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.

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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

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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/

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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

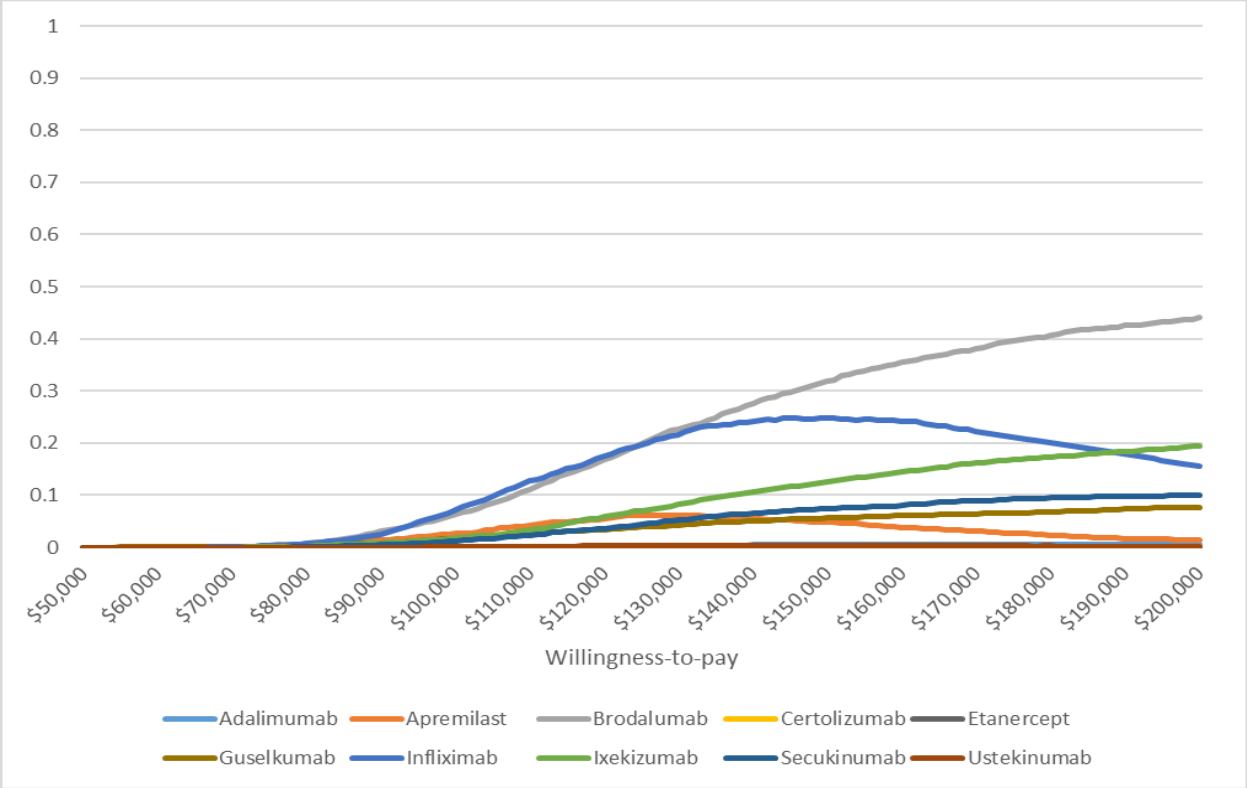
To demonstrate effects of model parameter uncertainty on incremental cost per QALY gained, we varied input parameters based on standard errors or reasonable ranges for two examples: ixekizumab versus non-targeted treatment and ixekizumab versus etanercept. These examples were selected because ixekizumab 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).

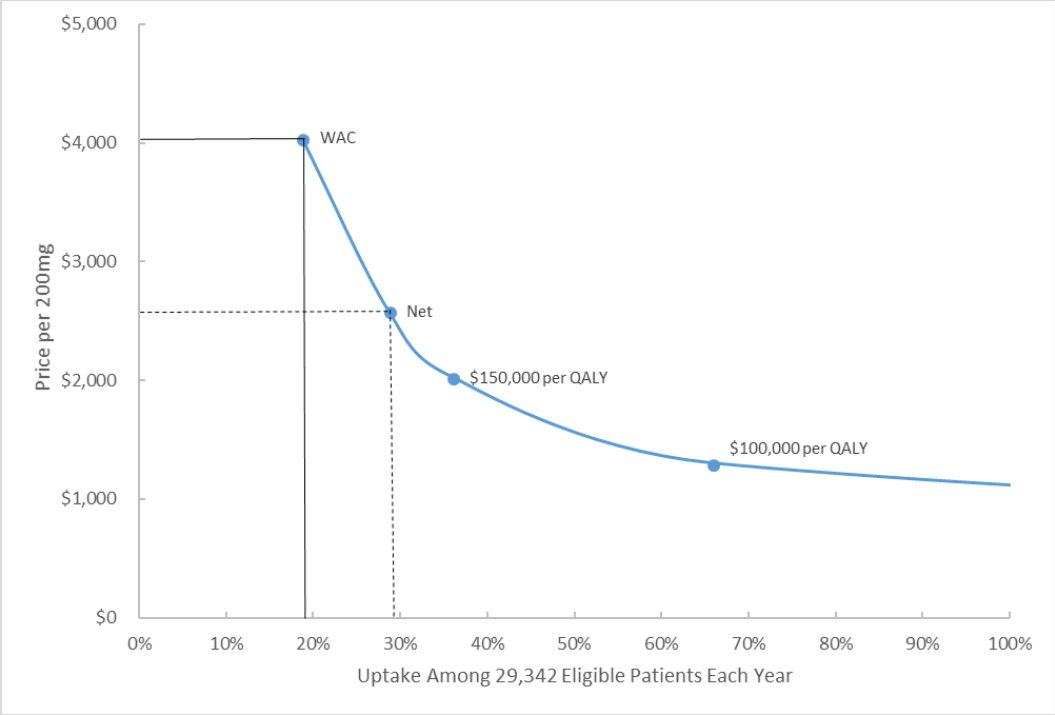
Table ES13. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon for Certolizumab Pegol in Adults with Moderate to Severe Plaque Psoriasis

	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).

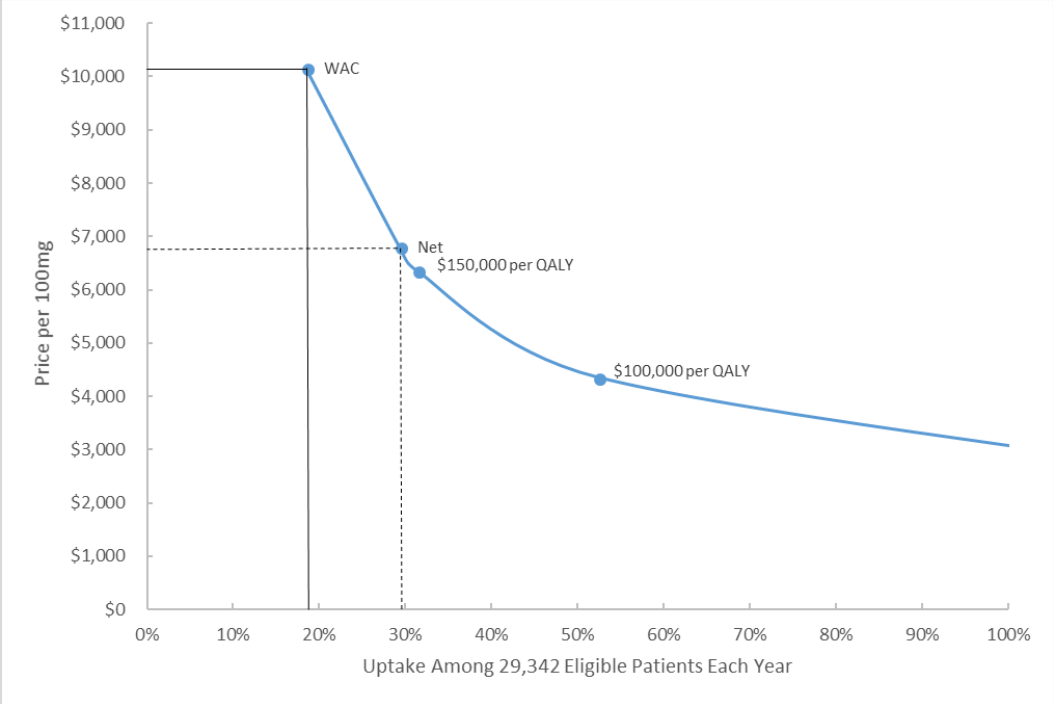
Table ES14. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon for Guselkumab in Adults with Moderate to Severe Plaque Psoriasis

	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]

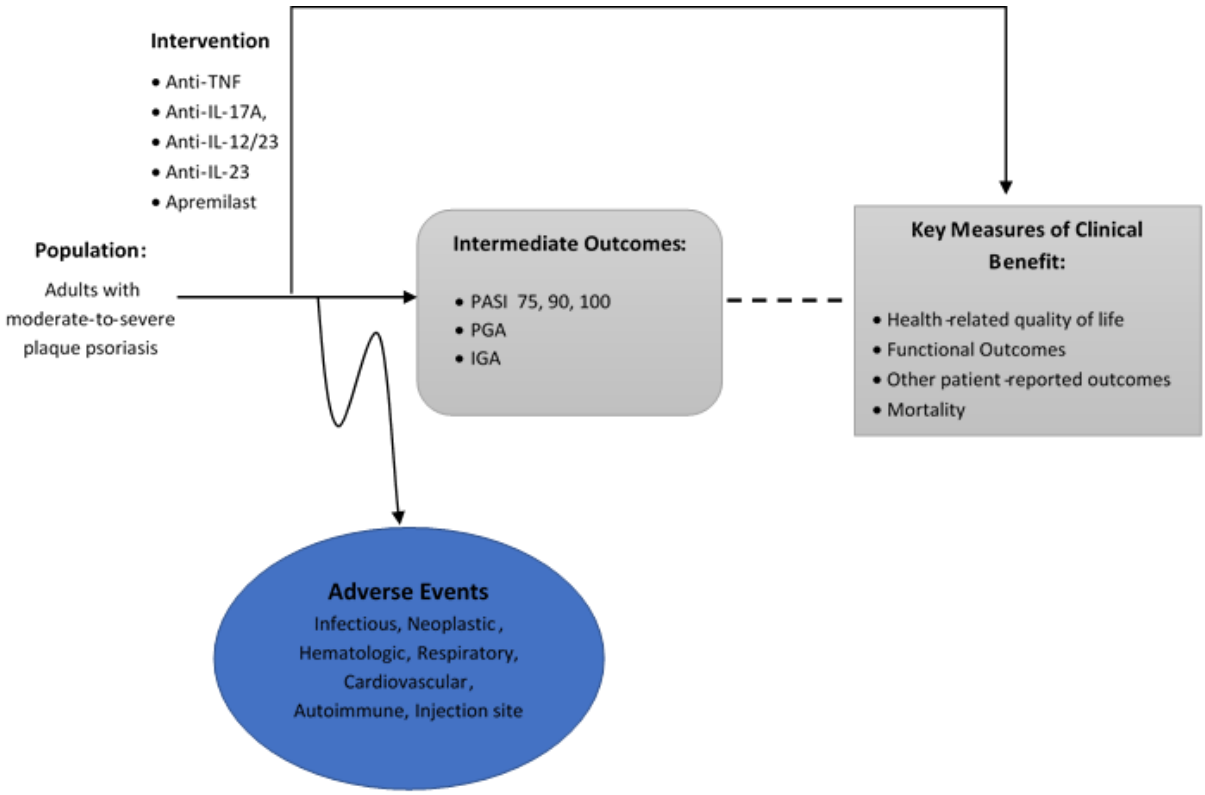
1.2 Scope of the Assessment

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.

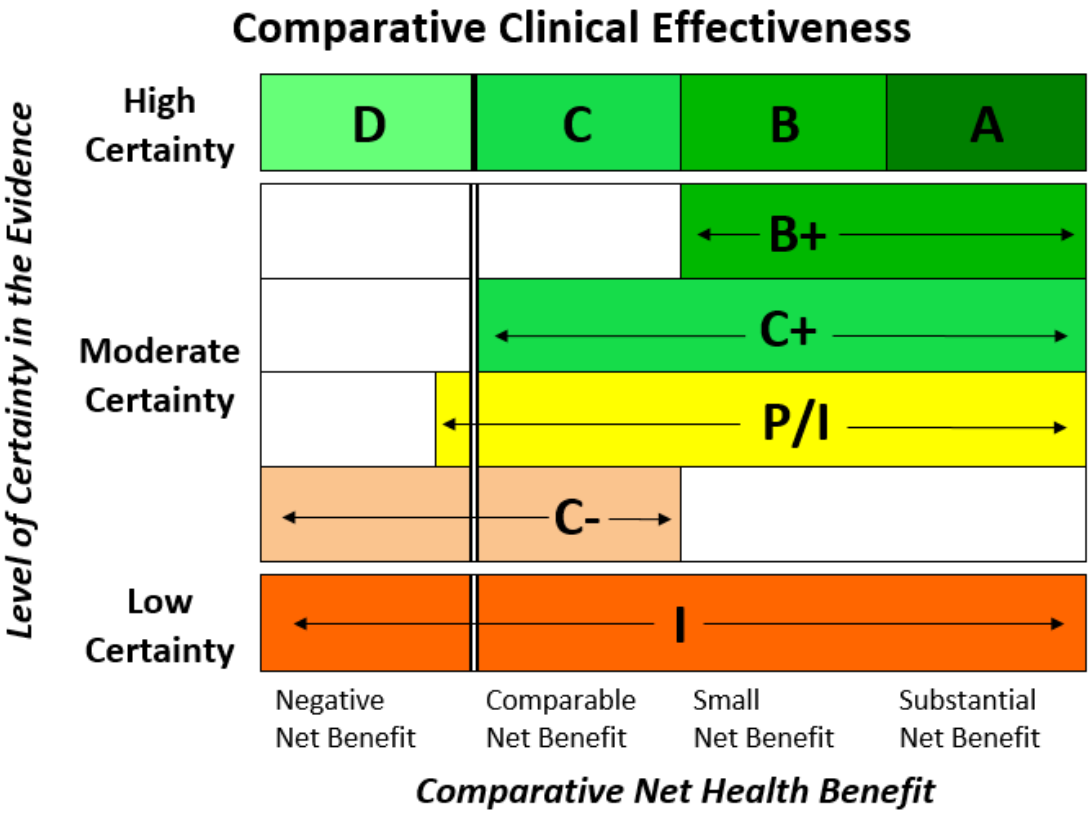
The NMA was conducted using JAGS software (version 4.3.0) via R using the R2jags package.[91] Criteria for trial selection, statistical methods and R code are detailed in Appendix F.

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

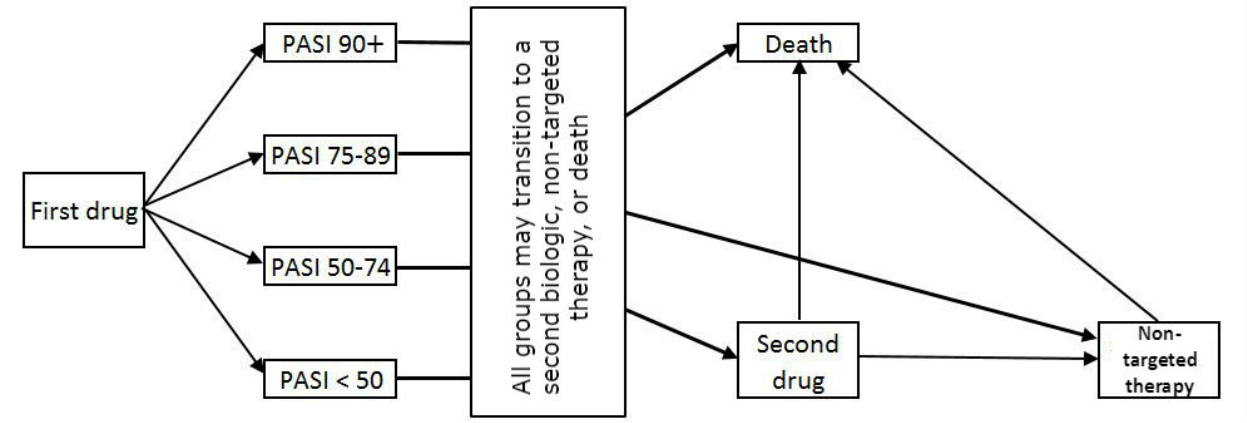
The model structure is unchanged since our prior report.

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

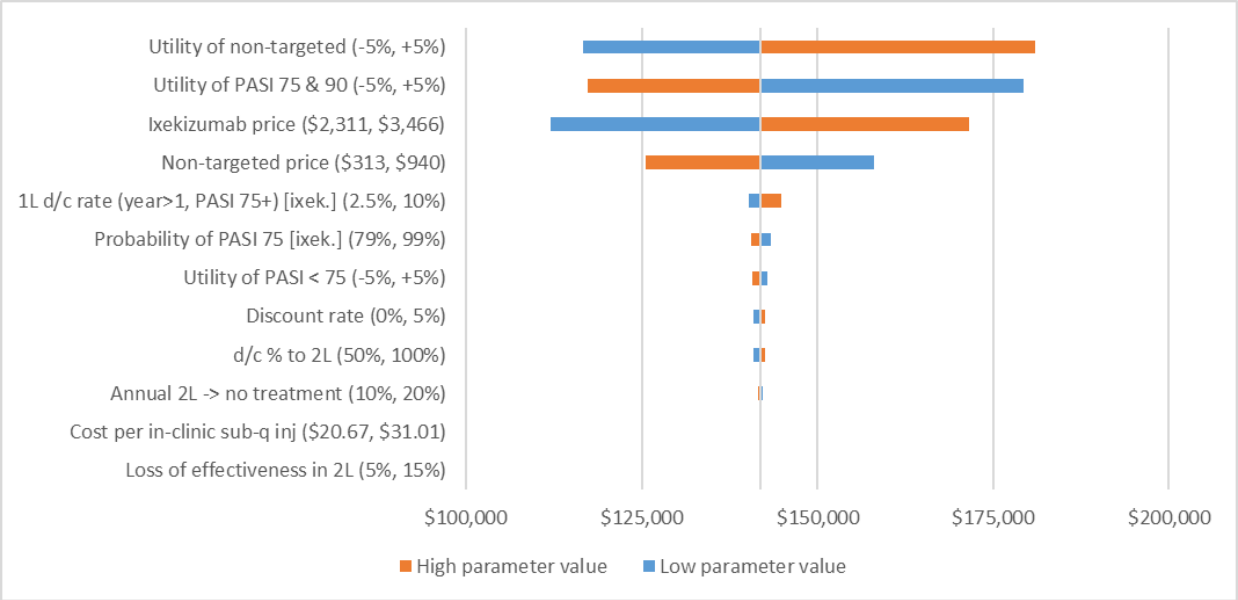
First-line Treatment	Cost / QALY	Cost / month in PASI 90+	Cost / month in PASI 75+
Adalimumab	$164,000	$4,600	$3,200
Apremilast	$135,000	$4,500	$2,800
Brodalumab	$131,000	$3,300	$2,600
Certolizumab pegol	$188,000	$5,400	$3,700
Etanercept	$175,000	$5,400	$3,500
Guselkumab	$161,000	$4,000	$3,200
Infliximab	$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.

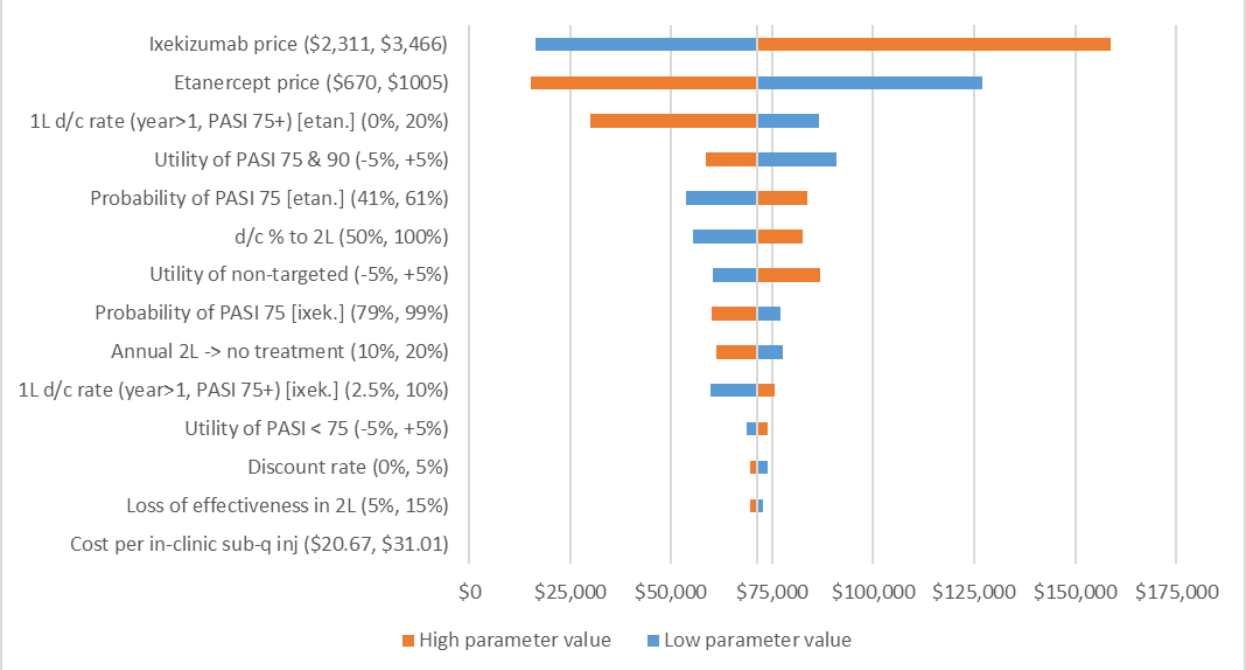
In the base-case, ixekizumab has an ICER of $142,000 per QALY compared to non-targeted, and an ICER of $72,000 per QALY compared to etanercept.

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

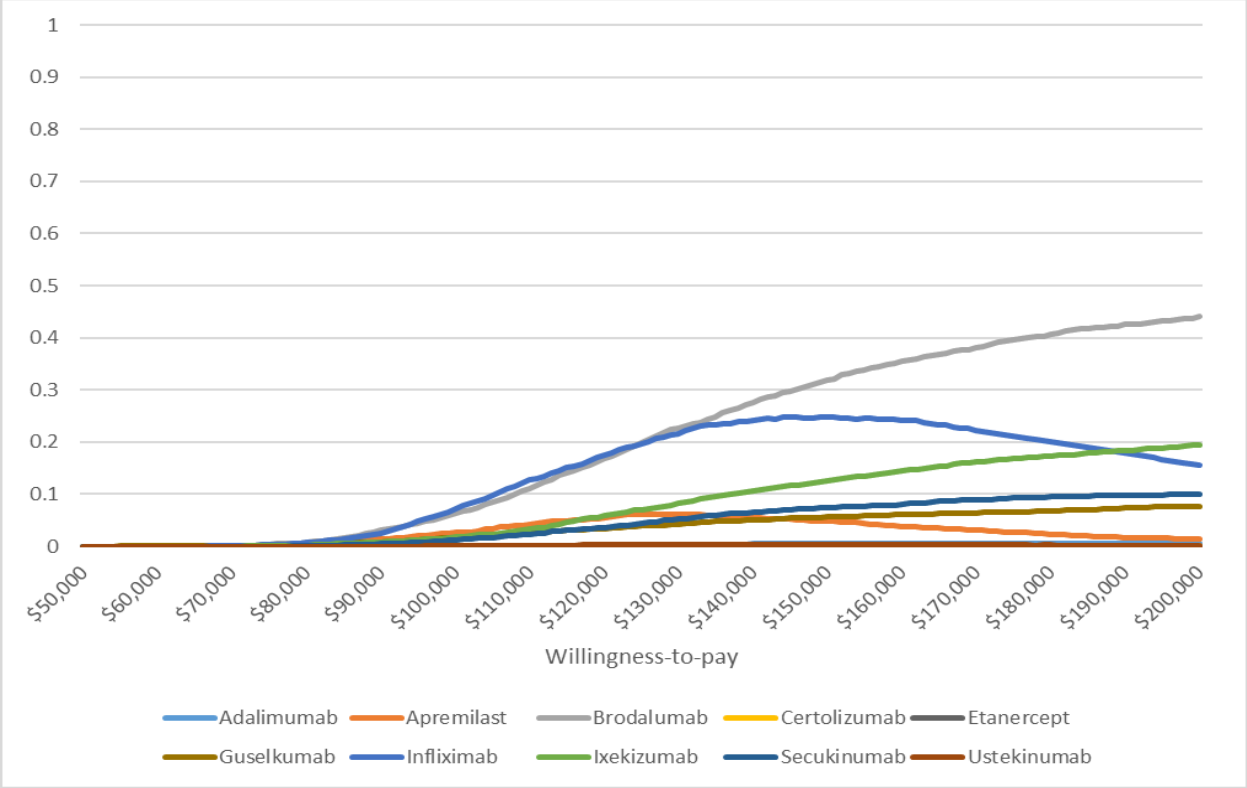


(Note: Ixekizumab Dominates Etanercept at a Price of $2,311 Per Unit)

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

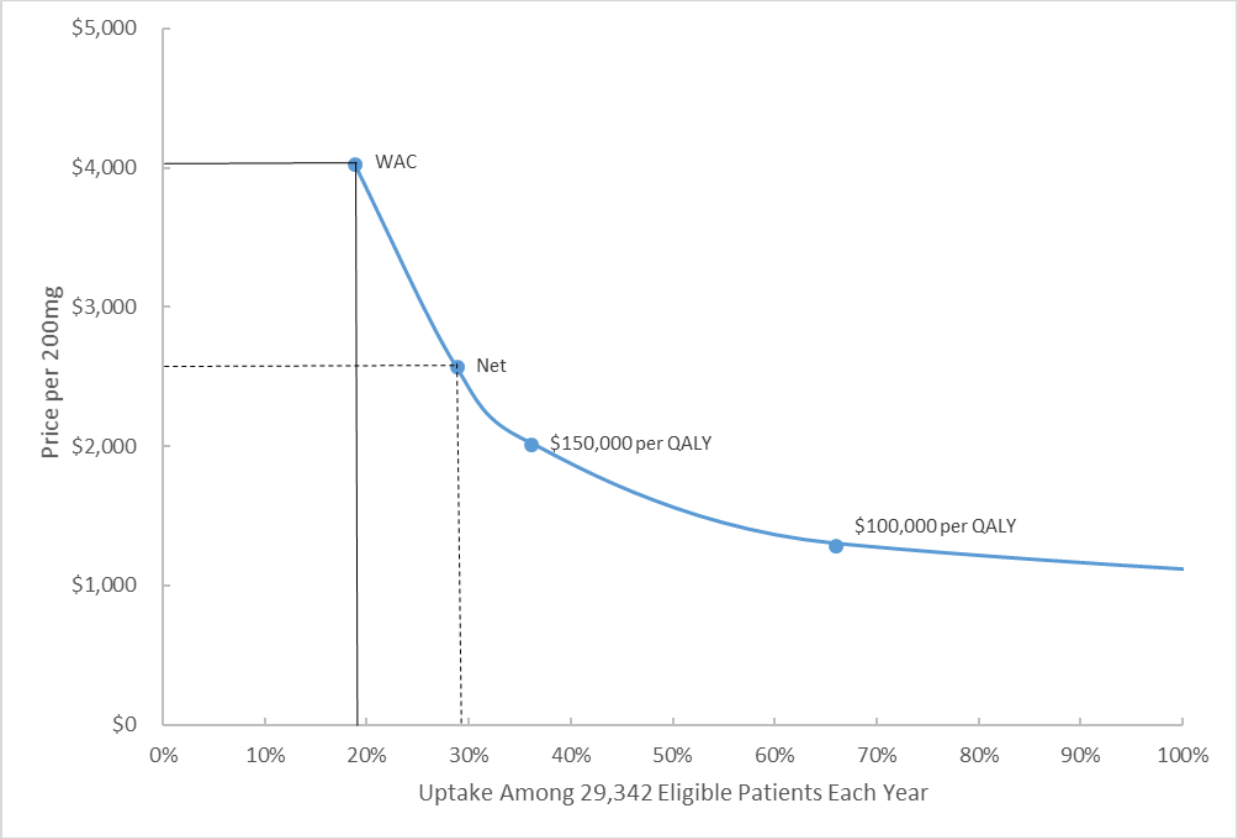
WAC: wholesale acquisition cost; QALY: quality-adjusted life year

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.

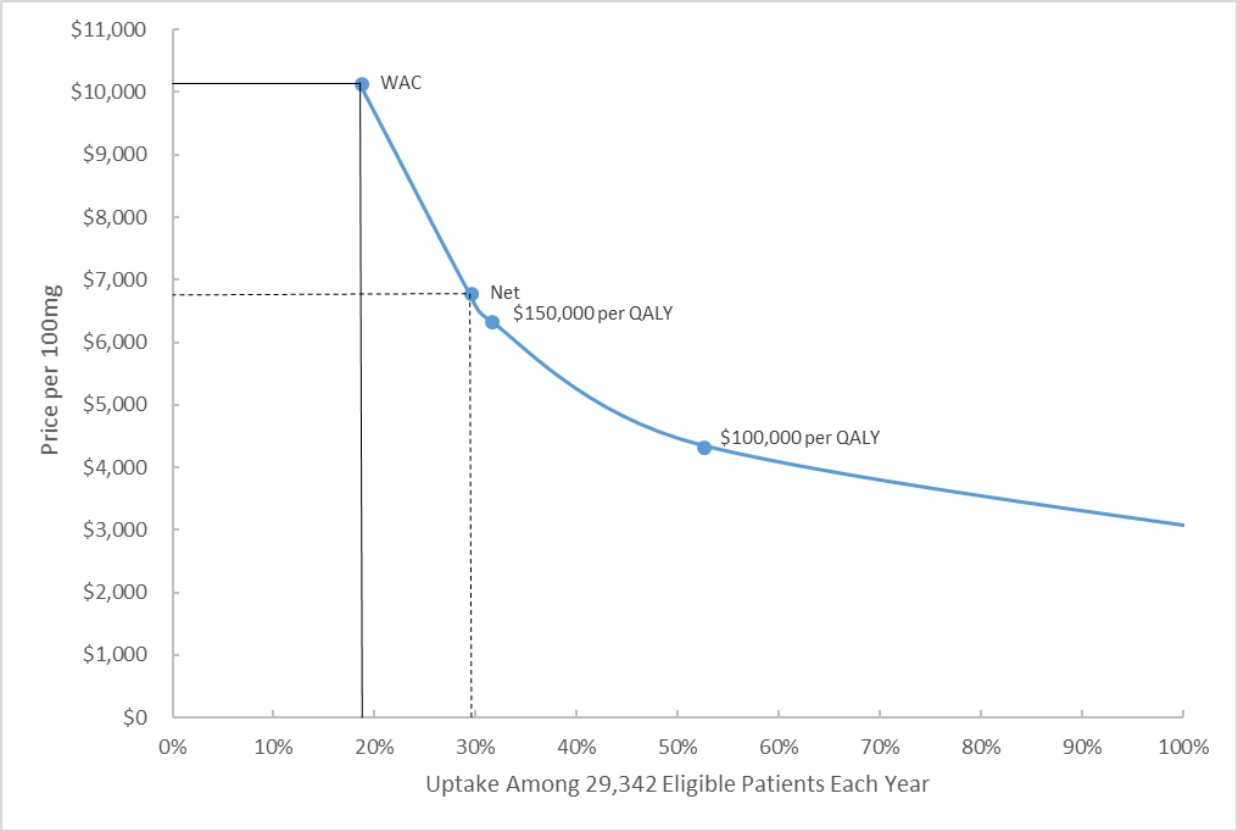
Figure 7.1. Potential Budget Impact Scenarios at Different Prices for Certolizumab Pegol in Adults with Moderate to Severe Plaque Psoriasis*



*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):

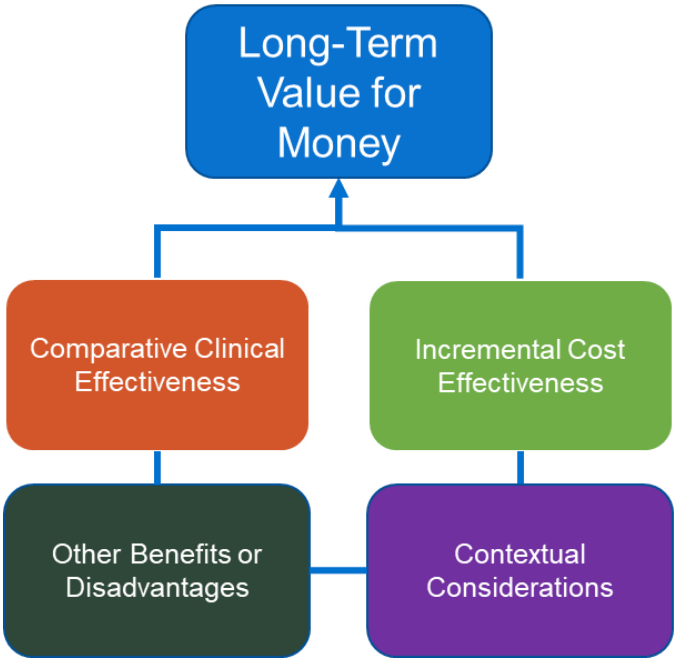
1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. The New England CEPAC uses the 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.

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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

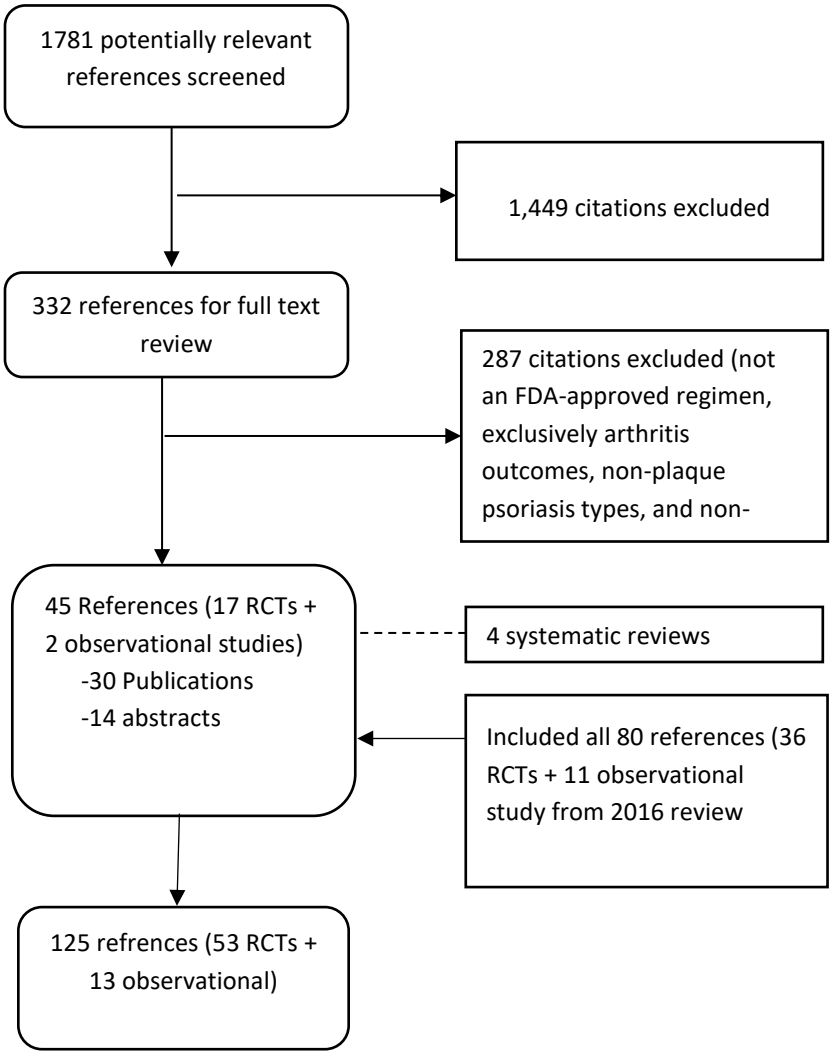
1	'psoriasis vulgaris'	8040
2	psorias*:ab,ti OR psoriat*:ab,ti	57572
3	#1 OR #2	58457
4	'secukinumab':ab,ti OR 'cosentyx':ab,ti	399
5	'ustekinumab':ab,ti OR 'stelara':ab,ti	1454
6	'ixekizumab':ab,ti OR 'taltz':ab,ti	156
7	'apremilast':ab,ti OR 'otezla':ab,ti	331
8	'brodalumab':ab,ti	127
9	#4 OR #5 OR #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 ***<u>NEW EVIDENCE</u>***		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.

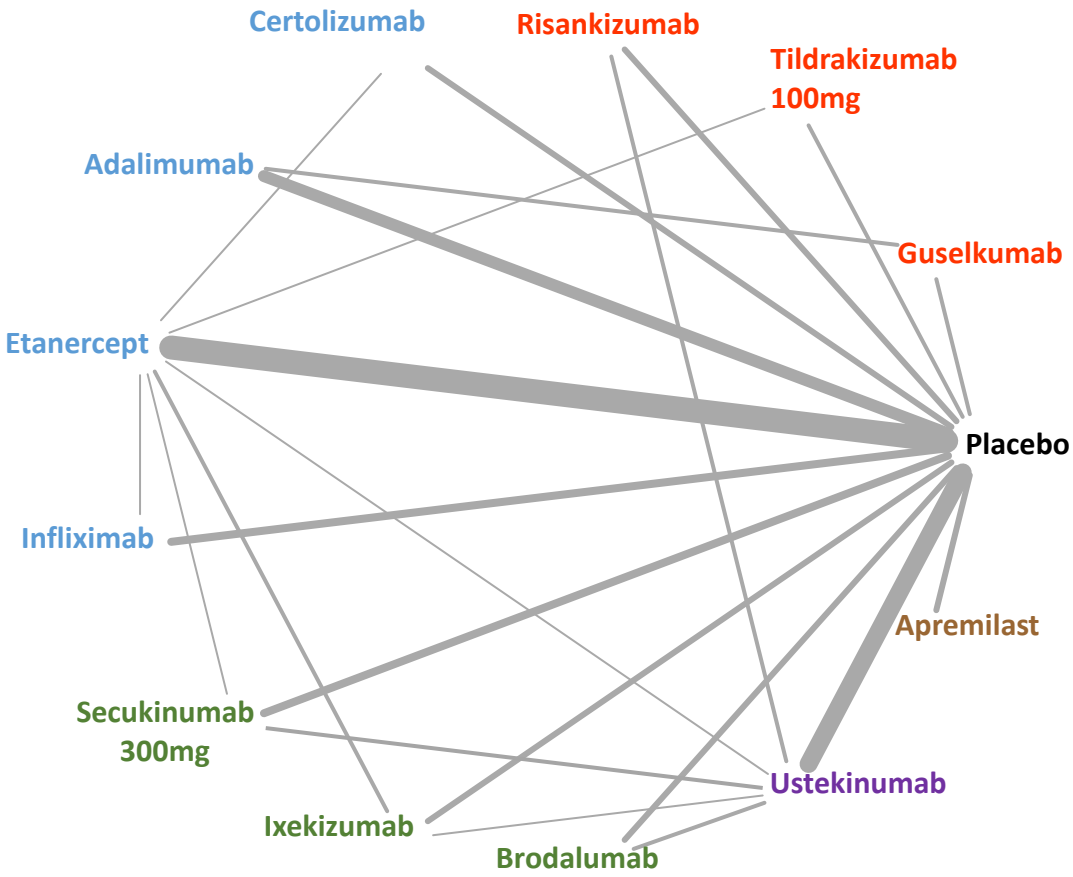
All statistical analyses were conducted within a Bayesian framework with JAGS software (version 4.3.0) via R using the R2jags package.[91] For all analyses we used noninformative prior distributions for all model parameters. We initially discarded the first 50,000 iterations as "burn-in" and base inferences 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.*