JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis

Draft Background and Scope

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Background

Atopic dermatitis is a common, chronic skin condition with persistent or relapsing lesions that are itchy and dry. Symptoms of itching and even pain vary in severity, but can affect sleep, cause psychological distress, and result in difficulty with performance at school or work.[1-3] The appearance of the skin can also lead to social embarrassment and isolation.[4] The net effect is that atopic dermatitis can have a profound effect on all aspects of patients' lives and those of their family and caregivers.[5,6]

Most lay people and many clinicians use the term "eczema" when referring to atopic dermatitis, but eczema more broadly refers to any skin condition with the appearance of crusting, oozing or blistering skin. Atopic dermatitis affects both children and adults. In the United States (US), it is estimated to affect around 11-15% of children and 7-10% of adults.[7-10] The overall costs associated with atopic dermatitis are estimated to be $5.3 billion dollars in the US, including over $1 billion in health care costs.[11,12]

Atopic dermatitis is thought to be caused by changes in the barrier properties of the skin and problems with the body's immune response.[13,14] Patients with atopic dermatitis often have a family history that can also include asthma and allergic rhinitis; atopic dermatitis is also associated with socioeconomic and environmental factors.[15] Atopic dermatitis frequently begins during childhood and persists into adulthood in about 50% of affected children.[16] The skin lesions can be localized or widespread, varying in their location by age, and can come and go or be persistent.[17] When acute, the appearance is of red papules and vesicles with weeping, oozing and crusting. When subacute or chronic, lesions are dry, scaly, or excoriated with skin thickening, erosions, cracking and bleeding. Disease severity is difficult to consistently define because it is based upon the amount of skin involved, its appearance, and the subjective impact of symptoms.

Most children with atopic dermatitis have mild disease, with 12-26% having moderate and 4-7% having severe disease.[15,18] Moderate or severe disease appears to be more common in adults.[19] For all patients with atopic dermatitis, treatment focuses on maintaining the skin barrier with moisturizers and emollients, avoiding triggers such as heat/cold, low humidity, and known allergens.[20] Antihistamines can be used for sedation and itch. Topical corticosteroids are used for short-term, intermittent use, and long-term maintenance may include the topical calcineurin inhibitors, tacrolimus and pimecrolimus, or the phosphodiesterase 4 (PDE-4) inhibitor, crisaborole.[21] For those with atopic dermatitis not controlled with topical therapies, phototherapy or systemic immunomodulators are used.[22] Short-term use of systemic oral corticosteroids or cyclosporine can be used to more quickly control skin disease, while oral methotrexate, azathioprine or mycophenolate mofetil can be used for long-term control. Dupilumab, an 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.[23]

Despite available treatments, many individuals do not respond to multiple different topical and systemic therapies supporting the need for new treatment options.[24] This is especially true for children, where there is greater concern about the effects of topical and systemic corticosteroids.[25] A new target for therapy are the Janus kinases (JAKs), cytoplasmic protein tyrosine kinases that are critical for signal transduction to the cell nucleus.[26] Oral JAK inhibitors being evaluated for patients with moderate-to-severe atopic dermatitis include abrocitinib, baricitinib, and upadacitinib. A topical JAK inhibitor, ruxolitnib is being evaluated for patients with mild-to-moderate atopic dermatitis. A second new target for therapy is the IL-13 receptor.[27] Tralokinumab, a monoclonal antibody that blocks the IL-13 receptor is given subcutaneously and is under investigation for patients with moderate-to-severe atopic dermatitis.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patient advocacy organizations, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and written input submissions. A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Initial comments from patients and patient advocacy groups has emphasized that atopic dermatitis can be a serious condition that can affect all aspects of a patient's life and that of their family and caregivers. When it affects children, atopic dermatitis can disrupt sleep, leading to daytime fatigue with negative impact on school performance. It can also have a profound impact on the child's caregivers and other family members. For adults, symptoms of atopic dermatitis can affect daily

activities at home and work, as well as one's productivity. Symptoms and the appearance of the skin can also lead to embarrassment, social isolation, psychological distress, disrupt relations with family, friends, intimate partners, all of which can be particularly impactful for children with bullying and other negative interactions with peers.

From clinical specialists, researchers, and manufacturers, we also heard that there is a need for new therapeutic options for those with atopic dermatitis, particularly individuals with moderate and severe symptoms who have not responded to topical treatments. Lack of adequate response as well as concerns about side effects of therapy, especially prolonged use of potent corticosteroids, highlight the need for new treatments. Dupilumab, a monoclonal antibody, approved for use in 2017 in the US, has helped many individuals with moderate-to-severe atopic dermatitis, but not all patients respond and it must be administered subcutaneously on a chronic basis. 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.

Report Aim

This project will evaluate the health and economic outcomes of abrocitinib, baricitinib, upadacitinib, tralokinumab, and ruxolitnib for Atopic Dermatitis. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses (NMA) of selected outcomes. Based on the availability of data, NMA specifications stratified by age

(children: <12 years, adolescents: ≥12 years to <18 years, and adults: ≥18 years), duration (≤16 weeks and >16 weeks), and/or severity (mild, moderate, and severe) will be considered. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The populations of focus for the review are:

1. Adults and children with moderate-to-severe atopic dermatitis whose disease has either not responded adequately to topical therapies or for whom topical therapies have not been tolerated or are medically inadvisable

2. Adults and children with mild-to-moderate atopic dermatitis

Additionally, based on the availability of data, we intend to include evidence stratified by age (children: <12 years, adolescents: ≥12 years to <18 years, and adults: ≥18 years), duration (≤16 weeks and >16 weeks), and disease severity (mild, moderate, and severe).

Interventions

The interventions of interest include the following JAK inhibitors and monoclonal antibodies:

Moderate-to-severe atopic dermatitis (Population 1):

- Abrocitinib (Pfizer)
- Baricitnib (Olumiant©, Eli Lilly)
- Upadacitinib (Rinvoq©, AbbVie)
- Tralokinumab (Leo Pharma)

Mild-to-moderate atopic dermatitis (Population 2):

- Ruxolitnib (Incyte)

Comparators

We intend to compare the interventions of interest to:

- For moderate-to-severe atopic dermatitis (Population 1):
    - Topical therapies (including emollients with or without a topical corticosteroid or calcineurin inhibitor)

    - Systematic immunomodulator therapies other than dupilumab (including cyclosporine, methotrexate, azathioprine, or mycophenolate)
    - Dupilumab
    - Phototherapy
- For mild-to-severe atopic dermatitis (Population 2):
    - Topical emollient therapy alone
    - Topical corticosteroids, calcineurin inhibitors, or crisaborole

Outcomes

The outcomes of interest are described in the list below.

- Investigator's Global Assessment (IGA)
- Eczema Area and Severity Index (EASI); 50, 75, and 90 or change from baseline
- Scoring Atopic Dermatitis (SCORAD) Score
- Patient-reported pruritis or itching
- Patient-Oriented Eczema Measure (POEM)
- Dermatology Life Quality Index (DLQI)
- Children's Dermatology Life Quality Index (CDLQI)
- Anxiety and depression (e.g., HADS)
- European Quality of Life-5 Dimensions (EQ-5D)
- Other patient-reported symptom and quality of life measures
- Safety
    - Adverse events (AEs)
    - Treatment-emergent adverse events (TEAEs)
    - Serious adverse events (SAEs)
    - Discontinuation due to AEs
    - Thrombotic events
    - Serious infections
    - Hematological abnormalities
    - Malignancy
    - All-cause mortality

Timing

Evidence on intervention effectiveness will be derived from studies of at least four weeks duration.

Settings

All relevant settings will be considered, with a focus on patients treated in outpatient settings in the United States.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Potential Other Benefits or Disadvantages and Contextual Considerations

1 (Suggests Lower Value)	2 (Neutral)	3 (Suggests Higher Value)
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.
Very similar mechanism of action to that of other active treatments.		New mechanism of action compared to that of other active treatments.
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials.		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials.
This intervention could reduce or preclude the potential effectiveness of future treatments.		This intervention offers the potential to increase access to future treatment that may be approved over the course of a patient's lifetime.
The intervention offers no special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.		The intervention offers special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.
This intervention will not differentially benefit a historically disadvantaged or underserved community.		This intervention will differentially benefit a historically disadvantaged or underserved community.
Small health loss without this treatment as measured by absolute QALY shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.

1 (Suggests Lower Value)	2 (Neutral)	3 (Suggests Higher Value)
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator.		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator.
Other		Other

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

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 atopic dermatitis relative to relevant comparator treatments, potentially including topical therapy, systemic immunomodulator therapies other than dupilumab, dupilumab, and phototherapy. Data permitting, we may include a population with episodic moderate-to-severe atopic dermatitis. The model structure 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.[28-30] The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. The model will consist of health states based on disease-specific measures. The target population will consist of adults and children with moderate-to-severe atopic dermatitis; based on data availability, the analysis may be stratified by age (children: <12 years, adolescents: ≥12 years to <18years, and adults: ≥18 years) and disease severity (moderate and severe). A cohort of patients will transition between health states during predetermined cycles over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., five years).

Key model inputs will likely include disease-specific measures (e.g., EASI, IGA), clinical probabilities, symptom improvement, treatment-related adverse events, and health-related quality of life. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis if available data allow. The health outcome of each intervention will be evaluated in terms of life-years gained,

quality-adjusted life years (QALYs) gained, equal value of life years gained (evLYG) and other clinically relevant measures (e.g. response time and/or itch-free time). Future costs and outcomes will be discounted at a rate of 3%. Relevant pairwise comparisons will be made between treatments or treatment sequences, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, and cost per life-year gained.

Based on the available clinical evidence, we will explore presenting a cost-consequence analysis of ruxolitnib versus its comparator(s) for patients with mild to moderate atopic dermatitis. This would feature the clinical outcomes presented within the clinical evidence review and include costs consistent with the trial evidence and the trial time horizon(s).

In separate analyses, we will explore the potential health care system budgetary impact of the new treatments over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by the treatments considered in this review (e.g., reduced need for emergency department visits for skin infections), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of atopic dermatitis beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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