Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value

Final Evidence Report and Meeting Summary

June 8, 2017

Prepared for

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Expert Review

In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input and feedback that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit:

https://icer-review.org/material/atopic-dermatitis-stakeholder-list/

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List of Acronyms Used in this Report

AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ASDI	Atopic Dermatitis Severity Index
BSA	Body surface area
CMS	Centers for Medicare and Medicaid Services
CSA	Cyclosporine
CLDQI	Children's Dermatology Life Quality Index
DFI	Dermatitis Family Impact Questionnaire
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EQ-5D	EuroQol five-dimension questionnaire
GISS	Global Individual Sign Score
HADS	Hospital Anxiety and Depression Scale
IGA	Investigator's Global Assessment
ISGA	Investigator's Static Global Assessment
NICE	National Institutes for Health and Care Excellence
NMA	Network meta-analysis
NRS	Numerical rating score
PDE 4	Phosphodiesterase 4
PICOTS	Population, Intervention, Comparators, Outcomes, Timing, and Settings
POEM	Patient-Oriented Eczema Measure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life-year
QoL	Quality of life
QW	Weekly dosing regimen
Q2W	Every two-week dosing regimen
RCT	Randomized controlled trial
SCORAD	Scoring Atopic Dermatitis
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
Th2	Type 2 helper T cell
USPSTF	US Preventive Services Task Force
WTP	Willingness to pay

Executive Summary

Background

Atopic dermatitis is a chronic/chronically-relapsing skin condition characterized by itching and dry skin. 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] The mainstays of therapy for atopic dermatitis are meticulous skin care with frequent application of a bland moisturizer (optimally an ointment) to maintain the skin's epidermal barrier, avoidance of triggers, and short-term intermittent treatment with a topical corticosteroid or long-term maintenance with a topical calcineurin inhibitor if needed.[5] Patients with skin disease that cannot be controlled with topical therapy can be treated with phototherapy or systemic immunomodulators such as cyclosporine, azathioprine, or, for short periods, prednisone.[6,7] Crisaborole (Eucrisa™, Pfizer, Inc.) 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 intermittently applied topical corticosteroids or daily topical calcineurin inhibitors. Dupilumab (Dupixent™, Sanofi-Regeneron) 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. Dupilumab, in particular, is expected to provide an important therapeutic option for many patients who have not previously had an adequate response to treatment, and is more expensive than existing treatment options.

Topic in Context

Atopic dermatitis is common, particularly in children.[1,2] There is a broad spectrum of disease, with the majority of patients able to be managed adequately with topical therapies. The two therapies we are examining in this report are intended for patients at different places on the disease spectrum. There is, however, no agreed-on definition of "mild-to-moderate" or "moderate-to-severe" atopic dermatitis.[7]

Management of atopic dermatitis can create burdens for the family,[8] and the disorder can decrease quality of life.[9] Itching, in particular, often disrupts sleep leading to daytime drowsiness[10] and irritability, with psychological stress and impaired performance in school and at work. The aesthetic impact of skin changes can lead to social stress and isolation.[9]

Crisaborole is a topical therapy that inhibits phosphodiesterase 4 (PDE4), the same mechanism as the oral agent apremilast that is used for psoriasis.[11] Crisaborole is intended for use in patients with mild-to-moderate atopic dermatitis as a safe alternative to the existing topical agents. Crisaborole comes as an ointment that is applied twice daily.

In addition to moisturizers used to augment the skin's epidermal barrier, existing topical therapies for atopic dermatitis include corticosteroids and calcineurin inhibitors (i.e., pimecrolimus [Elidel®]

and tacrolimus [Protopic®]). Prolonged use of topical corticosteroids can result in telangiectasias, increased hair, skin tears, easy bruising, poor wound healing, acne and rosacea, and thinning/atrophic changes, which can be permanent.[12,13] Topical corticosteroids can also produce systemic effects including adrenal suppression,[14] particularly when higher potency preparations are 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,[15] and concerns about the use of topical steroids are referred to as "steroid phobia" or "topical corticosteroid phobia", both in the literature[16] and by a number of clinicians and patient groups with whom we spoke. All topical preparations can sting, but there is evidence that this can be a particular problem with topical calcineurin inhibitors.[17] The US FDA label for topical calcineurin inhibitors includes a "black box" warning regarding a theoretical risk for skin cancers and lymphoma.

Dupilumab is a monoclonal antibody directed against interleukin-4 receptor alpha.[18] It is administered as a subcutaneous injection given every other week. Dupilumab inhibits signaling of interleukin-4 and interleukin-13, and by doing so alters type 2 helper T (Th2) cell mediated immune responses and improves epidermal barrier abnormalities in atopic dermatitis.[19] This is a novel mechanism of action, although other therapies directed at Th2 cells and type 2 cytokines are in development.[20,21] Dupilumab is intended for use in patients with moderate-to-severe atopic dermatitis and is believed to be more targeted and safer than existing systemic therapies.

Existing systemic therapies for atopic dermatitis include immunomodulators such as cyclosporine, azathioprine, and methotrexate, and patients with less severe disease can also be treated with phototherapy. Short courses of oral corticosteroids and oral antibiotics are commonly prescribed to many patients with severe atopic dermatitis. However, in addition to well-recognized adverse effects, treatment with systemic corticosteroids is typically inadequate for patients with chronic disease given its limited duration of use, and is often followed by rebound worsening upon discontinuation. All of the previous 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.[7] Phototherapy is typically available to patients in the US who live in large metropolitan areas, but is not generally felt to be appropriate for patients with more severe disease. Phototherapy can be prohibitively time consuming and may increase the risk of skin cancer,[22] and systemic immunomodulators can have potentially serious or even fatal side effects, including infections, malignancies, and blood dyscrasias, can cause irreversible liver and kidney damage, and require frequent laboratory monitoring.[7]

Insights Gained from Discussions with Patients and Patient Groups

Central to the comments we heard from patients and patient groups was the idea that thinking of atopic dermatitis as "just a skin condition" is a serious error that underappreciates the profound effects that severe atopic dermatitis can have on all aspects of a patient's life and on the lives of family and caregivers.

We heard that patients' lives can be affected by:

- Sleep disruption that can be profound
- Itch and pain that can affect both sleeping and waking hours
- Individual psychologic effects of illness, including depression, anxiety, suicidal ideation, and loss of self-esteem
- Interpersonal effects, including bullying in children, alterations in family dynamics, and effects on intimate relationships in adults
- Effects on performance, including effects on developmental milestones and school attendance in children, missed days of work, disability for one's chosen profession, and presenteeism effects on school and work performance
- Effects on life activities, including restrictions on diet, exercise, and recreation
- Burdens of therapy, including time spent on treatments (such as applying moisturizers and wraps) that may present particular adherence issues for children at school, costs of treatment and of travel to seek care

Additionally, atopic dermatitis can present substantial burdens for families and caregivers. Apart from the relationship issues discussed above, parents may need to spend substantial time applying topical therapies to children, may miss days of work when children miss school because of atopic dermatitis, and may experience chronic sleep disruption from cosleeping with their child. Lack of treatment options for infants and children younger than age two is a significant problem for patients and families.

Atopic dermatitis appears to be a disease that is frequently undertreated and, for many patients, is lacking treatments. Mild-to-moderate disease can often be effectively controlled with existing topical therapies,[23-25] but concerns about the side effects of those therapies inhibit treatment in many patients. In this landscape of a routinely undertreated disease with substantial burdens, more acceptable and effective therapies are clearly needed.

Comparative Clinical Effectiveness

To inform our analysis of the comparative clinical effectiveness of dupilumab versus placebo for moderate-to-severe atopic dermatitis and crisaborole versus the emollient it is prepared in for mild-to-moderate atopic dermatitis, we abstracted evidence from available clinical studies, whether in published, unpublished, or abstract form. We also qualitatively summarized findings from previously published systematic reviews to inform comparisons of crisaborole to topical corticosteroids and topical calcineurin inhibitors and comparisons of dupilumab to cyclosporine, phototherapy, and failed topical therapies.

We included evidence from randomized controlled trials (RCTs), comparative observational studies, and high-quality systematic reviews where available. We excluded single-arm studies and studies in healthy subjects from an early clinical development phase. We only focused on dosages that had been or were felt likely to be approved by the FDA. Evidence from previous systematic reviews which included other active treatments (e.g., phototherapy, cyclosporine, and topical calcineurin inhibitors) were discussed qualitatively to inform the comparisons with the newer agents, but were not analyzed quantitatively, with the exception of the topical calcineurin inhibitor pimecrolimus. We did not find additional registries or other datasets of patient-reported outcomes that could be used in our analysis.

Our review focused on key clinical outcomes common to atopic dermatitis trials as well as symptoms and burdens of atopic dermatitis that are not well-captured by standard trial outcomes. Data were abstracted and summarized into evidence tables for all outcomes. For most outcomes, we summarized comparative findings qualitatively. However, we quantitatively synthesized evidence for Eczema Area Severity Index (EASI) 50, 75, and 90 and Investigator's Global Assessment (IGA) outcomes through meta-analyses (see Appendix D):

- EASI assesses severity and body surface area affected by erythema, induration/papulation/edema, excoriations, and lichenification, which are graded systematically for each anatomical region and assembled in a composite score and reported as a percentage improvement from baseline (e.g., EASI 75 is a percentage improvement of EASI score from baseline that is ≥ 75%)
- IGA is a clinician-reported outcome measure that determines severity of atopic dermatitis. The most common versions used in the trials reviewed were static scales (they did not assess changes in severity with treatment; abbreviated in the key crisaborole trials as "ISGA") and used either a 5-point scale ranging from 0 (clear) to 4 (severe) or a 6-point scale ranging from 0 (clear) to 5 (very severe)

For the meta-analyses, we included evidence from phase II or III randomized controlled trials (RCTs) that directly compared dupilumab to placebo with or without background topical corticosteroids and reported either EASI or IGA at 16 weeks. We included phase III RCTs comparing crisaborole to vehicle. For the review of adverse events, we included additional dupilumab trials for nasal polyposis and asthma.

We identified three key clinical trials for dupilumab. Key trials for dupilumab are a phase IIb trial (Thaci) and SOLO 1 and SOLO 2, two identically designed multi-center, phase III RCTs. All three trials

were rated good quality. The remaining nine trials for dupilumab include the LIBERTY AD CHRONOS trial, which had only limited results available from a press release until a few weeks before the public meeting, which affected its addition in some meta-analyses, one phase II trial described in an abstract, four small phase I/IIa trials, and three trials of dupilumab used to treat asthma and nasal polyposis, reporting adverse events.

The two key trials for crisaborole are AD301 and AD302, which are identically designed, multi-center, phase III RCTs. We also identified a phase IIa, bilateral, multi-center, 6-week RCT (Murrell 2015).

Results

Dupilumab for moderate-to-severe atopic dermatitis

Investigator's Global Assessment (IGA)

Consistently across all trials, dupilumab met prespecified IGA targets representing successful outcomes in 30-44% of patients, compared to 2-12% for placebo. Results were similar with weekly or every other week dosing, and in patients treated or not treated with topical corticosteroids.

The primary outcome in the phase III trials of dupilumab, SOLO 1 & 2[18] and LIBERTY AD CHRONOS[26,27], was an IGA score of 0 or 1 *and* an improvement of 2 points or more from baseline IGA at 16 weeks. The primary IGA outcome in the phase II trials[28,29] was a score of 0 or 1 at 16 weeks. All trials showed statistically significantly greater IGA responses in the dupilumab arms compared to placebo. The response rates were 30% to 44% for the dupilumab arms, with little difference between weekly and every other week dosing, and was 2% to 12% in the placebo arms. Unlike the other trials, patients in LIBERTY AD CHRONOS were also treated with topical corticosteroids, but the results in this trial were very similar to those in SOLO 1 & 2. Meta-analysis pooling the two dosing regimens and including all five 16-week trials found an increased chance of achieving an IGA response (as defined in each trial) with dupilumab (relative risk [RR] 3.88, 95% CI 3.13-4.79).

Eczema Area Severity Index (EASI)

Dupilumab substantially increased the likelihood of achieving EASI 75 compared to placebo. Results were similar with weekly or every other week dosing and in patients treated or not treated with topical corticosteroids. Results for other EASI thresholds were generally consistent with results for EASI 75. More patients treated with dupilumab than placebo achieved EASI 50 and EASI 90 responses at 16 weeks.

EASI 75 (75% improvement from baseline EASI score) was a key secondary outcome in SOLO 1 & 2 and a primary outcome in the other three trials that provided 16-week outcomes. The response rates were 44% to 69% in the dupilumab arms, with little difference between dosing regimens,

compared to 12% to 20% in the placebo arm. The LIBERTY AD CHRONOS trial in patients also receiving topical corticosteroids found a slightly higher EASI 75 response in the dupilumab arms compared with the responses seen in SOLO 1&2, but this difference across trials was not statistically significant. However, it remains possible that dupilumab is more effective in some patients when used in combination with topical corticosteroids than when used alone.

We found no statistically significant differences between dupilumab 300 mg weekly and 300 mg biweekly on EASI 75 (or IGA) outcomes (Appendix Figure D1-D2). Similarly, the results of the LIBERTY AD CHRONOS trial were not statistically significantly different from the other trials where background topical corticosteroids were not allowed (Appendix Figure D3-D4).

Meta-analysis pooling the dosing regimens and including all five trials found an increased likelihood of achieving EASI 75 with dupilumab (RR 3.25, 95% CI 2.79-3.79). Other EASI thresholds show similar benefits with dupilumab. For EASI 50, the response rates were 61% to 83% in the dupilumab arms and 22% to 32% in the placebo arms; for EASI 90, the response rates were 30% to 37% with dupilumab and 3% to 8% with placebo.

LIBERTY AD CHRONOS demonstrates that dupilumab achieves better outcomes than continuing treatment with topical corticosteroids in patients who have had an inadequate response to therapy with topical corticosteroids with or without topical calcineurin inhibitors. The currently available results from LIBERTY AD CHRONOS do not provide direct evidence on dupilumab therapy as compared with topical calcineurin inhibitor therapy in such patients, since we are uncertain how many patients in the trial had failed topical calcineurin inhibitors.

Patient-reported Outcomes

Dupilumab improved patient quality of life as measured by DLQI and improved patient symptoms including individual measures of pruritus, and scoring systems looking at broader patient outcomes, patient-reported outcomes, and measures of anxiety and depression.

Dupilumab improved quality of life as measured by the Dermatology Life Quality Index (DLQI). SOLO 1&2,Thaci 2016, and LIBERTY AD CHRONOS measured the change in mean DLQI from baseline at 16 weeks and found statistically significantly greater improvement with dupilumab than placebo (absolute improvements of 8 to 12 points with dupilumab versus 1 to 5 points with placebo, $p<0.001$, where a 4-point improvement is considered clinically significant[30]).

Dupilumab also improved pruritus (itching) and psychological symptoms. SOLO 1&2,Thaci 2016, and LIBERTY AD CHRONOS assessed the reduction of pruritus symptoms using percent change from baseline peak numerical rating scale (NRS) score. Across the four trials, the reduction in peak NRS ranged from 40% to 56% in the dupilumab arms versus 5% to 29% in the placebo arms ($p<0.001$). Anxiety and Depression was measured by the Hospital Anxiety and Depression Scale (HADS) in SOLO 1&2 and LIBERTY AD CHRONOS. Mean reduction in HADS was statistically significantly greater with dupilumab than placebo (5-6 vs. 1-4; $p<0.001$).

52-Week Results

Results at 52 weeks from LIBERTY AD CHRONOS were published prior to this final version of the report. In addition to results of other outcomes, this provided information on flares of atopic dermatitis. Through 52 weeks, fewer patients had flares of atopic dermatitis with weekly or every other week dupilumab than with placebo (13% and 14% versus 41%, respectively, p<0.0001 compared to placebo for both dosing groups).

Harms

Severe or serious adverse events were rare during treatment up to 16 weeks. Injection site reaction, nasopharyngitis, and headache were the most common side effects. There appear to be increased rates of conjunctivitis with dupilumab. Across all dupilumab trials (including trials in asthma and nasal polyposis) there were four deaths in the dupilumab arms, felt to be unrelated to treatment with dupilumab, and no deaths in the placebo arms.

The most common adverse events (AEs) with dupilumab at 16 weeks were injection site reaction, nasopharyngitis, and headache, all having higher rates than placebo. Allergic conjunctivitis and infectious conjunctivitis were less common AEs, but the rates were increased compared to placebo. The rates of any AE, serious adverse events (SAEs), and discontinuation due to AE were slightly lower with dupilumab than placebo.

Across all 16-week dupilumab trials for atopic dermatitis, asthma, and nasal polyposis, among 2,400 patients in the dupilumab arms, there were five deaths. These deaths were reported to be unrelated to dupilumab treatment. One patient who did not receive asthma-control medication died of an asthma attack 84 days after the last dupilumab dose; one patient with a history of hospitalization for depression committed suicide eight days after the last dupilumab dose; one patient experienced acute cardiac failure; one patient died from metastatic gastric cancer with organizing pneumonia and cor pulmonale; one patient was in a motor vehicle accident. There were no deaths in any the 1,121 patients in the placebo arms of these same trials.

Comparison to cyclosporine and phototherapy

Dupilumab appears likely to be at least as effective as cyclosporine and more effective than phototherapy at controlling atopic dermatitis. Treatment with cyclosporine has important toxicities; short-term experience with dupilumab suggests it may be safer than cyclosporine.

There are no head-to-head trials comparing dupilumab with either systemic cyclosporine or phototherapy. A systematic review of treatments for moderate-to-severe atopic dermatitis found 5 RCTs comparing cyclosporine with placebo, with improvements of 53% to 95% in various clinical severity scores.[7] However, these trials were small, were performed many years ago, and used outcome measures different from those used in current trials.

A small, open-label randomized trial (Granlund 2001)[31] compared cyclosporine with phototherapy in 72 patients treated intermittently for one year, and assessed changes in the Scoring Atopic Dermatitis (SCORAD) score with a primary outcome of remission defined as a ≥ 50% decrease from

baseline SCORAD.[31] SCORAD was also assessed in SOLO 1&2, LIBERTY AD CHRONOS, and Thaci 2016, and the results from Granlund provide some limited indirect evidence for comparing cyclosporine and phototherapy with dupilumab. In Granlund, 36 patients treated with cyclosporine had a mean baseline SCORAD of 48.5, were in remission about 55%-60% of days, and appeared to typically have reductions of SCORAD of about 26-27 points (or about 55%). The median baseline SCORAD was higher in SOLO 1&2, LIBERTY AD CHRONOS, and Thaci (ranging from 65 to 68 in the dupilumab arms), and decreased by 52% to 63% with dupilumab. The higher SCORAD scores in the four dupilumab trials make this indirect comparison somewhat more difficult, as they reflect patients with more severe disease, but also provide greater opportunity for a percentage improvement in SCORAD. So, while the percentage improvements in SCORAD seem similar across these trials of cyclosporine and dupilumab, there is substantial remaining uncertainty as to the relative efficacy of these agents.

Table ES1. Dupilumab vs. Cyclosporine: SCORAD Response Rates

	Baseline score*	Reduction from baseline at 16 weeks*
Dupilumab		
SOLO 1	65	-57%
SOLO 2	68	-52%
CHRONOS	66	-63%
Thaci 2016	67	-54%
Cyclosporine		
Granlund 2001	49	-55%

*For dupilumab trials, values pooled across weekly and every two week dosing groups

Treatment with cyclosporine carries important risks of acute and chronic nephrotoxicity, can have hemodynamic effects that result in hypertension,[32] and can increase the risk of infections and cancer.[17,33] Cyclosporine nephrotoxicity can be irreversible, and this risk increases with longer durations of treatment.[34] As a result, treatment with cyclosporine for atopic dermatitis is typically limited to one year.

As noted, the Granlund trial also assessed phototherapy, and found that cyclosporine was substantially more effective than phototherapy. Patients treated with phototherapy had a mean baseline SCORAD of 46.8, were in remission about 37%-38% of days, and appeared to typically have reductions of SCORAD of about 11-18 points (or about 24%-38%). Based on these results, and based on other studies of phototherapy,[35] dupilumab appears to be more effective than phototherapy. Phototherapy can be prohibitively time consuming and may increase the risk of skin cancer.[22]

Controversies and Uncertainties

Dupilumab is a therapy with a novel mechanism of action affecting the immune response, and we lack adequate long-term safety data. There is the risk that so-far undetected toxicities and adverse events will be encountered over time.[36]

We have no head-to-head trials comparing dupilumab with other systemic therapies for atopic dermatitis, and this limits our ability to assess both comparative benefits and harms. Although we have some limited evidence that benefits with dupilumab may be similar to those seen with cyclosporine, in the absence of a head-to-head trial there is uncertainty in this comparison. Additionally, although the toxicities of the immunosuppressive agents used for atopic dermatitis are well established, and dupilumab appeared to be well tolerated in randomized trials, we have much less experience with dupilumab, making it difficult to be certain of the relative safety of dupilumab versus established immunotherapies.

Patients studied in the randomized trials of dupilumab had a substantial burden of disease. For instance, although the entry criteria for the SOLO trials required an EASI score of at least 16 and an affected body surface area of at least 10%, the median EASI score at baseline was around 30, with an interquartile range from 21.0-43.8, and the median affected body surface area was around 50%, with an interquartile range from 34%-77%. Thus, the vast majority of patients had more severe disease than was required by the entry criteria for the trial. Although the indication for dupilumab in the FDA label is for moderate-to-severe disease that is inadequately controlled with topical treatment or for whom topical treatment is medically inadvisable, it is uncertain whether the patients for whom dupilumab is recommended by their clinicians will have similarly severe disease to those in the randomized trials.

We have limited evidence on the expected duration of response to dupilumab, both once a course of therapy has been administered, and with repeated or ongoing therapy. It is uncertain how often patients require continuing treatment and whether such treatment is safe and efficacious.

We have heard from expert clinicians and from patient groups that the clinical trials do not adequately reflect how some patients with atopic dermatitis experience dramatic improvements with dupilumab. We have heard that these dramatic responses are beyond what is typically seen with systemic immunotherapies such as cyclosporine.

Comparative Clinical Effectiveness: *Summary*

- Treatment with dupilumab resulted in substantial improvements in atopic dermatitis in the majority of patients who were studied. In addition to improving the severity of atopic dermatitis and reducing pruritus, treatment improved quality of life and the effects of atopic dermatitis on sleep, anxiety, and depression.
- Dupilumab was generally well tolerated, although there was an increased rate of conjunctivitis with treatment. There were several deaths in the dupilumab arms of clinical trials that were not felt to be due to treatment; however, this is a novel therapy and important adverse effects could become apparent over time.
- Dupilumab appears to be at least as efficacious as cyclosporine (typically the preferred systemic therapy currently available) and more efficacious than phototherapy. Cyclosporine has important toxicities, and is generally not used for more than one year.

For adults with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy, or for whom topical therapies are medically inadvisable, we have high certainty that dupilumab provides at least a small net health benefit (“B+”) relative to treatment with emollients with or

without continued failed topical treatments. Given limitations of the evidence base, most notably the lack of long-term evidence on the safety of dupilumab, we have moderate certainty that the net health benefit of dupilumab is comparable or better than that provided by cyclosporine, but we have high certainty that dupilumab does not produce a lower net health benefit. Our comparative clinical effectiveness rating for dupilumab versus cyclosporine is therefore "C+".

Crisaborole for mild-to-moderate atopic dermatitis

Investigator's Static Global Assessment (ISGA)

In patients with mild-to-moderate atopic dermatitis, crisaborole modestly increased the likelihood of achieving ISGA success at four weeks compared with vehicle.

AD-301 and AD-302[11] randomized 1522 patients with mild-to-moderate atopic dermatitis 2:1 to crisaborole or vehicle and measured the proportion of patients with ISGA score of 0 or 1 *and* an improvement of ≥ 2 grades from baseline on Day 29 as the primary outcome. The success rate was moderately higher in the pooled crisaborole arms than in the placebo arms (32.1% vs. 21.7%; p<0.0001).

Quality of Life

Crisaborole improved quality of life as measured by the DLQI and CDLQI, however the differences on these scales were smaller than the changes usually considered clinically meaningful.

Quality of life was measured in AD-301 and AD-302 using the DLQI in those older than age 15, and the Children's Dermatology Life Quality Index (CDLQI) in those ages 2 to 15. Results have not been published but were presented in a poster.[37] Patients ages 2 to 15 had greater reductions from baseline on the CDLQI with crisaborole than vehicle (-4.6 vs. -3.0; p<0.001), and patients over age 15 treated with crisaborole had greater reductions on the DLQI (-5.2 vs. -3.5; p=0.016). The differences between crisaborole and vehicle are less than the differences considered clinically meaningful on each scale (2.5 points on the CDLQI[38] and 4 points on the DLQI[30]).

Pruritus

Crisaborole modestly reduced pruritus.

Patients or caregivers self-assessed the severity of pruritus, and the proportion of patients with a pruritus score of 0 or 1 and an improvement of 1 or more grades from baseline were reported from days 8 through 29. The improvement rate was moderately higher in the crisaborole arm than in the placebo arm on day 8 (58% vs. 42%; p<0.001), day 15 (60% vs. 44%; p<0.001), day 22 (61 vs. 48%; p<0.001), and day 29 (63% vs. 53%; p=0.002).

Caregiver Burden

Treatment with crisaborole reduced caregiver burden as measured by the DFI, however it is uncertain whether the change on this scale was clinically meaningful.

Burden on family/parents/caregivers of patients ages 2 to 17 was measured in AD-301 and AD-302 using the Dermatitis Family Impact Questionnaire (DFI). Results have not been published but were presented in a poster.[37] A reduction in DFI reflects lower caregiver burden, and there were greater reductions with treatment with crisaborole than vehicle (-3.7 vs. -2.7; p=0.0003). The difference in DFI score that is considered clinically meaningful has not been established.[37]

Network Meta-analyses

We identified no study directly comparing crisaborole to other active treatments. As indirect evidence, we identified two trials (Eichenfield 2002 and Ho 2003) comparing the calcineurin inhibitor pimecrolimus to placebo, using a 6-point static IGA score as an endpoint.[39,40] Crisaborole was evaluated in the key trials on a 5-point static IGA score. As shown in Table ES1, the severity of disease in the trials appeared to be reasonably similar with regard to baseline IGA score and percent body surface area involved. Given the lack of head-to-head data and the slightly different versions of the IGA score, we performed indirect comparisons using Bayesian network meta-analyses (NMAs), assuming "clear" and "almost clear" categories are similar on both scales. There was a trend suggesting pimecrolimus was superior to crisaborole. However, there were wide credible intervals, and the findings were not statistically significant.

Table ES2. Crisaborole/Pimecrolimus: Baseline Disease Severity across Trials

Trial	IGA score (%)		Mean body surface area involved (%)
	Mild	Moderate	
AD-301			
Crisaborole	39.0	61.0	18.8
Vehicle	36.3	63.7	18.6
AD-302			
Crisaborole	38.4	61.6	17.9
Vehicle	40.0	60.0	17.7
Ho 2003			
Pimecrolimus	32.5	67.5	NR
Vehicle	33.3	66.7	NR
Eichenfield 2002			
Pimecrolimus	30.0	60.3	26.1
Vehicle	31.6	57.4	25.5

In addition to statistical uncertainty, the trials were performed in very different time periods and used different versions of static IGA scales. Given the uncertainties, we cannot come to firm conclusions about the relative efficacy of crisaborole and pimecrolimus. Pimecrolimus appears to be less effective than tacrolimus or moderate potency topical corticosteroids. For instance, a systematic review found that pimecrolimus was less effective than topical triamcinolone acetonide

0.1% (a medium potency corticosteroid) based on one trial with 658 participants, and also less effective than betamethasone valerate 0.1% (a medium-to-high potency corticosteroid).[41] The same systematic review found that pimecrolimus was less effective than topical tacrolimus 0.1% based on two trials with 639 participants.

Table ES3. Pimecrolimus: IGA Response Rates across Trials

Trial	IGA 0 or 1	
	Pimecrolimus	Vehicle
Ho 2003	53	17
Eichenfield 2002	31	12

Table ES4. Crisaborole: IGA Response Risk Ratio

Treatment	IGA 0/1
Crisaborole vs. placebo	1.57 (0.27-3.98)
Pimecrolimus vs. placebo	2.59 (0.98-4.44)
Crisaborole vs. pimecrolimus	0.61 (0.10-2.28)

Harms

Severe or serious adverse events were rare in all three clinical trials of crisaborole.

The most common adverse events (AEs) with crisaborole at four weeks were application site pain, application site pruritus, and fever. Rates of serious AEs and discontinuation due to AEs were comparable between crisaborole and placebo, except that application site pain was higher with crisaborole (4.6% versus 1.7%).

Controversies and Uncertainties

We have no head-to-head trials comparing crisaborole with the other topical agents (corticosteroids and calcineurin inhibitors) that would typically be used in patients with mild-to-moderate atopic dermatitis. There is substantial uncertainty as to the relative efficacy of crisaborole. It is uncertain from the available evidence whether the patients who received crisaborole in the clinical trials had had an inadequate response to existing pharmacologic and non-pharmacologic therapies for atopic dermatitis.

There was a high response to the control arm (emollient vehicle) in the crisaborole trials. We heard from experts that this response was greater than that seen in placebo arms of most trials of topicals and may reflect that comparator preparations in some older trials included compounds that could be irritating and induce dermatitis. This would make the relative benefits of the active therapies in those older trials appear greater than they really were.

The main evidence on crisaborole comes from trials that randomized a total of 1016 patients to crisaborole therapy for 28 days. Although crisaborole was well tolerated over this period of time, it is difficult to assess its safety compared with the other topical agents. We have heard from experts and patient groups that concerns about the safety of the other topical agents may be greater than is warranted, and in the absence of longer trials and/or head-to-head trials, as with relative efficacy, the relative safety of crisaborole is uncertain.

Comparative Clinical Effectiveness: *Summary*

- Our review found inadequate evidence to assess the relative efficacy of crisaborole compared with the other topic therapies for atopic dermatitis, topical calcineurin inhibitors and topical corticosteroids.
- Crisaborole seems to cause less application site burning/pain than topical calcineurin inhibitors and skin changes seen with topical corticosteroids were not seen in 4-week trials of crisaborole. The safety of crisaborole used for longer periods is uncertain.
- For patients with mild-to-moderate atopic dermatitis, we have inadequate evidence on both the relative efficacy and the relative safety of crisaborole compared to other treatment options ("I").

Other Benefits or Disadvantages

Dupilumab is an injection given every two weeks. As such, administration is potentially far less time-consuming than topical therapies, but potentially more burdensome for patients bothered by injections.

Trials of dupilumab did not assess effects on productivity; however, there is reason to believe that for some patients with severe atopic dermatitis, dupilumab may reduce missed time from work and/or increase productive time at work.

Lifetime burden of illness can be prominent in atopic dermatitis. Many children experience resolution of atopic dermatitis as they grow into adolescence and adulthood; however, those with poorly controlled moderate-to-severe disease are more likely to have persistent, lifelong atopic dermatitis. The initial target group for dupilumab, adults with moderate-to-severe atopic dermatitis, have a substantial burden of illness that typically waxes and wanes over a lifetime.

Long-Term Cost-Effectiveness

The primary aim of this analysis was to estimate the cost-effectiveness of dupilumab for moderate-to-severe atopic dermatitis compared to usual care over a lifetime horizon. The modeled population had a mean age of 38 years and was 53% male. Given the target population of moderate-to-severe atopic dermatitis, as well as data availability challenges and anticipated clinical uptake, we decided to only model dupilumab rather than crisaborole, phototherapy, or cyclosporine. The model estimated the average length of time that a patient spent in health states defined by levels of response from baseline when administered treatments for atopic dermatitis.

Time spent in each health state was weighted using quality of life (QoL) measures and summed over a patient's remaining lifetime to provide estimates of the quality-adjusted life expectancy.

We developed a Markov model with health states based on treatment response. Health states were categorized by the percent decrease in EASI score after a patient began an intervention (either dupilumab or usual care): a 50% decrease (EASI 50), a 75% decrease (EASI 75), a 90% decrease (EASI 90), or no response. All patients entered the model in the non-responder state, and could then transition to responder states one cycle after beginning treatment.

Utility values for quality-of-life and costs were applied to each health state. Utility values representing patients' quality of life at baseline or with no response and in responder categories EASI 50, EASI 75, and EASI 90 were 0.684, 0.892, 0.893, and 0.907, respectively, for moderate patients, and 0.535, 0.882, 0.890, and 0.911, respectively, for severe patients. These utility values were collected in the dupilumab clinical trials using the EQ-5D. Utilities were collected at baseline and 16 weeks for three clinical trials. Baseline utilities were consistent across the three trials. These baseline utilities are in line with other estimates for moderate and severe atopic dermatitis, with examples ranging from 0.584 to 0.807 for moderate[42-46] and 0.421 to 0.697 for severe[42,43,45,46]. Additionally, utility decrements and associated costs were applied per cycle for therapy-related adverse events.

We applied an annual list price for dupilumab of $37,000 for 300 mg dosed every two weeks after a 600-mg loading dose. The manufacturer informed ICER that the average net price in the US market will be no more than $31,000.[47] Additionally, an annual cost of care was applied for all patients on either dupilumab or usual care. This cost included all direct costs of care, such as doctor visits, specialist visits, and hospitalizations. These costs were based on an analysis of Truven Health Marketscan® Commercial Claims and Encounters database during 2013 for patients with a diagnosis of atopic dermatitis. The non-responder/usual care health state had a baseline annual cost of $11,630, based on the annual cost for patients with atopic dermatitis treated with phototherapy or who were prescribed any systemic immunomodulatory medications used for this disease (i.e., prednisone, cyclosporine, methotrexate, azathioprine or mycophenolate) minus prescription drug costs.[47] Responder categories had a lower annual cost of $7,346, based on the annual cost (minus prescription drug costs) for patients with atopic dermatitis who did not have phototherapy or systemic immunomodulatory medications.[47] Outcomes were dependent on time spent in each health state in the model, dupilumab treatment, and adverse events.

Base Case Results

In the base case analysis, using the net price for dupilumab of $31,000, the average total lifetime cost for patients treated with dupilumab was $466,200. This included dupilumab drug costs of $224,400, accounting for discontinuation. Patients treated with dupilumab also accumulated a total of approximately $241,800 in other healthcare costs related to atopic dermatitis. Patients with atopic dermatitis treated with usual care had an average total lifetime cost of $271,500 (Table ES5). Dupilumab provided an additional 1.91 QALYs over the remaining lifetime of patients, leading to an incremental cost-effectiveness ratio of $101,800 per additional QALY gained. As would be expected from the relative impact on quality of life and associated costs of treatment, the cost per

additional QALY was lower for patients with severe atopic dermatitis ($78,300) than those with moderate atopic dermatitis ($130,800).

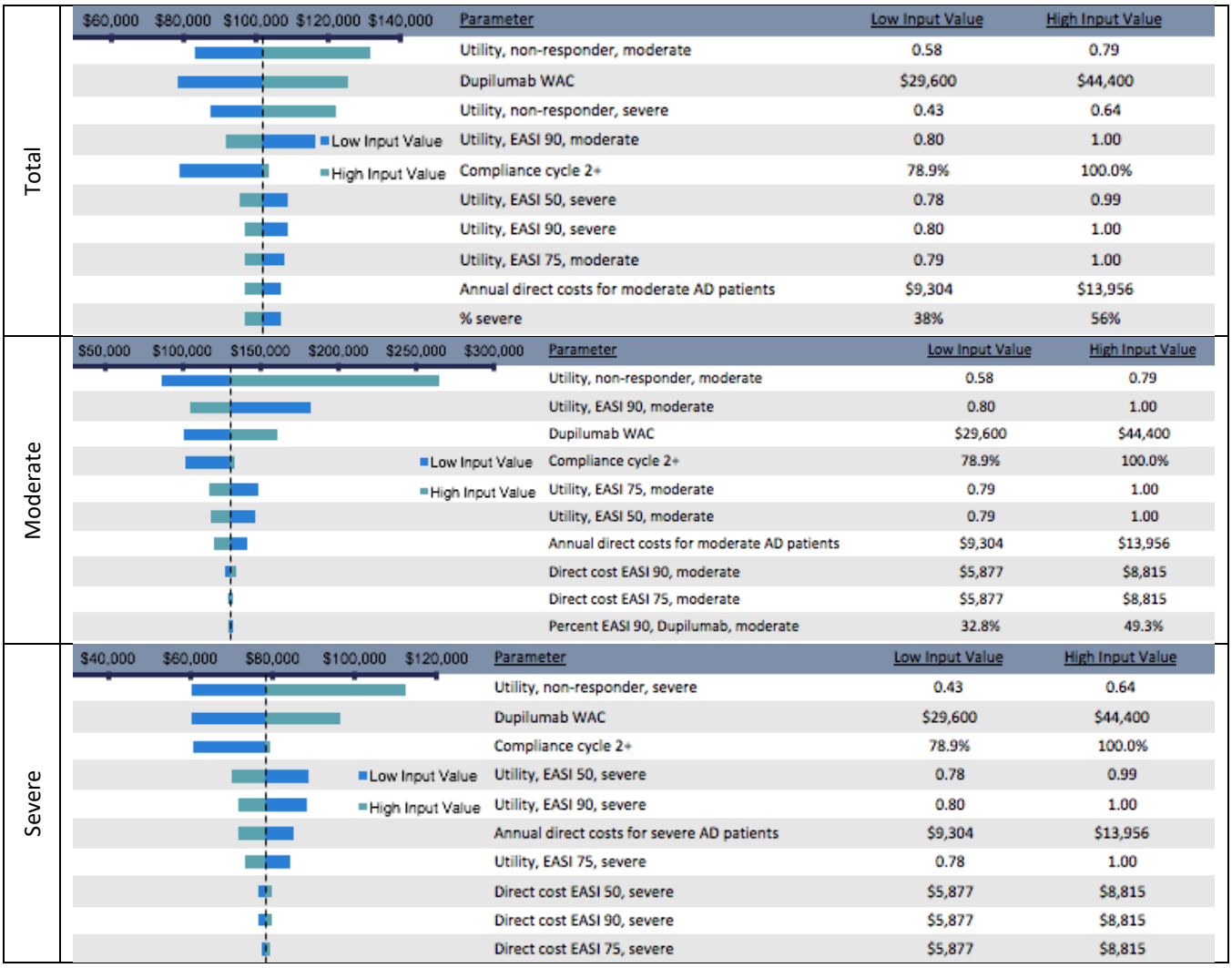
Table ES5. Base Case Results

	Usual Care	Dupilumab	Incremental
Total Costs	$271,461	$466,168	$194,708
Drug Costs	--	$224,372	$224,372
Other Healthcare Costs	$271,461	$241,796	-$29,665
QALYs	14.37	16.28	1.91
Cost per Additional QALY	--	--	$101,830

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate changes in cost per additional QALY for dupilumab compared to usual care. Results for the base case population (total, moderate, and severe) are shown in Figure ES1. Key drivers of the model were utility values for quality of life, particularly for non-responders, and the price of dupilumab. In a probabilistic sensitivity analysis, at the $150,000 per QALY threshold, dupilumab had an 88% probability of being cost effective compared to usual care overall, and a 70% and 94% probability for moderate and severe patients, respectively.

Figure ES1. One-Way Sensitivity Analysis: Cost per Additional QALY for Dupilumab Compared to Usual Care for the Total, Moderate, and Severe Atopic Dermatitis Populations



Parameter	Low Input Value	High Input Value
Utility, non-responder, moderate	0.58	0.79
Dupilumab WAC	$29,600	$44,400
Utility, non-responder, severe	0.43	0.64
Utility, EASI 90, moderate	0.80	1.00
Compliance cycle 2+	78.9%	100.0%
Utility, EASI 50, severe	0.78	0.99
Utility, EASI 90, severe	0.80	1.00
Utility, EASI 75, moderate	0.79	1.00
Annual direct costs for moderate AD patients	$9,304	$13,956
% severe	38%	56%

Parameter	Low Input Value	High Input Value
Utility, non-responder, moderate	0.58	0.79
Utility, EASI 90, moderate	0.80	1.00
Dupilumab WAC	$29,600	$44,400
Compliance cycle 2+	78.9%	100.0%
Utility, EASI 75, moderate	0.79	1.00
Utility, EASI 50, moderate	0.79	1.00
Annual direct costs for moderate AD patients	$9,304	$13,956
Direct cost EASI 90, moderate	$5,877	$8,815
Direct cost EASI 75, moderate	$5,877	$8,815
Percent EASI 90, Dupilumab, moderate	32.8%	49.3%

Parameter	Low Input Value	High Input Value
Utility, non-responder, severe	0.43	0.64
Dupilumab WAC	$29,600	$44,400
Compliance cycle 2+	78.9%	100.0%
Utility, EASI 50, severe	0.78	0.99
Utility, EASI 90, severe	0.80	1.00
Annual direct costs for severe AD patients	$9,304	$13,956
Utility, EASI 75, severe	0.78	1.00
Direct cost EASI 50, severe	$5,877	$8,815
Direct cost EASI 90, severe	$5,877	$8,815
Direct cost EASI 75, severe	$5,877	$8,815

Threshold Analysis Results

The annual net price of dupilumab that would achieve cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY gained was $17,307, $30,516, and $43,726, respectively. Note that the price of dupilumab would have to increase to reach the $150,000 per QALY cost-effectiveness threshold.

Potential Budgetary Impact Model Results

We used results from the cost-effectiveness model to estimate the potential total budgetary impact of dupilumab at various prices: WAC ($37,000 per year), discounted WAC ($31,000 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY for dupilumab ($43,726, $30,516, and $17,307 per year, respectively), compared to usual care. Potential budget impact was defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to see a more realistic impact on the number of patients treated with the new therapies.

The potential budget impact analysis included the entire candidate population for treatment, which consisted of US adults with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy or for whom topical therapies are medically inadvisable. To estimate the size of the potential candidate population for treatment with dupilumab, we used an estimate of the US prevalence of adults with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies from the Adelphi Real World Atopic Dermatitis Disease Specific Program, a cross-sectional real-world survey that captured data from clinicians and patients, which was reported to be 0.7%.[48] Applying this proportion to the projected 2017 US adult population resulted in an estimate of approximately 1,765,000 patients in the US over a five-year period. Note that this estimate includes all patients with moderate or severe atopic dermatitis. If dupilumab is used only in more severe patients, the number of patients eligible for treatment would be lower. The manufacturer has "estimated that 300,000 are most in need of treatment options."[49]

Table ES6 illustrates the per-patient budget impact calculations, based on WAC ($37,000 per year), discounted WAC ($31,000 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY for dupilumab ($43,726, $30,516, and $17,307 per year, respectively) compared to usual care. The average potential budgetary impact when using the WAC for dupilumab was an additional per-patient cost of approximately $22,300, and approximately $18,400 using the discounted WAC. Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug ranged from approximately $26,800 per patient using the annual price ($43,726) to achieve $150,000 per QALY to approximately $9,200 using the annual price ($17,307) to achieve a $50,000 per QALY cost-effectiveness threshold.

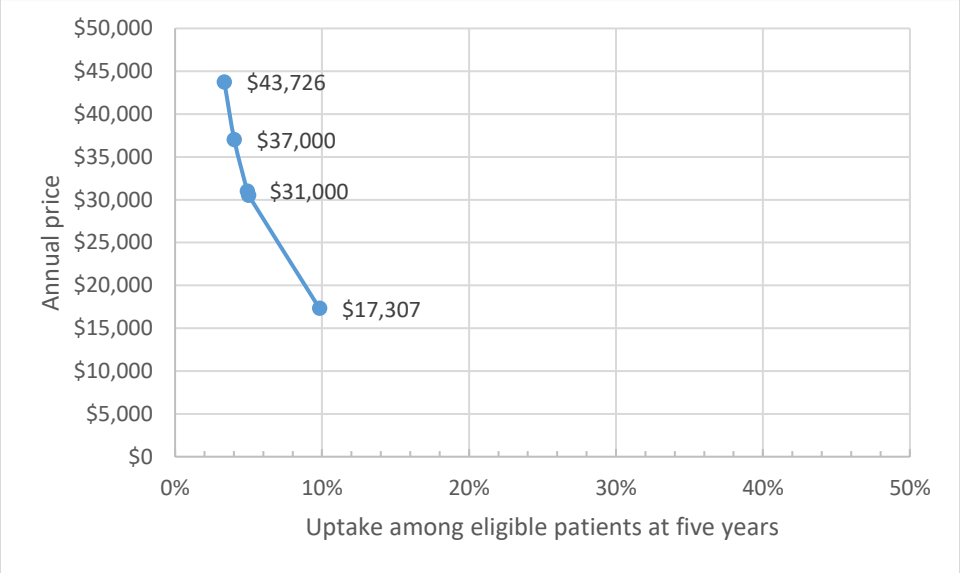
Table ES6. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon

	Average Annual Per Patient Budget Impact				
	WAC	Discounted WAC	$150,000/QALY	$100,000/QALY	$50,000/QALY
Dupilumab	$33,744	$29,752	$38,218	$29,431	$20,643
Usual Care	"	$11,395	"	"	"
Difference	$22,348	$18,357	$26,822	$18,035	$9,248

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

As shown in Figure ES2, approximately 4% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $915 million at WAC ($37,000) and approximately 5% of patients at the discounted WAC ($31,000). Approximately 3% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY threshold price ($43,726/year), while 10% of the population could be treated without crossing the threshold at the $50,000 per QALY threshold price ($17,307/year).

Figure ES2. Budgetary Impact of Dupilumab in Atopic Dermatitis Patients



Value-Based Price Benchmark

The value-based benchmark price for a drug is defined as the price range that would achieve cost-effectiveness ratios between $100,000 and $150,000 per QALY gained. The price required to achieve a $100,000 per QALY threshold for dupilumab is approximately equal to our assumed discounted price of $31,000, corresponding to a discount of 18% from WAC. To reach the $150,000 per QALY cost-effectiveness threshold, the annual net price of dupilumab could increase by 18%, to approximately $43,700 per year.

Comparative Value: *Summary and Comment*

We estimated the cost-effectiveness of dupilumab versus usual care over a lifetime time horizon for adult patients with moderate-to-severe atopic dermatitis. Compared to usual care, the cost per additional QALY for dupilumab was estimated to be approximately $101,800. The cost per additional QALY was lower for patients with severe atopic dermatitis ($78,300) than those with moderate atopic dermatitis ($130,800).

Results from our potential budget impact analysis suggest that the average potential budgetary impact over five years at the WAC price for dupilumab was an additional per-patient cost of approximately $22,300. At the discounted WAC price of $31,000, the average per-patient cost was approximately $18,400. Our analysis estimated that approximately 4% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $915 million at WAC ($37,000) and approximately 5% of patients at the discounted WAC ($31,000).

There were several key limitations of our analysis. First, there are limited data for health outcomes for patients with atopic dermatitis over long periods of time. We assumed patients did not switch between EASI 50, 75, and 90 responder categories. Second, there are limited data on costs of atopic dermatitis, particularly stratified by severity. Finally, atopic dermatitis is a heterogeneous condition and patients experience a wide range of symptoms and severities.

In summary, our economic modeling analysis indicates that dupilumab improves health outcomes compared to usual care, but with additional costs. At the discounted price of dupilumab used in this draft report, the incremental cost-effectiveness ratio was at or below commonly cited thresholds for cost-effectiveness. Dupilumab was projected to be more cost-effective in patients with severe atopic dermatitis, but even in patients with moderate atopic dermatitis, the ICER remained below the upper range of commonly cited thresholds.

Midwest Comparative Effectiveness Public Advisory Council Votes

The Midwest Comparative Effectiveness Public Advisory Council deliberated on key questions raised by ICER's report at a public meeting on May 25, 2017. The results of the votes are presented below.

1. In patients with mild-to-moderate atopic dermatitis, is the evidence adequate to demonstrate that the net health benefit of treatment with crisaborole is greater than that of treatment with topical corticosteroids or topical calcineurin inhibitors?

Yes: 2 votes	***No: 9 votes***

2. In adults with moderate-to-severe atopic dermatitis who have failed topical therapy, is the evidence adequate to demonstrate that treatment with dupilumab provides additional net health benefits beyond continued non-pharmacologic treatments such as emollients?

Yes: 11 votes	*No: 0 votes*

3. In adults with moderate-to-severe atopic dermatitis who have failed topical therapy, is the evidence adequate to demonstrate that the net health benefit of treatment with dupilumab is greater than that of treatment with cyclosporine?

Yes: 10 votes	*No: 1 votes*

4. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, in a mixed population of adults with moderate-to-severe atopic dermatitis who have failed topical therapy, what is the long-term value for money of dupilumab compared with no systemic treatment?

Low: 0 votes	***Intermediate: 8 votes***	*High: 3 votes*

5. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, in adults with moderate atopic dermatitis who have failed topical therapy, what is the long-term value for money of dupilumab compared with no systemic treatment?

Low: 0 votes	***Intermediate: 9 votes***	*High: 2 votes*

6. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, in adults with severe atopic dermatitis who have failed topical therapy, what is the long-term value for money of dupilumab compared with no systemic treatment?

Low: 0 votes	*Intermediate: 0 votes*	***High: 11 votes***

Key Policy Implications

The Midwest CEPAC engaged in a moderated discussion about how best to apply evidence on dupilumab and crisaborole for atopic dermatitis in policy and practice. The roundtable included two clinical experts, two patients, two payers, and a manufacturer representative. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. Below are the top-line policy implications; for more information, please see the full report.

Payers and Pharmacy Benefits Managers

While ICER's analyses found the price of dupilumab to be in line with its benefit, the broad range of severity of atopic dermatitis, limited long-term data on dupilumab's efficacy and appropriate use, and issues with affordability will lead payers to design evidence-based pre-authorization coverage criteria.

Criteria are likely to take the following into account:

- **Specialist prescribing:** Payers may consider requiring specialist prescribing of dupilumab.
- **Severity Measures:** There is no consensus on how to define severity. Payers using severity level as part of coverage policy should consider accepting the maximum severity of disease across multiple measures.
- **Trials of therapy:** Payers may consider inadequate response to one month of topical treatment with a moderate potency corticosteroid or tacrolimus 0.1% as an appropriate trial of treatment prior to coverage of dupilumab. Due to safety concerns with existing systemic therapies, clinical experts suggested that patients should not be required to try other systemic treatments such as cyclosporine before being covered for dupilumab.
- **Stopping rules:** Payers may require some measure of success for continuation of coverage past a certain number of months. Clinical experts noted EASI 50 as a potentially appropriate measure for some patients, but emphasized that the patient and provider should be involved in assessing the level of response. Experts also noted that after prolonged successful treatment, dupilumab should not be stopped abruptly, but trials of tapering may be appropriate.
- **Use in children:** Trials to evaluate dupilumab in children are ongoing. In the interim, health plans should ensure that clinicians assessing coverage exceptions for children are expert in this drug's risks and benefits and in the spectrum of atopic dermatitis.

Researchers, Clinicians, Manufacturers, and Patient Groups

- Work to develop a standard definition of disease severity and standard outcome measures. Patient groups should have a leading role in these efforts, and promote use of these definitions and measures in clinical trials.

Specialty Societies

- Educate members in the appropriate use of new medications for atopic dermatitis.

Clinicians and Patient Groups

- Communicate potential risks of new treatments, including uncertainty around the long-term benefit and potential harms of any new therapy.

Manufacturers and Researchers

- Perform direct comparisons of therapies when appropriate to better inform decision making.

Payers, Pharmacy Benefits Managers, Manufacturers

Access and affordability alert - Although the price for dupilumab is aligned with value, ICER notes that there is an access and affordability alert. Estimates from clinical experts and the manufacturer suggest that the number of patients whom clinicians may desire to treat will result in short-term costs that can create strains on health care budgets. Policymakers, payers, clinical experts, patient groups, and the manufacturer should continue to explore ways to manage affordability and maintain access to this treatment in a sustainable manner. As part of this effort, all stakeholders should seek collaborative ways to reduce ineffective and low-value care so that patients can benefit from this important new therapy.

1. Background

Introduction

Atopic dermatitis 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, erosions, erythema, crusting and exudate, swelling, scaling, and thickening/lichenification. Atopic dermatitis is frequently called "eczema" by lay persons and some clinicians, however, in the United States, the term eczema is typically used by the dermatologic community as a broader description, and atopic dermatitis is only one subtype of eczema.

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,[8] and the disorder can decrease quality of life.[9] Itching, in particular, often disrupts sleep leading to daytime drowsiness[10] and irritability, with psychological stress and impaired performance in school and at work. The aesthetic impact of skin changes can lead to social stress and isolation.[9] Disease severity is not consistently defined and frequently involves patient/parent self-report in epidemiologic studies, and global clinical assessments used in trials (such as the Investigator's Global Assessment [IGA]). However, even with global clinical assessment measures, there are many variations used in studies.[50] Approximately 67-82% of children with atopic dermatitis have mild disease, 12-26% have moderate disease, and 4-7% have severe disease.[51,52] 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. However, it is likely that there are more children than adults with moderate-to-severe atopic dermatitis given the overall greater burden of disease in children.

The mainstays of therapy for atopic dermatitis are meticulous skin care with frequent application of a bland moisturizer (optimally an ointment) to maintain the skin's epidermal barrier, avoidance of triggers, and short-term intermittent treatment with a topical corticosteroid or long-term maintenance with a topical calcineurin inhibitor if needed.[5] Patients with skin disease that cannot be controlled with topical therapy can be treated with phototherapy or systemic immunomodulators such as cyclosporine, azathioprine, or, for short periods, prednisone.[6,7]

Crisaborole (Eucrisa™, Pfizer, Inc.) 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 intermittently applied topical corticosteroids or daily topical calcineurin inhibitors. Dupilumab (Dupixent™, Sanofi-Regeneron) 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. Crisaborole was approved by the FDA in December, 2016 for use in adults and in children age two and older, and dupilumab was approved in March, 2017, for use in adults. Dupilumab, in particular, is expected to provide an important therapeutic option for many patients who have not previously had an adequate response to treatment, and is more expensive than existing treatment options.

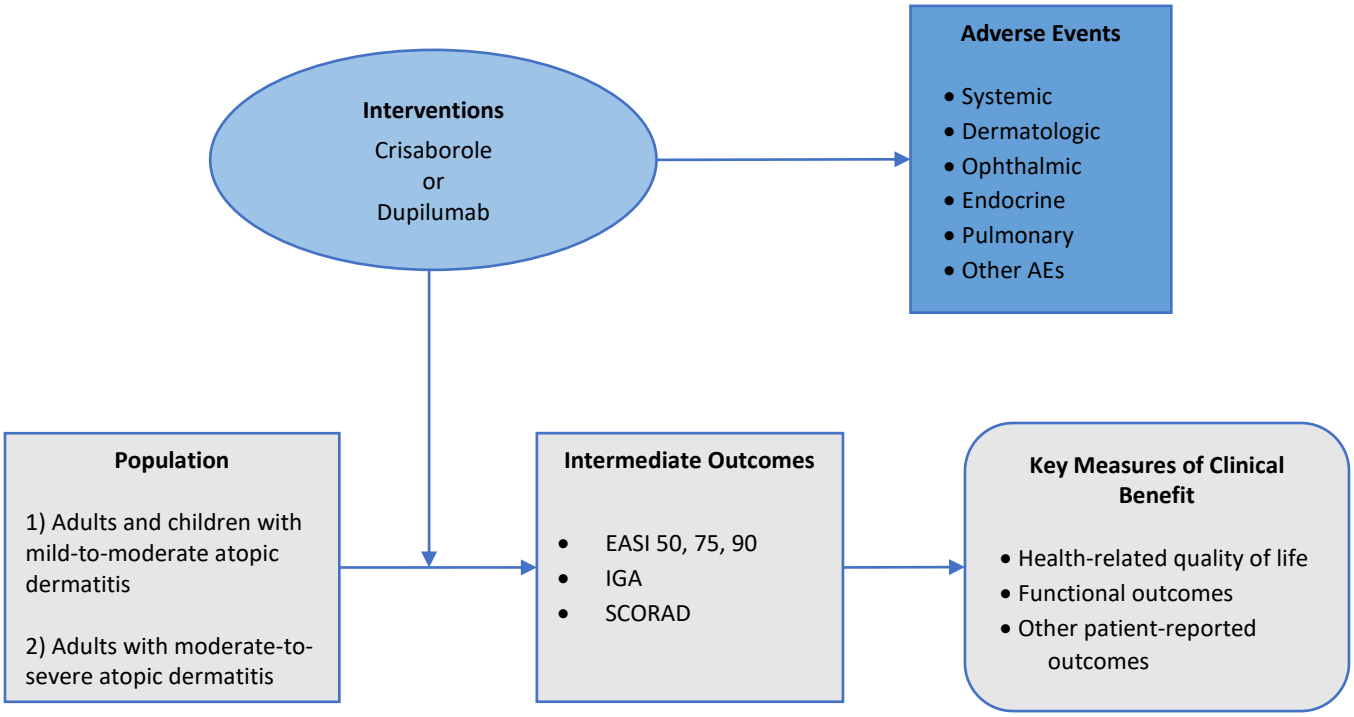
Scope of the Assessment

This report includes two separate assessments: it evaluates the comparative clinical effectiveness of crisaborole for its indication in the treatment of mild-to-moderate atopic dermatitis in children and adults. Separately, the report evaluates the comparative clinical effectiveness and value of dupilumab for its expected indication in the treatment of moderate-to-severe atopic dermatitis in adults. Given anticipated differences in the intended use of these drugs, the assessment does not compare the clinical effectiveness of crisaborole and dupilumab. The scope is described below using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework.

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 were:

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; we also compared crisaborole 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 assessment examined 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 recognized that many of these outcomes were not adequately addressed within randomized trials but looked for such evidence where available.

Outcomes from clinical trials:

- Investigator's Global Assessment (IGA; can be static or dynamic)
- 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
- Skin infections
- Treatment-related adverse events

We also looked for evidence on additional patient-reported outcomes, including other measures of health-related quality of life and measures of sleep. Additionally, we looked 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 also tried to assess whether there were differential effects on broader health outcomes. To do this, we sought evidence on quality of life measures (such as EQ-5D) in subgroups with and without asthma or nasal polyposis and also sought to compare such broader measures with measures more narrowly focused on dermatologic quality of life (such as DLQI).

We developed evidence tables for each selected study, and results were summarized in a qualitative fashion; meta-analysis was used to quantitatively summarize outcomes for the therapies of interest. We performed a network meta-analysis of indirect evidence to compare crisaborole with topical therapies (corticosteroids and calcineurin inhibitors).

Timing

Evidence on intervention effectiveness and harms were derived from studies of at least four weeks duration.

Settings

We examined results in patients treated in clinic and outpatient settings.

2. The Topic in Context

As discussed above, atopic dermatitis is common, particularly in children.[1,2] There is a broad spectrum of disease, with the majority of patients able to be managed adequately with topical therapies. The two therapies we are examining in this report are intended for patients at different places on the disease spectrum. There is, however, no agreed-on definition of "mild-to-moderate" or "moderate-to-severe" atopic dermatitis;[7] even recent trials have used different scaling systems to define severity of disease.[11,18,50]

Despite the lack of clear definitions, experts described to us that children with mild-to-moderate atopic dermatitis experience flares that can disrupt sleep and school attendance. Control of symptoms requires understanding of and adherence to 30-60 minutes of skin care a day. Children and adults with moderate atopic dermatitis can have intermittent disease with multiple flares per year or a more chronic persistent course with intermittent flares. Disease flares can result in missed days and poor performance at work and school, social isolation, and impaired quality of life. Patients often need to adjust aspects of their lives to cope with their disease, such as limiting physical activities, clothing choices, and travel, and may need to avoid certain jobs. Patients with severe atopic dermatitis typically have more than ten flares per year, with daily or almost daily active disease even between flares. The heavy burden of itch, pain, sleep disturbance, and mental health symptoms is debilitating and negatively impacts all areas of personal, academic, professional, and daily life for the patient and family members.

Crisaborole is a topical therapy that inhibits phosphodiesterase 4 (PDE4), the same mechanism as the oral agent apremilast that is used for psoriasis.[11] PDE4 is a regulator of inflammation, and intracellular inflammatory cell PDE4 activity is increased in atopic dermatitis. Crisaborole is intended for use in patients with mild-to-moderate atopic dermatitis as a safe alternative to the existing topical agents. Crisaborole comes as an ointment that is applied twice daily.

In addition to moisturizers used to augment the skin's epidermal barrier, existing topical therapies for atopic dermatitis include corticosteroids and calcineurin inhibitors (i.e., pimecrolimus [Elidel®] and tacrolimus [Protopic®]). Prolonged use of topical corticosteroids can result in telangiectasias, increased hair, skin tears, easy bruising, poor wound healing, acne and rosacea, and thinning/atrophic changes, which can be permanent.[12,13] Topical corticosteroids can also produce systemic effects including adrenal suppression,[14] particularly when higher potency preparations are 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,[15] and concerns about the use of topical steroids are referred to as "steroid phobia" or "topical corticosteroid phobia", both in the literature[16] and by a number of clinicians and patient groups with whom we spoke. All topical preparations can sting, but there is evidence that this can be a particular problem with topical calcineurin inhibitors.[17] The US FDA label for topical calcineurin inhibitors includes a "black box" warning regarding a theoretical risk for skin cancers and lymphoma. Topical calcineurin inhibitors have a labeled indication for patients who have failed to respond to topical corticosteroids or for whom topical corticosteroids are inadvisable. However, these medications are most often used as steroid-sparing agents for long-term maintenance in patients who require daily treatment.

Dupilumab is a monoclonal antibody directed against interleukin-4 receptor alpha.[18] Dupilumab inhibits signaling of interleukin-4 and interleukin-13, and by doing so alters type 2 helper T (Th2) cell mediated immune responses and improves epidermal barrier abnormalities in atopic dermatitis.[19] Dupilumab is intended for use in patients with moderate-to-severe atopic dermatitis and is believed to be more targeted and safer than existing systemic therapies. It is administered as a subcutaneous injection and was studied with weekly and every other week administration schedules. Although currently published randomized trials were performed in adults, its use in children is also being studied. Other therapies directed at Th2 cells and type 2 cytokines are in development.[20,21]

Existing systemic therapies for atopic dermatitis include immunomodulators such as cyclosporine, azathioprine, and methotrexate, and patients with less severe disease can also be treated with phototherapy. Short courses of oral corticosteroids and oral antibiotics are commonly prescribed to many patients with severe atopic dermatitis. However, in addition to well-recognized adverse effects, treatment with systemic corticosteroids is typically inadequate for patients with chronic disease given its limited duration of use, and is often followed by rebound worsening upon discontinuation. All of the previous 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.[7] Phototherapy is typically available to patients in the US who live in large metropolitan areas, but is not generally felt to be appropriate for patients with more severe disease. Phototherapy can be prohibitively time consuming and may increase the risk of skin cancer,[22] and systemic immunomodulators can have potentially serious or even fatal side effects, including infections, malignancies, and blood dyscrasias, can cause irreversible liver and kidney damage, and require frequent laboratory monitoring.[7]

Atopic dermatitis appears to be a disease that is frequently undertreated and, for many patients, is lacking treatments. Mild-to-moderate disease can often be effectively controlled with existing topical therapies,[23-25] but concerns about the side effects of those therapies inhibit treatment in many patients. Additionally, there is a lack of guidance on the safe and effective long-term use of topical medications, particularly with regard to the optimal quantity and frequency of topical corticosteroids and indications for the use of topical calcineurin inhibitors. Patients with mild-to-moderate disease may experience itching and visible changes that can result in important psychosocial effects described further below. We heard from multiple experts and patient groups that most patients with moderate-to-severe disease do not receive systemic therapies even when these might be beneficial. These are agents with important side effects. We heard that most clinicians are uncomfortable prescribing them for various reasons, including lack of experience with their use and the lack of a labeled indication for atopic dermatitis. Patients with moderate-to-severe disease experience substantial disruptions to their lives with the disorder disturbing sleep and affecting all aspects of social functioning. In this landscape of a routinely undertreated disease with substantial burdens, more acceptable and effective therapies are clearly needed.

Patient Outcome Measures Used in Clinical Trials

- ***Investigator's Global Assessment (IGA):*** This clinician-reported outcome measure determines severity of atopic dermatitis. The most common versions used in the trials reviewed were static scales (they did not assess changes in severity with treatment; abbreviated in the key crisaborole trials as "ISGA") and used either a 5-point scale ranging from 0 (clear) to 4 (severe) or a 6-point scale ranging from 0 (clear) to 5 (very severe).
- ***Eczema Area Severity Index score (EASI):*** Assesses severity and body surface area affected by erythema, induration/papulation/edema, excoriations, and lichenification, which are graded systematically for each anatomical region and assembled in a composite score.
    - ***EASI 50:*** a percentage improvement of EASI score from baseline that is ≥ 50%
    - ***EASI 75:*** a percentage improvement of EASI score from baseline that is ≥ 75%
    - ***EASI 90:*** a percentage improvement of EASI score from baseline that is ≥ 90%
- ***Global Individual Signs Score (GISS):*** Individual components of the atopic dermatitis lesions are rated globally (for the whole body, not by anatomical region) on a 4-point scale (0 [none] to 3 [severe]) using the EASI severity grading criteria. The cumulative score, which ranges from 0 to 12, is the sum of the four components.
- ***Dermatology Life Quality Index (DLQI):*** A 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of skin conditions on quality of life
- ***Hospital Anxiety and Depression Scale (HADS):*** Likert scale used to detect states of anxiety and depression; anxiety and depression subscales each with 7 items.
- ***Scoring Atopic Dermatitis (SCORAD):*** The extent and severity of atopic dermatitis over the body area and the severity of 6 specific symptoms (erythema, edema/papulation, excoriations, lichenification, oozing/crusts, and dryness) are assessed and scored by the investigator. Subjective assessment of itch and sleeplessness is scored by the patient. The SCORAD score is a combined score of body area affected, and investigator and patient symptom scoring, with a maximum of 103.
- ***Patient-Oriented Eczema Measure (POEM):*** A validated questionnaire, examining seven items, used in clinical settings to assess time spent with symptoms and the impact of symptoms on sleep.
- **Children's Dermatology Life Quality Index (CLDQI):** A questionnaire designed to measure the impact of skin disease on the lives of children ages 4 to 16 years.[53]
- **Dermatitis Family Impact Questionnaire (DFI):** A disease-specific measure to assess the impact of atopic dermatitis on the quality of life of parents and family members of affected children.[54]

Insights Gained from Discussions with Patients and Patient Groups

Atopic dermatitis is a common dermatologic condition. Central to the comments we heard from patients and patient groups was the idea that thinking of atopic dermatitis as "just a skin condition" is a serious error that underappreciates the profound effects that severe atopic dermatitis can have on all aspects of a patient's life and on the lives of family and caregivers.

Patients' lives can be affected by:

- Sleep disruption that can be profound
- Itch and pain that can affect both sleeping and waking hours
- Individual psychologic effects of illness, including depression, anxiety, suicidal ideation, and loss of self-esteem
- Interpersonal effects, including bullying in children, alterations in family dynamics, and effects on intimate relationships in adults
- Effects on performance, including effects on developmental milestones and school attendance in children, missed days of work, disability for one's chosen profession, and presenteeism effects on school and work performance
- Effects on life activities, including restrictions on diet, exercise, and recreation
- Burdens of therapy, including time spent on treatments (such as applying moisturizers and wraps) that may present particular adherence issues for children at school, costs of treatment and of travel to seek care

Additionally, atopic dermatitis can present substantial burdens for families and caregivers. Apart from the relationship issues discussed above, parents may need to spend substantial time applying topical therapies to children, may miss days of work when children miss school because of atopic dermatitis, and may experience chronic sleep disruption from cosleeping with their child. Lack of treatment options for infants and children younger than age two is a significant problem for patients and families.

We also heard that patients with atopic dermatitis often feel blamed for their condition by caregivers and others. Because topical therapy requires substantial time and energy and triggers are often unclear, worsening of the disease can set off a search for some behavior/indiscretion that led to the worsening. In a disease that tends to have some waxing and waning in severity, this can lead to patients feeling guilty and blamed when their disease severity increases.

3. Summary of Coverage Policies and Clinical Guidelines

3.1 Coverage Policies

To understand the insurance landscape for therapies for atopic dermatitis, we reviewed publicly available 2017 coverage policies and formularies for Midwestern state Medicaid programs (Missouri), Centers for Medicare and Medicaid Services (CMS) and major plans in individual marketplaces across Missouri and other Midwestern states, including Anthem Blue Cross Blue Shield, Aetna, Blue Cross Blue Shield Kansas City, Cigna Missouri, and Aetna Better Health Illinois.

Therapies for atopic dermatitis include nonpharmacologic interventions, such as moisturizers, bathing and wet wraps, topical pharmacologic treatments, such as topical corticosteroids and calcineurin inhibitors, systemic treatments, and phototherapy. We surveyed each plan's coverage policies for topical corticosteroids over a range of potencies. All private carriers covered most topical corticosteroids with preferred drug status. MissouriHealth, Missouri's state Medicaid program, only covered hydrocortisone as preferred agents, while other topical corticosteroids were non-preferred. There was variable coverage of the topical calcineurin inhibitors tacrolimus and pimecrolimus. For example, step therapy was required by some plans, while prior authorization was required by others. Blue Cross Blue Shield of Kansas City has a step therapy program intended to encourage the use of topical corticosteroids prior to the use of topical calcineurin inhibitors, allowing the use of topical calcineurin inhibitors once a patient has tried topical corticosteroids or if the target disease is in a sensitive area (such as the face, eyes, or genitalia).

More severe cases of atopic dermatitis can be treated with systemic therapies, such as cyclosporine, or with phototherapy. Cyclosporine was often covered as a preferred agent, and no plans surveyed required any prior authorization or step therapy for its use. Targeted phototherapy was covered by all plans when severe atopic dermatitis did not respond to any topical treatments. Anecdotally, we heard from clinical experts that, in practice, coverage for cyclosporine and for phototherapy was not as easily available as the coverage policies may indicate.

3.2 Clinical Guidelines

American Academy of Dermatology: Guidelines of care for the management of atopic dermatitis[6]

The American Academy of Dermatology issued guidelines for the treatment of atopic dermatitis in 2014, updating and expanding their previous guidelines, published in 2004. The guidelines were developed by a working group of recognized atopic dermatitis experts using an evidence-based approach. The guidelines recommend both nonpharmacologic interventions as well as a range of pharmacological treatment options.

The nonpharmacological treatments recommended include the application of moisturizers as a method to reduce the severity of atopic dermatitis and reduce the need for pharmacological treatments. Bathing, with the limited use of non-soap cleansers, followed by moisturizers, is also recommended. For patients with moderate-to-severe atopic dermatitis, use of wet-wraps, used in conjunction with topical corticosteroids at times, was also recommended during flares.

The pharmacological topical treatments recommended include topical corticosteroids and topical immunotherapies (calcineurin inhibitors). Topical corticosteroids are recommended for those individuals for whom nonpharmacological interventions have not been successful in controlling symptoms. Topical corticosteroids are recommended as both active treatment and maintenance therapy to prevent relapses. Topical calcineurin inhibitors are recommended for patients with atopic dermatitis as a second-line therapy where topical corticosteroids have failed to control symptoms, or when corticosteroids are not an appropriate treatment choice, for example on sensitive areas like the face or genitals.

Other topical treatments discussed include topical antimicrobials and antiseptics, which are not routinely recommended, and topical antihistamines, which are not recommended in any instance.

The guidelines also discuss the use of systemic agents and the use of phototherapy to treat atopic dermatitis. Phototherapy is recommended as a second-line treatment, to be used after the failure of topical first line therapies, such as emollients and topical corticosteroids and calcineurin inhibitors. For those patients with chronic disease, phototherapy is recommended as maintenance therapy. Systemic therapies are recommended for those patients with moderate-to-severe atopic dermatitis, particularly those where topical regimens and phototherapy are not adequately controlling the disease or when quality of life is affected. The guidelines identify cyclosporine, methotrexate, mycophenolate mofetil, and azathioprine as the more common and effective systemic options. The guidelines also discourage the use of systemic corticosteroids due to the short- and long-term adverse effects.

National Institutes for Health and Care Excellence (NICE)[55]

NICE has issued guidance on the treatment of atopic dermatitis, identifying emollients as a first-line therapy and as maintenance therapy for individuals with atopic dermatitis. Topical corticosteroids are recommended as first-line treatment for acute flares of atopic dermatitis, used in conjunction with emollients.

Other treatments, including topical immunomodulators and wet wraps are described as alternatives, but not recommended as first line treatments. Tacrolimus and pimecrolimus are recommended when corticosteroids have been ineffective or when the risk of using topical corticosteroids is significant. NICE describes systemic corticosteroids, phototherapy, and systemic immunosuppressants as "treatments of last resort."

Joint Task Force on Practice Parameters for Allergy and Immunology: Atopic dermatitis: A practice parameter update 2012[56]

The Joint Task Force on Practice Parameters, which represents the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy & Immunology American Academy of Dermatology issued guidelines for the treatment of atopic dermatitis in 2012 to update parameters published in 2004.

The practice parameters recommend that clinicians take a systemic, multifaceted approach, including elimination of exacerbating factors, skin hydration, topical anti-inflammatory medications, therapies to reduce itch, and antibacterial measures. Recommended first line treatment is skin hydration, including moisturizers and soaking baths. For atopic dermatitis that is not controlled by moisturizers, topical corticosteroids are recommended, particularly over shorter periods of time. Topical calcineurin inhibitors are recommended, particularly as treatment for areas susceptible to skin atrophy such as the face, eyelids, or skin folds.

The parameters also recommend identifying and avoiding or eliminating triggering factors such as common irritants like soap or chemicals. More difficult to treat atopic dermatitis, particularly in patients who are refractory to first line treatments discussed above may require consideration of treatments such as wet dressings, systemic immunomodulating agents, phototherapy, or allergen immunotherapy.

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our analysis of the comparative clinical effectiveness of dupilumab versus placebo for moderate-to-severe atopic dermatitis and crisaborole versus the emollient it is prepared in for mild-to-moderate atopic dermatitis, we abstracted evidence from available clinical studies, whether in published, unpublished, or abstract form. We also qualitatively summarized findings from previously published systematic reviews to inform comparisons of crisaborole to topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) and comparisons of dupilumab to cyclosporine, phototherapy, and failed topical therapies.

As described in the Background section, we included evidence from placebo-controlled trials, but we also incorporated evidence about the potential comparators when possible. Our review focused on key clinical outcomes common to atopic dermatitis trials as well as symptoms and burdens of atopic dermatitis that are not well-captured by standard trial outcomes.

- Clinical Benefits
    - 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

- Harms
    - Treatment-related adverse events
    - Skin infections (captured as adverse events, but reduction may be a benefit of therapy)

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on dupilumab for moderate-to-severe atopic dermatitis and crisaborole for mild-to-moderate atopic dermatitis followed established best methods used in systematic review research.[57] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) guidelines.[58] The PRISMA guidelines include a checklist of 27 items, further details of which is available in Appendix Table A1.

The timeframe for our search spanned the period from January 1996 to January 2017 and focused on MEDLINE, EMBASE, and Cochrane-indexed articles. We limited each search to studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We did not conduct a *de novo* search for phototherapy and calcineurin inhibitors. Rather, data from the key comparative studies not captured in the initial survey of the literature were abstracted from recently published high-quality systematic reviews. To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent relevant reviews and meta-analyses. Further details on the search algorithms, methods for study selection, data extraction, quality assessment, assessment for publication bias, and our approach to meta-analyses of the data are available in Appendix D. We included several articles published after our initial search date if the data appeared to inform this report.

Study Selection

We included evidence from randomized controlled trials (RCTs), comparative observational studies, and high-quality systematic reviews where available. We excluded single-arm studies and studies in healthy subjects from an early clinical development phase. We only focused on dosages that had been or were felt likely to be approved by the FDA. Evidence from previous systematic reviews which included other active treatments (e.g., phototherapy, cyclosporine, and topical calcineurin inhibitors) were discussed qualitatively to inform the comparisons with the newer agents, but were not analyzed quantitatively, with the exception of the topical calcineurin inhibitor pimecrolimus. We did not find additional registries or other datasets of patient-reported outcomes that could be used in our analysis.

In recognition of the evolving evidence base for atopic dermatitis, we supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature that met ICER standards for review (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/). We excluded abstracts which reported duplicative data available in published articles, or reported results from observational studies since it would be difficult, if not impossible, to evaluate the methodological quality of these studies. We also did not include any outcomes from conference proceedings or regulatory documents on phototherapy, calcineurin inhibitors, or topical corticosteroids given that these treatments have been available for at least a decade and primarily have peer-reviewed data available.

Data were abstracted and summarized into evidence tables for all outcomes. For most outcomes, we summarized comparative findings qualitatively. However, we quantitatively synthesized evidence for EASI 50, 75, and 90 and IGA outcomes through meta-analyses (see Appendix D).

For the meta-analyses, we included evidence from phase II or III randomized controlled trials (RCTs) that directly compared dupilumab to placebo with or without background topical corticosteroids and reported either EASI or IGA at 16 weeks. We included phase III RCTs comparing crisaborole to

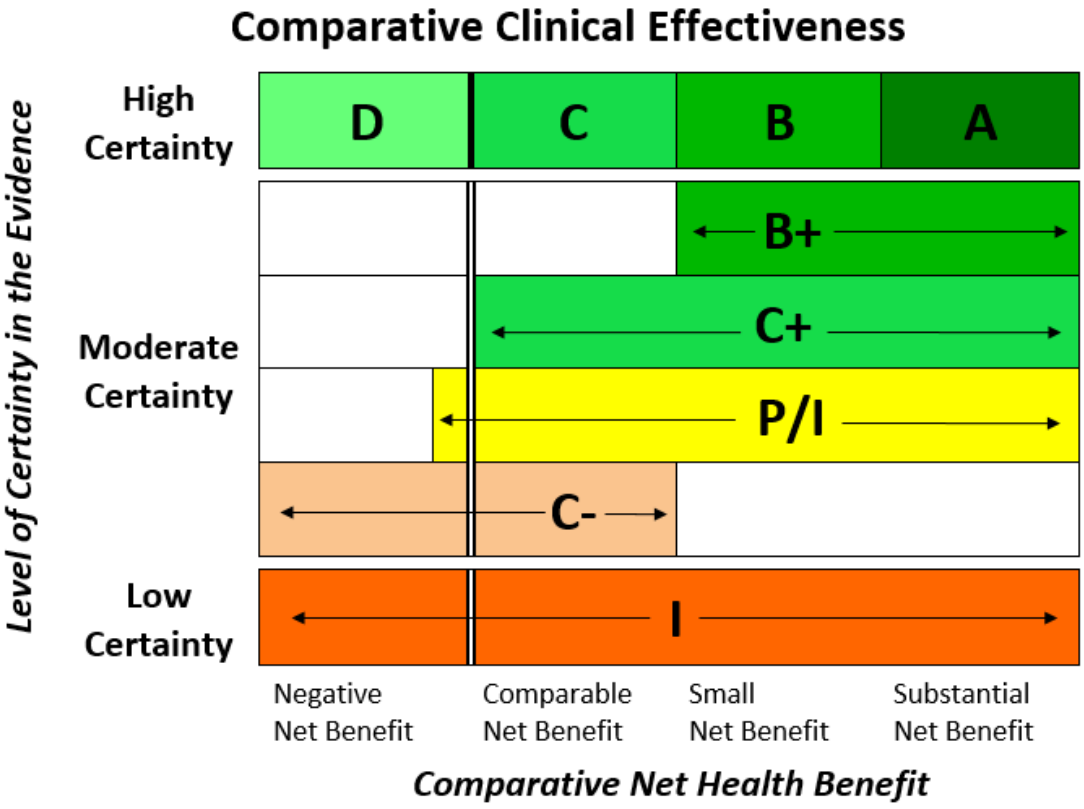
vehicle. For the review of adverse events, we included additional dupilumab trials for nasal polyposis and asthma.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 2) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

g) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
h) The level of **certainty** in the best point estimate of net health benefit.[59]

Figure 2. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D = "Negative"- High certainty of an inferior net health benefit
B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

Data Synthesis and Statistical Analyses

There was sparse evidence and no consistent outcome measure for clinical outcomes for dupilumab versus other active treatments, so NMAs were not performed. Instead, meta-analyses on EASI and IGA outcomes and subgroup analyses by dose and background topical corticosteroids were conducted for dupilumab. NMA was conducted for crisaborole, pimecrolimus, and vehicle, combining 5-point and 6-point IGA outcomes, assuming that the "clear" and "almost clear" categories in both scales were similar. Detailed descriptions of the statistical methods and sensitivity analyses are in Appendix D.

4.3 Results

Study Selection

Our literature search identified 616 potentially relevant references. A total of 30 references met our inclusion criteria, including 29 publications and one abstract. Primary reasons for study exclusion included indications not of interest, interventions not of interest, and non-comparative study design. Additional details of the included references are described in Appendix E, and the key studies are summarized in Table 1.

Dupilumab

Six publications and one abstract relating to 11 RCTs were identified for dupilumab, among which eight were focused on its efficacy and safety in atopic dermatitis and three on use in nasal polyposis and asthma.

Crisaborole

Two publications relating to three RCTs were included for crisaborole.

Others

The remaining 21 publications were all related to topical calcineurin inhibitors and phototherapy, including two publications of RCTs, two observational studies, and 17 systematic reviews.

Quality of Individual Studies

We rated all 16 trials, of which 5 were Phase III, to be of good, fair, or poor quality using criteria from U.S. Preventive Services Task Force (USPSTF).[60] Trial rankings can be found in Table E1, Appendix E. Trials of good quality had study arms that were comparable at baseline, the authors used valid instruments to evaluate outcomes, and no differential attrition was observed. Fair quality trials typically had inadequate descriptions of allocation and/or randomization, or had inadequate blinding. Of the 2 observational studies, both were judged to be of poor quality. We

did not assign a quality rating to systematic reviews or references that were obtained from the grey literature.

Dupilumab for moderate-to-severe atopic dermatitis

Key Studies

We identified three key clinical trials for dupilumab. Key trials for dupilumab are a phase IIb trial (Thaci) and SOLO 1 and SOLO 2, two identically designed multi-center, phase III RCTs. The remaining nine trials for dupilumab include the LIBERTY AD CHRONOS trial, which had only limited results available from a press release until a few weeks before the public meeting, which affected its addition in some meta-analyses, one phase II trial described in an abstract, four small phase I/IIa trials, and three trials of dupilumab used to treat asthma and nasal polyposis, reporting adverse events.

Study populations had similar inclusion criteria among the key atopic dermatitis trials (≥ 18 years old, moderate-to-severe atopic dermatitis with an Investigator's Global Assessment (IGA) score of 3 or 4, an EASI ≥ 16 at baseline, and involvement of at least 10% of the body surface area, for whom topical treatment provided inadequate control or was medically inadvisable) and were comparable with respect to age (range of means: 35-39 years), duration of atopic dermatitis (range of means: 24-31 years), and baseline severity (47%-49% baseline IGA of 4). In SOLO 1 & 2, many patients had received prior systemic treatments, including 32.9% and 33.0% receiving systemic corticosteroids and 25.9% and 31.4% receiving systemic immunosuppressants. The majority of patients treated with immunosuppressants received cyclosporine (20.3% and 23.3% of all patients).[18,47]

Table 1. Key Studies: Dupilumab

Trials	Total # of patients	Treatment duration (weeks)	EASI, (mean)	Mean age (years)	Atopic Dermatitis duration (years)	IGA score of 4 (%)
SOLO 1	671	16	31	39	27	48.3
SOLO 2	708	16	29	35	25	48.3
Thaci, 2016	379	16	32	38	29	47.2

Clinical Benefits

The primary outcomes of the trials varied: in SOLO 1&2 it was the proportion of patients at 16 weeks achieving IGA 0 or 1 and reduction of ≥ 2 from baseline, with EASI 75 being a key secondary outcome; in Thaci 2016 it was the proportion of patients achieving EASI 50, 75, and 90 at 16 weeks. Other clinical outcomes measured included change in the Global Individual Sign Score (GISS) which assessed atopic dermatitis signs including erythema, exudation, excoriation, induration/papulation, and lichenification, and change in the body surface area affected by atopic dermatitis. Patient-reported outcomes, including quality of life based on change in the DLQI, and measures of symptom

control, such as the pruritus numerical rating scale and pruritus score, the Hospital Anxiety and Depression Scale (HADS), the Scoring Atopic Dermatitis (SCORAD) score, the Patient-Oriented Eczema Measure (POEM), were also reported.

We reviewed the two dosing regimens in the trials that appeared most likely to be part of the possible label for dupilumab (300 mg weekly [QW] and 300 mg every other week [Q2W]). Dupilumab was approved with an initial loading dose of 600 mg, followed by 300 mg Q2W.

Investigator's Global Assessment (IGA)

Consistently across all trials, dupilumab met prespecified IGA targets representing successful outcomes in 30-44% of patients, compared to 2-12% for placebo. Results were similar with weekly or every other week dosing, and in patients treated or not treated with topical corticosteroids.

The primary outcome in the phase III trials of dupilumab, SOLO 1 & 2[18] and LIBERTY AD CHRONOS[26,27], was an IGA score of 0 or 1 *and* an improvement of 2 points or more from baseline IGA at 16 weeks. The primary IGA outcome in the phase II trials[28,29] was a score of 0 or 1 at 16 weeks. All trials showed statistically significantly greater IGA responses in the dupilumab arms compared to placebo (Table 2). The response rates were 30% to 44% for the dupilumab arms, with little difference between weekly and every other week dosing, and was 2% to 12% in the placebo arms. Unlike the other trials, patients in LIBERTY AD CHRONOS were also treated with topical corticosteroids, but the results in this trial were very similar to those in SOLO 1 & 2. Meta-analysis pooling the two dosing regimens and including all five 16-week trials found an increased chance of achieving an IGA response with dupilumab, as defined in each trial (relative risk [RR] 3.88, 95% CI 3.13-4.79). Additionally, four small phase I and II trials also suggested the dupilumab arms had higher proportions of patients achieving IGA 0 or 1 at 12 weeks and four weeks, even though most of the results in these small trials were not statistically significant.[19]

Table 2. Dupilumab: IGA Response Rates across Trials at 16 weeks

Trial	IGA 0 or 1 and ≥ 2 reduction from baseline (%)			IGA 0 or 1 (%)		
	Dupilumab 300 mg QW	Dupilumab 300 mg Q2W	Placebo	Dupilumab 300 mg QW	Dupilumab 300 mg Q2W	Placebo
SOLO 1	**37**	**38**	**10**	NR	NR	NR
SOLO 2	**36**	**36**	**8**	NR	NR	NR
Thaci 2016	NR	NR	NR	**33**	**30**	**2**
LIBERTY AD CHRONOS	**39**	**39**	**12**	NR	NR	NR
Blauvelt 2016	NR	NA	NR	**44**	NA	**10**

QW: weekly, Q2W: every two weeks.

Eczema Area Severity Index (EASI)

Dupilumab substantially increased the likelihood of achieving EASI 75 compared to placebo. Results were similar with weekly or every other week dosing and in patients treated or not treated with topical corticosteroids. Results for other EASI thresholds were generally consistent with results for EASI 75. More patients treated with dupilumab than placebo achieved EASI 50 and EASI 90 responses at 16 weeks.

EASI 75

EASI 75 was a key secondary outcome in SOLO 1 & 2 and a primary outcome in the other three trials. All trials showed statistically significantly greater EASI 75 response with dupilumab compared to placebo (Table 3). The response rates were 44% to 69% in the dupilumab arms, with little difference between dosing regimens, compared to 12% to 20% in the placebo arm (Table 3). The LIBERTY AD CHRONOS trial in patients also receiving topical corticosteroids found a slightly higher EASI 75 response in the dupilumab arms compared with the responses seen in SOLO 1&2, but this difference across trials was not statistically significant. However, it remains possible that dupilumab is more effective in some patients when used in combination with topical corticosteroids than when used alone.

We found no statistically significant differences between dupilumab 300 mg weekly and 300 mg biweekly on EASI 75 (or IGA) outcomes, as evidenced by p values of Q statistics greater than 0.05 (Appendix Figure D1-D2). Similarly, the results of the LIBERTY AD CHRONOS trial were not statistically significantly different from the other trials where background topical corticosteroids were not allowed (Appendix Figure D3-D4).

Meta-analysis pooling the dosing regimens and including all five trials found an increased likelihood of achieving EASI 75 with dupilumab (RR 3.25, 95% CI 2.79-3.79). Four small phase I and II trials showed numerically greater EASI 75 response with dupilumab than placebo at 12 weeks and four weeks.

LIBERTY AD CHRONOS demonstrates that dupilumab achieves better outcomes than continuing treatment with topical corticosteroids in patients who have had an inadequate response to therapy with topical corticosteroids with or without topical calcineurin inhibitors. The currently available results from LIBERTY AD CHRONOS do not provide direct evidence on dupilumab therapy as compared with topical calcineurin inhibitor therapy in such patients, since we are uncertain how many patients in the trial had failed topical calcineurin inhibitors.

Other EASI thresholds: EASI 50 and EASI 90

For EASI 50, the response rates were 61% to 83% in the dupilumab arms and 22% to 37% in the placebo arms; for EASI 90, the response rates were 30% to 43% with dupilumab and 3% to 11% with placebo. Four small phase I and II trials showed similar results at 12 weeks and four weeks.

Table 3. Dupilumab: EASI Response Rates across Trials

Trial	EASI 50			EASI 75			EASI 90		
	Dupilumab QW	Dupilumab Q2W	PBO	Dupilumab QW	Dupilumab Q2W	PBO	Dupilumab QW	Dupilumab Q2W	PBO
16 weeks									
SOLO 1	61	69	25	52	51	15	33	36	8
SOLO 2	61	65	22	48	44	12	31	30	7
Thaci 2016	83	78	30	61	54	12	37	30	3
LIBERTY AD CHRONOS	78	80	37	64	69	23	43	40	11
Blauvelt 2016	72	NA	32	54	NA	20	NR	NA	NR
12 weeks									
M12	85	NA	35	34	NA	8	NR	NA	NR
4 weeks									
M4A/M4B	59	NA	19	29	NA	6	NR	NA	NR
C4	59	NA	50	62	NA	40	NR	NA	NR

PBO: placebo.

Achieved EASI outcomes

We conducted a meta-analysis to estimate the percentages of patients in each mutually exclusive EASI category using the five trials reporting 16-week results in Table 3. This was to provide potential inputs for modeling quality of life outcomes with dupilumab therapy, given that we have estimates of utilities for the achieved EASI states. Statistical methods are described in Appendix D and the results are presented in Table 4. The models actually used the data stratified by severity (Tables 5 and 6, below), so the results of the meta-analysis provide information on the validity of those stratified results.

Table 4. Results from the Meta-analysis: Estimated EASI Outcomes across Five Trials

Treatment	% of patients in each mutually exclusive EASI response categories			
	Non-responders	EASI 50	EASI 75	EASI 90
Placebo	73	12	8	7
Dupilumab	31	16	17	36

We also received results from the manufacturer providing this same information pooled from the every other week dupilumab arms of the three key trials and stratified by baseline severity.[47] Results for patients with moderate disease are presented in Table 5 and for patients with severe disease in Table 6.

Table 5. Percentage of Patients with Moderate Baseline Disease in Each Mutually Exclusive EASI Response Category

Treatment	% of patients in each mutually exclusive EASI response categories			
	Non-responders	EASI 50	EASI 75	EASI 90
Placebo	70.3	12	8.3	9.4
Dupilumab	25.4	16	17.6	41

Table 6. Percentage of Patients with Severe Baseline Disease in Each Mutually Exclusive EASI Response Category

Treatment	% of patients in each mutually exclusive EASI response categories			
	Non-responders	EASI 50	EASI 75	EASI 90
Placebo	81.9	9.8	3.9	4.3
Dupilumab	38.3	24.1	14.2	23.3

Skin Infections

Evidence shows a trend toward small reductions in the risk of skin infection with dupilumab treatment, but no tests of statistical significance have been reported.

Patients with atopic dermatitis are at increased risk of skin infections, and therapies that improve atopic dermatitis may reduce this risk. Two phase III trials and one phase II trial showed slightly lower rates of skin infections with dupilumab than placebo (5%-8% vs. 8%-11%) at 16 weeks, while four small phase I and phase II trials showed moderate reductions in skin infections with dupilumab at four weeks (4%-5% vs. 10%-12%) and at 12 weeks (5% vs. 24%). Tests of statistical significance were not reported in any trial.

Other Clinical Outcomes

Outcomes using other measures of assessment showed similar benefits with dupilumab compared with placebo.

SOLO 1&2 and LIBERTY AD CHRONOS assessed outcomes using the Global Individual Signs Score (GISS) and mean percent change from baseline GISS. The reduction in GISS was 46% to 56% with dupilumab and 18% to 28% with placebo at 16 weeks. The affected body surface area (BSA) also showed a greater reduction from baseline with dupilumab than placebo in SOLO 1&2 (30%-34% vs. 13%-15%, with a baseline of 50%-57%; all p values <0.001) and in LIBERTY AD CHRONOS (37%-39% vs. 19% at 16 weeks, all p values <0.0001).

Patient-reported Outcomes

Quality of Life

Dupilumab improved patient quality of life as measured by DLQI.

SOLO 1&2,Thaci 2016, and LIBERTY AD CHRONOS measured the change in mean DLQI from baseline at 16 weeks and found statistically significantly greater improvement with dupilumab than placebo (absolute improvements of 8 to 12 points with dupilumab versus 1 to 5 points with placebo, p<0.001, where a 4-point improvement is considered clinically significant[30]).

Symptom Control

Dupilumab improved patient symptoms. These included individual measures of pruritus, and scoring systems looking at broader patient outcomes, patient-reported outcomes, and measures of anxiety and depression.

SOLO 1&2,Thaci 2016, and LIBERTY AD CHRONOS assessed the reduction of pruritus symptoms using percent change from baseline peak numerical rating scale (NRS) score. Across the four trials, the reduction in peak NRS ranged from 40% to 56% in the dupilumab arms versus 5% to 29% in the placebo arms (p<0.001). Anxiety and Depression was measured by Hospital Anxiety and Depression Scale (HADS) in SOLO 1&2 and LIBERTY AD CHRONOS. Mean reduction in HADS was statistically significantly greater with dupilumab than placebo (5-6 vs. 1-4; p<0.001). SOLO 1&2,Thaci 2016, and

LIBERTY AD CHRONOS also measured SCORAD, an instrument combining objective measures of area and intensity with subjective symptoms including itch and sleeplessness, and showed greater percentage improvement with dupilumab than placebo (51%-63% vs. 14%-32%; p<0.001). POEM, a self-reported measure of symptom severity, also showed greater reduction with dupilumab than placebo in SOLO 1&2 and LIBERTY AD CHRONOS (10-13 vs. 3-5; p<0.001).

52-Week Results

LIBERTY AD CHRONOS was the only clinical trial of dupilumab in atopic dermatitis that reported up to 52-week results for a variety of clinical outcomes, including IGA, EASI, Body Surface Area (BSA) affected, and GISS. In addition, LIBERTY AD CHRONOS also included long-term results on patient-reported outcomes such as SCORAD, POEM, DLQI, and HADS. These 52-week results from LIBERTY AD CHRONOS are presented in Table 7 below. Results were statistically significant across outcomes for both weekly and every other week dosing groups compared to placebo.

Through 52 weeks, fewer patients had flares of atopic dermatitis with weekly or every other week dupilumab than with placebo (13% and 14% versus 41%, respectively, p<0.0001 compared to placebo for both dosing groups).

Table 7. 52-Week Results of LIBERTY AD CHRONOS Trial

Outcome	% of patients achieved		
	Placebo	Dupilumab Q2W	Dupilumab QW
IGA score 0/1 and reduction of ≥2 points from baseline	13	36	40
EASI 50	30	79	70
EASI 75	22	65	64
EASI 90	16	51	51
	Mean change from baseline		
% Body Surface Area (BSA)	-20.3	-41.5	-39.9
GISS	-29.2%	-58.3%	-59.7%
HADS	-3.4	-5.3*	-5.5
POEM	-5.3	-13.7	-12.7
DLQI	-5.6	-10.9	-10.7
SCORAD	-34.1%	-66.2%	-66.1%

p<0.0001 vs. placebo unless otherwise noted. *p=0.0109.

LIBERTY AD CHRONOS also reported rates of skin infection at 52 weeks, which were lower with dupilumab than placebo (8%-11% vs. 18%), however tests of statistical significance were not reported.

Harms

Severe or serious adverse events were rare during treatment up to 16 weeks. Injection site reaction, nasopharyngitis, and headache were the most common side effects. There appear to be increased rates of conjunctivitis with dupilumab. Across all dupilumab trials (including trials in asthma and nasal polyposis) there were five deaths in the dupilumab arms, felt to be unrelated to treatment with dupilumab, and no deaths in the placebo arms.

The most common AEs with dupilumab at 16 weeks were injection site reaction, nasopharyngitis, and headache, all having higher rates than placebo. Allergic conjunctivitis and infectious conjunctivitis were less common AEs, but the rates were increased compared to placebo. The rates of any AE, SAEs, and discontinuation due to AE were slightly lower with dupilumab than placebo.

Across all trials of at least 16 weeks for dupilumab (for atopic dermatitis, asthma, and nasal polyposis), among 2,400 patients in the dupilumab arms, there were five deaths. These deaths were reported to be unrelated to dupilumab treatment. One patient who did not receive asthma-control medication died of an asthma attack 84 days after the last dupilumab dose; one patient with a history of hospitalization for depression committed suicide eight days after the last dupilumab dose; one patient experienced acute cardiac failure; one patient died from metastatic gastric cancer with organizing pneumonia and cor pulmonale; one patient was in a motor vehicle accident. There were no deaths in any the 1,121 patients in the placebo arms of these same trials.

Adverse events (AEs) that occurred in ≥ 5% of patients in any treatment group as well as specific AEs of interest are shown as trial-weighted averages in Table 8. Most adverse events were mild or moderate. Severe or serious adverse events, death, and AEs leading to discontinuation were rare and comparable between the treatment and placebo groups.

Table 8. Dupilumab: Harms at 16 Weeks

	AEs ≥ 1 (%)	SAEs ≥ 1 (%)	Discontinuation due to AE (%)	Any Severity			
				Injection site reaction[18,27,28] (%)	Conjunctivitis [18,28] (%)	Nasopharyngitis [18,28] (%)	Headache[18,28] (%)
Dupilumab 300 mg QW	74.6	2.4	1.5	16.6	11.2	11.3	7.8
Dupilumab 300 mg Q2W	73.0	2.8	2.0	11.1	8.2	10.9	8.4
Dupilumab dose groups pooled	73.9	2.6	1.8	14.2	9.9	11.1	8.1
Placebo	75.3	5.4	1.9	6.5	4.1	10.6	5.2

AE:adverse event, SAE:serious adverse event.

LIBERTY AD CHRONOS also reported rates of adverse events at 52 weeks, including higher rates of conjunctivitis with dupilumab than placebo (14%-19% vs. 8%).

Comparison to cyclosporine and phototherapy

Dupilumab appears likely to be at least as effective as cyclosporine and more effective than phototherapy at controlling atopic dermatitis. Treatment with cyclosporine has important toxicities; short-term experience with dupilumab suggests it may be safer than cyclosporine.

There are no head-to-head trials comparing dupilumab with either systemic cyclosporine or phototherapy. A systematic review of treatments for moderate-to-severe atopic dermatitis found 5 RCTs comparing cyclosporine with placebo, with improvements of 53% to 95% in various clinical severity scores.[7] However, these trials were small, were performed many years ago, and used outcome measures different from those used in current trials.

A small, open-label randomized trial (Granlund 2001[31]) compared cyclosporine with phototherapy in 72 patients treated intermittently for one year, and assessed changes in the Scoring Atopic Dermatitis (SCORAD) score with a primary outcome of remission defined as a ≥ 50% decrease from baseline SCORAD.[31] SCORAD was also assessed in SOLO 1&2, LIBERTY AD CHRONOS, and Thaci 2016, and the results from Granlund provide some limited indirect evidence for comparing cyclosporine and phototherapy with dupilumab. In Granlund, 36 patients treated with cyclosporine had a mean baseline SCORAD of 48.5, were in remission about 55%-60% of days, and appeared to typically have reductions of SCORAD of about 26-27 points (or about 55%). The median baseline SCORAD was higher in SOLO 1&2, LIBERTY AD CHRONOS, and Thaci (ranging from 65 to 68 in the dupilumab arms), and decreased by 52% to 63% with dupilumab. The higher SCORAD scores in the four dupilumab trials make this indirect comparison somewhat more difficult, as they reflect patients with more severe disease, but also provide greater opportunity for a percentage improvement in SCORAD. So, while the percentage improvements in SCORAD seem similar across these trials of cyclosporine and dupilumab, there is substantial remaining uncertainty as to the relative efficacy of these agents.

Table 9. Dupilumab vs. Cyclosporine: SCORAD Response Rates

	Baseline score*	Reduction from baseline at 16 weeks*
Dupilumab		
SOLO 1	65	-57%
SOLO 2	68	-52%
CHRONOS	66	-63%
Thaci 2016	67	-54%
Cyclosporine		
Granlund 2001	49	-55%

*For dupilumab trials, values pooled across weekly and every twoweek dosing groups

Treatment with cyclosporine carries important risks of acute and chronic nephrotoxicity, can have hemodynamic effects that result in hypertension,[32] and can increase the risk of infections and cancer.[17,33] Cyclosporine nephrotoxicity can be irreversible, and this risk increases with longer durations of treatment.[34] As a result, treatment with cyclosporine for atopic dermatitis is typically limited to one year.

As noted, the Granlund trial also assessed phototherapy, and found that cyclosporine was substantially more effective than phototherapy. Patients treated with phototherapy had a mean baseline SCORAD of 46.8, were in remission about 37%-38% of days, and appeared to typically have reductions of SCORAD of about 11-18 points (or about 24%-38%). Based on these results, and based on other studies of phototherapy,[35] dupilumab appears to be more effective than phototherapy. Phototherapy can be prohibitively time consuming and may increase the risk of skin cancer.[22]

Controversies and Uncertainties

Dupilumab is a therapy with a novel mechanism of action affecting the immune response, and we lack adequate long-term safety data. There is the risk that so-far undetected toxicities and adverse events will be encountered over time.[36]

We have no head-to-head trials comparing dupilumab with other systemic therapies for atopic dermatitis, and this limits our ability to assess both comparative benefits and harms. Although we have some limited evidence that benefits with dupilumab may be similar to those seen with cyclosporine, in the absence of a head-to-head trial there is uncertainty in this comparison. Additionally, although the toxicities of the immunosuppressive agents used for atopic dermatitis are well established, and dupilumab appeared to be well tolerated in randomized trials, we have much less experience with dupilumab, making it difficult to be certain of the relative safety of dupilumab versus established immunotherapies.

Patients studied in the randomized trials of dupilumab had a substantial burden of disease. For instance, although the entry criteria for the SOLO trials required an EASI score of at least 16 and an affected body surface area of at least 10%, the median EASI score at baseline was around 30, with an interquartile range from 21.0-43.8, and the median affected body surface area was around 50%, with an interquartile range from 34%-77%. Thus, the vast majority of patients had more severe disease than was required by the entry criteria for the trial. Although the indication for dupilumab in the FDA label is for moderate-to-severe disease that is inadequately controlled with topical treatment or for whom topical treatment is medically inadvisable, it is uncertain whether the patients for whom dupilumab is recommended by their clinicians will have similarly severe disease to those in the randomized trials.

We have limited evidence on the expected duration of response to dupilumab, both once a course of therapy has been administered, and with repeated or ongoing therapy. It is uncertain how often patients require continuing treatment and whether such treatment is safe and efficacious.

We have heard from expert clinicians and from patient groups that the clinical trials do not adequately reflect how some patients with atopic dermatitis experience dramatic improvements with dupilumab. We have heard that these dramatic responses are beyond what is typically seen with systemic immunotherapies such as cyclosporine.

Many patients with atopic dermatitis have a more general atopic disorder. Evidence from phase II trials suggests that dupilumab may have efficacy in the treatment of asthma and in the treatment of nasal polyposis.[61,62] In patients with atopic dermatitis who also have other atopic disorders,

dupilumab may provide additional health benefits. Estimates of improvements in quality of life based on EASI scores from the randomized trials will have pooled benefits across the patients in the trials. It is possible that patients with asthma and/or nasal polyposis who are treated with dupilumab for atopic dermatitis may get somewhat greater improvements in quality of life than these pooled numbers, and patients without these conditions may get somewhat smaller improvements.

Summary

- Treatment with dupilumab resulted in substantial improvements in atopic dermatitis in the majority of patients who were studied. In addition to improving the severity of atopic dermatitis and reducing pruritus, treatment improved quality of life and the effects of atopic dermatitis on sleep, anxiety, and depression.
- Dupilumab was generally well tolerated, although there was an increased rate of conjunctivitis with treatment. There were several deaths in the dupilumab arms of clinical trials that were not felt to be due to treatment; however, this is a novel therapy and important adverse effects could become apparent over time.
- Dupilumab appears to be at least as efficacious as cyclosporine (typically the preferred systemic therapy currently available) and more efficacious than phototherapy. Cyclosporine has important toxicities, and is generally not used for more than one year.

For adults with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy, or for whom topical therapies are medically inadvisable, we have high certainty that dupilumab provides at least a small net health benefit ("B+") relative to treatment with emollients with or without continued failed topical treatments. Given limitations of the evidence base, most notably the lack of long-term evidence on the safety of dupilumab, we have moderate certainty that the net health benefit of dupilumab is comparable or better than that provided by cyclosporine, but we have high certainty that dupilumab does not produce a lower net health benefit. Our comparative clinical effectiveness rating for dupilumab versus cyclosporine is therefore "C+".

Crisaborole for mild-to-moderate atopic dermatitis

Key Studies

The two key trials for crisaborole are AD301 and AD302, which are identically designed, multi-center, phase III RCTs. We also identified a phase IIa, bilateral, multi-center, 6-week RCT (Murrell 2015).

Study populations in AD301 and AD302 had similar inclusion criteria (≥ 2 years old, mild-to-moderate atopic dermatitis [Investigator's Static Global Assessment (ISGA) 2 or 3], and ≥ 5% treatable body surface) and were comparable with respect to age (range of means: 11.8-12.4 years), and baseline severity (36%-40% baseline ISGA of 2). Murrell 2015 included 25 adult patients ages 18 to 75, and assessed outcomes using Atopic Dermatitis Severity Index (ADSI). Given the

small number of patients in Murrell 2015 and the use of a different outcome measure, our analyses below focus on the key trials AD301 and AD302; information from Murrell 2015 is included in the analysis of adverse events and individual symptom/sign outcomes.

In the key trials, patients could not have recently received systemic corticosteroids (within 28 day), topical corticosteroids (within 14 days), or topical calcineurin inhibitors (within 14 days), and could not ever have been treated with biologic therapies (e.g., omalizumab or TNF inhibitors). However, data were not provided on how often patients had received other therapies and how they had responded to these therapies.

Table 10. Key Studies: Crisaborole

Trials	Total # of patients	Treatment duration (weeks)	Mean age (range) [years]	Mild, ISGA of 2 (%)	BSA (%)
AD301	759	4	12 (2-65)	38	18.7
AD302	763	4	12 (2-79)	39	17.8

Clinical Benefits

The primary outcomes of AD301 and AD302 were the proportion of patients achieving ISGA 0 or 1 and reduction of ≥ 2 from baseline ISGA at four weeks. Other clinical outcomes included improvement in atopic dermatitis signs, including erythema, exudation, excoriation, induration/papulation, and lichenification. Crisaborole data are reported based on the FDA-approved dosing of twice daily treatment.

Investigator's Static Global Assessment (ISGA)

In patients with mild-to-moderate atopic dermatitis, crisaborole modestly increased the likelihood of achieving ISGA success at four weeks compared with vehicle.

AD-301 and AD-302[11] randomized 1522 patients with mild-to-moderate atopic dermatitis 2:1 to crisaborole or vehicle and measured the proportion of patients with ISGA score of 0 or 1 *and* an improvement of ≥ 2 grades from baseline on Day 29 as the primary outcome. The success rate was moderately higher in the pooled crisaborole arms than in the placebo arms (32.1% vs. 21.7%; p<0.0001).

Table 11. Crisaborole: ISGA Response Rates across Trials

Trial	ISGA 0 or 1 and ≥ 2 reduction from baseline		ISGA 0 or 1	
	Crisaborole	Vehicle	Crisaborole	Vehicle
ADA 301	32.8	25.4	51.7	40.6
ADA 302	31.4	18.0	48.5	29.7

Skin Infections

Patients who received crisaborole had a slightly lower rate of staphylococcal skin infection at four weeks.

AD-301 and AD-302 reported on rates of staphylococcal skin infections, which were slightly lower with crisaborole than placebo at four weeks (0.1% vs. 1%; p=0.017).

Other Clinical Outcomes

Crisaborole showed statistically significantly higher rates of improvement in erythema, exudation, excoriation, induration/papulation, and lichenification than vehicle.

In the key trials, severity of individual signs of atopic dermatitis were assessed by investigators on days 1, 8, 15, 22, and 29, and improvement was defined as a score of 0 or 1 with an improvement of 1 or more grades from baseline. The improvement rate was moderately higher in the crisaborole arm than in the placebo arm for each individual atopic dermatitis sign evaluated, including erythema (59% vs. 40%; p<0.001), exudation (40% vs. 30%; p<0.001), excoriation (60% vs. 48%; p<0.001), induration/papulation (55% vs. 48%; p=0.008), and lichenification (52% vs. 41%; p<0.001). Murrell 2015 also measured improvement in severity of individual signs of atopic dermatitis, reported as mean severity score in each category for the lesion treated with crisaborole. Results were reported in a graph, but estimates on mean severity at day 28 included reductions from baseline in pruritus (2.3 to 0.6), erythema (2.2 to 0.8), lichenification (1.7 to 0.9, excoriation (1.5 to 0.4), and exudation (0.6 to 0.1).

Patient-reported Outcomes

Quality of Life

Crisaborole improved quality of life as measured by the DLQI and CDLQI, however the differences on these scales were smaller than the changes usually considered clinically meaningful.

Quality of life was measured in AD-301 and AD-302 using the DLQI in those older than age 15, and the Children's Dermatology Life Quality Index (CDLQI) in those ages 2 to 15. Results have not been published but were presented in a poster.[37] Patients ages 2 to 15 had greater reductions from baseline on the CDLQI with crisaborole than vehicle (-4.6 vs. -3.0; p<0.001), and patients over age 15 treated with crisaborole had greater reductions on the DLQI (-5.2 vs. -3.5; p=0.016). The differences between crisaborole and vehicle are less than the differences considered clinically meaningful on each scale (2.5 points on the CDLQI[38] and 4 points on the DLQI[30]).

Pruritus

Crisaborole modestly reduced pruritus.

Patients or caregivers self-assessed the severity of pruritus, and the proportion of patients with a pruritus score of 0 or 1 and an improvement of 1 or more grades from baseline were reported from days 8 through 29. The improvement rate was moderately higher in the crisaborole arm than in the placebo arm on day 8 (58% vs. 42%; p<0.001), day 15 (60% vs. 44%; p<0.001), day 22 (61 vs. 48%; p<0.001), and day 29 (63% vs. 53%; p=0.002).

Caregiver Burden

Treatment with crisaborole reduced caregiver burden as measured by the DFI, however it is uncertain whether the change on this scale was clinically meaningful.

Burden on family/parents/caregivers of patients ages 2 to 17 was measured in AD-301 and AD-302 using the Dermatitis Family Impact Questionnaire (DFI). Results have not been published but were presented in a poster.[37] A reduction in DFI reflects lower caregiver burden, and there were greater reductions with treatment with crisaborole than vehicle (-3.7 vs. -2.7; p=0.0003). The difference in DFI score that is considered clinically meaningful has not been established.[37]

Meta-Analyses and Network Meta-analyses

We identified no study directly comparing crisaborole to other active treatments. As indirect evidence, we identified two trials (Eichenfield 2002 and Ho 2003) comparing the calcineurin inhibitor pimecrolimus to placebo, using a 6-point static IGA score as an endpoint.[39,40] Crisaborole was evaluated in the key trials on a 5-point static IGA score. As shown in Table 12, the severity of disease in the trials appeared to be reasonably similar with regard to baseline IGA score and percent body surface area involved. Given the lack of head-to-head data and the slightly different versions of the IGA score, we performed indirect comparisons using Bayesian network meta-analyses (NMAs), assuming "clear" and "almost clear" categories are similar on both scales. We took a random-effects approach. There was a trend suggesting pimecrolimus was superior to crisaborole. However, there were wide credible intervals, and the findings were not statistically significant.

Table 12. Crisaborole/Pimecrolimus: Baseline Disease Severity across Trials

Trial	IGA score (%)		Mean body surface area involved (%)
	Mild	Moderate	
AD-301			
Crisaborole	39.0	61.0	18.8
Vehicle	36.3	63.7	18.6
AD-302			
Crisaborole	38.4	61.6	17.9
Vehicle	40.0	60.0	17.7
Ho 2003			
Pimecrolimus	32.5	67.5	NR
Vehicle	33.3	66.7	NR
Eichenfield 2002			
Pimecrolimus	30.0	60.3	26.1
Vehicle	31.6	57.4	25.5

In addition to statistical uncertainty, the trials were performed in very different time periods and used different versions of static IGA scales. Also, there are concerns that the pimecrolimus comparator vehicle can be irritating, and so the relative effects of pimecrolimus versus vehicle may appear greater than the relative effects of crisaborole which was compared to a less irritating vehicle. Given the uncertainties, we cannot come to firm conclusions about the relative efficacy of crisaborole and pimecrolimus. Pimecrolimus appears to be less effective than tacrolimus or moderate potency topical corticosteroids.[41]

Table 13. Pimecrolimus: IGA Response Rates across Trials

Trial	IGA 0 or 1	
	Pimecrolimus	Vehicle
Ho 2003	53	17
Eichenfield 2002	31	12

Table 14. Crisaborole: IGA Response Risk Ratio

Treatment	IGA 0/1
Crisaborole vs. placebo	1.57 (0.27-3.98)
Pimecrolimus vs. placebo	2.59 (0.98-4.44)
Crisaborole vs. pimecrolimus	0.61 (0.10-2.28)

Harms

Severe or serious adverse events were rare in all three clinical trials of crisaborole.

The most common adverse events (AEs) with crisaborole at four weeks were application site pain, application site pruritus, and fever. Rates of serious AEs and discontinuation due to AEs were comparable between crisaborole and placebo, except that application site pain was higher with crisaborole.

AEs that occurred in ≥ 5% of patients in any treatment group, as well as specific AEs of interest, are shown as trial-weighted averages in Table 15. Most adverse events were mild or moderate. Severe or serious adverse events, and AEs leading to discontinuation were rare and comparable between the treatment and placebo groups.

Table 15. Crisaborole: Harms at Four Weeks

	SAEs ≥ 1[11,63] (%)	Discontinuation due to AE[11,63] (%)	Treatment-related AEs				
			Application site pain[11,63] (%)	General disorders and administration site conditions[11] (%)	Infections and infestations[11] (%)	Nasopharyngitis[11] (%)	Upper respiratory tract infection[11] (%)
Crisaborole	0	1.2	4.6	7.4	11.7	1.8	3.0
Vehicle	0	1.1	1.7	5	11.8	1.2	3.0

SAE: serious adverse event, AE: adverse event.

Controversies and Uncertainties

We have no head-to-head trials comparing crisaborole with the other topical agents (corticosteroids and calcineurin inhibitors) that would typically be used in patients with mild-to-moderate atopic dermatitis. There is substantial uncertainty as to the relative efficacy of crisaborole. It is uncertain from the available evidence whether the patients who received crisaborole in the clinical trials had had an inadequate response to existing pharmacologic and non-pharmacologic therapies for atopic dermatitis.

There was a high response to the control arm (emollient vehicle) in the crisaborole trials. We heard from experts that this response was greater than that seen in placebo arms of most trials of topicals and may reflect that comparator preparations in some older trials included compounds that could be irritating and induce dermatitis. This would make the relative benefits of the active therapies in those older trials appear greater than they really were.

The main evidence on crisaborole comes from trials that randomized a total of 1016 patients to crisaborole therapy for 28 days. Although crisaborole was well tolerated over this period of time, it is difficult to assess its safety compared with the other topical agents. We have heard from experts

and patient groups that concerns about the safety of the other topical agents may be greater than is warranted, and in the absence of longer trials and/or head-to-head trials, as with relative efficacy, the relative safety of crisaborole is uncertain.

Summary

- Our review found inadequate evidence to assess the relative efficacy of crisaborole compared with the other topic therapies for atopic dermatitis, topical calcineurin inhibitors and topical corticosteroids.
- Crisaborole seems to cause less application site burning/pain than topical calcineurin inhibitors and skin changes seen with topical corticosteroids were not seen in 4-week trials of crisaborole. The safety of crisaborole used for longer periods is uncertain.
- For patients with mild-to-moderate atopic dermatitis, we have inadequate evidence on both the relative efficacy and the relative safety of crisaborole compared to other treatment options ("I").

5. Other Benefits or Disadvantages

Our reviews seek to provide information on other benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness.

1. *Unmeasured patient health benefits:* Trials of dupilumab captured the major health benefits, including psychologic and quality of life benefits, expected from a treatment for atopic dermatitis; although, pain was not assessed as an outcome. Although the overall benefit to quality of life of treating patients with dupilumab who also have other atopic diseases such as asthma and nasal polyposis should have been captured in our analyses, cost offsets, if any, from possibly stopping expensive therapies (e.g., omalizumab) for these conditions would not have been captured. We received expert input that at least some patients treated with dupilumab are able to discontinue such therapies.

Patients with uncontrolled atopic dermatitis may be treated with repeated courses of systemic corticosteroids, and the harms of such treatments may occur over many years. The models we performed relied on health outcomes typically over one year or less. As such, if treatment with dupilumab reduces the use of systemic corticosteroids, our models may not have full captured the longer-term benefits of avoiding corticosteroid side effects. Short-term benefits of avoiding systemic corticosteroids should have been captured in the models.

2. *Relative complexity of the treatment regimen that is likely or demonstrated to significantly affect adherence and outcomes:* Dupilumab is an injection given every two weeks. As such, administration is potentially far less time-consuming than topical therapies, but potentially more burdensome for patients bothered by injections. Lab monitoring is not required with dupilumab, which spares patients the need for blood tests needed with other systemic therapies. Crisaborole is a topical treatment with burdens similar to those of other topical therapies that would be used as alternatives.

3. *Impact on productivity and ability of the patient to contribute to personal and national economic activity:* Trials of dupilumab did not assess effects on productivity; however, there is reason to believe that for some patients with severe atopic dermatitis, dupilumab may reduce missed time from work and/or increase productive time at work. Trials of crisaborole also did not assess effects on productivity, but crisaborole is used in patients with mild-to-moderate atopic dermatitis where productivity effects are likely to be less pronounced.

4. *Impact on caregiver burden:* Dupilumab is being assessed in this report as a treatment for adults, and there is relatively low caregiver burden for adult patients with atopic dermatitis; however, atopic dermatitis can be quite disruptive of sleep for spouses/partners. Crisaborole is used in children; however, the burden of administration is similar to other topicals, and there is little reason to believe that crisaborole is more effective than other topical therapies, so parental caregivers would be expected to have similar burdens related to caring for ill children as with other topical treatments.

5. *Impact on public health:* Atopic dermatitis is a risk factor for skin carriage of antibiotic resistant organisms such as methicillin-resistant staphylococcus aureus (MRSA).[64-66]

6. *New mechanism of action that is likely to help patients who have not responded to other treatments*: Dupilumab has a new mechanism of action and is likely to help patients who have not responded to existing therapies. However, these benefits have generally been captured in the clinical trials and our analyses. Crisaborole also has a new mechanism of action; however, it is unclear how frequently it is efficacious in patients who have failed other topical therapies.

7. *Severity of the untreated condition:* Many patients with atopic dermatitis have a mild illness. However, a portion of patients have moderate-to-severe disease, and the most severe patients have substantial decrements in quality of life and a condition that affects all aspects of their lives.

8. *Lifetime burden of illness:* Many children experience resolution of atopic dermatitis as they grow into adolescence and adulthood; however, those with poorly controlled moderate-to-severe disease are more likely to have persistent, lifelong atopic dermatitis. The initial target group for dupilumab, adults with moderate-to-severe atopic dermatitis, have a substantial burden of illness that typically waxes and wanes over a lifetime.

9. *Lack of availability of any previous treatment for the condition:* Systemic treatments other than dupilumab exist for moderate-to-severe atopic dermatitis; however, data are relatively limited on the safety and efficacy of these treatments, and only systemic corticosteroids are approved by the FDA for this indication. This, and concerns about toxicity, may account for only a minority of patients with moderate-to-severe atopic dermatitis being offered systemic treatments. Mild-to-moderate atopic dermatitis has existing therapies other than crisaborole.

10. *Other ethical, legal, or social considerations that might strongly influence the overall value of an intervention to patients, families, and caregivers, the health system, or society:* Children and adults with atopic dermatitis can experience substantial interpersonal burdens, including problems with bullying in children and problems with intimacy in adults.

6. Economic Analyses

6.1 Long-Term Cost-Effectiveness

Overview

The primary aim of this analysis was to estimate the cost-effectiveness of dupilumab for moderate-to-severe atopic dermatitis compared to usual care over a lifetime horizon. For this analysis, usual care was assumed to include emollients, but did not include phototherapy or systemic immunomodulatory agents. The model was developed *de novo* for this analysis, using Microsoft Excel. Given the target population of moderate-to-severe atopic dermatitis, as well as data availability challenges and anticipated clinical uptake, we decided to only model dupilumab rather than crisaborole, phototherapy or cyclosporine.

The model estimated the average length of time that a patient spends in health states defined by levels of response from baseline when administered treatments for atopic dermatitis. Time spent in each health state was weighted using quality of life (QoL) measures and summed over a patient's remaining lifetime to provide estimates of the quality-adjusted life expectancy. We assumed that treatment for atopic dermatitis has no impact on mortality.

Model outcomes of interest include:

- Quality-adjusted life-years (QALYs)
- Dupilumab costs
- Total costs
- Costs per additional QALY for dupilumab versus usual care

Cost-Effectiveness Model: Methods

Model Structure

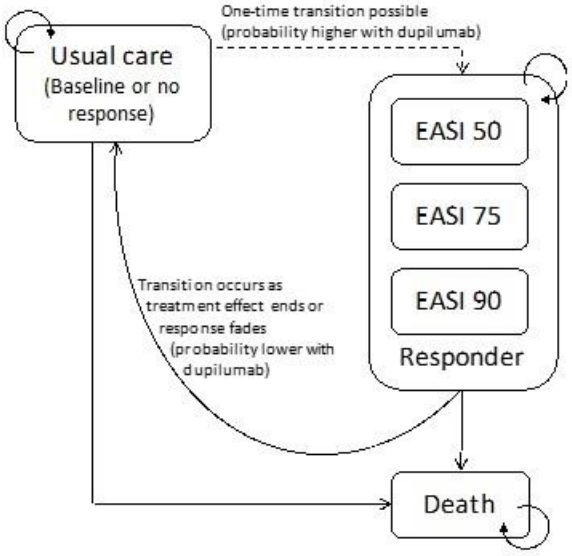
We developed a Markov model with health states based on treatment response. Treatment response was measured by the Eczema Area and Severity Index (EASI) score.[67] The EASI evaluates four anatomical regions for extent and severity of disease signs. We used EASI categories rather than IGA scores to provide inputs for modeling quality of life outcomes with dupilumab therapy, because it is a commonly used measure of clinical response. In addition, we have estimates of utilities for the achieved EASI states but no similar estimates for IGA scores.

Health states were categorized by the percent decrease in EASI score after a patient began an intervention (either dupilumab or usual care): a 50% decrease (EASI 50), a 75% decrease (EASI 75), a 90% decrease (EASI 90), or no response. All patients entered the model in the non-responder state, and could then transition to responder states one cycle after beginning treatment (Figure 3). In subsequent cycles, patients could transition from any responder state to the non-responder state,

and from any state to death. Patients could not transition between EASI 50, 75, and 90 responder categories.

Utility values representing patients' quality of life and costs were applied to each health state. Additionally, utility decrements and associated costs were applied per cycle for therapy-related adverse events. Outcomes were dependent on time spent in each health state in the model, dupilumab treatment, and adverse events. For dupilumab, total drug costs included acquisition costs and any relevant administration and monitoring costs.

Figure 3. Markov Model Structure



Target Population

The aim of this model was to evaluate a population with atopic dermatitis who had failed topical therapy. Therefore, the population for this analysis mirrored clinical trial populations of adults ages 18 years and older, in the United States, with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy, or for whom topical therapies were medically inadvisable. The modeled population had a mean age of 38 years and was 53% male.[19] The baseline patient population consisted of 53% with moderate disease (IGA3) and the remaining 47% with severe disease (IGA4).[68] Values for treatment effectiveness and quality of life utility value were different for moderate and severe patients. The overall moderate-to-severe atopic dermatitis population was modeled as a combination of the two severity levels. We additionally performed subgroup analyses focusing on only severe and only moderate patients. The model does not explicitly evaluate patients with common comorbidities such as asthma, with different levels of adherence to emollients, or with varying atopic dermatitis complications such as skin infections. However, the trial populations upon which the model and clinical inputs were derived included these patients; therefore, the effects of dupilumab treatment on these patients is captured at the population level.

Treatment Strategies

The interventions assessed in this model were dupilumab (300 mg dosed every two weeks after a 600-mg loading dose) and usual care with emollients, which was assumed to be the same for moderate and severe patients.

Key Model Choices and Assumptions

The model used a US health system perspective (i.e., focus on direct medical care costs only) with a 3% discount rate for costs and health outcomes, 4-month cycles, and a lifetime time horizon. Costs are presented in 2017 U.S. dollars. The model was informed by several assumptions, which are listed in Table 16, along with the rationale for each assumption.

Table 16. Key Model Assumptions

Assumption	Rationale
Patients who transitioned to response states did so after one cycle.	Patients may not respond to treatment immediately, therefore any patients entering a response state did so after one cycle.
Patients did not change EASI 50, 75, and 90 response levels after the initial response while on treatment.	There are limited data on sustained changes between response levels.
Costs and QoL for each responder category represented the weighted average effects for patients with moderate and severe disease at baseline.	This reflects an assumption that the proportion of moderate and severe patients within the modeled atopic dermatitis population treated with dupilumab is similar to that in clinical trials.
The utility and costs in the no response health state were equivalent for patients who never had a response and for those who transitioned back to the no response state after an initial response.	There is limited evidence that treatment for atopic dermatitis alters the course of the condition after treatment has ceased.
The discontinuation rate from dupilumab was constant over time, and was equivalent for all the responder categories.	There is limited evidence supporting differential discontinuation by response level or over time. We expect the three responder categories to have similar QoL and therefore likely similar discontinuation.
Patients on usual care who were responders transitioned to non-response at a rate equivalent to recurrence rate for usual care populations in trials.	We expect usual care patients to have very short durations of response, and therefore transition back to the no response state at a high rate.
Atopic dermatitis disease and treatments do not affect mortality.	There is limited evidence suggesting any effect on mortality.

Clinical Inputs

Clinical Probabilities

Treatment effectiveness was included in the model via the probability of entering the EASI 50, EASI 75, and EASI 90 states after initiating treatment (Tables 5 and 6).

Patients who responded to dupilumab transitioned from all three responder health states back to the non-responder state as they discontinued dupilumab, at a rate of 6.3% annually.[47] Patients on

usual care who were responders transitioned to the non-responder state at a rate of 65.8% every 16 weeks based on the recurrence rate in the trials.[69]

Patients transitioned to death according to U.S. age-dependent general population mortality rates weighed by gender.[70] Treatment was assumed to have no effect on mortality.

Utilities

Utility values representing patients' quality of life at baseline or with no response and in responder categories are shown in Table 17. These utility values were collected in the dupilumab clinical trials using the EQ-5D. Utilities were collected at baseline and 16 weeks for three clinical trials. Combined results were used for the values in Table 17. Baseline utilities were consistent across the three trials. These baseline utilities are in line with other estimates for moderate and severe atopic dermatitis, with examples ranging from 0.584 to 0.807 for moderate[42-46] and 0.421 to 0.697 for severe.[42,43,45,46] The utility values include patients with comorbidities such as asthma and skin infection, therefore the effects of these factors are included in the health outcomes for the model.

Table 17. Utility Values for Responder States

Baseline severity	Utility Value				Source
	Baseline/ no response	EASI 50	EASI 75	EASI 90	
Moderate	0.684	0.892	0.893	0.907	Sanofi-Regeneron[47]
Severe	0.535	0.882	0.890	0.911	Sanofi-Regeneron[47]

Adverse Events

We included adverse events for patients treated with dupilumab and usual care as defined in Table 18. We applied a per cycle disutility and cost based on the observed AE rates.

Table 18. Included Adverse Events

Adverse Event	Rate: Dupilumab[47]	Rate: Usual care[47]	Cost[47]	Disutility
Injection site reaction, One-time	11.0%	--	$108.13	0.004[71]
Allergic conjunctivitis, Per cycle	3.0%	0.9%	$73.40	0.03[72] *(rhinoconjunctivitis)*
Infectious conjunctivitis, Per cycle	4.3%	0.7%	$138.82	0.03[72] *(rhinoconjunctivitis)*

Economic Inputs

Drug Costs

We applied an annual list price for dupilumab of $37,000 for 300 mg dosed every two weeks after a 600-mg loading dose. The manufacturer informed ICER that the average net price in the US market will be no more than $31,000.[47] We present results here using the list price and that estimated net price. Our base case analysis presents results for both the list and net prices. We assumed compliance of 95.2% in the first cycle and 98.6% thereafter based on the observed compliance in the clinical trials.[47] We also applied a cost of $20 for one-time self-injection training (CPT 992110).[73]

Other Healthcare Costs

An annual cost of care was applied for all patients on either dupilumab or usual care. This cost included all direct costs of care, such as doctor visits, specialist visits, and hospitalizations. These costs were based on an analysis of Truven Health Marketscan® Commercial Claims and Encounters database during 2013 for patients with a diagnosis of atopic dermatitis. Though we did not link costs to specific health events or outcomes, in general these costs would include all costs of care for atopic dermatitis patients, including costs from non-adherence, or from treating infections or comorbidities such as asthma. Therefore, costs attributable to these underlying factors would be captured in the healthcare costs for the dupilumab and usual care groups.

The non-responder/usual care health state had a baseline annual cost of $11,630 (standard error $683), based on the annual cost for patients with atopic dermatitis treated with phototherapy or who were prescribed any systemic immunomodulatory medications used for this disease (i.e., prednisone, cyclosporine, methotrexate, azathioprine or mycophenolate) minus prescription drug costs.[47] Responder categories had a lower annual cost of $7,346 (standard error $25,187), based on the annual cost (minus prescription drug costs) for patients with atopic dermatitis who did not have phototherapy or systemic immunomodulatory medications.[47]

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We used normal distributions for age, gender, severity, utilization costs, and WAC; beta distributions for utilities, initial transitions, probabilities, and rates; and gamma distributions for other healthcare costs. Additionally, we performed a threshold analysis by systematically altering the price of dupilumab to estimate the maximum prices that would correspond to given willingness to pay (WTP) thresholds.

Model Validation

We used several approaches to validate the model. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these

groups, we refined data inputs used in the model. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. Finally, we compared results to other cost-effectiveness models in atopic dermatitis.

Cost-Effectiveness Model: Results

Base Case Results

In the base case analysis, the average total lifetime cost for patients treated with dupilumab was $509,600 using the list price for the drug and $466,200 using the net price for the drug. This included dupilumab drug costs of $267,800 or $224,400, respectively (accounting for discontinuation). Patients treated with dupilumab also accumulated a total of approximately $241,800 in other healthcare costs related to atopic dermatitis. Patients with atopic dermatitis treated with usual care had an average total lifetime cost of $271,500 (Table 19). Dupilumab provided an additional 1.91 QALYs over the remaining lifetime of patients, leading to an incremental cost-effectiveness ratio of approximately $124,500 per additional QALY gained using the list price for the drug, and $101,800 per additional QALY gained using the net price for the drug.

Table 19. Base Case Results

	Usual Care	Dupilumab	Incremental*
Results Using the List Price for Dupilumab			
Total Costs	$271,461	$509,593	$238,132
Drug Costs	--	$267,797	$267,797
Other Healthcare Costs	$271,461	$241,796	-$29,665
QALYs	14.37	16.28	1.91
Cost per Additional QALY	--	--	$124,541
Results Using the Net Price for Dupilumab			
Total Costs	$271,461	$466,168	$194,708
Drug Costs	--	$224,372	$224,372
Other Healthcare Costs	$271,461	$241,796	-$29,665
QALYs	14.37	16.28	1.91
Cost per Additional QALY	--	--	$101,830

*Inconsistencies are due to rounding error

As a subgroup analysis, we examined results for moderate and severe patients separately (Table 20). Patients with moderate disease had slightly lower healthcare costs but higher drug costs compared to the total population. Patients with moderate disease also gained fewer QALYs with dupilumab treatment compared with severe patients. Patients with severe disease had slightly

higher healthcare costs but lower drug costs compared to the total population. The resulting ICERs were $160,000 for patients with moderate atopic dermatitis and $95,800 for patients with severe disease if we use the list price for the drug, and $130,800 for patients with moderate atopic dermatitis and $78,300 for patients with severe disease if we use the net price for the drug.

Table 20. Results for Moderate and Severe Patients

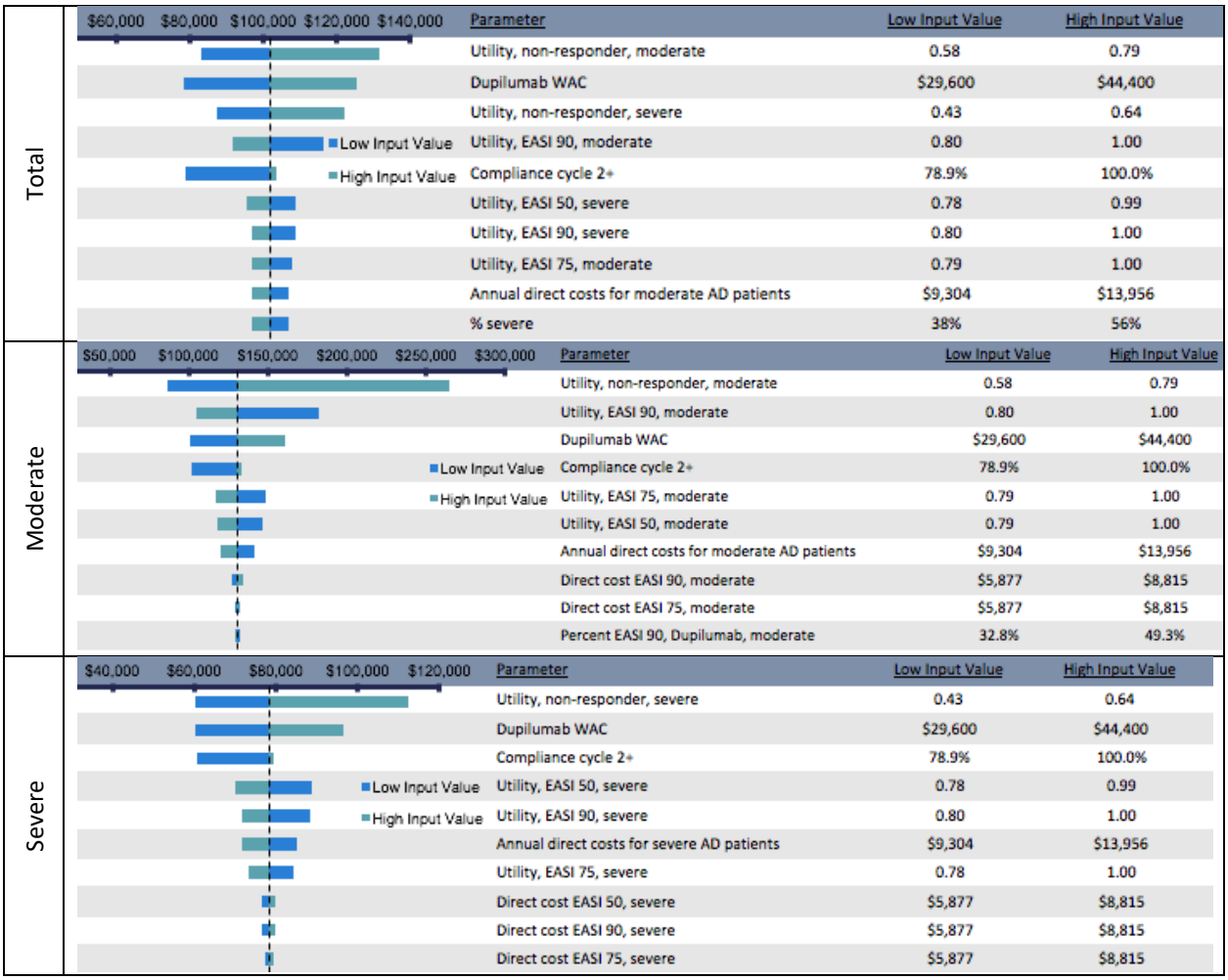
	Moderate			Severe		
	Usual Care	Dupilumab	Incremental*	Usual Care	Dupilumab	Incremental*
Results Using the List Price for Dupilumab						
Total Costs	$271,356	$530,044	$258,688	$271,579	$486,532	$214,953
Drug Costs	--	$290,969	$290,969	--	$241,668	$241,668
Other Healthcare Costs	$271,356	$239,075	-$32,281	$271,579	$244,864	-$26,715
QALYs	16.00	17.62	1.62	12.52	14.77	2.24
Cost per Additional QALY	--	--	$159,988	--	--	$95,751
Results Using the Net Price for Dupilumab						
Total Costs	$271,356	$482,861	$211,506	$271,579	$447,344	$175,765
Drug Costs	--	$243,786	$243,786	--	$202,480	$202,480
Other Healthcare Costs	$271,356	$239,075	-$32,281	$271,579	$244,864	-$26,715
QALYs	16.00	17.62	1.62	12.52	14.77	2.24
Cost per Additional QALY	--	--	$130,807	--	--	$78,295

*Inconsistencies are due to rounding error

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate changes in cost per addition QALY for dupilumab compared to usual care. Results for the base case population (total, moderate, and severe) are shown in Figure 4. Key drivers of the model were utility values for quality of life, particularly for on-responders, and the price of dupilumab. For the moderate population, the utility value for non-responders was the biggest driver, followed by utility for EASI 50 and the dupilumab price. For the severe population, the first key driver was the same, utility for non-responders, but the second driver was the dupilumab price, followed by utility for EASI 50.

Figure 4. One-Way Sensitivity Analysis: Cost per Additional QALY for Dupilumab Compared to Usual Care for the Total, Moderate, and Severe Atopic Dermatitis Populations



Parameter	Low Input Value	High Input Value
Utility, non-responder, moderate	0.58	0.79
Dupilumab WAC	$29,600	$44,400
Utility, non-responder, severe	0.43	0.64
Utility, EASI 90, moderate	0.80	1.00
Compliance cycle 2+	78.9%	100.0%
Utility, EASI 50, severe	0.78	0.99
Utility, EASI 90, severe	0.80	1.00
Utility, EASI 75, moderate	0.79	1.00
Annual direct costs for moderate AD patients	$9,304	$13,956
% severe	38%	56%

Parameter	Low Input Value	High Input Value
Utility, non-responder, moderate	0.58	0.79
Utility, EASI 90, moderate	0.80	1.00
Dupilumab WAC	$29,600	$44,400
Compliance cycle 2+	78.9%	100.0%
Utility, EASI 75, moderate	0.79	1.00
Utility, EASI 50, moderate	0.79	1.00
Annual direct costs for moderate AD patients	$9,304	$13,956
Direct cost EASI 90, moderate	$5,877	$8,815
Direct cost EASI 75, moderate	$5,877	$8,815
Percent EASI 90, Dupilumab, moderate	32.8%	49.3%

Parameter	Low Input Value	High Input Value
Utility, non-responder, severe	0.43	0.64
Dupilumab WAC	$29,600	$44,400
Compliance cycle 2+	78.9%	100.0%
Utility, EASI 50, severe	0.78	0.99
Utility, EASI 90, severe	0.80	1.00
Annual direct costs for severe AD patients	$9,304	$13,956
Utility, EASI 75, severe	0.78	1.00
Direct cost EASI 50, severe	$5,877	$8,815
Direct cost EASI 90, severe	$5,877	$8,815
Direct cost EASI 75, severe	$5,877	$8,815

The results of the probabilistic sensitivity analysis are shown in Table 21. The 95% credible range for cost per additional QALY for dupilumab compared to usual care for the total population ranged from $49,800 to $247,600. The 95% credible range for the ICER for moderate and severe patients was from $52,800 to $492,000 and from $36,200 to $208,600, respectively. At the $150,000 per QALY threshold, dupilumab had an 88% probability of being cost effective compared to usual care overall, and a 70% and 94% probability for moderate and severe patients, respectively.

Table 21. Results of Probabilistic Sensitivity Analysis for the Total, Moderate, and Severe Atopic Dermatitis Populations

	Dupilumab		Usual Care		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Total						
Total Costs	$466,886	$364,604 - $714,037	$271,334	$238,690 - $303,910	$195,553	$101,073 - $436,399
Total QALYs	16.28	14.43 - 18.14	14.37	12.21 - 16.52	1.91	1.23 - 2.64
ICER	--	--	--	--	$105,764	$49,805 - $247,604
Moderate						
Total Costs	$485,099	$363,682 - $883,929	$271,107	$232,554 - $312,740	$213,993	$103,512 - $612,720
Total QALYs	17.62	15.34 - 19.94	16.00	13.11 - 18.88	1.62	0.64 - 2.68
ICER	--	--	--	--	$129,299	$52,763 - $492,019
Severe						
Total Costs	$446,446	$349,393 - $723,588	$271,605	$233,140 - $313,696	$174,841	$87,420 - $447,697
Total QALYs	14.77	12.59 - 16.97	12.53	9.78 - 15.23	2.25	1.41 - 3.14
ICER	--	--	--	--	$80,772	$36,184 - $208,567

Threshold Analysis Results

The annual net price of dupilumab that would achieve cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY gained was $17,307, $30,516, and $43,726, respectively. Note that the price would have to increase to reach the $150,000 per QALY cost-effectiveness threshold. For moderate patients, the threshold prices to reach $50,000, $100,000, and $150,000 per QALY would be $14,385, $24,665, and $34,946 respectively, compared to $21,275, $38,460, and $55,646, respectively, for severe patients.

Model Validation and Prior Published Evidence on Costs and Cost-Effectiveness

The model demonstrated acceptable face validity during internal and external reviews. The results of the cross validation showed that our model results were similar to other available atopic dermatitis models.

We did not identify any prior, published economic evaluations of dupilumab or crisaborole for treatment of atopic dermatitis. However, we did identify three cost-effectiveness analyses, published since 2010, that examined the cost-effectiveness of other atopic dermatitis treatments. Researchers in Sweden[44] developed a Markov model to examine the cost-effectiveness of maintenance therapy with a barrier-strengthening moisturizing cream (Canoderm®) compared to no treatment after an initial three-week topical corticosteroid course in patients with moderate atopic dermatitis, using efficacy data from a randomized controlled trial. Their analysis used a societal perspective and a one-year time horizon. The model included two health states (eczema free and moderate eczema), with utility weights of 0.5843 for moderate eczema and 0.7960 for eczema free. They found that the estimated incremental cost-effectiveness ratio ranged from €5,479 in Sweden to €26,908 in Denmark.

Healy and colleagues[43] estimated the cost-effectiveness of twice-weekly maintenance treatment with tacrolimus ointment for adults and children with moderate or severe atopic dermatitis compared to a standard of twice-daily reactive treatment of exacerbations, using a UK National Health Service perspective over a 12-month time horizon. Ointment usage and number of treatment days were taken from clinical trial results. QALYs were calculated using utility values of 0.867, 0.807 and 0.697 for controlled, moderate, and severe atopic dermatitis in adults. Their analysis found that the twice-weekly maintenance treatment was more effective and less costly than the standard reactive treatment. Taneja and colleagues[74] examined the cost-effectiveness of tacrolimus 0.1% ointment compared to pimecrolimus 1.0% cream in adults with mild to severe atopic dermatitis, using data on efficacy from a randomized clinical trial. Over a six-week time horizon, patients receiving tacrolimus experienced an average of 4.9 fewer days with active atopic dermatitis than those receiving pimecrolimus. In addition, average costs were lower for patients receiving tacrolimus than for those receiving pimecrolimus ($501 vs. $546, respectively), indicating that tacrolimus dominated pimecrolimus (i.e., was more effective while costing less than) in these patients.

The results from these analyses are not directly comparable to the results of the cost-effectiveness analysis presented in this report, due to the different comparators, shorter time horizons, and different settings evaluated. However, it is interesting to note the range of utility values used in these studies. Values for moderate atopic dermatitis were 0.584 in Hjalte et al. and 0.807 in Healy et al., while the baseline value used in our model (0.684) was intermediate between these two. Healy et al. used a value of 0.697 for severe atopic dermatitis, which was higher than the 0.535 value used in our model (and comparable to the weight, 0.684, we used for moderate disease). These differences may be due to variations in the populations being evaluated, as well as in the methods used to measure quality of life in each study.

6.2 Value-based Benchmark Prices

Our value-based benchmark prices for dupilumab for atopic dermatitis treatment are provided in Table 22. As noted in the initial ICER methods document (http://icer-review.org/wp-content/uploads/2016/02/Value-Assessment-Framework-slides-for-July-29-webinar-FINAL-corrected-8-22-1.pdf), the value-based benchmark price for a drug is defined as the price range that would achieve cost-effectiveness ratios between $100,000 and $150,000 per QALY gained.

The price required to achieve a $100,000 per QALY threshold is approximately equal to our assumed discounted price of $31,000, corresponding to a discount of 18% from WAC. To reach the $150,000 per QALY cost-effectiveness threshold, the annual net price of dupilumab could increase by 18%, to approximately $43,700 per year.

Table 22. Value-based Benchmark Prices for Dupilumab for Atopic Dermatitis Treatment

	Annual WAC	Cost to Achieve $100,000/QALY	Cost to Achieve $150,000/QALY	Discount from WAC to reach WTP threshold
Dupilumab	$37,000	$30,516	$43,726	18% to 118%

6.3 Potential Budget Impact

We used the cost-effectiveness model to estimate the potential total budgetary impact of dupilumab for the treatment of adults ages 18 years and older with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy, or for whom topical therapies are medically inadvisable. We used the announced WAC and discount prices, along with the prices required to achieve cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY, in our estimates of budget impact.

Potential Budget Impact Model: Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to see a more realistic impact on the number of patients treated with the new therapies.

The potential budget impact analysis included the entire candidate population for treatment, which consisted of US adults with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy or for whom topical therapies are medically inadvisable. To estimate the size of the potential candidate population for treatment with dupilumab, we used an estimate of the US prevalence of adults with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies from the Adelphi Real World Atopic Dermatitis Disease Specific Program, a cross-sectional real-world survey that captured data from clinicians and patients, which was reported to be 0.7%.[48] Applying this proportion to the projected 2017 US adult population resulted in an estimate of approximately 1,765,000 patients in the US over a five-year period. Note that this estimate includes all patients with moderate or severe atopic dermatitis. If dupilumab is used only in more severe patients, the number of patients eligible for treatment would be lower. The manufacturer has "estimated that 300,000 are most in need of treatment options."[49]

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated. The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new drug or device to estimate the potential budget impact associated with adding to or displacing use of existing therapies with the new intervention. In this analysis, we compared the net cost associated with dupilumab treatment to that for usual care (assumed to include emollients but not phototherapy or systemic immunomodulatory agents). We tested the potential budget impact of dupilumab at WAC and discounted price points, as well as those that would reach cost-effectiveness thresholds of $50,000 per QALY, $100,000 per QALY, and $150,000 per QALY, compared to usual care.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (http://icer-review.org/wp-content/uploads/2016/02/ICER-Value-Assessment-Proposed-Updates-Webinar-021317.pdf), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 23.

For 2017-18, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $915 million per year for new drugs.

Table 23. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2017 (est.) +1%	3.20%	World Bank, 2016
2	Total health care spending, 2016 ($)	$2.71 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	17.7%	CMS National Health Expenditures (NHE), 2016; Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$479 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.3 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	33.5	FDA, 2016
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$457.5 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$915 million	Calculation

Potential Budget Impact Model: Results

Table 24 illustrates the per-patient budget impact calculations in more detail, based on WAC ($37,000 per year), discounted WAC ($31,000 per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY for dupilumab ($43,726, $30,516, and $17,307 per year, respectively) compared to usual care.

Table 24. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon

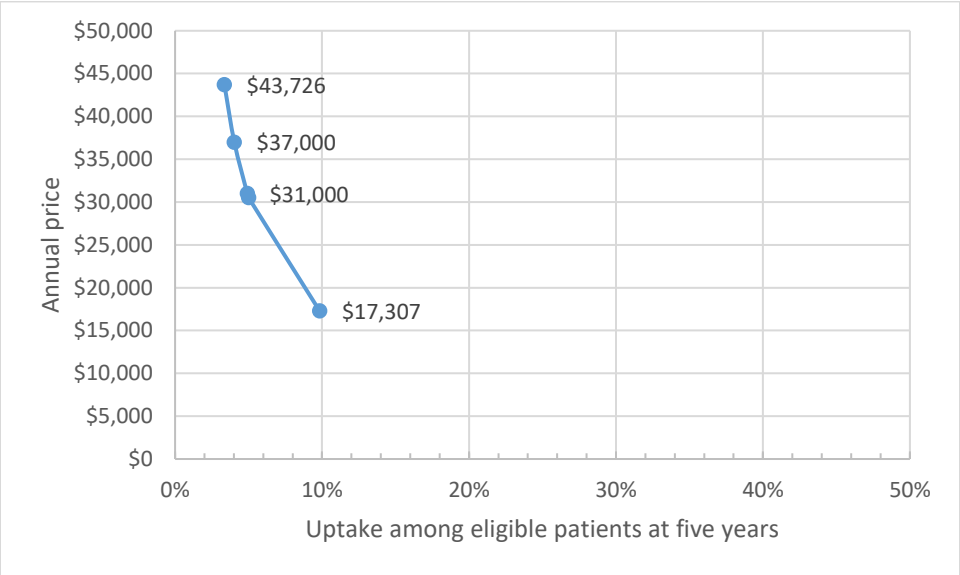
	Average Annual Per Patient Budget Impact				
	WAC	Discounted WAC	$150,000/QALY	$100,000/QALY	$50,000/QALY
Dupilumab	$33,744	$29,752	$38,218	$29,431	$20,643
Usual Care	"	$11,395	"	"	"
Difference	$22,348	$18,357	$26,822	$18,035	$9,248

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

The average potential budgetary impact when using the WAC for dupilumab was an additional per-patient cost of approximately $22,300, and approximately $18,400 using the discounted WAC. Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug ranged from approximately $26,800 per patient using the annual price ($43,726) to achieve $150,000 per QALY to approximately $9,200 using the annual price ($17,307) to achieve a $50,000 per QALY cost-effectiveness threshold.

As shown in Figure 5, approximately 4% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $915 million at WAC ($37,000) and approximately 5% of patients at the discounted WAC ($31,000). Approximately 3% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY threshold price ($43,726/year), while 10% of the population could be treated without crossing the threshold at the $50,000 per QALY threshold price ($17,307/year). The relatively low proportion of the affected population that could be treated at each price point partly reflects the budget impact that a new treatment may have in a therapy area where there are few current treatments. Because dupilumab is not displacing current drug treatments for moderate-to-severe atopic dermatitis, there are fewer offsetting treatment costs for these patients.

Figure 5. Budgetary Impact of Dupilumab in Atopic Dermatitis Patients



6.4 Summary and Comment: Long-Term Cost Effectiveness and Potential Budget Impact

We estimated the cost-effectiveness of dupilumab versus usual care over a lifetime time horizon for adult patients with moderate-to-severe atopic dermatitis. Compared to usual care, the cost per additional QALY for dupilumab was estimated to be approximately $101,800. The cost per additional QALY was lower for patients with severe atopic dermatitis ($78,300) than those with moderate atopic dermatitis ($130,800).

Results from our potential budget impact analysis suggest that the average potential budgetary impact over five years at the WAC price for dupilumab was an additional per-patient cost of approximately $22,300. At the discounted WAC price of $31,000, the average per-patient cost was approximately $18,400. Our analysis estimated that approximately 4% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $915 million at WAC ($37,000) and approximately 5% of patients at the discounted WAC ($31,000). Approximately 3% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY threshold price, while 10% of the population could be treated without crossing that threshold at the $50,000 per QALY threshold price.

There were several key limitations of our analysis. First, there are limited data for health outcomes for patients with atopic dermatitis over long periods of time. We assumed patients did not switch between EASI 50, EASI 75, and EASI 90 responder categories. Second, there are limited data on costs of atopic dermatitis, particularly stratified by severity. Finally, atopic dermatitis is a heterogeneous condition and patients experience a wide range of symptoms and severities.

Conclusions

In summary, our economic modeling analysis indicates that dupilumab improves health outcomes compared to usual care, but with additional costs. At the discounted price of dupilumab used in this draft report, the incremental cost-effectiveness ratio was at or below commonly cited thresholds for cost-effectiveness. Dupilumab was projected to be more cost-effective in patients with severe atopic dermatitis, but even in patients with moderate atopic dermatitis, the ICER remained below the upper range of commonly cited thresholds.

7. Summary of the Votes and Considerations for Policy

7.1 About the Midwest CEPAC Process

During Midwest CEPAC public meetings, the Midwest CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of the medical technologies or treatments under examination, and the supplementary information presented. Panel members typically serve for two or more years and are intentionally selected to represent a range of expertise and diverse perspectives. To maintain the objectivity of the Midwest CEPAC Panel and ground the conversation in the interpretation of the published evidence, they are not pre-selected based on the topic being addressed. Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to Midwest CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Midwest CEPAC Panel during their deliberation, and they help form recommendations with the Midwest CEPAC Panel on ways the evidence can be applied to policy and practice.

At each meeting, after the Midwest CEPAC Panel votes, a policy roundtable discussion is held with the Midwest CEPAC Panel, clinical experts, and representatives from provider groups, payers, and patient groups. This is intended to bring stakeholders into the discussion on how best to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the May 25, 2017 meeting, the Midwest CEPAC Panel discussed issues regarding the application of the available evidence to help patients, providers, and payers address the important questions related to the treatment of atopic dermatitis. Following the evidence presentation and public comments (public comments from the meeting can be accessed here, starting at 01:35:00), the Midwest CEPAC Panel voted on key questions concerning the comparative clinical effectiveness and comparative value of treatment options for atopic dermatitis. These questions are developed by the ICER research team for each assessment, with input from the Midwest CEPAC Advisory Board to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with comments reflecting considerations mentioned by Midwest CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the Midwest CEPAC Panel made use of a value assessment framework with four different components of long term value for money, a concept which represents the long-term perspective, at the individual patient level, on patient benefits and the incremental costs to achieve those benefits. The four components of long term value for money are comparative clinical effectiveness, incremental cost per outcomes achieved, other

benefits or disadvantages, and contextual considerations regarding the illness or therapy. These four components are defined below.

1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. The Midwest CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

2. Estimated incremental cost-effectiveness is the average per-patient incremental cost of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, ICER follows common academic and World Health Organization (WHO) standards by using cost per quality-adjusted life years (QALYs) and adopting thresholds at $100,000 per QALY and $150,000 per QALY as guides to reasonable ratios for cost-effectiveness.

3. Other benefits or disadvantages refers to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether other benefits or disadvantages such as these are important enough to factor into the overall judgment of care value. There is no quantitative measure for other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether the condition affects priority populations. There is no quantitative measure for contextual considerations.

7.2 Voting Results

1. In patients with mild-to-moderate atopic dermatitis, is the evidence adequate to demonstrate that the net health benefit of treatment with crisaborole is greater than that of treatment with topical corticosteroids or topical calcineurin inhibitors?

Yes: 2 votes	***No: 9 votes***

Comments: CEPAC members cited the limitations of the evidence, such as the lack of head-to-head data and lack of long term data, as reasons for their "no" votes.

2. In adults with moderate-to-severe atopic dermatitis who have failed topical therapy, is the evidence adequate to demonstrate that treatment with dupilumab provides additional net health benefits beyond continued non-pharmacologic treatments such as emollients?

Yes: 11 votes	*No: 0 votes*

3. In adults with moderate-to-severe atopic dermatitis who have failed topical therapy, is the evidence adequate to demonstrate that the net health benefit of treatment with dupilumab is greater than that of treatment with cyclosporine?

Yes: 10 votes	*No: 1 votes*

Comments: The CEPAC member who voted "no" shared that the comparative evidence was not adequate, particularly the lack of head-to-head data.

4. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, in a mixed population of adults with moderate-to-severe atopic dermatitis who have failed topical therapy, what is the long-term value for money of dupilumab compared with no systemic treatment?

Low: 0 votes	***Intermediate: 8 votes***	*High: 3 votes*

Comments: One of the CEPAC members who voted "high" noted that he gave weight to the significant other benefits that dupilumab provided to patients and caregivers (such as improved productivity and decreased burdens of care).

5. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, in adults with moderate atopic dermatitis who have failed topical therapy, what is the long-term value for money of dupilumab compared with no systemic treatment?

Low: 0 votes	***Intermediate: 9 votes***	*High: 2 votes*

Comments: One Midwest CEPAC voted "high," noting that the distinction between moderate and severe disease is so fluid and undefined.

6. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, in adults with severe atopic dermatitis who have failed topical therapy, what is the long-term value for money of dupilumab compared with no systemic treatment?

Low: 0 votes	*Intermediate: 0 votes*	***High: 11 votes***

7.3 Roundtable Discussion and Key Policy Implications

The Midwest CEPAC engaged in a moderated discussion about how best to apply evidence on dupilumab and crisaborole for atopic dermatitis in policy and practice. The roundtable included two clinical experts, two patients, two payers, and a manufacturer representative. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below.

Table 25. Policy Roundtable Participants

Policy Roundtable	
Debbie Byrnes Patient	**David Meeker, MD** Sanofi-Genzyme
Meg Duguid Patient	**Elaine Siegfried, MD** St. Louis University
Marsha Fisher, MD Anthem Blue Cross Blue Shield Missouri	**Jonathan Silverberg, MD** Northwestern University
Jeremy Fredell Express Scripts	

Payers and Pharmacy Benefits Managers

Even if the price of dupilumab is aligned with value, the broad range of severity of atopic dermatitis, limited long-term data on dupilumab's efficacy and appropriate use, and issues with affordability will lead payers to design evidence-based pre-authorization coverage criteria. As discussed during the policy roundtable, such criteria are likely to take the following into account:

Clinical Expertise:

Most primary care clinicians are unlikely to have experience prescribing specialty pharmaceuticals, nor are they likely to have had much clinical experience managing patients with atopic dermatitis of the severity in which the clinical benefits of dupilumab were studied. Payers may therefore consider requiring that dupilumab be prescribed only by a specialist so as to ensure that a correct diagnosis has been made, and that there has been an appropriate trial of optimal topical therapy prior to treatment with dupilumab.

Severity and Trials of Other Treatment Options:

As there is no consensus on how to define moderate-to-severe atopic dermatitis, many payers are likely to leave this term undefined in coverage criteria. Since the severity of atopic dermatitis can vary substantially over time and, from a patient's perspective, can be a complex combination of intensity of itch, location, expansiveness, and underlying skin integrity, payers that do consider creating a more specific definition of the level of severity as part of coverage policy should consider accepting the maximum severity of disease across multiple severity measures.

In addition to or in lieu of a definition of severity, payers are likely to require that patients receive an adequate trial of topical therapy prior to coverage for treatment with dupilumab. We heard from payer representatives that inadequate response to one month of an appropriate topical treatment (such as a moderate potency corticosteroid or tacrolimus 0.1%) would be a reasonable definition of an adequate trial of other treatments.

Notably, the MW CEPAC voted that current evidence is adequate to demonstrate greater net health benefit with dupilumab than cyclosporine, largely on the basis of documented side effects with cyclosporine. The clinical experts present stated that given safety concerns with existing systemic therapies for atopic dermatitis and the potential for greater response to dupilumab, they did not feel it was clinically appropriate to require that patients be treated with cyclosporine or other systemic therapies prior to gaining coverage for dupilumab.

Stopping rules:

Given the expense of dupilumab it is not unreasonable for payers to work with clinical experts and patient groups to design coverage criteria that require some measure of success for continuation of coverage past a certain number of months. However, patients may derive substantial benefits from dupilumab even when they do not meet criteria for success that were used as endpoints in randomized trials (such as EASI 75). Clinical experts suggested that achieving EASI 50 would be a more appropriate measure, but also noted that some patients who do not initially meet that measure continue to improve over time. As such, payers will want to involve the patient and the

treating provider in assessing the patient's level of response over at least several months of treatment as part of determining whether treatment should be stopped.

For patients who have a very successful response to treatment with dupilumab the question may arise as to whether treatment should be halted or tapered after some period of time to see if continued treatment is necessary. However, there is currently little evidence or clinical experience with managing treatment with dupilumab over the long term. We heard from expert clinicians that they believed trials of interrupting therapy might place patients at risk for a re-emergence of atopic dermatitis that would be less amenable to treatment, but that trials of tapering therapy would be reasonable to help inform future care.

Use in children:

Trials to evaluate the net health benefits of dupilumab in children are ongoing and results will likely not be available for several years. In the interim, health plans will have exception processes and should make sure that clinicians assessing exceptions are expert in the risks and benefits of this therapy as well as the spectrum of atopic dermatitis, given that many clinicians will not have seen severe disease.

Researchers, Clinicians, Manufacturers, and Patient Groups

Promote standardized measures of severity and of outcomes

We heard from expert clinicians that there are no standard definitions of severity of disease in atopic dermatitis, and that many different measures are used to assess outcomes in clinical trials, which makes it difficult to compare trial outcomes across therapies and over time. We also heard from patient advocacy groups that measures used in clinical trials do not always measure what is most important to patients and families. Patient groups should take a leading role in collaborative efforts to define a core set of severity and outcome measures and promoting their use in all clinical trials.

Specialty Societies

Educate your members in the appropriate use of new medications for atopic dermatitis

We heard from expert clinicians and patients that there were deficiencies in the diagnosis and treatment of atopic dermatitis. As new medications expand therapeutic options, specialty societies should work to ensure that their members understand the appropriate use of these new therapies.

Clinicians and Patient Groups

Communicating potential risks of new treatments

In the setting of appropriate excitement about effective new therapies, patients should be made aware as part of shared decision making of the uncertainties regarding the durability of clinical benefit and the potential risks of all new treatments. Patient organizations could help create materials to communicate this information to patients.

Manufacturers and Researchers

Perform direct comparisons of therapies when appropriate

Multiple stakeholders expressed concerns about the lack of information comparing crisaborole with existing topical treatments, particularly topical tacrolimus. Appropriate head-to-head trials of crisaborole would inform decision making by doctors and patients.

Payers, Pharmacy Benefits Managers, Manufacturers

Access and affordability alert

Although the price for dupilumab is aligned with value, ICER notes that there is an access and affordability alert as estimates from clinical experts and the manufacturer suggest that the number of patients whom clinical experts will desire to treat will result in short-term costs that can create strains on health care budgets. Policymakers, payers, clinical experts, patient groups, and the manufacturer should continue to explore ways that any potential concern about affordability can be managed so that access to this treatment can be maintained in a sustainable manner. As part of this effort, all stakeholders should seek collaborative ways to reduce ineffective and low-value care so that patients can benefit from this important new therapy.

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This is the first Midwest CEPAC review of dupilumab and crisaborole for the treatment of atopic dermatitis.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table A2. Atopic Dermatitis search strategy run on Jan 11,2017

Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials (Ovid)

1	observational study.pt.	26306
2	exp case-control studies/	714934
3	exp cohort studies/	1363044
4	exp cross-over studies/	66861
5	exp matched-pair analysis/	4386
6	multicenter study.pt.	257316
7	1 or 2 or 3 or 4 or 5 or 6	1737237
8	randomized controlled trial.pt.	735147
9	controlled clinical trial.pt.	134161
10	randomized.ab.	556472
11	placebo.ab.	270751
12	drug therapy.fs.	1244365
13	randomly.ab.	326478
14	trial.ab.	484151
15	groups.ab.	1351782
16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	3215161
17	comparative study.pt. or compare.ab,ti. or compares.ab,ti. or compared.ab,ti. or comparing.ab,ti. or comparison.ab,ti. or comparison.ab,ti. or comparative.ab,ti. or effective.ab,ti. or effectiveness.ab,ti. or versus.ab,ti. or vs.ab,ti.	4463550
18	7 and 17	990175
19	16 or 18	3663976
20	exp animals/	11666631
21	humans.sh.	9607372
22	20 not 21	2059259
23	19 not 22	3299754
24	limit 23 to english language	2943956
25	(case reports or comment or congresses or editorial or letter or review).pt.	3404522
26	24 not 25	2391448
27	exp Eczema/ or eczema.mp.	10057
28	exp Dermatitis, Atopic/	11850
29	neurodermatitis.mp. or exp Neurodermatitis/	361
30	exp Dermatitis/ or dermatitis.mp.	56920
31	27 or 28 or 29 or 30	59874
32	dupilumab.mp.	73
33	crisaborole.mp.	7
34	phototherapy.mp.	8466
35	uva.mp.	4949

36	uvb.mp.	6797
37	uva1.mp.	279
38	puva.mp.	2409
39	32 or 33	80
40	31 and 39	47
41	34 or 35 or 36 or 37 or 38	18673
42	31 and 41	1273
43	limit 42 to yr="2012 - 2017"	218
44	"nasal polyps".mp.	4657
45	"nasal polyposis".mp.	1877
46	44 or 45	5126
47	exp asthma/ or asthma.mp.	111598
48	46 or 47	115647
49	40 or 43	264
50	26 and 49	80
51	39 and 48	44
52	50 or 51	112

Cochrane Database of Systematic Reviews (Ovid)

1	eczema.mp.	155
2	neurodermatitis.mp.	17
3	dermatitis.mp.	211
4	'atopic dermatitis'.mp.	61
5	1 or 2 or 3 or 4	303
6	dupilumab.mp.	1
7	crisaborole.mp.	0
8	phototherapy.mp.	133
9	topical$.mp.	902
10	'calcineurin inhibitor$'.mp.	64
11	"uva".mp.	29
12	"uvb".mp.	26
13	"uva1".mp.	1
14	"puva".mp.	27
15	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	1031
16	5 and 15	131

Embase (trials)

1	'eczema'/exp OR eczema	43437

2	'atopic dermatitis'/exp OR 'atopic dermatitis'	37422
3	'neurodermatitis'/exp OR neurodermatitis	3914
4	'dermatitis'/exp OR dermatitis	167368
5	'eczema'/exp OR eczema OR 'atopic dermatitis'/exp OR 'atopic dermatitis' OR 'neurodermatitis'/exp OR neurodermatitis OR 'dermatitis'/exp OR dermatitis	171432
6	dupilumab:ti,ab	83
7	crisaborole:ti,ab	19
8	phototherapy:ti,ab	8572
9	dupilumab:ti,ab OR crisaborole:ti,ab	102
10	'eczema'/exp OR eczema OR 'atopic dermatitis'/exp OR 'atopic dermatitis' OR 'neurodermatitis'/exp OR neurodermatitis OR 'dermatitis'/exp OR dermatitis AND (dupilumab:ti,ab OR crisaborole:ti,ab)	70
11	uva:ti,ab	9048
12	uvb:ti,ab	11049
13	uva1:ti,ab	387
14	puva:ti,ab	4051
15	phototherapy:ti,ab OR uva:ti,ab OR uvb:ti,ab OR uva1:ti,ab OR puva:ti,ab	26596
16	'eczema'/exp OR eczema OR 'atopic dermatitis'/exp OR 'atopic dermatitis' OR 'neurodermatitis'/exp OR neurodermatitis OR 'dermatitis'/exp OR dermatitis AND (phototherapy:ti,ab OR uva:ti,ab OR uvb:ti,ab OR uva1:ti,ab OR puva:ti,ab)	2197
17	'eczema'/exp OR eczema OR 'atopic dermatitis'/exp OR 'atopic dermatitis' OR 'neurodermatitis'/exp OR neurodermatitis OR 'dermatitis'/exp OR dermatitis AND (phototherapy:ti,ab OR uva:ti,ab OR uvb:ti,ab OR uva1:ti,ab OR puva:ti,ab) AND [2012-2017]/py	630
18	'eczema'/exp OR eczema OR 'atopic dermatitis'/exp OR 'atopic dermatitis' OR 'neurodermatitis'/exp OR neurodermatitis OR 'dermatitis'/exp OR dermatitis AND (dupilumab:ti,ab OR crisaborole:ti,ab) OR ('eczema'/exp OR eczema OR 'atopic dermatitis'/exp OR 'atopic dermatitis' OR 'neurodermatitis'/exp OR neurodermatitis OR 'dermatitis'/exp OR dermatitis AND (phototherapy:ti,ab OR uva:ti,ab OR uvb:ti,ab OR uva1:ti,ab OR puva:ti,ab) AND [2012-2017]/py)	698
19	random*:ti OR placebo*:ti OR 'single blind*':ti OR 'double blind*':ti OR 'triple blind*':ab,ti	230413
20	'cohort analysis'/de OR 'cohort analysis'	267025
21	'longitudinal study'/de OR 'longitudinal study'	111437
22	'prospective study'/de OR 'prospective study'	408068
23	'follow-up'/de OR 'follow-up'	1469464
24	'case control study'/de OR 'case control study'	146162
25	'matched-pair analysis'/de OR 'matched-pair analysis'	232273
26	'cross-over study'/de OR 'cross-over study'	52778
27	'cohort*':ti,ab	607980
28	'case* and control*':ti,ab	21736
29	'cohort analysis'/de OR 'cohort analysis' OR 'longitudinal study'/de OR 'longitudinal study' OR 'prospective study'/de OR 'prospective study' OR 'follow-up'/de OR 'follow-up' OR 'case control study'/de OR 'case control study' OR 'matched-pair analysis'/de OR 'matched-pair analysis' OR 'cross-over study'/de OR 'cross-over study' OR 'cohort*':ti,ab OR 'case* and control*':ti,ab	2631363

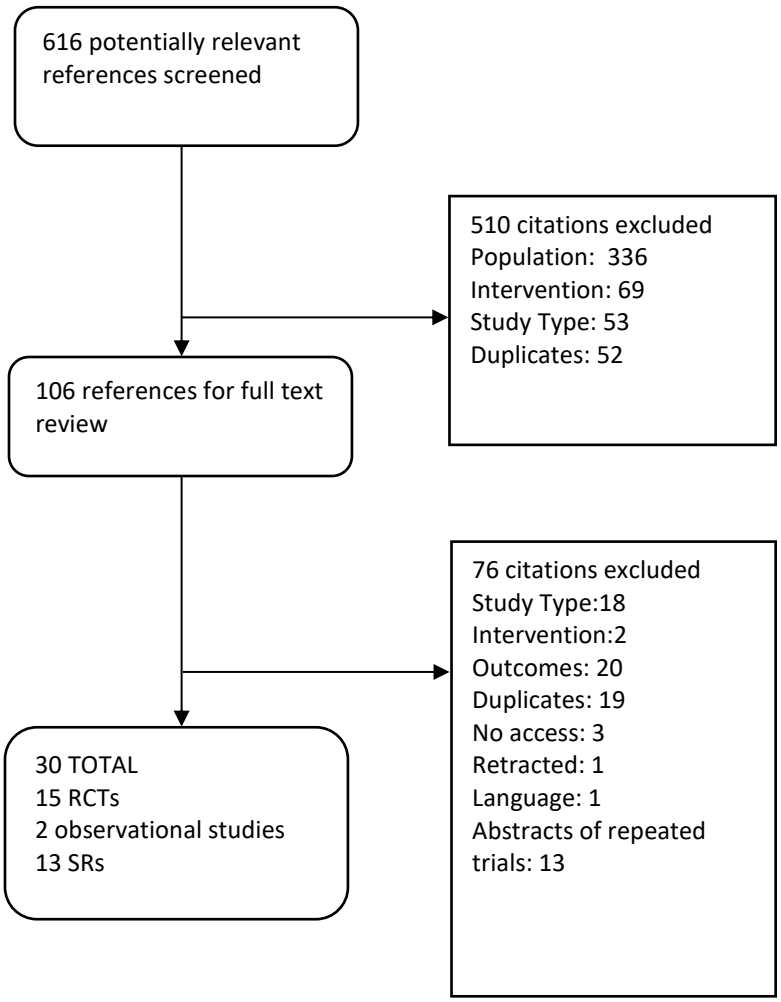
30	'compar*':ti,ab	5632213
31	'effective*':ti,ab	1962911
32	'versus':ti,ab	673974
33	'vs.':ti,ab	948187
34	'compar*':ti,ab OR 'effective*':ti,ab OR 'versus':ti,ab OR 'vs.':ti,ab	7619900
35	'cohort analysis'/de OR 'cohort analysis' OR 'longitudinal study'/de OR 'longitudinal study' OR 'prospective study'/de OR 'prospective study' OR 'follow-up'/de OR 'follow-up' OR 'case control study'/de OR 'case control study' OR 'matched-pair analysis'/de OR 'matched-pair analysis' OR 'cross-over study'/de OR 'cross-over study' OR 'cohort*':ti,ab OR 'case* and control*':ti,ab AND ('compar*':ti,ab OR 'effective*':ti,ab OR 'versus':ti,ab OR 'vs.':ti,ab)	1256865
36	random*:ti OR placebo*:ti OR 'single blind*':ti OR 'double blind*':ti OR 'triple blind*':ab,ti OR ('cohort analysis'/de OR 'cohort analysis' OR 'longitudinal study'/de OR 'longitudinal study' OR 'prospective study'/de OR 'prospective study' OR 'follow-up'/de OR 'follow-up' OR 'case control study'/de OR 'case control study' OR 'matched-pair analysis'/de OR 'matched-pair analysis' OR 'cross-over study'/de OR 'cross-over study' OR 'cohort*':ti,ab OR 'case* and control*':ti,ab AND ('compar*':ti,ab OR 'effective*':ti,ab OR 'versus':ti,ab OR 'vs.':ti,ab))	1425021
37	'eczema'/exp OR eczema OR 'atopic dermatitis'/exp OR 'atopic dermatitis' OR 'neurodermatitis'/exp OR neurodermatitis OR 'dermatitis'/exp OR dermatitis AND (dupilumab:ti,ab OR crisaborole:ti,ab) OR ('eczema'/exp OR eczema OR 'atopic dermatitis'/exp OR 'atopic dermatitis' OR 'neurodermatitis'/exp OR neurodermatitis OR 'dermatitis'/exp OR dermatitis AND (phototherapy:ti,ab OR uva:ti,ab OR uvb:ti,ab OR uva1:ti,ab OR puva:ti,ab) AND [2012-2017]/py) AND (random*:ti OR placebo*:ti OR 'single blind*':ti OR 'double blind*':ti OR 'triple blind*':ab,ti OR ('cohort analysis'/de OR 'cohort analysis' OR 'longitudinal study'/de OR 'longitudinal study' OR 'prospective study'/de OR 'prospective study' OR 'follow-up'/de OR 'follow-up' OR 'case control study'/de OR 'case control study' OR 'matched-pair analysis'/de OR 'matched-pair analysis' OR 'cross-over study'/de OR 'cross-over study' OR 'cohort*':ti,ab OR 'case* and control*':ti,ab AND ('compar*':ti,ab OR 'effective*':ti,ab OR 'versus':ti,ab OR 'vs.':ti,ab)))	66

Embase (systematic reviews)

1	'eczema'/exp OR eczema	43437
2	'atopic dermatitis'/exp OR 'atopic dermatitis'	37422
3	'neurodermatitis'/exp OR neurodermatitis	3914
4	'dermatitis'/exp OR dermatitis	167368
5	'eczema'/exp OR eczema OR 'atopic dermatitis'/exp OR 'atopic dermatitis' OR 'neurodermatitis'/exp OR neurodermatitis OR 'dermatitis'/exp OR dermatitis	171432
6	dupilumab:ti,ab	83
7	crisaborole:ti,ab	19
8	phototherapy:ti,ab	8572
9	'calcineurin inhibitor':ti,ab	4975
10	'steroid':ti,ab	162605
11	'topical':ti,ab	108916
12	uva:ti,ab	9048
13	uvb:ti,ab	11049

14	uva1:ti,ab	387
15	puva:ti,ab	4051
16	dupilumab:ti,ab OR crisaborole:ti,ab OR phototherapy:ti,ab OR 'calcineurin inhibitor':ti,ab OR 'steroid':ti,ab OR 'topical':ti,ab OR uva:ti,ab OR uvb:ti,ab OR uva1:ti,ab OR puva:ti,ab	294432
17	'eczema'/exp OR eczema OR 'atopic dermatitis'/exp OR 'atopic dermatitis' OR 'neurodermatitis'/exp OR neurodermatitis OR 'dermatitis'/exp OR dermatitis AND (dupilumab:ti,ab OR crisaborole:ti,ab OR phototherapy:ti,ab OR 'calcineurin inhibitor':ti,ab OR 'steroid':ti,ab OR 'topical':ti,ab OR uva:ti,ab OR uvb:ti,ab OR uva1:ti,ab OR puva:ti,ab)	15229
18	'eczema'/exp OR eczema OR 'atopic dermatitis'/exp OR 'atopic dermatitis' OR 'neurodermatitis'/exp OR neurodermatitis OR 'dermatitis'/exp OR dermatitis AND (dupilumab:ti,ab OR crisaborole:ti,ab OR phototherapy:ti,ab OR 'calcineurin inhibitor':ti,ab OR 'steroid':ti,ab OR 'topical':ti,ab OR uva:ti,ab OR uvb:ti,ab OR uva1:ti,ab OR puva:ti,ab) AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	252

Figure A1. PRISMA Flow Chart Showing Results of Literature Search for Atopic Dermatitis



Appendix B. Previous Systematic Reviews and Technology Assessments

Previous systematic reviews

Cyclosporine A

Cyclosporine A showed superiority against placebo and equivalence to 0.1% tacrolimus.

Schmitt et al 2007 (2 reviews)

Through 2005, 15 studies including 602 patients met the inclusion criteria. The primary outcome is the mean change in clinical severity from baseline, measured by a composite score including both intensity and extent of AEs. Eight RCTs comparing cyclosporine (CsA) to placebo consistently showed superiority of CsA, while 1 RCT comparing CsA to tacrolimus 0.1% showed equivalence. Among the 12 studies that were homogenous enough to be pooled quantitatively, the mean decrease in clinical severity was 55% (95% CI 48-62%) at week 6-8. Dose-response relationship was examined at 2 weeks after treatment, showing greater decrease in severity for higher-dose CsA (≥ 4 mg/kg, mean change 40%) than lower-dose (≤3 mg/kg, mean change 22%). Change in severity with placebo was not pooled but reported to be a 4% increase in one of the trials.

Phototherapy

Trials have been conducted to compare different types of phototherapy to each other but the evidence was insufficient to compare to placebo or other active treatments. Among all types, NB UV-B and UV-A1 showed the greatest effectiveness.

Perez-Ferriols 2015

Searched through 2013, 21 RCTs (961 patients) were identified. Most trials compared different types of phototherapies to each other, including high-dose (HD) UV-A1, medium-dose (MD) UV-A1, UV-B, UV-A and UV-B combination therapy (UV-AB), NB UV-B, PUVA, excimer laser (EL), full-spectrum-light phototherapy (FSL), and synchronous balneophototherapy (sBPT). Three trials compared phototherapy to other treatments, including cyclosporine, topical pimecrolimus, and topical corticosteroids combined with phototherapy.

Evidence supported the use of NB UV-B and UV-A1 but evidence supporting PUVA was scarce. UV-AB showed favorable results against UV-B. HD UV-A1 combined with fluocortolone was in favor of UV-AB but showed no difference than MD UV-A1. Cold-light UV-A1 dissipates the excessive heat load generated by UV-A1 and showed the most striking decrease in severity. NB UV-B was in favor of UV-A1 and showed no difference compared to PUVA.

Evidence was limited compared to other treatments. No evidence comparing phototherapy to topical corticosteroids. Cyclosporine resulted in more days in remission and was rated higher than UV-AB. NB UV-B showed no difference than 1% pimecrolimus. UV-AB combined with topical corticosteroids reduced phototherapy sessions and dose needed compared to UV-AB alone.

Garritsen 2014

This systematic review had a similar scope to Perez-Ferriols review and searched through 2013. Nineteen RCTs including 905 patients were identified. Conclusions were very similar to those in Perez-Ferriols: NB UV-B and UV-A1 showed the greatest effectiveness and no difference between HD and MD.

Calcineurin Inhibitors

Both tacrolimus and pimecrolimus were shown to be more effective than vehicle. There is some evidence suggesting that tacrolimus was more effective than both high-potency topical corticosteroids and pimecrolimus, while pimecrolimus did not show any difference or prove to be less efficacious than topical corticosteroids.

Broeders 2016

Twelve RCTs that compared calcineurin inhibitors to corticosteroids in 6954 children and adults with atopic dermatitis were included in this review, and meta analyzed. Calcineurin inhibitors had a slightly higher rate of overall improvement of IGA score versus corticosteroids (81% vs. 71%; RR 1.18; 95% CI, 1.04-1.34; p=0.01), but the difference was not large enough to be considered clinically meaningful. Calcineurin inhibitors also had a higher rate of adverse events (74% vs. 64%; RR 1.28; 95% CI 1.05-1.58; p=0.02), including skin burning (30% vs. 9%, p<0.0001) and pruritus (12% vs. 8%, p<0.0001).

Chia 2015

Similarly looking at the comparative effectiveness of topical calcineurin inhibitors versus topical corticosteroids, this review presents comparisons between tacrolimus versus topical corticosteroids, pimecrolimus versus vehicle and topical corticosteroids, as well as tacrolimus versus pimecrolimus. Tacrolimus showed superiority against class I/II/III topical corticosteroids. Pimecrolimus was shown to be superior to vehicle in achieving IGA 0/1, with a RR of 2.03 (95% CI, 1.50-2.74) at 6 weeks. Pimecrolimus was also more effective in terms of improving PGA, pruritus, and QoL. A 12-month trial showed pimecrolimus was less effective than topical corticosteroids on improving IGA, with RRs of 0.52 at 1 week, 0.75 at 3 weeks, 0.89 at 6 months, and 0.92 at 12 months. Similar results were found for PGA and pruritus in other studies. Pimecrolimus showed no difference than 0.03% tacrolimus but was less effective than 0.1% tacrolimus on IGA 0/1 at 3 weeks (RR=0.85) and 6 weeks (RR=0.58).

Martins 2015

This Cochrane review qualitatively reviewed trials comparing tacrolimus to topical corticosteroids and pimecrolimus. Tacrolimus 0.1% was shown to be better than low-potency corticosteroids, pimecrolimus 1%, and tacrolimus 0.03%. Tacrolimus 0.03% was better than mild corticosteroids and pimecrolimus. Outcomes measured included physician's assessment, participant's assessment, EASI, SCORAD, and adverse events.

Sher 2012

A systematic review and meta-analysis of RCTs of topical and systemic therapies focused on antipruritic effect. In total, 52 RCTs were included, 42 for topical treatments and 10 for oral treatment. Evidence were synthesized by drug class, including calcineurin inhibitors, topical corticosteroids, anti-histamines, and others. Among all the topical drug classes, calcineurin inhibitors showed the greatest antipruritic effect versus vehicle (RR 0.64; 95% CI, 0.61-0.68), followed by topical corticosteroids (RR 0.66; 95% CI, 0.58-0.75), and anti-histamines (RR 0.73; 95% CI, 0.65-0.83).

Svensson 2011

A systematic review of 17 trials comparing tacrolimus with topical corticosteroids and found tacrolimus of similar efficacy to topical corticosteroids.

Chen 2010

This review focused on the efficacy and safety of tacrolimus and pimecrolimus in children with atopic dermatitis. Twenty trials were included. ORs of response for tacrolimus were 4.56 (95% CI, 2.80 to 7.44) versus vehicle, 3.92 (95% CI, 2.96 to 5.20) versus hydrocortisone acetate, and 1.58 (95% CI, 1.18 to 2.12) versus 1% pimecrolimus.

Schmitt 2010

This review comparing calcineurin inhibitors with topical corticosteroids as proactive treatment for atopic eczema, with flare prevention being the outcome of interest. Meta-analysis found that topical fluticasone propionate was more effective than tacrolimus in preventing flares (RR 0.46 vs. 0.78).

Systematic reviews prior to 2010

Elbatawy 2009

Both tacrolimus and pimecrolimus were shown to be more effective than vehicle but no comparison between agents was made. 19 trials, 10 tacrolimus, 9 pimecrolimus.

In the analysis for IGA 0/1 outcome, pimecrolimus was more effective than vehicle at 3 weeks (RR 2.41, 95% CI, 1.31-4.43), 6 weeks (RR 2.05, 95% CI, 1.52 -2.76), 6 months and 12 months; In the analysis for Physician's global evaluation of response, tacrolimus 0.03% was also more effective than vehicle at 3 weeks (RR, 2.13, 95% CI, 1.24-3.68) and 12 weeks (RR, 4.53, 95% CI, 2.93-7.00); so was tacrolimus 0.1% (RR, 1.57, 95% CI, 0.88-2.81 at 3 weeks; RR, 5.69, 95% CI, 3.72-8.72 at 12 weeks).

Ashcroft 2007

Similar to Martins 2015, this is also a Cochrane review on tacrolimus and 1.0% pimecrolimus, showing pimecrolimus more effective than vehicle but less effective than topical corticosteroids and tacrolimus.

Ashcroft 2005

Both tacrolimus and pimecrolimus were more effective than placebo but the evidence was insufficient to show any advantages over topical corticosteroids.

Appendix C. Ongoing Studies

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
A Study to Assess the Efficacy and Safety of Dupilumab in Patients With Severe Atopic Dermatitis (AD) That Are Not Controlled With Oral Cyclosporine A (CSA) or for Those Who Cannot Take Oral CSA Because it is Not Medically Advisable Regeneron Pharmaceuticals NCT02755649	Phase 3 Double Blind RCT	1) Dupilumab dosing regimen 1 2) Dupilumab dosing regimen 2 3) Placebo With concomitant topical corticosteroids	Inclusion criteria • Severe, chronic AD • EASI≥ 20 • IGA ≥ 3 • BSA≥ 10% • Age ≥ 18 • No prior CsA use or should not be continued Exclusion criteria • Prior CsA, systemic corticosteroids, phototherapy, AZA, MTX, MMF, or JAK inhibitors • Hypersensitivity and/or intolerance to topical corticosteroids • Prior biologics • Active infection • Presence of TB • History of HIV • Positive hepatitis B or C antibodies	Primary at 16 weeks • EASI 75 • Secondary at 16 weeks • IGA 0/1 • Pruritus NRS • BSA • SCORAD • GISS • DLQI • POEM • HADS • TEAEs	April 2017

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. Comparative Clinical Effectiveness Supplemental Information

Methods: Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table E1).[75] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality. Nevertheless, we restricted our use of case series to those that met specific criteria, including a minimum of six months follow-up, clearly defined entry criteria, and use of consecutive samples of patients.

Additional Comparative Clinical Effectiveness Results

Table D1. Dupilumab: IGA Response Rates across Trials, 4 and 12 week results

Trial	IGA 0 or 1 and ≥ 2 reduction from baseline (%)			IGA 0 or 1 (%)		
	Dupilumab 300 mg QW	Dupilumab 300 mg Q2W	Placebo	Dupilumab 300 mg QW	Dupilumab 300 mg Q2W	Placebo
12 weeks						
M12	NR	NA	NR	40	NA	7
4 weeks						
M4A/M4B	NR	NA	NR	12	NA	6
C4	NR	NA	NR	52	NA	30

Additional Harms Data

Table D2. Dupilumab: Skin Infections Rates across Trials

Trial	Rate of skin infections (%)		
	Dupilumab 300 mg QW	Dupilumab 300 mg Q2W	Placebo
16 weeks			
SOLO 1	6	6	8
SOLO 2	6	6	11
Thaci 2016	5	8	8
12 weeks			
M12	5	NA	24
4 weeks			
M4A/M4B	4	NA	12
C4	5	NA	10

Meta-Analysis and Network Meta-Analysis Methods

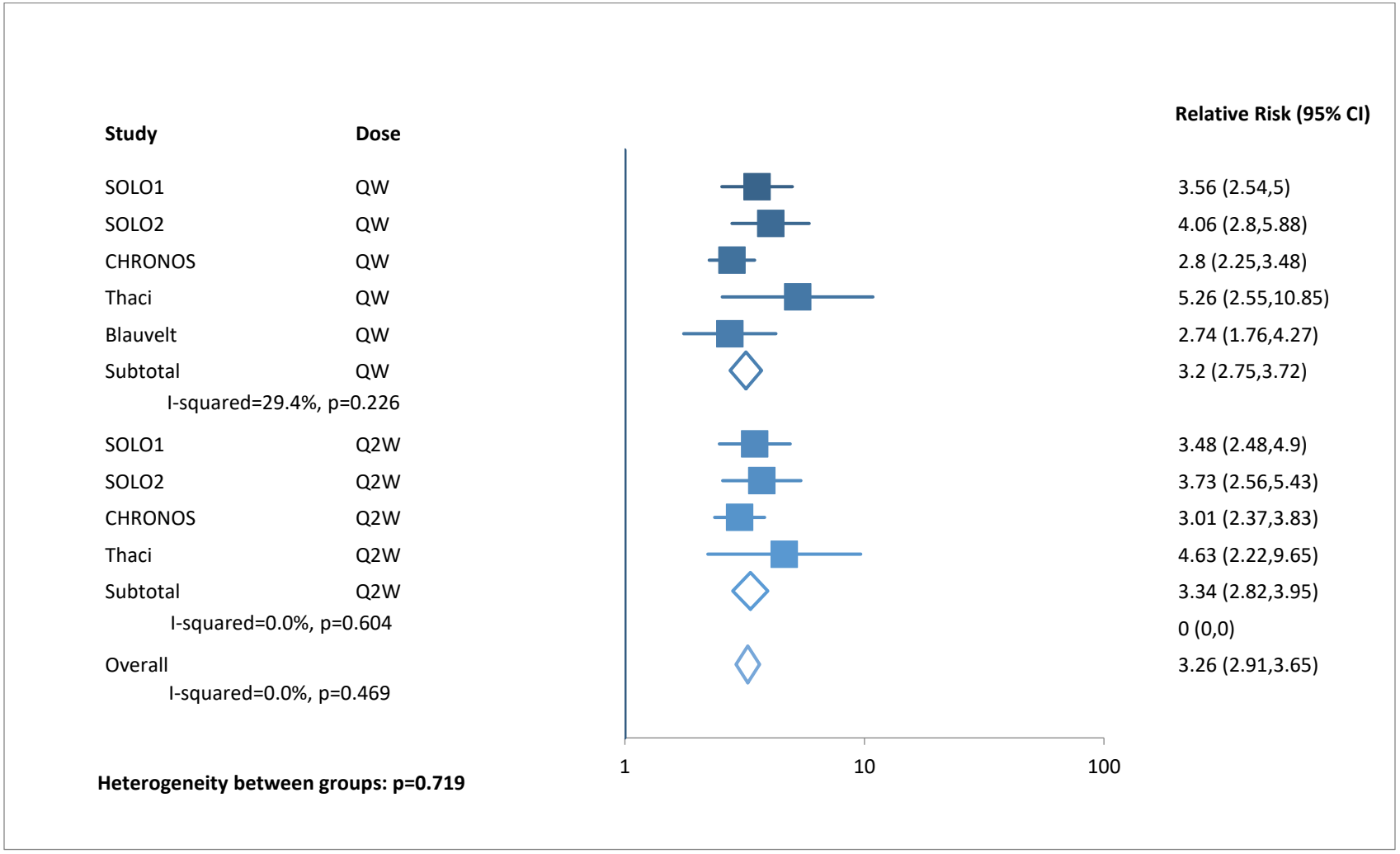
Dupilumab Meta-Analysis and Crisaborole Network Meta-Analysis

To decide whether all dupilumab trials could be pooled, we conducted subgroup analyses by weekly or every other weekly dose and presence or absence of background topical corticosteroid (TCS) use. We ran fixed-effects meta-analyses by dose and by background TCS for both EASI75 and IGA binary data using Stata 14.2. For subgroup analyses on background TCS, data across dosing groups were pooled. While SOLO1, SOLO2, and CHRONOS all included IGA score of 0 or 1 and ≥2 point reduction from baseline as a primary outcome, Thaci and Blauvelt only reported patients who had achieved an IGA score of 0 or 1. These data were pooled in subgroup analyses for IGA binary data. For each analysis, a Q-test was used to assess the statistical significance of between-group difference with a significance level of p=0.05. Forest plots were also generated to facilitate the comparisons visually. With no outstanding subgroup effect detected for dosing or background TCS, we pooled all trials in the subsequent analyses.

We then compared dupilumab to placebo using meta analysis under Bayesian framework for both EASI and IGA outcomes. Consistent with prior published methods for atopic dermatitis, EASI 50/75/90 response outcomes from clinical trials were tabulated to create numbers of patients in mutually exclusive categories (i.e., <50, 50-74, 75-89, ≥ 90). These data were analyzed using a random-effects, multinomial likelihood model to generate proportions of patients in each category. IGA outcome were analyzed as binary data using binomial likelihood model. We used numbers of patients with or without success as our input and corresponding proportions as output. The same model was used for the network meta-analysis of crisaborole using IGA outcomes. All statistical analyses were run within a Bayesian framework through WinBUGS 1.4.3.

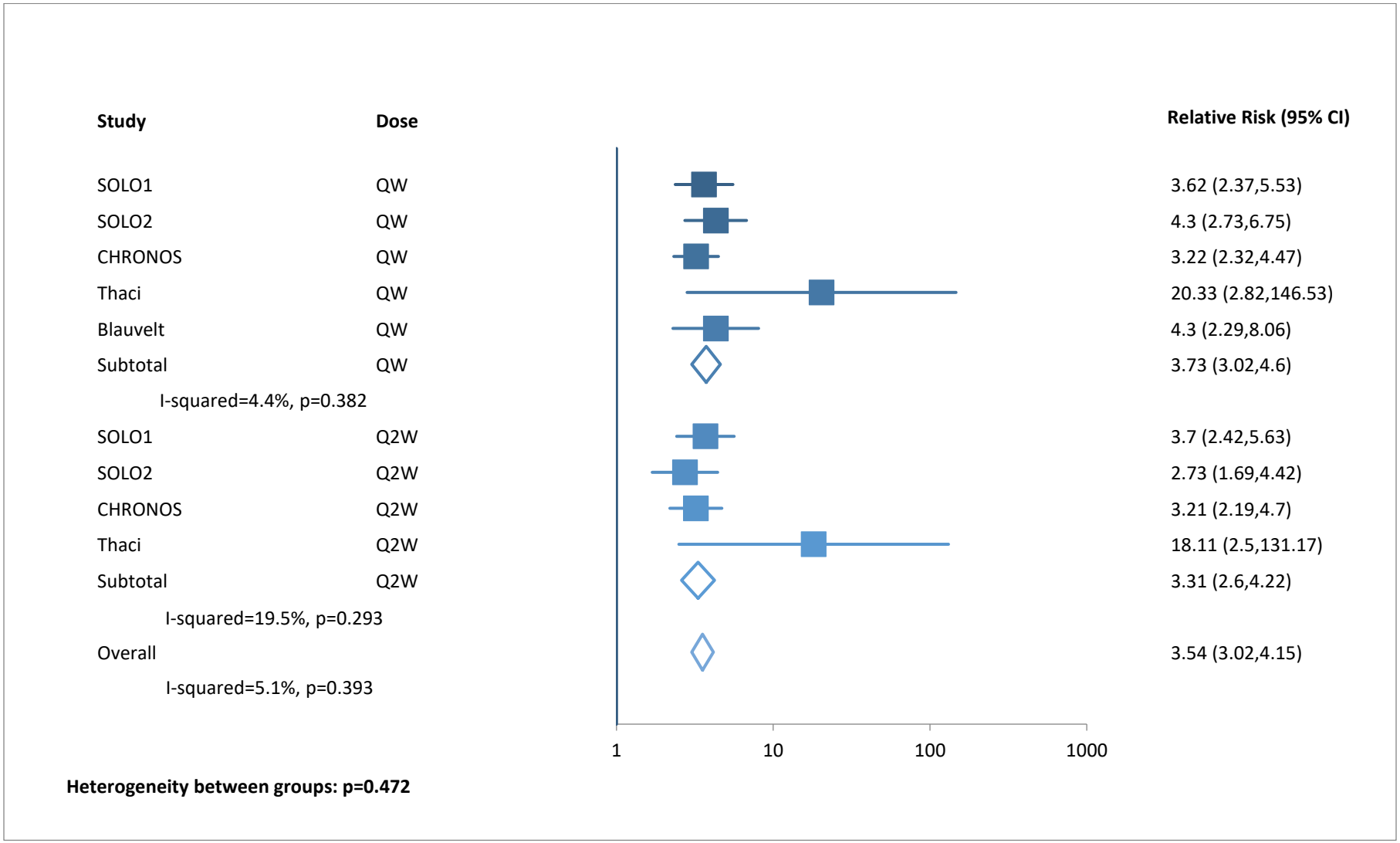
Subgroup Analyses

Figure D1. Subgroup Analysis by Dosing Schedule: Percentage Responders, EASI 75



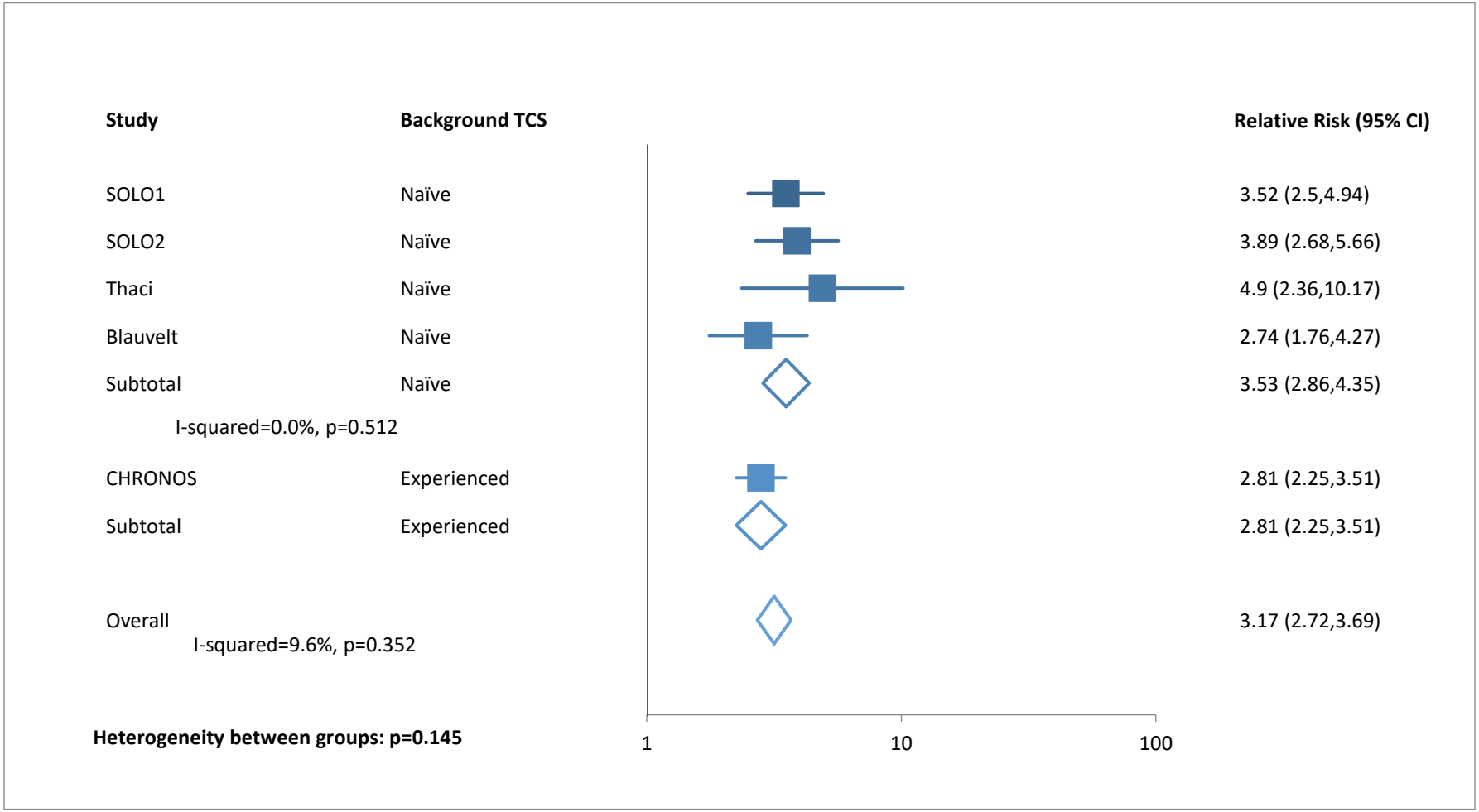
Q2W= Dupilumab 300 mg twice weekly dosing. QW= Dupilumab 300 mg weekly dosing.

Figure D2. Subgroup Analysis by Dosing Schedule: Percentage Responders, IGA 0 or 1



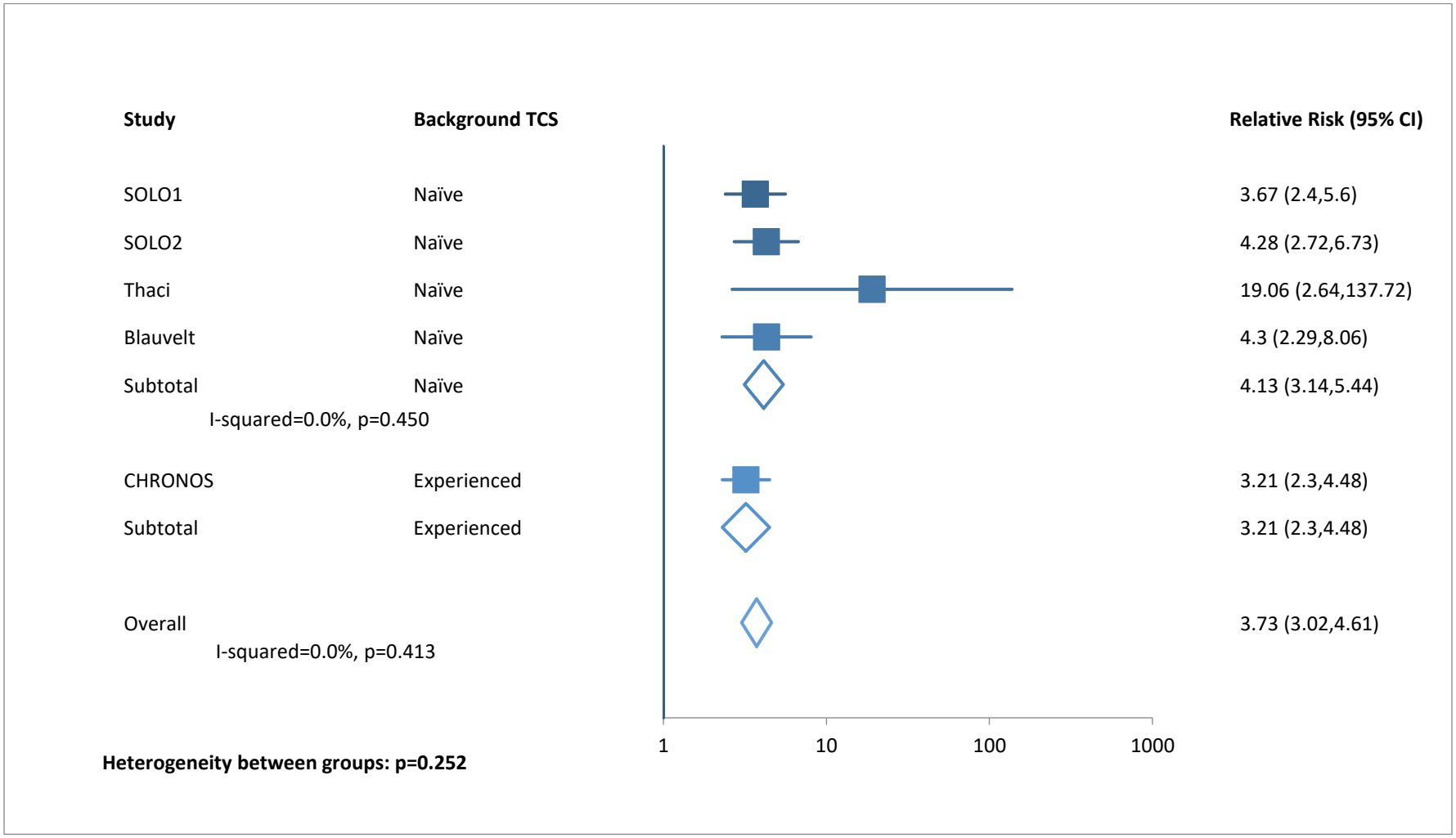
Q2W= Dupilumab 300 mg twice weekly dosing. QW= Dupilumab 300 mg weekly dosing.

Figure D3. Subgroup Analysis by Background Topical Corticosteroids Experienced/Naïve: Percentage Responders, EASI 75



Naïve= no previous use of topical corticosteroids. Experienced= previous use of topical corticosteroids. TCS= topical corticosteroids.

Figure D4. Subgroup Analysis by Background Topical Corticosteroid Experienced/Naïve: Percentage Responders, IGA 0 or 1



Naïve= no previous use of topical corticosteroids. Experienced= previous use of topical corticosteroids. TCS= topical corticosteroids.

Figure D5. Meta-Analysis, Dosing and Background Topical Corticosteroid Groups Pooled: Percentage Responders, EASI 75

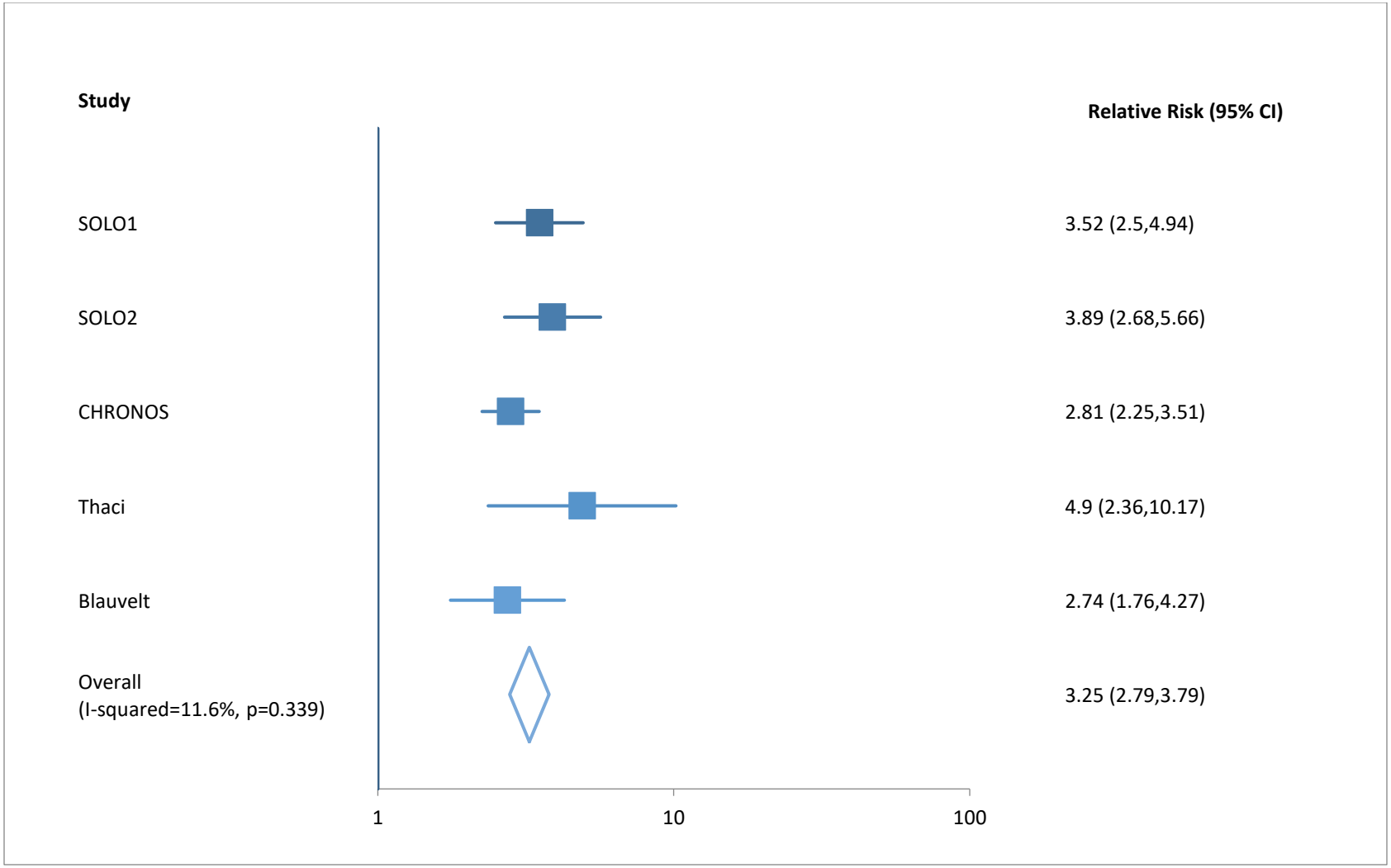
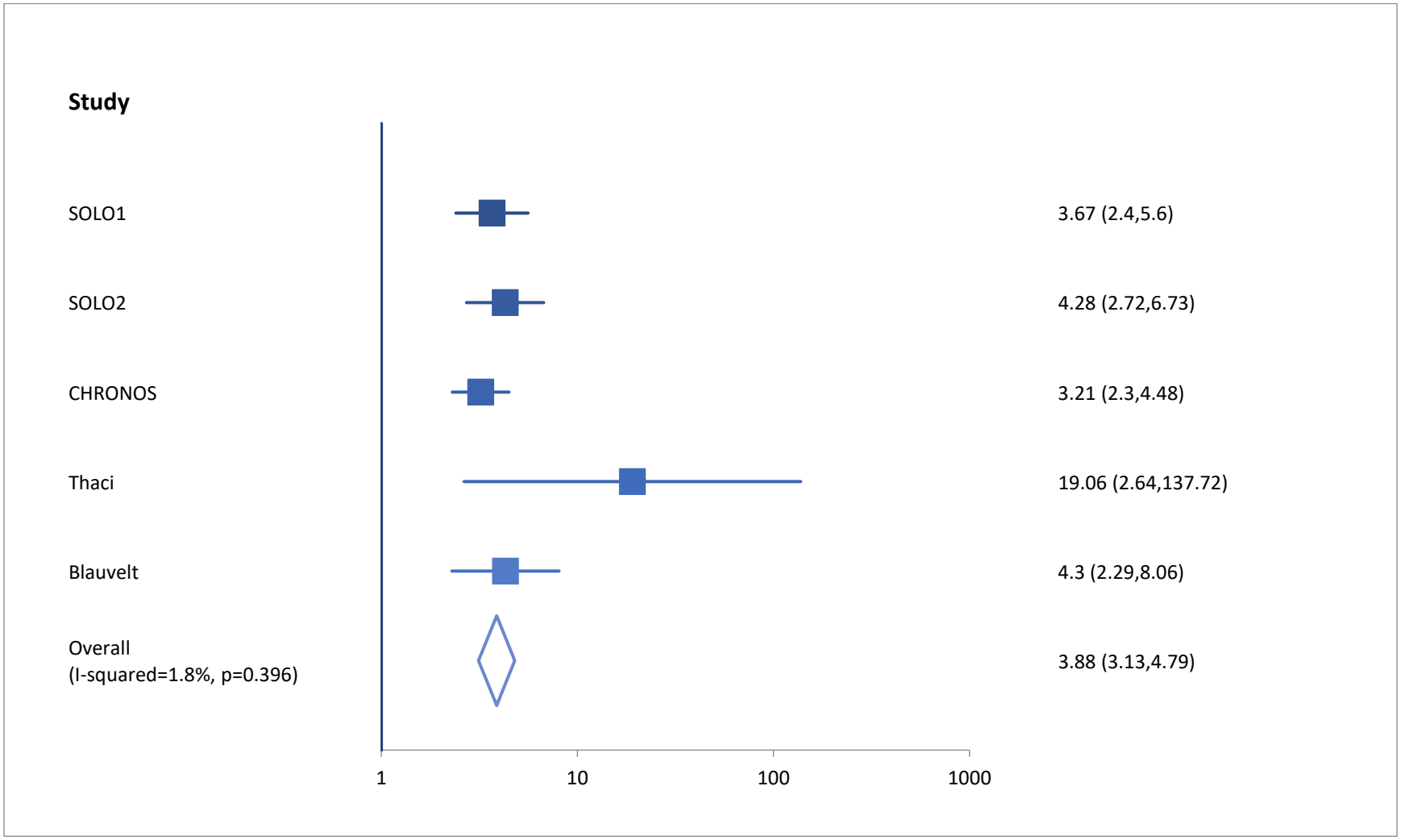


Figure D6. Meta-Analysis, Dosing and Background Topical Corticosteroid Groups Pooled: Percentage Responders, IGA 0 or 1



Winbugs Code

EASI, Random Effects, Multinomial Mode

```
# Binomial likelihood, probit link (different categories)
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS

for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
p[i,k,1] <- 1 # Pr(PASI >0)
for (j in 1:nc[i]-1) { # LOOP THROUGH CATEGORIES
r[i,k,j] ~ dbin(q[i,k,j],n[i,k,j]) # binomial likelihood
q[i,k,j] <- 1-(p[i,k,C[i,j+1]]/p[i,k,C[i,j]]) # conditional probabilities
theta[i,k,j] <- mu[i] + delta[i,k] + z[j] # linear predictor
rhat[i,k,j] <- q[i,k,j] * n[i,k,j] # predicted number events
dv[i,k,j] <- 2 * (r[i,k,j]*(log(r[i,k,j])-log(rhat[i,k,j])) #Deviance contribution of each category
+(n[i,k,j]-r[i,k,j])*(log(n[i,k,j]-r[i,k,j]) - log(n[i,k,j]-rhat[i,k,j])))
}
dev[i,k] <- sum(dv[i,k,1:nc[i]-1]) # deviance contribution of each arm
for (j in 2:nc[i]) { # LOOP THROUGH CATEGORIES
p[i,k,C[i,j]] <- 1 - phi.adj[i,k,j] # link function
# adjust link function phi(x) for extreme values that can give numerical errors
# when x< -5, phi(x)=0, when x> 5, phi(x)=1
phi.adj[i,k,j] <- step(5+theta[i,k,j-1])
* (step(theta[i,k,j-1]-5)
+ step(5-theta[i,k,j-1])*phi(theta[i,k,j-1]) )
}
}
for (k in 2:na[i]) { # LOOP THROUGH ARMS
delta[i,k] ~ dnorm(md[i,k],taud[i,k])
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LHR distributions, with multi-arm trial correction
taud[i,k] <- tau *2*(k-1)/k # precision of LHR distributions (with multi-arm trial correction)
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment, multi-arm RCTs
sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
}
resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
}
z[1] <- 0 # set z50=0
for (j in 2:Cmax-1) { # Set priors for z, for any number of categories
z.aux[j] ~ dunif(0,5) # priors
z[j] <- z[j-1] + z.aux[j] # ensures z[j]~Uniform(z[j-1], z[j-1]+5)
```

```
}



totresdev <- sum(resdev[]) #Total Residual Deviance
d[1] <- 0 # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
A~dnorm(meanA, precA)

# calculate prob of achieving ACR 20/50/70 on treat k
for (k in 1:nt) {
for (j in 1: Cmax-1) {
peasi[k,j] <- 1 - phi(A+d[k] + z[j])}
}


for (k in 1:nt-1) {
for (kk in k+1:nt){
RR50[k,kk] <- peasi[k,1]/peasi[kk,1]
RR50[kk,k]<- 1/RR50[k,kk]
 }
}


for (k in 1:nt-1) {
for (kk in k+1:nt){
RR75[k,kk] <- peasi[k,2]/peasi[kk,2]
RR75[kk,k]<- 1/RR75[k,kk]
}
}


for (k in 1:nt-1) {
for (kk in k+1:nt){
RR90[k,kk] <- peasi[k,3]/peasi[kk,3]
RR90[kk,k]<-1/RR90[k,kk]
 }
}


} # *** PROGRAM ENDS
```

EASI, Fixed Effects, Multinomial model

```
# Binomial likelihood, probit link (different categories)
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS

for(i in 1:ns){ # LOOP THROUGH STUDIES
mu[i] ~ dnorm(0,.001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
p[i,k,1] <- 1 # Pr(PASI >0)
for (j in 1:nc[i]-1) { # LOOP THROUGH CATEGORIES
r[i,k,j] ~ dbin(q[i,k,j],n[i,k,j]) # binomial likelihood
q[i,k,j] <- 1-(p[i,k,C[i,j+1]]/p[i,k,C[i,j]]) # conditional probabilities
theta[i,k,j] <- mu[i] + d[t[i,k]]-d[t[i,1]] + z[j]
rhat[i,k,j] <- q[i,k,j] * n[i,k,j] # predicted number events
dv[i,k,j] <- 2 * (r[i,k,j]*(log(r[i,k,j])-log(rhat[i,k,j])) #Deviance contribution of each category
+(n[i,k,j]-r[i,k,j])*(log(n[i,k,j]-r[i,k,j]) - log(n[i,k,j]-rhat[i,k,j])))
}
dev[i,k] <- sum(dv[i,k,1:nc[i]-1]) # deviance contribution of each arm
for (j in 2:nc[i]) { # LOOP THROUGH CATEGORIES
p[i,k,C[i,j]] <- 1 - phi.adj[i,k,j] # link function
# adjust link function phi(x) for extreme values that can give numerical errors
# when x< -5, phi(x)=0, when x> 5, phi(x)=1
phi.adj[i,k,j] <- step(5+theta[i,k,j-1])
* (step(theta[i,k,j-1]-5)
+ step(5-theta[i,k,j-1])*phi(theta[i,k,j-1]) )
}
}

resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
}
z[1] <- 0 # set z50=0
for (j in 2:Cmax-1) { # Set priors for z, for any number of categories
z.aux[j] ~ dunif(0,5) # priors
z[j] <- z[j-1] + z.aux[j] # ensures z[j]~Uniform(z[j-1], z[j-1]+5)
}

totresdev <- sum(resdev[]) #Total Residual Deviance
d[1] <- 0 # treatment effect is zero for reference treatment


for (k in 2:nt){
d[k] ~ dnorm(0,.0001)
```

```
} # vague priors for treatment effects

A ~ dnorm(meanA,precA)


# calculate prob of achieving easi 50/75/90 on treat k

for (k in 1:nt) {
for (j in 1: Cmax-1) {
peasi[k,j] <- 1 - phi(A+d[k] + z[j])}
}

for (k in 1:nt-1) {
for (kk in k+1:nt){
RR50[k,kk] <- peasi[k,1]/peasi[kk,1]
RR50[kk,k] <- peasi[kk,1]/peasi[k,1]
 }
}


for (k in 1:nt-1) {
for (kk in k+1:nt){
RR75[k,kk] <- peasi[k,2]/peasi[kk,2]
RR75[kk,k] <- peasi[kk,2]/peasi[k,2] }
}


for (k in 1:nt-1) {
for (kk in k+1:nt){
RR90[k,kk] <- peasi[k,3]/peasi[kk,3]
RR90[kk,k] <- peasi[kk,3]/peasi[k,3] }
}

} # *** PROGRAM ENDS
```

Appendix E. Evidence Tables

Table E1. Summary Evidence Table

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Dupilumab						
Simpson, 2016[18] ***SOLO 1 (NCT02277743)*** ***Good quality publication***	Phase 3 RCT Double-blind Multicenter international sites in NA, Europe, and Asia ITT	N=671 1) Dupilumab monotherapy 300 mg/wk, s.c.(n=223) 2) dupilumab 300 mg s.c. every other week alternating with placebo (n=224) 3) Placebo (n=224) Treatment duration: 16 weeks *dupilumab groups received 600 mg loading dose on day 1	Inclusion: ≥ 18 years of age, moderate-to-severe atopic dermatitis (IGA 3 or 4), inadequately controlled by topical treatment or medically inadvisable, AD ≥ 3 years Exclusion: See supp	Age (years): 1) 39.0, 2) 38.0, 3)39.0 % male: 1) 64, 2) 58, 3) 53 White (%**):** 1) 67, 2) 69, 3)65 AD **duration (years):** 1) 26.0, 2) 26.0, 3)28.0 E**ASI:** 1) 29.8, 2) 30.4, 3)31.8 DLQI: 1) 14.0, 2) 13.0, 3)14.0 IGA score of 4 **(%):** 1)48, 2)48, 3)49 Previous systemic glucocorticoids **(%):** 32.9 Previous systemic immunosuppressant agents **(%):** 25.9	Primary outcomes at week 16: IGA score of 0/1 and reduction of **≥ 2 from baseline n(%):** 1) 83(37), 2) 85 (38), 3) 23 (10) Secondary outcomes at week 16: EASI 75 n(%): 1) 117 (52), 2) 115 (51), 3) 33 (15) EASI 50 **n(%):** 1) 136 (61), 2) 154 (69), 3) 55 (25) EASI 90 **n(%):** 1) 74 (33), 2) 80 (36), 3) 17 (8) Peak score on NR**S for pruritus, LS mean percent change (SE):** 1) -48.9 (2.6), 2) -51.0 (2.5), 3) -26.1 (3.0) DLQI**, LS mean change (SE):** 1) -9.0 (0.4), 2) -9.3 (0.4), 3) -5.3 (0.5)	Primary outcomes at week 16: AEs ≥ **1 (%):** 1) 69, 2) 73, 3)65 SAEs ≥ **1 (%):** 1) 1, 2) 3, 3) 5 Discontinuation due to AEs (%): 1) 2, 2) 2, 3)1 Deaths: **0** Nasopharyngitis (%): 1) 11, 2)10, 3)8 Injection site reactions (%): 1) 19, 2)8, 3)6 Skin infection (%): 1) 6, 2)6, 3)8 Headache (%): 1) 5, 2)9, 3)6 Allergic conjunctivitis (%): 1) 3, 2)5, 3)1

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					HADS, **LS mean change (SE):** 1) -5.2 (0.5), 2) -5.2 (0.5), 3) -3.0 (0.7) Affected BSA, **LS mean change (SE):** 1) -34.3 (1.4), 2) -33.4 (1.4), 3) -15.4 (1.9) SCORAD, **LS mean percent change (SE):** 1) -57.0 (2.1), 2) -57.7 (2.1), 3) -29.0 (3.2) POEM, **LS mean change (SE):** 1) -11.0 (0.5), 2) -11.6 (0.5), 3) -5.1 (0.7) GISS, **LS mean percent change (SE):** 1) -52.0 (2.4), 2) -53.4 (2.4), 3) -26.4 (3.3) *All Dupilumab groups vs. placebo for both outcomes, p<0.001*	Infectious conjunctivitis (%): 1) 3, 2)5, 3)1
Simpson, 2016[18] ***SOLO 2*** **(NCT02277769)** ***Good quality publication***	Same as above	N=708 1) Dupilumab monotherapy 300 mg/wk, s.c.(n=239) 2) dupilumab 300 mg s.c. every other week alternating with placebo (n=233) 3) Placebo (n=236)	Same as above	Age (years): 1) 35.0, 2) 34.0, 3)35.0 % male: 1) 58, 2) 59, 3) 56 White (%**):** 1) 70, 2) 71, 3)66 AD **duration (years):** 1) 24.0, 2) 24.5, 3)26.0 E**ASI:** 1) 29.0, 2) 28.6, 3)30.5	Primary outcomes at week 16: IGA score of 0/1 and reduction of **≥ 2 from baseline n(%):** 1) 87(36), 2) 84 (36), 3) 20 (8) Secondary outcomes at week 16: EASI 75 n(%):	Primary outcomes at week 16: AEs ≥ **1 (%):** 1) 66, 2) 65, 3)72 SAEs ≥ **1 (%):** 1) 3, 2) 2, 3) 6 Discontinuation due to AEs (%): 1) 1, 2) 1, 3)2

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
		Treatment duration: 16 weeks *dupilumab groups received 600 mg loading dose on day 1		DLQI: 1) 16.0, 2) 15.0, 3)15.0 IGA score of 4 **(%):** 1)47, 2)49, 3)49 Previous systemic glucocorticoids **(%):** 33.0 Previous systemic **immunosuppressant agents (%):** 31.4	1) 115 (48), 2) 103 (44), 3) 28 (12) EASI 50 **n(%):** 1) 146 (61), 2) 152 (65), 3) 52 (22) EASI **90 n(%):** 1) 73 (31), 2) 70 (30), 3) 17 (7) Peak score on NRS for pruritus, **LS mean percent change (SE):** 1) -48.3 (2.4), 2) -44.3 (2.3), 3) -15.4 (3.0) DLQI**, LS mean change (SE):** 1) -9.5 (0.4), 2) -9.3 (0.4), 3) -3.6 (0.5) HADS, **LS mean change (SE):** 1) -5.8 (0.4), 2) -5.1 (0.4), 3) -0.8 (0.4) Affected BSA, **LS mean change (SE):** 1) -32.1 (1.3), 2) -30.6 (1.3), 3) -12.6 (1.6) SCORAD, **LS mean percent change (SE):** 1) -53.5 (2.0), 2) -51.1 (2.0), 3) -19.7 (2.5) POEM, **LS mean change (SE):** 1) -11.3 (0.5), 2) -10.2 (0.5), 3) -3.3 (0.6) GISS, **LS mean percent change (SE):**	Deaths (n): 1)1, 2)1, 3)0 Nasopharyngitis (%): 1) 8, 2)8, 3)9 Injection site reactions (%): 1) 13, 2)14, 3)6 Skin infection (%): 1) 6, 2)6, 3)11 Headache (%): 1) 9, 2)8, 3)5 Allergic conjunctivitis (%): 1) 1, 2)1, 3)1 Infectious conjunctivitis (%): 1) 4, 2)4, 3)0.4

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					1) -46.8 (2.1), 2) -45.6 (2.1), 3) -17.9 (2.5) *All Dupilumab groups vs. placebo for both outcomes, p<0.001*	
LIBERTY AD CHRONOS, 2017[26,27] ***Good quality publication***	Phase 3 RCT Double-blind Multicenter 161 international sites in Australia, Canada, Czech Republic, Hungary, Italy, Japan, the Netherlands, New Zealand, Poland, Romania, South Korea, Spain, the UK, and the US ITT	N=740 1) Dupilumab 300 mg weekly with topical corticosteroids (n=319) 2) Dupilumab 300 mg every two weeks with topical corticosteroids(n= 106) 3) topical corticosteroids alone (n=315) Treatment duration: 52 weeks	Inclusion: Age ≥18 yrs; atopic dermatitis present for ≥3 yrs prior to screening; inadequately controlled with medium-to-high-potency topical medications or documented score within the past 6 months; baseline IGA score of 3 or 4; EASI score of 16 or higher at screening and baseline.	Age (years): 1) 34.0, 2) 40.5, 3) 34.0 % male: 1) 60, 2) 58, 3) 61 % white: 1) 65, 2) 70, 3) 66 **AD duration (years):** 1) 26, 2) 28, 3) 26 **BSA (%)** 1) 52.0, 2) 58.8, 3) 55.0 **EASI score** 1) 29.0, 2) 30.9, 3) 29.6 **IGA Score, 4/3 (%)** 1) 46/54, 2) 50/50, 3) 47/53	***Primary outcomes week 16/week 52:*** **IGA score of 0/1 and reduction of ≥ 2 from baseline n(%):** 1) 125 (39)/108 (40), 2) 41 (39)/32 (36), 3) 39 (12)/33 (13) **EASI 75 n(%):** 1) 204 (64)/173 (64), 2) 73 (69)/58 (65), 3) 73 (23)/57 (22) **Mean improvement in EASI from baseline, (%)*** 1) 77.3/80.3, 2) 76.7/78.3, 3) 43.2/45.8 **EASI 50 (%):** 1) 78/70, 2) 80/79, 3) 37/30 **EASI 90 (%):** 1) 43/51, 2) 40/51, 3) 11/16 **Peak pruritus (NRS) score, mean % improvement from baseline*** 1) 54.8/54.4, 2) 56.2/56.2, 3) 28.6/27.1	***Primary outcomes at week 52:*** **AEs ≥ 1 (%):** 1) 83, 2) 88, 3)84 **SAEs ≥ 1 (%):** 1) 3, 2) 4, 3) 5 **Serious and/or severe infections (%):** 1) 1, 2) 1, 3) 2 **Discontinuation due to AEs (%):** 1) 3, 2) 2, 3) 8 **Deaths (n):** 1), 1, 2) 0,, 3) 0 Death occurred in motor vehicle accident **Infections and infestations (%)** 1) 53, 2) 57, 3) 58 **Injection site reaction, %**

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					POEM score, mean improvement from baseline* 1) , 2) 77, 3) 37 **DLQI score, mean improvement from baseline*** 1) 10.5/10.7, 2) 9.7/10.9, 3) 5.3/5.6 **BSA affected, improvement from baseline (%)*** 1) 37.4/39.9, 2) 38.6/41.5, 3) 18.6/20.3 **SCORAD score, improvement from baseline (%)** 1) 63.3/66.1, 2) 62.1/66.2, 3) 31.8/34.1 **HADS total score, improvement from baseline** 1) 5.2 [p=0.0004]/5.5*, 2) 4.9 [p=0.03]/5.3 [p=0.0109], 3) 3.6/3.4 **GISS total score, mean improvement from baseline (%)*** 1) 56.3/59.7, 2) 53.1/58.3, 3) 28.2/29.2	1) 19, 2) 15, 3) 8 **Conjunctivitis, %** 1) 19, 2) 14, 3) 8 **Respiratory-thoracic and mediastinal disorders (%)** 1) 14, 2) 12, 3) 17 **Non-herpetic skin infections (%)** 1) 8, 2) 11, 3) 18

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					Proportion of patients with AD flares through week 52 (%)* 1) 13, 2) 14, 3) 41 *p<0.0001 vs. placebo	
Thaci, 2016[28] ***(NCT01859988)*** ***Good Quality Publication***	Phase 2b RCT Double-blind Dose-ranging Multicenter 91 international sites in NA, Europe, and Asia ITT	N=379 1) Dupilumab monotherapy 300 mg/wk, s.c.(n=63) 2) dupilumab 300 mg s.c. every 2 weeks (n=64) 3) Placebo (n=61) 4) Dupilumab monotherapy 200 mg every 2 weeks, s.c.(n=61) 5) Dupilumab monotherapy 300 mg every 4 weeks, s.c.(n=65) 6) Dupilumab monotherapy 100 mg every 4 weeks, s.c.(n=65) Treatment duration: 16 weeks	Inclusion: ≥ 18 years of age; EASI ≥ 12 at screening, ≥ 16 at baseline; inadequately controlled by topical treatment; IGA ≥ 3 at baseline; atopic dermatitis 10% or more body surface area Exclusion: See supp	Age (years): 1) 36.2, 2) 39.4, 3)37.2 % male: 1) 68, 2) 64, 3) 66 White (%): NR AD duration (years): 1) 27.9, 2) 30.5, 3)29.8 EASI: 1) 30.1, 2) 33.8, 3)32.9 DLQI: 1) 15.0, 2) 14.5, 3)12.8 IGA score of 4 (%): 1)49, 2)47, 3)48 Previous systemic glucocorticoids (%): NR Previous systemic immunosuppressant agents (%): NR	Primary outcomes at week 16: EASI 50 n(%): 1) 52 (83), 2) 50 (78), 3) 18 (30) EASI 75 n(%): 1) 38 (61), 2) 34 (54), 3) 7 (12) (estimated from graph) EASI 90 **n(%):** 1) 23 (37), 2) 19 (30), 3) 2 (3) (estimated from graph) IGA score of 0/1 n(%): 1) 21(33), 2)19 (30), 3) 1 (2) All p<0.0001 Secondary outcomes at week 16: Peak score on NRS for pruritus, **LS mean percent change:** 1)-46.9, 2)-40.1, 3)-5.2 DLQI**, LS mean percent change:**	Primary outcomes at week 16: AEs ≥ **1 (%):** 1) 84, 2) 78, 3)80 SAEs ≥ **1 (%):** 1) 2, 2) 3, 3)7 Discontinuation due to AEs (%): 1) 2, 2) 6, 3)5 Nasopharyngitis (%): 1) 25, 2)25, 3)26 Injection site reactions (%): 1) 10, 2)5, 3)3 Headache (%): 1) 13, 2)8, 3)3 Conjunctival Infections, irr**itations, and inflammation (%):** 1) 11, 2)5, 3)3

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					1)-59.0, 2) -39.6, 3) 2.6 SCORAD, **LS mean percent change:** 1)-56.9, 2)-51.2, 3)-13.8 Affected BSA, LS mean % change from baseline 1) -65.6, 2) -52.1, 3) -7.7 *All Dupilumab groups vs. placebo for %change from baseline, p<0.001*	Skin structures and soft tissue infections (HLT), %: 1) 5, 2)8, 3)8
Beck,2014[19] ***(NCT01259323 NCT01385657)*** ***Good Quality Publication***	Phase I M4A in the U.S. M4B multinational	M4A 1)dupilumab 300 mg (n=8) 2)dupilumab 150 mg (n=8) 3)dupilumab 75 mg (n=8) 4)placebo (n=6) M4B 1)dupilumab 300 mg (n=13) 2)dupilumab 150 mg (n=14) 3)placebo (n=10) All administered subcutaneously once a week Duration: 4 weeks	Inclusion: adults with moderate-to-severe atopic dermatitis (IGA score of 3 or 4), and BSA≥ 15 in M4A and ≥ 10% in M4B that was not adequately controlled with topical medications (glucocorticoids and calcineurin inhibitors); disease duration ≥ 3 years	Pooled, 1=dupilumab, 2=placebo Age (years): 1)42.6, 2)37.4 % male: 1) 55, 2) 69 White (%): 1)76, 2)81 EASI: 1) 30.0, 2) 22.8 IGA mean score**:** 1)3.8, 2)3.6 BSA (%)**:** 1)51.4, 2)40.3 Pruritus NRS mean score**:** 1)6.0, 2)5.8	Pooled, 1=dupilumab, 2=placebo Primary **outcomes at 4 weeks** EASI 50 n(%): 1) 30 (59), 2) 3 (19) P<0.05 EASI 75 **n(%):** 1) 15 (29), 2) 1 (6) Percent change in pruritus NRS**(%):** 1) -41.3, 2) -18.6 P<0.05 IGA score of 0/1 n(%): 1) 6(12), 2)1 (6) Percent change in BSA**(%):** 1) -37.4, 2) -15.3 P<0.05	Pooled, 1=dupilumab, 2=placebo Primary outcomes at 4 weeks AEs ≥ **1 (%):** 1) 86, 2) 88 SAEs ≥ **1 (%):** 1) 2, 2) 6 Discontinuation due to AEs (%): 1) 0, 2) 6 Skin infection**(%):** 1) 4, 2) 12

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Beck,2014[19] ***(NCT01548404)*** ***Good Quality Publication***	Phase 2 In Europe	M12 1)dupilumab 300 mg/week (n=55) 2)placebo (n=54) Duration: 12 weeks	Inclusion: adults with moderate-to-severe atopic dermatitis (IGA score of 3 or 4) and BSA≥ 10% that was poorly controlled with topical agents; disease duration ≥ 3 years	Age (years): 1)33.7, 2)39.4 % male: 1) 56, 2) 50 White (%): 1)100, 2)100 EASI: 1) 28.4, 2) 30.8 IGA mean score**:** 1)3.9, 2)4.0 BSA (%)**:** 1)46.8 2)50.8 Pruritus NRS mean score**:** 1)6.1, 2)5.8	Primary outcomes at 12 weeks EASI 50 n(%): 1)47 (85), 2) 19 (35) P<0.001 EASI 75 **n(%):** 1) 34 (62), 2) 8 (15) Percent change in pruritus NRS**(%):** 1) -55.7, 2) -15.1 IGA score of 0/1 n(%): 1)22(40), 2)4 (7) P<0.001 Percent change in BSA**(%):** 1) -59.9, 2) -17.8	Primary outcomes at 12 weeks AEs ≥ **1 (%):** 1) 76, 2) 80 SAEs **≥ 1 (%):** 1) 2, 2) 13 Discontinuation due to AEs (%): 1) 2, 2) 6 Skin infection**(%):** 1) 5, 2) 24
Beck,2014[19] ***(NCT01639040)*** ***Good Quality Publication***	Phase 2a In Europe	C4 1)dupilumab 300 mg in combination with topical glucocorticoids weekly (n=21) 2)placebo 300 mg in combination with	Inclusion: Adults with moderate-to-severe atopic dermatitis (IGA score of 3 or 4) and BSA≥ 10%; disease duration ≥ 2 years	Age (years): 1)36.0, 2)37.8 % male: 1) 38, 2) 50 White (%): 1)95, 2)100 EASI: 1) 23.1, 2) 24.1	Primary outcomes at 4 weeks EA**SI 50 n(%):** 1)21 (100), 2) 5 (50) P<0.05 EASI 75 **n(%):** 1) 13 (62), 2) 4 (40)	Primary outcomes at 4 weeks AEs ≥ **1 (%):** 1) 57, 2) 70 SAEs ≥ **1 (%):** 1) 0, 2) 10

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
		topical glucocorticoids weekly (n=10) Duration: 4 weeks		IGA mean score**:** 1)3.4, 2)3.4 BSA (%)**:** 1)40.4 2)38.9 Pruritus NRS mean score**:** 1)6.4, 2)5.0	Percent change in pruritus NRS**(%):** 1) -70.7, 2) -24.7 P<0.05 IGA score of 0/1 n(%): 1) 11(52), 2)3 (30) Percent change in BSA**(%):** 1) -63.6, 2) -36.5	Discontinuation due to AEs (%): 1) 0, 2) 10 Skin infection**(%):** 1) 5, 2) 10
Blauvelt,2016[29] ***(NCT02210780)*** ***ABSTRACT***	RCT Double-blind PBO-controlled Phase 2	N=194 1) Dupilumab monotherapy 300 mg/wk, s.c.(n=97) 2) placebo (n=97) Group 1: 600 mg dupilumab loading dose	Inclusion: ≥ 18 years of age, inadequately controlled by topical treatment Exclusion: NR	*NR*	EASI 50 n(%): 1) 70 (72.2), 2) 31 (32.0) EASI 75 n(%): 1) 52 (53.6), 2) 19 (19.6) EASI 90 **n(%):** NR IGA score of 0/1 n(%): 1) 43(44.3), 2)10 (10.3)	At 32 weeks: AEs ≥ **1 (%):** 1) 55.7, 2) 61.9 SAEs ≥ **1 n,%:** 1) 3, 0.3, 2) 0 Discontinuation due to AEs (%): NR Nasopharyngitis (%): 1) 4.1, 2)5.2 Injection site reactions (%): 1) 12.4, 2)5.2 Headache (%): 1) 5.2, 2)3.1 Conjunctivitis (%): 1) 8.2, 2)0 Upper respiratory tract infec**tion (%):** 1) 11.3, 2)14.4

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Bachert, 2016[61] ***(NCT01920893)*** ***Good Quality Publication***	Phase 2 RCT Double-Blind PBO-Controlled Parallel Group 13 sites in U.S. and Europe	N=60 1) Dupilumab monotherapy 300 mg/wk, s.c. plus MFNS(n=30) 2) placebo plus MFNS(n=30) *MFNS: mometasone furoate nasal spray	Inclusion: Patients age 18 to 65 years with bilateral **nasal polyposis** and chronic symptoms of sinusitis despite intranasal corticosteroid treatment for at least 2 months Exclusion: had participated dupilumab trial before	Age (years): 1) 47.4, 2) 49.3 % male: 1) 60.0, 2) 53.3 White (%): 1)96.7, 2)100		At 16 weeks: AEs ≥ **1 (%):** 1) 100, 2) 83.3 SAEs ≥ **1 (%):** 1) 6.6, 2) 13.3 Discontinuation due to AEs (%): 1)6.6, 2)16.6 Death:0 Nasopharyngitis (%): 1) 47, 2)33 Injection site reactions (%): 1) 40, 2)7 Headache (%): 1) 20, 2)17
Wenzel, 2016[62] ***(NCT0185404)*** ***Good Quality Publication***	Phase 2b Randomized, double-blind, placebo-controlled, parallel-group 174 sites in Argentina, Australia, Chile, France, Italy, Japan, Republic of	1. Placebo (n=158) 2. Dupilumab 200 mg every 4wks (n=150) 2. Dupilumab 300 mg every 4wks (n=157) 3. Dupilumab 200 mg every 2 weeks (n=148) 4. Dupilumab 300 mg every 2 weeks (n=156) 5. Dupilumab regimens combined (n=611)	Inclusion: Adults with asthma diagnosis ≥ 12 months based on GIA 2009; existing treatment with medium-to-high dose corticosteroids plus long-acting β_2 agonist (fluticasone propionate ≥ 250 mcg or equivalent inhaled corticosteroids twice daily) with inhaled	Mean age, yrs (SD): 48.6 (13.0) Male, %: 37 White, %: 78		At 24 weeks: Any treatment-emergent AE, %: 1. 75 4. 78 5. 79 SAEs, %: 1. 6 4. 8 5. 7 Discontinuation due to AEs, %

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
	Korea, Mexico, New Zealand, Poland, Russia, South Africa, Spain, Turkey, Ukraine, USA 12- and 24-week follow-up		corticosteroids plus a long-acting β_2 agonist for ≥ 1 month before screening Exclusion: use of systemic corticosteroid within 28 days of screening			1. 3 4. 3 5. 4 Injection-site erythema, % 1. 8 4. 21 5. 13 Injection-site reactions, % 1. 13 4. 26 5. 18 Upper-respiratory tract infections, % 1. 35 4. 35 5. 35 Deaths: 2, both treatment group 3; one acute cardiac failure and one metastatic gastric cancer with organizing pneumonia and cor pulmonale
Wenzel, 2013[76] ***(NCT01312961)***	Randomized, double-blind, placebo-	1. Placebo (n=52) 2. Dupilumab 300 mg per week (n=52)	Inclusions: Adults aged 18 to 65; persistent, moderate-to-severe asthma; symptoms not	Mean age, yrs (SD): 1. 41.6 (13.1) 2. 37.8 (13.2) Male, %:		At 12 weeks: SAEs, % 1. 6

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Good quality publication	controlled, parallel group Phase 2A 28 sites in US 12-week follow-up	Patients received fluticasone (250 or 500 mcg) and salmeterol (50 mcg) twice daily for 4 weeks; patients instructed to discontinue LABAs at week 4 and to taper and discontinue inhaled glucocorticoids during weeks 6-9.	well controlled with medium-dose to high-dose inhaled glucocorticoids plus LABAs (fluticasone ≥ 250mcg and salmeterol 50mcg twice daily or the equivalent).	1. 50 2. 50 White, %: 1. 73 2. 87		2. 2 (1 patient worsening of bipolar disorder, led to discontinuation) Discontinuation due to AEs, % 1. 6 2. 6 Death: 0 Injection-site reactions, %: 1. 10 2. 29 Nasopharyngitis, %: 1. 4 2. 13 Headache, % 1. 6 2. 12 Nausea, % 1. 2 2. 8 Muscle spasms, % 1. 0 2. 6 Viral upper respiratory tract infection, % 1. 0 2. 6 Urticaria, % 1. 0

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
						2. 6
Crisaborole						
Paller, 2016[11] ***AD-301 (NCT02118766) AD-302 (NCT02118972)*** ***Good quality publication*** ***See also:*** **Simpson, 2016**[18]	Phase III RCT Double-blind Multicenter 47 and 42 investigational centers in the U.S. Per-protocol	N=1522 AD-301 1) crisaborole, twice daily (n=503) 2) vehicle, twice daily(n=256) AD-302 3) crisaborole, twice daily (n=513) 4) vehicle, twice daily (n=250) Treatment duration: 28 days	Inclusion: ≥ 2 years of age, mild-to-moderate atopic dermatitis (ISGA 2 or 3), ≥ 5% treatable body surface Exclusion: Previous use of biologics or systemic corticosteroids within 28 days or TCS or TCI within 14 days; active skin infection	AD-301 Age (**mean, years):** 1) 12.0, 2) 12.4 Age**≥ 18 (%):** 1)12.9, 2)14.8 % male: 1) 43.5, 2) 44.1 White, %**:** 1) 61.2, 2) 63.3 Baseline ISGA of 2 (mild), %: 1)39.0, 2)36.3 %BSA**:** 1)18.8, 2)18.6 AD-302 Age (**mean, years):** 1) 12.6, 2) 11.8 Age**≥ 18 (%):** 1)15.0, 2)11.6 % male: 1) 45.0, 2) 44.8 White, %**:** 1) 60.2, 2) 57.6 Baseline ISGA of 2 (mild), %: 1)38.4, 2)40.0	Primary outcomes at day 29: ISGA **score of 0/1 and improvement of ≥ 2 grades from baseline (%):** 1) 32.8*, 2) 25.4, 3) 31.4**, 4) 18.0 *P=0.038 **p<0.001 Secondary outcomes at day 29: ISGA **score of 0/1 and improvement (%):** 1)51.7*, 2)40.6 , 3) 48.5**, 4) 29.7 *P=0.005 **p<0.001 Pruritus **score of 0/1 and improvement of ≥ 1 grades from baseline (%), POOLED Crisaborole/Vehicle:** 63/53; p=0.002 Patients **with improvement in AD signs (%), POOLED Crisaborole/Vehicle:** Erythema: 59/40* Exudation: 40/30*	Primary outcomes Day 28, Crisaborole/Vehicle AEs ≥ **1 (%):** NR SAEs ≥ **1 (%): 0** Discontinuation due to AEs (%): 1.2/1.2 Deaths: 0 Application site pain (%): 4.4/1.2 General disorders and administration site conditions(%): 7.4/5.0 Infections and infestations**(%):** 11.7/11.8 Nasopharyngitis **(%):** 1.8/1.2 Upper respiratory tract infection(%): 3/3 Staphylococcal skin infection (%):

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
				%BSA**:** 1)17.9, 2)17.7 ***POOLED AD-301 and AD-302:*** *Crisaborole/Vehicle* CDLQI (Children's Dermatology Life Quality Index) 9.3/9.0 DLQI (Dermatology Life Quality Index): 9.7/9.3 DFI (Dermatitis Family Impact Questionnaire) for caregivers of patients 2-17 yrs: 8.1/7.8	Excoriation:60/48* **Induration/Papulation:** 55/48; p=0.008 Lichenification: 52/41 * *p<0.001 ***POOLED AD-301 and AD-302:*** *Crisaborole/Vehicle* **Mean change from baseline in CDLQI by baseline ISGA,** -4.6/-3.0; p<0.001 **Mean change from baseline in DLQI by baseline ISGA** -5.2/-3.5; p=0.016 **Mean change from baseline in DFI by baseline ISGA** -3.7/-2.7; p=0.003	0.1/1.0
Murrell, 2015[63] **(NCT01301508)** ***Fair Quality Publication***	Phase IIa RCT Double-blind Bilateral Multi-center Australia 6 weeks	N=25 1) crisaborole,twice daily 2) vehicle, twice daily *each to 1 of the 2 target lesions on the same subject Treatment duration: Twice daily for 6 weeks	Inclusion: Age 18-75 yrs; mild-to-moderate AD with 2 comparable lesions on trunk, upper, or lower extremities Exclusion: clinically significant or severe allergies; phototherapy within 2 wks,	Age, yrs**:** 43.6 Male, %: 60 White, %: 92 ADSI, **mean:** 1) 8.3, 2) 8.4	Day 28 Atopic Dermatitis Severity Index (ADSI): 1) Greater decrease in crisaborole lesion, % of patients: 68.0 2) Greater decrease in vehicle lesion, %: 20.0 P=0.017	Primary outcomes at day 28: AEs ≥ **1 (%): 44** % of AEs t**reatment-related: 31** SAEs ≥ **1 (%):0** Discontinuation due to AEs (%): **0**

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
			corticosteroids within 4 wks, topical therapy within 7 days; requirement for high-potency corticosteroids	Pruritus, mean on 0-3 rating scale: 1) 2.3, 2) 2.2 Erythema: 1) 2.2, 2) 2.3 Lichenification: 1) 1.7, 2) 1.7 Excoriation: 1) 1.5, 2) 1.6 Exudation: 1) 0.6, 2) 0.6	ASDI**=0 lesion total clearance, %:** 1) 4.0, 2) 8.0 ASDI **>0 and ≤2 lesion partial clearance:** 1) 48.0, 2) 8.0 Pruritus **mean severity score** (estimated from graph): 1) 0.6 Erythema: 1) 0.8 Lichenification: 1) 0.9 Excoriation: 1) 0.4 Exudation: 1) 0.1	Application-site reactions, % 1) 12, 2) 12
Pimecrolimus						
Eichenfield, 2002[39] ***Good Quality Publication***	RCT, multi-center, double-blind 6 weeks	1) Pimecrolimus 1% (n=267) 2) Vehicle (n=136) Application twice daily, 12 hours apart	Inclusion: age 1-17 yrs; AD affecting ≥ 5% total body surface area (TBSA); IGA score of 2 or 3; stable doses of additive-free, basic bland emollient ≥ 7 days before baseline. Exclusion: pregnancy; phototherapy or systemic therapy within 1 month; topical therapy within 7 days; systemic antibiotics within 2 weeks	Age, mean yrs 1) 6.8, 2) 6.6 Age distribution 2 to <12 years, % 1) 82.4, 2) 80.9 Male, % 1) 52.4, 2) 45.6 White, % 1) 54.7, 2) 48.5 Baseli**ne IGA, mild/moderate (%)** 1) 30.0/60.3 2) 31.6/57.4	Day 43 results IGA clear or almost clear of disease**:** 1) 34.8, 2) 18.4 p≤0.05 Day 29 results IGA clear or almost clear of disease (estimated from graph): 1) 31, 2) 12 p≤0.05 EASI **mean % score change from baseline** 1) -47, 2) 1 p≤0.001	At day 43 ≥ **1 AEs, %:** 1) 44.0, 2) 42.6 Discontinuation due to AEs, %: 1) 1.8, 2) 2.9 Headache**, %** 1) 13.9, 2) 8.8 Application site burning, % 1) 10.4, 2) 12.5 Nasopharyngitis, % 1) 10.1, 2) 7.4

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
				Baseline **body surface area, %** 1) 26.1, 2) 25.5 Baseline EASI score 1) 12.9, 2) 12.7	P**atients with mild to no pruritus (score 0 or 1), % [estimated from graph]** 1) 60.5 2) 31	
Ho 2003[40] ***Good Quality Publication***	RCT, double-blind, multi-center 25 centers in Australia, Brazil, Canada, Germany, South Africa, Spain 6 weeks	1) Pimecrolimus 1% (n=123) 2) Vehicle (n=63) Twice daily application, 12 hours apart After double-blind phase, 20-week extension to assess long-term safety, all patients on pimecrolimus	Inclusion: age 3-23 months; TBSA ≥ 5%; IGA of 2 or 3 based on erythema and infiltration/papulation Exclusion: phototherapy or systemic treatments within previous month; topical therapy within 1 week; sedative antihistamines to treat pruritus within 1 week	Mean age, months 1) 12.6, 2) 12.7 Male, % 1) 55.3, 2) 54.0 White, % 1) 52.8, 2) 69.8 IGA score, mild/moderate (%) 1) 32.5/67.5, 2) 33.3/66.7 EASI score, mean baseline 1) 11.2, 2) 10.2	Day 29 results IGA score of 0 or 1, % (estimated from graph) 1) 52.9, 2) 17.4 6 Week results IGA score of 0 or 1, % 1) 54.5*, 2) 23.8 EASI reduction from baseline**, mean** 1) -6.81*, 2) -0.75 Pruritus absent or mild, % 1) 72.4*, 2) 33.3 *P<0.001	6 weeks ≥ **1 treatment-emergent AEs, %** 1) 74.8, 2) 65.1 ≥ **1 SAEs, %** 1) 5.7, 2) 12.7 Bacterial skin **infection, %** 1) 0.8, 2) 6.3 After 20-week open label phase ≥ 1 AEs, %: 1) 80
Phototherapy						
Tupker, 2013[77] ***Fair quality Publication***	Randomized, observer-blind Multicenter	N=48 1)local bath-PUVA followed by Iontophoresis (n=19) 2) local PUVA only (n=14)	Inclusion: Adults ≥ 17 years diagnosed with ≥ 3 months' duration of moderate-to-severe **foot eczema** (endogenous eczema and atopic dermatitis);	Age, yrs 1) 37.9, 2) 38.6, 3) 41.6 Male, % 1) 42, 2) 71, 3) 87	Primary at 8 weeks: Eczema score**:** Decrease over time for all 3 groups: p<0.001 Difference between 3 groups: p=0.053 Secondary outcomes: DLQI**:**	Burning during therapy, (%) 1) 10.5, 2) 21.4, 3) NR Erythema, (%) 1) 5.3, 2) 7.1, 3) 6.7

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
		3) corticosteroid (n=15)	insufficient response to topical steroids, calcium inhibitors or coal-tar; summed score ≥ 8 on hand eczema score Exclusion: systemic therapy within 3 months; UV therapy within 3 months	Duration of disease, yrs 1) 4.6, 2) 4.9, 3) 6.4	Decrease over time for all 3 groups: p<0.001 Difference between 3 groups: p=0.563	
Fernández-Guarino, 2016[78] ***Poor Quality Publication***	Prospective observational study	N=26 1)NB-UVB (n=16) 2)NBUVB/UVA (n=10)	Inclusion: More than 50% total body surface area affected; no response to topical treatment/oral corticoids	Age, yrs 1) 34, 2) 46 Male, % 1) 62.5, 2) 30	**±CR defined as a clearance rate >75% of the initial TBSA or complete clearance, %:** 1) 68.8, 2) 50.0 *No statistically significant differences **Improvement grade of pruritus:** No statistically significant differences ±Complete response (CR) Total body surface area (TBSA)	Erythema**, %** 1) 12.5, 2) NR
Darné, 2014[79] ***Poor Quality Publication***	Prospective cohort	N=55 1)NB-UVB (n=29) 2)unexposed, chose not to take (n=26) Treatment duration: twice weekly for 12 weeks	Inclusion: Children aged 3-16 years, for whom NB-UVB was indicated and offered Exclusion: Mild disease,	Age (**mean, years):** 1) 11, 2) 9 Male **(n):** 1)16, 2) 14 White (n)**:** 1)24, 2)16	Primary outcomes at 12 weeks: SASSAD Mean score at 12 weeks: 1)11.6, 2)24.8, p<0.001 % **surface area at 12 weeks:** 1)11%, 2)36%, p<0.0001	1 patient development of erythema

Author, Publication Year (Trial) *Quality rating*	Study Design	Intervention (n) Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
			defined as a Six Area Six Sign Atopic Dermatitis score (SASSAD) < 10		Secondary outcomes at 12 weeks**, mean difference:** POEM -9.1, p<0.0001 CDLQI -4.3, p=0.02 DFI -4.0, p=0.04 VAS itch -3.5, p<0.0001 VAS sleep loss -4.0, p<0.0001 SCORAD -22, p<0.0001 *Results persisted at 3 months and 6 months	

Appendix F. Public Comment

This section includes summaries of the public comments prepared for the Midwest CEPAC Public Meeting on May 25, 2017 in Boston, MA. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Additional summaries may be included as they are received.

A video recording of these comments can be found on our site here, starting at 01:35:00. Conflict of interest disclosures are included at the bottom of each statement.

Yufang Lu, Executive Director, Medical Affairs Immunology, Regeneron Pharmaceuticals, Inc.

Sanofi Genzyme and Regeneron Pharmaceuticals are proud to bring DUPIXENT® to adults with uncontrolled moderate-to-severe atopic dermatitis. DUPIXENT® is the first systemic agent approved for AD in nearly 20 years, and the result of a sustained commitment by Regeneron and Sanofi to find breakthrough medicines for people living with immune and inflammatory diseases.

We believe that medicines should have strong value for the patients that use them, the healthcare system, and society overall. We are pleased that ICER concluded that DUPIXENT®'s price is aligned with the value it brings to patients. We would like to thank ICER for engaging us throughout the process, and hope we can continue to have an open dialogue.

We have two key comments:

- While we agree with ICER's conclusion that DUPIXENT® is cost-effective for patients with moderate-to-severe AD uncontrolled with topical therapy, we believe it is not clinically meaningful to perform an assessment of the long-term value of DUPIXENT® for patients with moderate and severe disease separately. Atopic dermatitis is a chronic condition where symptom severity fluctuates over the disease course, making severity scales based only on a static measure of signs at a particular time point of limited relevance in clinical setting.
- Second, regarding the voting question comparing the net health benefit of DUPIXENT® with cyclosporine, we do not believe that it is appropriate to compare DUPIXENT® to a therapy not approved for AD, especially one with significant safety issues that potentially render it unsuitable to treat a chronic disease requiring long-term management.

Amy Paller, President, International Eczema Council

Dear CEPAC members and guests:

I'm Amy Paller, International Eczema Council President and active member of the Scientific Advisory Board of the National Eczema Association. In full disclosure, I've been a Pfizer and Regeneron investigator and consultant. As a practicing dermatologist for over 30 years, I've specialized in caring for atopic dermatitis patients. I cannot overemphasize the high burden and comorbidities of this disease, and the unmet need for safe, effective topical and systemic long-term treatments.

High rates of anxiety, depression, and suicidal ideation are part of AD, plus infection and recurrent hospitalizations. Due to unbearable itch—likened to poison ivy everywhere—afflicted patients haven't slept a full night in months or even years.

Many patients remain inadequately treated or untreated because of fears associated with use of topical steroids and topical calcineurin inhibitors, even mild-to-moderate sufferers. Crisaborole is the only effective topical agent that does not have a theoretical or established side-effect profile that would limit its use.

All available systemic treatments have major drawbacks and potential side-effects, particularly cyclosporine. Systemic steroids have significant risks and can lead to severe disease rebound when stopped. Instead, I prescribe other immunosuppressants. None are suitable for long-term use, despite AD's chronicity.

Patients, their families, and we doctors are fearful of systemic immunosuppressants. Yet the horrendous impact of AD often leaves no choice. Many have only partial or no improvement with immunosuppressants. Dupilumab is the first targeted, long-term therapy available for them. Based on clinical trials, the safety profile of existing drugs can't be compared to dupilumab. The relief experienced by adult AD sufferers in trials has been priceless.

As clinicians, we struggle for creative relief of the burden of AD. I'm enthusiastic about the long-overdue emergence of new, promising treatments.

Conflict of Interest Disclosure: Dr. Paller serves on the advisory boards of: Eli Lilly, GSK/Steifel, Pierre Fabre, and Regeneron/Sanofi.

Tim Smith, Vice President Advocacy and Access, National Eczema Association

On behalf of the National Eczema Association, thank you for allowing us to speak today and for undertaking an evaluation of dupilumab and crisaborole. NEA's primary goals are to increase awareness of atopic dermatitis as a disease and access to new medications for patients.

We commend ICER for proactively including the patient voice in this report. ICER staff contacted NEA and our partner organization, the Allergy and Asthma Foundation of America, in advance of the study to find out about patient experiences with this disease and patients' perceptions of these medications. The researchers took the extraordinary step of holding a listening session with a lifelong patient with severe AD. We are very grateful for ICER's attention to the concerns of patients.

We are happy that dupilumab is determined to be clinically and cost effective but we regret that AD's disease burden remains poorly understood0. AD is a complex disease that affects patients and their families. Efforts are afoot to expound on our understanding of AD's direct and indirect medical, psychosocial, and economic costs, and particularly the costs of cooccurring disorders. We hope these efforts will inform future efforts to evaluate AD drugs.

We believe that the value of these drugs extends beyond estimates of their clinical and cost effectiveness. These are the first new drugs approved for the treatment of AD in 16 years. The clinical evidence for the effectiveness may be uncertain, but we believe that have value in that they represent new treatment options for patients.

Conflict of Interest Disclosure: The National Eczema Association accepts grants from pharmaceutical companies. Corporate Partners include: CVS Pharmacy, Lilly, Leo, Pfizer, Sanofi, Genzyme, Regeneron, Genentech, TaroPharma.