Dear ICER Review Panel,

We at AbbVie appreciate the opportunity to provide feedback on the Institute for Clinical and Economic Review's (ICER's) assessment of *JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis*: Draft Background and Scope.[1]

We have provided our comments below on all the relevant inputs outlined in your scope as they pertain to the evaluation of therapies for atopic dermatitis. In particular, there are notable differences across the trials being considered in this assessment. We strongly recommend that any indirect comparisons be conducted in such a way to mitigate these differences as certain comparisons may result in inappropriate conclusions. Finally, we would like to highlight that there are ways to quantify the contextual considerations of caregiver burden and worker productivity for this disease, and we believe that these should be included in this cost-effectiveness assessment to fully capture the burden of illness of this disease.

Populations

We agree with ICER that the population of review for upadacitinib is "[a]dults and children with moderate-to-severe atopic dermatitis whose disease has either not responded adequately to topical therapies or for whom topical therapies have not been tolerated or are medically inadvisable."[2] However, we would recommend that the specified subgroups of adolescents and adults may not be appropriate for ICER's modeling efforts at this time.

Despite the higher prevalence of AD in a young population, the actual percentage of patients with moderate to severe AD that are adolescents is roughly 8-10%.[3,4] For the phase III clinical trials conducted by AbbVie, adolescents made up close to 14% of the trial population.[5] For the JADE MONO-1 trial, adolescents were 22% of the trial population[6] and for the JADE MONO-2 trial, adolescents were 10% of the trial population.[7] Analyses of the adolescent-only population may result in statistically noisy estimates due to smaller sample size. Furthermore, any indirect comparison of adolescent-only data may be difficult due to the lack of publicly available results for this population.

Similarly, although the moderate and severe subgroups of the trials are sufficient for data analysis, the lack of publicly available data for these subgroups may make indirect comparison methodologically challenging.

*AbbVie Recommendation***:** Given the current paucity of data for subgroups, we recommend ICER focuses on the relevant overall population and not include subgroup analyses in their assessment.

Interventions

We would like to clarify that there are several forms of upadacitinib that have been evaluated in clinical trials and each should be evaluated separately.

- Upadacitinib 15 mg
- Upadacitinib 30 mg
- Upadacitinib 15 mg + topical corticosteroid (TCS)

- Upadacitinib 30 mg + TCS

This is also true of competitor products included in the list. Thus, we would like to emphasize the importance of evaluating different dosing, as well as monotherapy and combo therapy separately.

A comparison of the monotherapy trials is likely the approach with the fewest methodological challenges as the trials are relatively homogenous. This is not the case for trials that involved TCS use, where there are differences in TCS utilization, type, and likely adherence to TCS.

As an example, the AD Up phase III clinical trial protocol for upadacitinib in combination with TCS required participants to use medium potency TCS for a maximum of 3 consecutive weeks (participants could discontinue earlier if lesions were under control) before switching down to low potency for 7 days, with a resumption of this medium potency – low potency TCS cycle if lesions did not resolve.[8] This was also repeated if lesions reoccurred. Patients in the dupilumab CHRONOS and CAFÉ trials used medium potency TCS throughout the study.[9] There also are differences in the types of TCS creams used across trials. For instance, in the EZCTRA-3 trials for tralokinumab, participants used mometasone furoate 0·1% cream once daily to areas with active lesions[10] whereas they were recommended to use either fluocinolone acetonide 0.025% ointment or triamcinolone acetonide 0.1% cream (medium potency) and hydrocortisone 1% cream (low potency) in the AD Up trial.[11]

These potential sources of heterogeneity suggest that, at a minimum, any indirect comparison should view the monotherapy and combo therapy treatments as separate networks and consider adjustments to account for differences in placebo response rates, particularly in the TCS network. A comparison of monotherapy trials will be most robust as the trials in the monotherapy network are likely more homogenous.

AbbVie Recommendation: Both doses of upadacitinib should be compared separately in ICER's analysis. Monotherapy and combo therapy treatments should also be considered separately and should not be compared to one another.

Comparators

We agree that dupilumab is the most relevant comparator on the market for the JAK inhibitors and monoclonal antibodies. For the reasons stated above, we would also recommend that dupilumab be evaluated as a monotherapy versus other monotherapies and evaluated as a combo therapy versus other combo therapies.

We caution against making indirect comparisons of JAK inhibitors and monoclonal antibodies with systemic immunomodulator therapies other than dupilumab. Drucker et al. have published an NMA using a more expansive inclusion criteria that incorporated studies dating back to 1991.[12] As a result, there were differences in trial selection, trial population (e.g., different definitions of moderate to severe), and concomitant topical anti-inflammatory medications across trials. These differences could invalidate the transitivity assumption required of NMAs. Furthermore, the endpoints that are relevant in the determination of therapy response are not often captured in these earlier studies. Finally, cyclosporin is only approved for severe refractory AD in Europe. MTX, azathioprine, and mycophenolate are not approved for AD. Thus, there are multiple reasons to limit the scope of this comparison to dupilumab.

AbbVie Recommendation: Dupilumab is the appropriate comparator for the JAK inhibitors and the monoclonal antibodies. We would recommend not including systemic immunomodulator therapies in this analysis.

Outcomes

We appreciate that ICER plans on assessing multiple outcomes that aim to capture not just skin clearance, but other aspects of the patient experience such as itch, anxiety, and depression. Additionally, AD can also impact worker productivity through several means. These include, but are not limited to poor sleep quality, discomfort while working, and missed work due to flare episodes. This productivity burden associated with AD has been documented in the literature.[13-15] We would recommend incorporating these costs into the model as they are important to employer sponsored health plans in the US. Additionally, there is economic burden borne by caregivers, particularly among younger patients. Furthermore, sleep deprivation can have consequences from missed work and school, to poor performance at school and work and is more likely to lead to injury on the job and driving.[16]

AbbVie Recommendation: Work and productivity loss associated with AD should be incorporated into the model.

Timing

The majority of data from the phase III clinical trials for the proposed therapies in ICER's assessment provide information on the endpoints of interest at 16 weeks. Most trials report week 16 outcomes, however efficacy at earlier time points (e.g., week 1, week 2) are reported for several advanced therapies. The model should be flexible in accounting for these efficacy differences at earlier time points for the JAK inhibitors and the monoclonal antibodies.

AbbVie Recommendation: The model should account for efficacy differences at earlier time points across the clinical trial programs for the JAK inhibitors and monoclonal antibodies.

AbbVie appreciates the opportunity to provide input on ICER's draft clinical scope for the assessment of therapies for atopic dermatitis, particularly as it pertains to Population, Framework, Comparators, Outcomes, and Timing. Please contact me with questions or clarifications.

Sincerely,

Avani Joshi

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2. ICER. JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis: Draft Background and Scope. p. 4.
3. Silverberg JI. Public Health Burden and Epidemiology of Atopic Dermatitis. Dermatol Clin. 2017;35(3):283-289 The authors estimated prevalence for adults with AD to be 7.0% (midpoint of 6.0-8.0%) which was then applied to the overall US population between the ages of 18 and 75, resulting in an estimate of 16,388,597 adults with AD. They estimated prevalence for adolescents with AD to be 8.0% which was then applied to the overall US population between the ages of 12 and 17, resulting in an estimate of 2,000,507 adolescents with AD. The same authors estimated prevalence for adults with moderate/severe AD to be 50.0% of adults with AD. This was applied to the estimate for AD adult patients calculated above (16,388,597), resulting in an estimate of 8,194,299 adults with moderate/severe AD. They estimated prevalence for adolescents with moderate/severe AD to be 37.5% of adults with AD. This was applied to the estimate for AD adolescent patients calculated above (2,000,507), resulting in an estimate of 750,190 adolescents with moderate/severe AD. This suggests 8% of moderate/severe AD patients are adolescents. This estimate increased to 10% when an alternative calculation for the prevalence of AD in an adult population was used: see 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.
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January 6, 2020

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RE: ICER Draft Scope for Evaluation of "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis"

Dear Dr. Pearson,

Allergy & Asthma Network is a national nonprofit dedicated to ending needless death and suffering due to asthma, allergies and related conditions. Since 1985, we have worked to build patient-centered, collaborative care teams throughout the United States to serve the 60+ million Americans living with these conditions, including the 30 million Americans living with atopic dermatitis (AD).

AD has clinical consequences beyond physical signs and symptoms

It is important to recognize that AD is not just a skin condition. It affects many aspects of the lives of individuals living with condition, as well as their caregivers and families. AD extends far beyond signs and symptoms, negatively impacting mental health and resulting in other clinical consequences, such as frequent infections, asthma, allergic rhinitis, and food allergies. Results from our More Than Skin Deep survey, showed that anxiety (26%) and depression (22%) were commonly reported comorbidities. In addition, while 38% of survey respondents rated their current depressive symptoms as severe or moderate, 80% reported experiencing moderate or severe depressive symptoms when their AD was at its worst.

As the parent of a teen daughter who struggles with moderate AD, I can assure you it shapes not only her physical health, but also significantly impacts her sleep, self-esteem and emotional well-being. The impact of this disease reaches beyond the patient to the caregiver impacting loss of sleep, loss of intimacy, loss of work and measurable financial burden.

Do not compare interventions across classes

While we recognize ICER appropriately plans to separate out this review into two different populations (i.e., mild-to-moderate and moderate-to-severe AD), Allergy & Asthma Network recommends that ICER restrict its review to comparing treatments within the same product class only (i.e. JAK inhibitors and monoclonal antibodies). Given the heterogeneity of AD, the availability of multiple treatment options is paramount. Despite the existing treatment options, many people with AD are not being adequately controlled by current therapies. In fact, in the 2019 More Than Skin Deep survey only 12% reported being "very satisfied" with their current treatment plan. The millions of uncontrolled AD patients deserve innovative treatment options. Moreover, more than half of all patients on therapy have concerns over long-term use including lack of efficacy, side effects and cost. Since it is impossible to predict which class of products works for any particular person, it is simply inappropriate to compare across classes of products. Each may be used in different patients at different points in time in a patient's journey and the Network strongly believes this should be at the discretion of healthcare provider and patient preferences. Some may be geared more towards getting immediate control of the

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AD flare, whereas others may be used for maintaining control of the disease; therefore, comparing them based on their clinical trial data alone does not really reflect how physicians will select a treatment regimen for a specific patient based on their treatment history and individual characteristics.

Allergy & Asthma Network stands ready to partner with ICER to support the value assessment and ensure cost-effectiveness of these treatment solutions. We implore the committee to consider true patient-centered outcomes rather than QALYs. We advocate for appropriate use of innovative treatments and believe that when the right treatment is selected for the right patient at the right time, it benefits both the individual patient and the broader healthcare system and society.

It is truly a promising time for those in the atopic dermatitis community. Significant scientific advancements in diagnosis and treatment are exciting. We look forward to the opportunity to provide additional insights and/or patient testimonies. Please do not hesitate to contact me should you have any questions.

Sincerely,

Tonya A. Winders

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January 8, 2021

Lilly Public Comment to ICER's Draft Scoping Document – Atopic Dermatitis
Eli Lilly and Company appreciates the opportunity to provide comment to the Draft Scoping Document for ICER's assessment of Atopic Dermatitis (AD), announced on December 10, 2020. We have outlined several important considerations, as well as references to aid in the scoping for this assessment. Lilly has ongoing clinical and real-world studies to support the outcomes and contextual considerations listed which may be available during this assessment.

Burden of Illness and Unmet Need

Lilly supports the important background ICER has provided to frame the burden of illness and unmet need in AD.[1-10] However, additional background regarding disease manifestation should be considered. There is a significant seasonal impact on AD disease severity and healthcare utilization. A large population study in Denmark showed that a mean decline in temperature of 1°C was associated with 2 more AD clinic visits or hospitalizations, 10 more topical corticosteroids prescriptions and 53 additional topical calcineurin inhibitor prescriptions filled by AD patients.[11] In the United States (US), colder weather was associated with an increased number of AD visits in western states, while warmer weather was associated with an increased number of visits elsewhere in the country, with peaks noted in the spring and summer, suggesting an additional geographic impact on the seasonality of AD in the US, affecting healthcare resource utilization.[12] Thus, important consideration should be given to how patients with more seasonal manifestation of their AD can be managed.

In patients with moderate to severe AD, review of existing treatment patterns indicate a treatment cycle where the use of topical regimens is often followed by an inadequate response, leading to the need for treatment escalations including the use of short-term systemic therapies to attempt to control patients' worse symptoms.[13] After completion of short courses of systemic corticosteroids or conventional immunosuppressants, topical regimens are then resumed, often due to safety concerns with long-term therapy with systemic agents.[13,14] This cycle fails to provide appropriate management of symptoms, but still few patients advance in their care to using dupilumab, the only approved novel injectable systemic treatment for moderate to severe AD.[13,15] Therefore, there is a significant unmet need in AD for moderate to severe patients who are failing topical treatments, but who are not willing to commit to indefinite treatment with an injectable biologic. Following FDA approval, Lilly believes that Olumiant (baricitinib) will be uniquely placed to be a starter systemic agent for adult patients with moderate to severe AD where short-term systemics and topical regimens are inadequately controlling disease. With a rapid onset of action and good response in patients with moderate to severe AD and a body surface area of involvement (BSA) of 10-50%, baricitinib can offer a positive benefit-risk

balance as a starter systemic therapy in AD. Further, Lilly believes baricitinib could be an option for patients with seasonal or variable manifestations of moderate to severe AD.

Clinical Scope, Comparative Value Analysis, and Contextual Considerations

Given ICER's purpose to support value assessment in the US health care system, Lilly proposes that ICER reference BREEZE-AD5, the 16-week placebo-controlled clinical trial, examining baricitinib 2 mg for moderate to severe AD in a US-specific population.[16] Conducted in the US and Canada only, this study is most representative of patient experience in US, cared for by US providers, and is one of the pivotal clinical trials submitted to the FDA. Long-term maintenance of response data and safety analysis has been provided from a total of 8 clinical studies, including BREEZE-AD5 and its baricitinib 2 mg open label extension BREEZE-AD6. All other BREEZE clinical trials are conducted in other countries and excluded patients from the US.[17-19] Note that the 4mg dose of baricitinib will not be available in the US to treat AD.

The population assessed in baricitinib 2 mg clinical trials were adult (age ≥18 years) moderate to severe AD patients,[16] so Lilly recommends that ICER separate assessments for pediatric and adult moderate to severe AD patients. Lilly proposes that ICER consider a subgroup of patients with moderate to severe AD and baseline body surface area (BSA) involvement of 10% to 50% based on clinical data from the baricitinib 2 mg clinical trial program. The mean affected BSA at baseline in our studies ranged from ~40% to ~50%.[20] Post-hoc analyses showed that ~90% of the EASI75 responders, and ~95% of patients achieving a score of 0 or 1 (clear or almost clear) with the validated Investigator Global Assessment for AD (vIGA-AD™) scale had a baseline BSA between 10-50%.[20,21] The population with moderate to severe AD affecting a BSA of 10-50% may include primarily patients reluctant to transition to a long-term systemic biologic therapy, but who could benefit from chronic long-term treatment, or intermittent treatment, with oral baricitinib 2 mg. Patients who responded to baricitinib 2 mg showed a clinically meaningful improvement in skin inflammation (50% improvement from baseline in affected BSA) or itch (at least a 3-point improvement in itch) by week 4 to 8, allowing for rapid medical decision on whether patients should continue on baricitinib 2 mg therapy or not.[20] Rapid speed of onset in this subgroup allows for quick positive feedback to patients and providers given the importance of managing disease burden and symptoms of AD.[4]

In addition, approximately half of the baricitinib 2 mg patients achieving at least mild disease (vIGA-AD™ score of 2 or better) were able to maintain their response for at least 4 months after discontinuation of baricitinib 2 mg.[20] Approximately 90% of patients who worsened after discontinuation and required retreatment were able to recapture a mild disease response or better after at least 4 weeks of treatment.[20] Lilly encourages ICER to assess maintenance of response with intermittent treatment of baricitinib 2 mg on skin inflammation (vIGA-AD™, EASI75) and patient symptoms (Itch Numeric Rating Scale [NRS], Skin Pain NRS, Atopic Dermatitis Sleep Scale). Chronic therapy is a viable option for patients who respond to baricitinib 2 mg and maintain efficacy with continuous treatment with a positive benefit-risk profile, while intermittent dosing may be sufficient for patients with moderate to severe AD who may not require continuous long-term treatment with baricitinib 2 mg or other available therapies.[20]

Lilly believes the list of topical comparators are appropriate for the moderate to severe AD population assessment. Many of the guideline-supported systemic immunomodulator therapies

(other than dupilumab) listed as comparators are less appropriate as they are not FDA-approved for the treatment of AD.[14,22] The 2017 ICER Atopic Dermatitis review confirmed that due to safety concerns, clinical experts suggest that patients not be required to try these agents before being covered for agents that are FDA-approved for moderate to severe AD like dupilumab.[23] For the comparison to topical therapies, Lilly recommends referencing clinical studies of topical therapies used after failure of another topical therapy for AD to be similar to the populations being studied in the baricitinib 2 mg clinical trials. Lilly is aligned with many of the outcomes included in the Draft Scoping Document, though a serious limitation of a comparative analysis of the interventions listed will be the adaptations to the primary and key secondary endpoints (e.g. Investigator's Global Assessment vs. vIGA-AD™, Eczema Area and Severity Index 75 [EASI75]) for some of the clinical trial programs. Clinical assessment of AD should be inclusive of the entire body and not exclude difficult to treat areas (such as palms, soles, and scalp). Therefore, Lilly asks ICER to create clinical and economic comparisons where the selected populations, comparators, methods, and outcomes assessed are the same.

Lilly believes that patient-reported outcome measures are of particular importance in the assessment of AD and recommends the Itch NRS, Skin Pain NRS, and ADSS to assess the impact of AD on itch, skin pain, and sleep. These measures should be assessed at time points prior to 16 weeks (e.g. 4 or 8 weeks) in addition to 16 weeks to capture the overall benefit of therapy. Lilly also recommends capturing infection rates of Herpes Simplex and Herpes Zoster in addition to serious infections, separating non-melanocytic skin cancer from other malignancies, and assessing tolerability concerns such as acne, nausea, vomiting, conjunctivitis, and headache. To assess productivity impacts related to AD, Lilly is supportive of the Work Productivity and Activity Impairment Questionnaire (WPAI). Finally, Lilly encourages ICER to consider other potential benefits or contextual considerations related to route of administration, dosing, speed of onset, and anticipated real-world utilization.

ICER's comparative value assessment of AD should consider clinical and economic implications of rebates used to negotiate formulary access in the autoimmune therapeutic class. Rebates are rarely equal for all available treatment options and negotiations can create barriers to more cost-effective therapies due to exclusions and step edits. In the autoimmune market this dynamic is known as the "rebate wall," which is an issue that has received significant attention from policymakers and ICER itself.[24-29] To create a value assessment that appropriately assesses equal and open first-line access to treatment, ICER should consider uniform rebate discounts from WAC across all drugs assessed as opposed to average per unit net prices based on highly variable access. Further, we encourage ICER to evaluate the impact of non-evidence-based step therapy policies as scenario analyses. This is especially important in AD given the adverse clinical outcomes and associated out-of-pocket costs that result from such practices.[30]

Sincerely,

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January 8, 2021

Submitted electronically to: publiccomments@icer-review.org
Institute for Clinical and Economic Review (ICER)
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As the manufacturer of ruxolitinib cream, Incyte Corporation appreciates the opportunity to provide comment on ICER's draft background and scoping document on JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis.

At Incyte, we take a science-first approach and our research and development efforts in Dermatology are focused on leveraging our knowledge of the JAK-STAT pathway to identify and develop topical and oral therapies with the potential to modulate immune pathways driving uncontrolled inflammation and help restore normal immune function.

Ruxolitinib cream was developed as a JAK1 and JAK2 inhibitor to deliver drug directly to the affected skin to accelerate the onset of action and reduce the potential for adverse events typically observed with oral administration of JAK inhibitors.[1] Phase 3 studies showed that application of ruxolitinib cream exhibited antipruritic and anti-inflammatory effects in atopic dermatitis. Ruxolitinib cream was well tolerated with no safety findings suggestive of systemic exposure.[2] Clinical evidence suggests the potential of ruxolitinib cream as an important treatment option for atopic dermatitis that addresses some of the limitations with topical and systemic therapies.

We are sharing feedback, based on our deep understanding of JAK inhibition as well as the different profiles of systemic and topical administration of JAK inhibitors, to inform development of a scoping document with clear delineation between the systemic and topical therapies under evaluation.

I. Recommendation for consistent nomenclature of ruxolitinib:

An oral formulation of ruxolitinib is available in the United States, however the oral formulation is not indicated, nor being evaluated, for use in patients with atopic dermatitis. Therefore, we recommend that ***ruxolitinib cream*** is the preferred term, replacing *ruxolitinib* throughout the document.

Draft Scope Text: Page 2, Paragraph 2: *"A topical JAK inhibitor, ruxolitnib is being evaluated for patients with mild-to-moderate atopic dermatitis"*

Please note the correct spelling of 'ruxolitinib' cream should be used throughout the document.

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Suggested revision: "Ruxolitinib cream, a topical JAK inhibitor, is being evaluated in clinical studies in adolescents and adults with atopic dermatitis."

II. Recommendation to distinguish between topical and oral JAK inhibitors

The observed safety profile of ruxolitinib cream is different from that of orally administered JAK inhibitors.[2, 6] Oral JAK inhibitors have been associated with an increased risk of thrombotic events. These FDA-approved oral JAK inhibitors, tofacitinib, upadacitinib, and baricitinib, carry a black box warning.[3-5]

In the pivotal Phase 3 studies of ruxolitinib cream in atopic dermatitis, no treatment-emergent adverse events suggestive of systemic exposure were observed.[6] It is therefore important to differentiate the safety profile of ruxolitinib cream, from oral JAK inhibitors. Incyte recommends that the statement be revised to reflect the differences in safety-related information available regarding the oral JAK inhibitors and ruxolitinib cream.

Draft Scope Text: On page 3, the ICER draft scope states: *"Oral and topical JAK inhibitors are hoped to offer new and easier forms of delivery, but experts expressed caution about potential side effects of these new treatments with long-term use, both in children, given the lack of clinical trials, and in older patients at risk for thrombotic events."*

Suggested revision: "Oral and topical JAK inhibitors are hoped to offer new and easier forms of delivery. Experts caution about potential side effects of oral JAK inhibitors with long-term use, both in children, given the lack of clinical trials, and in older patients at risk for thrombotic events. In the pivotal Phase 3 studies of ruxolitinib cream in atopic dermatitis, no treatment-emergent adverse events suggestive of systemic exposure were observed.[6]"

III. Clarifications

A. Recommend stating topical therapies consistently throughout the document as comparator for Population 1

On page 4, the ICER draft scope lists "*Topical therapies (including emollients with or without a topical corticosteroid or calcineurin inhibitor)"* as a comparator for the comparative effectiveness evaluation in Population 1 (moderate-severe). On page 7, *"topical therapy"* is listed as a potential comparator in the comparative value assessment in Population 1.

In the revised scope, Incyte recommends naming the specific topical agents or classes

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listed on page 4 (i.e. *topical therapies including emollients with or without a topical corticosteroids or calcineurin inhibitor*) to also be specified on page 7.

B. Clarify prevalence estimates for mild, moderate and severe atopic dermatitis in adults

On page 2, the ICER draft scope states: *"Most children with atopic dermatitis have mild disease, with 12-26% having moderate and 4-7% having severe disease.*[7,8] *Moderate or severe disease appears to be more common in adults."*[9]

Incyte recommends ICER provide epidemiology figures by severity in adult populations as provided in children. Prevalence of atopic dermatitis in adults have been reported as 39-47% in mild, 31-46% in moderate, and 11-29% in severe disease.[10]

C. Editorial clarification

On page 5: please confirm that the heading "*For mild-to-severe atopic dermatitis (Population 2)"* is intended to read "*For mild-to-moderate atopic dermatitis (Population 2)"*.

We appreciate the opportunity to provide input on the scoping document and look forward to engaging with ICER. All future correspondence should continue to be directed to Vijay Joish at vjoish@incyte.com.

Sincerely,

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January 8, 2021

Steven D. Pearson, MD, MSc
President, Institute for Clinical and Economic Review
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Dear Dr. Pearson:

The International Eczema Council (IEC) is pleased to provide comments regarding the draft scoping document for the Institute for Clinical Economical Review's upcoming assessment "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis". As a global nonprofit organization comprised of over 100 dermatologists in 24 countries who are internationally recognized experts in managing atopic dermatitis, our mission is to convene these experts on AD in furtherance of the following goals:

- Identify and prioritize unmet needs for research related to atopic dermatitis.
- Facilitate atopic dermatitis research that addresses these needs through coordinative activities and infrastructure support.
- Disseminate evidence-based information about atopic dermatitis and its optimal management to health care professionals and the public through direct communication and in conjunction with other organizations.
- Promote good practices in the care of patients with atopic dermatitis worldwide.
- Collaborate with physicians, scientists, and stakeholder organizations worldwide toward fulfilling the IEC's goals.

Following are our comments to the draft scoping document:

Background:

1. The description of lesions can be made more accurate. Lesions are more than "dry and itchy." Acute lesions are inflamed and eczematous (red, swollen, fissured/cracked, and weeping). Skin lesions have the propensity to be infected, which is not mentioned. S. aureus infection is a common complication of poor disease control.

2. Antihistamines are not effective for itch in AD.[1] Their use is only to induce sleep in those sleep-deprived because of the itch and discomfort associated with atopic dermatitis.

3. It should be made clearer that traditional long-term immunosuppressants reduce atopic dermatitis by less than 50% (AZA, MMF, MTX), establishing the need for more effective therapies. CsA has more efficacy but is limited to one year of use and has associated toxicity, especially hypertension and renal toxicity.

4. Tralokinumab blocks the cytokine directly, not the receptor. By blocking the cytokine IL-13, it prevents IL-13 binding to the IL-13 receptors.

5. It should be noted that oral steroids are the most commonly used treatments, but are discouraged by all treatment guidelines, including guidelines issued by the American Academy of Dermatology, due to short and long-term toxicities and the rebound that occurs after stopping.[2]

Populations:

1. We recommend including older adults as a subgroup by which to stratify by age, based on the availability of data. Recent studies have found high rates of physician-diagnosed disease among older adults, and this patient population may have unique treatment considerations.[3,4]

Comparators:

1. Comparators for systemic therapy should only be systemic therapies. While both populations technically have patients with an IGA designation of "moderate", the baseline demographics are likely to be very different, thereby making comparisons between the two groups misleading. If comparison is undertaken, you will need to account for the lower body surface area/BSA and lower severity in the topical studies. The baseline utilities should reflect a systemic treatment population.

2. We have concerns regarding comparing the new systemic agents to TCS. The clinical trial population for the JAK inhibitors (with BSA of 40-50% on average) is not a population that can be effectively treated with topical medications.

3. We would not suggest comparing topical ruxolitinib to TCS only in the short term. The efficacy of potent or super-potent TCS is probably in the same range as ruxolitinib, but TCS cannot be used long term due to potential side effects, whereas there is no current evidence which states that topical ruxolitinib cannot be used long-term if needed for control.

4. We are concerned about the risks of under-emphasizing the importance of side effects for the long-term use of less expensive systemic medications, particularly cyclosporine but also methotrexate, azathioprine and mycophenolate mofetil.

Outcomes:

1. We suggest adding absolute reduction or percent reduction in EASI. An EASI 75 with a baseline EASI score of 7 will be much different than an EASI 75 with a baseline of 25. This difference must be made clear.

2. Minor, but a reminder that “pruritus” is spelled “tus”.

3. We suggest adding sleep as an outcome using the sleep-related items from the Patient-Oriented Eczema Measure (POEM) or SCORing AD (SCORAD), which have been validated for use as single-item measures.[5]

4. We suggest adding a measure of long-term control, such as the Recap of atopic eczema (RECAP) or Atopic Dermatitis Control Tool (ADCT), as recommended by the Harmonizing Outcome Measures in Eczema (HOME) initiative as part of the core outcome set for clinical trials.[6,7,8]

Safety:

1. We suggest adding herpes simplex and zoster - even if not serious. These are increased in patients treated with JAK inhibitors.

2. Counting skin infection would be important in a cost-effectiveness analysis.

Thank you very much for the opportunity to provide comments to the scoping document, and please do not hesitate to contact us if you have any questions.

Sincerely,

Emma Guttman, MD, PhD, IEC President
Robert Bissonnette, MD, FRCPC, MSc, IEC President-Elect
Amy Paller, MD, MS, IEC Past President
Katrina Abuabara, MD, MA, MSCE, IEC Associate
Eric Simpson, MD, MCR, IEC Councilor
Jonathan Silverberg, MD, PhD, MPH, IEC Councilor

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Submitted Electronically via: publiccomments@icer-review.org

ICER's Review of JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis

Dear Dr. Pearson:

LEO Pharma, Inc. ("LEO" or "we") appreciates the opportunity to provide comments on ICER's draft scope for the review entitled "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis." LEO is a global pharmaceutical company with a 100+ year history as a specialty pharmaceutical company, including the establishment of a US affiliate in 2008. As a pioneer and leader in medical dermatology, we are committed to working with patients, providers, payers, and policy makers to increase the awareness of the burden and severity of atopic dermatitis (AD) and ensuring patients have access to innovative treatments such as tralokinumab.

LEO is supportive of the ICER value framework as it is committed to understanding "the full range of benefits and harms… considered in the judgments about the clinical and economic value of the interventions." We believe that the dupilumab ICER framework provides a good start to understanding the value of treatment innovation for AD.

LEO respectfully offers these points of consideration to ICER regarding the scope of this review, with the goal of ensuring this review's meaningfulness to the intended audiences and support policy decision making.

Suggest acknowledging heterogeneity of AD and clinical trial outcomes and its effects on the ICER analysis

The course of disease of atopic dermatitis is driven by endogenous patient's condition and exogenous environmental condition heterogeneity that may affect trials outcomes

- AD is characterized by multiple, heterogeneous clinical phenotypes and a range of disease subtypes. Heterogeneity is based on a variety of factors including ethnicity, disease chronicity, age of onset, filaggrin mutational status, IgE status, and underlying molecular mechanism or endotypes. Variation in AD severity, signs and symptoms, course of illness and affected body parts are subsequently mediated by these factors.
- Seasons, climate, pollution, aero-allergen concentration and socioeconomics, all factors potentially influencing disease severity, symptoms and the course of illness.

While these endogenous and exogenous heterogeneous factors are controlled within randomized clinical trials they differ substantially between trials which contribute to high variability in clinical outcomes despite similar trial design and inclusion exclusion criteria as reflected by substantial

differences in placebo or vehicle response across trials. Such differences question any indirect treatment comparison as well as cost effectiveness analysis and we suggest this is taken into careful consideration.

Ensure an analytic framework that closely represents the endpoints meaningful to patients

AD is commonly cited as a heterogeneous disease and measured largely by Investigator and Patient reported outcomes. Contrary to the belief that all patients want aggressive treatment at all costs, the patient perspective must be incorporated into the ICER's value framework. Incorporating elements that are most relevant and preferred by patients. Therefore, we suggest that AD patients and their caregivers be included as stakeholders, in addition to additional patient advocacy groups.

While cost-effectiveness can inform decisions about different therapies, relying solely on this analysis to determine what AD treatments should be offered to patients is counter to good clinical practice. Not only does the trajectory of AD vary from patient to patient but there are well-known problems with cost effectiveness analysis that may lead to questionable findings - from the quality of the data analyzed to difficulties in generalizing from clinical trials populations to patients in real world settings.

While AD has seen some improvement in patients' outcomes in recent years, driven by an explosion of effective, new therapies, there remains a high unmet medical need for a significant segment of patients. Collaborative success has extended the relief for many patients; however, AD remains a high burden disease. The best treatment for one AD patient may not be the best treatment option for another patient.

LEO appreciates ICER’s consideration of the input provided, and we look forward to collaborating with ICER on this review.

Sincerely,
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January 8, 2021

Steven D. Pearson, MD, MSc
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Dear Dr. Pearson:

The National Eczema Association (NEA) is looking forward to working with the Institute for Clinical and Economic Review (ICER) as a "Key Stakeholder" during the development of the report entitled "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis: Effectiveness and Value." Given ICER's experience modeling the effectiveness and value of dupilumab and crisaborole for atopic dermatitis[1] in 2017 and interactions with multiple stakeholders in this clinical area, we have confidence that this updated evaluation will advance the value discussion for treatments available to our community.

Since ICER's last atopic dermatitis treatment assessment in 2017, five organizations serving the eczema community collaborated with the US Food and Drug Administration to host **More Than Skin Deep**, a patient-focused drug development meeting on September 23, 2019.[2] With over 160 in-person participants, more than 1,500 respondents to a companion survey, and thousands in attendance via webcast, our community gathered to share the lived experiences of patients and caregivers affected by atopic dermatitis. We hope our summary report will provide additional contextual factors for your team as you work to develop this updated atopic dermatitis model.[2]

Our team has had the opportunity to review the draft background and scoping document published on December 10, 2020 and we would like to submit the following public comments and questions for your consideration as you develop the research protocol that focus on the following 5 key areas:

1. Atopic Dermatitis Model Structure
2. Patient Heterogeneity
3. Caregiver Impact
4. Protecting the Most Vulnerable Among Us
5. Reporting of Health Care System and Modified Societal Perspective Reference Case

Atopic Dermatitis Model Structure

While the recent scoping document did not supply a new structural model, it did specify the model will be "based in part on ICER's previous atopic dermatitis model, as well as a literature review of prior published models of inflammatory skin disorders and moderate-to-severe atopic dermatitis."[3] In the 2017 ICER atopic dermatitis model, a Markov process was developed to

simulate the transitions between the health states based on treatment response (Figure 1).[1]

As your modeling team updates the model structure for this report, we would like to pose the following comments and questions for consideration:

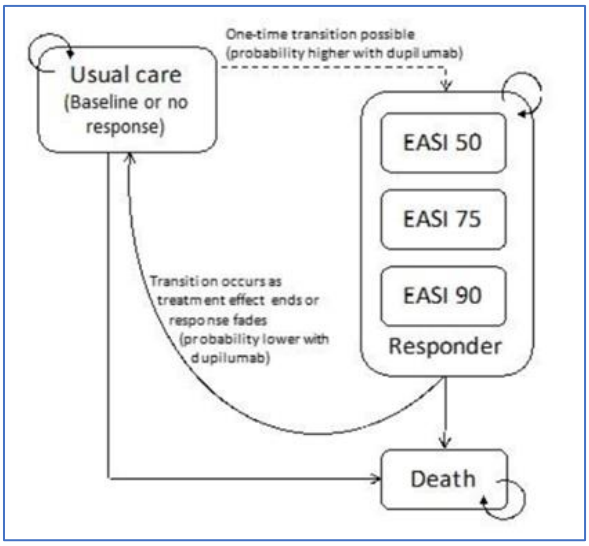

Figure 1. Markov model structure for 2017 ICER report on atopic dermatitis

- Will the same model structure be used for all patient populations and subgroups?
  - From the scoping document, it appears the age groups would be stratified but possibly entering the same model. For pediatric patients, it may be more realistic to consider different health states that more accurately reflect the experience of this population.
- Will the model address or have the ability to address the differences in costs or benefits for patients with severe vs. moderate or moderate vs. mild disease?
  - The current scope includes 2 populations, "mild-to-moderate" and "moderate-to-severe," likely reflecting clinical trial design. Will the modeling team be able to estimate the effects for each group separately where evidence exists, possibly additionally considering absolute changes in EASI scores that could account for different baseline levels of disease?
- Will treatment holidays or breaks in therapy be modeled along with consistent treatment?
  - We anticipate many patient groups to be prescribed periods of therapy with periods of therapy discontinuation throughout a patient's lifetime, or at least periods where maintenance therapy could be substantially less costly than the JAK regimen.
- Would there be additional health states for patients who experience anxiety and depression?
  - The scoping document specifies "anxiety and depression" as an outcome of interest, but it is not clear how this outcome would be reflected in the existing model, or how the model might include other frequently co-occurring health issues such as skin infections and sleep loss.[4-6]
- Would the model be flexible enough to allow for periods where patients may experience higher or lower out-of-pocket costs?
  - Out-of-pocket expenses reported by 1,118 NEA members vary greatly and can be compounded by multiple prescriptions copayments, frequent provider visits, and over-the-counter therapy.[7]

Patient Heterogeneity

When considering evaluating treatments for atopic dermatitis, the impact on different age groups could have a profound impact on the overall value assessment results. We applaud ICER's plan to focus on both adult and pediatric populations and further specifying plans to consider stratifying your assessment by children, adolescents, and adults.[3] Our initial subgroup concerns revolve

around the model structure listed above. Regardless of the model structure, we recognize it may be difficult to fully account for patient heterogeneity in all variables as there may be a lack of real-world evidence to support differing assumptions. We hope the NEA can serve as a resource to ICER's team to help answer some of these data gaps through engaging our members.

Caregiver Impact

Along the lines of our comments to patient heterogeneity, we anticipate the effects of atopic dermatitis to have extensive spillover effects for caregivers – especially for parents of pediatric patients. A recent review of cost-utility analyses in pediatric patients, 72% of studies included family spillover effects but these primarily focused on time costs.[8] The inclusion of these additional spillover effects had significant impacts on results, generally reducing the incremental cost-effectiveness ratio.[8] While we recognize that inclusion of these caregiver costs in the primary analysis could present the unintended consequence of justifying a higher treatment price, we do feel it is critical that special attention be paid to the potential value to caregivers.

Protecting the Most Vulnerable Among Us

In the revised Value Framework for 2020-2023, ICER has stated the importance of health inequality for policy makers and has committed to (when feasible) exploring scenario analyses to capture the impact of new technologies on disparities across different subpopulations in the US health care system.[9] While the "average" eczema patient experiences substantial financial difficulties due to the well documented economic burden of this disease and access differences based on payer type,[10,11] patients of lower socioeconomic status are particularly vulnerable.[9] Special consideration for the most economically vulnerable patients in this updated report on atopic dermatitis would greatly advance the discussion on treatment value in the eczema community and align with ICER's stated end goal: sustainable access to high-value care for ***all*** Americans.

Reporting of Health Care System and Modified Societal Perspective Reference Cases

We understand that it is ICER's position to report the health care system perspective as its reference or base case as ICER's value assessment methodology clearly states its intended use is to inform population-based medical policy and pricing decisions within the US health care system.[12] We agree with this emphasis on these health care system costs, however we ask that ICER consider aligning with the Second Panel on Cost Effectiveness, which recognized that the societal perspective (originally recommended as the preferred reference case) was rarely conducted and modified their recommendations such that economic models should report both perspectives and produce an impact inventory to aid in decision making.[13,14] From the scoping document, it appears that you would only report both perspectives as a co-base case when societal costs are "large relative to direct health care costs."[3] What is the harm in planning on reporting both as your standard? We feel this is a reasonable solution for health economists and value assessment frameworks to produce both reference cases and report side-by-side for comparison. This does not diminish the importance of the health care system or payer perspective, but rather recognizes that any "value assessment" that relegates the broader costs and outcomes important to patients to a secondary table or sensitivity analysis may actually bias the interpretation of the results.

We hope that these comments are helpful as you finalize your assessment, and we thank you for willingness to engage with our organization and our patient community.

Sincerely,

Julie Block
NEA President and CEO

Lawrence F Eichenfield, MD
Chair, NEA Scientific & Medical Advisory Council

With Support From:

Kenneth Mendez
President and CEO
Asthma and Allergy Foundation of America

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January 8, 2021

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Submitted via email: publiccomments@icer.org

RE: Draft Scoping Document for the Assessment of "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis"

Dear ICER AD Review Team,

On behalf of Pfizer Inc., thank you for the opportunity to comment on the draft scoping document for the assessment of "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis (AD)". We appreciate ICER's efforts to seek input from a broad range of stakeholders. Pfizer is committed to discovering medicines and vaccines that enhance the health of patients, their families, and society, with the ultimate goal of offering breakthroughs that will change patients' lives. In addition, we are dedicated to working with all stakeholders to identify solutions for creating a more effective, efficient, and equitable health care system for patients.

Based on our review of the draft scoping document, we offer the following feedback to select sections:

Background

- We recommend further emphasizing, both here and in the next section, that itch is the cardinal symptom of AD that often drives patients to seek treatment. Itch has been identified as the most burdensome AD symptom by patients, more so than "red, inflamed skin".[1] This is important context as patients consider "immediate and sustained relief from itch" as the most important result that a treatment could provide.[1]
- It is noted that "Antihistamines are used for sedation and itch". However, the American Academy of Dermatology guidelines for the treatment of AD state that "there is insufficient evidence to recommend the general use of antihistamines as part of the treatment of AD. Short-term, intermittent use of sedating antihistamines may be beneficial in the setting of sleep loss secondary to itch, but should not be substituted for management of AD with topical therapies".[2]
- In addition, while systemic immunosuppressants (cyclosporine A, methotrexate, mycophenolate mofetil, and azathioprine) are an option for patients whose previous treatments have failed or are considering phototherapy, all are off-label options in the United States, and data are sparse.[2-7]

Stakeholder Input

- As noted previously, we believe the burden of itch for AD patients of all severities should be further emphasized. Hundreds of members of the eczema community gathered to share their experiences at the

More Than Skin Deep patient-focused drug development meeting on September 23, 2019 (http://www.morethanskindeep-eczema.org/). The meeting was hosted by five organizations serving the eczema community in collaboration with the U.S. Food and Drug Administration. The five host organizations also developed and fielded a web-based survey to capture a broad set of experiences from patients and caregivers. 1,508 individuals (80% from the U.S.) completed the 32-item survey. Across all methods of gathering perspectives, itch was identified as the most problematic symptom; 79% of survey respondents placed it in their top three causes for greatest burden. "The burden of itch went far beyond a simple sensation. It was described as contributing to skin damage and physical harm, shame, difficulty with mood and attention, negative effects on social and intimate relationships, poor school and work performance, negative self-image, depression, and anxiety". When asked about the most important result that a treatment could provide patients with eczema, "immediate and sustained relief from itch" received the greatest number of responses by polling during the meeting and was selected by 51% of survey respondents.[1]

- When considering the unmet needs that still remain for AD patients, a recently conducted study aimed to identify meaningful treatment attributes and quantify patient preferences for attributes of systemic AD treatments through a discrete-choice experiment.[8] Adults with moderate-to-severe AD preferred a higher probability of skin clearance at 16 weeks, faster time to onset of itch relief, oral administration, and lower long-term safety risks. In particular, respondents valued an oral administration to such a degree, that they were willing to accept higher long-term safety risks. This research highlights the patient perspective surrounding the relevant benefits and risks of different AD systemic treatments, which can help inform shared patient-physician decision-making.

Comparators

- Many of the currently available treatments used for moderate-to-severe AD are limited to short-term or intermittent use due to inconvenience (phototherapy) or concern for adverse events.
  - Off-label systemic immunosuppressants (SISs) are generally used only intermittently rather than long-term due to the possible toxicities, which is important to consider when evaluating a lifetime time horizon.[2] A recently conducted retrospective claims study found that among moderate-to-severe AD patients, 64.6% had discontinued SIS therapy by 6 months after initiation.[9] For cyclosporine, clinical guidelines "recommend extensive monitoring, including blood pressure, renal function, lipids, and liver function, and that treatment duration should not exceed 1 year".[2]
  - With an increased understanding of the inflammatory pathways involved in AD pathogenesis, targeted systemic therapies, including monoclonal antibodies and small molecules, may allow for greater efficacy while minimizing adverse effects thereby permitting continuous long-term treatment for patients suffering from this chronic disease.
- We imagine Population 2 should be stated as "For mild-to-moderate atopic dermatitis (Population 2)" rather than "For mild-to-severe atopic dermatitis (Population 2)".
- We would like to confirm that TCS, TCI, and crisaborole are considered as separate comparator categories rather than pooling together given they are all listed within the same bullet. In addition, combining various

topical agents is often done in the real-world setting.

Outcomes

- Given that AD causes significant morbidity and impairment in quality of life, impacting patients, their caregivers/families, and society in general, we are pleased to see the broad range of patient-centric outcomes included in the Draft Scoping Document. Within "Other patient-reported symptom and quality of life measures" we would recommend considering the Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD), a validated 11-item, self-reported instrument using a 24-hour recall period, designed to assess the severity of key symptoms and signs of AD.[10] In addition, we recommend including the Work Productivity and Activity Impairment-Atopic Dermatitis questionnaire (WPAI-AD) in the list of outcomes given that AD has a significant adverse impact on work productivity, increasing with greater disease severity.[11,12]
- It is important to be aware of some of the inclusion/exclusion criteria differences across the various trial programs in order to appropriately interpret and contextualize particular outcomes. For example, the abrocitinib program excluded patients with suicidal ideation/behaviors or other psychiatric disorders (e.g., clinically significant depression), which should be considered when interpreting treatment effects on anxiety and depression (e.g., HADS).

Potential Other Benefits and Contextual Considerations

- Some additional benefits and contextual considerations not explicitly included in Table 1.1 follow:
  - Subpopulations of greater unmet need (e.g., dupilumab failures)
  - Rapidity of itch response, the most burdensome symptom for patients
  - Mode of administration: Oral medications allow for dose flexibility so healthcare providers can tailor treatments to individual AD patients in order to optimize both efficacy and safety and achieve long-term disease control for this heterogenous, unpredictable, relapsing-remitting chronic disease.
  - Considering mechanism of action, the differences between JAK selectivity should be noted, as not all JAK inhibitors are the same.

We hope that these comments are useful to ICER and look forward to further discussions throughout the review process.

Sincerely,

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January 8, 2021

Dear ICER Review Team:

Sanofi Genzyme and Regeneron Pharmaceuticals welcome the opportunity to provide comments on the ICER's draft scoping document "*JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis*, where dupilumab (Dupixent®) was identified as a comparator. We would like to provide some suggestions for the scoping document (available in Table 1 of the Appendix) as well as additional context and information about dupilumab for your consideration for the forthcoming review of new treatment options.

Dupilumab is a fully-human monoclonal antibody that inhibits the signaling of both interleukin-4 and interleukin-13, two key cytokines that mediate type 2 inflammatory processes. Dupilumab is approved in the US for the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. It is also approved for use with other asthma medicines for maintenance treatment of moderate-to-severe eosinophilic or oral steroid-dependent asthma in patients aged 12 years and older whose asthma is not controlled with their current asthma medications and for use with other medications for maintenance treatment of chronic rhinosinusitis with nasal polyps in adults whose disease is not controlled.[1] The clinical development program for dupilumab spans other type 2 inflammatory diseases, including eosinophilic esophagitis, chronic obstructive pulmonary disease, bullous pemphigoid, prurigo nodularis, and chronic spontaneous urticaria.

Since dupilumab's initial approval in the US in 2017 for the treatment of adults with moderate-to-severe AD, several new studies and reports have been published to support its long-term efficacy and safety profile and demonstrate treatment persistence in adults, as well as in adolescents (aged ≥ 12 to < 18 years)[2] and children (aged ≥ 6 to < 12 years)[3] as summarized below:

1) **Dupilumab's long-term safety profile (up to 3 years) was demonstrated in open-label extension (OLE) clinical studies and by post-marketing data**

   The ongoing, multicenter, OLE study (LIBERTY AD OLE; NCT01949311) assessed dupilumab treatment in adults previously enrolled in dupilumab clinical trials.[4] Among 2677 patients enrolled and treated with dupilumab 300 mg weekly, 347 patients completed 148 weeks (~ 3 years) of treatment. Safety data (270.1 adverse events [AEs]/100 patient-years; 6.9 serious AEs/100 patient-years) were consistent with previously reported trials and the known dupilumab safety profile.

   Long-term safety data were also reported in the adolescent (aged ≥ 12 to < 18 years) and pediatric (aged ≥ 6 to < 12 years) patients who were enrolled in the phase 3 OLE study (LIBERTY AD PED-OLE; NCT02612454) and who had completed 52 weeks of follow up. [5,6] The safety profile of dupilumab in both patient populations followed through Week

52 was similar to the safety profile observed at Week 16 and the long-term safety profile of dupilumab observed in adolescents and children was consistent with that seen in adults with atopic dermatitis.[1] The data further support the use of dupilumab as a continuous long-term treatment for adolescents and children with moderate-to-severe AD.

Post-marketing data from 01 January 2017 through 30 September 2020 estimated the exposure to dupilumab at approximately 250,000 patient-years[7]. The benefit-risk profile of dupilumab has remained favorable since the time of authorization. There is no requirement for initial lab testing or ongoing lab monitoring for treatment of atopic dermatitis according to the Prescribing Information.[1]

2) Dupilumab's real-world persistence at 12 months is 75-77%.

A retrospective cohort study that used the IBM MarketScan Commercial and Medicare database identified 1963 adults with AD who initiated dupilumab between March 28, 2017, and March 31, 2018.[8] Among those patients, dupilumab persistence at 6 and 12 months was 91.9% (95% confidence interval [CI]: 90.7%-93.2%) and 77.3% (95% CI: 75.0%-79.7%), respectively. Among patients who initially discontinued dupilumab (n=329), 78.8% reinitiated dupilumab within an average of 4 months (95% CI:75.8%-81.7%).

Another real-world study reported similar findings.[9] Among 265 patients with AD identified in the IQVIA Health Plan Claims database who received dupilumab, 78.1% were persistent with dupilumab treatment at 6 months, and 75.0% of patients were still on dupilumab at 12 months.

3) Dupilumab demonstrated long-term effectiveness in clinical trials, OLE studies and real-world studies

The previously mentioned OLE studies of adults, adolescents and children also indicated a sustained response to dupilumab over the long term. In adult patients with moderate-to-severe AD, signs and symptoms of AD showed substantial sustained improvements during treatment that resulted in a mean (standard deviation) EASI score of 1.4 (3.2) at Week 148.[4] This score represents a 95.4% reduction from the parent study baseline, and is indicative of the near-absence of clinical signs of AD. 96.6% of patients also achieved EASI-75 (i.e., a 75% improvement from baseline in EASI score). Additionally, a weekly average Pruritus Numerical Rating Scale (NRS) score ≤ 3 was reported in 81.9% of patients, with an absolute mean (standard deviation) score of 2.2 (1.8) at Week 148, representing a 65.4% reduction from the parent study baseline. Similarly, improvements were reported in the adolescent and pediatric OLE studies. 88% of adolescents and 94% of children treated with dupilumab for up to 52 weeks achieved an EASI-75 response, respectively. [5,6]

In the RELIEVE-AD study, a prospective longitudinal patient survey of 699 adult patients with AD who were treated with dupilumab, 77.4% and 62.9% of patients reported adequate disease control at Month 12 based on Atopic Dermatitis Control Tool

total score and symptom criteria, respectively.[10] Patient satisfaction with dupilumab treatment was at 85.1% at Month 12 and patients reported significant reductions in flares, itch, skin symptoms, and improved sleep, health-related quality of life, and daily activities relative to baseline.

In summary, recent evidence from both clinical trials and real-world studies have demonstrated dupilumab's long-term safety, effectiveness and persistence in patients with atopic dermatitis in populations representing a broad age range (age 6 and above), supporting its use in this disease that is characterized by substantial patient burden, often with other type 2 inflammatory comorbidities,[11] and high unmet needs. We appreciate the opportunity to be involved in this review and look forward to a continued dialogue with ICER.

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Appendix

Table 1: Suggestions for Text Changes and Comments on the Draft Scoping Document

Suggestions for change are highlighted in red.

Page	Original text	Suggestions for Text Changes or Comments
2	Short-term use of systemic oral corticosteroids or cyclosporine can be used to more quickly control skin disease, while oral methotrexate, azathioprine or mycophenolate mofetil can be used for long-term control.	Comment: These treatments are not currently indicated and not recommended in the guidelines for long term use in AD.
2	Dupilumab, an interleukin (IL) 4 receptor alpha antagonist given subcutaneously, was approved by the FDA in 2017 for those with moderate-to-severe disease with an inadequate response to prior treatment.	Suggestions for change: Dupilumab, an interleukin (IL) 4 receptor alpha antagonist given subcutaneously, was approved by the FDA in 2017 for adults with moderate-to-severe disease with an inadequate response to prior treatment. Subsequently, dupilumab was approved in the US in 2019 for adolescents 12-<18yo and in 2020 for children 6-<12yo with moderate to severe AD.
3	Oral and topical JAK inhibitors are hoped to offer new and easier forms of delivery, but experts expressed caution about potential side effects of these new treatments with long-term use, both in children, given the lack of clinical trials, and in older patients at risk for thrombotic events.	Comment: We recommend including a statement acknowledging that the US PIs (prescribing information) for JAK inhibitors therapies have the box warnings for serious infections, malignancy and thrombosis.
4	Topical therapies (including emollients with or without a topical corticosteroid or calcineurin inhibitor)	Suggestions for change: Topical therapies (including emollients with or without a topical corticosteroid or calcineurin inhibitor) and PDE inhibitor (Crisaborole)
5	Systematic immunomodulator therapies other than dupilumab (including cyclosporine, methotrexate, azathioprine, or mycophenolate)	Suggestions for change: Systemic immunomodulator therapies other than dupilumab (including cyclosporine, methotrexate, azathioprine, or mycophenolate)
5	Systematic immunomodulator therapies other than dupilumab (including cyclosporine, methotrexate, azathioprine, or mycophenolate)	Comment Dupilumab is not an immunossupressant and is classified in another ATC code (WHO drug). Suggest removing dupilumab from this line. (Boguniewicz et al, 2018. Ann Allergy Asthma Immunol. 2018 Jan;120(1):10-22)
5	Safety	Comment: Overall infections are also important to consider
7	As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of abrocitinib, baricitinib, upadacitinib, and tralokinumab for the treatment of chronic moderate-to-severe	Suggestions for change: As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of abrocitinib, baricitinib, upadacitinib, and tralokinumab for the treatment of

	atopic dermatitis relative to relevant comparator treatments, potentially including topical therapy, systemic immunomodulator therapies other than dupilumab, dupilumab, and phototherapy.	chronic moderate-to-severe atopic dermatitis relative to relevant comparator treatments, potentially including topical therapy, systemic immunossupressants, dupilumab, and phototherapy.