May 13, 2024

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

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

Re: PDAB Public Comments – Maryland Prescription Drug Affordability Board List of "Therapeutic Alternatives"

Dear Members of the Maryland Prescription Drug Affordability Board:

AbbVie Inc. is submitting comments in connection with the Maryland Prescription Drug Affordability Board's ("PDAB's") published list of "therapeutic alternatives" to AbbVie's product SKYRIZI®, and the PDAB's May 20th, 2024 meeting at which it plans to discuss whether to approve the list of therapeutic alternatives. **AbbVie has serious concerns with the PDAB's approach to defining "therapeutic alternatives" and the drugs that the PDAB has considered as alternatives to SKYRIZI. Accordingly, AbbVie objects to the list of therapeutic alternatives and urges the PDAB to vote to not approve the list.**

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

I. Background

SKYRIZI (Risankizumab-rzaa) is a prescription, biologic interleukin-23 antagonist that is indicated for the treatment of: (a) moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy; (b) active psoriatic arthritis in adults; and (c) moderately to severely active Crohn's disease in adults.[1] Since the U.S. Food and Drug Administration (FDA) first approved SKYRIZI in 2019, AbbVie has continued to sponsor research on the use of SKYRIZI to address unmet patient needs, including for rare diseases. For example, pursuant to an FDA orphan designation for the "[t]reatment of pediatric Crohn's disease,"[2] AbbVie currently is sponsoring a Phase 3, multicenter study to assess the pharmacokinetics, efficacy, and safety of SKYRIZI in pediatric participants with moderately to

[1] Skyrizi®, Full Prescribing Information, https://www.rxabbvie.com/pdf/skyrizi_pi.pdf.
[2] FDA, Search Orphan Drug Designations and Approvals: Risankizumab, https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=544716.

severely active Crohn's disease. The study began in December 2023, and is estimated to be completed in April 2029.[3]

Maryland released a list of "therapeutic alternatives" for SKYRIZI on April 11, 2024.[4] Maryland's PDAB regulations define "therapeutic alternative" as a "drug product that has the same or similar indications for use as a particular drug but is not a therapeutic equivalent to that drug." For the reasons stated below, we request that the Board vote to not approve the list of therapeutic alternatives as published.

II. The Maryland Definition of "Therapeutic Alternatives" Does Not Adequately Consider Key Product Differences and Does Not Serve Patient Needs

We have concerns that the "therapeutics alternatives" definition created by the PDAB to identify and compare drug products approved for treatment of the same condition does not account for significant variance in factors such as safety, efficacy, clinical outcomes, and manufacturing costs, nor does the definition account for alignment with clinical guidelines. The current definition also does not account for patient specific factors that may need to be considered during treatment selection such as comorbidities and/or contraindications.

A. The Maryland Therapeutic Alternative List Ignores Important Differences in Labeled Indications & Clinical Guidelines That Guide Patient Care & Treatment Decisions

In particular, various treatment guidelines for immune-mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis, psoriatic arthritis, and inflammatory bowel diseases have recommended a "treat-to-target" (T2T) approach, which involves starting effective treatment early for better long-term outcomes, given the availability of multiple treatment options.[5,6,7] Recent advancements in drug discovery have led to the development of Jak inhibitors and IL-23 and IL-17 agents, which have shown to be more effective than anti-TNFs in clinical trials. These developments in IMID therapies have made it possible to achieve clinical remission, whereas in the past, when conventional therapies and anti-TNFs dominated the treatment landscape, only

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

[4] https://dsd.maryland.gov/regulations/Pages/14.01.01.01.aspx

[5] Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Annals of the rheumatic diseases. 2016;75(1):3-15.

[6] Coates LC, Soriano ER, Corp N, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. Nature Reviews Rheumatology. 2022;18(8):465-479.

[7] Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology. 2021;160(5):1570-1583.

40-60% of patients were able to meet the guideline-defined endpoints.[8,9,10,11] Such advanced therapies like SKYRIZI have the potential to elevate the standard of care by enabling the attainment of more rigorous treatment targets as outlined in clinical guidelines. In IMIDs, there have been studies showing that patients who achieve a state of stringent disease control through these therapies are more cost-effective to manage compared to those with ongoing active disease.

SKYRIZI is categorized as "Only in Class" and has no therapeutic equivalents listed in FDA's Orange Book. And yet, the Maryland PDAB asserts methotrexate and cyclosporine are therapeutic alternatives for SKYRIZI. Moreover, and unlike SKYRIZI, neither drug has an FDA approved indication to treat psoriatic arthritis or Crohn's disease (FDA labels can be found here and here). The current (2019) American College of Rheumatology and National Psoriasis Foundation Guidelines on Psoriasis only cite use of cyclosporine as an option in combination therapy with a biologic, not as monotherapy. The guidelines also recognize that while efficacy may be augmented with combination treatment, there is an unknown level of safety risk due to significant adverse events. Therefore, if a patient is being treated for psoriasis by a provider who is following clinical guidelines, SKYRIZI is most likely being used in a population where treatment with methotrexate or cyclosporine has already failed to manage their condition. For this population, it would not be feasible to consider either drug as an effective therapeutic alternative.

For Crohn's disease, several drugs listed as therapeutic alternatives for SKYRIZI do not have FDA approved indications for Crohn's disease or are *contraindicated*. Sotyktu and Otezla do not have an FDA approved indication for Crohn's disease (FDA labels can be found here and here). Cosentyx, Taltz, Siliq and Bimzelx (i.e. IL-17) are contraindicated for Crohn's disease. Considering these drugs as a therapeutic alternative to SKYRIZI for the treatment of Crohn's would be irresponsible and dangerous.

B. Maryland Has Not Appropriately Considered Patient Choice and Access

Determinations related to cost-review may negatively impact patient access and ultimately patient outcomes. The PDAB must place utmost importance on patients and ensure their actions do not adversely impact patient health.

To our knowledge, in developing this list of therapeutic alternatives, the PDAB has not performed an assessment of what patients need and value from these medicines. Treatment decisions are best navigated between trained clinicians specializing in treatments and the patient, who presents with a unique set of clinical features often accompanied by impacts on their quality of life.

III. Conclusion

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[8]Curtis JR, Fox KM, Xie F, et al. The Economic Benefit of Remission for Patients with Rheumatoid Arthritis. Rheumatology and Therapy. 2022;9(5):1329-1345.

[9] Kremer JM, Pappas DA, Kane K, et al. The Clinical Disease Activity Index and the Routine Assessment of Patient Index Data 3 for achievement of treatment strategies. The Journal of Rheumatology. 2021;48(12):1776-1783.

[10] Zardin-Moraes M, da Silva ALFA, Saldanha C, et al. Prevalence of psoriatic arthritis patients achieving minimal disease activity in real-world studies and randomized clinical trials: systematic review with metaanalysis. The Journal of Rheumatology. 2020;47(6):839-846.

[11] Armuzzi A, Tarallo M, Lucas J, et al. The association between disease activity and patient-reported outcomes in patients with moderate-to-severe ulcerative colitis in the United States and Europe. BMC gastroenterology. 2020;20(1):1-11.

We appreciate the opportunity to provide our comments on the list of drugs that are being considered as therapeutic alternatives to SKYRIZI. However, as outlined in this letter, we have serious concerns with the list created by the PDAB. For those reasons, AbbVie objects to the list of therapeutic alternatives and urges the PDAB to vote to not approve the list.

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

Sincerely,

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

AiARTHRITIS
INTERNATIONAL FOUNDATION FOR AUTOIMMUNE & AUTOINFLAMMATORY ARTHRITIS

May 13, 2024

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

RE: Public Comments on Therapeutic Alternatives for Skyrizi

Dear Members and Staff of the Maryland PDAB and Stakeholder Council:

The International Foundation for Autoimmune & Autoinflammatory Arthritis (AiArthritis), a patient organization led by people affected by AiArthritis diseases, shares the committee's goal of lowering patient out-of-pocket costs so that they can more easily maintain their health. We appreciate the opportunity to provide comments on behalf of the thousands of people in Maryland who rely on Skyrizi to manage their active Psoriatic Arthritis and Crohn's Disease.

While we understand the board was asked to discuss therapeutic alternatives as part of the review, we appreciate the opportunity to explain why considering costs of "other options" has a limited place in drug affordability reviews.

People with Heterogeneous Diseases Cannot Be Treated with a One-Size-Fits-All Approach

We know many patients will not respond to existing therapies, so when they find the right one there should be no alternative. Of the thousands of people living with Psoriatic Arthritis and Crohn's Disease in Maryland, generally only between 40-60% respond well to any given treatment and of those up to 80% fail to achieve remission.[1] [2] This is, in part, due to the heterogeneity of these conditions combined with the current trial-by-error process of finding the drug that works best for the individual. Ask any patient who has found the right biologic and they will all tell you the same thing: "Do not disrupt my continuity of care!" Yet, unfortunately, year after year - and in some cases month after month - patients battle this very fight due to insurance formulary design and efforts by payers to move patients to less costly options (i.e., step therapy and non-medical switching).

Uncontrolled inflammation leads to comorbidities. Excess comorbidity is associated with poorer outcomes, including worse physical disability, functional decline, lower remission rates, poorer quality of life, and increased mortality. Up to 70% of AiArthritis disease patients, including

[1] https://www.gastroenterologyandhepatology.net/archives/june-2022/approach-to-treatment-failure-in-inflammatory-bowel-disease/
[2] https://pubmed.ncbi.nlm.nih.gov/35245701/

those with Psoriatic Arthritis and Crohn's Disease, will develop at least one comorbidity in their lifetime. Multiple diagnosis adds to the complexity of treatment matching.[3]

Continuity of Care Equates Better Outcomes and Lower Healthcare Costs

The right treatment matters. It often takes months, even years, for a person with AiArthritis diseases to be diagnosed. As a result, uncontrolled inflammation can lead to more aggressive disease and often to comorbidities (which makes the treatment of already heterogeneous diseases more complex). Even if diagnosis is not delayed, finding the right treatment still involves a trial-and-error process, taking months each time to determine level of efficacy.

The reality for patients and for their doctors is the right treatment matters. Failure to maintain access to a therapy that is working increases the chance for increased disease activity and decreases their chance to ever achieve remission (which equates to more long term health costs to state consumers and the state healthcare system).

Therapeutic alternative options are similar to non-medical switching (NMS) insurance protocols. NMS is the process of suggesting or requiring a stable patient to switch to a different drug for cost reasons, rather than for what is best for their disease stability and outcomes. Studies that include both Crohn's Disease and Psoriatic Arthritis have shown that NMS was associated with significantly worse clinical outcomes, including increased flares, poor control, and increased health care resource utilization.[4] In a recent study, switching or discontinuation from a therapy for nonmedical or economic reasons following stable response was associated with significantly worse clinical outcomes (disease flares and severity) and increased health care resource utilization among patients with Crohn's Disease (CD), Psoriasis (Ps), and Psoriatic Arthritis (PsA) - all diseases treated by Skyrizi. Recommendations from this study include, "Third-party payers might also want to consider the risk associated with policies that may result in nonmedical switching when making formulary decisions.

Alternative therapies should only be considered options when the patient and their doctor are determining an initial or new drug course. The drugs used to treat AiArthritis diseases are large molecule treatments that take time for adjustment and efficacy. Once a patient has achieved their disease targets (i.e., low disease activity or remission), requiring them to try another drug could cause decreased effectiveness if they must switch back to the original medication. These unintended health consequences translate to increased ER visits, hospitalizations, physician visits and lab tests – which also drive up health care costs.[5]

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[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6907158/
[4] https://www.sciencedirect.com/science/article/pii/S0149291817301790
[5] https://www.arthritis.org/health-wellness/treatment/treatment-plan/you-your-doctor/treatment-guidelines-for-psoriatic-arthritis-arth

Recommended Treat-to-Target Approach Improves Outcomes

Best treatment decisions for heterogeneous diseases should implement a Treat-to-Target (T2T) method, personalizing therapy options to the individual's disease severity and accompanying comorbidities.[6] Clinical practice guidelines include recommendations meant to optimize patient care that are informed by the benefits and harms of alternative care options, rather than prescribing a one-size-fits-all approach to patient care.[7] There is mounting evidence that targeted strategies are cost effective, reduce morbidity, and improve patient outcomes.[8]

Adding Payer-Initiated Cost Savings Strategies to the PDAB Process Is Not Putting Patient Needs First

For years patient organizations and persons affected by these diseases have been fighting insurance company protocols that limit access to the treatments that are working well. Every year, sometimes more than once a year, patients fear their insurance company will remove the drug that has enabled them to work, to go to school, to attend family events, to hold their child - to live relatively normal lives. The justification for requesting a patient switch to a different medication is based on "therapeutic alternative options."

We know under 60% of any given biologic will work for persons diagnosed with the same AiArthritis disease. We know it can take years to find 'the one' that works best for us. We know "options" are great for those who need them. We know the more our continuity of care is disrupted the less chance we have to ever achieve remission. We know this, we live it, and, therefore, we fight to be heard - *There are no alternatives to the treatment that works. Period.*

Thank you for considering our input and do not hesitate to reach out to me at tiffany@aiarthritis.org with any questions.

Sincerely,

Tiffany Westrich-Robertson

Tiffany Westrich-Robertson
Chief Executive Officer
Person living with non-radiographic axial spondyloarthritis
International Foundation for Autoimmune & Autoinflammatory Arthritis

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[6] https://erar.springeropen.com/articles/10.1186/s43166-022-00128-y
[7] https://erar.springeropen.com/articles/10.1186/s43166-022-00128-y
[8] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10022708/

Public Comments

Maryland Prescription Drug Affordability Board

Re: Drugs Referred to the Stakeholder Council Therapeutic Alternatives

Sent Via Email comments.pdab@maryland.gov

Dear Prescription Drug Affordability Board and Staff,

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

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

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

1. A UPL Unlikely to Reduce Cost for Patients:

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

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

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

2. A UPL is Likely to Hurt Patient Access:

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

3. JARDIANCE® Data Proves Its Value:

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

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

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

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

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

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

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

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

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

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

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

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

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

4. JARDIANCE'S Focus on Health Equity:

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

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

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

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

5. Costs and Data Analysis Transparency

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

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

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

Therapeutic Alternatives

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

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

JARDIANCE® has the following US FDA approved indications:

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

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

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

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

Conclusion

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

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

We respectfully request you remove JARDIANCE® from further review.

Regards,

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

ENSURING ACCESS THROUGH COLLABORATIVE HEALTH

May 10, 2024

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

RE: Public Comments on Therapeutic Alternatives

Dear Members and Staff of the Maryland Prescription Drug Affordability Board:

On behalf of the undersigned organizations, we appreciate the opportunity to provide comments to the board on therapeutic alternatives. We share the board's goal to lower costs for patients and applaud your efforts to ensure access to the care and therapies they need to manage their health.

It is critical, however, that the board understands that for many patients with chronic conditions, medications considered to be therapeutic alternatives are not actually viable alternatives for them personally. Therefore, we strongly urge the board to carefully consider the ultimate impact of your affordability review on those patients and reject actions that could limit treatment options for these patients.

Medicine is Not One-Size-Fits-All

Once diagnosed with a chronic condition, each patient starts an often life-long journey to identify the correct treatments and regimen to successfully manage their symptoms and improve their health. Many will also face multiple chronic conditions or need medications to treat specific symptoms or even side effects of their preferred treatment. For these reasons, patients with chronic conditions often rely on a complicated and personalized course of treatment that is not easily altered.

For these patients, therapeutic alternatives may not be alternatives at all. Very often drug interactions or other health conditions would prevent individual patients from being able to switch to an alternative medication that, on paper, seems like it would be an appropriate treatment. Further, patients with chronic conditions can build up a tolerance to medications over time, so they must retain access to all treatments in a class of drugs to prolong their treatment.

Patient Access Cannot Be Compromised

Ultimately, chronic conditions are incredibly complex to treat. Each patient will face a unique experience and should be able to work with their doctor to identify the treatment that works best for them. Substituting or requiring patients to change drugs based on cost considerations instead of medical needs can disrupt continuity of care and result in complications and higher overall medical costs. We urge this board to seriously consider the unique circumstances faced by these patients and work diligently to ensure that access to all treatments is protected.

As patient advocates, we are concerned that upper payment limits (UPL) will only exacerbate these risks. We are concerned that patients could see reduction in access to medications in the future due to unforeseen consequences of UPLs, like increased utilization management within drug classes or limits on treatment options due to reduced reimbursement rates for doctors.

ENSURING ACCESS THROUGH
COLLABORATIVE HEALTH

We strongly urge the board and staff to utilize the authority of the board to fully explore with all healthcare stakeholders how upper payment limits will be implemented and identify in advance any adverse impact to patients.

We appreciate your laudable efforts to improve our health system and your steadfast commitment to protecting patients. We look forward to working together to achieve these goals.

Sincerely,

Ensuring Access through Collaborative Health Coalition
Advocates for Compassionate Therapy Now
AiArthritis (International Foundation Autoimmune & Autoinflammatory Arthritis)
Cancer Support Community
Caring Ambassadors Program
Chronic Care Policy Alliance
Chronic Disease Coalition
Global Healthy Living Foundation
Infusion Access Foundation
International Cancer Advocacy Network (ICAN)
Looms For Lupus
National Infusion Center Association (NICA)
National Psoriasis Foundation
Neuropathy Action Foundation
Rare Access Action Project
Value of Care Coalition
Vasculitis Foundation

HBCU 1886
UNIVERSITY OF MARYLAND EASTERN SHORE
SCHOOL OF PHARMACY AND HEALTH PROFESSIONS
DEPARTMENT OF PHARMACY PRACTICE AND ADMINISTRATION

05/10/2024

To whom it may concern:

I am writing this letter of comment in regards to the therapeutic alternative lists suggested for Farxiga (dapagliflozin), Jardiance (empagliflozin), Trulicity (dulaglutide), and Ozempic (semaglutide). For each of these drugs the proposed lists of therapeutic alternatives include options that are not appropriate for the majority of patients who are prescribed these agents. Trulicity and Ozempic belong to the glucagon-like peptide-1 receptor agonist (GLP-1 RA) class of drugs. Jardiance and Farxiga belong to the sodium-glucose co-transporter-2 inhibitor class of drugs. (SGLT2-i).

The American Diabetes Association Standards of Care in Diabetes – 2024 recommends that drugs that have shown benefits for ASCVD, heart failure, and DKD should be considered first when determining appropriate therapy for Type 2 Diabetes Mellitus. Specific medications in both classes have shown benefits in preventing atherosclerotic cardiovascular disease (ASCVD) events such as heart attacks and strokes as well as preventing worsening of diabetic kidney disease (DKD) in people with Type 2 Diabetes Mellitus. Specific medications in the SGLT2i class have indications for reduction in heart failure hospitalizations in people with Type 2 Diabetes Mellitus. Drugs in the DPP-4 inhibitor class are listed as therapeutic alternatives for all four agents. None of the medications in that class have shown benefits for ASCVD, heart failure, or DKD. They can be great agents in specific situations, but they are not reasonable to include as alternatives to drugs that are intended not just to lower glucose but also to improve comorbid conditions.

Cost and Care Delays

Providing medications in either class as therapeutic or other classes alternatives that have not shown benefits for important comorbidities will likely result in insurance providers requiring prior authorizations or other additional paperwork to obtain these medications. Placing barriers to obtain these medications creates delays in care, adds to administrative burden, and ultimately increases overall healthcare costs as time and resources must be devoted to those processes.

Jardiance and Farxiga

Jardiance and Farxiga are approved for use in heart failure and chronic kidney disease in **persons without Diabetes Mellitus**. SGLT-2 inhibitors are included in the American Heart Association heart failure treatment guidelines as one of the main pillars for treatment of heart failure with reduced ejection fraction. Having agents that are solely used to treat Type 2 Diabetes Mellitus listed as therapeutic alternatives will create confusion and unnecessary issues with access for patients being placed on these medications by their heart and kidney specialists.

Jardiance and Invokana (canagliflozin) are the only two agents in the SGLT-2 inhibitor class that have studies showing benefits in ASCVD, heart failure, and DKD in persons with diabetes mellitus. Listing Invokana as a therapeutic alternative is reasonable for Type 2 Diabetes but not for heart failure or chronic kidney disease in **persons without diabetes**. Steglatro (ertugliflozin) is listed a possible therapeutic alternative, but that agent is only indicated for reduction of blood glucose not ASCVD, heart failure, or DKD. Farxiga does not carry an indication for ASCVD benefit so it is not a good therapeutic alternative in terms of being preferred over Jardiance or Invokana for treatment of Type 2 Diabetes Mellitus. For

heart failure and chronic kidney disease in those without diabetes it is a reasonable alternative to Jardiance and vice versa.

Trulicity and Ozempic

The only GLP-1 RA agents that have shown ASCVD benefit are Trulicity, Ozempic, and Victoza. Trulicity remains the only drug in the GLP-1 receptor agonist (RA)class of drugs that has an FDA indication for primary prevention of atherosclerotic cardiovascular disease (ASCVD) events for individuals with Type 2 Diabetes Mellitus. Providing Victoza as preferred over Trulicity or Ozempic would also create a reduction in adherence as it is once a day compared to once a week. Decreased adherence often results in the requirement for more medications and poorer outcomes which ultimately results in increased overall healthcare costs. Byetta (exenatide), Bydureon (exenatide LAR), and Adlyxin (lixisenatide) have not shown an ASCVD benefit. These agents are appropriate therapeutic alternatives for Trulicity, Ozempic, and Victoza. SGLT-2 inhibitors with ASCVD benefit are reasonable alternatives but their effect on blood glucose and weight are more modest so they will not always the best alternative.

Conclusion

The therapeutic alternatives list as written does not differentiate between medication indications. It also includes medications that are not usually appropriate as SGLT-2 inihibitor and GLP-1 RA agents are often the practice guideline recommended first or second like agents depending on patient co-morbidities. Cost of drugs must be considered in relation to the cost savings from avoiding hospitalizations for ASCVD events, heart failure exacerbations, and decline in kidney function or kidney failure. The current list will likely result in delays in care, barriers to access, and inappropriate therapeutic selections.

Sincerely,

Dana R. Fasanella, PharmD, CDCES, BCACP
Associate Professor
Department of Pharmacy Practice and Administration
University of Maryland Eastern Shore School of Pharmacy and Health Professions

May 10, 2024

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

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

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

Dear Members of the Prescription Drug Affordability Board:

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

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

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

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

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

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

Reasons Biktarvy should not be selected for a cost review:

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

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

***

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

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

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

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

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

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

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

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

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

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

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

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

Biktarvy supports rapid start

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

Biktarvy has a high barrier to resistance

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

Biktarvy is approved across broad populations

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

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

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

Table 1: Biktarvy and Therapeutic Alternatives Proposed by the Board

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

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

IV. Biktarvy is affordable and accessible to people with HIV

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

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

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

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

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

V. The State is overestimating its spending on Biktarvy

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Sincerely,

DocuSigned by:
Kristie Banks
3B4BECBA5AB74F3...

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

DocuSigned by:
Betty Chiang
DE32260A4A3E4AA...

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

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[29] An unboosted HIV regimen refers to a regimen that doesn't include a medication called a "booster." Boosters, usually ritonavir or cobicistat, work by decreasing the hepatic metabolism of certain HIV drugs, therefore

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Maryland

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

Therapeutic Alternatives for Drugs Referred

Chesahna Kindred, MD, MBA, FAAD [redacted]> Wed, Apr 24, 2024 at 2:16 PM
To: comments.pdab@maryland.gov

Greetings,

This is Dr. Kindred, a dermatologist serving Marylanders for more than 10 years. Never in my career have I seen a medication as effective and safe as dupilumab for moderate to severe atopic dermatitis. I still remember one of my patients was on the verge of divorce early in her marriage. Her husband did not understand why there were flakes all over the bed each morning (caused by her severe refractory atopic dermatitis). Within a month of starting dupilumab, she began to clear. They are now married with kids.

The alternate lists include treatments that are not quite as effective and *not quite as safe.* Furthermore, dupilumab is the only medication approved to treat across the Type 2 Inflammatory spectrum, from atopic dermatitis and prurigo nodularis (derm) to eosinophilic asthma (pulm) and other fields of medicine.

I am a firm proponent of lowering the costs of medications. Swapping dupilumab for the other medications on the list is not in the best interest of patients. There is no substitute for dupilumab in regards to safety and efficacy for atopic dermatitis.

Thank you for considering my experience with treating patients.

--

Eli Lilly and Company

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

May 10, 2024

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

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

Re: Drugs Referred to the Stakeholder Council

Dear Council and Staff:

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

Affordability for Maryland patients

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

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

Therapeutic Alternatives

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

Unintended consequence to patient access and cost

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

Value of Trulicity® to patients[3]

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

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

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

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

Sincerely,

Cynthia Ransom
Sr. Director, Government Strategy

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

National Eczema Association

May 13, 2024

Maryland Prescription Drug Advisory Board (MD-PDAB)
Subject Line: Therapeutic Alternatives - Dupixent
Sent Via Email comments.pdab@maryland.gov

Dear PDAB Board Members and Staff:

The National Eczema Association submits these comments in response to MD-PDAB's request for comments on therapeutic alternatives – Dupixent.

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

Eczema is the name for a group of conditions that cause the skin to become itchy, inflamed, and have rash-like lesions. Atopic dermatitis (AD) is the most common and chronic form of eczema, affecting more than 9.6 million children[1] and 16.5 million adults[2] of all races and ethnicities in the United States[3]. We are in the midst of a new era of care for eczema patients with several new FDA-approved therapies for AD, and dozens more in the drug discovery pipeline, which are transformative in their ability to ease numerous physical, psychological, and quality of life burdens of eczema[4 5 6].

We also recognize that these groundbreaking therapies are presenting emerging coverage, access, and out-of-pocket (OOP) cost barriers for the diverse eczema community. Forty-two percent of individuals affected by AD spend $1,000 or more on annual OOP costs for disease management[7]. Black race, worse AD severity, Medicaid insurance, and the use of three or more AD therapies are associated with higher OOP costs[8 9].

Therefore, while we applaud the state of Maryland for tasking the Prescription Drug Affordability Board to address the cost of prescription treatments, we would like to share our

[1] Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. J Invest Dermatol. 2011;131(1):67-73.
[2] Chiesa Fuxench ZC, Block JK, Boguniewicz M, et al. Atopic Dermatitis in America Study: A Cross-Sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. J Invest Dermatol. 2019;139(3):583-590.
[3] Hanifin JM, Reed ML, Eczema Prevalence and Impact Working Group. A population-based survey of eczema prevalence in the United States. Dermatitis. 2007;18(2):82-91.
[4] Drucker AM, Wang AR, Li WQ et al. The burden of Atopic Dermatitis: Summary of a report for the National Eczema Association. J Invest Dermatol. 2017;137(1):26-30.
[5] Chiesa Fuxench ZC, Block, JK, Boguniewicz M, et al. Atopic dermatitis in America study: A cross-sectional study examining the prevalence and disease burden of atopic dermatitis in the US adult population. J Invest Dermatol.2019;139(3):583-590.
[6] Silverberg J, Gelfand J, Margolis D et al. Patient burden and quality of life in atopic dermatitis in US adults. Ann Allergy Asthma Immunol. 2018;121(3):340-347.
[7] Smith Begolka, W., Chovatiya, R., Thibau, I.J. & Silverberg, J.I. Financial Burden of Atopic Dermatitis Out-of-Pocket Health Care Expenses in the United States. Dermatitis 32, S62-S70. 2021
[8] Chovatiya, R., Begolka, W.S., Thibau, I.J. & Silverberg, J.I. Financial burden and impact of atopic dermatitis out-of-pocket healthcare expenses among black individuals in the United States. Arch. Dermatol. Res. 2021: 10.1007/s00403-021-02282-3.
[9] Chovatiya, R., Begolka, W.S. Thibau, I.J. & Silverberg, J.I. Impact and Associations of Atopic Dermatitis Out-of-Pocket Health Care Expenses in the United States. Dermatitis. 2021. Doc: 10.1097/DER.0000000000000795.

concerns surrounding the proposed therapeutic alternatives for Dupixent (dupilumab) and potential unintended consequences for adults and children with AD.

1. **AD is clinically heterogenous and protean in nature. Treatment decisions that best address disease burden should be made between the healthcare provider and patient.[10]**

   The clinical and lived experience burdens of AD are numerous and multidimensional[11], necessitating the need for effective treatment options over the short- and long-term to achieve optimal disease control. In addition, the list of serious comorbid conditions associated with uncontrolled, more severe AD has grown to include multiple atopic, allergic, immune-mediated, bone and mental health conditions, infections and more[12]. Collectively this highlights the need for access to all available therapeutic options to best address disease and patient diversity for this chronic disease.

   Shared decision making (SDM) across medicine has been shown to lead to improved patient treatment adherence, enhance healthcare provider-patient communication and trust, and improve quality of care and outcomes. Decisions regarding selecting and/or changing therapies should be based on clinical, patient reported, quality of life and patient preference considerations. While several therapeutic options have been proposed should the availability of dupilumab change for Maryland residents on state-based insurance plans, this could negatively impact the SDM process and potentially clinical and patient-reported outcomes.

2. **Several of the therapeutic alternatives listed are not FDA-approved for AD or carry boxed warnings for their usage.**

   Omalizumab, mepolizumab and benralizumab are FDA-approved to treat asthma, but are not FDA-approved to treat AD. None of these biologics are included in recently published (2023) clinical practice guidelines from the American Academy of Dermatology[13] or the American Academy of Asthma, Allergy & Immunology[14]. Available data related to the use of omalizumab for AD is limited to case series, case reports, and smaller clinical trials, with conflicting results[15]. Phase 2 randomized clinical trial data

[10] The SHARE Approach: A Model for Shared Decisionmaking – Fact Sheet. Content last reviewed September 2020. Agency for Healthcare Research and Quality, Rockville, MD. AHRQ: https://www.ahrq.gov/health-literacy/professional-training/shared-decision/tools/factsheet.html
[11] Elsawi, R., Dainty, K. & Smith Begolka, W.; et al. The Multidimensional Burden of Atopic Dermatitis Among Adults. JAMA Dermatol. 2022 Aug 1;158(8):887-892. doi: 10.1001/jamadermatol.2022.1906.
[12] Davis, D., Drucker, A.M. & Alikhan, A.; et al. American Academy of Dermatology Guidelines: Awareness of comorbidities associated with atopic dermatitis in adults. J Am Acad Dermatol. 2022 Jun;86:1335-6. doi: 10.1016/j.jaad.2022.01.009
[13] Davis, D., Drucker, A.m., Alikhan, A.; et al. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies. J Am Acad Dermatol. 2023 Nov 7;0190-9622. doi: 10.1016/j.jaad.2023.08.102
[14] Chu, D.K., Schneider, L & Asiniwasis, R.N; et al. Atopic dermatitis (eczema) guidelines: 2023 American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on Practice Parameters GRADE – and Institute of Medicine-based recommendations. Ann Allergy Asthma Immunol. 2024 Mar;132(3)274-312. Doi: 10.1016/j.anai.2023.11.009
[15] Boguniewicz, M. Biologics for Atopic Dermatitis. Immunol Allergy Clin North Am. 2020 Nov;40(4):593-607. Doi: 10.1016/j.iac.2020.06.004

examining benralizumab[16] in adults and adolescents with moderate to severe AD indicated no evidence of treatment benefit on the signs, symptoms, or severity of disease. The phase 2 RCT of mepolizumab was terminated early due to lack of clinical benefit[17].

In addition, several of the proposed alternative therapies (i.e., tacrolimus, abrocitinib, and upadacitinib) carry boxed warnings. Although each of these medications has established efficacy for moderate to severe AD, these boxed warnings have clinical implications for appropriate patient selection and potential monitoring requirements[18] [19], as well as raise important long-term safety questions and concerns from patients and caregivers that may impact their treatment preference and adherence.

Additionally, NEA-conducted research suggests that nearly one-third of biologics prescriptions encounter some form of delay or denial, with step therapy accounting for the majority of utilization management approaches[20]. As such, almost all patients who are on dupilumab had to fail topical tacrolimus.

3. **Several of the therapeutic alternatives are not FDA-approved for children with AD .**

   Management of moderate to severe AD in children is challenging as limited therapeutic options are available, and parents/caregivers often have significant concerns about the long-term safety of AD treatments[21].

   Tralokinumab, abrocitinib, and upadacitinib are not FDA-approved for pediatric patients aged 0-11 years. Dupilumab is the only non-immunosuppressive systemic therapy approved for children to date (age 6 months+). Topical tacrolimus is also only FDA-approved for children ages 2 and above.

4. **We are concerned that patients will not be able to access the treatment that is currently working for them**.

   We are concerned that additional cost and/or access issues could be an unintended consequence of MD-PDAB deliberations, should the availability of Dupixent for Maryland residents' change for those using state-based insurance plans.

[16] Guttman-Yassky, E., Bahadori, L., Clark, K.L.; et al. Lack of effect of benralizumab on signs and symptoms of moderate-to-severe atopic dermatitis: Results from the phase 2 randomized, double-blind, placebo-controlled HILLIER trial. J Eur Acad Dermatol Venereol. 2023;37:e1211-e1214. doi: 10.1111/jdv.19195
[17] GlaxoSmithKline. Efficacy and Safety Study of Mepolizumab in Subjects With Moderate to Severe Atopic Dermatitis. ClinicalTrials.gov identifier: NCT03055195. Updated February 25, 2020. Accessed May, 3 2024. https://clinicaltrials.gov/study/NCT03055195
[18] Butala, S., Castelo-Soccio, L., Seshadri, R.; et al. J Allergy Clin Immunol Prac. 2023 May;11(5):1361-1373. doi: 10.1016/j.jaip.2023.03.011
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[20] Loiselle, A.R., Thibau, I.J. & Guadalupe, M. A patient survey to identify atopic dermatitis prescription treatment access barriers. J Am Acad Dermatol. 2022: 10.1016/j.jaad.2022.06.073
[21] McCleary, K.K. More Than Skin Deep 'Voice of the Patient' Report. (2020). https://www.morethanskindeep-eczema.org/report.html

National Eczema Association

Published scientific literature indicates that non-medical switching, which the NIH defines as, "a change in a stable patient's prescribed medication to a clinically distinct, non-generic, alternative for reasons other than poor clinical response, side-effects or non-adherence" has multiple negative influences on medical outcomes and healthcare utilization[22]. Non-medical switching had mostly negative effects in patients who were stable on a medication, including reduced medication adherence and poorer disease control[23] [24]. NEA-conducted research also indicates that 50% of AD patients experienced an insurance delay/denial in the past year across all currently available AD topical and systemic therapies[20]. Our research further highlighted the most commonly reported result of these access issues was a disease flare[25].

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

Sincerely,

Julie Block, President & CEO

Shawn Kwatra, MD
University of Maryland School of Medicine, Department of Dermatology Chairman,
Joseph W. Burnett Endowed Professor

Joy Wan, MD, MSCE
Assistant Professor of Dermatology
Johns Hopkins University School of Medicine

[22] J Mark Access Health Policy. 2020; 8(1): 1829883. Published online 2020 Oct 5. doi: 10.1080/20016689.2020.1829883
[23] Nguyen, Elaine et al. "Impact of non-medical switching on clinical and economic outcomes, resource utilization and medication-taking behavior: a systematic literature review." Current medical research and opinion vol. 32,7 (2016): 1281-90. doi:10.1185/03007995.2016.1170673
[24] Gilbert, Ileen et al. "The Impact of a Forced Non-Medical Switch of Inhaled Respiratory Medication Among Patients with Asthma or Chronic Obstructive Pulmonary Disease: A Patient Survey on Experience with Switch, Therapy Satisfaction, and Disease Control." Patient preference and adherence vol. 14 1463-1475. 20 Aug. 2020, doi:10.2147/PPA.S242215
[25] Loiselle, A.R., Thibau, I.J., Guadalupe, M., Butler L, Smith Begolka, W. A patient survey to identify atopic dermatitis prescription treatment access barriers. Br J Dermatol 188(Suppl 2) 2023. Ljac140.012. doi: 10.1093/bjd/ljac140.012

By Electronic Submission

May 10, 2024

Maryland Prescription Drug Affordability Board
16900 Science Drive, Suite 112-114
Bowie, MD 20715
comments.pdab@maryland.gov

Dear Members of the Maryland Prescription Drug Affordability Board ("Board"):

The Pharmaceutical Research and Manufacturers of America ("PhRMA") appreciates the opportunity to comment on the list of proposed therapeutic alternatives and sample dashboard (the "Sample Dashboard") of drugs identified for referral to the Stakeholder Council.[1] PhRMA represents the country's leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives.

PhRMA recognizes the Board's ongoing work to implement and carry out its responsibilities under the Maryland PDAB Statute ("PDAB Statute").[2] Consistent with our prior comment letters, however, PhRMA has concerns about the Board's implementation of the PDAB Statute, including a lack of adequate transparency and lack of sufficiently clear and meaningful standards.[3] As described below, these concerns pertain to both the Board's determination of therapeutic alternatives and the Sample Dashboard data relied upon by the Board for its ongoing drug selection and cost review processes.

I. TRANSPARENCY

PhRMA remains concerned that the Board's approach to implementing the PDAB Statute provides insufficient transparency with respect to the data and considerations that inform the Board's decision-making. Below, PhRMA highlights examples of the lack of transparency with respect to the Board's proposed list of therapeutic alternatives and the Board's Sample Dashboard of certain eligible drugs.

[1] *See* Board, Therapeutic Alternatives (for Drugs Referred to the Stakeholder Council), *available at* https://pdab.maryland.gov/Pages/cost_review_process.aspx#Therapeutic; Drugs Referred to the Stakeholder Council - Dashboard, *available at* https://pdab.maryland.gov/documents/comments/drugs_referred_stakeholder_council_dashboard_2024.xlsx.

[2] *See* Md. Code Ann., Health-Gen. § 21-2C-01-16 et seq.

[3] *See* Letter from PhRMA to Board Regarding Maryland Prescription Drug Affordability Board: Cost Review Study Process (Apr. 24, 2024); Letter from PhRMA to Board Regarding Rules of Construction and Open Meetings Proposed Rule; Confidential, Trade-Secret, and Proprietary Information; Public Comment Procedures; and Cost Study Review Process (Oct. 23, 2023); Letter from PhRMA to Board Regarding Definitions; Rules of Construction and Open Meetings; Confidential, Trade- Secret, and Proprietary Information; and Cost Review Study Process (June 30, 2023); Letter from PhRMA to Board Regarding Confidential, Trade-Secret, and Proprietary Information Proposed Rule (May 4, 2023); Letter from PhRMA to Board Regarding Rules of Construction and Open Meetings Proposed Rule (May 4, 2023); Letter from PhRMA to Board Regarding General Provisions; Fee Assessment, Exemption, Waiver, and Collection Amendments; and Cost Review Process (May 1, 2023). PhRMA incorporates by reference all comments, concerns, and objections that it has previously raised regarding the Board's implementation of the PDAB Statute.

A. Process for Identifying Therapeutic Alternatives

While the Board has published a list of proposed "therapeutic alternatives" for the eight drug products referred to the Stakeholder Council (the "Proposed List"), to date it has not provided a detailed description of how those proposed therapeutic alternatives were identified or how therapeutic alternatives will be identified for other drug products in the future. The Board staff's February 26, 2023 presentation on the process for selecting therapeutic alternatives includes an example of a selected drug's purported therapeutic alternatives that provided some details, such as whether a product was a biosimilar or generic, the therapeutic class, and indications for each of the purported therapeutic alternatives.[4] However, the Proposed List does not contain even these limited details. Rather, the only information that it provides is the names of the proposed therapeutic alternatives. This lack of information prevents the public from understanding the rationale that went into the selection of proposed therapeutic alternatives and impedes the ability of stakeholders to meaningfully comment on the Board's Proposed List or the Board's process for determining therapeutic alternatives.

The purpose of a comment period is to "give the agency free-flowing information from a broad range of interests."[5] Accordingly, the comment process is only meaningful to the extent proposals include adequate details and technical information to allow stakeholders to provide substantive feedback on the agency's proposals. Administrative law recognizes both the centrality of the comment process to an agency's activities and the necessity of providing members of the public with the information they need to meaningfully comment.[6]

In order to provide members of the public with a meaningful opportunity to review the Proposed List and provide substantive comments, PhRMA requests that the Board publicly release the information that informed the Board's creation of the list, subject to appropriate protections against the disclosure of confidential, proprietary, or trade secret information.[7] Following such publication, the Board should provide members of the public with a new opportunity to comment on the Proposed List.

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[4] *See* Board, Cost Review: Selection of Therapeutic Alternatives (Feb. 26, 2023), *available at* https://pdab.maryland.gov/documents/stakeholders/2024/pdasc_therapeutic_alternatives_02262024.pdf.

[5] *Adventist Healthcare Midatlantic, Inc. v. Suburban Hosp., Inc.*, 350 Md. 104, 123 (1998).

[6] *See* 75 Op. Atty Gen. Md. at 43 (Jan. 23, 1990) ("[T]he heart of an APA's rulemaking requirements is its public notice and comment procedures. Designed to assure fairness and mature consideration of rules of general application, these significant provisions serve the important twin functions of safeguarding public rights and educating the administrative lawmakers."), available at https://www.marylandattorneygeneral.gov/Opinions%20Documents/Volume75_1990.pdf. *See also Conn. Light and Power Co. v. Nuclear Reg. Com'n*, 673 F. 2d 525, 530–31 (D.C. Cir. 1982) (construing the federal Administrative Procedure Act, 5 U.S.C. § 553(b)(3)) ("An agency commits serious procedural error when it fails to reveal portions of the technical basis for a proposed rule in time to allow for meaningful commentary."); Md. Bar Ass'n, Practice Manual for the Maryland Lawyer, ch. 3, Administrative Law § 5 (6th Ed. 2023) (Maryland courts generally "seek to harmonize Maryland common administrative law and Maryland APA interpretation with federal administrative law").

[7] *See, e.g.*, Letter from PhRMA to Board Regarding Confidential, Trade-Secret, and Proprietary Information Proposed Rule (May 4, 2023).

B. Sample Dashboard and Other Data Considerations

PhRMA is also concerned about lack of transparency with respect to other data elements that the Board is relying on to carry out its responsibilities under the PDAB statute, including the data used to compile the Board's Sample Dashboard.[8] While the Board has published a Sample Dashboard containing data elements for the eight drug products referred to the Stakeholder Council for review, it has not made the data underlying the Sample Dashboard public, so stakeholders are unable to verify the data's accuracy or confirm how Board staff calculated various metrics. Notably, data in the Sample Dashboard contain several apparent limitations. For example, the Sample Dashboard does not state where cost information for each drug product was drawn from, and pricing data is from different years depending on the payer (2022 for commercial payers and 2020 for Medicare).[9] Because of the limited quantity and quality of data in the Sample Dashboards stakeholders will be unable to comprehensively review and determine whether the Board based its selection of drugs for referral to the Stakeholder Council on erroneous data.

To provide greater transparency with respect to the data being relied on by the Board for when performing its functions, PhRMA asks that the Board take the following additional steps:

- **Release of Full Dashboard**. PhRMA asks that the Board clarify the extent to which a comprehensive dashboard exists for all drugs determined to be eligible for cost reviews. To the extent more complete dashboard is available, we ask the Board to make public the full dashboards, subject to appropriate confidentiality and trade secret protections.[10] This would allow the stakeholders to review the data relied upon by the Board and provide information regarding any issues with the data used by the Board in its drug selection process. To the extent the Board does not have more complete dashboards, we ask that the Board provide more information about how it determined which products to refer for Stakeholder Council review and specifically, how it selected those drug products from among others it determined to be eligible for cost review.

- **Data Review Process**. PhRMA reiterates its prior requests that the Board establish a data review process for stakeholders to review and comment on potential errors in the data that the Board uses in its decision-making, including the data used as part of the dashboard and to select therapeutic alternatives.[11] The Board's activities rely on voluminous data from diverse sources. This creates an inherent risk that some data may be inaccurate, incomplete, or misleading. We ask that the Board provide manufacturers an opportunity to review, evaluate, confirm and meet with the Board about the data it is relying on before the Board decides on potential medicines to evaluate for affordability and before the Board decides on and publishes a list of medicines for affordability review. To provide protection for confidential, proprietary, and trade secret information as required under the PDAB Statute, the data review process should also include a confidential method for stakeholders to submit data regarding any issues found in the data that

[8] *See* Board, Drugs Referred to the Stakeholder Council- Dashboard, available at https://pdab.maryland.gov/documents/comments/drugs_referred_stakeholder_council_dashboard_2024.xlsx.
[9] *Id*. (eligible drug statistics worksheet).
[10] *See* Letter from PhRMA to Board (June 30, 2023), 4.
[11] *See* Letter from PhRMA to Board Regarding Maryland Prescription Drug Affordability Board: Cost Review Study Process (Apr. 24, 2024), 5; Letter from PhRMA to Board (May 1, 2023), 7.

the Board has relied on.[12] We ask that the Board not finalize any list of therapeutic alternatives or otherwise use therapeutic alternatives in its decision-making until this process is established and completed.

II. LACK OF CLEAR AND MEANINGFUL STANDARDS

A. Use of Therapeutic Alternatives

In addition to the issues described above, PhRMA continues to have concerns with the Board's consideration of therapeutic alternatives in its drug selection and cost review processes, including how it determines which drugs are a "therapeutic alternative" for drugs under consideration. The broad regulatory definition for "therapeutic alternative" could lead to certain therapies being identified as therapeutic alternatives that are not appropriate for all patients using the therapy.[13] In order to guide the Board's consideration of therapeutic alternatives in a manner that is consistent with clinical evidence, PhRMA recommends that the Board adopt a standard of "clinical appropriateness" for its identification of therapeutic alternatives for a selected drug. Specifically, when identifying the therapeutic alternatives for a drug subject to cost review, we ask that the Board do the following:

- Engage meaningfully with the manufacturer on potential therapeutic alternative(s);
- Look to clinician guidance, including physician-driven evidence-based clinical guidelines, as a resource; and
- Reference other widely recognized, scientifically rigorous, evidence-driven resources to identify therapeutic alternative(s).

We ask that, prior to publishing its proposed list of therapeutic alternatives in the future and prior to finalizing its current proposed list of therapeutic alternatives, the Board provide manufacturers an opportunity to review, provide feedback, and meet with the Board about the data it is relying on to select therapeutic alternatives and the therapeutic alternatives it has identified for the list.

Tailoring the therapeutic alternatives for drugs under consideration in this manner would help the Board avoid making comparisons between drugs in the drug selection and cost review process that may not be appropriate. As PhRMA has previously explained, not every drug product that has the same or a similar indication as a particular drug can be considered to be a therapeutic alternative.[14] A patient who can safely and effectively use one drug may experience increased risk of negative outcomes (e.g., drug

[12] *See* Md. Code Ann., Health-Gen. § 21-2C-10; *see also* Letter from PhRMA to Board Regarding Confidential, Trade-Secret, and Proprietary Information Proposed Rule (May 4, 2023).
[13] *See* Md. Code Regs. 14.01.01.01(B)(61) (defining "[t]herapeutic alternative" as "a drug product that has the same or similar indications for use as a particular drug but is not a therapeutic equivalent to that drug"); *see also* Md. Code Regs. 14.01.04.03(H), (I)(8), 14.01.04.05(C)(1)(c). For additional discussion regarding PhRMA's concerns with the consideration of therapeutic alternatives, *see, e.g.*, Letter from PhRMA to Board Regarding General Provisions; Fee Assessment, Exemption, Waiver, and Collection Amendments; and Cost Review Process (May 1, 2023).
[14] *See* Letter from PhRMA to Board (June 30, 2023), 6.

interactions, side effects, treatment failures) with another drug with a similar indication.[15] An approach to therapeutic alternatives that is targeted in this manner would reduce the risk of misleading comparisons that could skew the PDAB's consideration in a manner that has ramifications on the clinical choices of the prescribing health care provider and that interfere with the relationship between the patient and their health care provider.

Further, such an approach would better account for patients who rely on specific drug therapies to treat their conditions, such as those who are immune-compromised, pediatric patients, and women — particularly those who are pregnant — and the elderly. Patients in these groups in particular may respond differently to treatments and be limited to one specific drug therapy for their condition. In addition, patients also respond differently to treatment because of a number of factors, such as genetics, age, sex, socioeconomic status, drug-drug interactions, diet, environment, and co-morbidities. Specifically in the situation of co-morbidities that are managed effectively by a specific prescription drug regimen, switching to another medication could upset the stability of their ongoing treatment plan. Because the treatments that are the best option for some individuals are not as effective or safe for others, we ask that the Board carefully take these considerations into account in determining which drugs to compare as "therapeutic alternatives."

In addition to identifying therapeutic alternative(s) for a selected drug that are clinically appropriate, PhRMA strongly cautions the Board that drug cost should not play a role in determining of a selected drug's therapeutic alternative.

B. Consideration of Public Comments

PhRMA reiterates its request that the Board adopt additional procedures regarding how it will consider public comment in each step throughout the drug selection and cost review process, including in its deliberations on therapeutic alternatives.[16] The PDAB statute requires public notice and opportunity to comment on each meeting and pending decision of the Board; these requirements are further elaborated on in the Board's regulations.[17] In order to effectively implement these requirement, we ask that the Board provide additional transparency regarding how public comments are considered and how they impact the Board's decisions.[18] Greater transparency will give the public and stakeholders an understanding of how their concerns are being considered by the Board and how they are weighed in the Board's decision-making.

* * *

We thank you again for this opportunity to provide comments and feedback on the Board's drug selection and cost review processes and for your consideration of our concerns and requests for clarifications. Although PhRMA has concerns with the use of therapeutic alternatives in the Board's processes, we are

[15] McRae, J., Onukwugha, E. Why the Gap in Evaluating the Social Constructs and the Value of Medicines? PharmacoEconomics (2021), *available at* https://doi.org/10.1007/s40273-021-01075-w.
[16] *See e.g.*, Letter from PhRMA to Board Regarding Maryland Prescription Drug Affordability Board: Cost Review Study Process (Apr. 24, 2024), 5.
[17] *See* Md. Code Ann., Health-Gen. § 21-2C-03 (e)(2), (4)–(5); Md. Code Regs. 14.01.01.03(B), 14.01.01.05; 14.01.04.03(D)(4).
[18] This process should include protections for confidential, proprietary, or trade secret information received by the Board from stakeholders or other sources from inappropriate disclosure. *See* Letter from PhRMA to Board (June 30, 2023), 4.s

ready to be a constructive partner in this dialogue. If there is additional information or technical assistance that we can provide as therapeutic alternatives are considered and their use is deliberated, please contact Kristin Parde at Kparde@phrma.org.

Sincerely,

Kristin Parde
Deputy Vice President, State Policy

Merlin Brittenham
Assistant General Counsel, Law

sanofi

May 13, 2024

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

Re: Therapeutic Alternatives for Drugs Referred to the Stakeholder Council

Dear Members of the Maryland Prescription Drug Affordability Board,

Sanofi appreciates the opportunity to submit comments to the Maryland Prescription Drug Affordability Board ("Board") on the posted List of Proposed Therapeutic Alternatives to Dupixent ("Proposed List"). These comments were prepared by Sanofi's team of internal medical and scientific experts, which includes specialists in each of Dupixent's approved indications.

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

Sincerely,

Deanne Calvert
Head, State Government Relations, Sanofi

Executive Summary

Dupixent® (dupilumab) is a novel biologic agent, specifically designed to target the interleukin (IL)-4 and IL-13 pathways that are implicated in the direct causation of multiple type 2 inflammatory disease states (Dupixent United States Prescribing Information [USPI] 2024). It was first approved by the US Food and Drug Administration (FDA) on March 28, 2017, for atopic dermatitis (AD) and has been approved for four additional type 2 inflammatory disease states to date including: asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), prurigo nodularis (PN), and eosinophilic esophagitis (EoE) (Dupixent USPI 2024). Further, dupilumab has also received FDA approval for multiple age ranges: as young as 6 months in AD, as young as 6 years in asthma, and as young as 1 year in EoE. Approval in these indications and age ranges was based on thorough demonstration of efficacy and tolerability in a large clinical development program (Dupixent USPI 2024).

There are three additional potential indications under review by the FDA, with regulatory decisions anticipated by mid-2025: chronic obstructive pulmonary disease (COPD) with type 2 inflammation (FDA regulatory action date 06/27/24 [Sanofi Press Release 2024]), chronic spontaneous urticaria (CSU), and bullous pemphigoid (BP). The breadth of these indications, encompassing a range of diseases and therapeutic areas, highlights the unique mechanism of action of dupilumab and Sanofi's commitment to addressing unmet needs for patients impacted by diseases driven in part by type 2 inflammation.

Determination of therapeutic alternatives to a medicine is complex and involves multiple factors, including efficacy, safety, pharmacology, cost-effectiveness, and shared decision-making between a patient and their healthcare provider. Dupilumab is not an immunosuppressant (Cuellar-Barboza 2020), does not require laboratory monitoring as per the FDA prescribing information (Dupixent USPI 2024, Wollenberg 2020, Beck 2022), and has more than 7 years of real-world evidence demonstrating efficacy and safety in clinical practice. Compared with the therapeutic alternatives proposed by the Maryland Prescription Drug Affordability Board (MD PDAB), dupilumab is the only agent with a dual mechanism (blocks the signaling of both IL-4 and IL-13), making it pharmacologically separate from the other agents and not therapeutically interchangeable. These characteristics set it apart from the proposed alternatives identified by the MD PDAB, which have significant limitations including the following:

- Dupilumab is the only therapy with FDA-approved indications for five type 2 inflammatory diseases that frequently coexist
- Dupilumab is the only proposed alternative FDA approved and indicated for use in patients as young as 6 months with moderate-to-severe AD
- Dupilumab is the only AD biologic that is also FDA approved for use in asthma; up to 50% of patients with AD have coexisting asthma (Silverberg 2018)
  - The tralokinumab clinical development program failed and was discontinued in asthma (Panettieri 2018)
- Dupilumab is the only FDA-approved asthma biologic also approved in AD; up to 38% of patients with asthma have coexisting AD (Lee 2018)
  - All other FDA-approved asthma biologics have failed in AD (Guttman-Yassky 2023, Kang 2020, Heil 2010)
- Dupilumab is the only FDA-approved asthma biologic that is approved for oral corticosteroid (OCS)-dependent asthma
- Dupilumab is the only FDA-approved biologic for PN
- Dupilumab is the only FDA-approved biologic for EoE
- Dupilumab is the only FDA-approved AD biologic also approved in CRSwNP
- The Janus kinase (JAK) inhibitor listed alternatives (eg, upadacitinib and abrocitinib) are broad immunosuppressants. These agents are FDA approved in a limited manner (ie, to patients who have failed or are intolerant to other systemic therapies, including biologics). These agents are indicated in

a restrictive patient population, and require laboratory monitoring, tuberculosis testing, effective contraception, and herpes zoster vaccine before initiation of therapy
  - Further, the JAK inhibitor class of medicines has a Boxed Warning, which is the most serious warning issued by the FDA for an approved medicine in the US, due to this class having significant or potential life-threatening risks of adverse events such as serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis (Cibinqo USPI 2023, Rinvoq USPI 2024, FDA Guidance Document 2011)
- Topical therapies like tacrolimus ointment (Protopic®) are considered the mainstay of initial treatment for AD. Dupilumab is recommended as the first-line systemic therapy after failure of topical therapies; hence, tacrolimus is not interchangeable for dupilumab

Table 1 includes key characteristics of dupilumab and the proposed MD PDAB alternatives. In addition to these data, we have also provided background information related to the overlap of diseases with a type 2 inflammation component as well as considerations for the treatment of the five indications for dupilumab, including guidelines and practice parameters from the literature in **Appendix 1**. A summary of the clinical and economic value of dupilumab can be found in **Appendix 2**. We believe these comprehensive data, in addition to the above bulleted points, underscore the unique value proposition dupilumab provides to patients with a range of diseases driven in part by type 2 inflammation and ultimately supports our recommendation against including dupilumab in any drug cost review by the Board.

Table 1. Key characteristics of dupilumab and proposed MD PDAB alternatives[a]

Indications	Approvals and guideline recommendations	Dupixent® (dupilumab)[1–4]	Adbry® (tralokinumab)[2,5,6]	Cibinqo™ (abrocitinib)[2,7]	Rinvoq® (upadacitinib)[2,8]	Xolair® (omalizumab)[9–13]	Nucala® (mepolizumab)[14–21]	Fasenra® (benralizumab)[13,22–28]
	FDA approved for five type 2 inflammatory diseases	YES	No	No	No	No	No	No
AD	AAAAI/ACAAI recommended first-line systemic therapy	YES	YES	Second line after biologic failure	Second line after biologic failure	No	No	No
	FDA approved for ages ≥6 months	YES	Approved for ages ≥12 years	Approved for ages ≥12 years	Approved for ages ≥12 years	Failed clinical trial	Failed clinical trial	Failed clinical trial
ASTHMA	FDA approved for moderate-to-severe eosinophilic asthma ages ≥6 years	YES	Failed clinical trial	No	No	Approved for allergic asthma only	Approved for severe eosinophilic asthma only	Approved for severe eosinophilic asthma only
	FDA approved for OCS-dependent asthma	YES	No	No	No	No	No	No
EoE	FDA approved for EoE ages ≥1 years	YES	No	No	No	Failed clinical trial	Failed clinical trial	Failed clinical trial
PN	FDA approved for PN	YES	No	No	No	No	No	No
CRSwNP	FDA approved for CRSwNP	YES	No	No	No	YES	YES	No
COPD	Met primary end points in Phase 3 trials	YES	Not studied	Not studied	Not studied	Not studied	Failed clinical trial	Failed clinical trial

[a]Tacrolimus ointment (Protopic®) is not included, because it is not a systemic treatment for AD.

Table 1 abbreviations and references

AAAAI, American Academy of Allergy, Asthma, and Immunology; ACAAI, American College of Allergy, Asthma, and Immunology; AD, atopic dermatitis; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; EoE, eosinophilic esophagitis; FDA, US Food and Drug Administration; MD PDAB, Maryland Prescription Drug Affordability Board; OCS, oral corticosteroids; PN, prurigo nodularis.

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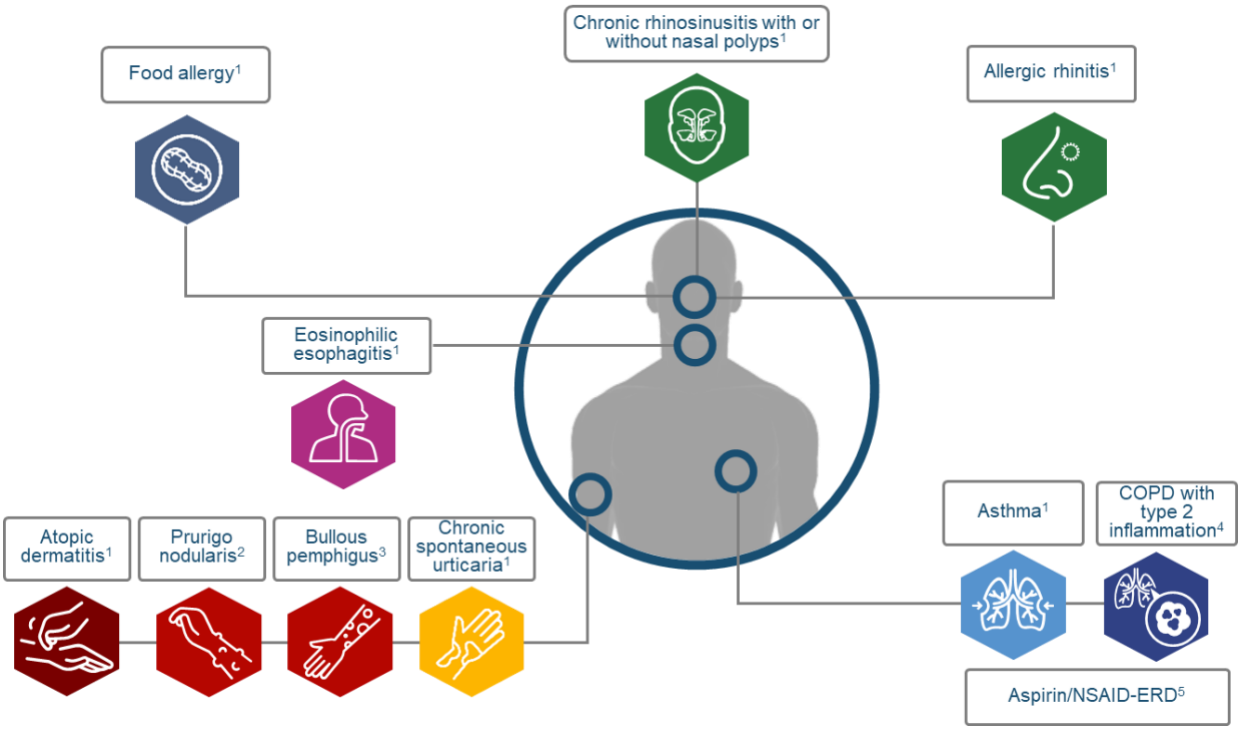
Appendix 1: Considerations for Treatment Choice in Patients With Atopic Dermatitis (AD), Asthma, Chronic Rhinosinusitis with Nasal Polyps (CRSwNP), Prurigo Nodularis (PN), and Eosinophilic Esophagitis (EoE)

Type 2 Inflammation

Type 2 inflammation plays a role in several chronic inflammatory disease states, including AD, asthma, CRSwNP, PN, EoE, and others. Figure 1 shows the broad range of diseases with a type 2 inflammatory component. Dupilumab is unique in that it is the only human monoclonal antibody that binds specifically to interleukin-4 receptor alpha (IL-4Rα), the shared receptor subunit for IL-4 and IL-13, thus inhibiting the dual signaling pathways of both IL-4 and IL-13 (Gandhi 2016, Le Floc'h 2020).

Figure 1. Diseases with a type 2 inflammation component



Co-existence of diseases driven in part by type 2 inflammation often affects treatment choices and shared decision-making between health care providers, patients, and caregivers. **Table 1** shows the percentage of patients in the dupilumab Phase 3 trials for AD, asthma, CRSwNP, and EoE who reported a history of select diseases with a type 2 component.

Table 1. Coexistence of type 2 inflammatory diseases in select dupilumab Phase 3 trials: Percentage of patients reporting a history of another atopic condition at screening visit for dupilumab clinical trials

	AD			Asthma		CRSwNP	EoE
	Adults aged ≥18 years (CHRONOS)[1]	Adolescents aged 12–17 years (ADOL)[2]	Children aged 6–11 years (AD-1652)[3,a]	Adults and adolescents aged ≥12 years (QUEST & VENTURE)[4–7]	Children aged 6–11 years (VOYAGE)[8]	Adults aged aged ≥18 years (SINUS)[9–11]	Adults and adolescents aged ≥12 years (TREET Part A)[12]
AD	NA	NA	NA	10%	36.3%	6%	19%
Any atopy	NA	NA	91.7%	NA	92.4%	N/A	84%
Asthma	39%	54%	46.7%	NA	NA	59%	31%
CRS[b]	6%	8%	3.0%	23%[b]	NA	100%	10%
CRSwNP	2%	2%	0.6%			NA	1%
Allergic rhinitis	43%	66%	60.2%	67%	81.9%	58%	59%
EoE	0.1%	0.4%	0.6%	0.1%	0.7%	0.6%	NA
Food allergy	33%	61%	64.4%	8%	17.9%	9%	44%
Allergic conjunctivitis	23%	23%	12.2%	13%	18.6%	11%	16%

Atopic Dermatitis

Dupilumab is the only US Food and Drug Administration (FDA)-approved AD systemic therapy that is also approved for asthma. The alternate biologic therapies approved for AD have failed in asthma clinical trials. Dupilumab is also the only AD biologic approved in patients aged 6 months and older.

The American Academy of Dermatology (AAD) 2023 guidelines gave dupilumab a strong recommendation for the treatment of moderate-to-severe AD, based on moderate certainty of evidence (Davis 2024). The guideline stated that dupilumab had an excellent safety track record in clinical trials and few major emergent safety concerns after more than 5 years in clinical practice. Despite having similar levels of recommendation for tralokinumab and Janus kinase (JAK) inhibitors, when surveyed, all participants from the guideline workgroup favored dupilumab as their first-line systemic agent. Dupilumab was also considered first-line by an international expert panel for use in special populations of adults, including older adults and those with renal disease, liver disease, viral hepatitis, HIV, or a history of cancer (Davis 2024). A summary of the AAD systemic therapy guidelines can be found in the supporting documents that follow this appendix.

The American Academy of Allergy, Asthma and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI) Joint Task Force also recently published practice parameters for atopic dermatitis (Chu 2024). A summary of the AAAAI/ACAAI 2023 practice parameters can be found in the supporting documents that follow this appendix.

This panel recommended adding dupilumab in patients aged 6 months of age or older with moderate-to-severe AD refractory, intolerant, or unable to use mid-potency or greater topical treatments (*strong recommendation, high certainty evidence*) (Chu 2024). When considering dupilumab vs other biologics, the panel did not issue a formal recommendation for one agent over another, but stated “The evidence for benefits, however, provides stronger support for dupilumab compared with agents targeting solely anti-IL-13, such as tralokinumab and lebrikizumab” (Chu 2024).

The panel considered oral JAK inhibitors, including abrocitinib and upadacitinib, second-line systemic therapy after biologics, specifically recommending use "in adults and adolescents with moderate-severe AD refractory, intolerant, or unable to use mid- to high-potency topical treatment and systemic treatment inclusive of a recommended biologic (dupilumab or tralokinumab)" *(conditional recommendation, low-certainty evidence)* (Chu 2024). They further stated that the risk-benefit profile of JAK inhibitors should be considered because of safety concerns and the boxed warnings for this class of agents. JAK inhibitors have a boxed warning for serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis (Chen 2023, Cibinqo US Prescribing Information [USPI] 2023, Rinvoq USPI 2024).

Asthma

Dupilumab is the only FDA-approved asthma biologic also approved in AD. This is important because real-world data estimate that up to 50% of patients with AD have coexisting asthma (Silverberg 2018). All the proposed therapeutic alternatives approved for asthma have failed in AD clinical trials.

The Global Initiative for Asthma (GINA), which launched in 1993 in collaboration between the National Heart, Lung, and Blood Institute, National Institutes of Health, and World Health Organization with the mission of improving the lives of people with asthma, releases a highly influential annual report that serves as guidance for clinical asthma treatment. In its 2023 report, GINA stressed the importance of comorbidities in asthma and recognized the additional FDA-approved indications for dupilumab, including for patients with comorbid CRSwNP, AD, and EoE as specific considerations for biologic agent selection. **Dupilumab is the only FDA-approved asthma biologic that is approved for patients with oral corticosteroid (OCS)-dependent asthma (without biomarker requirements)** (Dupixent USPI 2024). Overall, 30%–40% of patients aged ≥12 years with severe asthma require regular use of OCS, and up to 93% of patients aged >12 years with corticosteroid-dependent severe persistent asthma have at least 1 complication potentially due to OCS use (Lefebvre 2017, Sweeney 2016).

Several professional and patient advocacy organizations recognize the need to minimize OCS use in patients with severe asthma given the significant risk of adverse events. In its most recent release, the GINA report identifies multiple strategies to minimize OCS use, noting this as a high priority in severe asthma treatment to minimize common side effects. The report also includes chronic maintenance with OCS for asthma control as a criterion in favor of dupilumab when selecting a biologic in its treatment algorithm (GINA 2023).

The Allergy and Asthma Network, in its OCS Stewardship Statement, recognizes OCS overuse as a treatment plan failure and highlights the need to protect patients from both short-term and long-term health risks related to overexposure to OCS (OCS Stewardship Statement 2018).

The 2023 GINA Report can be found at this link, and the OCS Stewardship Statement can be found at this link.

Chronic Rhinosinusitis With Nasal Polyps

Dupilumab is the only FDA-approved biologic for patients with CRSwNP that is also approved for patients with AD.

The Joint Task Force on Practice Parameters (GRADE) guidelines for the management of CRSwNP, published in 2023 in the *Journal of Allergy and Clinical Immunology,* rendered an opinion in favor of the use of biologics in people with CRSwNP (Rank 2023). Furthermore, when considering patient-important and surrogate outcomes, dupilumab was considered most impactful in improving quality of life, symptoms, and smell improvement, and decreasing need for OCS and surgery when compared with the currently approved treatments, including the proposed therapeutic alternatives mepolizumab and omalizumab (Rank 2023).

Oykhman et al conducted a systematic review and network meta-analysis of 29 randomized controlled trials including data from >3400 patients and evaluating 8 advanced therapies (7 biologics and aspirin desensitization) for CRSwNP (Oykhman 2022).

The authors concluded that dupilumab uniquely ranked among the most beneficial for 7 out of 7 studied patient outcomes, in contrast to the proposed therapeutic alternatives omalizumab and mepolizumab, which were found to be most beneficial in 2 of 7 and 1 of 7 studied patient outcomes, respectively. This meta-analysis provides compelling evidence regarding the best CRSwNP treatments and better informs patients, clinicians, and policy makers on how to select from many CRSwNP treatment options (Oykhman 2022).

Complete results from Oykhman et al can be found in this manuscript.

Table 2. Summary of findings (Oykhman 2022)[1]

	Patient-important outcomes						Surrogate outcomes	
	HRQOL SNOT-22 (0–110)	**Symptoms** VAS (0–10 cm)	**Smell** UPSIT (0–40)[b]	**Rescue OCS**	**Rescue polyp surgery**	**Adverse events**	**Nasal polyp size** (0–8)	**CT score** LMK (0–24)
Standard care[a]	50.11	6.84	14.04	31.96%	21.05%	73.78%	5.94	18.35
Dupilumab	−19.91 (−22.50, −17.32)	−3.25 (−4.31, −2.18)	10.96 (9.75, 12.17)	−21.73 (−24.61, −18.22) RR 0.32 (0.23, 0.43)	−16.35 (−18.13, −13.48) RR 0.22 (0.14, 0.36)	0.13 (−8.12, 9.88) RR 1.00 (0.88, 1.13)	−2.04 (−2.73, −1.35)	−7.51 (−10.13, −4.89)
Omalizumab	−16.09 (−19.88, −12.30)	−2.09 (−3.15, −1.03)	3.75 (2.14, 5.35)	−12.46 (−23.65, 12.78) RR 0.61 (0.26, 1.40)	−7.40 (−11.04, −2.43) RR 0.65 (0.48, 0.88)	−2.60 (−15.58, 13.28) RR 0.96 (0.79, 1.18)	−1.09 (−1.70, −0.49)	−2.66 (−5.70, 0.37)
Mepolizumab	−12.89 (−16.58, −9.19)	−1.82 (−3.13, −0.50)	6.13 (4.07, 8.19)	−10.23 (−15.98, −2.88) RR 0.68 (0.50, 0.91)	−12.33 (−15.56, −7.22) RR 0.41 (0.26, 0.66)	−3.07 (−13.44, 9.07) RR 0.96 (0.82, 1.12)	−1.06 (−1.79, −0.34)	
Benralizumab	−7.68 (−12.09, −3.27)	−1.15 (−2.47, 0.17)	2.95 (1.02, 4.88)	−9.91 (−16.30, −0.96) RR 0.69 (0.49, 0.97)	−2.53 (−9.05, 7.16) RR 0.88 (0.57, 1.34)	−1.48 (−13.28, 12.54) RR 0.98 (0.82, 1.17)	−0.64 (−1.39, 0.12)	−1.00 (−3.83, 1.83)
Reslizumab					−18.82 (−20.93, 20.56) RR 0.11 (0.01, 1.98)	−2.55 (−19.49, 19.18) RR 0.97 (0.74, 1.26)		
AK001						2.54 (−27.11, 51.03) RR 1.03 (0.63, 1.69)	−0.20 (−1.61, 1.21)	
Etokimab	−1.30 (−8.99 to 6.40)					188.14 (−59.76, 4879.1) RR 3.55 (0.19, 67.13)	−0.33 (−1.58, 0.92)	
ASA Desensitization	−10.61 (−14.51, −6.71)	−2.74 (−3.92, −1.57)	2.72 (−1.17, 6.61)		−16.00 (−19.79, 0.21) RR 0.24 (0.06, 1.01)	209.21 (8.30, 901.87) RR 3.84 (1.11, 13.22)	−0.95 (−2.44, 0.55)	−0.31 (−3.50, 2.88)

Classification of intervention (color)[2]				Certainty (shading)[2,3]
Among most beneficial	Among intermediate beneficial	Among beneficial/not clearly different from placebo	No data (blank)	High/moderate (solid)
Among most harmful	Among intermediate harmful			Low/very low (shaded)

Eosinophilic Esophagitis

Dupilumab is the only FDA-approved asthma biologic also approved in EoE. Four different asthma biologics have failed in EoE clinical trials (omalizumab, reslizumab, mepolizumab, benralizumab) (Clayton 2014, Ridolo 2024).

EoE is a food allergen-triggered, immune-mediated, chronic inflammatory disease of the esophagus characterized by symptoms of esophageal dysfunction, such as swallowing difficulties and esophageal food impactions in adults and abdominal pain, food refusal, and vomiting in children, and histological/anatomical changes in the esophagus, such as strictures, due to chronic disease (Dellon

2018a; Muir 2021). EoE has emerged as a major cause of upper gastrointestinal morbidity over the past 3 decades, with current prevalence estimates in the US reaching 1 case per 1000 (Dellon 2018b). Epidemiological burden of EoE is also increasing rapidly, with the most recent nationwide data showing EoE-associated emergency department visits tripled between 2009 and 2019; these are projected to further double by 2030 (Lam 2023). Dupilumab was extensively studied in 52-week clinical trials and approved in May 2022 as the first and only medical therapy for EoE (for adolescents and adults), and later in January 2024, this indication was extended down to children as young as 1 year of age. **Dupilumab is the first and only biologic therapy approved for EoE, without any therapeutic alternatives approved for long-term use.** Real-world data from a study conducted at the Children's Hospital of Philadelphia have also demonstrated that dupilumab allowed safe introduction of EoE trigger foods in patients with EoE while controlling symptoms, preserving histologic integrity, and preventing endoscopic disease progression while also reducing the burden of dietary restrictions in children with this condition (Wolfset 2023).

Prurigo Nodularis

Dupilumab remains the first and only FDA-approved therapy for adult patients with PN, irrespective of disease severity and prior topical prescription treatment. PN is a chronic, inflammatory skin condition with an estimated prevalence of 72 per 100,000 adults in the US (Huang 2020). The diagnosis of PN is based on the following clinical features: firm, itchy lesions that can present as nodules, papules, or plaques, generally with a bilateral distribution on the arms and trunk; chronic pruritus lasting ≥6 weeks; history and/or signs of repeated scratching, picking, or rubbing (Pereira 2018, Kwon 2019, Elmariah 2021). Excoriations, crusts, lichenification, and pigmentary alterations develop due to ongoing scratching; areas less accessible to scratching, such as the middle of the back, are usually spared (Kwon et al 2019). PN mostly affects middle-aged to older patients (aged 50+ years) (Hughes 2020) and appears to be more common in skin of color (Whang 2019). PN signs and symptoms (intense itch, skin lesions, bleeding of excoriated lesions, scars) (Iking 2013, Pereira 2018, Pereira 2020) can have a severe impact on patients' quality of life and are associated with sleep disturbance, absenteeism from work, symptoms of depression and anxiety, and a feeling of shame and helplessness (Jørgensen 2017, Pereira 2018).

Dupilumab Pipeline

Dupilumab is expected to be the first FDA-approved therapy for the chronic treatment of the following diseases: COPD with type 2 inflammation and bullous pemphigoid (BP) (ClinicalTrials.gov NCT05649579). The FDA has accepted for Priority Review the supplemental Biologics License Application for dupilumab, with a target action date of June 27, 2024 for the FDA decision. Dupilumab is anticipated to be the first advanced therapy approved in patients with COPD in over a decade (Bhatt 2023, Sanofi Press Release 2023).

Results from dupilumab Phase 3 trials in patients with COPD with type 2 inflammation can be found in this manuscript (BOREAS) and this Sanofi press release (NOTUS).

Dupilumab is also in development for chronic spontaneous urticaria (CSU), chronic pruritus of unknown origin, eosinophilic gastritis, and ulcerative colitis with an eosinophilic phenotype (Maurer 2024, ClinicalTrials.gov NCT04180488, ClinicalTrials.gov NCT05263206, ClinicalTrials.gov NCT05831176, ClinicalTrials.gov NCT05731128).

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COPD, chronic obstructive pulmonary disease; NSAID-ERD, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease.

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Table 1 footnotes, abbreviations, and references

[a]Percentages were calculated using prevalence in each of the 3 treatment arms (placebo, dupilumab 300 mg q4w + TCS, and dupilumab 100 mg or 200 mg q2w + TCS). [b]Includes nasal polyps and/or CRS in QUEST study.
AD, atopic dermatitis; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; EoE, eosinophilic esophagitis; NA, not applicable; q2w, every 2 weeks; q4w, every 4 weeks; TCS, topical corticosteroids.

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Table 2 footnotes, abbreviations, and references

Numbers in the colored cells are the estimated mean differences (95% CI) for HRQOL, symptoms, smell, nasal polyp size, and CT score, and absolute risk differences (95% CI) per 100 patients (with accompanying relative risks [95% CI]) for rescue OCS, rescue nasal polyp surgery and adverse events vs standard care. GRADE certainty[2,3]: high certainty—further research is very unlikely to change our confidence in the estimate of effect; moderate certainty—further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low certainty—further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low certainty—any estimate of effect is very uncertain.
[a]The expected risk of each outcome with standard care is reported in the gray row. [b]The only scale presented where higher is better. Higher scores indicate worse outcomes for all other scales shown.
ASA, aspirin desensitization; CT, computed tomography; HRQOL, health-related quality of life; LMK, Lund-Mackay; OCS, oral corticosteroids; RR, risk ratio; SNOT-22, 22-item Sinonasal Outcome Test; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog score.

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SUPPORTING DOCUMENTS

AAD Guidelines Update for Atopic Dermatitis (AD)

Please complete a 2-minute survey to share your thoughts about this medical resource

Section I: AAD Guidelines on Topical Therapies and Comorbidities in Patients With AD

Topical Therapies

- The AAD workgroup developed 12 recommendations on the use of topical therapies in adults with AD, including nonprescription agents and prescription TCS, TCI, JAK inhibitors, PDE-4 inhibitors, antimicrobials, and antihistamines[1]
- For nonprescription therapies, moisturizers are strongly recommended with moderate certainty of evidence. However, the working group does not recommend using a particular moisturizer or active ingredient in an emollient based on the limited available evidence[1]
- There is a strong recommendation and high certainty of evidence for the use of prescription therapies, including TCS, TCI, and topical PDE-4 inhibitors[1]

Comorbidities

- In adults, there is clear evidence of an association between AD and atopic and immune-mediated conditions; ample evidence supporting an association between AD and mental health conditions (eg, depression, anxiety); and limited, but consistent evidence, supporting an association between AD and adverse bone health (eg, osteoporosis, fractures)[2]
- Targeted therapies that are effective for both severe AD and asthma, such as dupilumab, have the potential to benefit patients with both conditions[2]
- As biologics and other targeted agents continue to be evaluated, approved, and prescribed across different inflammatory conditions, medications with multiple indications have the potential to treat patients with 2 or more diseases simultaneously[2]

Section II: AAD Guidelines on Systemic Therapies in Patients With AD[3]

Monoclonal antibodies (biologics)

- For the treatment of moderate-to-severe AD (moderate certainty of evidence), **dupilumab** is strongly recommended
  - Dupilumab has an excellent safety track record in clinical trials and few major emergent safety concerns after more than 5 years in clinical practice. When surveyed, all participants from the guideline workgroup particularly favored dupilumab as their first-line systemic agent
  - It was also considered first-line therapy by an international expert panel (conducted before the approval of tralokinumab and JAK inhibitors) for use in special populations of adults, including older adults and those with renal disease, liver disease, viral hepatitis, HIV, or a history of cancer
  - Dupilumab at standard dosing (600 mg subcutaneously at initiation, then 300 mg every 2 weeks) is somewhat less efficacious than higher doses of abrocitinib and upadacitinib, with somewhat better efficacy than abrocitinib 100 mg daily and comparable efficacy to upadacitinib 15 mg daily
- For the treatment of moderate-to-severe AD (moderate certainty of evidence), **tralokinumab** is strongly recommended
- The AAD Guideline committee recommend both dupilumab and tralokinumab. These medications appear safe, and no laboratory monitoring is required before initiation or during treatment. Conjunctivitis is a common adverse event with both dupilumab and tralokinumab. For most patients, conjunctivitis is self-limited and can be managed conservatively with the use of artificial tears. Referral to ophthalmology should be considered, particularly if conjunctivitis is more severe, persistent, or refractory to conservative measures

JAK inhibitors

- **Upadacitinib** and **abrocitinib** are approved in patients with moderate-to-severe AD that did not respond to other systemic therapies. As such, in most circumstances, these medications are not considered to be a first-line systemic therapy. For the treatment of moderate-to-severe AD (moderate certainty of evidence), both **upadacitinib** and **abrocitinib** are strongly recommended
  - Both upadacitinib and abrocitinib demonstrated very high efficacy at reducing the signs and symptoms of AD and improving QOL, with rapid onset of action in their Phase 3 clinical trial programs among adolescents and adults with AD
  - The higher doses of upadacitinib (30 mg daily) and abrocitinib (200 mg daily) demonstrate the highest efficacy at reducing EASI scores for up to 16 weeks of treatment among all currently available treatments in a network meta-analysis and were superior to dupilumab in head-to-head trials
- For the treatment of moderate-to-severe AD (moderate certainty of evidence), **baricitinib** is strongly recommended. It is approved and available in the US for other immune-related conditions, but is not approved by the FDA to treat patients with AD
  - Although no head-to-head trials were done, network meta-analysis suggests baricitinib is less efficacious than upadacitinib and abrocitinib
- Because of potential safety concerns, the FDA recommended these medications be started at their lower doses. Serious adverse events, including death and thromboembolic events, have occurred in trials of patients with AD
- Based on safety data from other JAK inhibitors used in other populations, the FDA applied warnings of increased risk of serious heart-related events, cancer, blood clots, and death for the **JAK inhibitor class**
  - Other potential safety concerns with JAK inhibitors include an increased risk of serious and opportunistic infections, including herpes zoster. Vaccination for shingles is recommended before initiating a JAK inhibitor, particularly for older patients
  - The FDA recommends performing the following laboratory monitoring: complete blood count with differential and liver enzymes at baseline and after initiation or dose-escalation; lipids after initiation; testing for viral hepatitis, tuberculosis, and pregnancy at baseline

Systemic treatments with insufficient evidence to make recommendations

- There are insufficient data to make a recommendation on the use of PUVA phototherapy, systemic antibiotics, oral antihistamines, montelukast, apremilast, ustekinumab, IVIG, interferon-γ, omalizumab, TNF-α inhibitors, systemic calcineurin inhibitors (other than cyclosporine), or mepolizumab in the management of AD

References

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3. Davis DMR, Drucker AM, Alikham A, et al. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic agents. *J Am Acad Dermatol*. 2023. doi: https://doi.org/10.1016/j.jaad.2023.08.102.

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Section III: Recommendations From the AAD Guidelines on Systemic Therapies in Patients With AD[3]

Recommendations for the management of AD in adults with phototherapy and systemic agents

Intervention	US Regulatory Status[a]	Recommendation[b] and Strength	Certainty of Evidence	Remarks
Dupilumab	On-label	For adults with moderate-to-severe AD, we **strongly** recommend dupilumab	Moderate	
Tralokinumab	On-label	For adults with moderate-to-severe AD, we **strongly** recommend tralokinumab	Moderate	
Upadacitinib	On-label	For adults with moderate-to-severe AD, we **strongly** recommend upadacitinib	Moderate	Upadacitinib is approved by the FDA in patients with AD that has not responded to other systemic therapies or when use of those therapies is inadvisable
Abrocitinib	On-label	For adults with moderate-to-severe AD, we **strongly** recommend abrocitinib	Moderate	Abrocitinib is approved by the FDA in patients with AD that has not responded to other systemic therapies or when use of those therapies is inadvisable
Baricitinib	Off-label	For adults with moderate-to-severe AD, we **strongly** recommend baricitinib	Moderate	Baricitinib is not approved by the FDA in AD
Methotrexate	Off-label	For adults with moderate-to-severe AD, we **conditionally** recommend methotrexate with proper monitoring	Low	Comorbidities or drug interactions may exacerbate toxicity, making this intervention inappropriate for select patients. In the US, the FDA has not approved methotrexate in AD
Systemic corticosteroids (eg, prednisone)	On-label	For adults with AD, we **conditionally** recommend against systemic corticosteroids	Low	Their use should be reserved exclusively for acute, severe exacerbations and as a short-term bridge therapy to other systemic, steroid-sparing therapy
Mycophenolate mofetil[c]	Off-label	For adults with refractory moderate-to-severe AD, we **conditionally** recommend mycophenolate mofetil with proper monitoring	Very low	Mycophenolate mofetil is not approved by the FDA in AD. Comorbidities or drug interactions may exacerbate toxicity, making this intervention inappropriate for select patients
Azathioprine	Off-label	For adults with refractory moderate-to-severe AD, we **conditionally** recommend TPMT-dosed azathioprine with proper monitoring	Low	Comorbidities or drug interactions may exacerbate toxicity, making this intervention inappropriate for select patients
Cyclosporine	Off-label	For adults with refractory moderate-to-severe AD, we **conditionally** recommend limited term use of cyclosporine with proper monitoring	Low	The FDA has not approved cyclosporine in AD. Comorbidities or drug interactions may exacerbate toxicity, making this intervention inappropriate for select patients
Phototherapy (all types)	On-label	For adults with AD, we **conditionally** recommend phototherapy	Low	Most current literature reports the efficacy and safety of narrow band UVB. Wherever possible, use a light source that minimizes the potential for harm under the supervision of a qualified clinician

[a]For medications, whether they are used on- or off-label for AD based on FDA approval. [b]The supporting evidence used for this table can be found here. [c]Mycophenolic acid can be used interchangeably depending on availability. Note that dosing differs for mycophenolic acid and mycophenolate mofetil.

Links to relevant documentation

- Dupilumab USPI
- AAD Guidelines for AD Systemic Therapies
- AAD Guidelines for AD Topical Therapies
- AAD Guidelines for AD Comorbidities

Abbreviations

AAD	American Academy of Dermatology
AD	Atopic dermatitis
EASI	Eczema Area and Severity Index
FDA	US Food and Drug Administration
IVIG	Intravenous immunoglobin
JAK	Janus kinase
PDE-4	Phosphodiesterase-4
PUVA	Psoralen plus ultraviolet A
QOL	Quality of life
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TNF	Tumor necrosis factor
TPMT	Thiopurine methyltransferase
USPI	United States prescribing information
UV	Ultraviolet

AD Executive Summary: AAAAI / ACAAI Joint Task Force Atopic Dermatitis Guidelines

Please complete this 2-minute survey to share your thoughts about this medical resource

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Please see a summary of the evidence-based recommendations for the optimal management of AD in infants, children, and adults. This guidance was developed by a multidisciplinary guideline panel consisting of patients and caregivers, AD experts, PCPs, and allied health professionals using the GRADE approach. Access guidelines HERE.

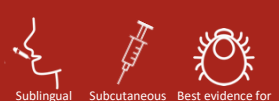
Background

How do the 2023 AAAAI/ACAAI JTF AD guidelines differ from the 2012 guidelines?

- Emphasis on evidence-based medicine and patient values and preferences
- Increased focus on diagnosis, education, trigger avoidance, proper medication use/adherence, and use of moisturizer for symptoms
- Inclusion of new therapies that have emerged in the past 10 years, including biologics

AD AAAAI/ACAAI JTF 2023 Guidelines: Summary of Recommendations

INTERVENTION Treatment or category of treatments considered	SEVERITY Severity of AD	RECOMMENDATION Text summary of recommendation	STRENGTH The strength of the recommendation	CERTAINTY GRADE rating for the certainty of evidence
SYSTEMIC TREATMENTS Consider if refractory, intolerant, or unable to use mid- to high-potency topical treatment	MODERATE, SEVERE	BIOLOGICS / MONOCLONAL ANTIBODIES **DUPILUMAB** (Age 6 mo+) We **recommend** adding dupilumab	**Strong** in favor	**High** certainty evidence
	MODERATE, SEVERE	BIOLOGICS / MONOCLONAL ANTIBODIES **TRALOKINUMAB** (Age 12 yo+) We **recommend** adding tralokinumab	**Strong** in favor	**High** certainty evidence
Consider if refractory, intolerant, or unable to use mid- to high-potency topical treatment and systemic treatment inclusive of a biologic recommended above See conditions to consider, eg, comorbidities, risk factors, values and preferences, and exceptional circumstances	MODERATE, SEVERE	**UVB TREATMENT** We **suggest** adding clinic-based narrow band UVB treatment	**Conditional** in favor	**Low** certainty evidence
	MODERATE, SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **ABROCITINIB, BARICITINIB, OR UPADACITINIB** (Age varies: 12 or 18 yo+) We **suggest** adding one of these three JAK inhibitors Suggested daily doses: Abrocitinib 100–200 mg; Baricitinib 2–4 mg; Upadacitinib 15–30 mg	**Conditional** in favor	**Low** certainty evidence
	MODERATE, SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **BARICITINIB 1 mg DAILY** We **recommend against** adding baricitinib 1 mg daily	**Strong** against	**Low** certainty evidence
	MODERATE, SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **AZATHIOPRINE** We **suggest against** adding azathioprine	**Conditional** against	**Low** certainty evidence
	MODERATE, SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **CYCLOSPORINE** We **suggest** adding cyclosporine Shared decision-making should determine whether to start therapy at high dose (5 mg/kg) or low dose (3 mg/kg)	**Conditional** in favor	**Low** certainty evidence
	MODERATE, SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **METHOTREXATE** We **suggest against** adding methotrexate	**Conditional** against	**Low** certainty evidence
	MODERATE, SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **MYCOPHENOLATE** We **suggest against** adding mycophenolate	**Conditional** against	**Low** certainty evidence
Chu et al Network meta-analysis	MILD, MODERATE, SEVERE	**SYSTEMIC CORTICOSTEROIDS** We **suggest against** systemic corticosteroids for all patients with atopic dermatitis	**Conditional** against	**Low** certainty evidence
TOPICAL TREATMENTS	MILD, MODERATE, SEVERE	**PRESCRIPTION MOISTURIZERS** We **suggest against** using prescription moisturizers rather than a fragrance-free over-the-counter moisturizer	**Conditional** against	**Low** certainty evidence
If refractory to moisturizers	MILD, MODERATE, SEVERE	**TOPICAL CORTICOSTEROIDS** (Age 3 mo+) We **recommend** adding a topical corticosteroid	**Strong** in favor	**High** certainty evidence
	MILD, MODERATE, SEVERE	**TOPICAL CALCINEURIN INHIBITORS** (Age 3 mo+) We **recommend** adding a topical calcineurin inhibitor	**Strong** in favor	**High** certainty evidence
	MILD, MODERATE	**TOPICAL PDE4 INHIBITORS** (Age 3 mo+) We **suggest** adding crisaborole	**Conditional** in favor	**Moderate** certainty evidence
	MILD, MODERATE	**TOPICAL JAK INHIBITORS** (Age 12 yo+) We **suggest against** adding topical ruxolitinib	**Conditional** against	**Low** certainty evidence
	MILD, MODERATE, SEVERE	**APPLICATION FREQUENCY** We **suggest** applying mid- to high-potency topical medicines once per day over twice per day	**Conditional** in favor	**Low** certainty evidence
Localized lesions refractory to mid- to high-potency topical treatment	MODERATE, SEVERE	**OCCLUSIVE APPLICATION** (WET WRAPS) We **suggest** a time and body surface area-limited trial of occlusive low- to mid-potency topical steroid	**Conditional** in favor	**Very low** certainty evidence
	MILD, MODERATE, SEVERE	**TOPICAL ANTIMICROBIALS** We **suggest against** adding topical antimicrobials to topical anti-inflammatories in patients with no clear signs of infection	**Conditional** against	**Very low** certainty evidence
Chu et al Network meta-analysis Devasenapathy & Chu meta-analysis	MILD, MODERATE, SEVERE	**MAINTENANCE OF REMISSION** We **recommend** use of proactive therapy to areas that flare with a topical calcineurin inhibitor or mid-potency topical steroid	**Strong** in favor	**Moderate** certainty evidence

INTERVENTION Treatment or category of treatments considered	SEVERITY Severity of dermatitis that this recommend-ation applies to	RECOMMENDATION Text summary of recommendation	STRENGTH The strength of the recommendation	CERTAINTY GRADE rating for the certainty of evidence
BLEACH BATHS  Bakaa et al 2022. Systematic review	MODERATE, SEVERE	We **suggest** adding dilute bleach bathing	**Conditional** in favor	**Low** certainty evidence
	MILD	We **suggest against** adding dilute bleach bathing	**Conditional** against	**Low** certainty evidence
ELIMINATION DIETS  Oykhman et al Systematic review	MILD, MODERATE, SEVERE	We **suggest against** the use of elimination diets	**Conditional** against	**Low** certainty evidence
ALLERGEN IMMUNOTHERAPY  Sublingual · Subcutaneous · Best evidence for dust mite allergy Ypes-Nuñez & Chu et al Systematic review	MODERATE, SEVERE	We **suggest** adding allergen immunotherapy If refractory, intolerant, or unable to use mid-potency topical treatments	**Conditional** in favor	**Moderate** certainty evidence
	MILD	We **suggest against** adding allergen immunotherapy See conditions to consider, eg, comorbidities, values and preferences	**Conditional** against	**Moderate** certainty evidence

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Systemic Treatment Recommendations for AD

	Dupilumab	Tralokinumab	Lebrikizumab	Abrocitinib		Baricitinib		Upadacitinib	
	Standard dose	Standard dose	Standard dose	Low dose (100 mg)	High dose (200 mg)	Low dose (1 mg)	High dose (2–4 mg)	Low dose (15 mg)	High dose (30 mg)
EASI	✓✓	✓	✓	✓	✓	–	✓	✓✓	✓✓
POEM	✓✓	✓	✓	✓	✓✓	–	✓	✓✓	✓✓
Itch NRS	✓	–	✓	✓	✓	–	–	✓	✓✓
Sleep NRS	✓✓	–	✓✓	–	✓✓	–	✓✓	N/A	N/A
DLQI	✓	–	✓	–	✓	–	–	✓✓	✓✓
AD flares	✓	✓	?	✓	✓✓	?	?	✓✓	✓✓
Any AE	–	–	?	–	✗	–	✗	✗	✗✗
SAE	–	–	?	?	?	?	?	?	?

High- to moderate-certainty evidence

- ✓✓ Among the most effective
- ✓ Among the intermediate (superior) effective
- ✓ Among the intermediate (inferior) effective
- – Not clearly different from placebo
- ✗ Among the intermediate harmful
- ✗✗ Among the most harmful

Low- to very-low-certainty evidence

- ? Possibly not clearly different from placebo

- **Dupilumab:** In patients aged 6 months or older with moderate-to-severe AD refractory, intolerant, or unable to use mid-potency or greater topical treatment, the JTF panel recommends adding dupilumab over continued standard topical treatment without dupilumab ***(Strong recommendation, high-certainty evidence)***
- **Tralokinumab:** In patients aged ≥12 years with moderate-to-severe AD refractory, intolerant, or unable to use mid-potency topical treatment, the JTF panel recommends adding tralokinumab over continued topical treatment without tralokinumab ***(Strong recommendation, high-certainty evidence)***

> *"Although the panel provides strong recommendations for dupilumab or tralokinumab, available evidence does not address combination therapy, and as such, the panel recommends using either agent, based on contextual factors, rather than both agents together. The panel did not yet issue a formal recommendation for one agent over the other. The evidence for benefits, however, provides stronger support for dupilumab compared with agents targeting solely IL-13, such as tralokinumab or lebrikizumab"*

- **Oral JAK inhibitors (abrocitinib, baricitinib, upadacitinib):** In adults and adolescents with moderate-to-severe AD refractory, intolerant, or unable to use mid- to high-potency topical treatment and systemic treatment inclusive of a recommended biologic (dupilumab or tralokinumab), the panel suggests replacing the systemic treatment with one of the following, over not using one of these JAK inhibitors ***(Conditional recommendation, low-certainty evidence)***
  - **Abrocitinib** 100–200 mg (aged ≥12 years)
  - **Baricitinib** 2–4 mg (aged ≥18 years)
  - **Updacitinib** 15–30 mg (aged ≥12 years)

Abbreviations, References, and Additional Resources

Abbreviations:

AAAAI, American Academy of Allergy, Asthma, and Immunology; ACAAI, American College of Allergy, Asthma, and Immunology; AD, atopic dermatitis; AE, adverse event; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IL, interleukin; JAK, Janus kinase; JTF, Joint Task Force; mo, months; NRS, numeric rating scale; PCP, primary care physician; PDE4, phosphodiesterase-4; POEM, Patient-Oriented Eczema Measure; SAE, serious adverse event; UV, ultraviolet; yo, years old.

Reference:

- Chu DK, et al. *Ann Allergy Asthma Immunol*. 2023 Dec 18:S1081–1206(23):01455–2. [click here for full text article]

Additional resources:

- Supplemental information on the AD guidelines can be downloaded here

DUPILUMAB PRESCRIBING INFORMATION

https://www.regeneron.com/downloads/dupixent_fpi.pdf

Please reach out if you have questions or would like additional information.

Warm regards,

Sanofi Medical Value & Outcomes (MVO) Team

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Appendix 2: Clinical and Economic Value of Dupixent® (Dupilumab)

Atopic Dermatitis

Atopic dermatitis (AD) is a type 2 immune-mediated skin disease with a multifactorial etiology, characterized by chronic systemic inflammation and skin barrier dysfunction (Gandhi 2016). AD onset can occur during infancy or childhood; in most patients with AD, disease onset occurs between ages 3 months to 2 years (Bieber 2017, Weidinger 2016). Particularly in children with severe disease, this chronic disease can persist through adolescence and into adulthood. After diagnosis, 20% of childhood-onset AD cases persist for 8 years and 5% persist for 20 years (Kim 2016). In the United States (US), the prevalence of AD is estimated to be 10.2% in young children aged 6 months to 5 years, 10.0% in children aged 6 to 11 years, 9.3% in adolescents, and 3.2% in adults (Silverberg 2017, Silverberg 2021). Uncontrolled moderate-to-severe disease is estimated to occur in 274,000 young children aged 6 months to 5 years, 320,000 children aged 6 to 11 years, 389,000 adolescents, and 1.6 million adults (Sanofi and Regeneron, Data on file, Infant and young childhood AD epidemiology funnel; Sanofi and Regeneron, Data on file, Childhood AD epidemiology funnel; Sanofi and Regeneron, Data on file, Adolescent AD epidemiology funnel; Sanofi and Regeneron, Data on file, Adult AD epidemiology funnel).

In the US, the 1-year prevalence of hand eczema is estimated to be 10%, with a lifetime prevalence of 15% (Thyssen 2010). In patients with a history of AD, the proportion of patients with current or previous hand dermatitis was 34.4% in adults and 79.9% in children and adolescents (Quaade 2021). For patients with active AD, the prevalence of hand dermatitis can be as high as 60% overall (age 0–2 years, 43.7%; 3–12 years, 54.1%; >12 years, 63.9%) (Simpson 2006). A total of 30% of patients present with foot dermatitis (Agner 2015).

Dupilumab is indicated for the treatment of adult and pediatric patients aged ≥6 months with moderate-to-severe AD, whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab can be used with or without topical corticosteroids (TCS) (Dupixent US Prescribing Information [USPI] 2024).

In several randomized, double-blinded clinical trials (6 in adults and 4 in pediatric patients), dupilumab provided significant, rapid, sustained, and clinically meaningful improvements in AD signs, symptoms, and health-related quality of life (HRQOL) in patients aged ≥6 months with moderate-to-severe AD.

Note: Study results for approved dose regimens are summarized below.

- **Adults aged ≥18 years**
  - Pooled analysis of Week 16 data from two phase 3 randomized trials (SOLO 1 and SOLO 2) (Thaçi 2019):
    - The proportion of patients achieving an Investigator's Global Assessment (IGA) score of 0 or 1 (clear or almost clear skin) and a ≥2-point reduction from baseline in IGA was statistically significantly greater in the dupilumab 300 mg once every 2 weeks (q2w) arm than in the placebo arm (37.0% vs 9.3%, respectively; *P*<0.0001)
    - The proportion of patients achieving ≥75% improvement from baseline in lesion extent and severity, measured by the Eczema Area and Severity Index (EASI-75), was statistically significantly greater in the dupilumab 300 mg q2w arm than in the placebo arm (47.7% vs 13.3%, respectively; *P*<0.0001)
    - The proportion of patients with improvement in itch based on achieving a ≥4- or ≥3-point reduction from baseline in the weekly average of the daily Peak Pruritus Numerical Rating Scale (PP-NRS) scores were statistically significantly greater in the dupilumab 300 mg q2w arm than in the placebo arm (≥4-point reduction: 38.4% vs 10.9%, respectively; ≥3-point reduction: 48.8% vs 15.0%, respectively; *P*<0.0001 for both comparisons)

- CHRONOS (Blauvelt 2017):
  - At Week 16, the proportion of patients achieving an IGA score of 0 or 1 and a ≥2-point reduction from baseline in IGA score was statistically significantly greater in the dupilumab 300 mg q2w + TCS arm than in the placebo + TCS arm (39% vs 12%, respectively; *P*<0.0001)
  - At Week 16, the proportion of patients achieving EASI-75 was statistically significantly greater in the dupilumab 300 mg q2w + TCS arm than in the placebo + TCS arm (69% vs 23%, respectively; *P*<0.0001)
  - At Week 16, the proportion of patients with ≥4- or ≥3-point reduction from baseline in the weekly average of the daily PP-NRS scores was statistically significantly greater in the dupilumab 300 mg q2w + TCS arm than in the placebo + TCS arm (≥4-point reduction: 59% vs 20%, respectively; ≥3-point reduction: 66% vs 28%, respectively; *P*<0.0001 for both comparisons)
  - At Week 52, the proportion of patients achieving an IGA score of 0 or 1 and a reduction from baseline of ≥2 points was statistically significantly greater in the dupilumab 300 mg q2w + TCS arm than in the placebo + TCS arm (36% vs 13%, respectively; *P*<0.0001)
  - At Week 52, the proportion of patients achieving EASI-75 was statistically significantly greater in the dupilumab 300 mg q2w + TCS arm than in the placebo + TCS arm (65% vs 22%, respectively; *P*<0.0001)
  - At Week 52, the proportion of patients with ≥4- or ≥3-point reduction from baseline in the weekly average of the daily PP-NRS scores was statistically significantly greater in the dupilumab 300 mg q2w + TCS arm than in the placebo + TCS arm (≥4-point reduction: 51% vs 13%, respectively; ≥3-point reduction: 56% vs 16%, respectively; *P*<0.0001 for both comparisons)

- **Adolescents aged 12 to 17 years**
  - The proportion of patients achieving an IGA score of 0 or 1 at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg (weight-based dosing) q2w arm than in the placebo arm (24% vs 2%, respectively; *P*<0.001) (Simpson 2020)
  - The proportion of patients achieving EASI-75 at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg q2w arm than in the placebo arm (41% vs 8%, respectively; *P*<0.001) (Simpson 2020)
  - The proportion of patients achieving a ≥4-point reduction in PP-NRS scores at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg q2w arm than in the placebo arm (37% vs 5%, respectively; *P*<0.001) (Simpson 2020)
  - Efficacy was sustained in the adolescent population through Week 52 (Blauvelt 2022)
- **Children aged 6 to 11 years**
  - In the general study population, the proportion of patients achieving IGA 0 or 1 at Week 16 was statistically significantly greater in the dupilumab once every 4 weeks (q4w) + TCS and dupilumab q2w + TCS arms than in the placebo + TCS arm (*P*<0.001 for both comparisons) (Paller 2020)
    - Among patients weighing <30 kg, the proportion achieving IGA 0 or 1 at Week 16 was significantly greater in those treated with dupilumab 300 mg q4w + TCS than in those treated with placebo + TCS (29.5% vs 13.1%, respectively; nominal *P*<0.05)
    - Among patients weighing ≥30 kg, the proportion achieving IGA 0 or 1 at Week 16 was significantly greater in those treated with dupilumab 200 mg q2w + TCS than in those treated with placebo + TCS (39.0% vs 9.7%, respectively; nominal *P*<0.001)

- In the general study population, the proportion of patients achieving EASI-75 at Week 16 was statistically significantly greater in the dupilumab q4w + TCS and dupilumab q2w + TCS arms than in the placebo + TCS arm (*P*<0.0001 for both comparisons) (Paller 2020)
    - Among patients weighing <30 kg, the proportion achieving EASI-75 at Week 16 was significantly greater in those treated with dupilumab 300 mg q4w + TCS than in those treated with placebo + TCS (75.4% vs 27.9%, respectively; nominal *P*<0.0001)
    - Among patients weighing ≥30 kg, the proportion achieving EASI-75 at Week 16 was significantly greater in those treated with dupilumab 200 mg q2w + TCS than in those treated with placebo + TCS (74.6% vs 25.8%, respectively; nominal *P*<0.0001)
- In the general study population, the proportion of patients achieving a ≥4-point reduction in the weekly average of daily PP-NRS scores at Week 16 was statistically significantly greater in the dupilumab q4w + TCS and dupilumab q2w + TCS arms than in the placebo + TCS arm (*P*<0.0001 for both comparisons) (Paller 2020)
    - Among patients weighing <30 kg, the proportion achieving a ≥4-point reduction in the weekly average of daily PP-NRS scores at Week 16 was significantly greater in those treated with dupilumab 300 mg q4w + TCS than in those treated with placebo + TCS (54.1% vs 11.7%, respectively; nominal *P*<0.0001)
    - Among patients weighing ≥30 kg, the proportion achieving a ≥4-point reduction in the weekly average of daily PP-NRS scores at Week 16 was significantly greater in those treated with dupilumab 200 mg q2w + TCS than in those treated with placebo + TCS (61.4% vs 12.9%, respectively; nominal *P*<0.0001)

- **Infants and young children aged 6 months to 5 years**
    - The proportion of patients achieving an IGA score of 0 or 1 at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg (weight-based dosing) q4w + TCS arm than in the placebo + TCS arm (28% vs 4%, respectively; *P*<0.0001) (Paller 2022a)
    - The proportion of patients achieving EASI-75 at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg + TCS arm than in the placebo + TCS arm (53% vs 11%, respectively; *P*<0.0001) (Paller 2022a)
    - The proportion of patients with a ≥4-point reduction in the weekly average of daily Worst Scratch/Itch scores at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg + TCS arm than in the placebo + TCS arm (48% vs 9%, respectively; *P*<0.0001) (Paller 2022a)
- **AD with hand and/or foot involvement in adult and adolescent patients aged ≥12 years**
    - The proportion of patients achieving an IGA score (hand and foot) of 0 or 1 at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg q2w arm than in the placebo arm (40.3% vs 16.7%, respectively; *P*=0.003), with separation between groups evident from Week 4 through Week 16 (Simpson 2023)
    - The proportion of patients achieving ≥75% reduction in hand eczema severity index-75 at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg q2w arm than in the placebo arm (46.9% vs 21.5%, respectively; *P*<0.01) (Simpson 2023)
    - The proportion of patients achieving a ≥4-point reduction in the weekly average of daily PP-NRS scores (hand and foot) at Week 16 was statistically significantly greater in the dupilumab 200 mg/300 mg arm than in the placebo arm (52.2% vs 13.6%, respectively; *P*<0.0001) (Simpson 2023)

Dupilumab had a positive benefit-risk ratio and was generally well tolerated in patients with moderate-to-severe AD, supported by data from clinical trials of infants and young children (aged 6 months–5 years), children (aged 6–11 years), and adolescents (aged 12–17 years) treated for up to 52 weeks and adults treated for up to 3 years.

- According to data released in May 2023, more than 600,000 patients are being treated with dupilumab globally (Sanofi Press Release 2023).
  - The most common adverse events (AEs) with dupilumab (incidence ≥1%) in AD clinical trials were injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infections, dry eye, and eosinophilia (Dupixent USPI 2024)
  - AEs reported with dupilumab were generally mild or moderate and occurred with an overall similar incidence compared with that of placebo (Blauvelt 2017, Simpson 2023, Thaçi 2019, Worm 2020); the long-term safety/tolerability profile observed in adult patients treated for up to 4 years and adolescent patients treated for up to 1 year were consistent with that seen in studies of shorter treatment duration (Beck 2022, Blauvelt 2022)
  - In adult patients, lower risk of serious and severe infections, as well as nonherpetic skin infections, were observed with dupilumab vs placebo; no increase in the incidence of overall infections was observed with dupilumab vs placebo (Eichenfield 2019). In pediatric patients, lower risk of total skin infections (patients aged 6–17 years) and nonherpetic skin infections (patients aged 6 months–17 years) was observed with dupilumab vs placebo; no increase in the incidence of overall infections or serious and severe infections was observed with dupilumab vs placebo (Paller 2022b, Siegfried 2022)
  - Conjunctivitis, including conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, and viral conjunctivitis, in patients with moderate-to-severe AD was generally mild to moderate and mostly resolved while patients continued dupilumab treatment; treatment discontinuation was rarely required for adults and not required for adolescents (Akinlade 2019, Bansal 2021, Simpson 2023)

Asthma

Asthma is a heterogeneous, chronic inflammatory disease characterized by chronic airway inflammation, a history of variable symptoms (wheezing, shortness of breath, chest tightness, and/or coughing), and variable expiratory airflow limitation with poor lung function (Global Initiative for Asthma [GINA] 2022).

In the US, asthma prevalence by age group is as follows:

- **Children:** The overall prevalence of asthma in the US is estimated to be 8.1% in children aged 5 to 11 years, according to 2018 National Health Interview Survey data (Centers for Disease Control and Prevention [CDC] 2020). According to an internal analysis, the prevalence of moderate-to-severe persistent asthma among children aged 6 to 11 years with asthma is estimated to be 8%. Among these patients, the prevalence of uncontrolled disease despite asthma treatments is estimated to be 37%. By extrapolating these prevalence rates to the US childhood asthma population aged 6 to 11 years (2.4 million), the number of children estimated to have uncontrolled moderate-to-severe asthma (including the eosinophilic phenotype) despite current therapies is approximately 75,000 (Data on file 2015a)
- **Adolescents and adults:** The overall prevalence of asthma is estimated to be 9.9% in adolescents aged 12 to 17 years and 7.7% in adults (CDC 2020). According to an internal analysis, 6.4%–7.0% of adolescents and adults aged ≥12 years with asthma are estimated to have moderate-to-severe persistent asthma. Among these patients, 51.2% to 54.9% are estimated to have uncontrolled disease despite asthma treatments. By extrapolating these prevalence rates to the US adolescent and adult asthma population aged ≥12 years (23.5–24.5 million patients), the number of adolescent and adult patients estimated to have moderate-to-severe asthma is 1.5 million to 1.6 million; of these patients, approximately 775,000 to 899,000 have uncontrolled disease despite current therapies. These patients are candidates for treatment with biologic therapy for asthma as recommended by GINA 2022 guidelines; 621,000 to 746,000 are eligible for dupilumab, according to the approved indication (Data on file 2015b)

Long-term asthma treatment goals are to achieve symptom control, minimize the risk of exacerbations, and normalize lung function while minimizing the risk of side effects associated with treatments (eg, long-term, high-dose inhaled corticosteroids and chronic use of oral corticosteroids [OCS]) (GINA 2022, National Heart, Lung, and Blood Institute [NHLBI] 2007). Patients with uncontrolled moderate-to-severe asthma continue to have an unmet need for treatment options to achieve comprehensive asthma control.

Dupilumab is indicated as an add-on maintenance treatment for adult and pediatric patients aged ≥6 years with moderate-to-severe asthma characterized by an eosinophilic phenotype or with OCS-dependent asthma (Dupixent USPI 2024).

The efficacy and safety of dupilumab have been studied in 3 randomized, double-blind, placebo-controlled trials (phase 2b dose-ranging clinical trial: Study DRI12544; phase 3 trials: LIBERTY ASTHMA QUEST and LIBERTY ASTHMA VENTURE) that enrolled a total of 2888 adult and adolescent patients aged ≥12 years with uncontrolled moderate-to-severe asthma (Study DRI12544 enrolled adult patients aged ≥18 years, and the other 2 studies enrolled adult and adolescent patients aged ≥12 years). The efficacy and safety of dupilumab have also been studied in a phase 3 randomized, double-blind, placebo-controlled, parallel-group trial (LIBERTY ASTHMA VOYAGE) in 408 children aged 6 to 11 years with uncontrolled moderate-to-severe asthma (Dupixent USPI 2024).

Dupilumab significantly improved lung function and significantly reduced the rate of severe asthma exacerbations vs placebo in adults, adolescents, and children aged 6 to 11 years; in adult and adolescent patients, dupilumab also reduced the rate of severe exacerbations that result in hospitalizations or emergency department (ED) visits. In addition, in an indirect treatment comparison of asthma biologics, dupilumab had a greater reduction in annualized severe asthma exacerbation rates (AERs) and improvement in lung function than other biologics approved for the treatment of moderate-to-severe asthma in adult and adolescent patients.

- **Adult and adolescent asthma**
  - For the subgroup with baseline blood eosinophil counts ≥300 cells/μL in the phase 2b dose-ranging clinical trial (Study DRI12544, N=776) in patients with uncontrolled moderate-to-severe asthma, the greatest increases in pre-bronchodilator (BD) forced expiratory volume in 1 second (FEV_1) from baseline to Week 12 were observed in the dupilumab 300 mg q2w group (least-squares mean [LSM] change, 0.39 L; LSM difference vs placebo, 0.21; 95% CI, 0.06–0.36; *P*=0.0063) and in the dupilumab 200 mg q2w group (LSM change, 0.43 L; LSM difference vs placebo, 0.26; 95% CI, 0.11–0.40; *P*=0.0008) compared with placebo (LSM change, 0.18 L) (Wenzel 2016)
  - In the LIBERTY ASTHMA QUEST phase 3 clinical trial of patients with uncontrolled moderate-to-severe asthma (N=1902), dupilumab statistically significantly decreased the AERs during the 52 weeks of treatment, with relative risk reductions (RRRs) for dupilumab vs matched placebo of 47.7% with 200 mg q2w and 46.0% with 300 mg q2w (*P*<0.001 for each comparison) in the overall intention-to-treat (ITT) population. The AERs for severe asthma exacerbations resulting in a hospitalization or ED visit during the 52 weeks of treatment was reduced in the combined dupilumab arm compared with the combined matched placebo arm, with an RRR of 46.8% (95% CI, 18.4–65.3) in the overall ITT population (Castro 2018)
  - In the LIBERTY ASTHMA VENTURE phase 3 clinical trial of patients with OCS-dependent asthma (N=210), the percentage change in the OCS dose was statistically significantly greater in the dupilumab 300 mg q2w arm than in the placebo arm (−70.1% vs −41.9%, respectively; *P*<0.001). Despite reductions in the OCS dose, dupilumab 300 mg q2w resulted in an AER that was 59% (95% CI, 37–74) lower than with placebo and a pre-BD FEV_1 that was 0.22 L (95% CI, 0.09–0.34) higher after 24 weeks of treatment. Reductions in the risk for severe asthma exacerbations with dupilumab 300 mg q2w vs placebo were observed regardless of baseline eosinophil count (Rabe 2018)
  - In an indirect treatment comparison, 14 randomized controlled trials were included in the analyses. The matched dupilumab subgroups were associated with greater reductions in AERs

compared with benralizumab, mepolizumab, reslizumab, and omalizumab (54%, 28%, 38%, and 26% greater reduction, respectively). A greater improvement in FEV_1 was also observed for dupilumab at Week 12 and/or Week 24/52 than for the other biologics (0.06–0.14 L) (Bateman 2020)

- **Childhood asthma**
  - In the LIBERTY ASTHMA VOYAGE phase 3 clinical trial of patients with uncontrolled moderate-to-severe asthma (N=408), dupilumab 100 mg or 200 mg q2w (based on body weight ≤30 kg or >30 kg, respectively) statistically significantly decreased AERs during the 52 weeks of treatment, with RRRs for dupilumab vs matched placebo of 59.3% in the population with type 2 inflammatory asthma phenotype (defined as baseline blood eosinophil count ≥150 cells/µL or baseline fractional exhaled nitric oxide ≥20 parts per billion) and 64.7% in the population with baseline blood eosinophil count ≥300 cells/µL (P<0.0001 for each comparison). Dupilumab 100 mg or 200 mg q2w statistically significantly increased pre-BD FEV_1 percent predicted from baseline to Week 12, with LSM differences for dupilumab vs matched placebo of 5.21% (95% CI, 2.14–8.27) in the population with type 2 inflammatory asthma phenotype and 5.32% (95% CI, 1.76–8.88) in the population with baseline blood eosinophil count ≥300 cells/µL (P<0.01 for each comparison) (Bacharier 2021)

Dupilumab had a positive benefit-risk ratio and was generally well tolerated in patients aged ≥6 years with moderate-to-severe asthma.

- **Dupilumab asthma clinical trial program**
  - The most common AEs with dupilumab (incidence ≥1%) in asthma clinical trials were injection site reactions, oropharyngeal pain, and eosinophilia. Injection site reactions were most common with the loading (initial) dose. The safety profile of dupilumab through Week 52 was generally consistent with the safety profile observed at Week 24 (Dupixent USPI 2024)
  - There were no indications that dupilumab increased the overall occurrence of any malignancy (Data on file 2017)
- **Adult and adolescent asthma**
  - In LIBERTY ASTHMA QUEST, the most frequent AE occurring in ≥5% of patients was injection site reaction in both dupilumab doses (200 mg q2w, 15.2%; 300 mg q2w, 18.4%) vs matched placebo (5.4% and 10.3%, respectively). Treatment-emergent eosinophilia occurred in 4.1% of patients treated with dupilumab vs 0.6% of patients treated with placebo. The rate of persistent antidrug antibody (ADA) responses was 4.2% with dupilumab 200 mg q2w and 2.1% with dupilumab 300 mg q2w compared with 1.1% in the combined placebo groups. Persistent ADA responses had no meaningful effect on efficacy or safety. During the 52-week treatment period, there were no meaningful between-group differences in AEs of conjunctivitis (2.3% of patients receiving dupilumab and 3.3% of those receiving placebo) (Castro 2018)
  - In LIBERTY ASTHMA TRAVERSE, the long-term open-label extension (OLE) study of patients with moderate-to-severe asthma who participated in a previous dupilumab asthma clinical trial (N=2282), the overall safety profile was consistent with the safety profile observed in placebo-controlled trials, and no new safety concerns were identified (Wechsler 2022), thus supporting the long-term safety of dupilumab
- **Childhood asthma**
  - In LIBERTY ASTHMA VOYAGE, the safety profile of dupilumab in children aged 6 to 11 years through Week 52 was similar to the safety profile of dupilumab from studies in adults and adolescents aged ≥12 years with moderate-to-severe asthma with the addition of helminth infections. Helminth infections were reported in 6 patients (2.2%) in the dupilumab group and 1 patient (0.7%) in the placebo group. The majority of cases were enterobiasis, reported in 5 patients (1.8%) in the dupilumab arm and 0 patients in the placebo arm. There was 1 case of ascariasis in the dupilumab arm. All helminth infection cases were mild-to-moderate and patients

recovered with anthelmintic treatment without dupilumab treatment discontinuation (Data on file 2020a, Dupixent USPI 2024)

- In LIBERTY ASTHMA EXCURSION, the ongoing long-term OLE study of patients with moderate-to-severe asthma who participated in LIBERTY ASTHMA VOYAGE (N=365), the overall safety profile of dupilumab was consistent with the safety profile observed in the LIBERTY ASTHMA VOYAGE placebo-controlled trial, and no new safety concerns were identified (Data on file 2020b), thus supporting the long-term safety of dupilumab

Chronic Rhinosinusitis With Nasal Polyps

Chronic rhinosinusitis with nasal polyps (CRSwNP) is defined as chronic rhinosinusitis with ≥2 of the following symptoms persisting for ≥12 weeks: facial pressure or pain, decreased or absent sense of smell, nasal obstruction and congestion, and mucopurulent discharge (rhinorrhea or postnasal drip); and ≥1 of the following findings: evidence of inflammation on paranasal sinus examination or computed tomography, evidence of purulence coming from paranasal sinuses or ostiomeatal complex, and presence of bilateral polyps (Orlandi 2016, Peters 2014, Rosenfeld 2015).

Among patients diagnosed with CRSwNP in the US, approximately 55,000 to 90,000 patients have uncontrolled CRSwNP despite prior sinus surgery or oral steroid use (CDC 2017; Data on file 2018a, Stevens 2015). The symptoms of CRSwNP are often moderate-to-severe and lead to a substantial HRQOL burden, with adverse effects on sleep quality, mood, and activities of daily living (Abdalla 2012, DeConde 2015a, Palmer 2019). In addition, patients with CRSwNP have a particularly high prevalence of type 2 atopic comorbidities (ie, 26% to 48% with asthma and 10% to 16% with aspirin-exacerbated respiratory disease); and patients with these comorbidities have more severe disease than those without these comorbidities, resulting in higher rates of polyp recurrence and an increased need for revision sinus surgeries (Bachert 2018, Batra 2013, Cahill 2017, Khan 2020, Promsopa 2016, Stevens 2016, Stevens 2017, White 2018).

For patients with CRSwNP, standard of care medical therapies, such as intranasal corticosteroids (INCS), may have limited effects and systemic corticosteroids are suitable only for short-term use (Li 2015, Orlandi 2016). Surgical interventions can have limited benefit, as they do not correct the underlying pathology of CRSwNP (DeConde 2017, van der Veen 2017). Symptoms in patients with CRSwNP who receive endoscopic sinus surgery (ESS) often persist, with frequent polyp and edema recurrence (DeConde 2015b, DeConde 2017, Wynn 2004).

As such, patients with inadequately controlled CRSwNP despite conventional pharmaceutical or surgical therapies, including those with comorbid asthma, lack a treatment option that provides robust and durable symptom relief combined with an acceptable safety profile.

Dupilumab is the first biologic approved as an add-on maintenance treatment in adult patients with inadequately controlled CRSwNP. Dupilumab has been studied in the largest clinical development program in CRSwNP, with nearly 500 patients with CRSwNP treated with dupilumab across clinical trials to date (Bachert 2016, Bachert 2019, Dupixent USPI 2024).

In patients with CRSwNP whose disease has not been adequately managed by current standard of care treatments, dupilumab demonstrated rapid and consistent benefits on all disease outcome measures, including improvement in objective measures of CRSwNP, key disease symptoms, and HRQOL, as well as reduction in the use of sinonasal surgery and systemic corticosteroids.

- In two phase 3 trials (SINUS-24 [N=276] and SINUS-52 [N=448]), dupilumab met both primary end points, statistically significantly reducing nasal polyp size (endoscopic nasal polyp score [NPS]) and nasal congestion (NC)/obstruction score from baseline vs placebo at Week 24 in SINUS-24 and SINUS-52 (P<0.0001 for each comparison), with improvements observed as early as the first postbaseline assessment at Week 4. In addition, patients treated with dupilumab in SINUS-52 continued to improve in NPS and NC score through Week 52 (Bachert 2019)

- Dupilumab also produced statistically significant improvements from baseline in sinus opacification, loss of smell, and total symptom score vs placebo at Week 24 in SINUS-24 and SINUS-52 (P<0.0001 for each comparison) (Bachert 2019)
- Patients treated with dupilumab had clinically meaningful improvement in disease-specific HRQOL (22-item Sinonasal Outcome Test [SNOT-22]), with key dimensions of improvement on SNOT-22 subscores, including loss of smell/taste, sleep impairment, lack of energy, and productivity loss (Data on file 2018b; Data on file 2018c)
- In a prespecified multiplicity-adjusted pooled analysis of SINUS-24 and SINUS-52, treatment with dupilumab resulted in significant reductions in systemic corticosteroid use and the need for sinonasal surgery vs treatment with placebo (hazard ratio [HR], 0.24; 95% CI, 0.17–0.35). The proportion of patients who required systemic corticosteroids was reduced by 74% (HR, 0.26; 95% CI, 0.18–0.38). The total number of systemic corticosteroid courses per year was reduced by 75% (RR, 0.25; 95% CI, 0.17–0.37). The proportion of patients who required surgery was reduced by 83% (HR, 0.17; 95% CI, 0.07–0.46) (Bachert 2019)
- In patients with CRSwNP and comorbid asthma, dupilumab produced rapid and continuous improvement in lung function (FEV_1) and asthma control (Asthma Control Questionnaire 6-items) vs placebo, observed by the first postbaseline assessment and sustained through 52 weeks of treatment (Data on file 2018b; Data on file 2018c)
- In an indirect treatment comparison, dupilumab had statistically significantly greater improvements in nasal polyp burden and symptoms according to NPS, NC, loss of smell, total symptom, and University of Pennsylvania Smell Identification Test scores than omalizumab q2w/q4w at Week 24 (statistical significance based on 95% CI of mean difference not containing 0). Dupilumab also had a greater improvement in SNOT-22 scores than omalizumab, but this difference was not statistically significant (Peters 2021)

Dupilumab had a positive benefit-risk ratio and was generally well tolerated in combination with INCS in patients with CRSwNP.

- In two phase 3 trials, patients receiving dupilumab had a lower overall incidence of treatment-emergent AEs (TEAEs), serious AEs (SAEs), and discontinuation rates vs patients receiving placebo; the most frequent TEAEs in both trials were nasopharyngitis and nasal polyps, both of which occurred less frequently in patients treated with dupilumab than with placebo (Data on file 2018b; Data on file 2018c)
- The most frequent TEAE considered to be related to study treatment was injection site erythema, which also occurred less frequently in the dupilumab group vs the placebo group (Data on file 2018b; Data on file 2018c)

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a chronic, progressive, type 2 inflammatory disease characterized by esophageal dysfunction and eosinophilic inflammation in the esophagus (Furuta 2015). The pathogenesis is related to a type 2 immune response involving immune dysregulation and epithelial barrier dysfunction (Gómez-Aldana 2019, Hill 2016, O'Shea 2018). Patients with coexisting type 2 inflammatory diseases are at a greater risk of EoE (Hill 2018). The predominant symptom of EoE in adults and adolescents is dysphagia, which is characterized by a sensation of difficulty when swallowing liquids, foods, or saliva (Furuta 2015, NIH 2017). The most common symptoms of EoE in children are feeding difficulties, vomiting, abdominal pain, dysphagia, food impaction, reflux-like symptoms, and failure to thrive (Lucendo 2017, Martin 2015). In the US, the estimated prevalence of diagnosed EoE for adult and adolescent patients (aged ≥12 years) is 0.114%, or 322,000 patients. Of these patients, 42,000 have uncontrolled disease on proton-pump inhibitors (PPIs) and swallowed topical corticosteroids (STCs). In children (aged 1–11 years), the estimated US prevalence of diagnosed EoE is 0.077%, or 34,000. Of these children, 7000 have uncontrolled disease on PPIs and STCs (Data on file 2021). The incidence of disease is more common in males with a 2- to 3-fold increase in risk for the male sex for both children and adults (Lucendo 2017).

Patients with EoE have persistent debilitating symptoms of dysphagia, chest and abdominal pain, heartburn, and vomiting. The underlying inflammatory and fibrostenotic process can lead to food impaction that may require medical intervention. In all age groups, the disease is associated with social challenges and a considerably reduced HRQOL, in addition to incurring higher health care utilization costs and economic burden.

The current standard of care for the treatment of EoE includes dietary therapy, use of medications (STCs and PPIs), and esophageal dilation. PPI therapy is one of the first-line therapeutic options (Hirano 2018). STCs are used to coat the esophagus and provide anti-inflammatory effects (Dellon 2018). Even though symptom control can be achieved with these therapies in some patients, they do not have a targeted impact on the underlying pathophysiology of EoE that leads to esophageal remodeling. Lastly, esophageal dilation is reserved for patients who require dilation of the esophagus to treat dysphagia and food impaction, but similar to the other therapies, it does not treat the underlying inflammation associated with EoE (Hirano 2020).

Management of EoE is challenging because of the limited treatment options and the high frequency of initial treatment failure and recurrence of symptoms (Dellon 2020). There is an unmet need for a treatment modality that improves treatment response while targeting the underlying pathophysiology of EoE. Dupilumab is indicated for the treatment of adult and pediatric patients aged ≥1 year, weighing ≥15 kg, with EoE (Dupixent USPI 2024).

In two 3-part, phase 3 studies in adult and adolescent (aged ≥12 years) and pediatric (aged 1–11 years) patients with EoE, dupilumab resulted in significant improvements in histologic and endoscopic outcomes compared with placebo.

Note: Results reported below do not include Part C data in the pediatric population as it is not yet reported.

Adult and Adolescent EoE

In Part A of a study in adult and adolescent patients with EoE, dupilumab met the coprimary end points of the proportion of patients achieving peak esophageal intraepithelial eosinophil count ≤6 eosinophils/high-power field (eos/hpf) at Week 24 and absolute change from baseline in the dysphagia symptom questionnaire (DSQ) total score.

- The proportion of patients who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at Week 24 was significantly greater in the dupilumab 300 mg once weekly (qw) arm (25/42 [60%] patients) than the placebo arm (2/39 [5%] patients) (adjusted between-group difference of 55 percentage points; 95% CI, 40–71; *P*<0.001) (Dellon 2022)
- The change from baseline DSQ total score was better in the dupilumab 300 mg qw arm than in the placebo arm at Week 24 (LSM change −21.92 vs −9.60 points; 95% CI, −19.11 to −5.54; *P*<0.001) (Dellon 2022)

In Part B of a study in adults and adolescents with EoE, the proportion of patients treated with dupilumab 300 mg qw achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at Week 24 and absolute change from baseline in DSQ total score significantly improved. The dupilumab 300 mg q2w dosing regimen showed numerical, but not significant, improvement in the histologic coprimary end point and symptom end point of absolute change from baseline in DSQ total score. The dupilumab 300 mg q2w dosing also did not significantly improve other EoE disease symptoms or HRQOL measures. All other secondary histologic, endoscopic, and molecular end points of EoE showed a similar degree of improvement to those observed with the dupilumab 300 mg qw dosing regimen.

- The proportion of patients who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at Week 24 was greater in the dupilumab 300 mg qw arm (47/80 [59%]) and 300 mg q2w arm (49/81 [60%]) than in the placebo arm (5/79 [6%]; difference between weekly dupilumab and placebo: 54 percentage points; 95% CI, 41–66; *P*<0.001; difference between dupilumab q2w and placebo: 56 percentage points; 95% CI, 43–69; not significant per hierarchical plan to adjust for multiple testing) (Dellon 2022)

- Treatment with dupilumab 300 mg qw resulted in a greater reduction from baseline in DSQ total score compared with treatment with placebo at Week 24 (LSM change −23.78 points vs −13.86 points; 95% CI, −14.81 to −5.02; *P*<0.001). The reduction from baseline in the DSQ score at Week 24 did not differ significantly between patients who received dupilumab 300 mg q2w compared with those who received placebo (LSM change −14.37 points vs −13.86 points; 95% CI, −5.42 to 4.41; *P*=0.84) (Dellon 2022)

In Part C of the study that enrolled participants from Part A (Part A–C) and participants from Part B (Part B–C), improvements in efficacy outcomes were observed for an additional 28 weeks of dupilumab treatment.

- In Part A–C, the proportion of patients who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at Week 52 was as follows: dupilumab 300 mg qw/dupilumab 300 mg qw (19/34 [56%]) and placebo/dupilumab 300 mg qw (18/30 [60%]) (Dellon 2022)
- In Part A–C, improvements in DSQ score were maintained to Week 52 in the dupilumab 300 mg qw/dupilumab 300 mg qw arm (mean change from baseline −23.44 points; 95% CI, −29.58 to −17.30) and were achieved in patients who switched to dupilumab in the placebo/dupilumab 300 mg qw arm (mean change from baseline −21.71 points; 95% CI, −29.13 to −14.30) (Dellon 2022)
- In Part B–C, peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at Week 52 was achieved by 55 (85%) patients in the dupilumab 300 mg qw/dupilumab 300 mg qw arm, 54 (74%) patients in the dupilumab 300 mg q2w/dupilumab 300 mg q2w arm, 25 (68%) patients in the placebo/dupilumab 300 mg qw arm, and 23 (72%) patients in the placebo/dupilumab 300 mg q2w arm (Rothenberg 2023)
- In Part B–C, improvements in DSQ score were maintained to Week 52 in patients in the dupilumab 300 mg qw/dupilumab 300 mg qw arm and the dupilumab 300 mg q2w/dupilumab 300 mg q2w arm, with the absolute change from Part B baseline in DSQ total score (mean [95% CI]) of −30.3 points [−34.5 to −26.1] and −20.9 points [−25.4 to −16.3], respectively. In patients who switched to dupilumab in the placebo/dupilumab 300 mg qw arm and placebo/dupilumab 300 mg q2w arm, improvements in DSQ total score (mean [95% CI]) were experienced from Part B baseline to Week 52: −27.3 points [−32.1 to −22.4] and −23.7 [−29.1, −18.3], respectively (Rothenberg 2023)

Pediatric EoE

In Part A of EoE KIDS, a study in pediatric patients with EoE who remain symptomatic despite treatment with PPIs, patients in both the higher-exposure and lower-exposure dupilumab arms met the primary end point of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at Week 16. Patients also achieved improvements in key secondary outcomes related to histologic and endoscopic improvement.

- The proportion of patients achieving peak esophageal eosinophil counts ≤6 eos/hpf at Week 16 was higher in the dupilumab arm than in the placebo arm (higher-exposure dupilumab 68% vs lower-exposure dupilumab 58% vs placebo 3%; *P*<0.0001) (Chehade 2023a)
- Patients in the higher-exposure dupilumab arm had reduced peak esophageal intraepithelial eosinophil counts at Week 16 compared with baseline, relative to those in the placebo arm (LSM percent change: −86% vs 21%, respectively; *P*<0.0001) (Chehade 2023a)
- Patients in the higher-exposure dupilumab arm also achieved a reduction in histologic scores at Week 16 compared with placebo (absolute change from baseline in Eosinophilic Esophagitis Histology Scoring System (EoE-HSS) grade score: −0.88 vs 0.02, respectively; *P*<0.0001; absolute change from baseline EoE-HSS stage score: −0.84 vs 0.05, respectively; *P*<0.0001) (Chehade 2023a)
- Patients in the higher-exposure dupilumab arm achieved improved endoscopic features of EoE at Week 16 compared with placebo (LSM absolute change from baseline in Eosinophilic Esophagitis Endoscopic Reference Score (EoE-EREFS) total score: −3.5 vs 0.3, respectively; *P*<0.0001) (Chehade 2023a)
- Results were generally comparable in the lower-exposure dupilumab arm (Chehade 2023a)

In Part B of the study, patients who switched to or continued in the higher-exposure dupilumab arm experienced or maintained improvements in histologic disease remission to Week 52.

- The proportion of patients who achieved peak esophageal counts ≤6 eos/hpf at Week 52 was 62.9% in patients who continued in the higher-exposure dupilumab arm and 52.9% in patients who were switched from placebo to the higher-exposure dupilumab arm (Chehade 2023b)
- Patients who switched from placebo to the higher-exposure dupilumab arm and those who continued in the higher-exposure dupilumab arm improved and maintained, respectively, histologic scores at Week 52 (absolute change from baseline in EoE-HSS grade scores: −0.89, −0.97, respectively; absolute change from baseline EoE-HSS stage scores: −0.86, −0.89, respectively) (Chehade 2023b)
- Patients who switched from placebo to the higher-exposure dupilumab arm and those who continued in the higher-exposure dupilumab arm improved and maintained, respectively, endoscopic features of EoE at Week 52 (LSM absolute change from baseline in EoE-EREFS total score: −3.6, −4.8, respectively) (Chehade 2023b)
- Patients who switched from placebo to the lower-exposure dupilumab arm and those who continued in the lower-exposure dupilumab arm also experienced or maintained histologic and endoscopic outcome improvements to Week 52 but to a numerically lower extent than those in the higher-exposure dupilumab arm (Chehade 2023b)
- Part C of the study is still ongoing, and full results are not yet available

Dupilumab was well tolerated in adult, adolescent, and pediatric patients with EoE, as supported by two, 3-part phase 3 trials.

Adult and Adolescent EoE

- In Part A–C of the study, most AEs were mild or moderate in intensity (placebo/dupilumab 300 mg qw [73%] vs dupilumab 300 mg qw/dupilumab 300 mg qw [60%]). During Part A–C, among patients who received placebo in Part A and dupilumab in Part C, 2 patients had AEs that led to discontinuation of dupilumab, and 1 patient had an SAE during the Part C treatment period. ADA responses were observed during the treatment period in 0% to 3% of the patients across the active treatment groups. No deaths were reported in any treatment arm (Dellon 2022)
- In Part B–C of the study, the most common TEAEs in the dupilumab/dupilumab and placebo/dupilumab treatment arms were injection-site reactions. Treatment-emergent SAEs occurred in 3 (4%) patients in the dupilumab 300 mg qw/dupilumab 300 mg qw arm and in 2 (5%) patients in the placebo/dupilumab 300 mg qw arm during Part B–C and none of them were considered to be related to study drug by the investigator. The TEAE of COVID-19 occurred in 18 (8%) patients, and all were nonserious, unrelated to study drug, and none led to permanent discontinuation of study drug. No deaths were reported in any treatment arm (Rothenberg 2023)

Pediatric EoE

- In Part A of the study, dupilumab was well tolerated in pediatric patients with EoE. There were 0 and 2 AEs leading to discontinuation in the dupilumab and placebo groups, respectively. The most common TEAEs among all arms were injection-site reactions and COVID-19. Most TEAEs were mild or moderate (Chehade 2023b)
- In Part B of the study, dupilumab was well tolerated in pediatric patients with EoE. Among the treatment arms, the incidence of AEs was 73%–100%. There was 1 AE leading to discontinuation in the dupilumab-dupilumab higher-exposure group. The most common TEAEs among all arms were similar to Part A, injection-site reactions and COVID-19. Most TEAEs were mild or moderate (Chehade 2023b)
- Part C of the study is still ongoing, and full results are not yet available

Prurigo Nodularis

Prurigo nodularis (PN), a chronic inflammatory skin condition characterized by intensely pruritic papulonodular lesions, substantially affects quality of life (QOL) and mental health (Elmariah 2021, Huang 2020, Whang 2020). According to a private insurance claims database, estimated PN prevalence in the US is 72 per 100,000 (Wongvibulsin 2021). According to an internal analysis, the prevalence of PN in the US adult population is 0.12% and the estimated number of adults with PN uncontrolled on topical prescription therapy is 139,000 (Data on file 2022). PN can occur in all age groups but primarily affects middle-aged and older adults (Hughes 2020). PN can arise without any concomitant comorbidities or separate underlying conditions; however, a range of comorbidities are often associated with PN that may contribute to initiation or perpetuation of itch (Elmariah 2021, Kwatra 2020, Kwon 2019). In an international cross-sectional survey study including adults with PN, coexisting type 2 inflammatory diseases were highly prevalent, with allergic rhinitis reported in 71%, eczema reported in 50%, and asthma reported in 31% (Aggarwal 2019). PN imposes a substantial economic and societal burden because of the high levels of health care resource utilization (Aggarwal 2021, Whang 2019, Whang 2020, Whang 2021).

Dupilumab is indicated for the treatment of adults with PN (Dupixent USPI 2024).

During the dupilumab PN clinical development program, the clinical efficacy and safety of dupilumab were studied in two phase 3 trials (Dupixent USPI 2024, Yosipovitch 2023).

Dupilumab provided significant and clinically meaningful improvements in itch and nodule clearance as well as both itch and nodule clearance in the same patients at 24 weeks. Improvements were also observed in skin pain, HRQOL, and symptoms of anxiety and depression. Safety was consistent with the known dupilumab safety profile (Yosipovitch 2023).

Dupilumab demonstrated significant and clinically meaningful improvement in itch, as measured by worst itch numerical rating scale (WI-NRS)

- In the PRIME and PRIME2 trials, itch severity was reduced by a clinically meaningful degree, as assessed by a ≥4-point reduction in weekly average WI-NRS from baseline, in a significantly greater proportion of patients treated with dupilumab than those treated with placebo (Dupixent USPI 2024, Yosipovitch 2023):
  - Week 12: PRIME, 44.0% dupilumab vs 15.8% placebo (treatment difference: 29.2%; *P*-value NR); PRIME2, 37.2% vs 22.0%, respectively (treatment difference: 16.8%; *P*=0.0216)
  - Week 24: PRIME, 60.0% dupilumab vs 18.4% placebo (treatment difference: 42.7%; *P*<0.0001); PRIME2, 57.7% vs 19.5%, respectively (treatment difference: 42.6%; *P*<0.0001)

Dupilumab demonstrated significant and clinically meaningful improvement of lesions, as measured by IGA PN-Stage (IGA PN-S)

- In the PRIME and PRIME2 trials, the number of lesions was reduced by a clinically meaningful degree, as assessed by achievement of IGA PN-S 0 or 1 (clear or almost clear) at Week 24, in a significantly greater proportion of patients treated with dupilumab than those treated with placebo (PRIME: 48.0% vs 18.4%, respectively [treatment difference: 28.3%; *P*=0.0004]; PRIME2: 44.9% vs 15.9%, respectively [treatment difference: 30.8%; *P*<0.0001]) (Dupixent USPI 2024, Yosipovitch 2023)

Dupilumab demonstrated clinically meaningful improvements in both itch and lesions, as measured by WI-NRS and IGA PN-S, respectively

- In the PRIME and PRIME2 trials, a greater proportion of patients achieved clinically meaningful responses in both itch and lesions, as assessed by the composite of ≥4-point reduction in weekly average WI-NRS from baseline and IGA PN-S 0 or 1 at Week 24, with dupilumab vs placebo (PRIME:

38.7% vs 9.2%, respectively [treatment difference: 29.6%]; PRIME2: 32.1% vs 8.5%, respectively [treatment difference: 25.5%]) (Dupixent USPI 2024)

Dupilumab had a safety profile in the PN indication that was consistent with the safety profile of dupilumab in other approved indications (Yosipovitch 2023)

- In the PRIME trial, dupilumab was evaluated through Week 24 and was generally well tolerated, with an overall acceptable safety profile
  - The overall rate of TEAEs in the dupilumab arm was similar to that of the placebo arm (70.7% vs 62.7%, respectively). The rate of TEAEs was also similar between the dupilumab and placebo arms (6.7% vs 10.7%, respectively). No TEAEs lead to treatment discontinuation in the dupilumab arm, whereas 3 (4.0%) patients in the placebo arm had a TEAE leading to treatment discontinuation
  - The incidence of conjunctivitis (narrow term) was similar between the dupilumab and placebo arms (4.0% vs 2.7%, respectively)
  - The incidence of injection site reactions was similar between the dupilumab and placebo arms (5.3% vs 6.7%, respectively)
  - The incidence of adjudicated nonherpetic skin infections was numerically lower in the dupilumab arm than the placebo arm (4.0% vs 9.3%, respectively)
  - No herpes viral infections were reported in either treatment arm
- In the PRIME2 trial, dupilumab was evaluated through Week 24 and was generally well tolerated, with an overall acceptable safety profile
  - The overall rate of TEAEs in the dupilumab arm was similar to that of the placebo arm (57.1% vs 51.2%, respectively)
  - The incidence of conjunctivitis (narrow term) was numerically higher in the dupilumab arm than in the placebo arm (3.9% vs 0%, respectively)
  - The incidence of adjudicated nonherpetic skin infections was numerically lower in the dupilumab arm than the placebo arm (5.2% vs 8.5%, respectively)
  - The incidence of herpes viral infections was higher in the dupilumab arm than in the placebo arm (6.5% vs 0%, respectively); none of the herpes viral infection events were severe or led to permanent treatment discontinuation

Economic Benefits

A pharmacy budget impact model from the health plan perspective was developed to assess the pharmacy-cost impact of including dupilumab on a US health plan's formulary. Eligible patients and treatments for uncontrolled AD, asthma, CRSwNP, EoE, and PN were included for evaluation. The budget impact model estimates the budget for dupilumab by indication and across all 5 indications.

For a hypothetical plan of 1 million patient lives, the budget impact results are presented in **Table 1**.

Table 1. Budget for dupilumab by indication and across all 5 indications

Outcome	Year	
	2022	2025
AD		
Total annual budget for dupilumab	$10,179,212	$15,613,787
Budget impact PMPM	$0.85	$1.30
Budget impact PMPY	$10.18	$15.61
Asthma		
Total annual budget for dupilumab	$3,472,267	$5,135,237
Budget impact PMPM	$0.29	$0.43
Budget impact PMPY	$3.47	$5.14
CRSwNP		
Total annual budget for dupilumab	$2,284,458	$4,864,592
Budget impact PMPM	$0.19	$0.41
Budget impact PMPY	$2.28	$4.86
EoE		
Total annual budget for dupilumab	$74,444	$1,097,065
Budget impact PMPM	$0.01	$0.09
Budget impact PMPY	$0.07	$1.10
PN		
Total annual budget for dupilumab	$291,020	$1,891,057
Budget impact PMPM	$0.02	$0.16
Budget impact PMPY	$0.29	$1.89
All 5 indications combined[a]		
Total annual budget for dupilumab	$16,301,400	$28,601,738
Budget impact PMPM	$1.36	$2.38
Budget impact PMPY	$16.30	$28.60

[a]These estimations account for patients with multimorbid indications.
AD, atopic dermatitis; CRSwNP, chronic rhinosinusitis with nasal polyps; EoE, eosinophilic esophagitis; PMPM, per member per month; PMPY, per member per year; PN, prurigo nodularis.

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