

Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness, Value, and Value-Based Price Benchmarks

Background and Scope
December 9, 2016

Background:

Atopic dermatitis (eczema) is a chronic/chronically-relapsing skin condition characterized by itching and dry skin. Lesions can be acute, subacute, or chronic, and these can involve papules, vesicles, erythema, crusting and exudate, swelling, scaling, and thickening/lichenification.

Atopic dermatitis is common. It affects 5-20% of children worldwide,¹ and approximately 11% of children in the US.² It is also estimated to affect around 3-7% of adults in the US.^{3,4} Management of atopic dermatitis can create burdens for the family,⁵ and the disorder can decrease quality of life.⁶ Itching, in particular, can disrupt sleep and lead to daytime sleepiness,⁷ irritability, and psychological stress, and cosmetically important lesions can lead to social stress and isolation.⁶

Atopic dermatitis has a strong genetic component,⁸ and a family history of atopic disease is an important risk factor.⁹ Approximately 67-82% of children with atopic dermatitis have mild disease, 12-26% have moderate disease, and 4-7% have severe disease.^{10,11} There is less evidence on severity of disease in adults or on the frequency with which adults are refractory to topical therapies, but severe disease appears to make up a greater percentage of disease in adults than in children. The majority of children experience improvement or resolution of atopic dermatitis by late childhood, although the exact percentage in whom disease persists into adulthood is uncertain.¹²

The mainstays of therapy for atopic dermatitis include emollients to improve the epidermal barrier, avoidance of triggers, and topical treatment with corticosteroids or calcineurin inhibitors, aimed at decreasing inflammation.¹² Patients with severe disease can be treated with phototherapy or systemic immunomodulators such as cyclosporine, azathioprine, or, for short periods, oral corticosteroids.^{13,14} While phototherapy is generally available to patients in the US, all of the systemic treatments other than oral corticosteroids lack approval by the FDA for atopic dermatitis and few patients in the US receive them. Cyclosporine appears to be the most commonly used of these non-steroid systemic agents and to have the best evidence of efficacy.¹⁴

Prolonged use of topical corticosteroids can result in telangiectasias, increased hair, and thinning/atrophic changes, which can be permanent,^{15,16} and higher potency topical corticosteroids can produce systemic effects including adrenal suppression,¹⁷ particularly when used for long periods on large surface areas or more permeable areas of the skin. However, many patients can use these preparations without developing atrophy or other side effects,¹⁸ and concerns about the use of topical steroids are referred to as “steroid phobia” or “topical corticosteroid phobia”, both in the literature¹⁹ and by a number of clinicians and patient groups with whom we spoke. Topical calcineurin inhibitors can sting when they are first used, and the US FDA label includes a warning regarding a theoretical risk for skin cancers and lymphoma. Phototherapy may increase the risk of skin cancer,²⁰ and systemic immunomodulators can have potentially serious side effects.¹⁴

Crisaborole is a topical phosphodiesterase 4 (PDE 4) inhibitor that has been evaluated as a new therapy for mild-to-moderate atopic dermatitis in adults and children, and is a potential alternative to topical corticosteroids and calcineurin inhibitors. Dupilumab is a monoclonal antibody against interleukin-4 receptor alpha that has been evaluated as a novel systemic therapy for moderate-to-severe atopic dermatitis in adults. Both treatments are undergoing review at the FDA with projected approval dates in the first quarter of 2017.

Report Aims:

This project will evaluate the comparative clinical effectiveness of crisaborole for its expected indication in the treatment of mild-to-moderate atopic dermatitis in children and adults; separately, the report will also evaluate the comparative clinical effectiveness and value of dupilumab for its expected indication in the treatment of moderate-to-severe atopic dermatitis in adults. The report will not compare the clinical effectiveness of crisaborole and dupilumab.

Scope of the Evidence Review Focusing on Comparative Clinical Effectiveness:

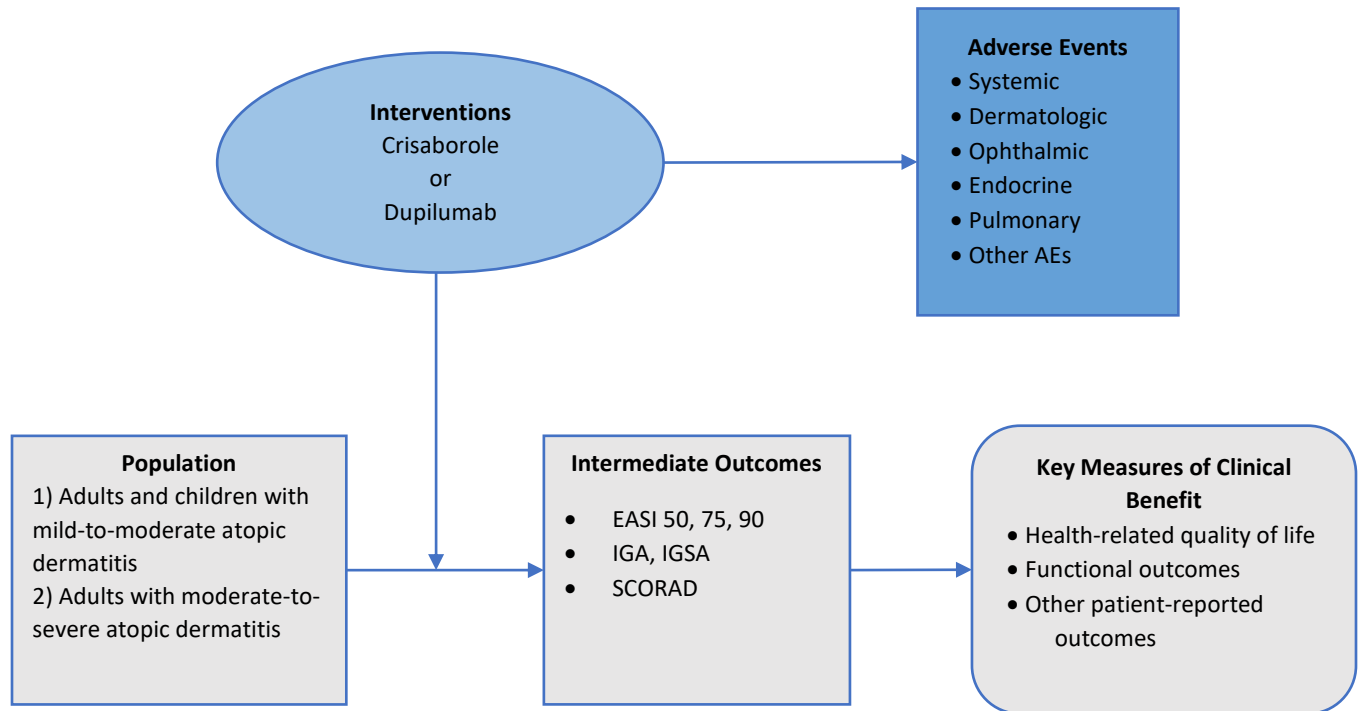
The proposed scope for this assessment is described below using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be collected from available randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered. We will not restrict studies according to study setting; however, we will limit our review to those that capture the outcomes of interest. However, when assessing adverse events and harms, we will also look for randomized trials of dupilumab therapy for conditions other than atopic dermatitis. In evaluating phototherapy and cyclosporine as comparators, we will look for randomized trials that compare these therapies with dupilumab, with placebo/no treatment, or with topical therapy so as to potentially inform a network meta-analysis.

Our evidence review will include input from patients and patient advocacy organizations, data from conference proceedings and regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see <http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/>).

Analytic Framework:

The general analytic framework for assessment of all the interventions is depicted in Figure 1 below.

Figure 1. Analytic Framework: Atopic Dermatitis



Populations

The populations of focus for the review will be:

- 1) For crisaborole: adults and children with mild-to-moderate atopic dermatitis
- 2) For dupilumab: adults with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy, or for whom topical therapies are medically inadvisable

Interventions

- 1) Crisaborole for mild-to-moderate atopic dermatitis
- 2) Dupilumab for moderate-to-severe atopic dermatitis

Comparators

- 1) For crisaborole: emollient therapy alone for mild-to-moderate atopic dermatitis; if possible, we will also compare to topical corticosteroids and calcineurin inhibitors
- 2) For dupilumab: topical therapy for moderate-to-severe atopic dermatitis (emollients with or without a topical corticosteroid or calcineurin inhibitor), phototherapy, or cyclosporine

Outcomes

This review will examine key clinical outcomes that occur in patients being treated for atopic dermatitis.

Discussions with patient groups and clinicians indicated that atopic dermatitis creates symptoms for patients and burdens for patients and families that may not be well-captured by standard trial outcomes. We heard that although itch and the effects of atopic dermatitis on sleep are central to quality of life, the latter is not always adequately captured in clinical trials. Burden and symptom outcomes that are typically not well captured include psychological issues (depression; anxiety; suicidal ideation; stress on relationships; effects on developmental milestones; effects on self-esteem and bullying), pain (distinct from itch), burden of treatment (time spent on treatment; caregiver burdens; difficulty of adherence by children at school [such as reapplying moisturizers]; perceived burdens of injections versus oral medications; cost; travel to seek medical care), and interference with life activities (missed days of school; missed days of work for parents; missed days of work for patients; disability for the patient's chosen profession; presenteeism effects on work and school; restrictions on diet, exercise, and recreation; effects on intimacy).

We recognize that many of these outcomes will not be adequately addressed within randomized trials, but will look for such evidence where available.

Outcomes from clinical trials:

- Investigator's Static Global Assessment (ISGA)
- Investigator's Global Assessment (IGA)
- Eczema Area and Severity Index (EASI): 50, 75, 90
- Scoring Atopic Dermatitis (SCORAD) score
- Pruritus (by any scale)
- Dermatology Life Quality Index (DLQI)
- Patient-Oriented Eczema Measure (POEM)
- Hospital Anxiety and Depression Scale (HADS)
- EuroQol five dimensions questionnaire (EQ-5D) if available
- Treatment-related adverse events

We will also look for evidence on additional patient-reported outcomes, including other measures of health-related quality of life and measures of sleep. Additionally, we will look for evidence regarding effects of therapy on the long-term course of atopic dermatitis through disease modification. Since dupilumab may have effects on other atopic disease, we will try to assess whether there are differential effects on broader health outcomes. To do this, we will seek evidence on quality of life measures (such as EQ-5D) in subgroups with and without asthma or nasal polyposis and/or compare such broader measures with measures more narrowly focused on dermatologic quality of life (such as DLQI).

We will develop evidence tables for each selected study, and results will be summarized in a qualitative fashion; meta-analysis will be considered to quantitatively summarize outcomes for the therapies of interest. If data permit, we may perform a network meta-analysis of indirect evidence to compare crisaborole with topical therapies (corticosteroids and calcineurin inhibitors) and to compare dupilumab with phototherapy.

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least four week's duration.

Settings

We will examine results in patients treated in clinic and outpatient settings.

Simulation Models Focusing on Comparative Value:

As a complement to the evidence review, we will develop a simulation model to assess the cost-effectiveness of dupilumab versus topical therapy and, if the evidence is adequate, versus phototherapy and systemic therapy with cyclosporine. The model structure will be informed by previously developed cost-effectiveness models assessing biologic therapies in inflammatory skin disorders²¹, as well as previously developed economic models assessing treatments for moderate-to-severe atopic dermatitis, such as that published by Hjelmgren et al.²² The model will allow for non-response and discontinuation of treatment, and will be developed from a health system perspective. The model population will include adults with moderate-to-severe atopic dermatitis who have failed topical therapy or for whom topical therapies are medically inadvisable.

Key model inputs will likely include disease-specific measures (e.g., EASI, IGA), symptom improvement, treatment-related adverse events, and health-related quality of life. Model cost inputs will include those of the treatment regimens, costs of treating adverse events, and ongoing care. If sufficient data are available, we will include productivity costs and associated offsets as a scenario analysis. Results will be expressed in terms of costs per quality-adjusted life year (QALY) gained.

We will also assess the potential budgetary impact of dupilumab over a five-year time horizon, utilizing modeled estimates of treatment costs and any cost offsets from reductions in use of other health care resources. Potential budgetary impact analyses will assume different rates of technology uptake over a five-year period based on ICER's criteria. Finally, we will develop a "value-based price benchmark" for dupilumab reflecting prices aligned with long-term cost-effectiveness thresholds.

More information on ICER's methods for estimating product uptake and calculating value-based price benchmarks can be found on [ICER's website](#).

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