *Journal of drugs in dermatology : JDD.* 2017;16(10):1002-1013.
24. Kimball AB, Sundaram M, Cloutier M, et al. Increased Prevalence of Cancer in Adult Patients With Psoriasis in the United States: A Claims Based Analysis. *Journal of drugs in dermatology : JDD.* 2018;17(2):180-186.
25. Linder J, Pearson S, Ollendorf D, et al. Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value. In: Institute for Clinical and Economic Review, ed. Boston2016: https://icer-review.org/wp-content/uploads/2016/11/NE_CEPAC_Psoriasis_Evidence_Report_FINAL_012317.pdf. Accessed 2017-11-27.
26. Institute for Clinical and Economic Review. Key Stakeholder Organizations for 2016 ICER Psoriasis Report. 2016; https://icer-review.org/wp-content/uploads/2016/10/NECEPAC_Psoriasis_Stakeholder_List_092916.pdf.
27. Siegel M. Comment of the National Psoriasis Foundation at the ICER public meeting on Treatment Options for Plaque Psoriasis, November 18, 2016. [YouTube video]. 2016; https://youtu.be/Rl7Fa9Ex2ts. Accessed March, 19, 2018.
28. (USPSTF) USPSTF. *Procedure Manual. Agency for Healthcare Research and Quality.* 2008.
29. Gottlieb AB, Blauvelt A, Thaci D, et al. Certolizumab Pegol for the Treatment of Chronic Plaque Psoriasis: Results through 48 Weeks from Two Phase 3, Multicenter, Randomized, Double-Blinded, Placebo-Controlled Studies (CIMPASI-1 and CIMPASI-2). *J Am Acad Dermatol.* 2018.
30. Lebwohl M, Blauvelt A, Paul C, et al. Certolizumab Pegol for the Treatment of Chronic Plaque Psoriasis: Results Through 48 Weeks of a Phase 3, Multicenter, Randomized, Double-Blinded, Etanercept- and Placebo-Controlled Study (CIMPACT). *J Am Acad Dermatol.* 2018.
31. Blauvelt A, Papp KA, Griffiths CEM, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *Journal of the american academy of dermatology.* 2016(pagination).
32. Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate

to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol.* 2017;76(3):418-431.
33. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *The Lancet.* 2017;390(10091):276-288.
34. Blauvelt A, Papp K, Gooderham M, et al. Efficacy and safety of risankizumab, an IL-23 inhibitor, in patients with moderate-to-severe chronic plaque psoriasis: 16-week results from the phase 3 IMMhance trial. Paper presented at: Psoriasis: from gene to clinic2017; London, UK.
35. Gordon K, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab: results from two double-blind, placebo- and ustekinumab-controlled, phase 3 trials in moderate-to-severe plaque psoriasis. Paper presented at: AAD Annual Meeting2018; San Diego, CA.
36. Reich K, Blauvelt A, Thac¸i D, Leonardi C, Gottlieb A. Maintenance of Response with Certolizumab Pegol for the Treatment of Chronic Plaque Psoriasis: 48-Week Results from Two Ongoing Phase 3, Multicenter, Randomized, Placebo-Controlled Studies (CIMPASI-1 and CIMPASI-2). European Academy of Dermatology and Venereology (EADV) Congress; 2017; Geneva, Switzerland.
37. Lebwohl M, Paul C, Piguet V, et al. Certolizumab Pegol for the Treatment of Chronic Plaque Psoriasis: Primary Results from an Ongoing Phase 3, Multicenter, Randomized, Active- and Placebo-Controlled Study. Paper presented at: 13th Annual Maui Derm for Dermatologists 2017; March 20 -24, 2017; Maui Hawaii.
38. Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet.* 2018;392(10148):650-661.
39. Lebwohl M, Strober B, Menter A, et al. Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis. *New England Journal of Medicine.* 2015;373(14):1318-1328.
40. National Institute for Health and Care Excellence (NICE). Brodalumab for treating moderate to severe plaque psoriasis. 2018;Technology appraisal guidance.
41. National Institute for Health and Care Excellence. Guselkumab for treating moderate to severe plaque psoriasis. 2018.
42. Amin M, No DJ, Egeberg A, Wu JJ. Choosing First-Line Biologic Treatment for Moderate-to-Severe Psoriasis: What Does the Evidence Say? *Am J Clin Dermatol.* 2018;19(1):1-13.
43. SSRHealth. US Brand Rx Net Price. *Access-restricted document.* 2018.
44. Wiatrowski A, Stockman C, Reimers K, et al. *Medical Pharmacy Trends Report.* Scottsdale, AZ: Magellan Rx Management;2015.
45. Services CfMaM. FY 2017 Final Rule, Correction Notice and Consolidated Appropriations Act of 2017 Tables. In: CMS.gov; 2017.
46. 2017 National Population Projections Datasets. 2018. https://www.census.gov/data/datasets/2017/demo/popproj/2017-popproj.html. Accessed 3/15/2018.
47. Strober B, Karki C, Mason M, et al. Characterization of disease burden, comorbidities, and treatment use in a large, US-based cohort: Results from the Corrona Psoriasis Registry. *J Am Acad Dermatol.* 2018;78(2):323-332.

48. Merola JF, Li T, Li WQ, Cho E, Qureshi AA. Prevalence of psoriasis phenotypes among men and women in the USA. *Clin Exp Dermatol.* 2016;41(5):486-489.
49. Sanchez IM, Sorenson E, Levin E, Liao W. The Efficacy of Biologic Therapy for the Management of Palmoplantar Psoriasis and Palmoplantar Pustulosis: A Systematic Review. *Dermatol Ther (Heidelb).* 2017.
50. Lee YW, Park EJ, Kwon IH, Kim KH, Kim KJ. Impact of Psoriasis on Quality of Life: Relationship between Clinical Response to Therapy and Change in Health-related Quality of Life. *Ann Dermatol.* 2010;22(4):389-396.
51. Lebwohl MG, Bachelez H, Barker J, et al. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *Journal of the American Academy of Dermatology.* 2014;70(5):871-881 e871-830.
52. Rapp SR, Feldman SR, Exum ML, Fleischer AB, Jr., Reboussin DM. Psoriasis causes as much disability as other major medical diseases. *Journal of the American Academy of Dermatology.* 1999;41(3 Pt 1):401-407.
53. Brezinski EA, Dhillon JS, Armstrong AW. Economic Burden of Psoriasis in the United States: A Systematic Review. *JAMA Dermatol.* 2015;151(6):651-658.
54. Amor KT, Ryan C, Menter A. The use of cyclosporine in dermatology: part I. *J Am Acad Dermatol.* 2010;63(6):925-946; quiz 947-928.
55. RAPS. FDA Begins Adding Suffixes to Newly Approved Biologics' Names. 2017; https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/11/fda-begins-adding-suffixes-to-newly-approved-biologics-names. Accessed March 11, 2018.
56. Feldman SR, Tencer T, Clancy Z, Zhang F. Cost per responder of apremilast versus etanercept, adalimumab, and ustekinumab in patients with moderate to severe psoriasis. *Journal of the American Academy of Dermatology.* 2015;72(5):AB229.
57. Mehren CR, Gniadecki R. Dose-creep of Infliximab during psoriasis treatment: an observational study. *Acta dermato-venereologica.* 2012;92(4):355-357.
58. Carter C, Wilson KL, Smith D, Lee S. Comparative Treatment Patterns Among Psoriasis Patients Using Adalimumab, Etanercept, or Ustekinumab. *Am J Pharm Benefits.* 2016;8(5):191-198.
59. Busard CI, Cohen AD, Wolf P, et al. Biologics combined with conventional systemic agents or phototherapy for the treatment of psoriasis: real-life data from PSONET registries. *J Eur Acad Dermatol Venereol.* 2018;32(2):245-253.
60. Clemmensen A, Spon M, Skov L, Zachariae C, Gniadecki R. Responses to ustekinumab in the anti-TNF agent-naive vs. anti-TNF agent-exposed patients with psoriasis vulgaris. *J Eur Acad Dermatol Venereol.* 2011;25(9):1037-1040.
61. FDA. Biosimilar Product Information. 2018; https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580432.htm. Accessed March 11, 2018.
62. Griffiths CEM, Thaci D, Gerdes S, et al. The EGALITY study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis. *The British journal of dermatology.* 2017;176(4):928-938.
63. Papp K, Bachelez H, Costanzo A, et al. Clinical similarity of the biosimilar ABP 501 compared with adalimumab after single transition: long-term results from a randomized controlled, double-

blind, 52-week, phase III trial in patients with moderate-to-severe plaque psoriasis. *The British journal of dermatology.* 2017;177(6):1562-1574.
64. Gisondi P, Bianchi L, Conti A, et al. Infliximab biosimilar CT-P13 in the treatment of chronic plaque psoriasis: data from the Psobiosimilars registry. *The British journal of dermatology.* 2017;177(6):e325-e326.
65. Jorgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet.* 2017;389(10086):2304-2316.
66. Chingcuanco F, Segal JB, Kim SC, Alexander GC. Bioequivalence of Biosimilar Tumor Necrosis Factor-alpha Inhibitors Compared With Their Reference Biologics: A Systematic Review. *Ann Intern Med.* 2016;165(8):565-574.
67. FDA. Considerations in Demonstrating Interchangeability With a Reference Product-Guidance for Industry DRAFT GUIDANCE. 2017; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf. Accessed April 10, 2018.
68. FDA. Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. 2018; https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm. Accessed March 11, 2018.
69. De Bandt M, Sibilia J, Le Loet X, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. *Arthritis Res Ther.* 2005;7(3):R545-551.
70. Kagami S, Rizzo HL, Kurtz SE, Miller LS, Blauvelt A. IL-23 and IL-17A, but not IL-12 and IL-22, are required for optimal skin host defense against Candida albicans. *J Immunol.* 2010;185(9):5453-5462.
71. Papp KA, Bachelez H, Blauvelt A, et al. Infections from seven clinical trials of ixekizumab, an anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriasis. *The British journal of dermatology.* 2017;177(6):1537-1551.
72. Danesh MJ, Kimball AB. Brodalumab and suicidal ideation in the context of a recent economic crisis in the United States. *J Am Acad Dermatol.* 2016;74(1):190-192.
73. FDA. Approved Risk Evaluation and Mitigation Strategies (REMS) - Siliq (brodalumab). 2018; https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=362. Accessed April 25, 2018.
74. Papp K, Reich K, Sobell JM, et al. Two-year safety of apremilast in patients with moderate to severe plaque psoriasis: Results from ESTEEM 1. *Australasian Journal of Dermatology.* 2016;57:67.
75. Feldman SR, Traci D, Gooderham M, et al. Tofacitinib improves pruritus and health-related quality of life up to 52 weeks: Results from 2 randomized phase III trials in patients with moderate to severe plaque psoriasis. *J Am Acad Dermatol.* 2016.
76. Papp KA, Menter MA, Raman M, et al. A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis. *The British journal of dermatology.* 2016;174(6):1266-1276.
77. Baker KF, Isaacs JD. Novel therapies for immune-mediated inflammatory diseases: What can we learn from their use in rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, psoriasis, Crohn's disease and ulcerative colitis? *Ann Rheum Dis.* 2018;77(2):175-187.

78. Woolf S. An organized analytic framework for practice guideline development: using the analytic logic as a guide for reviewing evidence, developing recommendations, and explaining the rationale. *Clinical Practice Guideline Development: Methodology Perspectives. AHCPR Pub* 1994; 105-113. Available at: https://ntrl.ntis.gov/NTRL/ under number PB95195848.
79. Nijsten T. Dermatology life quality index: time to move forward. *J Invest Dermatol.* 2012;132(1):11-13.
80. Finlay AY, Kelly SE. Psoriasis--an index of disability. *Clin Exp Dermatol.* 1987;12(1):8-11.
81. Lerner D, Amick BC, 3rd, Rogers WH, Malspeis S, Bungay K, Cynn D. The Work Limitations Questionnaire. *Med Care.* 2001;39(1):72-85.
82. FDA. Public Meeting on Patient-Focused Drug Development for Psoriasis. 2018; https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm470608.htm. Accessed March 31, 2018.
83. Armstrong AW, Robertson AD, Wu J, Schupp C, Lebwohl MG. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003-2011. *JAMA Dermatol.* 2013;149(10):1180-1185.
84. Takeshita J, Gelfand JM, Li P, et al. Psoriasis in the US Medicare Population: Prevalence, Treatment, and Factors Associated with Biologic Use. *J Invest Dermatol.* 2015;135(12):2955-2963.
85. Sampogna F, Chren MM, Melchi CF, et al. Age, gender, quality of life and psychological distress in patients hospitalized with psoriasis. *The British journal of dermatology.* 2006;154(2):325-331.
86. Korman NJ, Zhao Y, Pike J, Roberts J. Relationship between psoriasis severity, clinical symptoms, quality of life and work productivity among patients in the USA. *Clin Exp Dermatol.* 2016;41(5):514-521.
87. Avalere Health. PlanScape®Review of Formulary Coverage of Selected Treatments, 2015-2017. *Prepared for the National Psoriasis Foundation and Crohn's and Colitis Foundation* 2018; https://www.psoriasis.org/sites/default/files/201810409_avalere_planscape_psoriasis_crohns_colitis.pdf. Accessed June, 2018.
88. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
89. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International journal of surgery (London, England).* 2010;8(5):336-341.
90. Dias S, Welton NJ, Sutton AJ, Ades AE. *NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of. Randomised Controlled Trials.* 2011 (updated 2014).
91. Yu-sung S, Masanao Y. R2jags: Using R to Run 'JAGS'. R package version 0.5-7. 2015; https://CRAN.R-project.org/package=R2jags.
92. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Med Care.* 2010;48(6 Suppl):S145-152.
93. Zhu X, Zheng M, Song M, et al. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a phase 3 clinical trial (LOTUS). *Journal of drugs in dermatology : JDD.* 2013;12(2):166-174.
94. Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. *J Am Acad Dermatol.* 2008;58(1):106-115.

95. Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *The British journal of dermatology.* 2008;158(3):558-566.
96. Asahina A, Nakagawa H, Etoh T, Ohtsuki M. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a Phase II/III randomized controlled study. *The Journal of dermatology.* 2010;37(4):299-310.
97. Cai L, Gu J, Zheng J, et al. Efficacy and safety of adalimumab in Chinese patients with moderate-to-severe plaque psoriasis: results from a phase 3, randomized, placebo-controlled, double-blind study. *J Eur Acad Dermatol Venereol.* 2017;31(1):89-95.
98. Papp KA, Tyring S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *The British journal of dermatology.* 2005;152(6):1304-1312.
99. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med.* 2003;349(21):2014-2022.
100. Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet.* 2006;367(9504):29-35.
101. Strober BE, Crowley JJ, Yamauchi PS, Olds M, Williams DA. Efficacy and safety results from a phase III, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. *British Journal of Dermatology.* 2011;165(3):661-668.
102. Gottlieb AB, Leonardi C, Kerdel F, Mehlis S, Olds M, Williams DA. Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. *The British journal of dermatology.* 2011;165(3):652-660.
103. Bagel J, Lynde C, Tyring S, Kricorian G, Shi Y, Klekotka P. Moderate to severe plaque psoriasis with scalp involvement: a randomized, double-blind, placebo-controlled study of etanercept. *J Am Acad Dermatol.* 2012;67(1):86-92.
104. Bachelez H, van de Kerkhof PC, Strohal R, et al. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. *Lancet.* 2015;386(9993):552-561.
105. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet.* 2005;366(9494):1367-1374.
106. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol.* 2007;56(1):31.e31-15.
107. Yang HZ, Wang K, Jin HZ, et al. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. *Chinese medical journal.* 2012;125(11):1845-1851.
108. Torii H, Nakagawa H. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. *J Dermatol Sci.* 2010;59(1):40-49.
109. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet.* 2008;371(9625):1675-1684.

110. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1).[Erratum appears in Lancet. 2008 May 31;371(9627):1838]. *Lancet.* 2008;371(9625):1665-1674.
111. Igarashi A, Kato T, Kato M, Song M, Nakagawa H, Japanese Ustekinumab Study G. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. *Journal of Dermatology.* 2012;39(3):242-252.
112. Tsai TF, Ho JC, Song M, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). *J Dermatol Sci.* 2011;63(3):154-163.
113. Blauvelt A, Prinz JC, Gottlieb AB, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). *British Journal of Dermatology.* 2015;172(2):484-493.
114. Paul C, Lacour JP, Tedremets L, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: A randomized, controlled trial (JUNCTURE). *Journal of the European Academy of Dermatology and Venereology.* 2015;29(6):1082-1090.
115. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. *New England Journal of Medicine.* 2016;371(4):326-338.
116. Gordon K, Leonardi C, Blauvelt A, et al. Efficacy and safety of ixekizumab over four years of open-label treatment in a Phase 2 study in chronic plaque psoriasis. *Experimental Dermatology.* 2016;25:39.
117. Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet.* 2015;386(9993):541-551.
118. Lebwohl M, Reich K, Paul C, Rosen M, Hansen K. Brodalumab is efficacious in patients with moderate-to-severe psoriasis irrespective of prior use of, and response to, other biological therapies. *British Journal of Dermatology.* 2017;177:64-65.
119. Papp KA, Reich K, Paul C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *The British journal of dermatology.* 2016.
120. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *Journal of the American Academy of Dermatology.* 2015;73(1):37-49.
121. Reich K, Gooderham M, Green L, et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). *Journal of the european academy of dermatology and venereology : JEADV.* 2016(pagination).
122. de Vries AC, Thio HB, de Kort WJ, et al. A prospective randomized controlled trial comparing infliximab and etanercept in patients with moderate-to-severe chronic plaque-type psoriasis: the Psoriasis Infliximab vs. Etanercept Comparison Evaluation (PIECE) study. *The British journal of dermatology.* 2017;176(3):624-633.
123. Griffiths CE, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med.* 2010;362(2):118-128.

124. Thaci D, Blauvelt A, Reich K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *Journal of the American Academy of Dermatology.* 2015;73(3):400-409.
125. Reich K, Pinter A, Lacour JP, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. *British Journal of Dermatology.* 2017;177(4):1014-1023.
126. Bagel J, Nia J, Hashim P, et al. Secukinumab is Superior to Ustekinumab in Clearing Skin of Patients with Moderate to Severe Plaque Psoriasis: CLARITY, a Randomized, Controlled, Phase 3b Trial. *2018.* 2018;2.
127. Papp KA, Blauvelt A, Kimball AB, et al. Patient-reported symptoms and signs of moderate-to-severe psoriasis treated with guselkumab or adalimumab: results from the randomized VOYAGE 1 trial. *J Eur Acad Dermatol Venereol.* 2018.
128. Blauvelt A, Mehlis S, Vanaclocha F, al. E. Secukinumab provides greater 52-week sustained relief from dermatology-related quality of life impact on clothing choice and sexual function than ustekinumab. Paper presented at: 25th European Academy of Dermatology and Venereology Congress2016; Vienna, Austria.
129. Guenther L, Sofen H, Cathers J, et al. Impact of ixekizumab treatment on sexual function in moderate-to-severe psoriasis patients: 12 week results from two phase 3 trials UNCOVER-2 and UNCOVER-3. *Journal of the American Academy of Dermatology.* 2016;74(5):AB254.
130. Korman NJ, Sofen H, Fretzin S, et al. Secukinumab provides better relief from the impact of psoriasis on daily activities and personal relationships than etanercept: results of two phase 3 placebo-controlled randomized clinical trials in moderate-to-severe psoriasis. *J Dermatolog Treat.* 2017;28(5):384-389.
131. Blauvelt A, Reich K, Papp KA, et al. Safety of Tildrakizumab for Moderate-to-Severe Plaque Psoriasis: Pooled Analysis of Three Randomised Controlled Trials. *The British journal of dermatology.* 2018.
132. Kalb RE, Fiorentino DF, Lebwohl MG, et al. Risk of Serious Infection With Biologic and Systemic Treatment of Psoriasis: Results From the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *JAMA Dermatology.* 2015;151(9):961-969.
133. Papp K, Gottlieb AB, Naldi L, et al. Safety Surveillance for Ustekinumab and Other Psoriasis Treatments From the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *Journal of drugs in dermatology : JDD.* 2015;14(7):706-714.
134. Menter A, Papp KA, Gooderham M, et al. Drug survival of biologic therapy in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Eur Acad Dermatol Venereol.* 2016;30(7):1148-1158.
135. Wu JJ, Guerin A, Sundaram M, Dea K, Cloutier M, Mulani P. Cardiovascular event risk assessment in psoriasis patients treated with tumor necrosis factor-alpha inhibitors versus methotrexate. *J Am Acad Dermatol.* 2017;76(1):81-90.
136. Gulliver WP, Young HM, Bachelez H, Randell S, Gulliver S, Al-Mutairi N. Psoriasis Patients Treated With Biologics and Methotrexate Have a Reduced Rate of Myocardial Infarction: A Collaborative Analysis Using International Cohorts. *J Cutan Med Surg.* 2016;20(6):550-554.
137. Hu SC, Lan CE. Psoriasis and Cardiovascular Comorbidities: Focusing on Severe Vascular Events, Cardiovascular Risk Factors and Implications for Treatment. *Int J Mol Sci.* 2017;18(10).
138. Rungapiromnan W, Yiu ZZN, Warren RB, Griffiths CEM, Ashcroft DM. Impact of biologic therapies on risk of major adverse cardiovascular events in patients with psoriasis: systematic

review and meta-analysis of randomized controlled trials. *The British journal of dermatology.* 2017;176(4):890-901.
139. Gelfand JM. Does biologic treatment of psoriasis lower the risk of cardiovascular events and mortality? A critical question that we are only just beginning to answer. *J Am Acad Dermatol.* 2018.
140. Woolacott N, Hawkins N, Mason A, et al. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. *Health technology assessment (Winchester, England).* 2006;10(46):1-233, i-iv.
141. Warren RB, Barker J, Burden AD, et al. Secukinumab has demonstrated efficacy and safety in hard-to-treat anti-TNFα failure patients from the UK and Republic of Ireland: Results of the SIGNATURE study. Annual Meeting of the American Academy of Dermatology; February 16-20, 2018; San Diego, CA.
142. Griffiths CEM, Radtke MA, Youn SW, et al. Clinical response after guselkumab treatment among adalimumab PASI 90 non-responders: results from the VOYAGE 1 and 2 trials. Annual meeting of the American Academy of Dermatology; February 16-20, 2018; San Diego, CA.
143. Langley RG, Tsai TF, Flavin S, et al. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: Results of the randomized, double-blind, phase III NAVIGATE trial. *British Journal of Dermatology.* 2017.
144. Papp K, Gordon K, Langley R, et al. Impact of previous biologic use on efficacy and safety of brodalumab and ustekinumab in patients with moderate-to-severe plaque psoriasis: integrated analysis of AMAGINE-2 and AMAGINE-3. *British Journal of Dermatology.* 2018.
145. Egeberg A, Ottosen MB, Gniadecki R, et al. Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. *The British journal of dermatology.* 2018;178(2):509-519.
146. Langley R, Lebwohl M, Krueger G, et al. Long-term efficacy and safety of ustekinumab, with and without dosing adjustment, in patients with moderate-to-severe plaque psoriasis: results from the PHOENIX 2 study through 5 years of follow-up. *British Journal of Dermatology.* 2015;172(5):1371-1383.
147. Mrowietz U, Leonardi C, Girolomoni G, et al. Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis: a randomized, double-blind, noninferiority trial (SCULPTURE). *Journal of the American Academy of Dermatology.* 2015;73(1):27-36.
148. Bissonnette R, Luger T, Thac¸i D, et al. Secukinumab sustains good efficacy and favourable safety in moderate to severe psoriasis patients up to 3 years of treatment: results from a double-blind extension study. *British Journal of Dermatology.* 2017;177(4):1033-1042.
149. Leonardi C, Maari C, Philipp S, et al. Long-term Efficacy and Safety of Ixekizumab for the Treatment of Moderate-to-Severe Plaque Psoriasis Sustained for 3 Years: Results of a Randomized, Controlled Phase 3 Study (UNCOVER-3). 2018.
150. Gordon K, Menter A, Ferris L, et al. Consistency of response (PASI 90 or 100 and IGA 0/1 or 0) in patients with moderate to severe psoriasis treated with guselkumab: results from the VOYAGE 1 and 2 trials. Annual meeting of the American Academy of Dermatology; February 16-20, 2018; San Diego, CA.
151. Cao Z, Carter C, Wilson KL, Schenkel B. Ustekinumab dosing, persistence, and discontinuation patterns in patients with moderate-to-severe plaque psoriasis. *J Dermatolog Treat.* 2015;26(2):113-120.

152. Feldman S, Zhao Y, Gray S, Montejano L, Lin F, Herrera V. Adherence and persistence among U.S. patients initiating secukinumab for the treatment of moderate to severe psoriasis. 2017.
153. Bagel J, Liao W, Palmer J, et al. Persistence and adherence of secukinumab and subcutaneously administered anti-TNF treatments among biologic-naive and biologic experienced patients with plaque psoriasis: analyses from a US claims database. 2017.
154. Pickard AS, Gooderham M, Hartz DS, Nicolay C. EQ-5D health utilities: Exploring ways to improve upon responsiveness in psoriasis. *J Med Econ.* 2016:1-31.
155. Feldman SR, Zhao Y, Navaratnam P, Friedman HS, Lu J, Tran MH. Patterns of Medication Utilization and Costs Associated with the Use of Etanercept, Adalimumab, and Ustekinumab in the Management of Moderate-to-Severe Psoriasis. *Journal of Managed Care & Specialty Pharmacy.* 2015;21(3):201-209.
156. Feldman SR, Zhao Y, Zhou H, Herrera V, Tian H, Li Y. Economic Impact of Above-Label Dosing with Etanercept, Adalimumab, or Ustekinumab in Patients with Psoriasis. *J Manag Care Spec Pharm.* 2017;23(5):583-589.
157. Yu AP, Tang J, Xie J, et al. Economic burden of psoriasis compared to the general population and stratified by disease severity. *Curr Med Res Opin.* 2009;25(10):2429-2438.
158. Armstrong AW, Lynde CW, McBride SR, et al. Effect of Ixekizumab Treatment on Work Productivity for Patients With Moderate-to-Severe Plaque Psoriasis: Analysis of Results From 3 Randomized Phase 3 Clinical Trials. *JAMA Dermatol.* 2016;152(6):661-669.
159. Kimball AB, Yu AP, Signorovitch J, et al. The effects of adalimumab treatment and psoriasis severity on self-reported work productivity and activity impairment for patients with moderate to severe psoriasis. *J Am Acad Dermatol.* 2012;66(2):e67-76.
160. Bureau of Labor Statistics. May 2017 National Occupational Employment and Wage Estimates United States. *Occupational Employment Statistics.* 2017. http://www.bls.gov/oes/current/oes_nat.htm#00-0000.
161. Kimball A, Papp K, Tyring S, et al. Efficacy of tildrakizumab, an anti-IL23p19 monoclonal antibody, stratified by prior exposure to biologics in a randomized, placebo-controlled phase 3 clinical trial. *Journal of the American Academy of Dermatology.* 2017;76(6):AB121.
162. Reich K, Papp K, Thaçi D, et al. Safety and tolerability of tildrakizumab, an anti-IL-23p19 monoclonal antibody, in patients with chronic plaque psoriasis over two years of treatment: results from long-term extensions of two phase III clinical studies (reSURFACE 1 and reSURFACE 2). 2018.
163. Burge RT, Papadimitropoulos M, Henneges C, Garcia EG, Romiti R. Ixekizumab treatment leads to early resolution of bothersome symptoms versus ustekinumab. *Value in Health.* 2017;20(9):A902.
164. Revicki D, Willian MK, Saurat JH, et al. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. *The British journal of dermatology.* 2008;158(3):549-557.
165. Reich K, Nestle FO, Wu Y, et al. Infliximab treatment improves productivity among patients with moderate-to-severe psoriasis. *European journal of dermatology : EJD.* 2007;17(5):381-386.
166. Gisondi P, Conti A, Galdo G, Piaserico S, De Simone C, Girolomoni G. Ustekinumab does not increase body mass index in patients with chronic plaque psoriasis: a prospective cohort study. *The British journal of dermatology.* 2013;168(5):1124-1127.

167. Piaserico S, Conti A, Lo Console F, et al. Efficacy and safety of systemic treatments for psoriasis in elderly patients. *Acta dermato-venereologica.* 2014;94(3):293-297.
168. Esposito M, Giunta A, Mazzotta A, et al. Efficacy and safety of subcutaneous anti-tumor necrosis factor-alpha agents, etanercept and adalimumab, in elderly patients affected by psoriasis and psoriatic arthritis: an observational long-term study. *Dermatology (Basel, Switzerland).* 2012;225(4):312-319.
169. Gisondi P, Cotena C, Tessari G, Girolomoni G. Anti-tumour necrosis factor-alpha therapy increases body weight in patients with chronic plaque psoriasis: a retrospective cohort study. *J Eur Acad Dermatol Venereol.* 2008;22(3):341-344.
170. Blauvelt A, Reich K, Mehlis S, et al. Secukinumab demonstrates greater sustained improvements in daily activities and personal relationships than ustekinumab in patients with moderate-to-severe plaque psoriasis: 52-week results from the CLEAR study. *Journal of the European Academy of Dermatology and Venereology.* 2017;31(10):1693-1699.
171. Thaci D, Kimball A, Foley P, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, improves patient-reported outcomes in the treatment of moderate to severe psoriasis: results of two phase III randomized, controlled trials. *Journal of the european academy of dermatology and venereology : JEADV.* 2016(pagination).
172. Lacour JP, Paul C, Jazayeri S, et al. Secukinumab administration by autoinjector maintains reduction of plaque psoriasis severity over 52 weeks: results of the randomized controlled JUNCTURE trial. *Journal of the European Academy of Dermatology and Venereology.* 2017;31(5):847-856.
173. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. *N Engl J Med.* 2014;371(4):326-338.
174. Ohtsuki M, Morita A, Abe M, et al. Secukinumab efficacy and safety in Japanese patients with moderate-to-severe plaque psoriasis: Subanalysis from ERASURE, a randomized, placebo-controlled, phase 3 study. *Journal of Dermatology.* 2014;41(12):1039-1046.
175. Blauvelt A, Gottlieb A, Sigurgeirsson B, Papavassilis C, Martin R. Secukinumab efficacy in subjects with moderate-to-severe plaque psoriasis and concomitant psoriatic arthritis: A subanalysis of the ERASURE study. *Journal of the American Academy of Dermatology.* 2014;70(5 SUPPL. 1):AB2.
176. Papp K, Karpov A, Papavassilis C, Melendez E, Nakagawa H. Secukinumab efficacy in relationship with response to previous biologic psoriasis therapy: A subanalysis from the ERASURE Study. *Journal of the American Academy of Dermatology.* 2014;70(5 SUPPL. 1):AB186.
177. Wu NL, Hsu CJ, Sun FJ, Tsai TF. Efficacy and safety of secukinumab in Taiwanese patients with moderate to severe plaque psoriasis: Subanalysis from ERASURE phase III study. *Journal of Dermatology.* 2017;44(10):1129-1137.
178. Sigurgeirsson B, Gottlieb AB, Langley RG, et al. Effect of secukinumab on psoriasis symptoms and physical functioning compared with placebo and etanercept in subjects with moderate-to-severe plaque psoriasis and concomitant psoriatic arthritis: A subanalysis from the phase 3 fixture study. *Scandinavian journal of rheumatology.* 2014;43:64-65.
179. Strober B, Sigurgeirsson B, Popp G, et al. Secukinumab improves patient-reported psoriasis symptoms of itching, pain, and scaling: Results of two phase 3, randomized, placebo-controlled clinical trials. *International Journal of Dermatology.* 2016;55(4):401-407.
180. Lee JH, Morita A, Tsai TF, et al. Secukinumab efficacy and safety in Asian subjects with moderate to severe plaque psoriasis: Pooled analysis from the FIXTURE and ERASURE phase III clinical studies. *Journal of the American Academy of Dermatology.* 2015;72(5 SUPPL. 1):AB249.

181. van de Kerkhof PC, Griffiths CE, Reich K, et al. Secukinumab long-term safety experience: A pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis. *Journal of the American Academy of Dermatology.* 2016;75(1):83-98.e84.
182. Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis. *N Engl J Med.* 2016;375(4):345-356.
183. Langley R, Feldman SR, Paul C, et al. Treatment with ixekizumab over 60 weeks provides sustained improvements in health-related quality of life: Results from UNCOVER-1, a randomized phase 3 trial. *Journal of the American Academy of Dermatology.* 2016;74(5):AB279.
184. Imafuku S, Torisu-Itakura H, Nishikawa A, Zhao F, Cameron GS. Efficacy and safety of ixekizumab treatment in Japanese patients with moderate-to-severe plaque psoriasis: Subgroup analysis of a placebo-controlled, phase 3 study (UNCOVER-1). *Journal of Dermatology.* 2017;44(11):1285-1290.
185. Gottlieb A, Luger T, Sanz LP, et al. Impact of ixekizumab on skin pain in patients with moderate to severe psoriasis compared to placebo and etanercept in UNCOVER-2. *Journal of the American Academy of Dermatology.* 2016;74(5):AB57.
186. Blauvelt A, Gooderham M, Iversen L, et al. Efficacy and safety of ixekizumab for the treatment of moderate-to-severe plaque psoriasis: results through 108 weeks of a randomized, controlled phase 3 clinical trial (UNCOVER-3). *Journal of the american academy of dermatology.* 2017(pagination).
187. Gottlieb AB, Lacour JP, Korman N, et al. Treatment outcomes with ixekizumab in patients with moderate-to-severe psoriasis who have or have not received prior biological therapies: an integrated analysis of two Phase III randomized studies. *Journal of the european academy of dermatology and venereology : JEADV.* 2016(pagination).
188. Guenther L, Warren RB, Cather JC, et al. Impact of ixekizumab treatment on skin-related personal relationship difficulties in moderate-to-severe psoriasis patients: 12-week results from two Phase 3 trials. *Journal of the European Academy of Dermatology and Venereology.* 2017;31(11):1867-1875.
189. Kimball AB, Luger T, Gottlieb A, et al. Impact of ixekizumab on psoriasis itch severity and other psoriasis symptoms: Results from 3 phase III psoriasis clinical trials. *Journal of the American Academy of Dermatology.* 2016;75(6):1156-1161.
190. Griffiths C, Fava M, Miller A, et al. Impact of ixekizumab treatment on depressive symptoms: An integrated analysis of three phase 3 clinical studies in patients with moderate-tosevere psoriasis. *Journal of the American Academy of Dermatology.* 2016;74(5):AB253.
191. Gottlieb AB, Gerdes S, Lacour JP, et al. Efficacy of ixekizumab in moderate to severe psoriasis patients who have or have not received prior biologic therapies: An integrated analysis of 3 phase 3 studies. *Journal of the American Academy of Dermatology.* 2016;74(5):AB247.
192. Gottlieb A, Papp K, Duffin KC, et al. Ixekizumab in patients with psoriasis and psoriatic arthritis: Pooled analysis of three phase 3 studies in moderate-to-severe psoriasis. *Journal of Investigative Dermatology.* 2015;135:S26.
193. Papp KA, Leonardi C, Menter A, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *New England Journal of Medicine.* 2012;366(13):1181-1189.
194. Papp K, Leonardi C, Menter A, et al. Maintenance of clinical response with long-term brodalumab (AMG 827) therapy for psoriasis: Week 144 results from an open-label extension study. *Australasian journal of dermatology.* 2015;56(52).

195. Papp K, Menter A, Strober B, et al. Efficacy and safety of brodalumab in subpopulations of patients with difficult-to-treat moderate-to-severe plaque psoriasis. *Journal of the American Academy of Dermatology.* 2014;72(3):436-439.e431.
196. Papp K, Menter A, Strober B, et al. Improvement of psoriasis in patients with and without prior biologic experience: Subanalysis of a brodalumab (AMG 827) phase 2 study for moderate to severe plaque psoriasis. *Journal of the American Academy of Dermatology.* 2015;72(5 SUPPL. 1):AB238.
197. Strober B, Gordon K, Augustin M, et al. Improvements in patient-reported outcomes (PROs) among moderate to severe plaque psoriasis patients treated with brodalumab: Results from AMAGINE-1. *Journal of the American Academy of Dermatology.* 2016;74(5):AB256.
198. Nakagawa H, Niiro H, Ootaki K, Japanese brodalumab study g. Brodalumab, a human anti-interleukin-17-receptor antibody in the treatment of Japanese patients with moderate-to-severe plaque psoriasis: Efficacy and safety results from a phase II randomized controlled study. *J Dermatol Sci.*81(1):44-52.
199. Umezawa Y, Nakagawa H, Niiro H, Ootaki K, Japanese Brodalumab Study G. Long-term clinical safety and efficacy of brodalumab in the treatment of Japanese patients with moderate-to-severe plaque psoriasis. *J Eur Acad Dermatol Venereol.*30(11):1957-1960.
200. Langley RG, Feldman SR, Han C, et al. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: Results from a randomized, double-blind, placebo-controlled phase III trial. *Journal of the American Academy of Dermatology.* 2010;63(3):457-465.
201. Reich K, Schenkel B, Zhao N, et al. Ustekinumab decreases work limitations, improves work productivity, and reduces work days missed in patients with moderate-to-severe psoriasis: results from PHOENIX 2. *J Dermatolog Treat.* 2011;22(6):337-347.
202. Sofen H, Wasel N, Yeilding N, Lee S, Zhao N, Mendelsohn A. Ustekinumab improves overall skin response and healthrelated quality of life in a subset of moderate to severe psoriasis patients with psoriatic arthritis: Analysis of phoenix 1 and 2. *Value in Health.* 2010;13(3):A130.
203. Guenther L, Han C, Szapary P, et al. Impact of ustekinumab on health-related quality of life and sexual difficulties associated with psoriasis: results from two phase III clinical trials. *J Eur Acad Dermatol Venereol.* 2011;25(7):851-857.
204. Zhang W, Islam N, Ma C, Anis AH. Systematic review of cost-effectiveness analyses of treatments for psoriasis. *PharmacoEconomics.* 2015;33(4):327-340.
205. Gelfand JM, Wan J, Callis Duffin K, et al. Comparative effectiveness of commonly used systemic treatments or phototherapy for moderate to severe plaque psoriasis in the clinical practice setting. *Archives of Dermatology.* 2012;148(4):487-494.
206. Gniadecki R, Bang B, Bryld LE, Iversen L, Lasthein S, Skov L. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. *The British journal of dermatology.* 2015;172(1):244-252.
207. Strober BE, Bissonnette R, Fiorentino D, et al. Comparative effectiveness of biologic agents for the treatment of psoriasis in a real-world setting: Results from a large, prospective, observational study (Psoriasis Longitudinal Assessment and Registry [PSOLAR]). *Journal of the American Academy of Dermatology.* 2016;74(5):851-861e854.
208. Iskandar IYK, Ashcroft DM, Warren RB, et al. Comparative effectiveness of biological therapies on improvements in quality of life in patients with psoriasis. *British Journal of Dermatology.* 2017;177(5):1410-1421.

209. Papp K, Cather JC, Rosoph L, et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. *The Lancet.* 2012;380(9843):738-746.
210. Papp KA, Langley RG, Sigurgeirsson B, et al. Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study. *The British journal of dermatology.* 2013;168(2):412-421.
211. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: A phase III, randomized controlled trial (ESTEEM 2). *British Journal of Dermatology.* 2015;173(6):1387-1399.
212. Crowley J, Thaci D, Joly P, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: pooled safety analysis for >156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). *Journal of the american academy of dermatology.* 2017(pagination).
213. Green L, Thaci D, Zhang Z, Goncalves J, Nograles K, Nikkels A. Effect of apremilast and etanercept on pruritus and health-related quality of life in patients with moderate to severe plaque psoriasis: Results from the LIBERATE study. *Journal of the American Academy of Dermatology.* 2016;74(5):AB245.
214. Reich K, Gooderham M, Bewley A, et al. Safety and efficacy of apremilast through 104 weeks in patients with moderate to severe psoriasis who continued on apremilast or switched from etanercept treatment: findings from the LIBERATE study. *J Eur Acad Dermatol Venereol.* 2017.
215. Reich K, Soung J, Gooderham M, Zhang Z, Nograles K, Goodfield M. Sustained efficacy of apremilast in patients with moderate to severe psoriasis who continued on apremilast or switched from etanercept treatment: 52-week results from the LIBERATE study. *Journal of the American Academy of Dermatology.* 2016;74(5):AB276.
216. Ohtsuki M, Okubo Y, Komine M, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of Japanese patients with moderate to severe plaque psoriasis: Efficacy, safety and tolerability results from a phase 2b randomized controlled trial. *Journal of Dermatology.* 2017;44(8):873-884.
217. Ramaekers BLT, Wolff RF, Pouwels X, et al. Ixekizumab for Treating Moderate-to-Severe Plaque Psoriasis: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *PharmacoEconomics.* 2018.
218. Hinde S, Wade R, Palmer S, Woolacott N, Spackman E. Apremilast for the Treatment of Moderate to Severe Plaque Psoriasis: A Critique of the Evidence. *PharmacoEconomics.* 2016;34(6):587-596.
219. National Institute for Health and Care Excellence (NICE). Secukinumab for treating moderate to severe plaque psoriasis. In. Vol TA350. 22 July 2015 ed: NICE; 2015.
220. Turner D, Picot J, Cooper K, Loveman E. Adalimumab for the treatment of psoriasis. *Health technology assessment (Winchester, England).* 2009;13 Suppl 2:49-54.
221. Loveman E, Turner D, Hartwell D, Cooper K, Clegg A. Infliximab for the treatment of adults with psoriasis. *Health technology assessment (Winchester, England).* 2009;13 Suppl 1:55-60.
222. Gospodarevskaya E, Picot J, Cooper K, Loveman E, Takeda A. Ustekinumab for the treatment of moderate to severe psoriasis. *Health technology assessment (Winchester, England).* 2009;13 Suppl 3:61-66.
223. (NICE) NIfHaCE. Etanercept and efalizumab for the treatment of adults with psoriasis. 2006.
224. U.S. Preventive Services Task Force. *Procedure Manual.* Agency for Healthcare Research and Quality;2008.

225. Gottlieb A, Langley R, Philipp S, Martin R, Papavassilis C, Mpfofu S. Improvement in psoriasis symptoms and physical functioning with secukinumab compared with placebo and etanercept in subjects with moderate-to-severe plaque psoriasis and psoriatic arthritis: Results of a subanalysis from the phase 3 fixture study. *Arthritis and Rheumatism.* 2013;65(12):3322.
226. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. *Med Decis Making.* 2013;33(5):618-640.
227. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama.* 2016;316(10):1093-1103.

Appendices

Appendix A. Evidence Review Methods and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.
From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097		

Table A2. Updated Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials on the 2016 Review

1	Psoriasis/	18421
2	psoria$.ti,ab.	28290
3	(secukinumab or cosentyx).ti,ab.	518
4	(ustekinumab or stelara).ti,ab.	979
5	(ixekizumab or taltz).ti,ab.	234
6	brodalumab.ti,ab.	138
7	(apremilast or otezla).ti,ab.	334
8	1 or 2	30099
9	3 or 4 or 5 or 6 or 7	1953
10	8 and 9	1541
11	limit 10 to english language	1468
12	limit 11 to humans	1467
13	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt.conference or congresses).pt.	3057911
14	12 not 13	1059
15	remove duplicates from 14	884
16	limit 15 to ed=20160628-20180102	632
Date of Search: January 2, 2018		

Table A3. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials on New Drugs

1	Psoriasis/	18421
2	psoria$.ti,ab.	28290
3	(certolizumab pegol or cimzia).ti,ab.	647
4	(guselkumab or tremfya).ti,ab.	42
5	tildrakizumab.ti,ab.	28
6	risankizumab.ti,ab.	15
7	1 or 2	30099
8	3 or 4 or 5 or 6	705
9	7 and 8	154
10	limit 9 to english language	152
11	limit 10 to humans	152

12	(guideline or practice guideline or letter or editorial or news or case reports or clinical conferences or congresses).pt	2049847
13	11 not 12	149
14	remove duplicates from 13	129
Date of Search: January 2, 2018		

Table A4. Updated Search Strategy in EMBASE on the 2016 Review

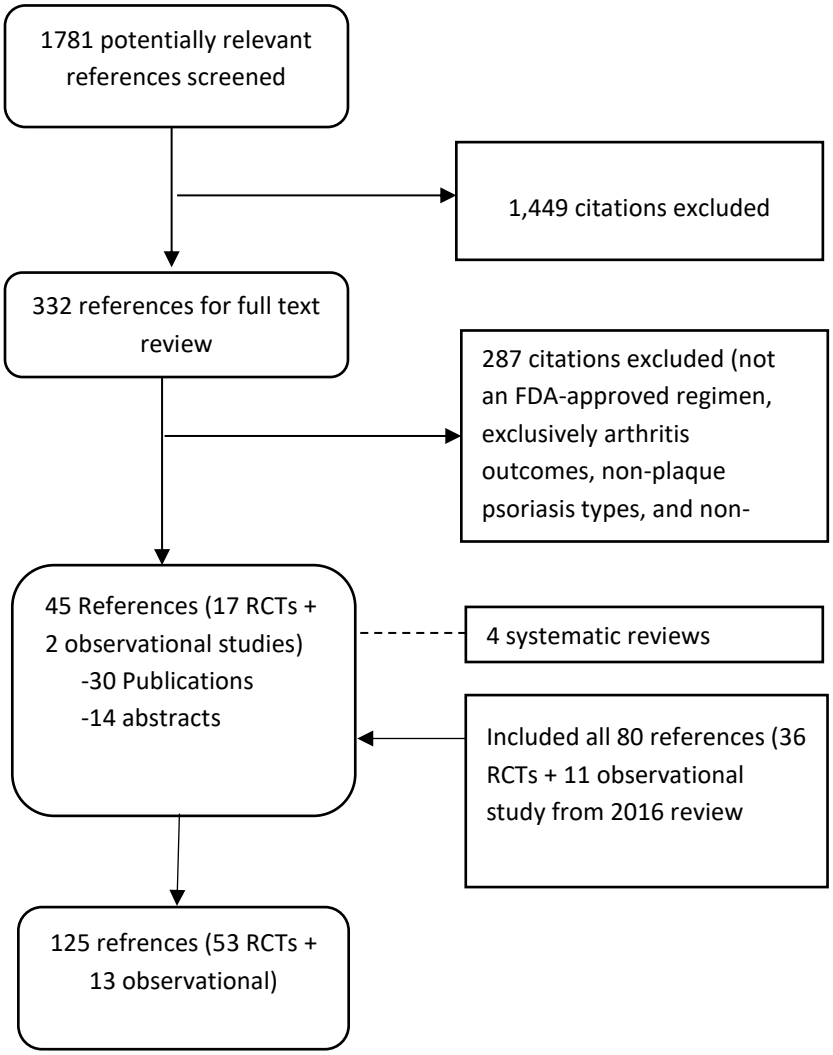
1	'psoriasis vulgaris'	8040
2	psorias*:ab,ti OR psoriat*:ab,ti	57572
3	#1 OR #2	58457
4	'secukinumab':ab,ti OR 'cosentyx':ab,ti	399
5	'ustekinumab':ab,ti OR 'stelara':ab,ti	1454
6	'ixekizumab':ab,ti OR 'taltz':ab,ti	156
7	'apremilast':ab,ti OR 'otezla':ab,ti	331
8	'brodalumab':ab,ti	127
9	#4 OR #5 OR #6 OR #7 OR #8	2235
10	#3 AND #9	1805
11	#3 AND #9 AND ([editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim)	122
12	#10 NOT #11	1683
13	#12 AND [english]/lim	1622
14	#12 AND [medline]/lim	413
15	#13 NOT #14	1224
16	#15 AND [animals]/lim	40
17	#15 AND [humans]/lim AND [animals]/lim	32
18	#15 NOT #16 NOT #17	1184
19	#18 NOT 'case report' NOT 'case study'	1679
20	#19 AND [humans]/lim	1568
21	#20 AND [28-6-2016]/sd	712
Date of Search: January 2, 2018		

Table A5. Search Strategy in EMBASE on New Drugs

1	'psoriasis vulgaris'	8040
2	psorias*:ab,ti OR psoriat*:ab,ti	57572
3	#1 OR #2	58457
4	'guselkumab':ab,ti OR 'tremfya':ab,ti	61
5	'tildrakizumab':ab,ti	40
6	'certolizumab pegol':ab,ti OR 'cimzia':ab,ti	1463
7	‘risankizumab’:ab,ti	21
8	#4 OR #5 OR #6 OR #7	1546
9	#3 AND #8	1805

10	#3 AND #8 AND ([editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim)	122
11	#9 NOT #8	1683
12	#11 AND [english]/lim	1622
13	#11 AND [medline]/lim	413
14	#12 NOT #13	1224
15	#14 AND [animals]/lim	40
16	#14 AND [humans]/lim AND [animals]/lim	32
17	#14 NOT #15 NOT #16	1184
18	#17 NOT 'case report' NOT 'case study'	1679
19	#18 AND [humans]/lim	211
Date of Search: January 2, 2018		

Figure A1. PRISMA Flow Chart Showing Results of Literature Search (updated May 21, 2018)



Appendix B. Evidence Summary Tables

Table B1. Evidence Summary Tables for New Drugs

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
TNFα inhibitors						
Certolizumab Pegol						
Gottlieb, 2018[29] **(NCT02326298)** **CIMPASI-1** ***Good quality publication***	Phase III, double-blind, placebo-controlled, multicenter trial Sites in North America and Europe ITT, MI & LOCF	1) Certolizumab 200 mg q2w after 400 mg at weeks 0, 2, and 4 (n=95) 2) Certolizumab 400 mg q2w (n=88) 3) Placebo (n=51) At 16 weeks, patients continued to receive treatment to 48 weeks based on their PASI response: All patients on certolizumab with PASI 50 response continued treatment; placebo PASI 75 responders continued placebo; placebo PASI 50-75 responders received 200 mg; all PASI 50 non-responders entered escape arm and	Inclusion: Adult patients (≥18 years) with moderate-to-severe plaque psoriasis (PASI ≥12, BSA ≥10%, PGA≥3 on a 5-point scale) who were candidates for systematic therapy or phototherapy Exclusion: Previous treatment with certolizumab or >2 biologics (including TNFα); history of primary failure to any biologic or secondary failure to >1 biologic; erythrodermic, guttate, or generalized pustular form of psoriasis	Age, mean 1)44.5; 2)43.6; 3)47.9 Male, % 1)70.5; 2)68.2; 3)68.6 Caucasian, % 1)91.6; 2)89.8; 3)88.2 Duration of PsO, years 1)16.6; 2)18.4; 3)18.5 With PsA, % 1)10.5; 2)17.0; 3)7.8 Previous biologic, % 1)31.6; 2)33.0; 3)29.4 PGA severe(4), % 1)34.7; 2)26.1; 3)31.4 PASI, mean (SD) 1)20.1 (8.2); 2)19.6 (7.9) 3)19.8 (7.5)	**At 16 weeks** PASI 75, % 1)66.5; 2)75.8; 3)6.5 PASI 90, % 1)35.8; 2)43.6; 3)0.4 PGA 0/1, % 1)47.0; 2)57.9; 3)4.2 DLQI, change from baseline, mean 1)-8.9; 2)-9.6; 3)-3.3 *For all above, p<0.0001 for certolizumab 200 mg & 400 mg vs. placebo*	**0-16 weeks** Any TEAE, % (IR/100PY) 1)54.7 (292.3) 2)64.8 (375.9) 3)54.9 (279.1) Serious AE, % (IR/100PY) 1)2.1 (6.9) 2)5.7 (19.0) 3)2.0 (6.8) TEAE leading to discontinuation, % 1)0 2)2.3 3)0 Serious infection, % (IR/100PY) 1)0; 2)0; 3)0 Malignancy, % (IR/100PY) 1)0; 2)0; 3)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		received unblinded 400mg		DLQI, mean (SD) 1)13.3 (7.4); 2)13.1 (6.5); 3)13.9 (8.3)		Depression, % (IR/100PY) 1)0; 2)1.1 (3.7); 3)0
Gottlieb, 2018[29] **(NCT02326272)** **CIMPASI-2** ***Good quality publication***	Phase III, double-blind, placebo-controlled, multicenter trial Sites in North America and Europe ITT, MI	1) Certolizumab 200 mg q2w after 400 mg at weeks 0, 2, and 4 (n=91) 2) Certolizumab 400 mg q2w (n=87) 3) Placebo (n=49) At 16 weeks, patients continued to receive treatment to 48 weeks based on their PASI response: All patients on certolizumab with PASI 50 response continued treatment; placebo PASI 75 responders continued placebo; placebo PASI 50-75 responders received 200 mg; all PASI 50 non-responders entered escape arm and received unblinded 400mg	*See CIMPASI-1*	Age, mean 1)46.7; 2)46.4; 3)43.3 Male, % 1)63.7; 2)49.4; 3)53.1 Caucasian, % 1)94.5; 2)93.1; 3)89.8 Duration of PsO, years 1)18.8; 2)18.6; 3)15.4 With PsA, % 1)24.2; 2)29.9; 3)18.4 Previous biologic, % 1)35.2; 2)34.5; 3)28.6 PGA severe(4), % 1)27.5; 2)29.9; 3)24.5 PASI, mean (SD) 1)18.4 (5.9) 2)19.5 (6.7) 3)17.3 (5.3) DLQI, mean (SD) 1)15.2 (7.2)	**At 16 weeks** PASI 75, % 1)81.4; 2)82.6; 3)11.6 PASI 90, % 1)52.6; 2)55.4; 3)4.5 PGA 0/1, % 1)66.8; 2)71.6; 3)2.0 DLQI, change from baseline, mean 1)-11.1 2)-10.0; 3)-2.9 *For all above, p<0.0001 for certolizumab 200 mg & 400 mg vs. placebo*	**0-16 weeks** Any TEAE, % (IR/100PY) 1)60.0 (308.7) 2)69.0 (405.7) 3)67.3 (388.9) Serious AE, % (IR/100PY) 1)2.2 (7.4) 2)4.6 (15.3) 3)0 TEAE leading to discontinuation, % 1)3.3 2)1.1 3)0 Serious infection, % (IR/100PY) 1)0 2)1.1 (3.8) 3)0 Malignancy, % (IR/100PY) 1)0 2)1.1 (3.8) 3)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				2)14.2 (7.2) 3)12.9 (7.3)		Depression, % (IR/100PY) 1)1.1 (3.7) 2)1.1 (3.8) 3)0
Lebwohl 2018[30] **(NCT02346240)** **CIMPACT** ***Good quality publication***	Phase III, double-blind, placebo- and active-controlled multicenter trial ITT, MI	1) Certolizumab 200 mg q2w after 400 mg at weeks 0, 2, and 4 (n=165) 2) Certolizumab 400 mg q2w (n=167) 3) Etanercept 50 mg BIW (n=170) 4) Placebo (n=57) Etanercept was single-blind (outcomes assessor). At week 16, patients achieving PASI 75 in the certolizumab arms were rerandomized to continue treatment or receive placebo. Patients achieving PASI 75 in the placebo arm continued to receive placebo, and patients achieving PASI	Inclusion: Adult patients (≥18 years) with moderate-to-severe chronic plaque psoriasis for ≥6 months and PASI ≥12, BSA ≥10%, PGA≥3 at baseline who were candidates for systematic therapy, phototherapy, or photochemotherapy Exclusion: Previous treatment with certolizumab (or etanercept or > 2 biologics (including TNFα); history of primary failure to any biologic or secondary failure to >1 biologic; erythrodermic, guttate, or generalized pustular form of psoriasis	Age, mean 1)46.7; 2)45.4; 3)44.6; 4)46.5 Male, % 1)68.5; 2)64.1; 3)74.7; 4)59.6 Caucasian, % 1)95.8; 2)97.0; 3)95.9; 4)100 Duration of PsO, years 1)19.5; 2)17.8; 3)17.4; 4)18.9 With PsA, % 1)16.4; 2)14.4; 3)15.9; 4)21.1 Previous biologic, % 1)26.7; 2)28.7; 3)30.0; 4)19.3 PGA, severe(4), % 1)30.9; 2)32.3; 3)32.4; 4)29.8	**At 12 weeks** PASI 75, % 1)61.3; 2)66.7; 3)53.3; 4) 5.0, *p=0.015 for certolizumab 400 mg vs. etanercept* PASI 90, % 1)31.2; 2)34.0; 3)27.1; 4)0.2 PGA 0/1, % 1)39.8; 2)50.3; 3)39.2; 4)1.9, *p<0.05 for certolizumab 200 mg vs. placebo* **At 16 weeks** PASI 75, % 1)68.2; 2)74.7; 4)3.8 PASI 90, % 1)39.8; 2)49.1; 4)0.3 PGA 0/1, % 1)48.3; 2)58.4; 4)3.4	**0-12 weeks** Any TEAE, % (IR/100PY) 1)47.3 (299.5) 2)49.1 (309.2) 3)46.4 (295.6) 4)56.1 (393.3) Serious AE, % (IR/100PY) 1)0.6 (2.7) 2)2.4 (10.6) 3)0.6 (2.7) 4)8.8 (41.0) AE leading to discontinuation, % 1)0.6 2)0.6 3)2.4 4)0 Serious infection, % (IR/100PY) 1)0 2)0.6 (2.6) 3)0 4)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		75 in the etanercept arm were rerandomized to certolizumab 200 mg or placebo. PASI 75 nonresponders entered the escape arm and received certolizumab 400 mg.		PASI, mean (SD) 1)21.4 (8.8); 2)20.8 (7.7) 3)21.0 (8.2); 4)19.1 (7.1) DLQI, mean (SD) 1)12.8 (7.0); 2)15.3 (7.3) 3)14.1 (7.4); 4)13.2 (7.6)	*For all above, p<0.0001 for certolizumab 200 mg and 400 mg vs. placebo unless otherwise stated*	Malignancy, % (IR/100PY) 1)0; 2)0; 3)0; 4)0 Depression, % (IR/100PY) 1)0.6 (2.7); 2)0; 3)0; 4)0
Anti-IL-23 Agents						
Tildrakizumab						
Reich, 2017[33] **(NCT01722331)** **reSURFACE 1** ***Good quality publication***	Phase III, randomized, controlled, double-blind, parallel-group, multicenter trial 118 global sites FAS, NRI	1) Tildrakizumab 200 mg (n=308) 2) Tildrakizumab 100 mg (n=309) 3) Placebo (n=155) Tildrakizumab was given at weeks 0, 4 and subsequently every 12 weeks. Patients on placebo crossed over to tildrakizumab at week 12 through week 28 followed by randomized treatment and withdrawal through week 64.	Inclusion: Adult patients (≥18 years) with moderate-to-severe chronic plaque psoriasis (PGA ≥3, PASI≥12, BSA ≥10%) at baseline who were candidates for systematic therapy or phototherapy Exclusion: Severe infection (within 2 weeks); live vaccination (within 4 weeks); active or latent TB; previous malignancy; previous	Age, mean 1)46.9; 2)46.4; 3)47.9 Male, % 1)73.0; 2)67.0; 3)65.0 Caucasian, % 1)68.0; 2)70.0; 3)65.0 Previous biologic, % 1)23.0; 2)23.0; 3)23.0 Duration of PsO & w/PsA NR PASI, mean (SD) 1)20.7 (8.5); 2)20.0 (7.9); 3)19.3 (7.1) DLQI, mean (SD) 1)13.2 (6.9); 2)13.9 (6.7)	**At 12 weeks** PASI 75, % 1)62.0; 2)64.0; 3)6.0 PASI 90, % 1)35.0; 2)35.0; 3)3.0 PASI 100, % 1)14.0; 2)14.0; 3)1.0 PGA 0/1, % 1)59.0; 2)58.0; 3)7.0 DLQI 0/1, % 1)44.0; 2)42.0; 3)5.0 *For all above, p<0.0001 for tildrakizumab 200*	**0-12 weeks** Any AE, %: 1)42; 2)47; 3)48 Serious AE, %: 1)3; 2)2; 3)1 AE leading to discontinuation, % 1)2; 2)0; 3)1 Severe infection, % 1)<1; 2) <1; 3)0 MACE, % 1)0; 2)<1; 3)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
			use of any anti-IL-23 or anti-IL-17 agents	3)13.2 (7.3)	*mg and 100 mg vs. placebo*	
Kimball, 2017 [161] **(NCT01722331)** **reSURFACE 1** ***Abstract***	*Subgroup analysis of reSURFACE 1: previous vs. no previous biologic use*	1) Tildrakizumab 200 mg (n=308) 2) Tildrakizumab 100 mg (n=309) 3) Placebo (n=155)	*See Reich, 2017*[33]	*See Reich, 2017*[33]	**At 12 weeks** *Prior biologic* PASI 75, % 1)56; 2)55; 3)0, *p=NR* PGA 0/1, % 1)51; 2)49; 3)3, *p=NR* *No prior biologic* PASI 75, % 1)64; 2)66; 3)8, *p=NR* PGA 0/1, % 1)62; 2)61; 3)8, *p=NR*	NR
Reich, 2017[33] **(NCT01729754)** **reSURFACE 2** ***Good quality publication***	Phase III, randomized, controlled, double-blind, parallel-group, multicenter trial 132 global sites FAS, NRI	1) Tildrakizumab 200 mg (n=314) 2) Tildrakizumab 100 mg (n=307) 3) Etanercept 50 mg BIW (n=313) 4) Placebo (n=156) *Same dosing schedule as reSURFACE 1 except patients receiving etanercept reduced dosing to once weekly at week 12 and patients were followed through week 52.*	*Same inclusion and exclusion criteria as reSURFACE 1* Reich, 2017[33] *except reSURFACE 2 also excluded patients with previous etanercept use.*	Age, mean 1)44.6; 2)44.6; 3)45.8; 4)46.4 Male, % 1)72.0; 2)72.0; 3)71.0; 4)72.0 Caucasian, % 1)90.0; 2)91.0; 3)92.0; 4)92.0 Duration of PsO, years NR With PsA, % NR Previous biologic, %	**At 12 weeks** PASI 75, % 1)66.0; 2)61.0; 3)48.0; 4)6.0 PASI 90, % 1)37.0; 2)39.0; 3)21.0; 4)1.0 PASI 100, % 1)12.0; 2)12.0; 3)5.0; 4)0 *For all above, p<0.0001 for tildrakizumab 200 mg and 100 mg vs. placebo & p≤0.001 for tildrakizumab 200 mg*	**0-12 weeks** Any AE, %: 1)49 2)44 3)54 4)55 Serious AE, %: 1)2 2)1 3)2 4)3 AE leading to discontinuation, % 1)1 2)1 3)2 4)1

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				1)12.0; 2)13.0; 3)12.0; 4)13.0 PASI, mean (SD) 1)19.8 (7.5) 2)20.5 (7.6) 3)20.2 (7.4) 4)20.0 (7.6) DLQI, mean (SD) 1)13.2 (7.0) 2)14.8 (7.2) 3)14.5 (7.2) 4)13.7 (7.0)	*and 100 mg vs. etanercept.* PGA 0/1, % 1)59.0; 2)55.0; 3)48.0; 4)4.0 DLQI 0/1, % 1)47.0; 2)40.0; 3)36.0; 4)8.0 *For all above, p<0.0001 for tildrakizumab 200 mg and 100 mg vs. placebo*	Severe infection, % 1)<1 2)0 3)0 4)<1 Malignancies, % 1)<1 2)<1 3)<1 4)0 Deaths, % 1)0; 2)<1; 3)0; 4)0
Reich, 2018 [162] **(NCT01722331 & NCT01729754)** **reSURFACE -1 & -2** ***Abstract***	Phase III, randomized, controlled, double-blind, parallel-group, multicenter trials	Patients who completed reSURFACE -1 or -2 base studies and achieved at least PASI 50 received tildrakizumab in an OLE. reSURFACE 1 1) Tildrakizumab 100 mg (n=256) 2) Tildrakizumab 200 mg (n=267) reSURFACE 2 3) Tildrakizumab 100 mg (n=399)	*See Reich, 2017*[33]	*See Reich, 2017*[33]	NR	**0-104 weeks** Total PYs 1)662.3; 2)750.0; 3)825.9; 4)807.2 Severe infections, EAR/100 PY 1)0.8; 2)0.8; 3)0.8; 4)1.1 Malignancies, EAR/100 PY 1)0.9; 2)0.3; 3)0.5; 4)0.9 NMSC, EAR/100 PY 1)0.3; 2)0.3; 3)0.4; 4)0.5 MACE, EAR/100 PY

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		4) Tildrakizumab 200 mg (n=454)				1)0.5; 2)0.3; 3)0.0; 4)0.1 Death, EAR/100 PY 1)0.0; 2)0.0; 3)0.2; 4)0.1
Blauvelt, 2018[131] **(NCT01225731, NCT01722331, & NCT01729754)**	*Pooled analysis of one Phase II P05495 study and reSURFACE-1 &-2.*	1) Tildrakizumab 100 mg (n=705 for placebo-controlled period; 1083 for full treatment period) 2) Tildrakizumab 200 mg (n=708; 1041) 3) Placebo (n=355; 588) 4) Etanercept 50 mg (n=313; 313) *See ReSURFACE-1 & -2 for dosing schedule.* Reich, 2017[33] In the P05495 Phase II trial, patients in Part 1 (1-16 weeks) received subcutaneous tildrakizumab 5 mg, 25 mg, 100 mg, 200 mg, or placebo at weeks 0 and 4. In Part 2 (weeks 16–52), patients were re-	Inclusion: Adult patients (≥18 years) with moderate-to-severe plaque psoriasis (PGA ≥3, PASI ≥12, BSA ≥10%) Exclusion (relating to safety): Active TB; HIV; any infection requiring treatment within 2 weeks or hospitalization within 8 weeks; prior or concurrent malignancy; uncontrolled hypertension; live vaccination within 4 weeks; uncontrolled diabetes; hospitalization due to cardiovascular event, illness, or surgery within 6 months	Age, mean 1)46; 2)46; 3)47; 4)46 Male, % 1)71; 2)73; 3)70; 4)71 Caucasian, % 1)81; 2)80; 3)78; 4)92 Duration of PsO, % NR History of PsA, % 1)17; 2)17; 3)15; 4)13 Previous biologic, % 1)18; 2)18; 3)19; 4)12 PASI, median 1)17.7 2)17.6 3)17.6 4)18.4	NR	**Placebo-controlled period** (16 weeks for P05495; 12 weeks for reSURFACE-1 & -2) Any TEAE, % 1)48.2; 2)47.9; 3)53.8; 4)54.0 Serious AE, % 1)1.4; 2)2.3; 3)1.7; 4)2.2 TEAE leading to discontinuation, % 1)0.6; 2)1.3; 3)1.1; 4)1.9 **Full treatment period** (52 weeks for P05495 and reSURFACE 2; 64 weeks for reSURFACE 1) Any TEAE, Exposure-adjusted rate (EAR)* 1)77.0; 2)79.3; 3)153.5; 4)148.6 Serious AE, EAR

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		randomized to various tildrakizumab doses based on responder status.				1)5.8; 2)7.2; 3)6.4; 3)13.0 TEAE leading to discontinuation, EAR 1)2.2; 2)2.2; 3)2.3; 4)5.9 *Patients/100 patient years
Guselkumab						
Blauvelt, 2016[31] **(NCT02207231)** **VOYAGE 1** ***Good quality publication***	Phase III, randomized double-blind, placebo- and active-controlled, multicenter trial 101 global sites ITT, NRI (binary) & mLOCF (continuous)	1) Guselkumab 100 mg at week 0, 4, and then every 8 weeks (n=329) 2) Adalimumab 80 mg at week 0, 40 mg at week 1, and then 40 mg q2w (n=334) 3) Placebo (n=174) Patients on placebo crossed over to guselkumab at week 16 and continued to receive guselkumab through week 48.	Inclusion: Adult patients (≥18 years) with moderate-to-severe plaque psoriasis (IGA ≥3, PASI ≥12, BSA ≥10%) for ≥6 months who were candidates for systematic therapy or phototherapy Exclusion: Previous or current signs of severe medical condition or malignancy; active TB; previous use of guselkumab or adalimumab, other TNFα agents (3 months), IL-12/23, IL-17, or IL-23 agents (6 months), or other systemic therapies (4 weeks)	Age, mean 1)43.9; 2)42.9; 3)44.9 Male, % 1)72.9; 2)74.6; 3)68.4 Caucasian, % 1)79.6; 2)82.9; 3)83.3 Duration of PsO, years 1)17.9; 2)17.0; 3)17.6 With PsA, % 1)19.5; 2)18.6; 3)17.2 Previous biologics, % 1)21.6; 2)21.0; 3)19.5 IGA, severe(4), % 1)23.4; 2)26.9; 3)24.7	**At 16 weeks** PASI 75, % 1)91.2; 2)73.1; 3)5.7 PASI 90, % 1)73.3; 2)49.7; 3)2.9 PASI 100, % 1)37.4; 2)17.1; 3)0.6 IGA 0/1, % 1)85.1; 2)65.9; 3)6.9 DLQI change from baseline, mean 1)-11.2; 2)-9.3; 3)-0.6 DLQI 0/1, % 1)56.3; 2)38.6; 3)4.2 *For all above, p<0.001 for guselkumab vs. PBO*	**0-16 weeks** Any AE, %: 1)51.7 2)51.1 3)49.4 Serious AE, %: 1)2.4 2)1.8 3)1.7 AE leading to discontinuation, % 1)1.2 2)0.9 3)1.1 Serious infection, % 1)0 2)0.6 3)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				PASI, mean (SD) 1)22.1 (9.5); 2)22.4 (9.0); 3)20.4 (8.7) DLQI, mean (SD) 1)14.0 (7.5); 2)14.4 (7.3); 3)13.3 (7.1)		NMSC, % 1)0.3 2)0 3)0 MACE, % 1)0.3 2)0.3 3)0
Papp, 2018[127] **(NCT02207231)** **VOYAGE 1**	*Patient-reported outcomes from VOYAGE 1[31]*	1) Guselkumab 100 mg at week 0, 4, and then every 8 weeks (n=249*) 2) Adalimumab 80 mg at week 0, 40 mg at week 1, and then 40 mg q2w (n=274*) 3) Placebo (n=129*) *See VOYAGE 1[31]* *Psoriasis Symptoms and Signs Diary (PSSD) scores were available for a subset of the full trial population.	*See VOYAGE 1[31]*	Age, mean 1)44.0; 2)43.3; 3)45.3 Male, % 1)70.7; 2)74.1; 3)69.0 Caucasian, % 1)77.9; 2)81.4; 3)82.9 Duration of PsO, years 1)18.5; 2)17.3; 3)17.1 PASI, mean (SD) 1)21.7 (9.24) 2)22.2 (8.88) 3)20.0 (8.69) PSSD symptom score, mean (SD) 1)54.4 (24.6) 2)53.9 (25.8) 3)48.3 (23.8)	**At 16 weeks** PSSD symptom score change from baseline, mean 1)-41.9; 2)-35.9; 3)-3.0 PSSD sign score change from baseline, mean 1)-44.6; 2)-39.8; 3)-4.1 *For all above, p<0.001 for guselkumab vs. placebo* **At 24 weeks** PSSD symptom score change from baseline, mean 1)-44.0; 2)-36.0 PSSD sign score change from baseline, mean 1)-47.2; 2)-40.1	NR

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				PSSD sign score, mean (SD) 1)56.9 (21.3) 2)58.5 (21.7) 3)53.6 (20.3)	*For all above, p<0.001 for guselkumab vs. adalimumab*	
Reich, 2016[32] **(NCT02207244)** **VOYAGE 2** ***Good quality publication***	Phase III, randomized double-blind, placebo- and active-controlled multicenter trial 115 global sites ITT, NRI	1) Guselkumab 100 mg at weeks 0, 4, and then every 8 weeks (n=496) 2) Adalimumab 80 mg at week 0, 40 mg at week 1, and then 40 mg q2w (n=248) 3) Placebo (n=248) Patients on placebo crossed over to guselkumab at week 16 and continued to receive guselkumab through week 48. At week 28, patients on guselkumab & adalimumab were re-randomized based on PASI response level.	*Same inclusion and exclusion criteria as VOYAGE 1[31]*	Age, mean 1)43.7; 2)43.2; 3)43.3 Male, % 1)70.4; 2)68.5; 3)69.8 Caucasian, % 1)82.3; 2)80.6; 3)83.1 Duration of PsO, years 1)17.9; 2)17.6; 3)17.9 With PsA, % 1)17.9; 2)17.7; 3)18.5 Previous biologics, % 1)20.4; 2)19.8; 3)21.8 IGA severe(4), % 1)23.2; 2)21.4; 3)23.0 PASI, mean (SD) 1)21.9 (8.8) 2)21.7 (9.0) 3)21.5 (8.0) DLQI, mean (SD)	**At 16 weeks** PASI 75, % 1)86.3; 2)68.5; 3)8.1, *p=NR* PASI 90, % 1)70.0; 2)46.8; 3)2.4, *p<0.001 for guselkumab vs. placebo* PASI 100, % 1)34.1; 2)20.6; 3)0.8, *p=NR* IGA 0/1, % 1)84.1; 2)67.7; 3)8.5 *p<0.001 for guselkumab vs. placebo* DLQI 0/1, % 1)51.7; 2)39.0; 3)3.3, *p=NR* DLQI change from baseline 1)-11.3; 2)-9.7; 3)-2.6, *p=NR*	**0-16 weeks** Any AE, %: 1)47.6 2)48.4 3)44.8 Serious AE, %: 1)1.6 2)2.4 3)1.2 AE leading to discontinuation, % 1)1.4 2)1.6 3)0.8 Serious infection, % 1)0.2 2)0.8 3)0.4 MACE, % 1)0 2)0.4 3)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				1)14.7 (6.9) 2)15.0 (6.9) 3)15.1 (7.2)		
Langley, 2017[143] **(NCT02203032)** **NAVIGATE** ***Fair quality publication***	Phase III, randomized, double-blind, active-controlled multicenter trial 100 global sites ITT, NRI	All patients received open-label ustekinumab dosed by weight at weeks 0 and 4. At week 16, patients with IGA≥2 were randomized to guselkumab 100 mg at weeks 16, 20, and every 8 weeks thereafter or to continue ustekinumab at week 16 and every 12 weeks thereafter. Patients with an IGA of 0 or 1 continued receiving open-label ustekinumab at week 16 and every 12 weeks thereafter. *Non-randomized* 1) Open-label ustekinumab continuation (n=585) *Randomized* 2) Guselkumab 100 mg (n=135)	Inclusion: Adults (≥18 years) with moderate-to-severe plaque psoriasis (PASI≥12, IGA≥ 3, BSA≥ 10%) for ≥ 6 months who were candidates for phototherapy or systemic treatment Exclusion: Severe medical conditions; history of malignancy within 5 years (except NMSC); history of active TB; positive for hepatitis B or seropositive for antibodies to hepatitis C; prior treatment with guselkumab or ustekinumab, IL-12, IL-17 or IL-23 agents (6 months), TNFα (3 months or 5 half-lives), or any systemic immunosuppressants or phototherapy (4 weeks)	Age, mean 1)42.9; 2)44.2; 3)43.0 Male, % 1)63.6; 2)70.4; 3)66.2 Caucasian, % 1)89.4; 2)80.7; 3)74.4 Weight>100 kg, % 1)25.5; 2)27.4; 3)27.8 Duration of PsO, years 1)16.7; 2)18.2; 3)15.6 With PsA, % 1)13.2; 2)20.7; 3)15.8 Previous TNFα, % 1)10.8; 2)23.7; 3)19.5 IGA, severe(4), % 1)18.5; 2)23.7; 3)24.8 PASI, mean (SD) 1)21.1 (9.2) 2)22.6 (9.3) 3)22.8 (9.4)	**At 28 weeks** PASI 75, % 2)81.4; 3)50.3; *p=NR* PASI 90, % 2)48.1; 3)22.6; *p≤0.001* PASI 100, % 2)11.3; 3)5.6; *p=NR* IGA, 0/1, % 2)31.1; 3)14.3; *p=0.001* **At 52 weeks** PASI 75, % 2)76.9; 3)53.8; *p=NR* PASI 90, % 2)51.1; 3)24.1; *p<0.001* PASI 100, % 2)20.0; 3)7.5; *p=0.003* IGA, 0/1, % 2)36.3; 3)17.3; *p<0.001* DLQI 0 or 1, % 2)38.8; 3)19.0; *p=0.002*	**16-60 weeks** Any AE, %: 1)41.4 2)64.4 3)55.6 Serious AE, % 1)3.4 2)6.7 3)4.5 AE leading to discontinuation, % 1)1.2 2)2.2 3)1.5 Serious infection, % 1)0.9 2)0.7 3)0 NMSC, n 1)2 2)0 3)0 Malignancy other than NMSC, n

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		3) Ustekinumab (n=133)		DLQI, mean (SD) 1)14.2(7.1) 2)15.5(7.9) 3)14.4(6.7)		1)2; 2)2; 3)0 MACE, % 1)0.2; 2)1.5; 3)0.8
Risankizumab						
Blauvelt, 2017[34] **(NCT02672852)** **IMMhance** ***Abstract***	Phase III, randomized, double-blinded, placebo-controlled multicenter trial Sites in Australia, Belgium, Canada, Czechia, France, Germany, Japan, Korea, and United States NRI	1) Risankizumab 150 mg at weeks 0 and 4 (n=407) 2) Placebo (n=100) At week 16, patients receiving risankizumab with sPGA≥2 continued treatment and those with sPGA 0 or 1 were rerandomized to continue treatment or receive placebo. Patients receiving placebo during the double-blind phase were treated with risankizumab at week 16 and thereafter.	Inclusion: Adults (≥ 18 years) with chronic plaque psoriasis for >6 months and moderate-to-severe chronic plaque psoriasis (PASI≥ 12, sPGA≥3, BSA≥ 10%) at baseline who were candidates for systemic therapy or phototherapy Exclusion: Non-plaque or drug-induced psoriasis; active inflammatory disease other than psoriasis or PsA	Age, mean 1)49.6; 2)47.6 Male, % 1)69.5; 2)73 Caucasian, % 1)78.6; 2)82 Duration of PsO, years NR With PsA, % NR Prior TNFα, % 1)36.9; 2)35 Prior biologics, % 1)56.5; 2)51.0 sPGA severe, % 1)20.6; 2)23 PASI, mean (SD) 1)19.9 (7.9)	**At 16 weeks** PASI 75, % 1)88.7; 2)8.0 PASI 90, % 1)73.2; 2)2.0 PASI 100, % 1)47.2; 2)1.0 sPGA 0/1, % 1)83.5; 2)7.0 sPGA 0, % 1)46.4; 2)1.0 DLQI 0/1, % 1)65.4; 2)3.0 *For all above, p<0.001*	**0-16 weeks** Any AE, % 1)45.5; 2)48.0 Serious AE, % 1)2.0; 2)8.0 AE leading to discontinuation, % 1)0.5; 2)4.0 Serious infection, % 1)0; 2)1.0 MACE, % 1)0; 2)1.0 Malignancies, % 1)0.7; 2)0 Malignancies excluding NMSC, % 1)0.5; 2)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				2)21.2 (8.7)		
Gordon, 2018[38] **(NCT02684370)** **UltIMMa-1** ***Good quality publication***	Phase III, randomized, triple-blinded, placebo- and active-controlled, multicenter trial Sites in Australia, Canada, Czechia, France, Germany, Japan, Korea, and United States ITT, NRI	1) Risankizumab 150 mg at weeks 0 and 4 (n=304) 2) Ustekinumab 45/90 mg dosed by weight at weeks 0 and 4 (n=100) 3) Placebo (n=102) At week 16, patients receiving risankizumab and ustekinumab continued treatment and patients receiving placebo switched to treatment with risankizumab.	Inclusion: Adults (≥18 years) with chronic plaque psoriasis for ≥6 months and moderate-to-severe chronic plaque psoriasis (PASI≥ 12, sPGA≥3, BSA≥ 10%) at baseline who were candidates for systemic therapy or phototherapy Exclusion: Non-plaque or drug-induced psoriasis; active inflammatory disease other than psoriasis or PsA; prior exposure to risankizumab or ustekinumab	Age, mean 1)48.3; 2)46.5; 3)49.3 Male, % 1)69.7; 2)70; 3)77.5 Caucasian, % 1)65.8; 2)74.0; 3)69.6 Weight>100 kg, % 1)25.7; 2)26.0; 3)25.5 Duration of PsO, years NR With PsA, % 1)28.0; 2)23.0; 3)35.0 Prior biologic, % 1)34.2; 2)30.0; 3)39.2 sPGA severe, % 1)15.8; 2)15.0; 3)15.7 PASI, mean 1)20.6 2)20.1 3)20.5	**At 16 weeks** PASI 75, % 1)89.0; 2)76.0; 3)9.0, p=0.0034 vs. UST PASI 90, % 1)75.3; 2)42.0; 3)4.9 PASI 100, % 1)35.9; 2)12.0; 3)0 sPGA 0/1, % 1)87.8; 2)63.0; 3)7.8 sPGA 0, % 1)36.8; 2)14.0; 3)2.0 DLQI 0/1, % 1)65.8; 2)43.0; 3)7.8 *For all above, p<0.001 unless otherwise noted*	**0-16 weeks** Any AE, % 1)49.7; 2)50.0; 3)51.0 Serious AE, % 1)2.3; 2)8.0; 3)2.9 AE leading to discontinuation, % 1)0.7; 2)2.0; 3)3.9 Serious infection, % 1)0.3; 2)3.0; 3)0 MACE, % 1)0; 2)0; 3)0 Malignancies, % 1)0.3; 2)0; 3)1.0 Malignancies excluding NMSC, % 1)0; 2)0; 3)0

Study, *Quality Rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Gordon, 2018[38] **(NCT02684357)** **UltIMMa-2** ***Good quality publication***	Phase III, randomized, double-blinded, placebo- and active-controlled, multicenter trial Sites in Austria, Belgium, Canada, France, Germany, Mexico, Poland, Portugal, Spain, and United States ITT, NRI	1) Risankizumab 150 mg at weeks 0 and 4 (n=294) 2) Ustekinumab 45/90 mg dosed by weight at weeks 0 and 4 (n=99) 3) Placebo (n=98) At week 16, patients receiving risankizumab and ustekinumab continued treatment and patients receiving placebo switched to treatment with risankizumab.	*See UltIMMa-1*	Age, mean 1)46.2 2)48.6; 3)46.3 Male, % 1)69.0 2)66.7; 3)68.4 Caucasian, % 1)86.7 2)91.9; 3)88.8 Weight>100 kg, % 1)31.0; 2)30.3; 3)31.6 Duration of PsO, years NR With PsA, % 1)25.0; 2)27.0; 3)33.0 Prior biologic, % 1)40.1; 2)43.4; 3)42.9 sPGA severe, % 1)22.4; 2)18.2; 3)21.4 PASI, mean 1)20.5; 2)18.2; 3)18.9	**At 16 weeks** PASI 75, % 1)91.0; 2) 70.0; 3)6.0 PASI 90, % 1)74.8; 2)47.5; 3)2.0 PASI 100, % 1)50.7; 2)24.2; 3)2.0 sPGA 0/1, % 1)83.7; 2)61.6; 3)5.1 sPGA 0, % 1)51.0; 2)25.3; 3)3.1 DLQI 0/1, % 1)66.7; 2)46.5; 3)4.1 *For all above, p<0.001*	**0-16 weeks** Any AE, % 1)45.6; 2)53.5; 3)45.9 Serious AE, % 1)2.0; 2)3.0; 3)1.0 AE leading to discontinuation, % 1)0.3; 2)0; 3)1.0 Serious infection, % 1)1.0; 2)1.0; 3)0 MACE, % 1)0; 2)0; 3)0 Malignancies, % 1)0.3; 2)0; 3)0 Malignancies excluding NMSC, % 1)0; 2)0; 3)0 Non-treatment emergent deaths, % 1)0.3; 2)0; 3)0

AE: adverse event; BSA: body surface area; DLQI: Dermatology Life Quality Index , no or minimal impact (0/1); EAR: exposure-adjusted rate; FAS: full analysis set; IGA: Investigator's Global Assessment, clear (0) or almost clear (1); IR: incidence rate; ITT: intention-to-treat; LOCF: last observation carried forward; MACE: major adverse cardiac events; MI: multiple imputation; mLOCF: modified last observation carried forward; BIW: twice weekly; NMSC: non-melanoma skin cancer; NR: not reported; NRI: nonresponder imputation; PASI: Psoriasis Area Severity Index; PGA: Physician's Global Assessment, clear (0) or almost clear (1); PsA: psoriatic arthritis; PsO: psoriasis; PY: patient years; q2w: every two weeks; q4w: every four weeks; SAE: serious adverse event; SD: standard deviation; sPGA: static Physician's Global Assessment, clear (0) or almost clear (1); TB: tuberculosis; TEAE: treatment emergent adverse event
*p-values only reported if significant

Table B2. Evidence Summary Tables for New Head-to-Head Trials

Study, *Quality rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Reich, 2017[125] ***Also see Burge, 2017 (conference abstract)*** [163] **(NCT02561806)** **IXORA-S** ***Good quality publication***	Phase IIIb, randomized, double-blind, controlled, parallel-group, multicenter trial 51 global sites ITT, NRI (binary) & mLOCF (continuous)	1) Ixekizumab: 160 mg at week 0, 80 mg q2w through week 12, and then 80 mg q4w (n= 136) 2) Ustekinumab dosed by weight at weeks 0, 4, and then every 12 weeks (n=166)	Inclusion: Adult patients (≥18 years) with chronic plaque psoriasis (PASI≥10) for ≥6 months who had previously failed or had a contraindication or intolerability to at least one systemic therapy Exclusion: Predominant presence of nonplaque psoriasis; contraindication for ustekinumab; prior treatment with ustekinumab, ixekizumab, or any other IL-17 or IL-12/23 antagonists	Age, mean 1)42.7; 2)44.0 Male, % 1)66.2; 2)67.5 Caucasian, % 1)93.3; 2)95.7 Weight>100 kg, % 1)23.0; 2)27.1 Duration of PsO, years 1)18.0; 2)18.2 Previous biologics, % 1)13.2; 2)15.1 PASI, mean (SD) 1)19.9 (8.2) 2)19.8 (9.0) DLQI total, mean (SD) 1)11.1 (7.2) 2)12.0 (7.3) Itch NRS, mean (SD) 1)6.3(2.7); 2)6.2 (2.6) Skin pain VAS, mean (SD) 1)42.9 (33.3) 2)39.4 (30.8)	**At 12 weeks** PASI 75, % 1)88.2; 2)68.7, *p<0.001* PASI 90, % 1)72.8; 2)42.2, *p<0.001* PASI 100, % 1)36.0; 2)14.5, *p<0.01* DLQI 0/1, % 1)61.0; 2)44.6, *p<0.01* sPGA 0/1, % 1)83.6; 2)57.2, *p<0.001* Itch NRS, change from baseline, mean (SD) 1)-4.8(3.0); 2)-4.2(3.0) Skin pain VAS, change from baseline, mean (SD) 1)-35.4 (32.1); 2)-29.1 (30.7)	**0-24 weeks** Any TEAE, % 1)69.6 2)75.3 Serious TEAE, % 1)4.4 2)6.0 Serious AE, % 1)2.2 2)3.0 AE leading to discontinuation, % 1)1.5 2)0.6 Infection, % 1)42.2 2)52.4

Study, *Quality rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
de Vries, 2017[122] **(Netherlands registry: NTR 1559)** **PIECE** ***Fair quality publication***	Investigator-initiated, single-blind, multicenter trial Sites in the Netherlands ITT, LOCF	1) Etanercept 50 mg BIW (n=23) 2) Infliximab 5 mg/kg at weeks 0, 2, 6 and every 8 weeks thereafter (n=25) If patient discontinued due to adverse events or insufficient response (less than 50% improvement in PASI) up to week 12, they could switch to other treatment arm. At week 12 patients with insufficient response could crossover to other treatment arm.	Inclusion: Adult patients (≥18 years) with moderate-to-severe plaque psoriasis (PASI≥10 or BSA ≥10% or PASI ≥8 and Shindex-29 score≥35) who have failed, were contraindicated for, or intolerant to UV therapy and methotrexate or ciclosporin Exclusion: Malignancy within previous 10 years; active/chronic infections; demyelinating disease; congestive heart failure; liver or kidney function disorders; prior etanercept or infliximab treatment failure	Age, mean 1)42.4; 2)45.9 Male, % 1)56; 2)72 Duration of PsO, years 1)10.6; 2)12.9 With PsA, % 1)13; 2)8 PASI, mean (SD) 1)15.9 (5.1) 2)17.8 (9.7) IGA, mean (SD) 1)3.3 (0.65) 2)3.2 (0.52)	**At 12 weeks** PASI 50, % 1)61; 2)96, *p=0* PASI 75, % 1)22; 2)76, *p=0* PASI 90, % 1)0; 2)20, *p=0.05* PASI 100, % 1)0; 2)4 IGA 0/1, % 1)9; 2)68, *p=0*	**0-24 weeks** Any AE, % 1)100 2)96 Any treatment-related AE, % 1)12 2)8 Any SAE, % 1)0.7 2)0.5 AE leading to discontinuation, n 1)2 2)3

Study, *Quality rating*	Study Design, Location, Statistical Method	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Bagel, 2018[126] **(NCT02826603)** **CLARITY** ***Abstract***	Phase IIIb, parallel-group, double-blind, multicenter trial Global sites MI	1) Secukinumab 300 mg at weeks 0, 1, 2, 3, 4, and then q4w (n=550) 2) Ustekinumab dosed by weight at weeks 0, 4, and then every 12 weeks (n=552)	Inclusion: Adult patients (≥18 years) with chronic plaque-type psoriasis for ≥6 months and moderate-to-severe plaque psoriasis (PASI≥12, BSA ≥10%, mIGA≥3) at baseline who were candidates for systemic therapy Exclusion: Forms of psoriasis other than plaque psoriasis; ongoing use of prohibited treatments; previous use of biologic targeting IL-17, IL-17 receptor, IL-12, or IL-23	Age, mean 1)45; 2)45 Male, % 1)64.7; 2)68.1 Caucasian, % 1)75.3; 2)74.3 Weight>100 kg, % 1)34.4; 2)34.1 Duration of PsO, years 1)16.8; 2)17.3 With PsA, % NR Prior biologic, % 1)20.0; 2)23.6 PASI, mean (SD) 1)20.8 (8.95) 2)21.3 (9.19) mIGA severe, % 1)38.0; 2)43.3	**At 12 weeks** PASI 75, % 1)88.0 2)74.2 PASI 90, % 1)66.5 2)47.9 PASI 100, % 1)38.1 2)20.1 mIGA 0/1, % 1)72.3 2)55.4 *For all above, p<0.0001*	NR

AE: adverse event; BIW: twice weekly; BSA: body surface area; DLQI: Dermatology Life Quality Index, no or minimal impact (0/1); IGA: Investigator's Global Assessment, clear (0) or almost clear (1); ITT: intention-to-treat; LOCF: last observation carried forward; MI: multiple imputation; mIGA: Investigator's Global Assessment, 2011 modification, clear (0) or almost clear (1); mLOCF: modified last observation carried forward; NRI: nonresponder imputation; NRS: numeric rating scale; PASI: Psoriasis Area Severity Index; PsA: psoriatic arthritis; PsO: psoriasis; q2w: every two weeks; q4w: every four weeks; SAE: serious adverse event; SD: standard deviation; sPGA: static Physician's Global Assessment, clear (0) or almost clear (1); TEAE: treatment emergent adverse event; VAS: visual analog scale

*p-values only reported if significant

Table B3. Updated Evidence Summary Tables for Older Drugs

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
TNFα Inhibitors						
Adalimumab						
Saurat, 2008[95] and Revicki, 2008[164] **(NCT00235820)** **CHAMPION** ***Good quality publication***	Phase III, randomized, controlled, double-blind, multicenter trial 28 study sites in Europe and Canada ITT with NRI	1) Adalimumab 40 mg q2w following an 80 mg dose (n=108) 2) Placebo (n=53) 3) Methotrexate 7.5 to 25 mg once weekly (n=110)	Inclusion: Psoriasis for ≥12 months and stable moderate to severe chronic plaque psoriasis (PASI≥10 and BSA≥10%) at baseline; candidate for systematic therapy or phototherapy Exclusion: Previous systemic TNFα therapy or methotrexate; pregnancy	Age, mean 1)42.9; 2)40.7 Male, % 1)64.8; 2)66.0 Caucasian, % 1)95.4; 2)92.5 Duration of PsO (year), mean 1)17.9; 2)18.8 With PsA, % 1)21.3; 2)20.8 Previous systemic and/or phototherapy, % 1)82.2; 2)90.4 PASI, mean (SD) 1) 20.2 (7.5) 2) 19.2 (6.9) DLQI, mean (SD) 1)11.8 (6.6) 2)11.7 (7.0) ED-5D index score, mean (SD) 1)0.7 (0.3) 2)0.7 (0.3)	**At 16 weeks** PASI 50, % 1)88 2)30.2 PASI 75, % 1)79.6 2)18.9 PASI 90, % 1)51.9 2)11.3 PASI 100, % 1)16.7 2)1.9; *p=0.004* PGA 0/1. % 1) 73.1 2) 11.3 DLQI, change from baseline, mean (95% CI) 1)-9.1 (-10.4, -7.8) 2)-3.4 (-5.2, -1.6) ED-5D index score, change from baseline, mean (95% CI) 1)0.2 (0.2, 0.3) 2)0.1 (0.0, 0.2), *p<0.01* *p<0.001 unless otherwise specified*	**0-16 weeks** SAEs, % 1)1.9 2)1.9 AEs leading to discontinuation, % 1)0.9 2)1.9

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Menter, 2008[94] **(NCT00237887)** **REVEAL** ***Good quality publication***	Phase III, multicenter, double-blind RCT 67 centers in the United States and 14 centers in Canada ITT with NRI	1) Adalimumab: 40 mg q2w following an 80 mg dose (n=814) 2) Placebo (n=398)	Inclusion: Psoriasis for ≥6 months, stable moderate-to-severe plaque psoriasis for ≥ 2 months (PASI≥12, BSA≥10% and PGA of at least moderate severity) Exclusion: A history of CNS disease, cancer or lymphoproliferative disease	Age, mean 1)44.1 2)45.4 Male, % 1)67.1 2)64.6 Caucasian, % 1)91.2 2)90.2 Duration of PsO (years), mean 1)18.1 2)18.4 With PsA, % 1)27.5 2)28.4 Previous systemic biologic, % 1)11.9 2)13.3 PASI, mean (SD) 1) 19.0 (7.08) 2) 18.8 (7.09)	**At 16 weeks** PASI 75, % 1)71; 2)7 P<0.001 PASI 90, %: 1)45; 1)2 P<0.01 PASI 100, %: 1)20; 2)1 P<0.01	**0-16 weeks** SAEs,% 1)1.8 2)1.8 Serious infectious, % 1)0.6 2)1.0 AEs leading to discontinuation, % 1)1.7 2)2.0
Asahina, 2010[96] ***Good quality publication***	Phase II/III, multicenter, double-blind RCT 42 sites in Japan ITT with NRI	1) Adalimumab 40 mg q2w (n=38) 2) Adalimumab 80 mg at week 0 and 40 mg q2w thereafter (n=43)	Inclusion: Moderate-to-severe chronic plaque psoriasis ≥6 months stable for ≥2 months (PASI≥12, and BSA≥10%) Exclusion:	Age, mean 2)44.2 4)43.9 Male, % 2)35 4)41	**At 16 weeks** PASI 50, %: 2)81.4; 4)19.6 PASI 75,%: 2)62.8; 4)4.3 PASI 90,%:	**0-16 weeks** SAEs, % 2)2.3 4)2.2 AEs leading to discontinuation, 2)11.6

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		3) Adalimumab 80 mg q2w (n=42) 4) Placebo (n=46)	Previous TNFα therapy, other major disease, or infection	Duration of PsO (year), mean 2)14.0 4)15.5 Previous systemic non-biologic, % 2)41.9 4)37.0 PASI, mean (SD) 2)30.2 (10.9) 4)29.1 (11.8)	2)39.5; 4)0 PGA 0/1, % 2) 60.5; 4) 8.7 DLQI, change from baseline, mean (SD) 2)-5.1 (5.7); 4)1.0 (7.0) *p<0.001 for all*	4)10.9
Cai, 2017[97] **(NCT01646073)** ***NEW EVIDENCE*** ***Fair quality publication***	Phase III, randomized, controlled, double-blind multicenter trial 16 sites in China ITT, NRI (categorical) & LOCF (continuous)	1) Adalimumab 40 mg q2w following 80 mg loading dose (n=338) 2) Placebo (n=87) At week 13, all patients received adalimumab 40 mg q2w, following an 80 mg loading dose only for patients originally randomized to placebo.	Inclusion: Adult patients (≥18 years) with psoriasis for at least 6 months, plaque psoriasis for at least 2 months, and moderate-to-severe plaque psoriasis at baseline for whom previous systemic therapy has failed. Exclusion: Previous exposure to a biologic treatment or received other systemic treatment within one month of baseline	Age, mean 1)43.1; 2)43.8 Male, % 1)75.1; 2)66.7 Duration of Pso (years), mean 1)14.8; 2)15.8 History of PsA, % 1)12.7; 2)11.5 PASI, mean (SD) 1) 28.2 (12.0); 2) 25.6 (10.98) PGA, moderate (3), % 1)63.5; 2)65.5 PGA, marked (4), % 1)32.5; 2)32.2	**At 12 weeks** PASI 75, % 1)77.8;2)11.5 PASI 90, % 1)55.6; 2)3.4 PASI 100, % 1)13.3; 2)1.1 *p≤0.001 for all above* PGA 0/1, % 1)80.5; 2)14.9, p=NR *See publication for efficacy data through 24 weeks.*	**0-12 weeks** Any AE, % 1)46.7; 2)37.9 AE leading to discontinuation, % 1)0.6; 2)0 Serious AE, % 1)1.2; 2)3.4 Infection, % 1)17.5; 2)16.1 Serious Infection, % 1)0; 2)0

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				PGA, severe (5), % 1)4.1; 2)2.3 DLQI, mean (SD) 1)14.7 (7.1); 2)13.4 (7.1)		
Etanercept						
Papp, 2005[98] ***Fair quality publication***	Phase III, multicenter, double-blind RCT 50 sites in the US, Canada, and Europe mITT with LOCF	1) Etanercept 50 mg BIW (n=203) 2) Etanercept 25 mg BIW (n=204) 3) Placebo (n=204)	Inclusion: Active and clinically stable plaque psoriasis with ≥10% BSA involvement; baseline PASI≥10; at least one previous phototherapy or systemic therapy; adequate hematological, renal, and hepatic function Exclusion: Active severe infection; other skin conditions; previous TNFα therapy	Age, median 1)44.5; 3)44.0 Male, % 1)67; 3)64 Duration of PsO, yr 1)18.1; 3)17.5 History of PsA, % 1)26; 3)26 PASI, median (range) 1)16.1 (7.0-57.3) 3)16.0 (7.0-62.4)	**At 12 weeks** PASI 50, % 1)72; 3)9 P<0.0001 PASI 75, % 1)46; 3)3 P<0.0001 PASI 90,% 1)19; 3)<1 P<0.0001 sPGA "clear" or "almost clear," % 1)54; 3)3 *p<0.0001 for all*	**0-12 weeks** Grade 3 or 4 laboratory abnormalities at week 24, n 1)1 3)1
Leonardi, 2003[99] ***Fair quality publication***	Phase III, multicenter, double-blind RCT 47 sites in the US mITT with LOCF	1) Etanercept 25 mg once weekly (n=160) 2) Etanercept 25 mg BIW (n=162) 3) Etanercept 50 mg BIW (n=164)	Inclusion: Active but clinically stable moderate-to-severe plaque psoriasis (PASI≥10 and BSA≥10%); previous phototherapy or systemic therapy, or	Age, median 3)44.8; 4)45.6 Male, % 3)65; 4)63 Caucasian, % 3)87; 4)90	**At 12 weeks** PASI 50, %: 3)74; 4)14 PASI 75, % 3)49; 4)4 PASI 90, %	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		4) Placebo (n=166)	candidate for such therapy Exclusion: guttate, erythrodermic, or pustular psoriasis; active skin conditions; previous TNFα therapy	Duration of PsO, yr 3)18.6; 4)18.4 History of PsA, % 22 Prior systemic therapy/ phototherapy, % 76 PASI, median (SE) 3)18.4 (0.7); 4)18.3 (0.6)	3)22; 4)1 sPGA "clear" or "almost clear" at week 12,%: 3)49; 4)5 % improvement DLQI, mean (SD) 3)61.0 (4.3) 4)10.9 (4.8) *p<0.001 for all*	
Tyring, 2006[100] **(NCT00111449)** ***Fair quality publication***	Phase III, multicenter, double-blind RCT 39 sites in the US and Canada mITT with LOCF	1) Etanercept 50 mg BIW (n=300) 2) Placebo (n=300)	Inclusion: Active, clinically stable plaque psoriasis with PASI≥10 and BSA≥10%; previous systemic therapy or phototherapy, or candidate for such therapy; adequate hematological, renal, and hepatic function Exclusion: History of psychiatric disease; active guttate, erythrodermic, or pustular psoriasis; previous TNFα therapy	Age, median 1)45.8 2)45.6 Male, % 1)65 2)70 Duration of PsO, yr 1)20.1 2)19.7 With hx of PsA, % 1)35 2)33 PASI, median (SD) 1)18.3 (7.6) 2)18.1 (7.4)	**At week 12** PASI 50, % 3)74; 4)14 PASI 75, % 3)47; 4)5 PASI 90, % 3)21; 4)1, *p<0.001* % improvement DLQI, mean (SD) 3)69.1 4)22.1 *All p<0.0001 unless otherwise stated*	**0-12 weeks** SAE,% 1)0; 2)0.3 AEs leading to discontinuation through 12 weeks, % 1)1.3; 2)1.6
Bagel, 2012[103] ***Good quality publication***	Phase III, multicenter, double-blind RCT Conducted in North America	1) Etanercept 50 mg BIW through week 12, followed by etanercept 50 mg QW and placebo QW through week 24 (n=62)	Inclusion: Stable moderate to severe plaque psoriasis with BSA≥10% for ≥ 6 months; PASI ≥10 and SSA ≥ 30% with PSSI ≥15;	Age, median 1)39; 2)42 Male, % 1)53.2; 2)58.1	**At week 12** PASI 50, % 1)85 2)7 P<0.0001	**0-12 weeks** SAEs, % 1)0 2)0

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
	mITT with LOCF	2) Placebo BIW through week 12, followed by etanercept 50 mg BIW (n=62)	candidates for phototherapy or systemic therapy Exclusion: guttate, erythrodermic, or pustular psoriasis; significant medical problems; a history of tuberculosis; or a history of cancer 5 years or less before enrollment	Caucasian, % 1)69.4; 2)75.8 Duration of PsO, yr 1)17.5; 2)11.9 Previous biologic therapy, % TNFα 1)6.8; 2)6.5 PASI, median (range) 1)15.5 (8,46) 2)15.2 (10,41)	PASI 75, % 1)59 2)5 P<0.0001 PASI 90, % 1)25 2)2 P<0.0001 PGA 0/1, % 1)54 2)5 P<0.0001	AEs leading to discontinuation, % 1)3.2 2)0
Gottlieb, 2011[102] **(NCT00691964)** ***Good quality publication***	Phase III, multicenter, double-blind RCT 33 sites in the United States ITT with NRI & LOCF	1) Briakinumab 200 mg at week 0 and 4, followed by 100 mg at week 8 (n=138) 2) Etanercept 50 mg BIW at week 0-11 (n=141) 3) Placebo (n=68)	Inclusion: A diagnosis of chronic plaque psoriasis for ≥6months, stable for ≥2 months; BSA ≥ 10%; PGA at least moderate (≥3); PASI ≥ 12 Exclusion: Previous systemic anti-IL-12/23p40 therapy, etanercept, or inability to discontinue topical therapy, phototherapies, or systemic therapies	Age, median 2)43.1; 3)44.0 Male, % 2)69.5; 3)69.1 Caucasian, % 2)90.1; 3)95.6 Duration of PsO, yr 2)17.0; 3)19.1 With hx of PsA, % 2)22.7; 3)20.6 Previous biologic therapy, % 2)14.2; 3)14.7 PASI, mean (SD) 2)20 (14.2); 3)10 (14.7)	**At 12 weeks** PASI 75, % 2)56.0 3)7.4 P<0.001 PASI 90, % 2)23 3)1.4 P≤0.002 PASI 100, % 2)6.7 3)0 p≤0.002 PGA 0/1 at, % 2)39.7; 3)2.9, p<0.0001 DLQI of 0, % 2)21.3; 3)2.9, p≤0.008	**0-12 weeks** Severe AE, % 2)2.1 3)4.3 Serious, % 2)0.7 3)2.9 AEs leading to discontinuation, % 2)2.8 3)0

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Strober, 2011[101] **(NCT00710580)** ***Good quality publication***	Phase III, multicenter, double-blind RCT 41 sites in the US ITT with NRI & LOCF	1) Briakinumab 200 mg at week 0 and 4, followed by 100 mg at week 8 (n=139) 2) Etanercept 50 mg BIW at week 0-11 (n=139) 3) Placebo (n=72)	Inclusion: A diagnosis of chronic plaque psoriasis for ≥6months, stable for ≥2 months; BSA ≥ 10%; PGA at least moderate (≥3); PASI ≥ 12 Exclusion: Previous systemic anti-IL-12/23p40 therapy, etanercept, or inability to discontinue topical therapy, phototherapies, or systemic therapies	Age, median 2)45.2; 3)45.0 Male, % 2)61.2; 3)63.9 Caucasian, % 2)91.4; 3)93.1 Duration of PsO, yr 2)15.2; 3)15.5 With hx of PsA, % 2)33.1; 3)20.8 Previous biologic, % 2)7.9; 3)4.2 PASI, mean (SD) 2)18.5 (6.0); 3)18.3 (6.4)	**At 12 weeks** PASI 75, % 2)39.6 3)6.9 PASI 90, % 2)13.7 3)4.2 PASI 100, % 2)5.8 3)0 PGA 0-1, % 2)39.7; 3)2.9, P<0.0001 DLQI of 0, % 2)29.5; 3)4.2	**0-12 weeks** Severe AE, % 2)0.7 3)2.8 Serious AE, % 2)0.7 3)2.8 AEs leading to discontinuation, % 2)2.9 3)2.8
Bachelez, 2015[104] **(NCT01241591)** ***Good quality publication***	Phase III, multicenter, double-blind RCT 122 sites worldwide (not included the US and Canada) ITT with NRI	1) Tofacitinib 5 mg twice daily (n=329) 2) Tofacitinib 10 mg twice daily (n=330) 3) Etanercept 50 mg BIW at week 0-11 (n=335) 4) Placebo (n=107)	Inclusion: Chronic stable plaque psoriasis for ≥ 12 months; candidates for systemic therapy or phototherapy; PASI ≥12 and PGA of moderate or severe; BSA ≥10%; failed to respond or had a contraindication to or were intolerant to at least one conventional systemic therapy Exclusion: Non-plaque or drug-induced forms of psoriasis, could not continue systemic	Age, median 3)42.0 4)46.0 Male, % 3)70 4)66 Caucasian, % 3)87 4)84 Duration of PsO, yr 3)18.0 4)17.0 With hx of PsA, % 3)21 4)24	**At 12 weeks** PASI 50, % 3)80.3 4)20.6 PASI 75, % 3)58.8 4)5.6 PASI 90, % 3)32.2 4)0.9 PGA 0-1, % 3)66.3 4)15.0 PGA 0, %	**0-12 weeks** Severe TEAE, % 2)2 3)5 Serious TEAE, % 2)2 3)2 AEs leading to discontinuation, % 2)3 3)4

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
			therapies, previous or had a contraindication to etanercept, previously not responded to TNFα therapy, active infection, previous tofacitinib	Previous biologic therapy, % 3)11 4)11 PASI, median (range) 3)19.4 (12.0-63.6) 4)19.5 (12.4-54.6)	3)19.4 4)1.9 DLQI reduction ≥5 from baseline, % 3)74.7 4)31.8	
Infliximab						
Reich, 2005[105] **EXPRESS I** ***Fair quality publication***	Phase III, multicenter, double-blind RCT 32 sites (countries NR) ITT and NRI only for PASI measures only	1) infusions of infliximab 5mg/kg at weeks 0,2 and 6, then every 8 weeks to week 46 (n=301) 2) infusions of placebo at weeks 0,2 and 6, then every 8 weeks to week 46 (n=77) Crossover at week 24	Inclusion: A diagnosis of moderate-to-severe plaque psoriasis for ≥6 moths; candidates for phototherapy or systemic therapy; PASI≥12 and BSA≥10% Exclusion: A history or risk of serious infection, lymphoproliferative disease, or active tuberculosis; previous TNFα treatment	Age, median 1)42.6 2)43.8 Male, % 1)69 2)79 White, % NR Duration of PsO, yr 1)19.1 2)17.3 With PsA, % 1)31 2)29 Previous biologic therapy, % NR PASI, mean (SD) 1)22.9 2)22.8	**At 10 weeks** PASI 50, % 1)91 2)8 PASI 75, % 1)80 2)3 PASI 90, % 1)57 2)1 PGA of 0-1, % 1)83 2)4 *All p<0.0001* Change in DLQI from baseline, mean** 1)10.3 2)0.4 *p<0.001* **Reported in Reich 2006	**0-24 weeks** Serious AEs % 1)6 2)3 AEs leading to discontinuation,% 1)9 2)7

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Reich, 2006[165] **EXPRESS I**	*See above* Work productivity outcomes from EXPRESS	*See above*	*See above*	**Additional characteristics:** Productivity VAS 1) 5.8; 2) 6.3 SF-RP (role physical) 1) 64.8; 2) 69.8 SF-RE (role emotional) 1) 72.1; 2) 71.9	**At 10 weeks** Productivity VAS 1) -0.1; 2) 2.7 SF-RP (role physical) 1) -5.2; 2) 20.6 SF-RE (role emotional) 1) -2.2; 2) 18.2 *All p<0.001*	Discontinuation due to AEs through week 50 (%) Placebo/INF: 10.4 INF/INF: 11.3 Discontinuation due to unsatisfactory therapeutic effects (%) Placebo/INF: 9.7 INF/INF: 4.7
Menter, 2007[106] **EXPRESS II** ***Good quality publication***	Phase III, multicenter, double-blind RCT 63 sites in the US, Canada, and Europe ITT with NRI	1) infusions of infliximab 3mg/kg at weeks 0,2 and 6 (n=313) 2) infusions of infliximab 5mg/kg at weeks 0,2 and 6 (n=314) 3) infusions of placebo at weeks 0,2 and 6 (n=208) 1) and 2) were re-randomized to receive either every-8-week continuous maintenance therapy or intermittent as-needed maintenance therapy; 3)crossed over to receive infliximab 5mg/kg at weeks 16,18,and 22, and every 8 weeks thereafter	Inclusion: A diagnosis of moderate-to-severe plaque psoriasis; candidates for phototherapy or systemic therapy; PASI≥12 and BSA≥10% Exclusion: A history or risk of serious infection, lymphoproliferative disease, or active tuberculosis; previous TNFα treatment	Age, median 2)44.5 3)44.4 Male, % 2)65.0 3)69.2 Caucasian, % 2)93.3 3)90.9 Duration of PsO, yr 2)19.1 3)17.8 With PsA, % 2)28.3 3)26.0 Previous biologic therapy, % 2)14.3 3)13.0 PASI, mean (SD)	**At 10 weeks** PASI 75, % 2)75.5 3)1.9 PASI 90, % 2)45.2 3)0.5 PGA of 1-2, % 2)76.0 3)1.0 DLQI of 0, % 2)39.0 3)1.0 DLQI mean change 2) -9.0 3) 0 *p<0.001* *PGA ranging from 1 to 6	**0-14 weeks** Any SAE, % 2) 2.9 3) 2.4 AEs leading to discontinuation, % 1)5.1 2)2.4

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				2)20.4 (18.6) 3)19.8 (17.4)		
Yang, 2012[107] ***Fair quality publication***	Phase III, multicenter, double-blind RCT ITT; handling of missing data NR	1)infusion of infliximab 5mg/kg at weeks 0,2, and 6, then at weeks 14 and 22 (n=84) 2)placebo at weeks 0,2, and 6, then infliximab 5mg/kg at weeks 10,12, and 16 (n=45)	Inclusion: A diagnosis of plaque psoriasis for ≥6 months; had failed to respond to conventional systemic treatment; PASI≥12 and BSA≥10%; Exclusion: Non-plaque psoriasis; a history of chronic infectious disease or opportunistic infection or lymphoproliferative disease; a serious infection within 2 months; active or latent tuberculosis; pregnancy or planned pregnancy within 12 months; an active malignancy or a history of malignancy within 5 years	Age, median 1)39.4 2)40.1 Male, % 1)71.4 2)77.8 White, % NR Duration of PsO, yr 1)16.0 2)16.0 With PsA, % NR Previous psoriasis therapy, % 1) 40.5 2) 31.1 PASI, mean (SD) NR DLQI, mean 1)14.4 2)14.4	**At 10 weeks** PASI 50, % 1)94.0 2)13.3 PASI 75, % 1)81.0 2)2.2 PASI 90, % 1)57.1 2)0 PGA of 0-1, % 1)88.1 2)6.7 DLQI mean 1) 6.5 2) 13.1 *P<0.001 for all*	**0-10 weeks** Serious AEs% 1)1.2 2)0 **0-26 weeks** AEs leading to discontinuation through 26 weeks, % 1)6.7 2)NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Torii, 2010[108] ***Fair quality publication*** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind multicenter trial 28 sites in Japan ITT, NRI	1) Infliximab 5 mg/kg at weeks 0, 2, and 6 (n=35) 2) Placebo (n=19)	Inclusion: Patients with moderate-to-severe plaque psoriasis (PASI≥12, BSA≥10%) for at least 6 months requiring systematic therapy or phototherapy Exclusion: History or risk of serious infection, lymphoproliferative disease, or active TB	Age, mean 1)46.9; 2)43.3 Male, % 1)62.9; 2)73.7 Duration of Pso, years 1)14.2; 2)11.1 With PsA, % 1)28.6; 2)36.8 PASI, mean (SD) 1) 31.9 (12.8) 2) 33.1 (15.6) PGA moderate, % 1)40.0; 2)52.6 PGA marked, % 1)45.7; 2)36.8 PGA severe, % 1)8.6; 2)5.3 DLQI, mean (SD) 1) 12.7 (6.8) 2) 10.5 (6.8)	**At week 10** PASI 50, % 1)82.6; 2)10.8 PASI 75, % 1)68.6; 2)0 PASI 90, % 1)54.6; 2)0 PGA, cleared or minimal, % DLQI, change from baseline, mean (SD) 1) -9.9 (7.1); 2)-0.4 (6.2) *p<0.001 for all above* *See publication for efficacy data up to week 66.*	**0-14 weeks** Duration of follow-up (days), mean 1)101.3; 2)105.5 Any AE, % 1)97.1; 2)57.9 AE leading to discontinuation, % 1)2.9; 2)5.3 SAE, % 1)2.9; 2)5.3 Infection, % 1)62.9; 2)21.1 Serious infection, % 1)0; 2)5.3 Infusion reaction, % 1)8.6; 2)5.3 Serious infusion reaction, % 1)2.9; 2)0 *See publication for safety data up to week 78.*

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Observational Studies						
Gisondi, 2013[166] ***Good quality publication***	Observational, prospective, multi-center study	1) infliximab 5 mg/kg at weeks 0,2, and 6 and every 8 weeks thereafter (n=83) 2) ustekinumab 45 mg for patients ≤100 kg and 90 mg for patients > 100 kg at weeks 0, 4, and every 12 weeks thereafter (n=79)	Inclusion: Patient data recoded at four tertiary referral psoriasis centers in Italy (Universities of Verona, Modena and Padua, and Catholic University of Rome); a diagnosis of chronic plaque psoriasis; all patients who received etanercept or infliximab were biological therapy naïve, with PASI≥10 and BSA ≥10% and resistance to methotrexate, cyclosporine, acitretin or phototherapy Exclusion: Patients diagnosed with PsA	Age, mean 1) 47.8 2) 45.7 Male, % 1) 64 2) 72 White, % NR Duration of PsO, yr 1) 17.5 2) 18.6 Previous biologic therapy, % 0 PASI, mean (SD) 1) 16.5 (9.1) 2) 18.4 (8.2)	**At one month** PASI, mean (SD) 1) 4.1 (4.7) 2) 2.1 (3.2) Improvement in PASI, % 1) 64 2) 60 PASI 75, % 1) 32 2) 28 **At seven months** PASI, mean (SD) 1) 8.1 (5.2) 2) 4.1 (5.5) Improvement in PASI, % 1) 85 2) 82 PASI 50, % 1) 96 2) 82 PASI 75, % 1) 69 2) 58 *between-group PASI 50 and PASI 75 are not statistically significant	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Piaserico, 2014[167] ***Fair quality publication***	Observational, prospective study Adjustment: for the presence of comorbidities, smoking, steroid use and disease severity	1) etanercept (n=83) 2) adalimumab (n=18) 3) infliximab (n=16) 4) ustekinumab (n=4)	Inclusion: All patients who received a new treatment with systemic traditional drugs or biologics for chronic plaque psoriasis in various Italian Dermatology Departments	Age, mean 71.3 Male, % 58.3 White, % NR Duration of PsO, yr 22.1 Previous biologic therapy, % 26.2 PASI, mean (SD) 1)14.9 (6.4) 2)14.3 (4.1) 3)14.8 (5.7) 4)17.2 (1.9)	**At 12 weeks** PASI 75, % 1) 64 2) 65 3) 93 4) 100	Serious AEs, % 1)7.2 2)0 3)12.5 4)0
Esposito, 2012[168] ***Poor quality publication***	Observational, retrospective study Adjustment: none	1) Etanercept: 50 mg weekly as continuous regimen for PsA and 50 mg twice weekly for 12 weeks for PsO (n=61) 2) Adalimumab: a loading dose of 80 mg followed by 40 mg every other week for PsA and PsO (n=28)	Inclusion: Patients with PsO with/without PsA, ≥65 years undergoing TNF-α therapy (i.e. adalimumab or etanercept) for at least 6 months in the outpatient collaborative Dermatology and Rheumatology Unit of the University of Rome	Age, mean (range) 1) 70 (65-82) 2) 69 (65-75) Male, % 1)54 2)57 White, % NR Duration of PsO, yr 1)29.2 2)24.1 Previous biologic therapy, %	**At week 12** PASI 50, % 1)82.0 2)85.7 PASI 75, % 1)54.1 2)60.7 **At week 24** PASI 50, % 1)90.2 2)82.1 PASI 75, % 1)78.7 2)71.4 **At one year**	Severe AEs leading to discontinuation, % 1)4.9 2)7.1

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				1) Adalimumab: 1.6 Efalizumab: 9.8 Infliximab: 9.8 2) Efalizumab: 25.0 Etanercept: 67.9 Infliximab: 50.0 PASI, mean (range) 1)11.3 (0.4-68.3) 2)10.4 (0.4-23.8)	PASI 50, % 1)90.2 2)78.6 PASI 75, % 1)83.6 2)67.9 **At two years** PASI 50, % 1)91.8 2)82.1 PASI 75 % 1)86.9 2)71.4 **At three years** PASI 50, % 1)91.8 2)82.1 PASI 75, % 1)83.6 2)71.4	
Gisondi, 2008[169] ***Poor quality publication***	Observational, retrospective study Adjustment: none	1) Etanercept 25 mg twice weekly (n=58) 2) Infliximab 5 mg/kg at week 0,2,and 6 and then every 8 weeks (n=40) 3) Methotrexate 15 mg once weekly (n=43)	Inclusion: psoriatic patients affected by chronic plaque psoriasis consecutively admitted to the outpatient clinics of the University Hospital of Verona; all patients who received etanercept or infliximab were biological therapy naïve, with PASI≥10 and BSA ≥10% and resistance to methotrexate,	Age, mean 1) 50.2 ; 2) 46.8; 3) 53.1 Male, % 1) 67; 2) 70; 3)60 White, % NR Duration of PsO, yr 1) 22 2) 17.5 3) 18.6	**At six months** PASI, mean (SD) 1) 4.8 (4.7) 2) 2.1 (3.2) 3) 4.3 (6) Improvement in PASI, % 1) 74.5 2) 88.8 3) 47.6	Severe AEs, % 0

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
			cyclosporine, acitretin or phototherapy Exclusion: patients diagnosed with PsA	Previous biologic therapy, % 0 PASI, mean (SD) 1) 18.8 (7.4) 2) 17.7 (7.3) 3) 8.2 (3.1)		
Anti IL-17A Agents						
Secukinumab (Cosentyx)						
Blauvelt, 2015[113] **(NCT01555125)** **FEATURE** ***Good quality publication***	Phase III RCT Double-blind Multicenter 32 sites in North America and Europe ITT with NRI	1) secukinumab 300mg at week 0,1,2,3, and then every 4 weeks starting from week 4 (n=59) 2) secukinumab 150mg at week 0,1,2,3, and then every 4 weeks starting from week 4 (n=59) 3) placebo (n=59) Maintenance: dosing every 4 weeks from week 12 to week 52	Inclusion: Plaque psoriasis for ≥6 months; moderate-to-severe disease defined by baseline PASI≥12, IGA mod 2011≥3, and BSA≥10%; inadequately controlled by topical treatment, phototherapy, or previous systemic therapy Exclusion: Non-chronic-plaque psoriasis, except for palmoplantar psoriasis; prior anti-IL-17A therapy; medical conditions that confound the evaluation or risky for immunotherapy; active infections or history of infections; history of lymphoproliferative	Age, mean 1) 45.1 2) 46.0 3) 46.5 Male, % 1) 64.4 2) 67.8 3) 66.1 White, % 1) 91.5 2) 86.4 3) 96.6 Duration of PsO (yr), mean 1) 18.0 2) 20.4 3) 20.2 PASI, mean (SD) 1) 20.7 (7.95) 2) 20.5 (8.29) 3) 21.1 (8.49)	**At 12 weeks** PASI 75, % 1) 75.9 2) 69.5 3) 0 PASI 90, % 1) 60.3 2) 45.8 3) 0 PASI 100, % 1) 43.1 2) 8.5 3) 0 IGA mod 2011 0/1 response, % 1) 69.0 2) 52.5 3) 0 *p<0.0001 for all secukinumab vs. placebo comparisons*	**0-12 weeks** Serious AE at week 12, % 1) 5.1 2) 0 3) 1.7 AE leading to discontinuation at week 12, % 1) 1.7 2) 0 3) 1.7

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
			diseases or malignancy; pregnancy	Previous biologic, % 1) 39.0 2) 47.5 3) 44.1		
Thaci, 2015[124] **(NCT02074982)** **CLEAR** ***Good quality publication***	Phase IIIb RCT Double-blind Multicenter 134 sites worldwide ITT with NRI	1) secukinumab SQ 300mg dosed at Week 0, 1, 2, 3, & q4wks to Week 48 (n=337) 2) ustekinumab SQ weight-based dosing at Week 0, 4, & q12wks from Wk 16-40 (placebo given at other wks) (n=339)	Inclusion: Moderate-to-severe psoriasis defined by baseline PASI≥12, IGA mod 2011 of 3 or 4, and BSA≥10%; a diagnosis of psoriasis for ≥6 months; had been inadequately controlled by topical treatment, phototherapy, and/or previous systemic therapy Exclusion: Previous biologics targeting IL-17A or IL-12/IL-23	Age, mean 1) 45.2; 2) 44.6 Male, % 1) 68.0; 2) 74.3 Caucasian, % 1) 88.7; 2) 85.0 Duration of PsO (yr), mean 1) 19.6; 2) 16.1 PASI, mean (SD) 1) 21.7 (8.50) 2) 21.5 (8.07) Previous biologic, % 1) 14.2; 2) 13.0	**At 16 weeks** PASI 75, % 1)93.1 2)82.7 PASI 90, % 1)79.0 2)57.6 PASI 100, % 1)44.3 2)28.4 IGA mod 2011 0/1, % 1)82.9; 2)67.5 DLQI 0/1, % 1)71.9; 2)57.4 *p≤0.0001 for all*	**At 16 weeks** Nonfatal serious AE, % 1)3.0 2)3.0 AE leading to discontinuation at week 16, % 1)0.9 2)1.2
Blauvelt, 2017 [170] **(NCT02074982)** **CLEAR** ***NEW EVIDENCE***	Phase IIIb, randomized, controlled, double-blind, multicenter trial	1) Secukinumab 300 mg (n=336) 2) Ustekinumab dosed by weight (n=339)	*See Thaci, 2015* [171]	*See Thaci, 2015* [171] **Additional patient characteristics:** DLQI, daily activities domain total, mean (SD) 1)2.9 (1.88); 2) 2.8 (1.83) DLQI, personal relationships domain (PRD) total, mean (SD) 1)1.8 (1.90); 2)1.9 (1.94)	**At 16 weeks** DLQI, change from baseline in daily activities total, mean 1)-2.63; 2)-2.43, *p<0.001* DLQI, daily activities total responders, % 1)83.6; 2)73.1, p*<0.01* DLQI, change from baseline in PRD, mean	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					1)-1.67; 2)-1.49, p<*0.01* DLQI, PRD total responders, % 1)86.5; 2)75.4, p<*0.01* *Total responders defined as patients reporting no impact*	
Paul, 2015[114] **(NCT01636687)** **JUNCTURE** ***Fair quality publication***	Phase III RCT Double-blind Multicenter 38 sites worldwide ITT, NRI	1) secukinumab 300 mg at week 0,1,2,3, and then every 4 weeks starting from week 4 (n=60) 2) secukinumab 150mg at week 0,1,2,3, and then every 4 weeks starting from week (n=61) 3) placebo (n=61) Maintenance: dosing every 4 weeks, week 12-52 OTE: week 52-208 and an 8-week treatment-free FU	Inclusion: Moderate-to-severe psoriasis defined by baseline PASI≥12, IGA mod 2011 of 3 or 4, and BSA≥10%; a diagnosis of psoriasis for ≥6 months; had been inadequately controlled by topical treatment, phototherapy, and/or previous systemic therapy Exclusion: Non-plaque or drug-induced psoriasis; ongoing prohibited treatment; prior exposure IL-17 agents; systemic infection, tuberculosis, history of HIV, Hep B, Hep C; immunocompromised	Age, mean 1) 46.6; 2) 43.9; 3) 43.7 Male, % 1) 76.7; 2) 67.2; 3) 62.3 Caucasian, % 1) 93.3; 2) 95.1; 3) 96.7 Duration of PsO (yr), mean 1) 21.0; 2) 20.6; 3) 19.86 PASI, mean (SD) 1) 18.9 (6.37) 2) 22.0 (8.85) 3) 19.4 (6.70) Previous biologic, % 1) 25.0; 2) 24.6; 3) 21.3 PsA reported, % 1) 23.3; 2) 26.2; 3) 19.7	**At 12 weeks** PASI 75, % 1)86.7 2)71.7 3)3.3 PASI 90, % 1)55.0 2)40.0 3)0 PASI 100, % 1)26.7 2)16.7 (p=0.0006 vs. (3)) 3)0 IGA mod 2011 0/1 response 1)73.3; 2)53.3; 3)0 *p<0.0001 for secukinumab vs. placebo comparisons unless specified otherwise*	**At 12 weeks** Nonfatal serious AEs, % 1)1.7 2)4.9 3)1.6 AE leading to discontinuation, % 1)0 2)0 3)1.6
Lacour, 2017 [172] **(NCT01636687)**	Phase III, randomized, controlled, double-blind,	1) Secukinumab 150 mg (n=61)	*See Paul, 2015* [114]	*See Paul, 2015* [114] **Additional patient characteristics:**	**At 52 weeks** PASI 75, % 1)70; 2)80	**0-52 weeks** Any AE, % 1)78.7; 2)88.6

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
JUNCTURE ***NEW EVIDENCE***	parallel-group, multicenter trial	2) Secukinumab 300 mg (n=60) 3) Placebo (n=61) *See Paul, 2015* [114]		mIGA, moderate (3), % 1)57.4; 2)65.0; 3)62.3 mIGA, severe (4), % 1)42.6; 2)35.0; 3)37.7	PASI 90, % 1)53.3; 2)63.3 PASI 100, % 1)30.0; 2)38.3 mIGA 0 or 1, % 1)55.0; 2)68.3	Serious AEs, % 1)13.5; 2)8.0 AE discontinuation, % 1)1.1; 2)0 Serious infections, % 1)3.4; 2)2.3 MACE, % 1)1.1; 2)0
Langley, 2014[173] **(NCT01365455)** **ERASURE** ***Good quality publication***	Phase III RCT Double-blind Multicenter 88 sites worldwide ITT with NRI	1) secukinumab 300mg (n=245) 2) secukinumab 150mg (n=245) 3) placebo (n=248) Administered once weekly and at week 1, 2, 3, 4, then q4wks until week 48 At week 12, placebo pt who did not exceed PASI75 were randomized to secukinumab, and these patients were excluded from analysis	Inclusion: Adults w/ moderate-to-severe plaque psoriasis PASI score ≥ 12, IGA of 3 or 4, and BSA ≥10%; a diagnosis of psoriasis for ≥6 months; poorly controlled with topical treatments, phototherapy, systemic therapy, or a combination of these therapies Exclusion: Non-plaque or drug induced psoriasis	Age (yr), mean 1) 44.9 2) 44.9 3) 45.4 Male, % 1) 69.0 2) 68.6 3) 69.4 White, % 1)69.8 2)69.8 3)71.0 PASI score, mean (SD) 1) 22.5 (9.2) 2) 22.3 (9.8) 3) 21.4 (9.1) Body surface area involved, % (SD) 1) 32.8 (19.3) 2) 33.3 (19.2) 3) 29.7 (15.9)	**At 12 weeks** PASI 75, % 1) 81.6 2) 71.6 3) 4.5 IGA 0/1, % 1) 65.3 2) 51.2 3) 2.4 PASI 90, % 1) 59.2 2) 39.1 3) 1.2 DLQI, change in mean score 1) -11.4 2) -10.1 3) -1.1 DLQI, score of 0/1, %	**0-12 weeks** Nonfatal serious AE, % 1) 1.2 2) 2.1 3) 0.9 AE leading to discontinuation, % 1)1.2 2)0.6 3)1.9

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				Psoriatic arthritis, % 1) 23.3 2) 18.8 3) 27.4 Previous biologic, % 1) 28.6 2) 29.8 3) 29.4	1) 58.8 2) 46.1 3) 10.3 **all p<0.001 for comparisons with placebo*	
Ohtsuki, 2014[174] **ERASURE**	*Sub analysis of Japanese patients (18 sites in Japan) enrolled in ERASURE trial*	*See Langley, 2014[173]* Bio-naïve 1) 23 2) 24 3) 23 Bio-exposed 1) 6 2) 5 3) 6	*See Langley, 2014[173]*	Age 1) 51.9 2) 48.2 3) 50.2 Male, % 1) 89.7 2) 79.3 3) 79.3 Mean PASI 1) 26.7 2) 28.2 3) 21.4 PsO duration (years) 1) 15.6 2) 15.6 3) 14.1 PsA 1) 13.8 2) 17.2 3) 13.8 Previous biologic: 1) 20.7	**At 12 weeks** PASI 75 (%) 1) *82.8, 2) *86.2, 3) 6.9 PASI 90 (%) 1) *62.1, 2) *55.2, 3) 0 PASI 100 PASI 100 (%) 1) **27.6, 2) 10.3, 3) 0 IGA mod 0/1 (%) 1) *55.2, 2) *55.2, 3) 3.4 **p<0.0001, **p<0.01* DLQI score of 0/1 (%) 1) 71.4, 2) 65.5, 3) 24.1 *1 vs. 3, p<0.001* *2 vs. 3, p<0.01* **At one year** PASI 75 Bio-naïve: 1) 82.6, 2) 83.3, 3) 8.7 Bio-exposed: 1) 83.3, 2) 100, 3) 0	AEs (%) 1) 48.3 2) 55.2 3) 41.4 SAEs (per 100 PYs) 1) 2.7 2) 8.5 3) 0

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				2) 17.2 3) 20.7	PASI 90 Bio-naïve: 1) 65.2, 2) 54.2, 3) 0 Bio-exposed: 1) 50, 2) 60, 3) 0	
Blauvelt, 2014[175] **ERASURE** ***Abstract***	*See Langley, 2014[173]* *Reports outcomes of subpopulation w/ PsA*	*See Langley, 2014[173]* 1)secukinumab 300 mg 2)secukinumab 150 mg 3)placebo	*See Langley, 2014[173]*	PsA patients (n=171)	**At 12 weeks** PASI 75,% 1) 68; 2) 70; 3)4 PASI 90,% 1) 53; 2) 44; 3) 0	NR
Papp, 2014[176] **ERASURE** ***Abstract***	*See Langley, 2014[173]* Reports outcomes based on prior biologic exposure	*See Langley, 2014[173]*	*See Langley, 2014[173]*	Previous exposure to biologic (n=216/738) Previous inadequate response to biologic (n=72/216)	**At 12 weeks** No prior exposure PASI 75, % 1) 84.0; 2) 74.7; 3) 4.6 IGA 0/1, % 1) 67.4; 2) 55.0; 3) 2.9 Prior exposure PASI 75, % 1) 75.7; 2) 64.4; 3) 4.1 IGA 0/1, % 1) 60.0; 2) 42.5; 3) 1.4 **p<0.0001 for each secukinumab dose vs. placebo*	NR
Wu, 2017 [177] **(NCT01365455)** **ERASURE** ***NEW EVIDENCE***	Phase III, randomized, controlled, double blind, multicenter trial *Subgroup analysis-Taiwanese patients in ERASURE*	1) Secukinumab 150 mg q4w (n=20) 2) Secukinumab 300 mg q4w (n=16) 3) Placebo (n=15)	*See Langley, 2014 [173]*	Age, mean 1)39.5; 2)38.1;3)40.6 Male, % 1)70; 2)87.5; 3)86.7 With PsA, % 1)15; 2)18.8; 3)26.7	**At 12 weeks** PASI 75, % 1)70; 2)87.5; 3)0 *p<0.001 for SEC 150, SEC 300 vs. PBO* PASI 90, % 1)45; 2)68.8; 3)0	**0-12 weeks** Any AE, % 2)80; 2)93.8; 3)80 Serious AE, % 1)0; 2)0; 3)0

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		SEC was administered at week 0, 1, 2, 3, 4 and then q4w through week 48. In the placebo arm, patients who did not achieve PASI 75 were rerandomized to received SEC 150 mg or 300 mg at week 12. Those patients who achieved PASI 75 underwent continuous placebo treatment.		Duration of PsO, yr 1)14.5 (5.8); 2)13.6 (6.9); 3)8.3 (5.8) Previous TNFα, % 1)25; 2)25; 3)6.7 PASI, mean (SD) 1)20.9 (7.7); 2)24.7 (8.5); 3)21.1 (6.5) mIGA, severe (4), % 1)20; 2)12.5; 3)33.3	*p=0.004 for SEC 150 and p<0.001 for SEC 300 vs. PBO* PASI 100, % 1)15; 2)31.3; 3)0 *p<0.05 for SEC 300 vs. PBO* mIGA 0 or 1, % 1)65; 2)68.8; 3)0 *p<0.001 for SEC 150, SEC 300 vs. PBO.*	AE leading to discontinuation, % 1)0; 2)0; 3)0
Langley, 2014[173] **(NCT01358578)** **FIXTURE** ***Good quality publication***	Phase III RCT Double-blind Multicenter 88 sites worldwide ITT with NRI	1) secukinumab 300mg (n=327) 2) secukinumab 150mg (n=327) 3) etanercept 50mg BIW until week 12, then QW until week 51 (n=326) 4) placebo (n=326) Secukinumab was administered once weekly and at week 1, 2, 3, 4, then q4wks until week 48	Inclusion: Adults w/ moderate-to-severe plaque psoriasis PASI score ≥ 12, IGA of 3 or 4, and BSA ≥10%; a diagnosis of psoriasis for ≥6 months; poorly controlled with topical treatments, phototherapy, systemic therapy, or a combination of these therapies Exclusion: Non-plaque or drug induced psoriasis; previous etanercept	Age (yr), mean 1) 44.5 2) 45.4 3) 43.8 4) 44.1 Male, % 1) 68.5 2) 72.2 3) 71.2 4) 72.7 White, % 1)68.5 2)67.0 3)67.2 4)66.9 PASI score, mean (SD) 1) 23.9 (9.9) 2) 23.7 (10.5) 3) 23.2 (9.8)	**At 12 weeks** PASI 75, % 1) 77.1 2) 67.0 3) 44.0 4) 4.9 IGA 0/1, % 1) 62.5 2) 51.1 3) 27.2 4) 2.8 PASI 90, % 1) 54.2 2) 41.9 3) 20.7 4) 1.5 DLQI, change in mean score	**0-12 weeks** Nonfatal serious AE, # events/100 person-year 1) 6.8 2) 6.0 3) 7.0 4) 8.3 AE leading to discontinuation, # events 1) 14 2) 10 3) 12 4) 3

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				4) 24.1 (10.5) Psoriatic arthritis, % 1) 15.3 2) 15.0 3) 13.5 4) 15.0 Previous biologic, % 1) 11.6 2) 13.8 3) 13.8 4) 10.7	1) -10.4 2) -9.7 3) -7.9 4) -1.9 **all p<0.001 for comparisons between secukinumab and etanercept/placebo* DLQI, score of 0/1, % 1) -10.4 2) -9.7 3) -7.9 4) -1.9	
Sigurgeirsson, 2014 [178] **(NCT01358578)** **FIXTURE** ***Abstract*** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trial *Subgroup analysis- Concomitant PsA*	1) Secukinumab 150 mg q4w (n=49) 2) Secukinumab 300 mg q4w (n=50) 3) Etanercept 50 mg biw until week 12, then once weekly thereafter (n=44) 4) Placebo (n=47) Secukinumab was administered at weekly for 4 weeks and then q4w thereafter.	*See Langley, 2014* [173]	*See Langley, 2014* [173]	**At 12 weeks** PASI 75, % 1)59; 2)72; 3)39; 2)2 *p<0.01 for secukinumab 150, secukinumab 300 vs. PBO. p<0.01 for secukinumab 300 vs. ETN.* PASI 90, % 1)39; 2)44; 3)18; 2)2 *p<0.01 for secukinumab 150, secukinumab 300 vs. PBO. p<0.01 for secukinumab 300 vs. ETN.*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Strober, 2016[179] **ERASURE and FIXTURE** ***Good quality publication***	*Secondary analysis*	*As above* 39% patients who (n=678/1718) completed Psoriasis Symptom Diary (PSD) were included in this analysis 1) secukinumab 300mg (n=224) 2) secukinumab 150mg (n=229) 3) placebo (n=225)	See ERASURE and FIXTURE	Age (yr), mean 1) 43.0; 2) 45.7; 3) 43.1 Male, % 1) 62.5; 2) 65.9; 3) 71.1 PASI, mean (SD) 1) 21.9 (9.0); 2) 21.8 (9.0); 3) 21.6 (8.7) PSD, itching mean (SD) 1) 6.4 (2.4); 2) 6.5 (2.4); 3) 6.1 (2.5) PSD, pain mean (SD) 1) 5.5 (3.0); 2) 5.3 (3.1) 3) 5.0 (3.0) PSD, scaling mean (SD) 1) 6.4 (2.6); 2) 6.5 (2.4) 3) 6.2 (2.4)	**At week 12** Response rate* for itching, % 1) 83.0; 2) 78.2; 3) 16.9 Response rate* for pain % 1) 72.8; 2) 65.5; 3) 15.6 Response rate* for scaling, % 1) 83.0; 2) 78.2; 3) 13.8 *reduction of ≥2.2 points from baseline	*NR*
Lee, 2015 [180] **ERASURE & FIXTURE** **(NCT01365455& NCT01358578)** ***Abstract*** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trials *Pooled, subgroup analysis- Asian patients*	1) Secukinumab 150 mg (n=NR) 2) Secukinumab 300 mg (n=NR) 3) Etanercept 50 mg BIW (n=NR) 4)Placebo (n=NR) Secukinumab administered at weeks 0, 1, 2, 3, 4 and then q4w thereafter.	*See Langley, 2014 [173]*	*See Langley, 2014 [173]*	**At 12 weeks** PASI 75, % 1)67.5; 2)74.4; 3)27.4; 4)6.8 *p<0.0001 for SEC 150, SEC 300 vs. PBO and ETN* PASI 90, % 1)40.5; 2)53.6; 3)13.7; 4)0.9, *p=NR* IGA, 0 or 1, % 1)46.0; 2)52.8; 3)17.8; 4)2.6	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					p<0.0001 for SEC 150, SEC 300 vs. PBO and ETN	
Korman, 2017 [130] **ERASURE & FIXTURE** **(NCT01365455& NCT01358578)** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trials *Pooled analysis*	1) Secukinumab 300 mg (n=572) 2) Etanercept (n=326) 3)Placebo (n=572) Secukinumab administered at weeks 0, 1, 2, 3, 4 and then q4w thereafter. Subjects randomized to placebo and those who did not respond were rerandomized to secukinumab at week 12.	*See Langley, 2014* [173]	Age, mean (SD) 1)44.5 (13.5); 2)42.9 (12.9); 3)44.8 (12.9) Male, % 1)68.7; 2)71.2; 3)71.2 PASI, mean (SD) 1) 23.3 (9.7) 2) 23.2 (9.8) 3) 22.9 (10.0) DLQI total, mean (SD) 1) 13.6 (7.3) 2) 13.4 (7.3) 3) 12.8 (7.1) DLQI PRD score, mean (SD) 1)1.9 (1.9); 2)2.1 (1.9); 3)1.8 (1.8) DLQI skin-related sexual difficulties, mean (SD) 1)1.2 (1.1); 2)1.1 (1.1); 3)1.1 (1.0)	**At 12 weeks** DLQI PRD score, change from baseline, mean (SD) 1)-1.5 (1.7); 2)-1.2 (1.8); 3)-0.1 (1.4) *p<0.05 for SEC vs. ETN, p<0.0001 for SEC vs. PBO* DLQI PRD score 0, % 1)47.5; 2)37.6; 3)15.5 *p<0.01 for SEC vs. ETN, p<0.0001 for SEC vs. PBO* DLQI skin-related sexual difficulties, change from baseline, mean (SD) 1)-1.0; 2)-0.7; 2)0 *p<0.01 for SEC vs. ETN, p<0.0001 for SEC vs. PBO* DLQI skin-related sexual difficulties 0, % 1)36.7; 2)34.0; 3)9.7 *p<0.0001 for SEC vs. PBO* **At 52 weeks*** DLQI PRD score, change from baseline, mean (SD)	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					1)-1.62; 2)-1.40 DLQI PRD score 0, % 1)54.6; 2)48.6; *p<0.05* DLQI skin-related sexual difficulties, change from baseline, mean (SD) 1)-1.0; 2)-0.8; *p<0.01* DLQI skin-related sexual difficulties 0, % 1)39.8; 2)35.5 *See publication for number analyzed at 52 weeks.	
van de Kerkhof, 2016 [181] **ERASURE, FIXTURE, FEATURE, JUNCTURE, SCULPTURE, STATURE, and 4 phase II trials** **(NCT01365455, NCT01358578, NCT01555125,**	Phase II and III, randomized, double-blind trials All studies except two phase III trials were not placebo-controlled *Pooled analysis*	1) Secukinumab 300 mg (n=1173)* 2) Secukinumab 150 mg(n=1174)* 3) Secukinumab 300 or 150 mg (n=2877)† 4) Etanercept (n=323)‡	NR *See van de Kerkhof, 2016* [181] *for additional information*	Age, mean 1)45.6; 2)45.2; 3)45.2; 4)43.8; 5)44.6 Male, % 1)68.9; 2)67.3; 3)69.8; 4)70.9; 5)69.6 Caucasian, %	NR	**0-12 weeks** Any AE, % 1)54.2; 2)56.3; 3)56.3; 4)57.6; 5)50.4 Nonfatal SAE, % 1)2.0; 2)1.9; 3)2.2; 4)0.9; 5)1.6

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
NCT0163668, NCT01406938, NCT01412944, NCT00941031, NCT01132612, NCT01071252, NCT00805480) ***NEW EVIDENCE***		5) Placebo (n=793) *Includes subjects from phase III studies only who were randomized to the specified secukinumab dose at the study start. †Includes subjects from phase II and III studies who were randomized to any secukinumab dose at the study start. ‡Etanercept data are from one phase III trial (FIXTURE).		1)72.2; 2)72.2; 3)75.1; 4)66.9; 5)74.8 With PsA, % 1)22.7; 2)32.6; 3)29.3; 4)17.9 Duration of PsO, yr 1)18.8; 2)18.9; 3)19.2; 4)13.6; 5)18.8 Previous biologics, % 1)24.5; 2)24.7; 3)25.4; 4)13.9; 5)22.0 PASI, mean (SD) 1) 22.9 (9.5); 2) 23.3 (10.2); 3) 22.6 (9.6); 4) 23.3 (9.8); 5) 22.2 (9.6)		AEs leading to discontinuation, % 1)1.5; 2)1.5; 3)1.5; 4)1.9; 5)1.3 **0-52 weeks** Total P-Y 1) 117.5; 2) 1142.0 3) 2724.6; 4) 293.5 Any AE, IR/100 PY 1)236.1; 2)239.9; 3)252.9; 4)243.4 Nonfatal SAE, IR/100 PY 1)7.4; 2)6.8; 3)7.8; 4)7.0 AEs leading to discontinuation, n 1)46; 2)43; 3)118; 4)12 Death, n 1)0; 2)1; 3)1; 4)0
Ixekizumab (Taltz)						
Gordon, 2016[182] **(NCT01474512)** **UNCOVER-1** ***Good quality publication***	Phase III RCT Double-blind Multicenter 100 sites worldwide	N=1296 1) placebo (n=431) 2) ixekizumab, 80mg Q4W (n=432)	Inclusion: ≥18 years BSA ≥10%, PASI ≥12 sPGA ≥3 ≥6 months of plaque psoriasis diagnosis	Age ,years 1) 46, 2) 46, 45 Male, % 1) 70.3, 2) 66.9, 3) 67.2 Weight <100kg, %	**At 12 weeks** PASI 75 (%): 1) 3.0, 2) 82.6, 3) 89.1 PASI 90 (%): 1)0.5 2) 64.6, 3) 70.9	**0-12 weeks** (pooled across UNCOVER trials): AEs, % 1) 46.8, 2) 58.3, 3) 58.4 All IXE- 80.9 SAEs, %

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
	ITT with NRI	3) ixekizumab, 80mg Q2W (n=433) *Patients who had an sPGA score of 0 or 1 at week 12 and entered the randomized withdrawal period through 60 weeks* 2a) maintained on ixekizumab 80mg Q4W 2b) switch to ixekizumab 80mg Q2W	Candidates for phototherapy or systemic therapy	1) 67.1, 2) 66.5, 3) 66.5 PsO duration, years 1) 20, 2) 19, 3) 20 PASI score 1) 20, 2), 20, 3) 20 Previous biologics (%): 1) 42.0, 2) 38.9, 3) 40.0	PASI 100 (%): 1) 0.0, 2) 33.6, 3) 35.3 sPGA score of 0/1 (%): 1) 3.2, 2) 76.4, 3) 81.8 *All IXE groups vs. placebo, p<0.001* **At wk 60** (pooled UNCOVER-1 and -2): PASI 75 (%): 2a) 80, 2b) 83 PASI 90 (%): 2a) 71, 2b) 73 sPGA score of 0/1 (%): 2a) 73, 2b) 75	1) 1.5, 2) 2.2, 3) 1.7 All IXE (wk 0-60)- 6.7 Discontinuation of study due to AEs, % 1) 1.1, 2) 2.1, 3) 2.1 All IXE (wk 0-60)- 4.4 Infections , % 1) 22.9, 2) 27.4, 3) 27.0 All IXE (wk 0-60)- 55.2 MACE , % 1) 0.1, 2) 0.2, 3) 0.0 All IXE (wk 0-60)- 0.6 Grade 3 or 4 neutropenia, n 1) 1, 2) 1, 3) 2 All IXE (wk 0-60)- 10 Deaths, n 0 in all groups All IXE (wk 0-60)- 0.1 (3 patients)
Langley, 2016[183] **(NCT01474512)** **UNCOVER-1** ***Abstract***	*Reports improvement in HRQoL for IXE Q4W*	See above	See above	See above	**At 12 weeks** DLQI, mean change -11.3* **At 60 weeks** DLQI, mean change -11.2* DLQI, score of 0/1, %	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					66.4 *p<0.001 from baseline	
Imafuku, 2017 [184] **(NCT01474512)** **UNCOVER-1** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trial *Subgroup analysis-Japanese patients*	1) Ixekizumab 80 mg q4w after 160 mg loading dose (n=12) 2) Ixekizumab 80 mg q2w after 160 mg loading dose (n=8) 3) Placebo (n=13)	*See Gordon, 2016* [182]	Age, mean 1)44.5 (10.6); 2)45.5 (10.4); 3)51.4 (14.9) Male, % 1)83.3; 2)100; 3)69.2 Duration of PsO, yr 1)18.7; 2)13.9; 3)13.2 Previous biologics, % 1)0; 2)0; 3)0 PASI, mean (SD) 1) 22.3 (9.4); 2) 27.6 (14.7); 3) 24.8 (12.9) sPGA, moderate (3), % 1)41.7; 2)50.0; 3)46.2 sPGA, severe (4), % 1)58.3; 2)37.5; 3)38.5 sPGA, very severe (5), % 1)0; 2)12.5; 3)15.4 DLQI total, mean (SD) 1) 11.5 (7.6); 2) 13.9 (8.0); 3) 12.9 (7.9)	**At 12 weeks** PASI 75, % 1)75; 2)100; 3)0 PASI 90, % 1)58.3; 2)75; 3)0 PASI 100, % 1)33.3; 2)37.5; 3)0 sPGA (0, 1), % 1)66.7; 2)100; 3)0 DLQI, change from baseline, mean (SD) 1) -9.0 (6.91 2) -13.3 (7.38) 3) -2.6 (8.22)	**0-12 weeks** Any TEAE, % 1)75; 2)87.5; 3)76.9 SAE, % 1)8.3; 2)0; 3)7.7 TEAE leading to discontinuation, % 1)25; 3)0; 3)7.7 Infection, % 1)25; 3)25; 3)23.1
Griffiths, 2015[117] **and Gordon, 2016**[182] **(NCT01597245)**	Phase III RCT Double-blind Multicenter	N=1224 1) placebo (n=168) 2) etanercept (n=358)	Inclusion: ≥18 years BSA ≥10%, PASI ≥12 sPGA ≥3	Age (years): 1) 45, 2) 45, 3), 45, 4), 45 % male:	**At week 12**: PASI 75 (%): 1) 2.4, 2) 41.6‡, 3) 77.5‡§, 4) 89.7‡§	**At week 12** (pooled across UNCOVER-1 and -2 trials): AEs, % 1) 44, 2) 54, 3) 58, 4) 58

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
UNCOVER-2 ***Good quality publication***	Sites in USA, Canada, Mexico, Argentina, Chile, Europe, Czech Republic, Hungary, Romania, Russia, Australia, and Japan ITT	3) ixekizumab 80mg Q4W (n=347) 4) ixekizumab, 80mg Q2W (n=351) *Patients who had an sPGA score of 0 or 1 at week 12 and entered the randomized withdrawal period*	≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy Exclusion: Patients who had used etanercept at any time before screening	1) 71.4, 2) 65.9, 3) 70.3, 4) 63.0 Weight (kg): <100kg- 1) 66.9, 2) 65.0, 3) 65.6, 4) 72.9 ≥100kg- 1) 33.1, 2) 35.0, 3) 34.4, 4) 27.1 PsO duration (years): 1) 19, 2) 19, 3) 19, 4) 18 PASI: 1) 21, 2) 19, 3) 20, 4) 19 Previous biologics (%): 1) 25.6, 2) 21.2, 3) 24.5, 4) 23.9	PASI 90 (%): 1) 0.6, 2) 18.7‡, 3) 59.7‡§, 4) 70.7‡§ PASI 100 (%): 1) 0.6, 2) 5.3, 3) 30.8, 4) 40.5 sPGA score of 0/1 with ≥2-point reduction (%): 1) 2.4, 2) 36.0‡§, 3) 72.9‡§, 4) 83.2‡§ DLQI, score of 0/1 (%): 1) 6.0, 2) 33.8‡, 3) 59.9‡§, 4) 64.1‡ *‡p<0·0001 compared with placebo §p<0·0001 compared with etanercept*	SAEs, % 2% in all groups Discontinuation of study due to AEs, % 1) 0.01, 2) 0.07, 3) 0.05, 4) 0.03 URIs, % 1) 3, 2) 5, 3) 3, 4) 4 Deaths, % 0 in all groups
Gottlieb, 2016[185] **(NCT01597245)** **UNCOVER-2** ***Abstract***	Reports improvement in skin pain VAS	See above	See above	See above Mean VAS 1) 49.2	**At 12 weeks** Skin pain VAS 1) 44.5, 2) 18.9, 3) 10.3, 4) 7.2 *Least squares mean change from baseline:* 1) -4.6, 2) -29, 3) -37.7, 4) -42.2 *All comparisons, p<0.001*	NR
Griffiths, 2015[117] and Gordon, 2016[182]	Phase III RCT Double-blind	N=1346 1) placebo (n=193)	Same as UNCOVER-2	Age (years): 1) 46, 2) 46, 3), 46, 4), 46	**At 12 weeks** PASI 75 (%):	See above

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
(NCT01646177) **UNCOVER-3** ***Good quality publication***	Multicenter Sites in USA, Canada, Mexico, Argentina, Chile, Europe, Czech Republic, Hungary, Romania, Russia, Australia, and Japan ITT	2) etanercept (n=382) 3) ixekizumab, 80mg Q4W (n=386) 4) ixekizumab, 80mg Q2W (n=385)		% male: 1) 71.0, 2) 70.4, 3) 66.8, 4) 66.0 Weight (kg): <100kg- 1) 71.9, 2) 67.0, 3) 71.9, 4) 71.6 ≥100kg- 1) 28.1, 2) 33.0, 3) 28.1, 4) 28.4 PsO duration (years): 1) 18, 2) 18, 3), 18, 4) 18 PASI: 1) 21, 2), 21, 3) 21, 4) 21 Previous biologics (%): 1) 17.1, 2) 15.7, 3) 15.0, 4) 15.1	1) 7.3, 2) 53.4†, 3) 84.2†‡, 4) 87.3†‡ PASI 90 (%): 1) 3.1, 2) 25.7†, 3) 65.3†‡, 4) 68.1†‡ PASI 100 (%): 1) 0.0, 2) 7.3†, 3) 35.0†‡, 4) 37.7†‡ sPGA score of 0/1 with ≥2-point reduction (%): 1) 6.7, 2) 41.6†, 3) 75.4†‡, 4) 80.5†‡ DLQI, score of 0/1 (%): 1) 7.8, 2) 43.7‡, 3) 63.7‡§, 4) 64.7‡§ *†p<0·0001 compared with placebo* *‡p<0·0001 compared etanercept*	
Blauvelt, 2017 [186] **UNCOVER-3** **(NCT01646177)** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trial *Long term safety*	1) Ixekizumab 80 mg q2w (0-12 weeks), IXE 80 mg q4w (12-108 weeks) (n=385 for efficacy; n=362 for safety) 2) Ixekizumab 80 mg q4w (0-12 weeks), IXE 80 mg q4w (12-108 weeks) (n=360)	*See Griffiths, 2015* [117] *and Gordon, 2016* [182]	*See Griffiths, 2015* [117] *and Gordon, 2016* [182]	**At 108 weeks** PASI 75, % 1)83.6 PASI 90, % 1)70.3 PASI 100, % 1)48.9 sPGA 0 or 1, %	**At 108 weeks** Any TEAE, % 1)84.5; 2)84.7; 3)84.8; 4)83.6 Any severe TEAE, % 1)9.9; 2)14.4; 3)14.1; 4)14.8 Any serious AE, %

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		3) Etanercept 50 mg BIW (0-12 weeks), IXE 80 mg q4w (12-108 weeks) (n=369) 4) Placebo (0-12 weeks), IXE 80 mg q4w (12-108 weeks) (n=183) After the 12-week induction period, patients entered the LTE and received IXE 80 mg q4w. After week 60, patients could increase dose to IXE 80 mg q2w at the investigator's discretion.			1)74.1 * Efficacy results are only reported for patients who received recommended dose of IXE 80 mg q2w during the induction period and IXE 80 mg q4w during the LTE. Safety results are reported for all treatment arms.	1)8.3; 2)11.9; 3)12.7; 4)15.3 Candida infections, % 1)3.3; 2)5.0; 3)3.0; 4)4.4 Malignancies, % 1)1.4; 2)2.8; 3)1.4; 4)1.1 Cerebrocardiovascular events, % 1)1.9; 2)1.7; 3)2.7; 4)4.4 Death, n 1)1; 2)1; 3)2; 4)1
Leonardi, 2018 [149] **UNCOVER-3** **(NCT01646177)** ***Abstract*** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trial *Long term safety*	After the 12-week induction period, patients entered the LTE and received IXE 80 mg q4w. After week 60, patients could increase dose to IXE 80 mg q2w at the investigator's discretion. 1) Ixekizumab 80 mg q2w (0-12 weeks), IXE 80 mg q4w (12-156 weeks)*	*See Griffiths, 2015* [117] *and Gordon, 2016* [182]	*See Griffiths, 2015* [117] *and Gordon, 2016* [182]	**At 156 weeks** PASI 75, % 1)80.5 PASI 90, % 1)66.0 PASI 100, % 1)45.1 sPGA 0/1, % 1)67.4 sPGA 0, %	**0-156 weeks** Any TEAE, % 1)87.8; 2)86.4; 3)87.0; 4)88.5 Severe TEAE, % 1)11.6; 2)16.9; 3)16.8; 4)19.7 Discontinuation due to AE, % 1)6.4; 2)8.3; 3)7.9; 4)8.2

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		(n=385 for efficacy, 362 for safety) 2) Ixekizumab 80 mg q4w (0-12 weeks), IXE 80 mg q4w (12-156 weeks) (n=360) 3) Etanercept 50 mg BIW (0-12 weeks), IXE 80 mg q4w (12-156 weeks) (n=369) 4) Placebo (0-12 weeks), IXE 80 mg q4w (12-156 weeks) (n=183) *Patients randomized to IXE q2w/IXE q4w were considered for primary efficacy analysis			1)48.5 *Results presented here are for patients who received IXE 80 mg q4w during entire OLE. See publication for results including patients who increased dose to IXE 80 mg q2w.*	Viral upper respiratory tract infection, % 1)28.5; 2)25.3; 3)28.2; 4)29.0 Upper respiratory tract infection, % 1)8.8; 2)11.1; 3)7.9; 4)8.7 Injection-site reaction, % 1)6.4; 2)8.9; 3)6.5; 4)9.3 Candida infection, % 1)3.6; 2)6.1; 3)4.1; 4)4.9 Death, % 1)0.6; 2)0.3; 3)0.5; 4)1.1
Gottlieb, 2016 [187] **(NCT01597245 & NCT01646177)** **UNCOVER -2 and -3** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trials *Pooled analysis*	*Prior biologic* 1) Ixekizumab 80 mg q4w after 160 mg loading dose (n=143) 2) Ixekizumab 80 mg q2w after 160 mg loading dose (n=142) 3) Etanercept 50 mg BIW (n=136) 4) Placebo (n=76)	*See Griffiths, 2015* [117] *and Gordon, 2016* [182]	*See Griffiths, 2015* [117] *and Gordon, 2016* [182]	**At 12 weeks** PASI 75, % 1)76.2; 2)91.5; 3)34.6; 5)82.2; 6)87.7; 7)50.7 PASI 90, % 1)55.2; 2)76.1; 3)13.2; 5)64.4; 6)67.7; 7)24.3 PASI 100, %	**0-12 weeks** Any TEAE, % 1)55; 2)55; 3)56; 4)45; 5)58; 6)58; 7)54; 8)44 Any SAE, % 1)1.4; 2)1.4; 3)1.5; 4)1.3; 5)2.0; 6)2.0; 7)2.0; 8)2.1 Infections, %

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		No prior biologic 5) Ixekizumab 80 mg q4w after 160 mg loading dose (n=590) 6) Ixekizumab 80 mg q2w after 160 mg loading dose (n=594) 7) Etanercept 50 mg BIW (n=604) 8) Placebo (n=284)			1)25.2; 2)47.2; 3)3.7; 5)34.9; 6)37.0; 7)7.0 Itch NRS responders*, % 1)80.3; 2)82.4; 3)55.0; 5)77.9; 6)84.1; 7)62.4 *p<0.001 for all IXE vs. ETN* *Total number of patients analyzed differs for this outcome. See publication for details.	1)27; 2)25; 3)24; 4)25; 5)26; 6)26; 7)21; 8)19
Guenther, 2017 [188] **(NCT01597245 & NCT01646177)** **UNCOVER -2 and -3** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trials *Pooled analysis*	1) Ixekizumab 80 mg q4w after 160 mg loading dose (n=733) 1) Ixekizumab 80 mg q2w after 160 mg loading dose (n=736) 3) Etanercept 50 mg BIW (n=740) 4) Placebo (n=361)	*See Griffiths, 2015* [117] *and Gordon, 2016* [182]	*See Griffiths, 2015* [117] *and Gordon, 2016* [182] **Additional patient characteristics:** DLQI personal relationship domain (PRD) score, mean (SD) 1) 1.6 (1.8) 2) 1.7 (1.8) 3) 1.7 (1.8) 4) 1.8 (1.9)	**At 12 weeks** Change in PRD score, mean (SE) 1)-1.3 (0.05); 2)-1.4 (0.04); 3)-1.1 (0.03); 4)-0.1 (0.05) *p<0.001 for IXE q4w, IXE q2w vs. ETN & PBO* Skin-related sexual difficulties, % 1)18.1; 2)12.9; 3)23.6; 4)49.3 *p≤0.001 for IXE q4w, IXE q2w vs. ETN & PBO* Improvement in skin-related sexual difficulties, %	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					1)71.7; 2)79.6; 3)59.4; 4)24.7, *p=NR* Sexual health impairment, % 1)3.8; 2)1.8; 3)5.0; 4)18.8 *p<0.001 for IXE q4w, IXE q2w vs. PBO; p<0.001 for IXE q2w vs. ETN* Improvement in skin-related sexual health impairment, % 1)83.4; 2)91.2; 3)77.9; 3)48.5, *p=NR*	
Kimball, 2016 [189] **(NCT01474512, NCT01597245, & NCT01646177)** **UNCOVER -1, -2, & -3** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trials	UNCOVER-1 1) Ixekizumab 80 mg q4w after 160 mg loading dose 1) Ixekizumab 80 mg q2w after 160 mg loading dose 3) Placebo UNCOVER-2 and -3 1) Ixekizumab 80 mg q4w after 160 mg loading dose	*See Gordon, 2016* [182] *for UNCOVER-1,* *See Griffiths, 2015* [117] *and Gordon, 2016* [182] *for UNCOVER-2 and -3*	*See Gordon, 2016* [182] *for UNCOVER-1,* *See Griffiths, 2015* [117] *and Gordon, 2016* [182] *for UNCOVER-2 and -3* **Additional patient characteristics:** UNCOVER-1 Itch NRS, range 7.0-7.2 Skin pain VAS, range 46.9-48.9 UNCOVER-2 Itch NRS, range	**At 12 weeks** UNCOVER-1 Itch NRS, mean 1)1.38; 2)1.38; 3)6.67 *p<0.001 for IXE q4w, IXE q2w vs. PBO* Skin pain VAS, mean 1)8.18; 2)6.62; 3)47.3 *p<0.001 for IXE q4w, IXE q2w vs. PBO* UNCOVER-2 Itch NRS, mean 1)1.67; 2)1.38; 3)2.94; 4)6.10 *p<0.001 for IXE q4w, IXE q2w vs. PBO*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		1) Ixekizumab 80 mg q2w after 160 mg loading dose 3) Etanercept 50 mg BIW 4) Placebo		6.4-6.7 Skin pain VAS, range 43.3-46.9 UNCOVER-3 Itch NRS, range 6.2-6.5 Skin pain VAS, range 38.4-43.2	Skin pain VAS, mean 1)9.44; 2)6.78; 3)17.4; 4)44.3 *p<0.001 for IXE q4w, IXE q2w, ETN vs. PBO* UNCOVER-3 Itch NRS, mean 1)1.57; 2)1.14; 3)2.42; 4)5.86 *p<0.001 for IXE q4w, IXE q2w vs. PBO* Skin pain VAS, mean 1)7.66; 2)5.15; 3)12.5; 4)40.4 *p<0.001 for IXE q4w, IXE q2w, ETN vs. PBO*	
Armstrong, 2016[158] **UNCOVER trials (all)** ***Good quality publication***	See above Secondary analysis to evaluate change in work productivity from baseline as measured by Work Productivity and Activity Impairment–Psoriasis (WPAI-PSO) scores	N=3866	See main trials	See main trials	WPAI-PSO* *UNCOVER-1* Absenteeism: 1)0.2, 2)-3.5, *p< 0.001 vs.1*, 3)-2.6, *p=0.003 vs.1* Presenteeism: 1) 0.5 2) -18.8, 3) -18.3 *2 and 3 vs. 1, p<0.001* Work productivity loss: 1) -0.8, 2) -20.6, 3) -19.8 *2 and 3 vs. 1, p<0.001* Activity impairment: 1) 0.8, 2) -24.5, 3) -25.2 *2 and 3 vs. 1, p<0.001*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					Similar results were obtained for UNCOVER-2 and -3, with the exception of absenteeism with ixekizumab Q4W in UNCOVER-2 *UNCOVER-2 (from graph)* Work productivity loss: 1)-2, 2) -14, 3) -19, 4) -19.5 *2 and 3 vs. 1 and 2, p<0.001* *UNCOVER-3 (from graph)* Work productivity loss: 1) +0.7, 2) -17, 3) -16, 4) -19 *4 vs. 1, p<0.001; all other comparisons NS* **Data presented as LSM change from baseline relative to placebo*	
Griffiths, 2016[190] **Pooled UNCOVER trials (all)** ***Abstract***	Secondary analysis to evaluate improvement in depression (etanercept group not included)	N=3119 1) placebo (n=791) 2) ixekizumab, 80mg Q4W (n=1161) 3) ixekizumab, 80mg Q2W (n=1167)	See main trials	Quick Inventory of Depressive Symptomology e Self Report 16 items (QIDS-SR16), median 14.0 (no difference b/w groups)	**At week 12** QIDS-SR16 mean change: 1) -3.6, 2) -6.5, 3) -6.9 *2 and 3 vs. 1, p<0.001* QIDS-SR16 ≥50% improvement from baseline (%)*: 1) 27.1, 2) 49.1, 3) 59.8 *2 and 3 vs. 1, p≤0.001*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					QIDS-SR16 remission (score ≤5) (%)*: 1) 17.8, 2) 33.5, 3) 45.2 *2 and 3 vs. 1, p<0.05* **Outcomes presented for NRI analysis*	
Gottlieb, 2016[191] **Pooled UNCOVER trials (all)** ***Abstract***	Secondary analysis to evaluate subgroups of patients who were biologic-naïve vs. biologic-experienced	N=3126 1) placebo (n=792) 2) ixekizumab, 80mg Q4W (n=1165) 3) ixekizumab, 80mg Q2W (n=1169) a) biologic-experienced (n=883) b) biologic-naïve (n=2243)	See main trials	NR	**At week 12** PASI 75 (%): 1a) 2.7, 1b) 5.2, 2a) 77.5, 2b) 83.1, 3a) 89.5, 3b) 88.4 PASI 90 (%): 1a) 0, 1b) 1.7, 2a) 53.7, 2b) 66.9, 3a) 73.0, 3b) 68.7 PASI 100 (%): 1a) 0, 1b) 0.3, 2a) 32.0, 2b) 34.7, 3a) 36.6, 3b) 39.1 *All IXE groups vs. placebo, p<0.001*	NR
Gottlieb, 2015[192] **Pooled UNCOVER trials (all)** ***Abstract***	Secondary analysis to evaluate subgroups of patients with PsA (etanercept group not included)	N=792	See main trials	Joint Pain VAS: 49.6 PASI: 21.6 DLQI: 14.2	**At 12 weeks** Joint Pain VAS, mean change: Placebo, +1.1 IXE Q4W, -25.2 IXE Q2W, -26.8 DLQI, mean change: Placebo, -0.8 IXE Q4W, -10.5	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					IXE Q2W, -11.8 PASI 75 (%): Placebo, 2.9 IXE Q4W, 81.1 IXE Q2W, 89.8 SF-36 MCS, mean score: Placebo, +0.8 IXE Q4W, +4.2 IXE Q2W, +5.2 SF-36 PCS, mean score: Placebo, -1.1 IXE Q4W, +5.1 IXE Q2W, +5.4 IXE groups vs. *placebo for all outcomes, p<0.001*	
2016 **IXORA-S** **(NCT02561806)** ***Abstract***	Phase III RCT Double-blind Multicenter	N=302 1)ixekizumab, 80mg Q2W (n=136) 2)ustekinumab, dosed by weight according to the label(n=166)	Inclusion: ≥6 months of plaque psoriasis diagnosis Failure of at least 1 systemic therapy Baseline PASI ≥10 Exclusion: Prior use of ustekinumab, prior use of IL-17A or IL12/23 antagonists, use of biologics within washout periods, ongoing or serious infection.	NR	PASI 75 (%): 1)91% 2)69% PASI 90 (%): 1)75 2)42 PASI 100(%); 1)37 2)15 sPGA of 0 (%): 1)43 2)18 DLQI of 0/1 (%): 1)63; 2)45	NR
Brodalumab						
Papp, 2012[193] **(NCT00975637)**	Phase II RCT Double-blind	N=198 1) brodalumab 70mg (n=39)	Inclusion: ≥18 years BSA ≥10%,	Age (years): 1) 42.1, 2) 44.0, 3) 42.1, 4) 41.8	**At week 12:** PASI 75 (%): 1) 33, 2) 77, 3) 82, 4) 0	**At week 12:** AEs ≥1 (%): 1) 68, 2) 69, 3) 82, 4) 62

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Good quality publication	Multicenter 23 international sites ITT	2) brodalumab 140mg (n=39) 3) brodalumab 210mg (n=40) 4) placebo (n=38) Also evaluated 280mg brodalumab monthly	PASI ≥12 sPGA ≥3 ≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy Exclusion: patients could not have received biologic agents within 3 months, and no previous treatment with ustekinumab or etanercept	% male: 1) 56, 2) 72, 3) 62, 4) 58 Weight (kg): 1) 88.8, 2) 92.4, 3) 88.8, 4) 86.9 PsO duration (years): 1) 20.7, 2) 19.2, 3) 17.1, 4) 18.3 PASI: 1) 18.8, 2) 19.4, 3) 20.6, 4) 18.9 DLQI: 1) 12.4, 2) 11.1, 11.4, 13.3 PsA (%): 1) 21, 2) 28, 3) 30, 4) 18 Previous biologics (%): Etanercept- 1) 18, 2) 8, 3) 10, 4) 18 Adalimumab- 1) 8, 2) 13, 3) 18, 4) 11 Ustekinumab- 1) 15, 2) 5, 3) 15, 13	PASI 50 (%): 1) 51, 2) 90, 3) 90, 4) 16 PASI 90 (%): 1) 18*, 2) 72, 3) 75, 4) 0 sPGA score of 0/1 (%): 1) 26*, 2) 85, 3) 80, 4) 3 *All BROD groups vs. placebo for both outcomes, p<0.001; *p<0.01* DLQI, mean change: 1) -5.9*, 2) -9.1, 3) -9.4, 4) -3.0 *All BROD groups vs. placebo, p<0.001; *p<0.01* SF-36, Physical: 1) +1.7, 2) +4.2, 3) +4.0, 4) +1.5 *2 vs. placebo, p<0.01* SF-36, Mental: 1) +2.4, 2) +4.4, 3) +5.0, 4) +1.7 *2 vs. placebo, p<0.05; 3 vs. placebo, p<0.01* *Other outcomes reported: Mean % BSA*	URIs (%): 1) 8, 2) 8, 3) 5, 4) 5 SAEs ≥1 (%): 1) 3, 2) 0, 3) 2, 4) 3 Discontinuation due to AEs (%): 1) 0, 2) 0, 3) 5, 4) 3 Deaths: NR
Papp, 2015 [194]	Phase II, double-blind, randomized, controlled,	1) Brodalumab 140 mg or 210 mg (n=181)	*See Papp, 2012* [193]	*See Papp, 2012* [193]	**Week 12 OLE** PASI 75, %	**0-144 weeks** Any TEAE, %

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
(NCT00975637) ***Abstract*** ***NEW EVIDENCE***	multicenter trial with open-label extension 23 international sites	Subjects previously received placebo or brodalumab 70, 140, 210 mg q2w or 280 mg q4w. Subjects enrolled in OLE initially received brodalumab 210 mg q2w. A protocol amendment after 1 year reduced the dose to 140 mg for subjects ≤100 kg (n=119). A subsequent protocol amendment allowed for subjects with inadequate response to 140 mg to increase to 210 mg (n=19).			1)95.4 PASI 90, % 1)85.1 PASI 100, % 1)62.9 **Week 48 OLE** PASI 75, % 1)93.3 PASI 90, % 1)83.0 PASI 100, % 1)61.8 **Week 144 OLE** PASI 75, % 1)85.4 PASI 90, % 1)73.6 PASI 100, % 1)51.4	1)94.5 Most frequently reported AEs were nasopharyngitis (26.5%), upper respiratory tract infection (19.9%), arthralgia (17.1%), back pain (11.0%), and influenza (10.5%).

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Gordon, 2013 **(NCT00975637)** ***Good quality publication***	Secondary analysis of Phase II data evaluating quality of life	See above	See above	See above	**At week 12** PSI total score = 0 (%): 1) 18, 2) 41, 3) 55, 4) 0 2 and 3 vs. 4, p<0.0001; 1 vs. 4 p=0.006 PSI change: 1) 8.5, 2) 15.8, 3) 16.2, 4) 4.8 2 and 3 vs. 4, p<0.0001; 1 vs. 4, p=0.042	NR
Papp, 2014[195] **(NCT00975637)** ***Fair quality publication***	Secondary analysis of Phase II data evaluating subgroups with and without PsA and with and without previous biologic use Subgroups were not compared statistically due to low statistical power	1) PsA- yes (n=46) 2) PsA- no (n=152) 3) Biologic use- yes (n=70) 4) Biologic use- no (n=158) a) placebo b) brodalumab 140mg c) brodalumab 210mg	See original trial	Age (years): 1) 89.7, 2) 90.1, 3) 93, 4) 21.3 PsO duration (years): 1) 24.3, 2) 17.3, 3) 21.4, 4) 17.6 PASI: 1) 26.6, 2) 22.9, 3) 26.5, 4) 22.2 DLQI: 1) PsA (%) 1) 100, 2) 0, 3) 24.3, 4) 22.7 Previous biologics (%): TNFα- 1) 32.6, 2) 21.7, 3) 68.6, 4) 0 Ustekinumab- 1) 4.3, 2) 13.8, 3) 32.9, 4) 0	**At week 12** PASI 75 (%): 1a) 0, 1b) 82, 1c) 92 2a) 0, 2b) 75, 2c) 79 3a) 0, 3b) 70, 3c) 88 4a) 0, 4b) 60, 4c) 79 PASI 90 (%): 1a) 0, 1b) 73, 1c) 83 2a) 0, 1b) 71, 2c) 71 3a) 0, 1b) 70, 1c) 81 4a) 0, 1b) 72, 3c) 71 DLQI response: 1a) 0, 1b) 100, 1c) 100 2a) 42, 2b) 75, 2c) 79 3a) 33, 3b) 80, 3c) 94 4a) 35, 4b) 83, 4c) 79 PSI score ≤8, with no item having a score >1 (%): 1a) 14, 1b) 100, 1c) 94 2a) 13, 2b) 86, 2c) 79 3a) 8, 3b) 100, 3c) 86 4a) 15, 4b) 94, 4c) 79	AEs of any grade were higher among patients who received brodalumab versus placebo and were similar among subgroups (data NR)

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					All BROD vs. placebo were SS. *Outcomes not compared between subgroups*	
Papp, 2015[196] **(NCT00975637)** ***Abstract***	Secondary analysis of Phase II data evaluating subgroups with and without previous biologic use	1) Biologic use- yes (n=70) 2) Biologic use- no (n=158) a) brodalumab 70mg b) brodalumab 140mg c) brodalumab 210mg d) placebo	See original trial	See original trial	**At week 12** sPGA score of 0/1 **(%):** 1a) 8, 1b) 80, 1c) 81, 1d) 0 2a) 35, 2b) 86, 2c) 79, 2d) 4 *No outcomes were evaluated statistically* Other outcomes reported: sPGA score of 0	**At week 12** AE, % 1) brodalumab (combined) – 79% placebo – 67% 2) brodalumab (combined) – 70% placebo – 60%
Papp, 2016[119] **(NCT01708590)** **AMAGINE 1** ***Good quality publication***	Phase III RCT Double-blind Multicenter 73 sites in the US, Canada, and Europe ITT (all randomized patients)	N=661 1) brodalumab 140mg Q2W (n=219) 2) brodalumab 210mg Q2W 3) placebo (n=222) Patients who achieved sPGA success (≥2) at week 12 were rerandomized to their induction doses of brodalumab or placebo	Inclusion: 18 - 75years BSA ≥10%, PASI ≥12 sPGA ≥3 ≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy Exclusion: A washout period was required for patients receiving specific drugs (reported in supplementary appendix)	Age (years): 1) 46, 2) 46, 3) 47 % male: 1) 74, 2) 73, 3) 73 Weight (kg): 1) 90.6, 2) 91.4, 3) 90.4 PsO duration (years): 1) 19, 2), 20, 3) 21 PASI: 1) 19.7, 2) 18.9, 3) 19.0 DLQI: NR PsA (%): 1) 27, 2) 26, 3) 29	**At week 12** PASI 75 (%): 1) 60, 2) 83, 3) 3 PASI 90 (%): 1) 42.5, 70.3, 2) 0.9 PASI 100 (%): 1) 0.5, 2) 23.3, 3) 41.9 sPGA score of 0/1 (%): 1) 54, 2) 76, 3) 1 HADS-A (treatment difference, after imputation): 1) -1.3, 2) -1.5 *BROD vs. placebo, p<0.001* HADS-D (treatment difference, after imputation):	**At week 12** AEs ≥1 (%): 1) 58, 2) 59, 3) 51 SAEs (%): 1) 2.7, 2) 1.4, 3) 1.8 Discontinuation due to AEs (%): 1) 1.8, 2) 0.9, 3) 1.4 Depression (%) 1) 0.5, 2) 0.5, 3) 0.5 URIs (≥5% in any group): 1) 8.2, 2) 8.1, 3) 6.4 No deaths AE outcomes at week 52 reported based on

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				Previous biologics (%): 1) 45, 2) 47, 3) 46	1) -1.9, 2) -2.1 *BROD vs. placebo, p<0.001* PSI responder (score ≤8, with no item having a score >1) (%): 1) 53, 2) 61, 3) 4	number of patients with exposure-emergent adverse events per 100 patient-years 5 deaths (2 suicides, 1 in the placebo group and 1 in the brodalumab 210mg group)
Strober, 2016[197] **(NCT01708590)** **AMAGINE 1** ***Abstract***	PROs from AMAGINE-1	See original trial	See original trial	See original trial	**At week 12** DLQI improvement ≥5, % 1) 74, 2) 84, 3) 22 DLQI score of 0/1, % 1) 43, 2) 56, 3) 5 PSI score = 0, % 1) 17, 2) 22, 3) 1 *All BROD groups vs. placebo, p<0.001* PSI responder data same as Papp, 2016	NR
Lebwohl, 2015[39] **NCT01708603** **AMAGINE-2** ***Good quality publication***	Phase III RCT Double-blind Multicenter 142 international sites (US, Canada, Europe, Australia) ITT	N=2,492 1) placebo (n=309) 2) ustekinumab (n=300) 3) brodalumab 140mg Q2W (n=610) 4) brodalumab 210mg Q2W (n=612) At week 12, patients receiving brodalumab underwent	Inclusion: 18 - 75years BSA ≥10%, PASI ≥12 sPGA ≥3 ≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy	Age (years): 1) 44, 2) 45, 3) 45, 4) 45 % male: 1) 71, 2) 68, 3) 68, 4) 69 Weight (kg): 1) 92, 2), 91, 3) 92, 4) 91 PsO duration (years): 1) 18, 2) 19, 3) 19, 4) 19 PASI: 1) 20.4, 2) 20.0, 3) 20.0, 4) 20.3 DLQI: NR PsA (%): 1) 17, 2) 17, 3), 21, 4) 19	**At week 12:** PASI 75 (%) 1) 8, 2) 70, 3) 67, 4) 86 PASI 90 (%) 1) 3, 2) 47, 3) 49, 4) 70 PASI 100 (%) 1), 2, 2) 22, 3) 26, 4) 44 sPGA score of 0 or 1 (%) 1) 4, 2) 61, 3) 58, 4) 79 p1 (%) 1) 7, 2) 55, 3) 51, 4) 68	**At week 12** *AMAGINE-2* AEs ≥1 (%): 1) 53.4, 2) 59.0, 3) 60.1, 4) 57.8 SAEs (%): 1) 2.06, 2) 1.3, 3) 2.1, 4) 1.0 Discontinuation due to AEs (%): 1) 0.3, 2) 1.3, 3) 1.2, 4) 1.2

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		rerandomization to receive one of four brodalumab maintenance regimens		Previous biologics (%): 1)29, 2) 28, 3) 29, 4) 29	*All BROD groups vs. placebo, p<0.001* *BROD 210mg was SS better than UST in both trials on PASI 75, 90, 100 and sPGA score of 0/1 (p-values in Table 2; no comparison b/w BROD and UST for PSI)	1 attempted suicide in the brodalumab 210mg group ; 1 death in the brodalumab 210mg group (cerebral infarction) 2 additional attempted suicides in the same patient as the induction period and 1 in the UST group at 52 weeks
Lebwohl, 2015[39] **(NCT01708629)** **AMAGINE-3** ***Good quality publication***	Phase III RCT Double-blind Multicenter 142 international sites (US, Canada, Europe, Australia) ITT	N=1,881 1) placebo (n=315) 2) ustekinumab (n=313) 3) brodalumab 140mg Q2W (n=629) 4) brodalumab 210mg Q2W (n=624)	See above	Age (years): 1) 44, 2) 45, 3) 45, 4) 45 % male: 1) 66, 2) 68, 3) 70, 4) 69 Weight (kg): 1) 89, 2), 90, 3) 89, 4) 90 PsO duration (years): 1) 18, 2), 18, 3) 17, 4) 18 PASI: 1) 20.1, 2) 20.1, 3) 20.1, 4) 20.4 DLQI: NR PsA, % 1) 19, 2) 20, 3) 21, 4) 20 Previous biologics, % 1) 24, 2) 24, 3) 25, 4) 25	**At week 12** PASI 75, % 1) 69, 2) 85*, 3) 69, 4) 6 PASI 90, % 1) 2, 2) 48, 3) 52, 4) 69 PASI 100, % 1) 0.3, 2)19, 3) 27, 4) 37 sPGA score of 0/1, % 1) 6), 2) 69, 3) 69, 4) 85 PSI score ≤8, with no item having a score >1, % 1) 6, 2) 52, 3) 53, 4) 61 *All BROD groups vs. placebo, p<0.001* **At week 52** (after switching to brodalumab 210 mg): PASI 75, % 1) 93	**At week 12** AEs ≥1 , % 1) 48.6, 2) 53.7, 3) 52.6, 4) 56.8 SAEs, % 1) 1.0, 2) 0.6, 3) 1.6, 4) 1.4 Discontinuation due to AEs, % 1) 1.0, 2) 0.6, 3) 0.8, 4) 1.1 AE outcomes at week 52 based on number of patients with exposure-emergent adverse events per 100 patient-years (reported in supplementary appendix)

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					2) 92 PASI 100, % 1) 68 2) 40 sPGA score of 0/, % 1) 90 2) 70 PSI score ≤8, with no item having a score >1, % 1) 86; 2) 73	No attempted suicides at any point during the study
Lebwohl, 2017 [118] **AMAGINE 1, 2, 3** **(NCT01708590 & NCT01708603 & NCT01708629)** ***Abstract*** ***NEW EVIDENCE***	Phase III, randomized, controlled, double-blind, multicenter trials *Pooled analysis*	1) Placebo (n=844) 2) Brodalumab 140 mg (n=1458) 3) Brodalumab 210 mg (n=1458)	*See Papp, 2016 for AMAGINE 1*[119] *and Lebwohl, 2015*[39] *for AMAGINE 2 and 3*	*See Papp, 2016 for AMAGINE 1*[119] *and Lebwohl, 2015*[39] *for AMAGINE 2 and 3*	**At 12 weeks** *Prior biologic use* PASI 75, % 1) 2.6 2) 60.7 3) 83.1 PASI 90, % 1) 0.4 2) 43.2 3) 66.7	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					PASI 100, % 1) 0.0 2) 20.3 3) 40.3 *No prior biologic use* PASI 75, % 1) 7.5 2) 69.3 3) 86.3 PASI 90, % 1) 2.8 2) 52.2 3) 70.9 PASI 100, % 1) 0.7 2) 28.3 3) 40.9	
Nakagawa, 2016[198] ***Fair quality publication*** ***NEW EVIDENCE***	Phase II, randomized, controlled, double-blind multicenter trial Sites in Japan LOCF (continuous), NRI (binary)	1) Brodalumab (210mg) (n=37) 2) Brodalumab (140mg) (n=37) 3) Brodalumab (70mg) (n=39)	Inclusion: Adult patients (20-70 years) with moderate to severe plaque psoriasis (PASI ≥12, BSA ≥10%) for at least 6 months and were candidate for systematic therapy or phototherapy. Negative	Age, mean 1)46.4; 2)46.4; 3)43.4; 4) 46.6 Male, % 1)75.0; 2)72.0; 3)63.0 Caucasian, % 1)78.4; 2)81.1;	**At 12 weeks** PASI 75 (%): 1)94.6*; 2)78.4*; 3)25.6; 4)7.9 PASI 90 (%): 1)91.9*; 2)64.9*; 3)15.4; 4)2.6	**0-12 weeks** Any AE. % 1) 73 2) 57 3) 54 4) 45 Serious AE, % 1) 2.7

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		4) Placebo (n=38)	HBV, HCV, HIV, TB & human T-cell lymphotropic virus tests were required Exclusion: Erythrodermic, guttate, pustular, or dug induced psoriasis, CHF, MI, unstable angina (within a year), current or previous history of malignancy (within 5 years). Previous use of systemic therapy, phototherapy, or biologic agents were allowed after washout.	3)87.2; 4)71.1 Duration of PsO, yr 1)15.0; 2)14.5; 3)13.3; 4)16.9 With PsA, % 1)13.5; 2)16.2; 3)15.4; 4)18.4 Prior Biologic, % 1)13.5; 2)8.1; 3)12.8; 3)7.9 PASI, mean (SD) 1)28.0 (14.4) 2)28.5 (10.7) 3)27.6 (11.6) 4)24.0 (8.9)	PASI 100 (%): 1) 59.5*; 2) 35.1*; 3) 2.6; 4) 0 sPGA of '0' or '1' (%) 1)94.6*; 2)78.4*; 3)25.6†; 4)5.3 Change from baseline DLQI 1) -9.0*; 2)-8.4*; 3) -2.2; 4) -2.0 SF36 - (PC) 1) -8.1†; 2)-3.8; 3) -1.8; 4)-0.2 SF36 - (MC) 1) -5.0†; 2)-7.0†; 3) -1.9; 4)-1.1 *†p<0.05 vs placebo* **p<0.001 vs placebo*	2) 0 3) 5.1 4) 2.6
Umezawa, 2016[199] ***NEW EVIDENCE***	Phase II, randomized, controlled, double-blind multicenter trial with open label extension *See Nakagawa, 2016[198]*	**Week 0 – 12** 1) Brodalumab (210mg) (n=37) 2) Brodalumab (140mg) (n=37)	*See Nakagawa, 2016[198]*	*See Nakagawa, 2016[198]*	**Week 52** PASI 75 (%): 1)94.4; 2)78.1 PASI 90 (%): 1)87.5; 2)71.2	**0-52 weeks** Any AE, % 1) 92 2) 86 Discontinuation due to AE, %

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
	Observed case analysis	3) Brodalumab (70mg) (n=39) 4) Placebo (n=38) At 12 weeks, patients in the 70mg brodalumab or placebo group in the main RCT were allocated to either the 140mg or 210mg brodalumab group. **After Week 12** 1) Brodalumab (210mg) (n=73) 2) Brodalumab (140mg) (n=72)			PASI 100 (%): 1) 55.6; 2) 43.8 sPGA of 'clear' or 'minimal' (%) 1)91.7; 2)69.9 Change from baseline DLQI 1) -7.9; 2)-8.3 SF36 - (PC) 1) -6.4; 2)-5.8 SF36 - (MC) 1) -6.8; 2)-3.6	1) 0 2) 0 No death
Anti IL-12/13 Agent						
Ustekinumab (Stelara)						
Griffiths, 2010[123] **(NCT00454584)**	Phase III RCT Multicenter	N=903 1) ustekinumab 45mg (n=209)	Inclusion: ≥18 years BSA ≥10%,	Age (years): 1) 45.1, 2) 44.8, 3) 45.7	**At week 12** PASI 75 (%) 1) 67.5 2) 73.8, 3) 56.8	**At week 12** AEs ≥1 (%): 1) 66.0, 2) 69.2), 3) 70.0

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
ACCEPT ***Fair quality publication***	*Dose of UST was blinded, but otherwise patients knew which drug they were receiving* 67 sites worldwide ITT but unclear about handling of missing data	2) ustekinumab 90mg (n=347) 3) etanercept 50mg (n=347) *Patients who did not respond on etanercept crossed over to receive ustekinumab*	PASI ≥12, sPGA ≥3 ≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy Exclusion: patients could not have received biologic agents within 3 months, and no previous treatment with ustekinumab or etanercept	% male: 1) 63.6, 67.4, 3) 70.9 Weight (kg): 1) 90.4, 2) 91.0, 3) 90.8 PsO duration (years): 1) 18.9, 2) 18.7, 3) 18.8 PASI: 1) 20.5, 2) 19.9, 3) 18.6 DLQI: NR PsA (%): 1) 29.7, 2) 27.4, 3) 27.4 Previous biologics (%): 1) 12.4, 2) 10.4, 3) 11.8	*1 vs. 3, p=0.01* *2 vs. 3, p<0.001* PASI 90 (%) 1) 36.4, 2) 44.7, 23.1 sPGA score of 0/1 (%) 1) 65.1, 2) 70.6, 3) 49.0 *Both UST groups vs. ETN, p<0.001* Patients who did not respond on ETN and crossed over to UST 90mg: PASI 75 (%): 48.9 PASI 90 (%): 23.4 PGA- cleared or minimal (%): 40.4	URIs (%): 1) 6.2, 2) 6.3, 3) 5.8 SAEs ≥1 (%): 1) 1.9, 2) 1.2, 3) 1.2 Infections (%): 1) 30.6, 2) 29.7, 3) 29.1 Discontinuation due to AEs (%): 1) 1.9, 2) 2.0, 3) 2.3 3 deaths, 1 in each active treatment arm Common AEs at wk 64: adverse events were similar in the lower-dose and higher-dose ustekinumab groups and also before and after crossover from etanercept to ustekinumab
Leonardi, 2008[110] **(NCT00267969)**	Phase III RCT Double-blind Multicenter	N=766 1) ustekinumab 45mg (n=255)	Inclusion: ≥18 years PASI ≥12 BSA ≥10%	Age: 1) 44.8, 2) 46.2, 3) 44.8 % male:	**At week 12** PASI 75 (%) 1) 67.1, 2) 66.4, 3) 3.1	**At week 12** AEs ≥1 (%): 1) 57.6, 2) 51.4, 3) 48.2

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
PHOENIX 1 ***Good quality publication***	48 sites in the US, Canada, and Belgium ITT with NRI	2) ustekinumab 90mg (n=256) 3) placebo (n=255) Ustekinumab patients with PASI ≥75% improvement re-randomized at wk 40 1) maintenance (n=162) 2) withdrawal (n=160) *Cross-over to ustekinumab 45 or 90 mg at week 12*	≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy Exclusion: previous treatment with any agent that targets IL-12 or -23, received biological or investigational agents within previous 3 months, had received conventional systemic psoriasis therapy, or phototherapy within the previous 4 weeks, or had received topical psoriasis treatment within the previous 2 weeks	1) 68.6, 2) 67.6, 3) 71.8 Weight (kg): 1) 93.7, 2) 93.8, 3) 94.2 PsO duration (years): 1)19.7, 2) 19.6, 3) 20.4 PASI: 1) 20.5, 2) 19.7, 3) 20.4 DLQI: 1) 11.1, 2) 11.6, 3) 11.8 PsA: 1) 29.0, 2) 36.7, 3) 35.3 Previous biologics (%): 1) 52.2, 2) 50.8, 3) 50.2	PASI 50 (%) 1) 83.5, 2) 85.9, 3) 10.2 PASI 90 (%) 1) 41.6, 2) 36.7, 3) 2.0 *All UST groups vs. placebo, p<0.0001* PGA- cleared or minimal (%): 1) 60.4, 2) 61.7, 3) 3.9 *1 vs. 3: 56.5%, 95% CI 50.0–62.9, p<0.0001* *2 vs. 3: 57.8%, 95% CI 51.4–64.2, p<0.0001* DLQI score of 0 or 1 (%): 1) 53.1, 2) 52.4, 3) 6.0 *1 and 2 vs. 3: p<0.0001* Maintenance vs. withdrawal on PASI and PGA (data NR): *p<0.0001*	URIs (%): 1) 7.1, 2) 6.3, 3) 6.3 SAEs (%): 1) 0.8, 2) 1.6, 3) 0.8 Infections (%): 1) 31.4, 2) 25.9, 3) 26.7 No dose response was seen in the rates of adverse events, serious adverse events, or adverse events leading to study agent discontinuation Similar AEs in withdrawal phase AEs also reported wk 12-40 (crossover) and wk 40-74 (withdrawal) 3 deaths, 1 in the 45mg and 2 in the placebo groups
Kimball, 2013 **PHOENIX 1**	5-year long-term safety extension of PHOENIX 1	N=517 (those who received one dose of ustekinumab) 1) ustekinumab 45mg (n=259) 2) ustekinumab 90mg (n=258)	See above	Similar to original trial	**At week 244:** PASI 75 (%) 1) 63.4, 2) 72.0 PASI 90 (%) 1) 39.7, 2) 49.0 PASI 100 (%) 1) 21.6, 2) 26.4 PGA- score of 0/1 (%): 1) 42.5, 2) 51.0 *Other outcomes reported: % PASI improvement*	**At week 244** Serious infections (n): 1) 13, 2) 19 (in 30 patients) MACE (n): 1) 8, 2) 2 (reported in 10 patients) Discontinuation: 68.7% of ustekinumab-treated patients completed the 5-year f/u 5 deaths unrelated to treatment

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Papp, 2008[109] **PHOENIX 2** ***Good quality publication***	Phase III RCT Double-blind Multicenter 70 sites in Europe and North America ITT with NRI	N=766 1) ustekinumab 45mg (n=409) 2) ustekinumab 90mg (n=411) 3) placebo (n=410) *Partial responders (i.e., patients achieving ≥50% but <75% improvement from baseline in PASI) were re-randomized at week 28*	Inclusion: ≥18 years PASI ≥12 BSA ≥10% ≥6 months of plaque psoriasis diagnosis Exclusion: patients who had received treatment with any agent that specifically targeted IL-12 or -23, had received biological or investigational agents within the previous 3 months	Age (years): 1) 45.1, 2) 46.6, 3) 47.0 % male: 1) 69.2, 2) 66.7, 3) 69.0 Weight (kg): 1) 90.3, 2) 91.5, 3) 91.1 PsO duration (years): 1) 19.3, 2) 20.3, 3) 20.8 PASI: 1) 19.4, 2) 20.1, 3) 19.4 DLQI: 1) 12.2, 2) 12.6, 3) 12.3 PsA (%): 1) 26.2, 2) 22.9, 3) 25.6 Previous biologics (%): 1) 38.4, 2) 36.5, 3) 38.8 Baseline characteristics for partial responders at wk 28 also reported	**At week 12** PASI 75 (%): 1) 66.7, 2) 75.7, 3) 3.7 PASI 50 (%): 1) 83.6, 2) 89.3, 3) 10.0 PASI 90 (%): 1) 42.3, 2) 50.9, 3) 0.7 PGA, cleared/minimal (%): 1) 68.0, 2) 73.5, 3) 4.9 DLQI, score of 0/1 (%): 1) 55.3, 2) 56.4, 3) 3.2 *All UST groups vs. placebo, p<0.0001*	**At week 12** AEs ≥1 (%): 1) 53.1, 47.9, 3) 49.8 URIs (%): 1) 4.4, 2) 2.9, 3) 3.4 SAEs (%): 1) 2.0, 1.2, 3) 2.0 Infections (%): 1) 21.5, 2) 22.4, 3) 20.0 Discontinuation due to AEs (%): NR *Patients not achieving PASI 50 at wk 28 discontinued the study* AEs at wk 52: No dose response had been observed in rates of adverse events, serious adverse events, or adverse events leading to treatment discontinuation. 1 death (cardiac-related)
Langley, 2015[146] **PHOENIX 2**	5-year long-term safety extension of PHOENIX 2 Also compared dose adjusters to non-adjusters after wk 28	N=1212 1) ustekinumab 45mg (n=606) 2) ustekinumab 90mg (n=606) 3) combined N=1112 a) adjusters (n=568)	See above	BSA (%): a) 29.0, b) 22.9 PASI: a) 20.5, b) 18.4 Hyperlipidemia a) 24.6, b) 16.4	**At week 244:** PASI 75 (%): 1) 76.5, 2) 78.6 PASI 90 (%): 1) 50.0, 2) 55.5 PASI 100 (%): 1) 28.1, 2) 31.3 PGA, cleared/minimal (%):	**At week 264** AE, n 1) 222, 2) 195, 3) 206 a) 216, b) 187 3) 202 *Discontinuation due to AEs (%): 1) 2.17, 2) 2.58, 3) 2.43 a) 1.66, b) 2.51, c) 2.06 *SAEs (%):

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		b) non-adjusters (n=544) c) combined		Hypertension (%)ǂ: a) 29.6, b) 24.3 PsA (%)*: a) 28.7, b) 21.9 Systemic therapies: a) 63.2, b) 47.8 Previous biologics (%): a) 44.4, b) 30.3 **p=0.009, ǂp=0.046, all other comparisons p<0.001*	1) 54.0, 2) 58.6	1) 7.99, 2) 6.87, 3) 7.31 a) 7.43, b) 6.57, c) 7.02 *MACE (%): 1) 0.56, 2) 0.42, 3) 0.48 a) 0.54, b) 0.38, c) 0.46 *Infections (%): 1) 85.6, 2) 75.9, 3) 79.7 a) 83.4, b) 73.9, c) 78.9 ** per 100 patient-years*
Langley, 2010[200] **PHOENIX 2** ***Good quality publication***	Secondary analysis of patients from PHOENIX 2 evaluating anxiety, depression and QoL	See original study	See original study	See original study	**At week 12** HADS-A, mean 1) -1.6, 2) -1.6, 3) -0.11 HADS-D, mean 1) -1.7, 2) -2.1, 3) -0.21 DLQI, mean 1) -9.3, 2) -10.0, 3) -0.5 *UST vs. placebo, p<0.001*	All psychologic AEs were mild and did not result in treatment discontinuation
Reich, 2011[201] **PHOENIX 2** ***Good quality publication***	Secondary analysis of patients from PHOENIX 2 evaluating productivity	See original study	See original study	See original study Median productivity VAS score: 1) 2.7, 2) 3.2, 3) 2.6	**At week 12** Median improvement from baseline in work days missed (%): 1) 81.6, 2) 78.4, 3) 10.6 Median improvement from baseline in productivity VAS (%): 1) 72.6, 2) 71.4, 3) 0.0 *WLQ-physical demands 1) 7.6, 2) 5.1ǂ, 3) 0.2 *WLQ-time management 1) 6.6, 2) 9.1, 3) -0.7	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					*WLQ-mental-interpersonal 1) 7.8, 2) 7.5, 3) -1.1 *WLQ-output demands 1) 6.8, 2) 7.0, 3) -1.1 *UST vs. placebo, p<0.001 (ŧ=NS)*	
Sofen, 2010[202] **PHOENIX 1 and 2** ***Abstract***	Pooled analysis of patients from PHOENIX 1 and 2 for a subgroup with PsA	N=563	See original studies	PASI: 20.7 DLQI: 12.6	**At week 12** Primary: PASI 75 (%): 1) 63.0, 2) 61.5, 3) 3.6 DLQI, mean score: 1) -9.2, 2) -9.7, 3) -0.01 DLQI, ≥5 improvement: 1) -9.2, 2) -9.7, 3) -0.01 *All UST groups vs. placebo, p<0.001*	NR
Guenther, 2011[203] **PHOENIX 1 and 2** ***Good quality publication***	Pooled analysis of patients from PHOENIX 1 and 2 for patients with sexual difficulties	See original trials	See original trials	Impaired sexual function (score of 2 or 3 on DLQI item 9) (%): All UST, 22.6 UST45, 22.8 UST90, 22.1 Placebo, 23.0	**At week 12** Patients with impaired sexual function (%): UST, 2.7 UST45, 2.6 UST90, 2.8 Placebo, no change (23.0) *UST vs. placebo, p<0.001* **At week 28** Patients with impaired sexual function (%): UST (crossover), 4.4 UST45, 3.4 UST, 90, 2.3	NR
Igarashi, 2012[111] ***Good quality publication***	Phase II/III RCT Double-blind Multicenter	N=158 1) ustekinumab 45mg (n=64)	Inclusion: ≥20 years PASI ≥12 BSA ≥10%	Age (years): 1) 45, 2) 44, 3) 49 % male: 1) 82.8, 2) 75.8, 3) 83.9	**At week 12** PASI 75 (%): 1) 59.4, 2) 67.7, 3) 6.5 PASI 50 (%):	**At week 12** AEs ≥1 (%): 1) 65.6, 2) 59.7, 3) 65.6 SAEs (%):

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
	35 sites in Japan ITT with NRI	2) ustekinumab 90mg (n=62) 3) placebo (n=32) *Cross-over to ustekinumab 45 or 90 mg at week 12*	≥6 months of plaque psoriasis diagnosis	Weight (kg): 1) 73.2, 2) 71.1, 3) 71.2 PsO duration (years): 1) 15.8, 2) 17.3, 3) 16.0 PASI: 1) 30.1, 2) 28.7, 3) 30.3 DLQI: 1) 11.4, 2) 10.7, 10.5 PsA (%): 1) 9.4, 2) 11.3, 3) 3.1 Previous biologics (%): 1) 1.6, 2) 0.0, 3) 0.0	1) 82.8, 2) 83.9, 3) 12.9 PASI 90 (%): 1) 32.8, 2) 43.5, 3) 3.2 PGA, cleared/minimal (%): 1) 57.8, 2) 69.4, 3) 9.7 DLQI score of 0/1 (%): 1) 30.6, 2) 32.8, 3) 6.7 *All UST groups vs. placebo, p<0.0001* VAS improvement (mean) 1) -38.5, 2) -9.3. 3) +8.0 *p=NR* *Other outcomes reported: DLQI mean change, SF-36 summary, MCS, and PDI scores also included through wk 64*	1) 0.0, 2) 4.8, 3) 6.3 Infections (%): 1) 20.3, 2) 24.2, 3) 18.8 Discontinuation from AEs (%): 1) 0.0, 2) 6.5, 3) 6.3 AEs also reported through wk 72 (generally comparable between groups) No deaths through wk 72
Tsai, 2011[112] **PEARL** ***Good quality publication***	Phase III RCT Double-blind Multicenter *Conducted at 13 sites in Korea and Taiwan* ITT with NRI	N=121 1) ustekinumab 45mg (n=61) 2) placebo (n=60) *Placebo group crossed-over to ustekinumab 45mg at wk 12-36*	Inclusion: ≥20 years PASI ≥12 BSA ≥10% ≥6 months of plaque psoriasis diagnosis Exclusion: patients could not have received biologic agents within 3 months	Age (years): 1) 40.9, 2) 40.4 % male: 1) 82.0, 2) 88.3 Weight (kg): 1) 73.1, 2) 74.6 PsO duration (years): 1) 11.9, 13.9 PASI: 1) 25.2, 2) 22.9 DLQI: 1) 16.1, 15.2 PsA (%): 1) 16.4, 2) 11.7	**At 12 weeks** PASI 75 (%): 1) 67.2, 2) 5.0 *p<0.001* PASI 50 (%): 1) 83.6, 2) 13.3 *p<0.001* PASI 90 (%): 1) 49.2, 2) 1.7 *p<0.001* PASI 100 (%):	**At week 12** AEs ≥1 (%): 1) 65.6, 2) 70.0 SAEs (%): 1) 0.0, 2) 3.3 URIs (%): 1) 11.5, 2) 11.7 Discontinuation from AEs (%): 1) 0.0, 2) 5.0 Infections (%): 1) 32.8, 2) 23.3 **At week 36** AEs ≥1 (%):

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				Previous biologics (%): 1) 21.3, 2) 15.0 The population was evenly distributed Between Taiwanese/Chinese (49.6%) and Korean (50.4%)	1) 8.2, 2) 0.0 *p=0.024* PGA, cleared/minimal (%): 1) 70.5, 2) 8.3 *p<0.001* DLQI, mean change: 1) -11.2, 2) -0.5 *p<0.001*	Placebo/UST, 67.3 UST45, 67.8 SAEs (%): Placebo/UST, 9.1 UST45, 3.4 URIs (%): Placebo/UST, 3.6 UST45, 8.5 Discontinuation from AEs (%): Placebo/UST, 0.0 UST45, 1.6 Infections (%): Placebo/UST, 25.5 UST45, 32.2 No deaths during the study

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Zhu, 2013[204] **LOTUS** ***Good quality publication***	Phase III RCT Double-blind *14 sites in China* ITT with NRI	N=322 1) ustekinumab 45mg (n=160) 2) placebo (n=162) Placebo patients crossed over to receive ustekinumab for wks 12-16	Inclusion: ≥18 years PASI ≥12 BSA ≥10% ≥6 months of plaque psoriasis diagnosis	Age (years): 1) 40.1, 2) 39.2 % male: 1) 78.1, 2) 75.9 Weight (kg): 1) 69.9, 2) 70.0 PsO duration (years): 1) 14.6, 14.2 PASI: 1) 23.2, 2) 22.7 DLQI: 1) 13.7, 2) 13.1 PsA (%): 1)8.8, 2)8.6 Previous biologics (%): 1) 11.9, 6.8	**At week 12** PASI 75 (%): 1) 82.5 2) 11.1 PASI 50 (%): 1) 91.3 2) 19.8 PASI 90 (%): 1) 66.9 2) 3.1 PGA, cleared/minimal (%) 1) 78.8 2) 14.8 *All UST groups vs. placebo, p<0.001* Response was maintained through wk 28	**At week 12** AEs (%) 1) 42.5, 2) 38.5 SAEs (%) 1) 0.6 2) 0.6 Infections (%) 1) 19.3 2) 25.6 Discontinuation due to AEs (%) 1) 1.2 2) 1.9 No deaths, serious infections, malignancies, or cardiovascular events reported through wk 36
Observational Studies						
Clemmensen, 2011[60] **DERMBIO** ***Poor quality***	Database of Danish patients to evaluate drug adherence in TNFα-naïve vs. TNFα exposed over 1 year	N=179 1) All ustekinumab (n=71) 2) ustekinumab TNFα-naïve (n=24) 3) ustekinumab TNFα exposed (n=37) 4) TNFαs (n=47)	Inclusion: Failure of two or more conventional systemic agents or lack of efficacy or intolerance to methotrexate and narrow- band ultraviolet B; for biologic-naive patients, PASI >10 or DLQI >10	Age (years): 1) 43.1, 2) 41.8, 3) 43.7, 4) 43.7 % male: 1) 50.7, 2) 41.7, 3) 55.3, 4) 53.7 PASI: 1) 10.9, 2) 13.7, 3) 9.6, 4) 10.4	"No difference in the PASI75 response between the subjects exposed to 1, 2 or 3 TNFαa agents (data NR)" "Previous failure to one or more TNFα inhibitors did not influence treatment responses measured by the time to	Discontinuation (%): Ustekinumab survival was significantly better than the adherence to TNFα drugs (p<0.001, HR 0.32, 95% CI 0.15–0.67)

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				Observation time (days): 1) 142.6, 2) 132.8, 3) 147.5, 4) 173.1 *Differences between groups not measured statistically*	PASI 75 or the proportion of patients achieving PASI 75"	
Gelfand, 2012[205] ***Good quality***	Cross-sectional study of 10 outpatient dermatology sites across the US participating in the Dermatology Clinical Effectiveness Research Network	N=713 1) ADA (n=152) 2) ETN (n=191) 3) UST (n=73)	N/A	*Not compared between groups* Age (years): 48.6 % male: 50.6 Weight (kg): NR PsO duration (years): 19 PsA (%): 22.6 Previous biologics (%): 37.3	PGA clear or almost clear (%): 1) 47.7%; 2) 34.2%; 3)36.1% p<0.001 PGA clear or almost clear (*adjusted relative rates): 1) 2.15; 95% CI, 1.60-2.90 ; 2) 1.45; 95% CI 1.06-1.97; 3) 1.57; 95% CI 1.06-2.32 Differences in median PGA: (p<0.001), PASI (p=.02), and BSA (p=0.01) across therapies Treatment doses were double the recommended doses in 36.1% of patients taking etanercept and 11.8% of those taking adalimumab; 10.6% of patients undergoing phototherapy received the recommended treatment frequency	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					*Adjusted for sex, race, ethnicity, body mass index, skin type, frequency of topical use, practice setting of dermatologist, marital status, income, and insurance	
Gniadecki, 2011[206] **DERMBIO** ***Good quality***	Database of Danish patients to evaluate long-term drug survival (time to drug discontinuation) followed up to 10 years	N=1277 1) ADA (n=567) 2) ETN (n=364) 3) INF (n=176) 4) UST (n=170)	Inclusion: Patients on biologics with: PASI > 10 DLQI > 10 BSA > 10% in whom treatments previously failed or who have contraindications to topical therapies, ultraviolet B phototherapy and methotrexate *The choice of drug was the decision of the physician*	Age (years): 1) 44.4, 2) 46.3, 3) 45.5, 4) 44.6 % male: 1) 63.8, 2) 65.9, 67.6, 4) 60.6 PsO duration (years): 1) 18.7, 2) 19.5, 3) 18.7, 4) 17.9 PASI: 1) 12.5, 2) 12.6, 3) 15.8, 4) 11.4 DLQI: 1) 12.6, 2) 11.9, 3) 13.9, 4) 11.5 PsA (%): 1) 38.1, 2) 39.6, 3) 43.8, 4) 14.1	*OR for treatment termination: 1 vs. 4: 1.77, 95% CI 1.39-2.26, p<0.0001 2 vs. 4: 2.55, 95% CI 1.98-3.29, p<0.0001 3 vs. 4: 1.99, 95% CI 1.5-2.63, p<0.0001 2 vs. 1: 1.42, 95% CI, 1.20-1.68, p<0.0001 2 vs. 3: 1.30, 95% CI 1.04-1.61, p=0.02 Bio-naïve vs. bio-exposed: 1.24, 95% CI 1.05-1.46, 0.011 Male vs. female: 1.51, 95% CI 1.31-1.74, p<0.0001 *Adjusted for covariates*	NR
Goren, 2015 ***Fair quality***	Web-based survey from a US claims database study evaluating differences between ustekinumab and adalimumab for patients previously or not previous on etanercept	N=250 1) bio-naïve (n=68) 1a) ADA (n=26) 1b) UST (n=42) 2) etanercept-experienced 2a) ADA (n=49) 2b) UST (n=65)	Inclusion: ≥18 years	Age (years): 1a) 45.8, 1b) 47.6, 2a) 51.1, 2b) 46.4 % male: 1a) 61.5, 1b) 54.8, 2a) 42.9, 2b) 55.4 Weight (kg): NR PsO duration (years):	Significantly higher proportion of bio-naïve ustekinumab users reported a score of 0 on the DLQI compared with bio-naïve adalimumab users (45.2% vs 19.2%, p<0.05). After adjusting for covariates in	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				1a) 11.4, 1b) 18.5, 2a) 21.2, 2b) 17.9 Bio-naïve ADA patients had a significantly shorter duration of psoriasis then ustekinumab	multivariable models, the results were still significant. Adjusting for covariates, no significant overall differences were realized on health outcomes across UST and ADA users.	
Kalb, 2013[132] **PSOLAR** ***Good quality***	Multicenter, longitudinal, psoriasis-based registry study evaluating the risk of infection in biologics and other systemic therapies followed up to 8 years (June 20, 2007, through August 23, 2013)	N=11466 1) UST (n=3474) 2) ETN (n=1854) 3) ADA (n=2675) 4) INF (n=1151) Nonmethotrexate/nonbiologics, (n=1610) 5) Methotrexate/ nonbiologics, (n=490) (22,311 patient-years)	Inclusion: Non-biologic therapies included (but were not limited to) methotrexate, systemic retinoids, psoralen plus UV-A, and UV-B, which may also impact infection risk in different ways and to different degrees. *Treatment dosing was determined by the treating physician*	Age (years): 1) 47.2, 2) 48.7, 3) 47.6, 4) 48.5, 5) 50.1, 6) 55.1 % male: 1) 57.5, 2) 56.0, 3) 56.3, 4) 56.6, 5) 51.6, 6) 42.2 PsA (%): 1) 32.6, 2) 42.3, 3) 41.6, 4) 52.2, 5) 14.7, 6) 28.6 Previous biologics (%): 71.4 *SS differences between the biologics and nonmethotrexate/ nonbiologics cohorts (age, sex, BMI, and disease characteristics [PGA score, PsO duration]), as well as among the individual biologic groups (higher prevalence of psoriatic arthritis, history of serious infection)*	NR	*Incidence rate of serious infections (unadjusted): Overall: 1.45 1) 0.83, 2) 1.47, 3) 1.97, 4) 2.49, 5) 1.05, 6) 1.28 Biologic-exposed (incident): 1.35 Bio-naïve: 1.12 *The trend was similar across the biologic cohorts in the incident and bio-naive populations (i.e., lowest rates for the ustekinumab or etanercept cohorts, followed by either the infliximab or adalimumab cohort)* *Most common AEs: Pneumonia: 1) 0.19, 2) 0.27, 3) 0.39, 4) 0.44, 5) 0.21, 6) 0.16 Cellulitis:

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
						1) 0.19, 2) 0.37, 3) 0.19, 4) 0.40, 5) 0.13, 6) 0.24 *per 100 patient-years for those that occurred at least 4 times across treatment cohorts Multivariate analysis for the overall population: Increasing age: HR, 1.37; 95% CI, 1.24-1.52) Presence of diabetes: HR, 1.70; 95% CI, 1.25-2.32 History of significant infections: HR, 1.67; 95%CI, 1.28-2.18 *Increased risk of serious infections, all outcomes p<0.001*
Papp, 2015[133] **PSOLAR** ***Good quality***	Multicenter, longitudinal, psoriasis-based registry study evaluating adverse events in a real-world setting for 8 years (06/2007-08/2013) Missing values for covariates were imputed as the mean for continuous factors and as the median for categorical factors.	N=12094 1) UST (n=4134) 2) INF (n=1435) 3) ŧother biologics (n=2151) 4) *non-biologics (n=2151) (31,818 patient-years) ŧ4188 were treated with adalimumab and/or etanercept *511 were exposed to methotrexate	NR *Treatment dosing was determined by the treating physician*	Age (years): 1) 47.2, 2) 49.2, 3) 48.4, 4) 51.2 % male: 1) 57.5, 2) 55.1, 3) 55.25, 4) 49.3 PsA (%): 1) 34.0, 2) 55.2, 3) 39.6, 4) 18.1 Previous biologics (%): 1) 88.4, 2) 94.8, 3) 85.8, 4) 0.0	NR	*Cumulative incidence rates All-cause mortality (overall): 0.46 1) 0.36, 2) 0.45, 3) 0.42, 4) 0.70 MACE (overall): 0.36 1) 0.34, 2) 0.38, 3) 0.33, 4) 0.45 Serious infections (overall): 1.50 1) 0.95, 2) 2.78, 3) 1.80, 4) 1.26 ** rate/100 patient-years*

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Strober, 2016[207] **PSOLAR** ***Fair quality***	Multicenter, longitudinal, psoriasis-based registry study evaluating effectiveness of biologics in a real-world setting (June 20, 2007, through August 23, 2013)	N=2076 (patients initiating a new biologic) 1) UST (n=1041) 2) ETN (n=116) 3) ADA (n=662) 4) INF (n=257)	Inclusion: Patients may have been bio-naive or may have been exposed before enrollment to a biologic other than their newly initiated treatment in the registry Excluded: Patients restarting a biologic received before enrollment	Age (years): 1) 46.3, 2) 46.8, 3) 46.7, 4) 47.9 % male: 1) 56.8, 2) 56.0, 3) 58.0, 4) 62.9 PsO duration (years): 1) 19.1, 2) 14.7, 3) 16.1, 4) 17.2 PsA (%): 1) 33.5, 2) 35.8, 3) 35.0, 4) 44.0 *Baseline clinical values numerically reflected more severe disease in the infliximab group.*	**12 Month Analysis** PGA of 0/1 (%): 1) 59.9, 2) 57.6, 3) 56.5, 4) 42.0 *Odds of achieving a PGA score of 0/1 (logistic regression): 1 vs. 4: OR 0.449, 95% CI 0.260-0.774, p=0.040 *No other comparisons to UST were SS* *DLQI mean improvement (least mean square): 1 vs. 2: -5.011, 1.917 (95% CI 0.909-2.925), p=0.0002 1 vs. 3: -6.185, 0.743 (95% CI 0.025-1.492), p=0.427 *No other comparisons to UST were SS* *Adjusted multivariate analysis *Missing data excluded in the analysis* *Other outcomes reported: 6-month data and BSA*	NR
Iskandar, 2017[208] **BADBIR**	Prospective cohort registry that compares two adult psoriasis	N=2152 1) Etanercept (n=517)	Inclusion: Adult patients with chronic plaque psoriasis,	Age, mean 1)45.1; 2)44.8; 3)46.7	**At 6 months** DLQI change from baseline, median (IQR)	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Good quality publication ***NEW EVIDENCE***	cohorts: patients treated with biologics, and a second comparator group with similar disease characteristics but exposed only to nonbiologic systemic therapies. This study focused on evaluating the impact of biologics on quality of life.	2) Adalimumab (n= 1239) 3) Ustekinumab (n=396)	receiving adalimumab, etanercept or ustekinumab with follow-up data ≥6 months	Female, % 1)42.0; 2)39.1.0; 3)36.6 Duration of PsO, yr 1)22.9; 2)22.3; 3)22.0 With PsA, % 1) 25.0; 2)25.3; 3)21.2 Biologic naive, % 1)93.0; 2)83.1; 3)57.1 DLQI total score, median 1) 18; 2) 18; 3) 19 DLQI '0' or '1', % 1) 1.6; 2) 1.7; 3) 1.9 EQ-5D , median (IQR) 1) 0.73 (0.52, 0.8); 2) 0.73 (0.62, 0.8); 3) 0.73 (0.59, 0.8)	1) -11 (-17, -6) 2) -14 (-20, -7) 3) -14 (-19, -7) DLQI, '0' or '1', % 1) 29.5 2) 51.9 3) 46.8 All p<0.001 vs. baseline EQ-5D change from baseline, median (IQR) 1) 0.07 (0, 0.24) 2) 0.11 (0, 0.27) 3) 0.07 (0, 0.24)	
Anti-PDE4 Agent						
Apremilast (Otezla)						
Papp, 2012[209] **(NCT00773734)** ***Good quality publication***	Phase IIb RCT Double-blind Multicenter 35 sites in the US and Canada ITT with LOCF	N=352 1) placebo (n=88) 2) apremilast 10mg BID (n=89) 3) apremilast 20mg BID (n=87) 4) apremilast 30mg BID (n=88)	Inclusion: ≥18 years BSA ≥10%, PASI ≥12 ≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy	Age (years): 1) 44.1, 2) 44.4, 3) 44.6, 4) 44.1 % male: 1) 60, 2) 71, 3) 63, 4) 57 Weight (kg): 1) 90.4, 2) 95.9, 3) 20.2, 4) 91.4 PsO duration (years):	**At week 16*:** PASI 50 (%): 1) 25, 2) 38.2, 3) 47.1, 4) 60.2 *2 vs. 1, p=NS* *3 & 4 vs. 1, p<0.002* PASI 75 (%): 1) 5.7, 2) 11.2, 3) 28.7, 4) 40.9	**At week 16** AEs ≥1 (%): 1) 65, 2) 66, 3) 77, 4) 82 SAEs ≥1 (%): 1) 2, 2) 0, 3) 2, 4) 2 Infections ≥1 (%): 1) 33, 2) 33, 2) 41, 4) 48 Discontinuation due to AEs (%):

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		Patients in the placebo group were rerandomized to APR 20mg or 30mg (n=70); those in the APR groups continued to the active treatment phase wk 16-24 (n=210)	Exclusion: use of *adalimumab*, *etanercept*, efalizumab, or *infliximab* within 12 weeks; or had used alefacept within 24 weeks of randomization	1) 19.6, 2) 18.0, 3) 19.2, 4) 19.2 PASI: 1) 18.1, 2) 18.1, 3) 18.5, 4) 19.1 DLQI: NR PsA (%): 1) 19, 2) 23, 3) 18, 4) 24 Previous biologics (%): NR [see exclusion criteria]	*2 vs. 1, p=NS* *3 and 4 vs. 1, p<0.001* PASI 90 (%): 1) 1.1, 2) 4.5, 3) 9.2, 4) 11.4 *2 vs. 1, p=NS* PASI 100 (%): 1) 1, 2) 0, 3) 3.4, 4) 2.3 *p=NS* sPGA score of 0/1 (%): 1) 12.5, 2) 10.1, 3) 24.1, 4) 33.0 p=NR sPGA mean change (%): 1) -0.6, 2) -0.8, 3) -1.2, 4) 37.7 *2 vs. 1, p=NS* *3 and 4 vs. 1, p<0.001* Pruritus VAS, mean % change (%): 1) -6.1, 2) -10.2, 3) -35.5, 4) -43.7 *2 vs. 1, p=NS* *3 &4 vs. 1, p<0.005* DLQI ≥ 5-point decrease (only patients with score >5) (%): 1) 25, 2) 34, 3) 49, 4) 44 2 vs. 1, p=NR 3& 4 vs. 1, p=0.01	1) 5.7, 2) 2.2, 3) 9.2, 4) 11.47 Deaths (n): 1 in the placebo group **At week 24** (those continuing apremilast): AEs ≥1 (%): 2) 39, 3) 39, 4) 46 SAEs ≥1 (%): 1) 1, 2-4) 0 Infections ≥1 (%): 2) 18, 3) 15, 4) 22 Discontinuation due to AEs (n): 2) 4, 3) 0, 4) 0 Deaths (n): None

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Strand, 2013 **(NCT00773734)** ***Good quality publication***	Reporting of PRO measures	See above	See above	See above	**At week 16** DLQI mean change (%): 1) -1.9, 2) -3.2, 3), -5.9, 4) -4.4 *Other outcomes reported: MCID between groups for PROs*	NR
Papp, 2013[210] **(NCT00773734)** **Phase IIb** ***Abstract***	Reporting of symptom measures	See above	See above	See above	**At week 24** (those continuing apremilast): Pruritus VAS, mean change (%): 2) -36.7, 3) -41.5, 4) -41.0 p=NR *Other outcomes reported: MCID between groups for pruritus VAS*	NR
Papp, 2015[120] **(NCT01194219)** **ESTEEM 1** ***Good quality publication***	Phase III RCT Double-blind Multicenter 72 sites in the US, Canada, and Europe ITT with LOCF and NRI results	N=844 1) placebo (n=282) 2) apremilast 30mg BID (n=562)	Inclusion: ≥18 years BSA ≥10%, PASI ≥12 sPGA ≥3 ≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy Exclusion: use of biologics within 12 to 24 weeks	Age (years): 1) 46.5, 2) 45.8 % male: 1) 68.8, 2) 67.4 Weight (kg): 1) 93.7, 2) 93.2 PsO duration (years): 1) 18.7, 2) 19.8 PASI: 1) 19.4, 2) 18.7 DLQI: 1) 12.1, 2) 12.7	**At week 16** PASI 50 (%): 1) 17.0, 2) 58.7ǂ PASI 75 (%)*: 1) 5.3, 2) 33.1ǂ PASI 90 (%): 1) 0.4, 2) 9.8 sPGA score of 0/1 with ≥2-point reduction (%)*: 1) 3.9, 2) 21.7ǂ DLQI ≥ 5-point decrease (only patients with score >5) 1) 33.5, 2) 70.2	**At week 16** AEs ≥1 (%): 1) 55.7, 2) 69.3 SAEs ≥1 (%): 1) 2.8, 2) 2.1 Discontinuation due to AEs (%): 1) 3.2, 2) 5.3 Deaths (n): 1) 1, 2) 1 At week 52: AEs ≥1 (%): Apremilast- 78.7 SAEs ≥1 (%): Apremilast- 4.2 Discontinuation due to AEs (%):

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				PsA (%): NR Previous biologics (%): 1) 28.4, 28.8	Pruritus VAS, mean change (mm) 1) -7.3, 2) -31.5ǂ *ǂ1 vs. 2, p<0.0001* *Patients remaining on APR over 52 weeks maintained or continued improvement.* *Other outcomes reported: NPSI, c, BSA mean change, PASI mean % improvement*	Apremilast- 7.3 Deaths (n): Apremilast- 1
Thaci, 2017 [171] **(NCT01194219)** **ESTEEM 1** ***NEW EVIDENCE***	Phase III, randomized, double-blind, placebo-controlled, multicenter trial *See Papp, 2015*[120]	1) Placebo (n=282) 2) Apremilast 30 mg BID (n=562)	*See Papp, 2015*[120]	*See Papp, 2015*[120] **Additional patient characteristics:** SF-36v2 MCS, mean (SD) 1)47.0 (11.6) 2)45.8 (12.5) SF-36v2 PCS, mean (SD) 1)48.8 (8.9) 2)48.8 (9.7) WLQ-25, mean (SD) 1)0.037 (0.043) 2)0.040 (0.048)	**At 16 weeks** DLQI, change from baseline, mean (SD) 1)-2.1 (5.69) 2)-6.6 (6.66) *p<0.0001* DLQI 0 or 1, % 1) 6.7 2) 25.8 *p≤0.0095* SF-36v2 MCS, change from baseline, mean (SD) 1)-1.0 (9.16) 2)2.4 (9.50) *p<0.0001*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
					SF-36v2 PCS, change from baseline, mean (SD) 1)0.17 (6.22) 2)1.15 (7.20) WLQ-25 change from baseline, mean (SD) 1)0.006 (0.036) 2)-0.004 (0.039) *p=0.0148*	
Papp, 2016[74] (NCT01194219) **ESTEEM 1** ***NEW EVIDENCE***	Phase III randomized trial with an open-label extension *See Papp, 2015[120]*	Week 0 – 16 1) Placebo (n=282) 2) Apremilast 30mg BID (n=562) At week 16, the placebo group switched to apremilast through week 32, followed by a randomized treatment withdrawal phase to week 52 LTE was continued for up to 5 years	*See Papp, 2015[120]*	*See Papp, 2015[120]*	NR	**Harms from apremilast** **0-52 weeks (N=804)** Serious AEs, %: 4.5 AEs leading to discontinuation, %: 7.8 Depression, %: 2 Serious infection, %:0 Suicidal ideation, %: 0 Death: 1 case **>52 - 104 weeks (N=444)** Serious AEs, %: 5.4 AEs leading to discontinuation, %: 2.9 Depression, %: 0.5 Serious infection, %:1.4 Suicidal ideation, %: 0 Death: 1 case

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Paul, 2015[211] **(NCT01232283)** **ESTEEM 2** ***Fair quality publication***	Phase III RCT Double-blind Multicenter 40 sites in the US, Canada, and Europe Modified ITT	N=411 1) placebo (n=137) 2) apremilast 30mg BID (n=274) At week 16, placebo patients switched to apremilast (N=380)	Inclusion: ≥18 years BSA ≥10%, PASI ≥12 sPGA ≥3 ≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy Exclusion: use of biologics within 12 to 24 weeks	Age (years): 1) 45.7, 2) 45.3 % male: 1) 73.0, 2) 64.2 Weight (kg): 1) 90.5, 2) 91.4 PsO duration (years): 1) 18.7, 2) 17.9 PASI: 1) 20.0, 2) 18.9 DLQI: NR	**At week 16:** PASI 50 (%)*: 1) 19.7, 2) 55.5 PASI 75 (%)*: 1) 5.8, 2) 28.8 PASI 90 (%)*: 1) 1.5, 2) 8.8 (p=0.0042) sPGA score of 0/1 (%)*: 1) 4.4, 2) 20.4 DLQI, mean change: 1) -12.2, 2) -33.5	Primary outcomes at week 16: AEs ≥1 (%): 1) 60.3, 2) 68.0 SAEs ≥1 (%): 1) 2.2, 2) 1.8 Discontinuation due to AEs (%): 1) 5.1, 2) 5.5 Deaths (n): 1) 0, 2) 0 At week 52: AEs ≥1 (%): Apremilast- 77.9 SAEs ≥1 (%): Apremilast- 4.7

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				PsA (%): NR Previous biologics (%): 1) 32.1, 2) 33.6	DLQI ≥ 5-point decrease (only patients with score >5) 1) 42.9, 2) 70.8 (p<0.001 from baseline only) Pruritus VAS, mean change (mm) 1) -12.5, 2) -33.5 *APR groups vs. placebo, p<0.001* *LOCF for missing data (NRI also reported for PASI 75 and 90) PASI 75 by prior therapy (%): Biologic naïve- 1) 6.5, 2) 31.9 1 vs. 2, p<0.001 Biologic-experienced- 1) 4.5, 2) 22.8 1 vs. 2, p=0.0069	Discontinuation due to AEs (%): Apremilast- 7.1 Deaths (n): Apremilast- 0
Thaci, 2017 [171] **(NCT01232283)** **ESTEEM 2** ***NEW EVIDENCE***	Phase III, randomized, double-blind, placebo-controlled, multicenter trial *See Paul, 2015*[211]	1) Placebo (n=137) 2) Apremilast 30 mg BID (n=274)	*See Paul, 2015*[211]	*See Paul, 2015*[211] **Additional patient characteristics:** DLQI, mean (SD) 1)12.8 (7.1) 2)12.5 (7.1) 36-Item Short-Form Health Survey version 2 (SF-36v2) mental	**At 16 weeks** DLQI, change from baseline, mean (SD) 1)-2.8 (7.22) 2)-6.7 (6.95) *p<0.0001* DLQI 0 or 1, % 1)8.0 2)28.1	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
				component summary (MCS), mean (SD) 1)45.3 (12.4) 2)45.4 (12.8) SF-36v2 physical component summary (PCS), mean (SD) 1)48.5 (9.5) 2)48.5 (9.1) Work Limitations Questionnaire-25 (WLQ-25), mean (SD) 1)0.038 (0.046) 2)0.045 (0.046)	*p≤0.0095* SF-36v2 MCS, change from baseline, mean (SD) 1)0.0 (10.50) 2)2.6 (10.13) *p≤0.0095* SF-36v2 PCS, change from baseline, mean (SD) 1)0.28 (7.29) 2)1.60 (7.24) WLQ-25 change from baseline, mean (SD) 1)-0.005 (0.036) 2)-0.006 (0.039)	
Crowley, 2017[212] (NCT01194219 & NCT01232283) **ESTEEM 1 & 2** ***NEW EVIDENCE***	2 Phase III, randomized, double-blind, placebo-controlled, multicenter trial *See Papp, 2015[120]* *See Paul, 2015[211]*	**Week 0 – 16** 1) Placebo (n=418) 2) Apremilast 30 mg BID (n=832) **Week 16 - 156**	*See Papp, 2015[120]* *See Paul, 2015[211]*	*See Papp, 2015[120]* *See Paul, 2015[211]*	NR	**0 – 156 weeks** Any AE, % (100 PY): 83.2 (237.5) AEs leading to discontinuation, % (100 PY): 11.1 (7)

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
	Pooled analysis of the LTE	1) Apremilast BID (n=1184) Patient-years=1902.2				Any AE leading to death, % (100 PY): 0.3 (0.2) Serious AE, % (100 PY): 9 (5.9) MACE: 0.5/100 PY Malignancies: 1.2/100 PY Serious infection: 0.9/100 PY Depression: 1.8/100 PY
Reich, 2016 [121] **(NCT01690299)** **LIBERATE**	Phase IIIb, randomized, controlled, double-blind, multicenter trial LOCF	1) Apremilast 30 mg BID (n=83) 2) Etanercept 50 mg QW (n=83)	Inclusion: Adults (≥18 years) with chronic plaque psoriasis for ≥12 months (PASI≥12, BSA ≥10%, sPGA ≥3) who had	Age, mean 1)46.0; 2)47.0; 3)43.4 Male, % 1)59.0; 2)59.0; 3)70.2	**At 16 weeks** PASI 50, % 1)62.7; 2)83.1; 3)33.3 *p<0.0001 for ETN vs. PBO, p=0.0002 for APR vs. PBO*	**0-16 weeks** Any AE, % (EAIR/100 PY) 1) 71.1 (469.0) 2) 53.0 (288.8) 3) 53.6 (292.0)

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
Good quality publication ***NEW EVIDENCE***		3) Placebo (n=84)	inadequate response to ≥1 conventional systemic agent, were candidates for phototherapy or systemic therapy, and had no prior exposure to biologics. Exclusion: Prior failure of >3 systemic agents; history of demyelinating diseases or history of or concurrent congestive heart failure; other clinically significant or major uncontrolled disease; serious infection; latent, active or history of incompletely treated tuberculosis.	Caucasian, % 1)95.2; 2)90.4; 3)95.2 Duration of PsO in years, mean 1)19.7; 2)18.1; 3)16.6 PASI, mean (SD) 1) 19.3 (7.0) 2) 20.3 (7.9) 3) 19.4 (6.8) DLQI, mean (SD) 1) 13.6 (6.7) 2) 12.5 (7.0) 3) 11.4 (6.3) sPGA severe (4), % 1)20.5; 2)15.7; 3)27.4 Prior use of conventional systemic therapies, % 1)79.5; 2)69.9; 3)83.3	PASI 75, % 1)39.8; 2)48.2; 3)11.9 *p<0.0001 for APR, ETN vs. PBO* PASI 90, % 1)14.5; 2)20.5; 3)3.6 *p<0.001 for ETN vs. PBO, p=0.017 for APR vs. PBO* sPGA 0/1 and ≥2 reduction from baseline, % 1)21.7; 2)28.9; 3)3.6 *p<0.0001 for ETN vs. PBO, p=0.0005 for APR vs. PBO* DLQI, change from baseline, mean (SD) 1)-8.3 (7.7); 2)-7.8 (6.5); 3)-3.5 (5.6) *p<0.0001 for ETN vs. PBO, p=0.0004 for APR vs. PBO*	Serious AE, % 1) 3.6 (12.6) 2) 2.4 (7.9) 3) 0.0 (0.0) AE leading to discontinuation, % 1) 3.6 (12.5) 2) 2.4 (7.9) 3) 2.4 (8.3)
Green, 2016[213] **LIBERATE** ***Abstract***	*As above*	*As above* Reports pruritus and HRQoL up to wk 52	As above Patients who received ≥1 dose at baseline and	NR	**At week 16** DLQI (mean change): 1) -3.8, 2) -8.3, 3) -7.8 *1 & 2 vs. 3, p<0.0004*	NR

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
			f/u included in this analysis		Pruritus VAS (mean change from baseline, mm): 1) -22.5, 2) -35.6, 3) -36.4 *1 vs. 2 & 3 , p=0.002* % of patients achieving MCID (p=NR): DLQI (≥5 points): 1) 41.7, 2) 65.1, 3) 65.1 Pruritus VAS (>20% improvement): 1) 53.6, 2) 79.5, 3) 83.1 **At week 52** Outcomes (p=NR): Pruritus VAS (>20% improvement): 1) -35.8, 2) -35.9, 3) -34.6 DLQI (mean change): 1) -6.6, 2) -8.9, 3) -8.0	
Reich, 2017[214] **(NCT01690299)** **LIBERATE** ***NEW EVIDENCE***	Phase III randomized trial with an open-label extension *See Reich, 2016*[215]	At week 16 of the main trial, the placebo and etanercept group switched to apremilast; apremilast patients continued through week 104 **Week 16 -104** 1) Apremilast/ apremilast (n=74)	*See Reich, 2016*[215]	*See Reich, 2016*[215]	**At 104 weeks** PASI 75, %: 1) 45.9 2) 51.9 3) 50.7 sPGA 'clear' or 'minimal', %: 1) 18.9 2) 26.6 3) 27.4	**16-104 weeks** Any AE, % (PY): 1) 49 (0.54) 2) 54 (0.53) 3) 45 (0.47) Serious AEs, % (PY): 1) 4.1 (0.034) 2) 5.1 (0.039) 3) 6.8 (0.052)

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
		Patient-years =89.4 2) Etanercept/ apremilast (n=79) Patient-years=102.3 3) Placebo/ apremilast (n=73) Patient-years=95.6			DLQI, change from baseline, mean (SD): 1) -7.5 (7.0) 2) -5.2 (7.3) 3) -5.6 (6.3) Pruritus VAS change from baseline, mean (SD) 1) -26.6 (29.1) 2) -24.4 (31.2) 3) -32.3 (33.4)	AEs leading to discontinuation, % (PY): 1) 5.4 (0.045) 2) 2.5 (0.020) 3) 4.1 (0.031) AE leading to death, % (PY): 1) 0 2) 0 3) 0
Ohtsuki, 2017 [216] **(NCT01988103)** ***Fair quality publication*** ***NEW EVIDENCE***	Phase IIb, randomized, placebo-controlled, double-blind, multicenter trial Sites in Japan mITT, NRI (binary), LOCF (continuous)	1) Apremilast 20 mg BID (n=85) 2) Apremilast 30 mg BID (n=85) 3) Placebo (n=84)	Inclusion: Adults (≥20 years) with chronic moderate to severe plaque psoriasis (PASI ≥12, BSA ≥10%) for ≥ 6 months and was inappropriate for or inadequately controlled by topical therapy. Exclusion: Major illness; history of suicide attempt, or major psychiatric illness requiring hospitalization (within last 3 years); significant infection; active or latent TB; prolonged UV exposure;	Age, mean 1)52.2; 2)51.7; 2)48.3 Male, % 1)81.2; 2)83.5; 3)73.8 Duration of PsO, yr 1)12.6; 2)13.9; 3)12.4 With PsA, % NR Previous biologics, % 1)3.5; 2)2.4; 3)4.8 PASI, mean (SD) 1)22.1(9.6) 2)21.6 (8.9) 3)19.9 (8.9)	**At 16 weeks** PASI 50 (%) 1)37.6; 2)48.2; 3)21.4 PASI 75 (%) 1)22.4; 2)28.2; 3)7.1 *(PASI 50, 75, p<0.05 APR20 vs. placebo, p≤0.0003 APR30 vs. placebo)* PASI 90 (%) 1)7.1; 2)14.1; 3)1.2 sPGA 0 or 1 (%) 1)23.9; 2)26.8; 3)8.8	**0-16 weeks** Any AEs, % 1)57.6 2)51.8 3)41.7 Serious AEs, % 1)4.7 2)0.0 3)0.0 AEs leading to discontinuation, % 1)11.8 2)7.1 3)4.8 **0-68 weeks** Any AEs, % 1)77.7; 2)74.2

Study, *Quality rating*	Study Design, Location	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes*	Harms
			or previous use of biologics (12– 24 weeks), other systemic treatment or phototherapy (4 weeks), or active topical treatments (2 weeks).	DLQI total, mean (SD) 1)7.4 (5.6) 2)7.4 (5.7) 3)7.5 (5.3)	*(p<0.05 for APR20 & APR30 vs. placebo)* DLQI, change from baseline, mean (SD) 1)-0.4(5.3); 2)-2.2(5.0); 3)+1.3(5.7) *(p<0.05 APR20 vs. placebo, p<0.0001 APR30 vs. placebo)*	Serious AEs, % 1)9.1; 2)1.7 AEs leading to discontinuation, % 1) 15.7; 2)8.3 AE leading to death, n 1)1; 2)0
Komine, 2017[216] **(NCT01988103)** ***Abstract*** ***NEW EVIDENCE***	Phase II randomized trial with an open-label extension *See Ohtsuki, 2017* [216]	1) Apremilast 20 mg BID (n=85) 2) Apremilast 30 mg BID (n=85) 3) Placebo (n=84) At week 16, patients on placebo were re-randomized to either apremilast 20mg or apremilast 30mg	*See Ohtsuki, 2017* [216]	*See Ohtsuki, 2017* [216]	**At 68 weeks** PASI 75 (%) 1) 30.6 2) 41.2 sPGA 0 or 1 (%) 1) 36.6 2) 39.4	NR

AE: adverse event; BSA: body surface area; DLQI: Dermatology Life Quality Index, no or minimal impact (0/1); EAR: exposure-adjusted rate; IGA: Investigator's Global Assessment, clear (0) or almost clear (1); IR: incidence rate; ITT: intention-to-treat; LOCF: last observation carried forward; LTE: long term extension; MACE: major adverse cardiac events; MI: multiple imputation; mIGA: Investigator's Global Assessment, 2011 modification, clear (0) or almost clear (1); mLOCF: modified last observation carried forward; BIW: twice weekly; NR: not reported; NRI: nonresponder imputation; PASI: Psoriasis Area Severity Index; PGA: Physician's Global Assessment, clear (0) or almost clear (1); PsA: psoriatic arthritis; PsO: psoriasis; PY: patient years; q2w: every two weeks; q4w: every four weeks; SAE: serious adverse event; SD: standard deviation; sPGA: static Physician's Global Assessment, clear (0) or almost clear (1); TB: tuberculosis; TEAE: treatment emergent adverse event

*p-values only reported if significant

Appendix C. Previous Systematic Reviews and Technology Assessments

We identified six systematic reviews, four of which conducted network meta-analyses, and nine health technology appraisals conducted by the National Institute for Health and Care Excellence (NICE) comparing the effectiveness of targeted immunomodulators in moderate-to-severe psoriasis.

Bilal, J., et al. (2018). "A Systematic Review and Meta-Analysis of the Efficacy and Safety of the Interleukin (IL)-12/23 and IL-17 Inhibitors Ustekinumab, Secukinumab, Ixekizumab, Brodalumab, Guselkumab, and Tildrakizumab for the Treatment of Moderate to Severe Plaque Psoriasis." Journal of Dermatological Treatment: 1-37.

The objective of this systematic review and meta-analysis was to analyze the efficacy and safety of IL-12/13, IL-17, and IL-23 inhibitors in treating moderate to severe plaque psoriasis. The authors performed a meta-analysis based on a random effects model and generated risk ratios to compare the treatments to placebo. Ustekinumab 90 mg was found to have the highest likelihood of achieving PASI 75 (versus placebo RR: 20.20), followed ixekizumab 80 mg every two weeks (19.83), ixekizumab 80 mg every four weeks (18.22), secukinumab 300 mg (17.65), secukinumab 150 mg (15.36), brodalumab 210 mg (14.79), ustekinumab 45 mg (13.75), guselkumab 100 mg (12.40), brodalumab 140 mg (11.55), tildrakizumab 200 mg (11.45), then tildrakizumab 100 mg (11.02). Regarding the risk of adverse events, treatments were comparable to placebo except for ixekizumab which was associated with a slightly increased risk of withdrawal due to toxicity.

Sbidian, E., et al. (2017). "Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis." Cochrane Database of Systematic Reviews, Issue 12, Art. No.: Cd011535.

The authors of this systematic review identified 109 randomized controlled trials (RCTs) conducted in adults with moderate-to-severe psoriasis. Interventions of interest included all drugs of interest in our review (except risankizumab) in addition to conventional systemic treatments (acitretin, ciclosporin, fumaric acid esters, methotrexate), other small molecules (tofacitinib, ponesimod), and other biologics (alefacept, itolizumab). Two-thirds of the identified studies were placebo-controlled trials, 23% were head-to-head trials, and 10% were multi-armed trials (including both active comparator and placebo arms). Collectively, these trials enrolled approximately 40,000 patients, 68% of which were men, and the mean PASI score at baseline was 20. Using network meta-analyses, all 19 interventions were compared and ranked according to their effectiveness as measured by proportion of patients achieving PASI 90 and incidence of serious adverse events

(SAEs). The analyses showed that all interventions, on both class- and drug-levels, were superior to placebo in achieving PASI 90. Ranking on the class-level showed that anti-IL-17 agents were the most effective treatments (versus placebo RR: 30.81), followed by anti-IL-12/23 agents (23.16), anti-IL-23 agents (16.53), TNFα agents (11.58), small molecules (8.76), other biologics (4.78), then conventional systemic agents (3.78). On the drug-level, ixekizumab had the highest probability of achieving PASI 90 (versus placebo RR 32.45), followed by secukinumab (26.55), brodalumab (25.45), certolizumab (24.58), guselkumab (21.03), ustekinumab (19.91), then tildrakizumab (15.63). Results from the network meta-analysis for SAEs showed there was no statistically significant difference in the risk of SAEs between all the interventions and placebo. Compared to conventional systemic therapies, anti-IL-17 agents and TNFα agents were associated with a higher risk of SAEs (RR: 2.31 and 2.06, respectively). Generally, more effective treatments were associated with a higher risk of SAEs when compared to other treatments. The authors noted that the evidence for SAEs was of very low to moderate quality and recommended researchers to analyze data from non-randomized or post-marketing studies to assess the long-term risk of SAEs associated with these interventions.

Sawyer, L., et al. (2018). "The comparative efficacy of brodalumab in patients with moderate-to-severe psoriasis: a systematic literature review and network meta-analysis." Journal of Dermatological Treatment.

This systematic review and network meta-analysis assessed the efficacy of brodalumab relative to other biologic therapies (adalimumab, etanercept, infliximab, ixekizumab, secukinumab, and ustekinumab) and apremilast for the treatment of moderate-to-severe chronic plaque psoriasis. Sixty-two publications relating to 54 RCTs met the inclusion criteria for the network meta-analysis. A Bayesian network meta-analysis and an ordered probit model was used to generate the likelihood of achieving PASI response levels (50, 75, 90 and 100). The primary analysis excluded studies with a non-biologic systemic therapy arm and only included the doses of biologics licensed by the European Medicine Agency or recommended by NICE except for brodalumab 140 mg. As a result, the evidence network for the primary analysis included 41 RCTs, and a sensitivity analysis was conducted including all 54 RCTs. Results from the primary analysis with placebo-response adjustment showed that ixekizumab and brodalumab 210 mg were the most effective treatments, followed by secukinumab and infliximab for PASI 50, 75, 90, and 100 when compared to placebo. Specifically, the primary analysis of PASI 75 showed treatment with ixekizumab and brodalumab 210 mg had the highest likelihood of reaching PASI 75 (versus placebo RR: 16.51 and 16.48, respectively), followed by secukinumab (15.27) and infliximab (14.96). Results from the sensitivity analysis including all 54 RCTs showed similar results with anti-IL-17 agents outperforming all other therapies. The primary analysis also demonstrated brodalumab 210 mg was associated with a higher likelihood of achieving PASI 50, 75, 90, and 100 than adalimumab, apremilast, brodalumab 140 mg, etanercept, ustekinumab, infliximab, and secukinumab.

Gomez-Garcia, F., et al. (2017). "Short-term efficacy and safety of new biological agents targeting the interleukin-23-T helper 17 pathway for moderate-to-severe plaque psoriasis: a systematic review and network meta-analysis." Br J Dermatol 176(3): 594-603.

This systematic review and network meta-analysis evaluated the effectiveness and safety of secukinumab, ustekinumab, and TNFα agents. Efficacy measures, including PASI 75 and 90, and safety data at week 10-16 from 27 RCTs were analyzed using frequentist method to generate odds ratios (OR) of direct and indirect comparisons. Other efficacy outcomes such as IGA, PGA, and DLQI were also analyzed but not presented as main results due to missing data for some interventions. All biologics showed superior efficacy compared to placebo but also had higher ORs for adverse events. Based on PASI 75 and 90, infliximab (versus placebo OR 118.89 and 84.11, respectively) and secukinumab (87.07 and 96) were found to be the most effective but also the most likely to produce adverse events. Ustekinumab 90 mg ranked third in effectiveness in terms of achieving PASI 75 and 90 (versus placebo OR 73.67 and 61.34, respectively) and was the only agent showing no increased risk for all safety outcomes compared to placebo. Of the remaining drugs analyzed, ustekinumab 45 mg was associated with the highest likelihood of achieving PASI 75 and 90 (versus placebo OR 56.16 and 55.95), followed by adalimumab (30.69 and 22.11), then etanercept (17.88 and 16.53). Mixed treatment comparisons based on PASI 75 showed no difference between infliximab and secukinumab, but both were significantly more effective than the other biologics. Etanercept had significantly lower effectiveness compared to other biologics, and adalimumab and ustekinumab were not distinguished from each other.

Zweegers, J., et al. (2016). "Effectiveness of Biologic and Conventional Systemic Therapies in Adults with Chronic Plaque Psoriasis in Daily Practice: A Systematic Review." Acta Derm Venereol 96(4): 453-458.

The authors conducted a literature review of prospective and retrospective observational studies of TNFα agents, ustekinumab, and conventional systemic therapies from 1990 to 2014. A total of 32 studies were identified including two retrospective and two prospective studies comparing PASI responses of biologics of interest. Only one of these four studies found a statistically significant difference between biologics--percentage improvement in PASI at 24 weeks was greater with infliximab compared to etanercept (89% vs. 75%, p=0.02). The other studies either did not conduct statistical tests or found non-statistically significant results. The authors identified the gap in the availability of direct evidence on effectiveness among agents.

Signorovitch, J. E., et al. (2015). "Comparative efficacy of biological treatments for moderate-to-severe psoriasis: a network meta-analysis adjusting for cross-trial differences in reference arm response." Br J Dermatol 172(2): 504-512.

This systematic review identified 15 phase II or III trials of biologic treatments for moderate-to-severe psoriasis conducted in the U.S. or Europe. The authors proposed a network meta-analysis model adjusted for placebo response rate to control for measured and unmeasured patient- and trial-level characteristics. The network meta-analysis results showed all biologics were more effective than placebo with infliximab associated with the highest likelihood of achieving PASI 75 (versus placebo RR 19.49), followed by ustekinumab 90 mg (17.54), ustekinumab 45mg (16.33), adalimumab (16.01), then etanercept (12.54). Etanercept had statistically significant lower effectiveness than the other biologics, and the differences between the others were not statistically significant.

NICE health technology appraisals

NICE has issued technology appraisals for guselkumab, brodalumab, ixekizumab, apremilast, secukinumab, adalimumab, infliximab, ustekinumab, and etanercept for the treatment of moderate-to-severe psoriasis. During the technology appraisal process, a selected academic evidence review group (ERG) evaluates evidence submitted by the intervention technology company and generates a report on the clinical and cost-effectiveness of the technology. The ERG report is sent to an appraisal committee who issues either an appraisal consultation document or a final appraisal determination with their recommendations.

In the final appraisal determination for guselkumab[41], NICE recommended guselkumab for the treatment of psoriasis in adults only if the disease is severe (PASI>10 and DLQI>10) and has not responded to prior systemic treatment. The company modelled guselkumab with adalimumab and ustekinumab as comparators in their base case, but the ERG felt that these treatments were not acceptable comparators. In an exploratory analysis, the ERG modelled guselkumab with ixekizumab and secukinumab as comparators. The appraisal committee concluded that the recommendations for guselkumab are consistent with NICE's recommendations for ixekizumab and secukinumab.

The company's brodalumab submission[40] showed the treatment sequence starting with brodalumab dominated or had an ICER less than £25,000/QALY versus the sequences starting with other biologics, apremilast, or dimethyl fumarate. Since the cost-effectiveness of a treatment included early in a sequence would be driven by avoiding potentially cost-ineffective treatments later in the sequence, the committee considered the results from the ERG model that compared individual treatments and best supportive care to determine the cost-effectiveness of brodalumab. Results from the ERG model showed brodalumab was cost-effective, and the committee recommended brodalumab as a treatment option for patients with severe disease (PASI≥10) who have not responded to systemic therapy.

The company's ixekizumab submission[217] reported an ICER of £32,541/QALY for the sequence of treatments with ixekizumab as first-line therapy versus the sequence beginning with etanercept. After reviewing the company's model, the ERG added another sequence with ixekizumab as a second-line therapy following adalimumab which the ERG felt was a treatment sequence more likely to be used in real world practice. Results from the ERG model showed the sequence with ixekizumab as a second-line therapy had an ICER of £25,532/QALY versus the etanercept sequence, and the sequence with ixekizumab as a first-line therapy had an ICER of £39,129/QALY versus the second-line ixekizumab sequence. The appraisal committee concluded the cost-effectiveness of ixekizumab was similar to that of other biologics and recommended ixekizumab as a treatment for adults with severe disease (PASI≥10 and DLQI>10) who have not responded to systemic therapy.

Results from the company's apremilast model[218] suggested the sequence of treatments including apremilast dominated the comparator sequence in both modeled populations, distinguished by DLQI>10 or DLQI≤10. Upon review of the company's submission, the ERG noted the company used a high cost of basic supportive care, a US EQ-5D measure instead of a UK measure for utility estimates, and a lower number of annual physician visits than seen in real world practice. Correcting for these and other assumptions, the ERG's model showed apremilast was more clinically effective in both populations but not cost-effective. The ERG's final guidance stated the sequence including apremilast had an ICER of £30,300/QALY in the DLQ1>10 population and £60,000/QALY in the DLQ1≤10 population.

The company's secukinumab model [219] showed secukinumab dominated adalimumab, ustekinumab 45 mg and 90 mg, and infliximab. Additionally, the company found secukinumab had an ICER of £2,515/QALY versus etanercept and £7,231/QALY versus best supportive care. The ERG performed an exploratory analysis of the company's base case by correcting for assumptions including rates of mortality, cost of serious adverse events, and cost for best supportive care. Due to structural and parameter uncertainties, the appraisal committee was unable to determine a precise ICER but recommended secukinumab as a cost-effective therapy.

The company's adalimumab submission[220] reported an ICER of £30,538/QALY for adalimumab versus supportive care. The number of hospitalization days avoided influenced model outcomes significantly with no days avoided resulting in an ICER of £60,600/QALY and 39 days avoided resulting in a ICER of £4,800/QALY. The ERG expressed uncertainty of this model input and noted it to be a key factor driving model results. NICE issued an appraisal consultation document and recommended treatment with adalimumab for patients with PASI>10 and DLQI>10 who have not responded to systemic therapy.

Results from the company's infliximab model[221] showed infliximab to be cost-effective when compared to etanercept with an ICER of £26,095/QALY. The ERG notes the company's model

defines the population as patients with DLQI scores in the fourth quartile which does not clearly indicate if these patients fall under the moderate-to-severe psoriasis category. NICE recommended treatment with infliximab for patients with very severe disease (PASI>20 and DLQI>18) in appraisal consultation document.

The company's ustekinumab submission[222] reported an ICER of £29,587/QALY for ustekinumab versus supportive care. The model assumed 80% of the population weighed less than 100 kg and were treated with 45 mg of ustekinumab, and the remaining patients received 90 mg of ustekinumab. In the base case, the manufacturer proposed a patient access scheme that discounted the cost of ustekinumab 90 mg to that of ustekinumab 45 mg. ERG analysis showed the probability of ustekinumab being cost-effective at £20,000/QALY and £30,000/QALY was 10% and 47%, respectively.

The manufacturer of etanercept modelled etanercept 25 mg and 50 mg over 12- and 96-week periods. The model[223] showed the ICER for etanercept 25 mg versus no systematic therapy was almost £125,000/QALY in the 12-week model and £37,2000 in the 96-week model. The respective ICERs for etanercept 50 mg were substantially higher. The assessment group at NICE found the ICER for etanercept 25 mg to be £65,320/QALY over a longer time horizon and the ICER for etanercept 50 mg to be substantially higher.

Appendix D. Ongoing Trials

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Anti-IL-17 agents					
Secukinumab					
Study of Efficacy and Safety of Secukinumab in Subjects with Moderate to Severe Chronic Plaque-type Psoriasis/Novartis (NCT03066609)	Phase III, randomized, parallel assignment, quadruple-blind trial	1. Secukinumab 150 mg 2. Secukinumab 300 mg 3. Placebo	N=554 Inclusion: • ≥18 years • Chronic plaque-type psoriasis for at least 6 months • Moderate-to-severe psoriasis at baseline (PASI≥12; IGA mod 2011≥3; BSA≥10%) • Candidate for systemic therapy Exclusion: • Previous exposure to biologic targeting IL-17 or IL-17 receptor	PASI 75 and IGA mod 2011 0/1 at week 12	October 30, 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
A Study to Evaluate Clear Skin Effect on Quality of Life in Patients with Plaque Psoriasis (PROSE)/Novartis (NCT02752776)	Phase IV, non-randomized, single group assignment, open label trial	1. Secukinumab	N=1661 Inclusion: • ≥18 years • Moderate-to-severe plaque-type psoriasis for at least 3 months Exclusion: • Previous use of biologic targeting IL-17 or IL-17 receptor	DLQI 0/1 responders at week 16	March 26, 2018
Study of Secukinumab with 2 mL Pre-filled Syringes (ALLURE)/Novartis (NCT02748863)	Phase III, randomized, parallel assignment, quadruple-blind trial	1. Secukinumab 150 mg 2. Secukinumab 300 mg 3. Placebo	N=210 Inclusion: • ≥18 years • Chronic plaque-type psoriasis for at least 6 months • Moderate-to-severe psoriasis at baseline (PASI≥12; IGA mod 2011≥3; BSA≥10%) • Candidate for systemic therapy Exclusion: • Previous use of biologic targeting IL-17 or IL-17 receptor	PASI 75 responders and IGA mod 2011 0/1 responders at week 12	August 24, 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Study of Secukinumab Compared to Ustekinumab in Subjects with Plaque Psoriasis (CLARITY)/Novartis (NCT02826603)	Phase III, randomized, parallel assignment, quadruple-blind trial	1. Secukinumab 300 mg at weeks 0, 1, 2, 3, 4, and then q4w 2. Ustekinumab dosed by weight at weeks 0, 4 and then every 12 weeks	N=1109 Inclusion: • ≥18 years • Chronic plaque-type psoriasis for at least 6 months • Moderate-to-severe psoriasis at baseline (PASI≥12; IGA mod 2011≥3; BSA≥10%) • Candidate for systemic therapy Exclusion: • Previous use of biologic targeting IL-17, IL-17 receptor, IL-12, or IL-23	PASI 90 responders and IGA mod 2011 0/1 responders at week 12	August 22, 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Ixekizumab					
A Study of Ixekizumab (LY2439821) in Chinese Participants with Moderate-to-Severe Plaque Psoriasis/Eli Lilly (NCT03364309)	Phase III, randomized, parallel assignment, double-blind trial	1. Ixekizumab 2. Placebo	N=420 Inclusion: • ≥18 years • Chronic plaque psoriasis for at least 6 months • PASI≥12; sPGA≥3; BSA≥10% at baseline • Candidates for phototherapy and/or systemic therapy Exclusion: • Previous use of biologic targeting IL-17 or IL-17 receptor	sPGA 0/1 responders and PASI 75 responders at week 12	June 15, 2020

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
A Study of Ixekizumab (LY2439821) in Participants with Moderate-to-Severe Plaque Psoriasis Naive to Systemic Treatment/Eli Lilly (NCT02634801)	Phase III, randomized, parallel assignment, single-blind (outcomes assessor) trial	1. Ixekizumab 80 mg q2w until week 12, q4w until week 24 2. Fumaric acid esters 215 mg 1-3 times daily 3. Methotrexate 30 mg weekly	N=162 Inclusion: • ≥18 years • Moderate-to-severe chronic plaque-type psoriasis for at least 6 months • PASI>10 or BSA>10% and DLQI>10 • Candidates for and naïve to any systemic treatment Exclusion: • Serious illness of disorder other than psoriasis or immunocompromised	PASI 75 responders at week 24	November 2017
Brodalumab					

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Brodalumab in Subjects with Moderate to Severe Plaque Psoriasis Who Have Failed IL-17A Therapies/Icahn School of Medicine at Mount Sinai (NCT03403036)	Phase IV, single group assignment, open label trial	1. Brodalumab 210 mg q2w	N=40 Inclusion: • ≥18 years • sPGA≥3 and BSA>5% at baseline • Previously failed treatment with an IL-17A agent • Last dose of secukinumab or ixekizumab ≥ 28 days Exclusion: • Use of most psoriasis treatments within previous 4 weeks • Risk of suicide	PASI score at week 16 AEs through week 16	June 30, 2018
A Trial Comparing the Efficacy of Subcutaneous Injections of Brodalumab to Oral Administrations of Fumaric Acid Esters in Adults with Moderate to Severe Plaque Psoriasis/LEO Pharma (NCT03331835)	Phase IV, randomized, parallel assignment, single-blind (outcome assessor) trial	1. Brodalumab 210 mg q2w 2. Fumaric acid esters 215 mg 1-3 times daily	N=240 Inclusion: • ≥18 years • Chronic plaque-type psoriasis for at least 6 months • Moderate-to-severe psoriasis at baseline (PASI>10, BSA>10%, DLQI>10) • Candidates for systemic therapies Exclusion: • Previous use of systemic treatment for psoriasis • Use of most psoriasis treatments within previous 4 weeks • History of depressive disorder or suicidal behavior	PASI 75 responders and sPGA 0/1 responders at week 24	October 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Study to Assess the Long-Term Safety of Brodalumab Compared with Other Therapies in the Treatment of Adults with Moderate-to-Severe Psoriasis/Valeant (NCT03254667)	Prospective observational cohort	1. Brodalumab 2. Non-IL-17-inhibitor biologic medications	N=3500 Inclusion: • ≥18 years • Moderate-to-severe psoriasis • Started on or switched to a systemic treatment within previous 12 months Exclusion: • Participating in clinical trial	Incidence of malignancy through 8 years	November 2031

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
A Study of KHK4827 (Brodalumab) in Subjects with Moderate to Severe Psoriasis in Korea/ Kyowa Hakko Kirin Korea Co., Ltd. (NCT02982005)	Phase III, randomized, parallel assignment, triple-blind trial	1. Brodalumab 2. Placebo	N=60 Inclusion: • ≥20 years • Moderate-to-severe chronic plaque-type psoriasis for at least 6 months • PASI≥12; sPGA≥3; BSA≥10% at baseline Exclusion: • Previous use of IL-17 antagonist • History of suicidal ideation • Severe depression at baseline	PASI 75 responders and sPGA 0/1 responders at week 12	December 2018
Anti-IL-12/23 agent					
Ustekinumab					
No ongoing trials identified					
Anti-IL-23 agents					
Guselkumab					

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
A Study to Compare the Efficacy of Guselkumab to Fumaric Acid Esters for the Treatment of Participants with Moderate to Severe Plaque Psoriasis (POLARIS)/Janssen (NCT02951533)	Phase III, randomized, parallel assignment, open label trial	1. Guselkumab 100 mg 2. Fumaric acid esters	N=119 Inclusion: • ≥18 years • Plaque-type psoriasis for at least 6 months • PASI>10, BSA>10%, DLQI>10 at baseline	PASI 90 responders at week 24	February 14, 2019
An Efficacy and Safety of CNTO 1959 (Guselkumab) in Participants with Moderate to Severe Plaque-type Psoriasis/Janssen (NCT02325219)	Phase III, randomized, parallel assignment, double-blind trial	1. Guselkumab 50 mg 2. Guselkumab 200 mg 3. Placebo	N=226 Inclusion: • ≥20 years • Plaque-type psoriasis for at least 6 months • PASI≥12; IGA≥3; BSA≥10% at baseline • Candidate for phototherapy or systemic treatment	IGA 0/1 responders and PASI 90 responders at week 16	September 21, 2018
Tildrakizumab					
No ongoing trials identified					

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Risankizumab					
A Study to Assess the Efficacy of Risankizumab Compared to FUMADERM® in Subjects with Moderate to Severe Plaque Psoriasis Who Are Naïve to and Candidates for Systemic Therapy/AbbVie (NCT03255382)	Phase III, randomized, parallel assignment, open label trial	1. Risankizumab 2. Fumaric acid ester	N=120 Inclusion: • ≥18 years • Chronic plaque psoriasis for at least 6 months • Stable moderate to severe psoriasis at baseline • Naïve to and candidate for systemic therapy Exclusion: • Previously received systemic therapy	PASI 90 responders at week 24	June 27, 2018
BI 655066 (Risankizumab) Compared to Placebo in Japanese Patients with Moderate to Severe Chronic Plaque Psoriasis/AbbVie (NCT03000075)	Phase II, randomized, parallel assignment, double-blind trial	1. Risankizumab 'high dose' 2. Risankizumab 'low dose' 3. Placebo	N=171 Inclusion: • ≥20 years • Chronic plaque-psoriasis for at least 6 months • Stable moderate to severe psoriasis (PASI≥12; sPGA≥3; BSA≥10%) at baseline Exclusion: • Previous exposure to risankizumab	PASI 90 responders at week 16	June 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Extension Trial Assessing the Safety and Efficacy of BI 655066/ABBV-066/Risankizumab in Patients with Moderate to Severe Chronic Plaque Psoriasis/AbbVie (NCT02203851)	Phase II, single group assignment, open label trial	1. Risankizumab	N=104 • Inclusion: • ≥18 years • Moderate to severe chronic plaque psoriasis • Completed the preceding trial Exclusion: • Experienced SAE during preceding trial	PASI 90 responders at week 48 AEs and SAEs through week 48	August 15, 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Anti-PDE-4 agent					
Apremilast					
A Study of the Real-life Management of Psoriasis Patients Treated with Otezla® (Apremilast) in Belgium (OTELO)/Celgene (NCT03097003)	Prospective observational cohort	1. Apremilast	N=250 Inclusion: • ≥18 years • Moderate to severe chronic plaque psoriasis (PASI>10 BSA>10%) Exclusion: • Received apremilast within last month	Patient Benefit Index for skin diseases responders at month 6	June 30, 2018
Observational Study of Apremilast in Patients with Psoriasis in The Netherlands (APRIL)/Celgene (NCT02652494)	Prospective observational cohort	1. Apremilast	N=200 Inclusion: • ≥18 years • Starting treatment for psoriasis with apremilast Exclusion: • Prior exposure to apremilast • PsA treated by rheumatologist	DLQI responders for up to 12 months	December 31, 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
A Study of Real-World Experience of Psoriasis Patients Treated with Apremilast in Clinical Dermatology Practice (APPRECIATE)/Celgene (NCT02740218)	Retrospective observational cohort	1. Apremilast	N=515 Inclusion: • ≥18 years • Plaque psoriasis • Initiated treatment with apremilast 6 months previously Exclusion: • Participating in clinical trial	Patient Benefit Index score up to 7 months	February 28, 2018
A Study of Otezla® in Patients with Plaque Psoriasis Under Routine Conditions/Celgene (NCT02626793)	Prospective observational cohort	1. Apremilast	N=500 Inclusion: • ≥18 years • Moderate to severe plaque psoriasis • Failed previous systemic treatment	DLQI score at 4 months	December 30, 2017
Post-Marketing Surveillance Study of OTEZLA/Celgene (NCT03284879)	Prospective observational case-only	1. Apremilast	N=1000 Inclusion: • All ages • Psoriasis vulgaris with an inadequate response to topical therapies or psoriasis arthropathica	AEs through 12 months, PGA and DLQI score at 12 months	August 31, 2021
TNF- α agents					
Adalimumab					

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Comparative Clinical Trial of Efficacy and Safety of BCD-057 and Humira® in Patients with Moderate to Severe Plaque Psoriasis (CALYPSO)/Biocad (NCT02762955)	Phase III, randomized, parallel assignment, triple-blind trial	1. BCD-057 (adalimumab biosimilar) 40 mg q2w 2. Adalimumab 40 mg q2w	N=344 Inclusion: • 18-75 years • Moderate to severe plaque psoriasis for at least 6 months • PASI≥12; sPGA≥3; BSA≥10% at baseline • Candidates for phototherapy or systemic treatments Exclusion: • Previous use of TNFα therapy or previous use of 2 or more biologics • Participating in clinical trial within 3 months before trial	PASI 75 responders at 16 weeks	December 2018
Real-World Outcome of Psoriasis Subjects in Korea on Adalimumab (RAPSODI)/AbbVie (NCT03099083)	Prospective observational cohort	1. Adalimumab	N=100 Inclusion: • ≥19 years • Diagnosis of psoriasis by investigator Exclusion: • Participating in clinical trial at enrollment	EQ-5D score at week 24	November 1, 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
MAP Study: Methotrexate and Adalimumab in Psoriasis (MAP)/Jeffery J Crowley (NCT03217734)	Phase II/III randomized, parallel assignment, triple-blind trial	1. Adalimumab 40 mg q2w 2. Adalimumab 40 mg q2w + methotrexate 10 mg weekly	N=56 Inclusion: • ≥18 years • Psoriasis for at least 6 months • Moderate to severe psoriasis (PASI≥12; BSA≥10%) at baseline Exclusion: • Previous exposure to adalimumab or adalimumab biosimilar	PASI score at week 16	October 10, 2018
A Study to Evaluate the Effectiveness and Patient-Reported Outcome of Adalimumab in Patients with Moderate to Severe Plaque Psoriasis in China (ADAPT)/AbbVie (NCT03236870)	Prospective observational cohort	1. Adalimumab	N=310 Inclusion: • ≥18 years • Patients with moderate to severe plaque psoriasis eligible to use adalimumab Exclusion: • Participating in clinical trial at enrollment	PASI 75 responders at week 12	December 1, 2019

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Study of Efficacy and Safety of HLX03 in Subjects with Moderate to Severe Plaque Psoriasis/ Shanghai Henlius Biotech (NCT03316781)	Phase III, randomized, parallel assignment, quadruple-blind trial	1. HLX03 (adalimumab biosimilar) 40 mg q2w 2. Adalimumab 40 mg q2w	N=216 Inclusion: • 18-75 years • Moderate to severe plaque psoriasis for at least 6 months and at baseline (PASI≥12; PGA≥3; BSA≥10%) • Previously failed at least one traditional psoriasis treatment	PASI score at week 16	October 2018
Canadian Humira Post Marketing Observational Epidemiological Study: Assessing Effectiveness in Psoriasis (Complete-PS)/AbbVie (NCT01387815)	Prospective observational cohort	1. Topical agents 2. Traditional systemic agents 3. Adalimumab	N=662 Inclusion: • ≥18 years • Moderate to severe plaque psoriasis determined by physician • Treating physician decided to change or add current treatment for any reason	PGA 0/1 responders at month 6	June 30, 2018

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
A Study to Provide Real-world Evidence on the Treatment Goal Achievement Rate, Adherence to and Utilization Patterns of Adalimumab in Patients with Moderate to Severe Plaque Psoriasis in Greece (CONCORDIA)/AbbVie (NCT02713295)	Prospective observational cohort	1. Adalimumab	N=280 Inclusion: • ≥18 years • Plaque psoriasis for at least 6 months • Moderate to severe psoriasis at time of adalimumab treatment onset (BSA>10% or PASI>10 and DLQI>10) Exclusion: • Initiated adalimumab more than 2 weeks prior to enrollment • Previous exposure to adalimumab unless a period of at least 6 months from the last dose has elapsed	PASI 75 responders or DLQI≤5 responders at week 16	March 15, 2019
Documentation of Humira in Psoriasis Patients in Routine Clinical Practice (LOTOS)/AbbVie (NCT01077232)	Prospective observational case-only	1. Adalimumab	N=3000 Inclusion: • ≥18 years • Moderate to severe plaque psoriasis • Failed other systemic therapy or photochemotherapy	PASI score and PASI 75 responders at 24, 48, and 60 months	October 31, 2020

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Chronic Plaque Psoriasis (Ps) Registry/AbbVie (NCT00799877)	Prospective observational	1. Adalimumab	N=6000 Inclusion: • ≥18 years • Chronic plaque psoriasis • Initiated adalimumab within 4 weeks of enrollment or received continuous adalimumab treatment in the past with documentation of AEs since initiation	AEs, SAEs, and AEs leading to discontinuation every 6 months through 10 years	September 29, 2022
Etanercept					
Safety and Efficacy of Etanercept in Patients with Psoriasis/Chengdu PLA General Hospital (NCT02258282)	Randomized, parallel assignment, single-blind trial	1. Etanercept 2. Placebo	N=80 Inclusion: • 18 to 75 years old • Plaque psoriasis • Unsatisfactory response to traditional DMARDs • Eligible for systemic therapy • PGA≥3; BSA≥3% at baseline	PGA at 24 weeks	December 2022
Infliximab					
No ongoing trials identified					

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Certolizumab pegol					
A Study to Test the Efficacy and Safety of Certolizumab Pegol in Japanese Subjects with Moderate to Severe Chronic Psoriasis/UCB (NCT03051217)	Phase II/III, randomized, parallel assignment, quadruple-blind trial	1. Certolizumab 200 mg q2w 2. Certolizumab 400 mg q2w 3. Placebo	N=149 Inclusion: • ≥20 years • Chronic plaque psoriasis for at least 6 months • PASI≥12, PGA≥3; BSA≥10% at baseline • Also includes patients with generalized pustular or erythrodermic psoriasis	PASI 75 responders at week 16	January 2019
Head-to-head					
A Study to Evaluate the Comparative Efficacy of CNTO 1959 (Guselkumab) and Secukinumab for the Treatment of Moderate to Severe Plaque-type Psoriasis (ECLIPSE)/Janssen (NCT03090100)	Phase III, randomized, parallel assignment, double-blind trial	1. Secukinumab 2. Guselkumab + placebo	N=1048 Inclusion: • ≥18 years • Plaque-type psoriasis for at least 6 months Exclusion: • Previous use of guselkumab or secukinumab	PASI 90 responders at week 48	November 23, 2018
Risankizumab Versus Secukinumab for Subjects with Moderate to Severe Plaque Psoriasis/AbbVie	Phase III, randomized, parallel assignment, single-blind	1. Risankizumab 2. Secukinumab	N=310 Inclusion: • ≥18 years • Chronic plaque psoriasis for at least 6 months • Moderate to severe psoriasis at baseline	PASI 90 responders at week 16 and 52	May 27, 2020

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
(NCT03478787)	(outcomes assessor) trial		• Candidate for systemic therapy Exclusion: • Previous exposure to risankizumab or secukinumab		
A Registry of Patients with Moderate to Severe Plaque Psoriasis (PURE)/Novartis (NCT02786186)	Prospective observational cohort	1. Secukinumab 2. Approved standard of care (other therapies including systemic, phototherapy, or biologic therapy)	N=2500 Inclusion: • ≥18 years • Moderate-to-severe chronic plaque-type psoriasis • Patients initiating a treatment for psoriasis as per regional policy Exclusion: • Participation in clinical trial within 30 days	Incidence of TEAE through month 60	December 30, 2024
The Corrona Psoriasis (PSO) Registry/Corrona, LLC. (NCT02707341)	Prospective observational cohort	1. Systemic psoriasis treatments	N=10000 Inclusion: • ≥18 years • Patients with psoriasis who have started or switched to a systemic psoriasis treatment within prior 12 months	Number of patients with AEs or SAEs through at least 8 years	December 2100
PsoBest - The German Psoriasis Registry/University Medical Center Hamburg-Eppendorf (NCT01848028)	Prospective observational cohort	1. Systemic psoriasis or psoriatic arthritis treatments	N=3500 Inclusion: • ≥18 years • Patients with plaque-type psoriasis or psoriatic arthritis initiating a systemic treatment for the first time Exclusion: • Participating in clinical trial at enrollment	PASI score every 6 months for 10 years	July 2026

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Psoriasis Longitudinal Assessment and Registry (PSOLAR)/Janssen (NCT00508547)	Prospective observational cohort	1. Infliximab 2. Ustekinumab And other systemic treatments	N=12052 Inclusion: • ≥18 years • Diagnosis of psoriasis • Candidates for or currently receiving systemic treatments for psoriasis Exclusion: • Participating in clinical trial at enrollment	Number of patients with AEs or SAEs through at least 8 years	May 31, 2021
Swiss Dermatology Network of Targeted Therapies (SDNTT)/SDNTT (NCT01706692)	Prospective observational cohort	1. Adalimumab 2. Etanercept 3. Infliximab 4. Ustekinumab And other systemic treatments	N=500 Inclusion: • ≥18 years • Plaque-type psoriasis or psoriatic arthritis confirmed by dermatologist • Receiving specific systemic drug for the first time Exclusion: • Participating in a clinical trial at day of registration	PASI score every 6 months for 5 years	June 2021
Spanish Registry of Systemic Treatments in Psoriasis (Biobadaderm)/Spanish Academy of Dermatology (NCT02075697)	Prospective observational cohort	1. Systemic treatments for psoriasis	N=1887 Inclusion Criteria: • Any age • Psoriasis patients who begin any biological or nonbiologic systemic treatment for the first time	SAEs through 5 years	October 2020

Title/ Trial Sponsor	Study Design	Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Ustekinumab Safety and Surveillance Program Using the Ingenix NHI Database/Janssen (NCT01081730)	Prospective observational cohort	1. Ustekinumab And other biological and nonbiologic psoriasis treatments	N=2000 Inclusion: • All ages • Complete medical coverage and pharmacy benefits • Enrollment for at least 6 months	Serious infections and other AEs through at least 8 years	April 30, 2018

AE: adverse event; BSA: body surface area; DLQI: Dermatology Life Quality Index; EQ-5D: EuroQol Five Dimensions; IGA: Investigator's Global Assessment; PASI: Psoriasis Area Severity Index; PsA: psoriatic arthritis; q2w: every two weeks; SAE: serious adverse event; sPGA: static Physician's Global Assessment

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix E. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. Two investigators screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Two investigators reviewed full papers and provided justification for exclusion of each excluded study.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2) [224] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention-to treat-analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Modified intention-to-treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention-to treat-analysis is lacking.*

Table E1. PASI Outcomes by Trials included in the NMA

Trial	Treatment	Week	N	PASI 50, %	p-value	PASI 75, %	p-value	PASI 90, %	p-value
CHAMPION[95]	Adalimumab	16	108	88	<0.001	79.6	<0.001	51.9	<0.001
	placebo	16	53	30.2		18.9		11.3	
REVEAL[94]	Adalimumab	16	814	NR	NR	71	<0.001	45	<0.001
	placebo	16	398	NR		7		2	
Asahina 2010[96]	Adalimumab	16	43	81.4	<0.001	62.8	<0.001	39.5	<0.001
	placebo	16	46	19.6		4.3		0	
Cai 2017[97]	Adalimumab	12	337	NR	NR	77.8	<0.001	55.6	<0.001
	placebo	12	87	NR		11.5		3.4	
CONSORT[98]	Etanercept	12	203	72	<0.0001	46	<0.0001	19	<0.0001
	placebo	12	204	9		3		1	
Leonardi 2003[99]	Etanercept	12	164	74	<0.001	49	<0.001	22	<0.001
	placebo	12	166	14		4		1	
Tyring 2006[100]	Etanercept	12	311	74	<0.0001	47	<0.0001	21	<0.0001
	placebo	12	306	14		5		1	
Strober 2011[101]	Etanercept	12	139	NR	NR	39.6	NR	13.7	NR
	placebo	12	72	NR		6.9		4.2	
Gottlieb 2011[102]	Etanercept	12	141	NR	NR	56	NR	23	NR
	placebo	12	68	NR		7.4		1	
Bagel 2012[103]	Etanercept	12	62	85	<0.0001	59.7	<0.0001	25	<0.0001
	placebo	12	62	7		4.8		2	
Bachelez 2015[104]	Etanercept	12	335	80.3	<0.0001	58.8	<0.0001	32.2	<0.0001
	placebo	12	107	20.6		5.6		0.9	
PIECE[122]	Etanercept	12	23	60.9	0	21.7	0	0	0.05
	Infliximab	12	25	96		76		20	
EXPRESS 1[105]	Infliximab	10	301	91	<0.0001	80.4	<0.0001	57.1	<0.0001
	placebo	10	77	8		2.6		1.3	
EXPRESS 2[106]	Infliximab	10	314	NR	NR	75.5	<0.001	45.2	<0.001
	placebo	10	208	NR		1.9		0.5	
Yang 2012[107]	Infliximab	10	84	94	<0.001	81	<0.001	57.1	<0.001
	placebo	10	45	13.3		2.2		0	
Torii 2010[108]	Infliximab	10	35	82.9	<0.001	68.6	<0.001	54.6	<0.001
	placebo	10	19	10.5		0		0	
ACCEPT[123]	Etanercept	12	347	NR	NR	56.8	≤0.01	23.1	<0.001
	Ustekinumab	12	556	NR		71.4		41.5	
PHOENIX 1[110]	Ustekinumab	12	511	84.7	<0.0001	66.7	<0.0001	39.1	<0.0001
	placebo	12	255	10.2		3.1		2	
PHOENIX 2[109]	Ustekinumab	12	820	86.5	<0.0001	71.2	<0.0001	46.6	<0.0001
	placebo	12	410	10		3.7		0.7	
Igarashi 2012[111]	Ustekinumab	12	126	83.3	<0.0001	63.5	<0.0001	38.1	≤0.001
	placebo	12	31	12.9		6.5		3.2	
PEARL[112]	Ustekinumab	12	61	83.6	<0.001	67.2	<0.001	49.2	<0.001
	placebo	12	60	13.3		5		1.7	

Trial	Treatment	Week	N	PASI 50, %	p-value	PASI 75, %	p-value	PASI 90, %	p-value
LOTUS[93]	Ustekinumab	12	160	91.3	<0.001	82.5	<0.001	66.9	<0.001
	placebo	12	162	19.8		11.1		3.1	
FEATURE[113]	Secukinumab	12	59	NR	NR	75.9	<0.0001	60.3	<0.0001
	placebo	12	59	NR		0		0	
CLEAR[124]	Secukinumab	16	334	NR	NR	93.1	0.0001	79	<0.0001
	Ustekinumab	16	335	NR		82.7		57.6	
JUNCTURE[114]	Secukinumab	12	60	NR	<0.0001	86.7	<0.0001	55	<0.0001
	placebo	12	61	NR		3.3		0	
ERASURE[173]	Secukinumab	12	245	NR	NR	81.6	<0.001	59.2	<0.001
	placebo	12	246	NR		4.5		1.2	
FIXTURE[173]	Secukinumab	12	323	NR	NR	77.1	<0.001 vs. ETN and PBO	54.2	<0.001 vs. ETN and PBO
	Etanercept	12	323	NR		44		20.7	
	placebo	12	324	NR		4.9		1.5	
UNCOVER 1[182]	Ixekizumab	12	433	NR	NR	89.1	<0.001	70.9	<0.001
	placebo	12	431	NR		3.9		0.5	
UNCOVER 2[117]	Ixekizumab	12	351	NR	NR	89.7	<0.0001 vs. ETN and PBO	70.7	<0.0001 vs. ETN and PBO
	Etanercept	12	358	NR		41.6		18.7	
	placebo	12	168	NR		2.4		0.6	
UNCOVER 3[117]	Ixekizumab	12	385	NR	NR	87.3	<0.0001 vs. ETN and PBO	68.1	<0.0001 vs. ETN and PBO
	Etanercept	12	382	NR		53.4		25.7	
	placebo	12	193	NR		7.3		3.1	
IXORA-S[125]	Ixekizumab	12	136	NR	NR	88.2	<0.001	72.8	<0.001
	Ustekinumab	12	166	NR		68.7		42.2	
AMAGINE 1[119]	Brodalumab	12	222	NR	NR	83.3	<0.0001	70.3	<0.0001
	placebo	12	220	NR		2.7		0.9	
AMAGINE 2[39]	Brodalumab	12	612	NR	NR	86	<0.001 vs. PBO; NS vs. UST	70	NR
	Ustekinumab	12	300	NR		70		47	
	placebo	12	309	NR		8		3	
AMAGINE 3[39]	Brodalumab	12	624	NR	NR	85	<0.001 vs. PBO; 0.007 vs. UST	69	NR
	Ustekinumab	12	313	NR		69		48	
	placebo	12	315	NR		6		2	
ESTEEM 1[120]	Apremilast	16	562	58.7	<0.0001	33.1	<0.0001	9.8	NR
	placebo	16	282	17		5.3		0.4	
ESTEEM 2[211]	Apremilast	16	274	55.5	<0.001	28.8	<0.001	8.8	0.004
	placebo	16	137	19.7		5.8		1.5	
LIBERATE[121]	Apremilast	16	83	62.7	0.0002	39.8	<0.0001	14.5	NS
	placebo	16	84	33.3		11.9		3.6	
VOYAGE 1[31]	Guselkumab	16	329	NR	NR	91.2	<0.001 vs. ADA and PBO	73.3	<0.001 vs. ADA and PBO
	Adalimumab	16	334	NR		73.1		49.7	
	placebo	16	174	NR		5.7		2.9	
VOYAGE 2[32]	Guselkumab	16	496	NR	NR	86.3	<0.001 vs. ADA and PBO	70	<0.001 vs. ADA and PBO
	Adalimumab	16	248	NR		68.5		46.8	
	placebo	16	248	NR		8.1		2.4	
reSURFACE 1[33]	Tildrakizumab	12	308	NR	NR	64	<0.0001	35	<0.0001

Trial	Treatment	Week	N	PASI 50, %	p-value	PASI 75, %	p-value	PASI 90, %	p-value
	placebo	12	154	NR		6		3	
reSURFACE 2[33]	Tildrakizumab	12	314	NR	NR	61	<0.0001 vs. PBO, 0.001 vs. ETN	39	<0.0001 vs. ETN and PBO
	Etanercept	12	313	NR		48		21	
	placebo	12	156	NR		6		1	
CIMPASI 1*[29]	Certolizumab 200 mg	16	95	NR	NR	66.5	<0.0001 vs. PBO for both doses	35.8	<0.0001 vs. PBO for both doses
	Certolizumab 400 mg	16	88	NR		75.8		43.6	
	placebo	16	51	NR		6.5		0.4	
CIMPASI 2*[29]	Certolizumab 200 mg	16	91	NR	NR	81.4	<0.0001 vs. PBO for both doses	52.6	<0.0001 vs. PBO for both doses
	Certolizumab 400 mg	16	87	NR		82.6		55.4	
	placebo	16	49	NR		11.6		4.5	
CIMPACT*[30]	Certolizumab 200 mg	12	165	[redacted]		61.3	<0.0001 vs. PBO, NS vs. ETN for 200 mg; <0.0001 vs. PBO, 0.02 vs. ETN for 400 mg	31.2	<0.0001 vs. PBO, NR vs. ETN for both doses
	Certolizumab 400 mg	12	167	[redacted]		66.7		34.0	
	Etanercept	12	170	[redacted]		53.3		27.1	
	placebo	12	57	[redacted]		5.0		0.2	
IMMhance[34]	Risankizumab	16	407	NR	NR	88.7	<0.001	73.2	<0.001
	placebo	16	100	NR		8		2	
UltIMMa 1[38]	Risankizumab	16	304	NR	NR	89	<0.0001 vs. PBO; 0.0034 vs. UST	75.3	<0.001 vs. UST and PBO
	Ustekinumab	16	100	NR		76		42	
	placebo	16	102	NR		9		4.9	
UltIMMa 2[38]	Risankizumab	16	294	NR	NR	91	<0.0001 vs. UST and PBO	74.8	<0.001 vs. UST and PBO
	Ustekinumab	16	99	NR		70		47.5	
	placebo	16	98	NR		6		2	
CLARITY[126]	Secukinumab	12	550	NR	NR	88.0	<0.0001	66.5	<0.0001
	Ustekinumab	12	552	NR		74.2		47.9	

NR: not reported; NS: not significant; *Certolizumab 200 mg and 400 mg arms pooled in NMA

Additional Comparative Clinical Effectiveness Results

Table E2. Placebo-Controlled Trials: Ranges of PASI 50/75/90/100 Response Rates across Trials*

Treatment	PASI 50		PASI 75		PASI 90		PASI 100	
	Tx	Placebo	Tx	Placebo	Tx	Placebo	Tx	Placebo
Adalimumab	88	30	71-80	7-19	45-52	2-11	17-20	1-2
Etanercept	71-85	7-21	40-59	3-7	19-32	1-2	6-7	0
Infliximab	91	8	76-80	2-3	45-57	1	NR	NR
Certolizumab¥	NR	NR	67-81	4-12	36-53	0-5	NR	NR
Ustekinumab 45 mg	84	10	67	3-4	42	1-2	11-18	0
Ustekinumab 90 mg	86-89	10	66-76	3-4	37-51	1-2	13-18	0
Secukinumab	NR	NR	76-87	0-5	54-60	0-2	24-43	0-1
Ixekizumab	NR	NR	87-90	2-7	68-71	1-3	35-41	0-1
Brodalumab	NR	NR	83-86	3-8	69-70	1-3	37-44	0-2
Apremilast	56-63	17-33	29-40	5-12	9-15	0-4	NR	NR
Guselkumab¥	NR	NR	86-91	6-8	70-73	2-3	34-37	1
Tildrakizumab¥	NR	NR	62-66	6	35-37	1-3	12-14	0-1
Risankizumab¥	NR	NR	89-91	6-9	73-75	2-5	47	1

*Excludes trials conducted in exclusively Asian population; ¥New drugs

Table E3. Comparative Trials: PASI Responses

Trial	Treatment	PASI 75	p-value	PASI 90	p-value	PASI 100	p-value
VOYAGE 1 & 2¥	Adalimumab	69-73	<0.001	47-50	<0.001	17-21	<0.001
	Guselkumab	86-91		70-73		34-37	
PIECE¥	Etanercept	22	0.0	0	0.05	0	NS
	Infliximab	76		20		4	
CIMPACT*¥	Etanercept	61	NS	27.1	N/A	NR	NR
	Certolizumab Pegol	53		31.2		NR	
ACCEPT	Etanercept	57	≤0.01	23	<0.001	NR	NR

	Ustekinumab 45 mg	68		36		NR	
	Ustekinumab 90 mg	74		45		NR	
FIXTURE	Etanercept	44	<0.001	21	<0.001	4	<0.001
	Secukinumab 300 mg	77		54		24	
UNCOVER 2&3	Etanercept	42-53	<0.0001	19-26	<0.0001	5-7	<0.0001
	Ixekizumab	87-90		68-70		38-41	
RESURFACE 2¥	Etanercept	48	<0.001	21	<0.001	5	<0.001
	Tildrakizumab	61		39		12	
CLEAR	Ustekinumab WBD	79	0.0001	53	<0.0001	26	<0.0001
	Secukinumab 300 mg	91		73		39	
AMAGINE 2†&3	Ustekinumab WBD	69-70	0.007	47-48	<0.001	19-22	<0.001
	Brodalumab 210 mg	85-86		69-70		37-44	
IXORA-S	Ustekinumab	69	<0.001	42	<0.001	15	0.009
	Ixekizumab	91		75		37	
ULTIMMA 1* & 2¥	Ustekinumab	70-76	<0.005	42-48	<0.001	12-24	<0.001
	Risankizumab	89-91		75		36-51	

; †P-value NS for PASI 75 in in AMAGINE 2; ¥New trials

Table E4. DLQI Outcomes Across Direct Comparative Trials

Trial	Drug	Mean change	p-value	DLQI 0/1 (%)	p-value
VOYAGE 1	Adalimumab	-9.3	P<0.001	39	P<0.01
	Guselkumab	-11.2		56	
VOYAGE 2	Adalimumab	-9.7		39	P<0.01
	Guselkumab	-11.3	P<0.001	52	
CLEAR	ustekinumab	NR	NR	56.5	p=0.0109
	secukinumab	NR		66.2	
FIXTURE	etanercept	-7.9	p<0.001	34.5	p<0.001
	secukinumab	-10.4		56.7	
UNCOVER 2	etanercept	-7.7	p<0.0001	33.8	p<0.0001
	ixekizumab	-10.4		64.1	
UNCOVER 3	etanercept	-8.0	p<0.0001	43.7	p<0.0001
	ixekizumab	-10.2		64.7	
RESURFACE 2	Etanercept	NR	NR	36	NS
	Tildrakizumab	NR		40	
IXORA-S	ixekizumab	NR	NR	61	p<0.001
	ustekinumab	NR		45	
ULTIMMA 1	Ustekinumab	NR	NR	43	P<0.001
	Risankizumab	NR		66	
ULTIMMA 2	Ustekinumab	NR	NR	43	P<0.001
	Risankizumab	NR		66	

Table E5. Adverse Events During the Placebo-Controlled Period

%	ADA	ETN	IFX	UST	SEC	IXE	BROD	GUS	TIL	RIS	CZP	APR	PBO
Any AE	65	57	71	53	58	58	58	49	46	47	53	69	51
Tx-related death	0	0	0	0.1	0	0	0.1	NR	0.1	NR	0	0.1	0
D/C due to AEs	2	2	7	1	1	2	1	1.3	0.5	0.5	1.1	5	2
Serious AEs	2	2	3	1	2	2	1	1.9	1.5	2	1.4	2	2
Serious Infections	1	0.5	6	0.6	NR	0.4	0.5	0.1	0.5	0.4	0	NR	0.3
≥Grade 3 AEs	2	2	NR	NR	NR	NR	4	NR	NR	NR	NR	4	3
Common AEs, %													
Any Infections	32	27	36	36	29	27	NR	24	NR	22	29	NR	25
Nasopharyngitis	8	8	NR	12	11	10	9	8	10	NR	12	7	8
Upper respiratory tract infection	7	6	14	5	3	4	6	4.5	1.5	4.7	4.9	8	5
Headache	6	7	13	7	6	4	4	5	NR	NR	NR	6	4
Nausea	4	2	4	NR	5	NR	NR	NR	NR	NR	NR	17	4
Injection site reactions	19	14	NA	4	NR	10	1	NR	NR	NR	NR	NA	2
Infusion Reaction	NA	NA	10	NA	NA	NA	NA	NA	NA	NA	NA	NA	7
AEs of Interest													
Malignancy excluding NMSC	0.2	0.5	1	0.2	NR	0.1	NR	0	NR	0.5	0	NR	0.2
NMSC	0.5	0.3	NR	0.4	NR	0.1	NR	0.1	0.1	0.2	0	NR	0.2
MACE	NR	0.2	NR	0.2	NR	0	0	0.1	0.2	0	NR	NR	0

Subgroup Analyses

Patients with Psoriatic Arthritis

We identified no new secondary analysis evaluating outcomes in patients with psoriatic arthritis. In the previous report, we identified and discussed in details five secondary analyses evaluating outcomes for patients with psoriatic arthritis, four of which were from the grey literature.[51,175,176,192,202,225]

All agents (secukinumab, ixekizumab, ustekinumab, and brodalumab) were statistically significantly better relative to placebo (or active comparator) on the PASI 75 among patients with psoriatic arthritis, and the differences were similar to those observed in the overall population (Table E6). See the 2016 report for additional details.[25]

Table E6. Proportion of patients with and without psoriatic arthritis reaching PASI 75

Drug (Trial)	# of PsA patients	PsA Achieving PASI 75 (%)		Overall Population	
		Intervention	Placebo	Intervention	Placebo
Secukinumab (FIXTURE)	175	72	2	82	5
Etanercept (FIXTURE)	Same trial	39	4	44	Same trial
Secukinumab (ERASURE)	171	70	4	82	5
Ustekinumab 45/90mg (PHOENIX 1 and 2)	563	63/62	4	67/66	3
Ixekizumab (all UNCOVER trials)	749	90	3	87-90	4
Brodalumab (Phase IIb)	198	92	0	82	0

Patients with Previous Biologic Therapy Exposure

In total, we identified ten studies that evaluated outcomes in patients who were and were not previously exposed to biologic therapy.[60,118,132,161,176,185,187,196,206,211] Subgroup analyses from four RCTs were primarily reported in the grey literature, though we found three peer-reviewed publications: a key clinical trial of apremilast (ESTEEM 2), a Phase II study on brodalumab, and a pooled analysis of UNCOVER 2 & 3. Across placebo-controlled studies, a statistically significantly greater proportion of patients achieved a PASI 75 response with the intervention for

patients with and without prior biologic therapy (except for tildrakizumab where p-value was not reported). Rates between groups were numerically similar, but not compared statistically, and other outcomes (PASI 50, 90, and sPGA score of 0/1) followed the same trend where reported. In one head-to-head comparison between ixekizumab and etanercept, ixekizumab remained superior to etanercept in both groups of patients with (90% vs. 35%, p<0.001) and without (88% vs. 51%; p<0.001) prior biologic use.

Table E7. Proportion of Patients Reaching PASI 75 in the Bio-Exposed and Bio-Naïve Groups

Drug	Exposed (%)	Naïve (%)
Apremilast	22.8	31.9
Placebo	4.5	6.5
p-value[211]	=0.0069	<0.001
Brodalumab	88	79
Placebo	0	0
p-value[196]	<0.001	<0.001
Ixekizumab	89.5	88.4
Placebo	2.7	5.2
p-value[191]	<0.001	<0.001
Secukinumab	75.7	84.0
Placebo	4.1	4.6
p-value[176]	<0.0001	<0.0001
Tildrakizumab	55	66.4
Placebo	0	7.5
p-value	NR	NR

In addition to the above-described analyses from RCTs, we identified and described three observational studies in the previous report. All were database studies, of which two were based on one small database (DERMBIO registry), while one was based on a large database (PSOLAR registry). Similar to the RCTs, the studies did not find a statistical significant difference in the in PASI 75 response for patients taking one, two, or three prior TNF-α.[60] However, one study found that all patients who were previously exposed to biologic therapy had a higher probability of treatment discontinuation (primarily due to loss of efficacy) across all agents (OR: 1.24, 95% CI 1.05-1.46, p=0.011).[206] See the 2016 report for additional details. [25]

Asian Studies

We identified seven Phase III and two Phase II placebo-controlled RCTs that were conducted in Asia, plus a sub analysis of the Japanese portion of the ERASURE study. No head-to-head Asian studies were available.[93,96,107,111,112,174] Two trials of adalimumab included Chinese patients[97] and Japanese patients[96], three distinct trials of ustekinumab included patients in Japan,[111] China (LOTUS),[93] and Taiwan and Korea (PEARL) patients,[112] the subgroup analysis for the secukinumab trial[174] included Japanese patients, the trials for infliximab

included Chinese[107] and Japanese patients,[108] while the phase II trials of brodalumab[198] and apremilast[216] included Japanese patients. We did not identify any trials conducted in Asia for etanercept, certolizumab, ixekizumab, guselkumab, tildrakizumab or risankizumab.

As in multinational studies, all studies demonstrated statistically significant differences on all PASI measures (where reported) for each therapy compared to placebo; these results are presented in the table below. The proportion of patients achieving a PASI 75 response across RCTs of adalimumab (71-80%), infliximab (76-80%), secukinumab (76-91%), ustekinumab 45mg (67-68%) and 90mg (66-76%), brodalumab (83-86%), and apremilast (29-40%) did not demonstrate any identifiable differences from the results reported in the Asian studies. Other commonly reported outcomes included improvements on the DLQI and the proportion of patients achieving a PGA or IGA score of 0/1, which were consistent with PASI score improvement. See the evidence table in Appendix B for details of the other outcomes reported in these studies.

Table E8. Proportion of Patients Achieving PASI Scores Across Asian Studies

Study	Study group	PASI 50	p-value	PASI 75	p-value	PASI 90	p-value	PASI 100	p-value
Asahina, 2010	Adalimumab	81	<0.001	63	<0.001	40	<0.001	NR	NR
	Placebo	20		4		0		NR	
Cai, 2017	Adalimumab	NR	NR	78	0.002	56	0.002	13	0.002
	Placebo	NR		12		3		1.1	
Torii, 2010	Infliximab	83	<0.001	69	<0.001	55	<0.001	NR	NR
	Placebo	11		0		9		NR	
Yang, 2012	Infliximab	94	<0.001	81	<0.001	57	<0.001	NR	NR
	Placebo	13		2		0		NR	
Igarashi, 2012	Ustekinumab 45mg	83	<0.001	59	<0.001	33	<0.001	NR	NR
	Ustekinumab 90mg	84		68		44		NR	
	Placebo	13		7		3		NR	
Tsai, 2011	Ustekinumab 45mg	84	<0.001	67	<0.001	49	<0.001	8	=0.024
	Placebo	13		5		2		0	
Zhu, 2013	Ustekinumab 45mg	91	<0.001	83	<0.001	67	<0.001	24	<0.001
	Placebo	20		11		3		1	
Ohtsuki, 2014	Secukinumab	NR	NR	83	<0.0001	62	<0.0001	28	<0.01
	Placebo	NR		7		0		0	
Nakagawa, 2016	Brodalumab	NR	NR	95	<0.001	92	<0.001	60	<0.001
	Placebo	NR		8		3		0	

Ohtsuki, 2017	Apremilast	48	<0.003	28	<0.003	14	<0.05	NR	NR
	Placebo	21		7		1		NR	

*NA=not available; NR=not reported

Appendix F. Network Meta-Analysis Supplemental Information

Network Meta-Analysis Methods

Network meta-analyses were conducted to determine comparative effectiveness using measures of treatment response based on the Psoriasis Area and Severity Index (PASI). For the NMA, we included Phase III RCTs that reported the proportion of patients with an improved PASI score at the end of induction period (10-16 weeks). RCTs were included if they reported one or more commonly used PASI benchmark scores (the proportion of patients with >50%, >75%, or >90% improvement on the PASI scale).

PASI outcomes are ordered categorical data with up to four distinct groups: i.e. PASI<50, PASI 50, PASI 75, and PASI 90, representing a reduction in the Psoriasis Area and Severity Index (PASI) of less than 50%, at least 50%, at least 75%, and at least 90% respectively. Using the PASI outcomes reported in studies, we created mutually exclusive groups by re-classifying the data as <50, 50-74, 75-89, 90-100. Therefore, a multinomial likelihood model with a probit link was used. Model functions have been previously published.[90] This model allows for the inclusion of data from trials that use different thresholds or a different number of thresholds. Our model adjusted for the placebo response rate in each study. Model assumptions are provided below.

Assumption (s):

1) PASI was a continuous variable which has been categorized by specifying cut-points (e.g., 50, 75, 90)
2) The distance (on a standard normal scale) between consecutive categories was the same for every trial and every treatment
3) Treatment effect was the same regardless of the PASI cut-off (i.e., 50 vs. 75 vs. 90).
4) Study-specific treatment effects came from a common distribution, and the amount of between-study variance (i.e., heterogeneity) was assumed to be constant across all treatment comparisons
5) The model includes a covariate for placebo response, which was assumed to be common across all treatments.

Two subgroup analyses were also conducted by: 1) excluding all Asian studies; and 2) excluding studies that had previous biologic exposure in less than 5% of their patient population. In addition, we conducted two sensitivity

analyses suggested as part of the public comments to our draft report. These includes: 1) a model with no placebo adjustment; and 2) a placebo adjusted model using multiple covariates (three betas) across PASI levels.

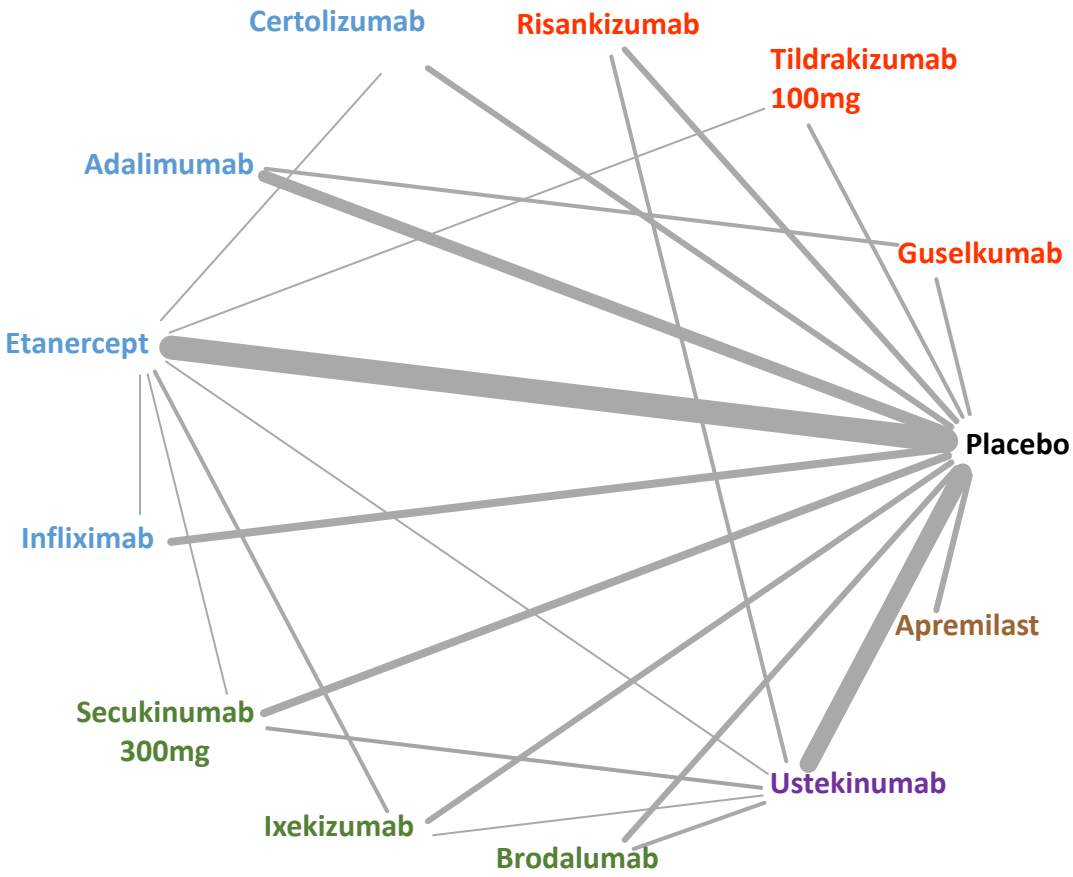
All statistical analyses were conducted within a Bayesian framework with JAGS software (version 4.3.0) via R using the R2jags package.[91] For all analyses we used noninformative prior distributions for all model parameters. We initially discarded the first 50,000 iterations as "burn-in" and base inferences on an additional 50,000 iterations using three chains. Convergence of chains was assessed visually using trace plots.

Relative risks and proportions of patients having a given PASI response state compared to placebo were generated. We based our analysis on existing code.[90,226]

Supplemental NMA Results

The network diagram (Figure E1), additional results on the base case NMA including league tables for PASI 50 and 90 and results of subgroup analyses are presented below. To interpret the network figures, note that the lines indicate the presence of a trial directly assessing the connecting interventions, with the thickness of the line corresponding to the number of trials. The location of treatments and the distances between them does not have any meaning.

Figure F1. Network of Studies Included in the NMA of PASI Outcome



Legend: The TNF inhibitors are depicted in blue, the Interleukin-17 inhibitors are depicted in green, the interleukin 12/23 agent is depicted in purple; the phosphodiesterase inhibitor (anti- PDE4) is depicted in brown; and the new class (interleukin-23 inhibitors) are depicted in red.

Table F1. Base Case NMA: League Table of PASI 50 Response

Risankizumab												
1 (0.98, 1.02)	**Ixekizumab**											
1.01 (0.99, 1.03)	1 (0.99, 1.03)	**Guselkumab**										
1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	1.01 (0.98, 1.03)	**Brodalumab**									
1.03 (1.01, 1.06)	**1.03 (1.01, 1.05)**	1.02 (1, 1.05)	1.02 (1, 1.04)	**Secukinumab**								
1.05 (1.02, 1.09)	**1.05 (1.02, 1.09)**	**1.04 (1.01, 1.08)**	**1.03 (1.01, 1.07)**	1.02 (0.99, 1.05)	**Infliximab**							
1.1 (1.07, 1.16)	**1.1 (1.06, 1.16)**	**1.1 (1.06, 1.15)**	**1.09 (1.05, 1.15)**	**1.07 (1.03, 1.13)**	**1.05 (1.01, 1.11)**	**Adalimumab**						
1.11 (1.07, 1.16)	**1.11 (1.07, 1.15)**	**1.1 (1.06, 1.15)**	**1.09 (1.06, 1.14)**	**1.08 (1.05, 1.12)**	**1.06 (1.02, 1.1)**	1 (0.96, 1.04)	**Ustekinumab†**					
1.12 (1.07, 1.2)	**1.12 (1.07, 1.2)**	**1.12 (1.07, 1.19)**	**1.11 (1.06, 1.18)**	**1.09 (1.05, 1.16)**	**1.07 (1.02, 1.14)**	1.02 (0.97, 1.08)	1.01 (0.97, 1.07)	**Certolizumab‡**				
1.18 (1.1, 1.28)	**1.18 (1.1, 1.28)**	**1.17 (1.1, 1.28)**	**1.16 (1.09, 1.27)**	**1.14 (1.08, 1.25)**	**1.12 (1.06, 1.22)**	1.06 (1, 1.16)	1.06 (1, 1.14)	1.05 (0.98, 1.14)	**Tildrakizumab**			
1.32 (1.23, 1.43)	**1.31 (1.23, 1.43)**	**1.31 (1.22, 1.42)**	**1.3 (1.22, 1.41)**	**1.28 (1.2, 1.38)**	**1.25 (1.18, 1.34)**	**1.19 (1.12, 1.27)**	**1.19 (1.13, 1.25)**	**1.17 (1.1, 1.25)**	**1.11 (1.04, 1.2)**	**Etanercept**		
1.61 (1.42, 1.9)	**1.61 (1.41, 1.9)**	**1.6 (1.41, 1.87)**	**1.6 (1.4, 1.87)**	**1.57 (1.38, 1.83)**	**1.54 (1.36, 1.8)**	**1.46 (1.3, 1.67)**	**1.46 (1.29, 1.67)**	**1.43 (1.27, 1.66)**	**1.37 (1.21, 1.58)**	**1.23 (1.1, 1.39)**	**Apremilast**	
6.22 (4.84, 8.14)	**6.21 (4.84, 8.18)**	**6.18 (4.82, 8.08)**	**6.15 (4.79, 8.05)**	**6.05 (4.74, 7.87)**	**5.94 (4.7, 7.65)**	**5.61 (4.49, 7.17)**	**5.61 (4.47, 7.13)**	**5.54 (4.42, 7.03)**	**5.27 (4.25, 6.66)**	**4.72 (3.92, 5.77)**	**3.83 (3.2, 4.67)**	**PBO**

Legend: The interventions are arranged from most effective (top left) to least effective (bottom right). Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

†dosing by weight; ‡200 mg and 400 mg combined; PBO: placebo

Table F2. Base Case NMA: League Table of PASI 90 Response

Risankizumab												
1.01 (0.91, 1.11)	**Ixekizumab**											
1.03 (0.92, 1.16)	1.03 (0.92, 1.15)	**Guselkumab**										
1.07 (0.96, 1.19)	1.06 (0.96, 1.17)	1.03 (0.92, 1.16)	**Brodalumab**									
1.16 (1.04, 1.3)	**1.15 (1.04, 1.28)**	1.12 (0.99, 1.27)	1.09 (0.98, 1.21)	**Secukinumab**								
1.25 (1.09, 1.47)	**1.24 (1.09, 1.44)**	**1.21 (1.05, 1.42)**	**1.17 (1.03, 1.36)**	1.08 (0.95, 1.24)	**Infliximab**							
1.54 (1.36, 1.8)	**1.53 (1.34, 1.8)**	**1.49 (1.32, 1.74)**	**1.45 (1.26, 1.7)**	**1.34 (1.16, 1.56)**	**1.23 (1.04, 1.46)**	**Adalimumab**						
1.56 (1.39, 1.78)	**1.55 (1.4, 1.75)**	**1.51 (1.33, 1.73)**	**1.46 (1.31, 1.64)**	**1.35 (1.21, 1.51)**	**1.24 (1.09, 1.42)**	1.01 (0.88, 1.15)	**Ustekinumab†**					
1.63 (1.39, 1.99)	**1.62 (1.39, 1.97)**	**1.58 (1.34, 1.92)**	**1.53 (1.31, 1.85)**	**1.41 (1.2, 1.69)**	**1.3 (1.09, 1.59)**	1.06 (0.89, 1.27)	1.05 (0.9, 1.25)	**Certolizumab‡**				
1.91 (1.55, 2.42)	**1.89 (1.54, 2.41)**	**1.84 (1.5, 2.36)**	**1.78 (1.46, 2.25)**	**1.64 (1.34, 2.08)**	**1.52 (1.23, 1.92)**	1.23 (1, 1.56)	1.22 (1, 1.51)	1.17 (0.92, 1.48)	**Tildrakizumab**			
2.62 (2.19, 3.16)	**2.6 (2.2, 3.12)**	**2.54 (2.11, 3.08)**	**2.46 (2.09, 2.94)**	**2.26 (1.94, 2.68)**	**2.09 (1.78, 2.47)**	**1.69 (1.44, 2)**	**1.68 (1.48, 1.91)**	**1.6 (1.34, 1.91)**	**1.37 (1.11, 1.68)**	**Etanercept**		
4.36 (3.24, 6.07)	**4.32 (3.18, 6.05)**	**4.21 (3.13, 5.78)**	**4.08 (3.01, 5.65)**	**3.76 (2.8, 5.19)**	**3.46 (2.57, 4.84)**	**2.82 (2.14, 3.76)**	**2.79 (2.12, 3.75)**	**2.66 (1.98, 3.66)**	**2.28 (1.66, 3.17)**	**1.66 (1.27, 2.2)**	**Apremilast**	
55.87 (37.9, 83.87)	**55.62 (37.95, 82.83)**	**54.01 (36.8, 80.71)**	**52.5 (35.51, 77.94)**	**48.37 (33.56, 70.4)**	**44.59 (31.37, 64.62)**	**36.1 (26.04, 50.76)**	**35.81 (26.01, 49.7)**	**34.28 (24.14, 48.26)**	**29.32 (21.01, 41.4)**	**21.34 (16.54, 28.02)**	**12.79 (9.32, 17.63)**	**PBO**

Legend: The interventions are arranged from most effective (top left) to least effective (bottom right). Each box represents the estimated risk ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

†dosing by weight; ‡200 mg and 400 mg combined; PBO: placebo; Bolded results are statistically significant

Table F3. Base Case NMA Proportions of Patients Having a Given PASI Response State at the End of Induction Period

Treatments	<50%	50%-74%	75%-89%	≥90%
Risankizumab¥	3.3%	7.4%	15.8%	73.4%
Ixekizumab	3.4%	7.6%	16.1%	72.9%
Guselkumab¥	3.9%	8.3%	16.9%	71.0%
Brodalumab	4.4%	9.0%	17.7%	69.0%
Secukinumab	6.1%	10.9%	19.7%	63.3%
Infliximab	7.8%	12.7%	21.2%	58.4%
Adalimumab	12.6%	16.5%	23.5%	47.3%
Ustekinumab (45/90)	12.9%	16.7%	23.5%	46.9%
Certolizumab (200/400)¥	14.0%	17.4%	23.7%	44.7%
Tildrakizumab¥	18.0%	19.4%	24.1%	38.4%
Etanercept	26.6%	22.2%	23.3%	27.9%
Apremilast	40.4%	23.3%	19.6%	16.7%
Placebo	84.5%	10.1%	4.0%	1.3%

¥New drugs

Table F4. Sensitivity Analysis. Three Beta Model (PASI 50, 75, and 90) to Adjust for Placebo Response, Proportions

Treatments	<50%	50%-74%	75%-89%	≥90%
Ixekizumab	3.3%	7.0%	16.3%	73.4%
Risankizumab¥	3.4%	7.2%	16.6%	72.7%
Guselkumab¥	3.9%	7.9%	17.6%	70.5%
Brodalumab	4.6%	8.7%	18.6%	68.0%
Secukinumab	6.0%	10.3%	20.4%	63.3%
Infliximab	8.0%	12.4%	22.2%	57.4%
Adalimumab	12.3%	15.7%	24.5%	47.4%
Ustekinumab (45/90)	13.1%	16.2%	24.7%	46.1%
Certolizumab (200/400)¥	13.8%	16.6%	24.8%	44.7%
Tildrakizumab¥	17.7%	18.6%	25.2%	38.5%
Etanercept	26.7%	21.5%	24.4%	27.7%
Apremilast	38.7%	22.6%	21.1%	17.7%
Placebo	84.5%	9.9%	4.3%	1.3%

¥New drugs

Table F5. Subgroup Analysis. Biologic Experienced Studies (Excludes 11 Studies With 5% or Less Biologic Experienced Patient Population), Proportions

Treatment	<50%	50%-74%	75%-89%	≥90%
Risankizumab¥	3.2%	7.3%	16.1%	73.4%
Ixekizumab	3.5%	7.7%	16.6%	72.2%
Guselkumab¥	3.9%	8.2%	17.3%	70.6%
Brodalumab	4.4%	8.9%	18.1%	68.5%
Secukinumab	6.2%	11.0%	20.3%	62.6%
Infliximab	9.6%	14.2%	22.8%	53.4%
Ustekinumab (45/90)	12.9%	16.6%	24.0%	46.5%
Adalimumab	13.1%	16.8%	24.1%	46.0%
Certolizumab (200/400)¥	14.0%	17.2%	24.2%	44.5%
Tildrakizumab¥	18.1%	19.3%	24.5%	37.9%
Etanercept	27.3%	22.2%	23.6%	26.8%
Apremilast	40.8%	23.1%	19.8%	16.1%
Placebo	85.7%	9.5%	3.8%	1.1%

¥New drugs

Table F6. Subgroup Analysis. Multi-National Studies (Excludes All 7 Asian Studies), Proportions

Treatments	<50%	50%-74%	75%-89%	≥90%
Risankizumab¥	3.2%	7.4%	15.9%	73.5%
Ixekizumab	3.5%	7.9%	16.4%	72.2%
Guselkumab¥	3.7%	8.2%	16.9%	71.1%
Brodalumab	4.4%	9.2%	18.0%	68.4%
Secukinumab	6.3%	11.4%	20.2%	62.0%
Infliximab	8.2%	13.4%	21.7%	56.7%
Adalimumab	12.3%	16.7%	23.6%	47.3%
Ustekinumab (45/90)	13.5%	17.4%	23.9%	45.2%
Certolizumab (200/400)¥	13.6%	17.5%	23.9%	45.0%
Tildrakizumab¥	17.9%	19.7%	24.2%	38.0%
Etanercept	26.5%	22.6%	23.3%	27.4%
Apremilast	39.4%	23.7%	19.9%	17.0%
Placebo	84.3%	10.4%	4.1%	1.3%

¥New drugs

Table F7. Sensitivity analysis. No Placebo Adjustment & Placebo Adjustment with Multiple Covariates across PASI Levels

PASI 75: Relative Risks and Credible Intervals of Treatments Compared to Placebo			
Treatments	Base case	No placebo adjustment	Three beta model
Adalimumab	13.1 (9.9 -17.6)	11.8 (8.9 -15.7)	12.9 (9.7 - 17.6)
Etanercept	9.5 (7.6 - 12.1)	9.9 (7.8 - 12.7)	9.3 (7.4 - 12.0)
Infliximab	14.8 (11-20.3)	15.9 (11.5 - 22.2)	14.2 (10.6 - 19.5)
Secukinumab	15.4 (11.3 - 21.4)	15.7 (11.5 - 21.9)	15.0 (11.1 - 20.9)
Ixekizumab	16.5 (11.9 -23.3)	16.6 (12.1 - 23.6)	16.1 (11.7 - 22.7)
Brodalumab	16.1 (11.6 - 22.6)	16.0 (11.7 - 22.4)	15.5 (11.4 - 21.8)
Ustekinumab	13.1 (9.9 - 17.5)	13.2 (10.0 - 17.7)	12.7 (9.7 - 17.0)
Apremilast	6.7 (5.3 -8.7)	5.8 (4.4 - 7.6)	6.9 (5.4 - 8.9)
Guselkumab¥	16.3 (11.8 – 22.9)	15.5 (11.3 - 21.6)	15.8 (11.5 – 22.2)
Tildrakizumab	11.6 (8.8 - 15.5)	11.9 (8.9 - 16.1)	11.4 (8.6 - 15.3)
Risankizumab¥	16.5 (12 – 23.4)	16.2 (11.8 - 22.9)	16.0 (11.6 - 22.8)
Certolizumab Pegol	12.7 (9.5 -17)	12.0 (9.1 -16.2)	12.4 (9.3 -16.9)

¥New drugs

NMA code

Model

```
model <- function() { # *** PROGRAM STARTS
 for(i in 1:ns){ # LOOP THROUGH STUDIES
  w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
  delta[i,1] <- 0 # treatment effect is zero for control arm
  mu[i] ~ dnorm(0,.001) # vague priors for all trial baselines (smaller than original)
  for (k in 1:na[i]) { # LOOP THROUGH ARMS
   p[i,k,1] <- 1 # Pr(PASI >0)
   for (j in 1:(nc[i]-1)) { # LOOP THROUGH CATEGORIES
    r[i,k,j] ~ dbin(q[i,k,j],n[i,k,j]) # binomial likelihood
    q[i,k,j] <- 1-(p[i,k,C[i,(j+1)]]/p[i,k,C[i,j]]) # conditional probabilities
    z.index[i,j,k]<- C[i,(j+1)]-1 # index the cut point
    theta[i,k,j] <- mu[i] + delta[i,k] + z[z.index[i,j,k]]+(beta[t[i,k]]-beta[t[i,1]])*(mu[i]-mx) # linear predictor
    rhat[i,k,j] <- q[i,k,j] * n[i,k,j] # predicted number events
    dv[i,k,j] <- 2 * (r[i,k,j]*(log(r[i,k,j])-log(rhat[i,k,j])) #Deviance contribution of each category
                +(n[i,k,j]-r[i,k,j])*(log(n[i,k,j]-r[i,k,j]) - log(n[i,k,j]-rhat[i,k,j])))
   }
   dev[i,k] <- sum(dv[i,k,1:(nc[i]-1)]) # deviance contribution of each arm
   for (j in 2:nc[i]) { # LOOP THROUGH CATEGORIES
    p[i,k,C[i,j]] <- 1 - phi.adj[i,k,j] # link function
    # adjust link function phi(x) for extreme values that can give numerical errors
    # when x< -5, phi(x)=0, when x> 5, phi(x)=1
    phi.adj[i,k,j] <- step(5+theta[i,k,(j-1)])*(step(theta[i,k,(j-1)]-5)
                                + step(5-theta[i,k,(j-1)])*phi(theta[i,k,(j-1)]) )
   }
  }
  for (k in 2:na[i]) { # LOOP THROUGH ARMS
   delta[i,k] ~ dnorm(md[i,k],taud[i,k])
   md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LHR distributions, with multi-arm trial correction
   taud[i,k] <- tau *2*(k-1)/k # precision of LHR distributions (with multi-arm trial correction)
   w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment, multi-arm RCTs
   sw[i,k] <- sum(w[i,1:(k-1)])/(k-1) # cumulative adjustment for multi-arm trials
  }
  resdev[i] <- sum(dev[i,(1:na[i])]) # summed residual deviance contribution for this trial
 }
 z[1] <- 0 # set z50=0
 for (j in 2:(Cmax-1)) { # Set priors for z, for any number of categories
  z.aux[j] ~ dunif(0,5) # priors
  z[j] <- z[j-1] + z.aux[j] # ensures z[j]~Uniform(z[j-1], z[j-1]+5)
 }
 totresdev <- sum(resdev[]) #Total Residual Deviance
 d[1] <- 0 # treatment effect is zero for reference treatment
 beta[1]<-0 # coefficient is zero for reference treatment


 for (k in 2:nt){
  d[k] ~ dnorm(0,.0001) # vague priors for treatment effects
  beta[k]<-B #common covariate effect
```

```
 }
 B ~ dnorm(0,.0001) #vague prior for covariate effect

 sd ~ dunif(0,5) # vague prior for between-trial SD
 tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)

 A ~ dnorm(meanA,precA)
 for (k in 1:nt) {
  # calculate prob of achieving PASI >50,>75,>90 on treat k (at mean covariate value)
  for (j in 1: (Cmax-1)) { T[j,k] <- 1 - phi(A + d[k] + z[j]) }
  # calculate prob of achieving PASI50,50-75,75-90,>90 on treat k (at mean covariate value)
  T50[k] <- phi(A + d[k] + z[1]+beta[k]*(A-mx))
  T50_75[k] <- phi(A + d[k] + z[2]+beta[k]*(A-mx))-T50[k]
  T75_90[k] <- phi(A + d[k] + z[3]+beta[k]*(A-mx))-T50_75[k]-T50[k]
  T90[k] <- 1- phi(A + d[k] + z[3]+beta[k]*(A-mx))
 }

 # calculate risk ratios for PASI >50, >75, >90
 for (k in 1:(nt-1)){
  for (kk in (k+1):nt){
   rrPASI50[kk,k] <- T[1,kk]/T[1,k]
   rrPASI75[kk,k] <- T[2,kk]/T[2,k]
   rrPASI90[kk,k] <- T[3,kk]/T[3,k]

   rrPASI50[k,kk] <- T[1,k]/T[1,kk]
   rrPASI75[k,kk] <- T[2,k]/T[2,kk]
   rrPASI90[k,kk] <- T[3,k]/T[3,kk]
  }
 }
}
```

Analysis

```
NMAresults<- jags(data=datalist, inits=jaginits, parameters.to.save = c("d", "z", "T50", "T50_75","T75_90","T90",
                  "B","rrPASI50", "rrPASI75", "rrPASI90"), model.file = model,  n.iter = 150000)
```

Appendix G. Comparative Value Supplemental Information

Table G1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health outcomes	Longevity effects	☐	☐	Insufficient evidence
	Health-related quality of life effects	X	X	
	Adverse events	☐	☐	No meaningful impact in 2016 analysis
Medical costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-related costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	X	Notable impact
	Cost of unpaid lost productivity due to illness	NA	☐	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al.[227]

Appendix H. Coverage Policies in New England

Table H1. Coverage Policies in New England Commercial Plans

	Connecticut		Maine		Massachusetts			New Hampshire		Rhode Island		Vermont	
	Anthem (Wellpoint Inc Group)	Connecticare	Anthem (Wellpoint Inc Group)	HPHC Maine	BCBS of MA	Neighborhood Health Plan	Tufts Health Plan	Anthem (Wellpoint Inc Group)	HPHC New Hampshire	BCBS of RI	Neighborhood Health Plan of RI	BCBS of VT	MVP Grp
TNFα inhibitors													
etanercept (Tradename: Enbrel; Manufacturer: Amgen)													
Tier	4	5	4	3	2	3	2	4	3	4	3	2	2
Systemic therapies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
How many TNFs	0	0	0	0	1	0	0	0	0	0	0	0	0
How many trials of biologics?	0	0	0	0	1	0	0	0	0	0	0	0	0
Preferred Agent	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
infliximab (Tradename: Remicade; Manufacturer: Janssen)													
Tier	MB	5	MB	MB	MB	4	2	MB	MB	4	4	3	MB
Systemic therapies	MB	Yes	MB	MB	Yes	Yes	Yes	MB	MB	Yes	Yes	Yes	no info
How many TNFs	MB	0	MB	MB	2	0	0	MB	MB	0	2	2	no info
How many trials of biologics?	MB	0	MB	MB	2	1	0	MB	MB	0	5	2	no info

Preferred Agent	Yes	Yes	Yes	MB	No	No	Yes	Yes	MB	No	No	No	no info
adalimumab (Tradename: Humira; Manufacturer: AbbVie)													
Tier	4	5	4	3	2	3	2	4	3	4	3	2	2
Systemic therapies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
How many TNFs	0	0	0	0	0	0	0	0	0	0	0	0	0
How many trials of biologics?	0	0	0	0	0	0	0	0	0	0	0	0	0
Preferred Agent	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
certolizumab pegol (Tradename: Cimzia; Manufacturer: UCB) | ***Approved for psoriasis in May 2018; Not included on any formularies specific to psoriasis at the time of survey.***													
IL17As													
secukinumab (Tradename: Cosentyx; Manufacturer: Novartis)													
Tier	4	5	4	4	2	3	2	4	4	4	4	2	3
Systemic therapies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
How many TNFs	2	1	2	1	0	0	1	2	1	2	0	0	0
How many trials of biologics?	2	1	2	1	0	0	2	2	1	0	0	0	0
Preferred Agent	No	No	No	No	Yes	Yes	No	No	No	Yes	Yes	Yes	No
ixekizumab (Tradename: Taltz; Manufacturer: Eli Lilly)													
Tier	NF	NF	NF	4	4	4	2	NF	4	4	NF	3	2
Systemic therapies	NF	NF	NF	Yes	Yes	Yes	Yes	NF	Yes	Yes	Yes	Yes	Yes

How many TNFs	NF	NF	NF	1	1	2	1	NF	1	2	2	1	1
How many trials of biologics?	NF	NF	NF	1	2	2	2	NF	1	3	5	PA- no info	1
Preferred Agent	NF	NF	NF	No	No	No	No	NF	No	No	No	No	Yes
brodalumab (Tradename: Siliq; Manufacturer: Valeant)													
Tier	NF	NF	NF	4	4	NF	4	NF	4		NF	3	NF
Systemic therapies	NF	NF	NF	Yes	Yes	NF	Yes	NF	Yes	Yes	NF	Yes	NF
How many TNFs	NF	NF	NF	no info	1	NF	1	NF	no info	2	NF	PA- no info	NF
How many trials of biologics?	NF	NF	NF	no info	2	NF	2	NF	no info	3	NF	PA- no info	NF
Preferred Agent	NF	NF	NF	no info	No	NF	No	NF	no info	No	NF	No	NF
IL12/23													
ustekinumab (Tradename: Stelara; Manufacturer: Janssen)													
Tier	NF	NF	4	MB	2	3	2	MB	MB	4	4	2	2
Systemic therapies	NF	NF	Yes	Yes	Yes	Yes	Yes	MB	Yes	Yes	Yes	Yes	Yes
How many TNFs	NF	NF	0	1	0	0	0	MB	1	0	0	PA- no info	1
How many trials of biologics?	NF	NF	0	1	0	0	0	MB	1	0	0	PA- no info	1
Preferred Agent	No	NF	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
risankizumab (Tradename: *Investigational;* Manufacturer: AbbVie) | Investigational													
IL23													

guselkumab (Tradename: Tremfya; Manufacturer: Janssen)													
Tier	NF	NF	NF	NF	3	NF	4	NF	NF		NF	3	NF
Systemic therapies	NF	NF	NF	NF	Yes	NF	Yes	NF	NF	Yes	NF	PA- no info	NF
How many TNFs	NF	NF	NF	NF	1	NF	1	NF	NF	2	NF	PA- no info	NF
How many trials of biologics?	NF	NF	NF	NF	1	NF	2	NF	NF	3	NF	PA- no info	NF
Preferred Agent	NF	NF	NF	NF	No	NF	No	NF	NF	No	NF	Yes	NF
tildrakizumab (Tradename: Ilumya*;* Manufacturer: Sun Pharma/Merck) | *Not marketed*													
PDE-4													
apremilast (Tradename: Otezla; Manufacturer: Celgene)													
Tier	NF	NF	NF	4	2	3	2	NF	4	4	4	2	3
Systemic therapies	NF	NF	NF	Yes	Yes	Yes	Yes	NF	Yes	Yes	Yes	Yes	Yes
How many TNFs	NF	NF	NF	1	0	no info	1	NF	1	1	0	PA- no info	0
How many trials of biologics?	NF	NF	NF	1	0	no info	2	NF	1	1	1	PA- no info	0
Preferred Agent	NF	NF	NF	No	Yes	Yes	No	NF	No	No	No	Yes	No

Table H2. New England Medicaid Policies for Drug Therapies to treat Moderate-Severe Plaque Psoriasis

	Massachusetts	Connecticut	Rhode Island	Vermont	New Hampshire	Maine
Prefers adalimumab and etanercept	No	Yes	Yes	Yes	Yes	Yes
Prefers secukinumab (after treatment failure with adalimumab)	No	No	No	Yes	No	Yes
Requires PA even for preferred drugs	N/A	Yes	No	Yes	Yes	Yes
# of trials required of systemic therapy	1	1	0	2	1	1

Appendix I. Public Comments

This section includes summaries of the public comments prepared for the New England CEPAC Public Meeting on July 12, 2018 in Burlington, VT. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery.

A video recording of all comments can be found here, beginning at minute 01:12:50. Conflict of interest disclosures are included at the bottom of each statement for each speaker.

Leah McCormick Howard, JD
Chief Operating Officer, National Psoriasis Foundation

It has been a year and a half since ICER conducted the first review of psoriasis treatments in 2016. In many ways, our space has not changed all that much. Psoriasis is still a complex disease with much uncertainty. And while we have seen new therapies come to market – something patients and providers are always eager to see – we still have significant room to go in getting patients to treat their disease to target.

From a patient community standpoint, the 2016 findings were as good as it gets. All the therapies were determined to be of good value, the work reflected patient concerns and included patient input thanks to the work of the NPF and contributions of individual patients, and the policy recommendations accurately captured the challenges of accessing the reviewed therapies. Unfortunately, an analysis of several markets has confirmed what we hear from patients through our Patient Navigation Center – even with these new therapies coming to market, patients do not have that many more options to choose from when it comes to treating since most formularies only offer access to a limited number of treatments.

As ICER concludes this update, we ask how these value assessments become something that is real and meaningful to patients because it positively impacts their health, opens up access to therapies, and helps experienced clinicians take an individual who has been struggling, felt frustrated, angry and helpless, and enables them to change their life around because they are on the right therapy from the beginning.

You can find a full transcript of remarks here

Conflict of Interest: The National Psoriasis Foundation works with all the manufacturers that have a therapy in the psoriatic disease space, including AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, Merck, Novartis, Ortho Dermatologics, Pfizer, Sandoz, Sun Pharma, and UCB. A full list of their funders can be found in their Annual Report.

Brad Stolshek, PharmD
Director, Global Health Economics, Inflammation, Amgen

We appreciate the opportunity to comment on ICER's Psoriasis Condition Update. Enbrel® is a recommended important treatment option to help psoriasis patients benefit from clearer skin and potentially experience daily activities with less concern over visible plaques.

ICER's 2016 psoriasis analysis showed the high to moderate value of targeted immunomodulators (TIMs). However, many stakeholders, including Amgen, suggested improvements to the analysis to more accurately value the TIMs, which would have resulted in an even higher value. While noted in the current contextual considerations, the below factors should be incorporated into the model:

1. the long-term psychosocial impact of psoriasis on patients who have not been adequately treated
2. the comorbidities due to or associated with long-term inflammation and multiple immunologic pathways, such as psoriatic arthritis, metabolic abnormalities, and atherosclerotic disease

Incorporating these additional comorbidities and disease impact into the model would more accurately demonstrate these TIMs value as compared to a model that focuses on psoriasis as only a skin disease.

Enbrel® has efficacy in several moderate-to-severe psoriatic patient types: bio-naïve, continuing, after failure of other immunomodulators, and in psoriatic arthritis. Some patients have benefited from Enbrel® continuously since launch and access should be preserved for these patients who may not benefit from a formulary-induced switch.

Patients and physicians need options when considering and maintaining psoriasis treatments without the risk of payer interruption. This assessment should account for all factors, including comorbidities, psychosocial, and economic, to more accurately demonstrate the value of and preserve patient access to these important TIMs.

Conflict of Interest: Brad Stolshek is an employee and shareholder of Amgen.

David L. Kaplan, MD, MS, FACP, FAAD
Clinical Assistant Professor, University of Missouri, Kansas City School of Medicine; Clinical Assistant Professor, University of Kansas Medical Center

Delivered oral comments at public meeting which are available here at minute 01:25:45. Did not submit written summary.

Conflict of Interest: Dr. Kaplan has been a speaker for AbbVie, Pfizer, and Celgene.

Appendix J. Conflict of Interest Disclosures

Tables J1 through J3 contain conflict of interest (COI) disclosures for all participants at the July 12, 2018 public meeting of the New England CEPAC.

Table J1. ICER Staff and Consultant COI Disclosures

Name	Organization	Disclosures
Dan Ollendorf, PhD	ICER	None
Reiner Banken, MD MSc	ICER	None
David Veenstra, PharmD, PhD	University of Washington	None

Table J2. New England CEPAC Panel Member COI Disclosures

Name	Organization	Disclosures
Robert H. Aseltine Jr., PhD	UCONN Health	*
Teresa Fama, MD	Central Vermont Medical Center	*
Claudio W. Gualtieri, JD	AARP	*
Claudia B. Gruss, MD, FACP, FACG, CNSC	Western Connecticut Medical Group	*
Stephen Kogut, PhD, MBA, RPh	University of Rhode Island College of Pharmacy	*
Stephanie Nichols, PharmD, BCPS, BCPP	Husson University; Maine Medical Center	*
Brian P. O'Sullivan, MD	Dartmouth College	*
Jeanne Ryer, MSc, EdD	New Hampshire Citizens Health Initiative	*
Jason Wasfy, MD, MPhil	Massachusetts General Hospital	*
Rev. Albert Whitaker, MA	American Diabetes Association	*

* No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Table J3. Patient and Clinical Expert COI Disclosures

Name	Organization	Disclosures
Alexa B. Kimball, MD	Beth Israel Deaconess Medical Center	*Alexa B. Kimball is a consultant for Novartis, AbbVie, UCB, Lilly, Janssen. Investigator to AbbVie, and UCB. Fellowship funding from Janssen and AbbVie. President of the International Psoriasis Council.*
Leah McCormick Howard, J.D.	National Psoriasis Foundation	*The NPF works with all manufacturers with a therapy in the psoriatic disease space, including AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, Merck, Novartis, Ortho Dermatologics, Pfizer, Sandoz, Sun Pharma, and UCB. A full list of their funders can be found in their Annual Report.*