Drugs to Treat Atopic Dermatitis

Final Report

December 2017

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# Table of Contents

Key Findings ...................................................................................................................................................................... 4

- Treatment-Resistant Symptoms .......................................................................................................................................................... 4
- Moderate-to-Severe Symptoms – Topical Calcineurin Inhibitors ............................................................................................................ 4
- Moderate-to-Severe Symptoms – Comparisons with Corticosteroids ............................................................................................... 4
- Mild-to-Moderate Symptoms – Crisaborole ........................................................................................................................................ 4
- Mild-to-Moderate Symptoms – Topical Calcineurin Inhibitors ........................................................................................................... 4
- Mild-to-Moderate Symptoms – Topical Calcineurin Inhibitors and Crisaborole .................................................................................. 4

Background ....................................................................................................................................................................... 5

- Scope and Key Questions ............................................................................................................................................................. 6

Methods Summary ................................................................................................................................................................. 6

- Inclusion Criteria ........................................................................................................................................................................ 6
  - Populations: Adults and children (all ages, including infants) with stable atopic dermatitis or eczema. ........................................ 6
  - Comparators: Another included drug, a topical steroid, or placebo (vehicle). ........................................................................... 7
- Literature Search: Searches were conducted from November 2007 through September 2017. .......................................................... 7

Data Analysis ..................................................................................................................................................................... 7

Detailed Assessment .................................................................................................................................................................. 7

- Overview .................................................................................................................................................................................. 7
- Patients with Treatment-Resistant Symptoms .................................................................................................................................... 8
  - Dupilumab Versus Placebo .......................................................................................................................................................... 8
- Moderate-to-Severe Symptoms ........................................................................................................................................................ 14
  - Topical Calcineurin Inhibitors: Head-to-Head Comparisons ...................................................................................................... 14
  - Topical Calcineurin Inhibitors: Comparisons with Corticosteroids ................................................................................................. 18
- Mild-to-Moderate Symptoms ........................................................................................................................................................ 19
  - Crisaborole: Placebo (Vehicle) Comparisons .............................................................................................................................. 19
  - Topical Calcineurin Inhibitors: Head-to-Head Comparisons ...................................................................................................... 20
  - Network Meta-analysis: Crisaborole, Pimecrolimus, Tacrolimus and Placebo (Vehicle) ............................................................. 23
- Location of Affected Skin ............................................................................................................................................................ 25
- High Percentage of Body Surface Area with Atopic Dermatitis .................................................................................................... 25
- Baseline Disease Severity .............................................................................................................................................................. 25
- Age .......................................................................................................................................................................................... 25
- Ethnicity .................................................................................................................................................................................. 26

Summary ........................................................................................................................................................................ 26

References ........................................................................................................................................................................ 26

*Appendices and Evidence Tables are published in a separate document.*
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Key Findings

Treatment-Resistant Symptoms
- Compared with placebo, patients with atopic dermatitis inadequately controlled with topical treatments taking dupilumab were more likely to respond to treatment, and experience improved symptoms, with no significant differences in adverse events.

Moderate-to-Severe Symptoms – Topical Calcineurin Inhibitors
- Short-term treatment response was not consistently different between tacrolimus and pimecrolimus based on 4 head-to-head trials and a network meta-analysis.
- Short-term improvement in symptoms was modestly better with tacrolimus, using a symptom scale, the reduction in the percent of body surface area affected, and ratings of pruritus.
- Quality of life was not found different between the drugs, but evidence is very limited.
- Adverse event withdrawals and application site reaction incidence and severity were not found different between the drugs, but evidence is limited.

Moderate-to-Severe Symptoms – Comparisons with Corticosteroids
- In patients with moderate-to-severe symptoms, response to treatment and symptom improvement were similar between calcineurin inhibitors (tacrolimus and pimecrolimus) and corticosteroids, but patients taking calcineurin inhibitors experienced more adverse events.

Mild-to-Moderate Symptoms – Crisaborole
- Significantly more patients had treatment response, improved symptoms and quality of life with crisaborole than with placebo (vehicle) based on 3 short-term trials.
- Application site reactions were more common with crisaborole (4.6% vs. 1.7%).

Mild-to-Moderate Symptoms – Topical Calcineurin Inhibitors
- In children with mild to moderate atopic dermatitis, differences in treatment response were not found between tacrolimus and pimecrolimus in 2 short-term trials. Symptom measures had inconsistent results, with patient-reported measures favoring tacrolimus and investigator-assessed measures finding no differences. Significantly more children withdrew due to adverse events with and reported burning with application of pimecrolimus.
- In adults, response and symptom improvement was significantly better with tacrolimus, but differences in pruritus were very small. There were no differences with withdrawal due to adverse events, but more patients reported burning with tacrolimus application.
- Patients with atopic dermatitis may have slightly increased risk of lymphoma, but evidence does not find that the topical calcineurin inhibitors increase this risk.

Mild-to-Moderate Symptoms – Topical Calcineurin Inhibitors and Crisaborole
- Network meta-analysis of 11 trials found that tacrolimus resulted in more patients achieving treatment response than crisaborole, pimecrolimus or placebo. Crisaborole was superior to placebo and similar to pimecrolimus.
Background
Atopic dermatitis (AD) is a chronic inflammatory skin disease, characterized by itching and dry skin, which poses a significant burden on health care resources and patients’ quality of life. It affects 5% to 20% of children worldwide and approximately 11% of children in the United States. It is also estimated to affect around 3% to 7% of adults in the United States. First manifestations of AD usually appear early in life and often precede other allergic diseases such as asthma or allergic rhinitis.

There is no known cure for AD and no optimal regimen for long-term maintenance of the disease. Treatment of AD usually involves a multipronged approach of reducing exposure to exacerbating factors, maintaining skin hydration with emollients, alleviating symptoms such as pruritus, and controlling active disease with topical anti-inflammatory agents. Intensity of treatment with or without a topical anti-inflammatory agent depends on the severity of the disease. Of the topical agents, topical steroids were generally considered the mainstay of treatment. Concerns about side effects associated with long-term topical steroid exposure persisted among patients and practitioners. Hence, treatments with alternate nonsteroid based agents were sought.

In December 2000 and 2001, two topical calcineurin inhibitors were approved for use in patients with AD in the United States and Canada. Since the approval of these agents, several case reports of malignancies (skin and lymphoma) have been reported to the United States Food and Drug Administration (FDA), causing a black box warning to be placed in each product’s labeling. Several pharmacokinetic analyses, commentaries, and editorials have been published refuting the addition of the black box warning.

Currently, both topical corticosteroids and topical calcineurin inhibitors are recommended by The American College of Dermatology’s 2014 guideline. Topical corticosteroids are recommended for AD-affected individuals who have failed to respond to good skin care and regular use of emollients alone, and topical calcineurin inhibitors are recommended for acute and chronic treatment, along with maintenance, in both adults and children with AD.

Recent advances in the understanding of the molecular basis of cutaneous barrier disorders and of congenital and acquired immune disorders have led to new approaches to the treatment of AD. 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.

Crisaborole (Eucrasia™, Pfizer, Inc.) is a topical phosphodiesterase 4 (PDE 4) inhibitor that has been evaluated as a new therapy for mild-to-moderate AD 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 AD in adults. It is administered as a subcutaneous injection given every other week. 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.
Treatments for AD are often targeted to symptom severity. The role of individual topical corticosteroids and calcineurin inhibitors, relative to each other, is still evolving, and questions remain about the most effective therapies for maintenance, treatment of flares, and therapy in patients inadequately managed with topical treatments. The objective of this report is to review evidence on the comparative effectiveness and comparative harms of dupilumab, crisaborole, pimecrolimus, and tacrolimus when compared to each other and when compared to topical corticosteroids, and to determine if there are any subgroups of patients (for example, age, racial groups, gender) and comorbidities (for example, immunodeficiencies) for which dupilumab, crisaborole, pimecrolimus, or tacrolimus are more effective or associated with fewer adverse events.

**Scope and Key Questions**

1. For adults and children with atopic dermatitis, do dupilumab, crisaborole, pimecrolimus, and tacrolimus differ in effectiveness versus each other or to topical corticosteroids? Are there differences based on the location of application (e.g., face, hands, feet), body surface area involved, or treatment duration?

2. For adults and children with atopic dermatitis, do dupilumab, crisaborole, pimecrolimus, or tacrolimus differ in harms versus each other or to topical corticosteroids? Are there differences based on the location of application (e.g., face, hands, feet), body surface area involved, or treatment duration?

3. Are there subgroups of patients based on demographics and comorbidities for which dupilumab, crisaborole, pimecrolimus, or tacrolimus are more effective or have fewer adverse events?

**Methods Summary**

We followed systematic review methodology developed for Drug Effectiveness Review Project (DERP)\(^1\) and that are in accordance with current guidance for systematic reviews, for example, dual review of inclusion decisions, quality assessments and data abstraction. Detailed methods are available upon request.

**Inclusion Criteria**

*Populations:* Adults and children (all ages, including infants) with stable atopic dermatitis or eczema.

**Table 1. Included Drugs**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Mechanism</th>
<th>Dosage Form</th>
<th>Approved Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dupilumab</td>
<td>Dupixent®</td>
<td>Monoclonal antibody</td>
<td>Subcutaneous</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Crisaborole</td>
<td>Eucrasia™</td>
<td>PDE4 inhibitor</td>
<td>Ointment</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Pimecrolimus(^\circ)</td>
<td>Elidel®</td>
<td>Calcineurin inhibitor</td>
<td>Cream</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Tacrolimus(^\circ)</td>
<td>Protopic®</td>
<td>Calcineurin inhibitor</td>
<td>Ointment</td>
<td>Moderate to severe</td>
</tr>
</tbody>
</table>

\(PDE4,\) phosphodiesterase 4 \(^\circ\) *Indicated for short-term, non-continuous treatment*
Comparators: Another included drug, a topical steroid, or placebo (vehicle).

Literature Search: Searches were conducted from November 2007 through September 2017.

Data Analysis
We organized and analyzed the evidence according to patient severity (resistant to topical treatment, mild-to-moderate symptoms, and moderate-to-severe symptoms). Input from a clinical expert, and scanning the study findings, indicated that disease severity is a more relevant factor than age in determining outcomes. When studies enrolled patients with any severity, we categorized them into 1 of the 3 severity groups according to the mean EASI score or mean affected body surface area of patients at baseline.

Pairwise meta-analyses were conducted for dupilumab and crisaborole versus placebo studies, and studies comparing topical calcineurin inhibitors using the DerSimonian and Laird random effects model in StatsDirect. We conducted network meta-analyses of data from trials of topical calcineurin inhibitors and topical crisaborole compared with topical steroids or placebo (vehicle) using the “mvmeta” command in Stata (version 14.0). We pooled several different response measures, including results of any tool that assessed disease severity and dichotomized treatment response. We also combined studies of adults and children, as noted above. We excluded studies longer than 12 weeks in duration, since the bulk of the evidence was in short-term studies and because topical calcineurin inhibitors are indicated for short-term use. Additionally, we did not incorporate studies of dupilumab in the network because the place in therapy of dupilumab differs from that of the other drugs and violates the transitivity assumption of network meta-analysis. We combined studies that were homogeneous enough that combining their results could be justified, and stratified according to severity (as above). When meta-analysis could not be performed, the data were summarized qualitatively. Caution should be used in interpreting the results of indirect and network meta-analyses, particularly where there may be variation at baseline (e.g., duration of study or risk level of participants). In this report, the analyses are rated low strength evidence at best for these reasons.

Detailed Assessment
Overview
The results are organized according to the place of the drugs in therapy, according to the severity of patient symptoms and treatment history. We present the evidence for patients that are the most difficult to treat first and those with less severe symptoms last. Evidence for adults and children are presented within these categories.

Through comprehensive searching, we identified and screened for inclusion a total of 594 publications for this review. In addition, 13 studies included in the October 2008 Topical Calcineurin Inhibitors report were carried over to this report. By applying eligibility and exclusion criteria, we ultimately included 43 original trials (reported in 39 publications), 5 observational studies, and 2 systematic reviews. These included 3 trials of crisaborole in 2 publications, and 8 trials of dupilumab in 7 publications, with 1 secondary analysis. We also identified a recent systematic review that also included these trials of crisaborole and dupilumab. For the topical calcineurin inhibitors, we included 14 trials of pimecrolimus in
13 publications with 1 observational study, 16 trials of tacrolimus in 15 publications, 5 head-to-head trials of pimecrolimus and tacrolimus (reported in 3 publications), with 1 secondary analysis, and 6 observational or systematic review publications which included both pimecrolimus and tacrolimus. Please refer to Appendix C for a full accounting of the flow of literature through the selection process, Appendix D for a list of studies excluded after full-text review with reasons for exclusion, Appendix E for quality assessment and results of included studies, and Appendix F for a list of all included studies.

**Key Question 1 & 2: Comparative Effectiveness and Harms According to Patient History**

**Patients with Treatment-Resistant Symptoms**

**Dupilumab Versus Placebo**

Six randomized controlled trials (RCTs) published in 3 papers compared dupilumab to placebo in adult patients with moderate-severe AD inadequately controlled with topical treatments. Three trials were of fair quality, and the other 3 were of good quality. Three trials were 16 weeks in duration, 1 trial was 12 weeks, and 2 were 4 weeks. Trials were conducted at various sites across Europe, Asia, and North America. There were no important differences in baseline characteristics between treatment and control groups in any of the 6 trials.

Two RCTs compared dupilumab plus topical corticosteroids to topical corticosteroids alone in adult patients with moderate-severe AD, inadequately controlled with topical treatments. One was a fair-quality trial and 1 was a good-quality trial. Trial durations varied; the fair-quality trial assessed primary outcomes at 4 weeks, and the good-quality trial assessed primary outcomes at both 16 and 52 weeks. The trials were conducted at sites in Asia, Europe, and North America. There were no important differences in baseline characteristics between treatment and control groups in either of the 2 trials.

A systematic review conducted by the Institute for Clinical and Economic Review evaluated the effectiveness and value of dupilumab in AD. The review included similar trials to those in this report and drew the same conclusions.

**Table 2. RCTs in Patients with Treatment-Resistant Symptoms**

<table>
<thead>
<tr>
<th>Author Year Quality</th>
<th>Population</th>
<th>N Duration</th>
<th>Disease Severity</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blauvelt 2017 Good</td>
<td>Adults, ≥18 years</td>
<td>740</td>
<td>Moderate-Severe, with inadequate response to topical corticosteroids</td>
<td>Dupilumab 300 mg weekly with topical corticosteroids (n=319)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16- and 52-week assessment of primary outcomes</td>
<td></td>
<td>Dupilumab 300 mg every 2 weeks with topical corticosteroids (n=106)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>topical corticosteroids alone (n=315)</td>
</tr>
<tr>
<td>Author Year Quality</td>
<td>Population</td>
<td>N</td>
<td>Duration</td>
<td>Disease Severity</td>
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</tr>
<tr>
<td>Beck 2014(^2)(^3) (a) 4-week Monotherapy Study M4A and M4B Fair</td>
<td>Adults, ≥18 years</td>
<td>67</td>
<td>4 weeks</td>
<td>Moderate-Severe, despite treatment with topical steroids or calcineurin inhibitors</td>
</tr>
<tr>
<td>Beck 2014(^2)(^3) (b) 12-week Monotherapy Study M12 Fair</td>
<td>Adults, ≥18 years</td>
<td>109</td>
<td>12 weeks</td>
<td>Moderate-Severe, despite treatment with topical steroids or calcineurin inhibitors</td>
</tr>
<tr>
<td>Beck 2014(^2)(^3) (c) 4-week Combination Therapy [M4B] Study C4 Fair</td>
<td>Adults, ≥18 years</td>
<td>31</td>
<td>4 weeks</td>
<td>Moderate-Severe, despite treatment with topical steroids or calcineurin inhibitors</td>
</tr>
<tr>
<td>Simpson 2016(^1)(^7) SOLO 1 Good</td>
<td>Adults, ≥18 years</td>
<td>671</td>
<td>16 weeks</td>
<td>Moderate – Severe, inadequately controlled with topical treatments or topical treatments inadvisable</td>
</tr>
<tr>
<td>Simpson 2016(^1)(^7) SOLO 2 Good</td>
<td>Adults, ≥18 years</td>
<td>708</td>
<td>16 weeks</td>
<td>Moderate – Severe, inadequately controlled with topical treatments or topical treatments inadvisable</td>
</tr>
<tr>
<td>Author Year</td>
<td>Quality</td>
<td>Population</td>
<td>N</td>
<td>Duration</td>
</tr>
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</tr>
<tr>
<td>Thaci 2016</td>
<td>Good</td>
<td>Adults, ≥18 years</td>
<td>379</td>
<td>16 weeks</td>
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</table>

**Response**

All 6 trials comparing dupilumab to placebo reported response to treatment, with all 6 using a score of 0 or 1 on the Investigator’s Global Assessment (IGA) to indicate disease clearing. All trials showed statistically significantly greater IGA responses in the dupilumab arms compared to placebo. The response rates were 11.8% to 40% for the dupilumab arms, with little difference between weekly and every other week dosing, and were 1.6% to 10.3% in the placebo arms. Meta-analysis including all 6 trials found an increased chance of achieving an IGA response (as defined in each trial) with dupilumab (EPC pooled RR 4.10, 95% CI 3.10 to 5.42, P<0.0001, I²=0%). See Figure 1 below (note: Beck 2004 presented pooled results of 2 trials).

**Figure 1. Treatment Response: Dupilumab Versus Placebo (Relative Risk)**

![Relative risk meta-analysis plot (random effects)](image)

The 2 trials comparing dupilumab plus corticosteroid to corticosteroid alone also reported a response to treatment, with both studies using a score of 0 or 1 on the IGA to indicate disease clearing. Pooling these 2 studies results in a significantly increased chance of...
response with dupilumab and corticosteroid than with corticosteroid alone (EPC pooled RR 3.94, 95% CI 2.93 to 5.31, P<0.0001, I²=0%).

**Symptoms**

These trials reported additional outcomes assessing symptom improvement, including percent change in EASI score, percent change in pruritus numerical-rating scale, and percent change in percentage of body-surface area affected (Table 3).

Dupilumab substantially increased the likelihood of achieving improvement on the EASI compared to placebo. Results were similar with weekly or every other week dosing and in patients treated or not treated with topical corticosteroids. Dupilumab also improved pruritus. Four trials assessed the reduction of pruritus symptoms using percent change from baseline peak numerical rating scale (NRS) score. Across the 4 trials, the reduction in peak NRS ranged from 40% to 56% in the dupilumab arms versus 5% to 29% in the placebo arms.17,26,50

### Table 3. Symptom Improvements with Dupilumab in Treatment-Resistant Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Percent Improvement in EASI Score</th>
<th>Percent Reduction in Body Surface Area Affected</th>
<th>Pruritus Numerical-Rating Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck 2014 23 (a) 4-week Monotherapy Study M4A and M4B</td>
<td>Dupilumab vs. Placebo: −57.7±3.9 vs. −25.4±10.1; (P&lt;0.001)</td>
<td>Dupilumab vs. Placebo: −37.4±4.7 vs. −15.3±9.0; (P&lt;0.05)</td>
<td>Dupilumab vs. Placebo: −41.3±4.3 vs. −18.6±12.1 (P&lt;0.05)</td>
</tr>
<tr>
<td>Beck 2014 23 (b) 12-week Monotherapy Study M12</td>
<td>Dupilumab vs. Placebo: −74.0±3.6 vs. −23.3±6.7; (P&lt;0.001)</td>
<td>Dupilumab vs. Placebo: −59.9±6.4 vs. −17.8±7.2</td>
<td>Dupilumab vs. Placebo: −55.7±3.8 vs. −15.1±5.7</td>
</tr>
<tr>
<td>Beck 2014 23 (c) 4-week Combination Therapy [M4B] Study C4</td>
<td>Dupilumab + Topical Glucocorticoids vs. Placebo + Topical Glucocorticoids: −75.6±2.9 vs. −52.5±12.5</td>
<td>Dupilumab + Topical Glucocorticoids vs. Placebo + Topical Glucocorticoids: −63.6±5.8 vs. −36.5±16.1</td>
<td>Dupilumab + Topical Glucocorticoids vs. Placebo + Topical Glucocorticoids: −70.7±4.7 vs. −24.7±15.0 (P&lt;0.05)</td>
</tr>
<tr>
<td>Blauvelt 2017 LIBERTY AD CHRONOS*</td>
<td>Dupilumab once weekly vs. Dupilumab once every 2 weeks vs. Placebo: −77.3% (±2.22); P&lt;0.0001 vs. −76.7% (±3.77); P&lt;0.0001 vs. −43.2% (±2.26)</td>
<td>NR</td>
<td>Dupilumab once weekly vs. Dupilumab once every 2 weeks vs. Placebo: −54.8% (±1.99) vs. −56.2% (±3.38) vs. −28.6% (±2.03)</td>
</tr>
</tbody>
</table>

Atopic dermatitis 11 of 31
### Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Percent Improvement in EASI Score</th>
<th>Percent Reduction in Body Surface Area Affected</th>
<th>Pruritus Numerical-Rating Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simpson 2016</td>
<td>Dupilumab weekly vs. Dupilumab every other week vs. Placebo:</td>
<td>NR</td>
<td>Dupilumab weekly vs. Dupilumab every other week vs. Placebo:</td>
</tr>
<tr>
<td>SOLO 1</td>
<td>−69.1±2.5 vs. −67.1±2.5 vs. −30.9±3.0</td>
<td>−48.9±2.6 vs. −51.0±2.5 vs. −26.1±3.0</td>
<td></td>
</tr>
<tr>
<td>Simpson 2016</td>
<td>Dupilumab weekly vs. Dupilumab every other week vs. Placebo:</td>
<td>NR</td>
<td>Dupilumab weekly vs. Dupilumab every other week vs. Placebo:</td>
</tr>
<tr>
<td>SOLO 2</td>
<td>−69.1±2.5 vs. −67.1±2.5 vs. −30.9±3.0</td>
<td>−48.3±2.4 vs. −44.3±2.3 vs. −15.4±3.0</td>
<td></td>
</tr>
<tr>
<td>Thaci 2016</td>
<td>300 mg once weekly vs. 300 mg every 2 weeks vs. 200 mg every 2 weeks vs. 300 mg every 4 weeks vs. 100 mg every 4 weeks vs. Placebo:</td>
<td>300 mg once weekly vs. 300 mg every 2 weeks vs. 300 mg every 4 weeks vs. 100 mg every 4 weeks vs. Placebo:</td>
<td>300 mg once weekly vs. 300 mg every 2 weeks vs. 300 mg every 2 weeks vs. 200 mg every 2 weeks vs. Placebo:</td>
</tr>
<tr>
<td></td>
<td>−73.7% (+/- 5.2) vs. −68.2% (+/- 5.1) vs. −65.4% (+/- 5.2) vs. −63.5% (+/- 4.9) vs. −44.8% (+/- 5.0) vs. −18.1% (+/- 5.2)</td>
<td>15.1 (+/- 17.2) vs. 22.5 (+/- 23.0) vs. 21.1 (+/- 23.0) vs. 23.2 (+/- 21.3) vs. 32.3 (+/- 27.0) vs. 43.9 (27.1)</td>
<td>3.07 (+/- 2.15) vs. 3.64 (+/- 2.39) vs. 4.21 (+/- 2.76) vs. 3.99 (+/- 2.45) vs. 5.26 (+/- 2.47) vs. 6.05 (+/- 2.31)</td>
</tr>
</tbody>
</table>

### Quality of Life

Dupilumab improved patient quality of life as measured by the Dermatology Life Quality Index (DLQI), and improved measures of anxiety and depression. See Table 4 below. Four trials measured the change in mean DLQI from baseline at 16 weeks and found greater improvement with dupilumab than placebo.\(^{17,26,50}\) Anxiety and Depression were measured by the Hospital Anxiety and Depression Scale (HADS) in 3 trials,\(^{17,26}\) and improvement was noted in patients taking dupilumab in all 3 studies.
Table 4. Quality-of-Life Improvements with Dupilumab in Treatment-Resistant Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Dermatology Life Quality Index</th>
<th>Hospital Anxiety and Depression Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blauvelt 2017</td>
<td>Dupilumab once weekly vs.</td>
<td>Dupilumab once weekly vs. dupilumab</td>
</tr>
<tr>
<td></td>
<td>dupilumab once every 2 weeks vs. placebo:</td>
<td>once every 2 weeks vs. placebo:</td>
</tr>
<tr>
<td></td>
<td>−10.5 (±0.30); P&lt;0.0001 vs. −9.7 (±0.51); P&lt;0.0001 vs. −5.3 (±0.31)</td>
<td>−5.2 (±0.33); P=0.0004 vs. −4.9 (±0.56); P=0.03 vs. −3.6 (±0.34)</td>
</tr>
<tr>
<td>LIBERTY AD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHRONOS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simpson 201617</td>
<td>Dupilumab weekly vs. dupilumab every other week vs. placebo:</td>
<td>Dupilumab weekly vs. dupilumab every other week vs. placebo:</td>
</tr>
<tr>
<td>SOLO 1</td>
<td>−9.0±0.4 vs. −9.3±0.4 vs. −5.3±0.5</td>
<td>−0.0 ± 0.8 vs. −2.4± 0.8 vs. −2.7 ± 0.8 vs. -4.0 ± 0.8 vs. -4.3 ± 0.8 vs. -4.6 ± 0.8</td>
</tr>
<tr>
<td>Simpson 201617</td>
<td>Dupilumab weekly vs. dupilumab every other week vs. placebo:</td>
<td>Dupilumab weekly vs. dupilumab every other week vs. placebo:</td>
</tr>
<tr>
<td>SOLO 2</td>
<td>−1.3 ± 0.9 vs. −2.2 ± 0.8 ± −6.2 ± 0.8 vs. −6.9 ± 0.8 vs. -9.3 ± 0.9</td>
<td>−9.0±0.4 vs. −9.3±0.4 vs. −5.3±0.5</td>
</tr>
<tr>
<td>Thaci 201650</td>
<td>300 mg once weekly vs. 300 mg every 2 weeks vs. 200 mg every 2 weeks vs. 300 mg every 4 weeks vs. 100 mg every 4 weeks vs. placebo:</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>−59.0% (± 7.14) vs. −39.6% (± 7.01) vs. −43.3% (± 7.18) vs. −37.4% (± 6.88) vs. -11.9% (± 6.88) vs. 2.6 (± 7.34)</td>
<td></td>
</tr>
</tbody>
</table>

Adverse Events
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. The most common adverse events 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 adverse events, but the rates were increased compared to placebo. The rates of any adverse event, serious adverse events serious adverse events, and discontinuation due to adverse event were slightly lower with dupilumab than placebo.

The 6 trials comparing dupilumab to placebo, found no statistically significant difference in withdrawals to adverse events between the 2 groups (EPC pooled RR 0.98; 95% CI 0.50 to 1.92, P=0.9618, I²=0%).

In 2 trials comparing dupilumab plus corticosteroid to corticosteroid alone, withdrawal due to adverse events was less likely for patients receiving dupilumab plus corticosteroids compared to corticosteroids alone (EPC pooled relative risk 0.43, 95% CI 0.15 to 1.4, P=0.1176, I²=0%). This result was not statistically significant.

Long-Term Management
One good-quality trial reported on results at 52 weeks.26 Through 52 weeks, fewer patients had flares of AD 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).
Moderate-to-Severe Symptoms

**Topical Calcineurin Inhibitors: Head-to-Head Comparisons**

There are 3 fair-quality RCTs, and 1 subgroup analysis from another RCT, comparing tacrolimus ointment (0.03% or 01%) with pimecrolimus 0.1% cream in patients with moderate-to-severe AD (Table 5).\textsuperscript{19,31,38,63} All of the patients in these studies were enrolled with the purpose of short-term treatment of active disease, with 1 requiring that patients have failed topical corticosteroids for enrollment.\textsuperscript{38} Three of the studies enrolled only children, 1 enrolled only adults, and 1 enrolled both. All but 1 study were 6 weeks in duration, with the other study being 12 weeks in duration. The smallest trial was open-label, while the other 3 were investigator-blinded. There were no head-to-head trials of crisaborole in this population.

<table>
<thead>
<tr>
<th>Author, year Quality</th>
<th>Population N</th>
<th>Duration</th>
<th>Disease severity</th>
<th>Tacrolimus Dosing</th>
<th>Pimecrolimus Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kempers 2004\textsuperscript{31} Fair</td>
<td>Children, 2 to 17 years 139</td>
<td>6 weeks</td>
<td>99% Moderate, 1% Severe per IGA</td>
<td>Tacrolimus 0.03% ointment twice daily</td>
<td>Pimecrolimus 1% cream twice daily</td>
</tr>
<tr>
<td>Paller 2005 (b)\textsuperscript{19} Fair</td>
<td>Children, 2 to 15 years 224</td>
<td>6 weeks</td>
<td>99% Moderate, Severe, or Very Severe per IGA</td>
<td>Tacrolimus 0.1% ointment twice daily</td>
<td>Pimecrolimus 1% cream twice daily</td>
</tr>
<tr>
<td>Abramovits, 2008a</td>
<td>Adults &gt; 16 years 98</td>
<td>6 weeks</td>
<td>100% Moderate subgroup\textsuperscript{a} per IGA</td>
<td>Tacrolimus 0.1% ointment twice daily</td>
<td>Pimecrolimus 1% cream twice daily</td>
</tr>
<tr>
<td>Onumah, 2013 Fair</td>
<td>Adults and children 20</td>
<td>12 weeks</td>
<td>Moderate* and failed topical steroids\textsuperscript{**}</td>
<td>Tacrolimus 0.03% (children) or 0.1% (adults) ointment twice daily</td>
<td>Pimecrolimus 1% cream twice daily</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Subgroup of Paller 2005-(c); * Criteria not reported; **Per patient report; IGA, Investigator’s Global Assessment

**Response**

All 4 trials reported response to treatment, with 3 using a score of 0 or 1 on the IGA to indicate disease clearing, and the 4th trial not describing the method of determining treatment success.\textsuperscript{38} Pooling these 4 studies results in a significantly lower chance of response with pimecrolimus than with tacrolimus (Figures 2 and 3, below). The pooled relative risk was 0.73, P=0.02, with low statistical heterogeneity (\(I^2=33.1\%\)). However, the absolute difference in risk was very small and not statistically significant (-0.09%, P=0.18), with moderate statistical heterogeneity (\(I^2=68\%\)). This difference in results based on the effect measure chosen indicates less certainty in the benefit of tacrolimus over pimecrolimus.
We conducted a network meta-analysis of the 4 head-to-head trials, and 11 placebo- or steroid-controlled trials of drugs used to treat AD for the outcome of response (Table 3). The diagram of the network for response in patients with moderate-to-severe AD is shown in Figure 3. The size of the nodes and lines reflect the numbers of trials for each comparison in the network. We did not include studies comparing a corticosteroid with
placebo in the network, so there is not line connecting that comparison. In this network, tacrolimus had the largest number of trials, and the comparison to placebo was the most frequent. In this network meta-analysis, we found that there was not a significant difference between tacrolimus and pimecrolimus (Table 6, Figure 4). Both drugs were found superior to placebo, but only tacrolimus was superior to corticosteroids in this population. The studies in this network reported response using a variety of tools, or tools that were described using differing names, with the most common being the IGA, with scores of 0 (clear) or 1 (almost clear) indicating response to treatment and most being investigator assessments. Details on scales can be found in Appendix B. These studies ranged in duration from 3 to 12 weeks. The results of this network analysis were found to be statistically consistent (an assessment of the model's internal consistency). These findings support the conclusion that there is not a significant difference between tacrolimus and pimecrolimus in the incidence of response to treatment.

Table 6. Network Meta-Analysis: Response in Moderate-to-Severe Atopic Dermatitis

<table>
<thead>
<tr>
<th></th>
<th>Pimecrolimus Versus Left Column</th>
<th>Tacrolimus Versus Left Column</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Pimecrolimus</td>
<td>0.78 (0.47,1.31)</td>
<td>1.28 (0.77,2.14)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>1.42 (0.68,2.98)</td>
<td>1.83 (1.07,3.10)</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>2.53 (1.51,4.23)</td>
<td>3.24 (2.08,5.06)</td>
</tr>
</tbody>
</table>

Bold = statistically significant difference

Symptoms
These trials reported additional outcomes assessing symptom improvement, including 2 patient-reported measures of improvement in symptoms (EASI scale and assessments of pruritus on a visual analog scale, VAS; Table 4), and the investigator-reported outcome of percent reduction in body surface area affected. Data were not combinable in meta-analyses, due to inadequate reporting of variance measures. Only 2 of the trials measured improvements in symptoms using the EASI scale, with both finding tacrolimus superior to pimecrolimus by 11% to 16%.
Improvements in the percent of body surface area affected by AD varied widely across the studies, from a 64.6% reduction with tacrolimus in 1 study down to a 7% improvement with tacrolimus in another study. The differences in improvement were statistically significantly greater with tacrolimus in 2 of 3 investigator-blinded trials. A fourth, very small, open-label trial reported that improvement was significantly better with pimecrolimus, but the difference was only 5% and the P-value was not reported. Improvements in the head and neck area were not different between the drugs in 1 study, but were found significantly better with tacrolimus in another (Table 7). Pruritus was improved more with tacrolimus in 1 of 3 studies reporting this outcome.

### Table 7. Symptom Improvement: Pimecrolimus vs. Tacrolimus In Moderate-to-Severe Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Percent Improvement in EASI Score</th>
<th>Percent Reduction in Body Surface Area affected</th>
<th>Pruritus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kempers, 2004 Children</td>
<td>NR</td>
<td>Whole body: 43.3% vs. 44.5%</td>
<td>Pruritus score of 0 or 1 (absent or mild) at day 43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Head/neck: 53.7% vs. 34.9%</td>
<td>64% vs. 70% (reported as NSD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower limbs: 29.3% vs. 41.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper limbs: 35.3% vs. 38.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(all reported as NSD)</td>
<td></td>
</tr>
<tr>
<td>Paller, 2005 Children</td>
<td>56.4% vs. 67.2%; P=0.04</td>
<td>47.5%, vs. 64.6%; P&lt;0.001</td>
<td>VAS: -2.0 cm vs. -3.7 cm; P≤0.01</td>
</tr>
<tr>
<td>Onumah 2013 Adults and</td>
<td>NR</td>
<td>11.94% vs. 7% (reported to be SS)</td>
<td>NR</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abramovits, 2008 Adults</td>
<td>42.8% vs. 59.0%; P=0.01</td>
<td>36.1% vs. 49.6% (P 0.10)</td>
<td>3 cm decrease on VAS reported for tacrolimus, and</td>
</tr>
<tr>
<td>98</td>
<td></td>
<td>Head and neck: 54.1% vs. 75.2% (P=0.04)</td>
<td>that change with pimecrolimus was similar.</td>
</tr>
</tbody>
</table>

NSD, not statistically significantly different; NR, not reported; SS, statistically significant; VAS, visual analog scale (0-100)

### Quality of Life

Only the very small 12-week, open-label trial reported quality of life, using the Dermatology Life Quality Index. The difference between groups was not statistically significant (mean change: -4.7 points vs. -3.6 points, P-value not reported).

### Adverse Events

Withdrawal due to adverse events was not different between pimecrolimus and tacrolimus, based on 3 trials (EPC pooled relative risk 1.16, 95% CI 0.43 to 3.14, I²=0%). Specific adverse events reported included application site reactions and skin infections. Application site reactions were evaluated in 3 trials, with 1 trial reporting these as the primary outcome. This trial in children with moderate AD reported similar proportions of patients with any application site reaction at 4 days (28% versus 24%), and also reported that the incidence decreased over time. The types of reactions reported were burning or stinging, itching, and erythema or irritation.
Across the 3 trials, significant differences were not consistently found in specific application site reactions, or other adverse events, such as skin infections.19,31,63

**Topical Calcineurin Inhibitors: Comparisons with Corticosteroids**

We found 1 good-quality systematic review, and 3 additional trials not included in the systematic review that met our inclusion criteria.30,32,41 The systematic review included 12 RCTs comparing calcineurin inhibitors (n=3492) versus corticosteroids (n=3462) in children and adults.60 Eleven of the 12 trials were conducted among patients with moderate-severe AD. The systematic review did not specify the potency of the corticosteroids used in the studies. The included trials were published between 2001 and 2015. Mean follow-up was 101 weeks (range 2-260 weeks). All participants applied calcineurin inhibitors or corticosteroids twice daily and all but 1 trial was funded by a pharmaceutical company. Mean age, sex, and percentage affected body surface were divided equally between both arms.

Two of the additional RCTs identified were of poor quality.30,41 The third RCT was of fair quality (n=60) and compared the efficacy of 0.1% mometasone furoate (n=30) to tacrolimus 0.03% ointment in children and adults with AD in Bangladesh.32 Both treatments were applied daily for 12 weeks. Patients were followed up monthly. Disease severity was assessed using the SCORAAD, and a 4-point scale was used to measure the level of response to treatment. Baseline characteristics were similar for patients in both groups; baseline severity was reported using the SCORAD (30.90 ± 17.17 for the mometasone furoate group vs. 30.57 ± 13.62 for the tacrolimus group).32 We made the assumption that a SCORAD of 30 indicated most patients had moderate AD.65

**Response**

Treatment success was similar in the systematic review for calcineurin inhibitors and corticosteroids (72% vs. 68%; RR from review 1.15; 95% CI 1.00 to 1.31; P=0.04). Subgroup analysis with stratification of tacrolimus and pimecrolimus were in line with these results. There was high heterogeneity across studies (I²=93%).60 The methods or score(s) used to determine treatment success across studies were not disclosed.

There was no statistically significant difference in response between mometasone furoate and tacrolimus in the fair-quality RCT. At final follow-up 56.7% of patients in the mometasone furoate group and 63.3% of patients in the tacrolimus group achieved excellent response; 13.3% of the mometasone furoate group and 16.7% of the tacrolimus group achieved good response.32

**Symptoms**

In the systematic review, calcineurin inhibitors and corticosteroids had a similar percentage of patients with improvement of dermatitis (81% vs. 71%; RR from review 1.18; 95% CI 1.04 to 1.34; P=0.02). Subgroup analysis with stratification of tacrolimus and pimecrolimus were in line with these results. There was a high degree of heterogeneity across studies (I²=96%).60 The methods or score(s) used to determine improvement across studies were not reported.

In the fair-quality RCT, patients in the tacrolimus group experienced a slightly greater SCORAD percent reduction, compared to patients receiving mometasone furoate (74.77 ± 23.30 vs. 69.20 ± 23.41, P=0.360), but this was not statistically significant.
Quality of Life
Neither the systematic review nor the fair-quality RCT reported quality-of-life measures.

Adverse Events
In the systematic review, there were no differences in adverse events requiring discontinuation (1.8% vs. 1.9%; RR in review 0.95; 95% CI 0.66 to 1.38; P=0.79), severe adverse events (8.2% vs. 7.2%; RR in review 1.15; 95% CI 0.98 to 1.34; P=0.08), atrophy (0.8% vs. 0%; RR in review 5.66; 95% CI 1.00 to 31.91; P=0.05), or skin infection (12% vs. 11%; RR in review 1.08; 95% CI 0.94 to 1.24; P=0.29) between the corticosteroid and calcineurin treatment groups. The number of adverse events (74% vs. 64%; RR in review 1.28; 95% CI 1.05 to 1.58; P=0.02) and adverse events related to treatment (11% vs 8%; RR in review 1.45; 95% CI 1.15 to 1.83; P=0.002) were higher in the calcineurin inhibitor group compared with the corticosteroid group, with a higher rate of skin burning (30% vs. 9%; RR in review 3.27; 95% CI 2.48 to 4.31; P<0.00001) and pruritus (12% vs. 8%; RR in review 1.49; 95% CI 1.24 to 1.79; P<0.00001). Subgroup analysis after stratification of tacrolimus and pimecrolimus were in line with the main analysis, but the difference in adverse events did not reach significance in the pimecrolimus group.60

The newer fair-quality RCT, not included in the systematic review, did not report on adverse events.32

Mild-to-Moderate Symptoms
Crisaborole: Placebo (Vehicle) Comparisons
We found no studies comparing crisaborole with a topical calcineurin inhibitor, dupilumab, or corticosteroids. To date, there are only 3 trials of crisaborole, all comparing to placebo (vehicle) in patients with mild-to-moderate AD.18,37 The 2 larger studies were similar designs and enrolled children (N=1522) with mild-to-moderate AD (39% mild), with 18% body surface area affected. These trials compared crisaborole to vehicle for 4 weeks. The other study was a very small 6-week trial in adults (N=25) with mild-to-moderate disease and was fair quality. We also found a recent, good-quality systematic review that evaluated these studies.59

Response
Crisaborole resulted in significantly more patients achieving response (Figure 5); 44% vs 21%, relative risk 1.67 (95% CI 1.15 to 2.47) using the Investigator’s Static Global Assessment tool in children or the AD Severity Index (ADSI) score in adults, with total or partial clearance of disease constituting response. There was moderate statistical heterogeneity in this analysis, I²=68%, likely due to the larger treatment effect seen in the very small study of adults. The recent systematic review came to the same conclusion, based on the 2 studies in children only.59
Symptoms

Crisaborole was superior to placebo on all measures of individual symptom improvement in all 3 trials.\textsuperscript{18,37,59} In the 2 trials of children, improvement was seen in more patients using crisaborole than placebo in 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\%; \(P<0.001\)).\textsuperscript{59} These were investigator assessments. Patient assessment of pruritus improvement at day 29 was also greater with crisaborole (63\% vs. 53\%; \(P=0.002\)).

Quality of Life

The systematic review reported that quality of life was improved with crisaborole, based on the Children’s Dermatology Life Quality Index (CDLQI), based on data presented in a poster, but that the magnitude of difference was unlikely to be clinically meaningful.\textsuperscript{59}

Adverse Events

In these trials there were no serious adverse events reported, and very few patients withdrew due to adverse events (no differences between groups). Application site reactions were the most common adverse event reported (4.6\% versus 1.7\%). Other adverse events reported were not different between groups.

Topical Calcineurin Inhibitors: Head-to-Head Comparisons

There are 2 fair-quality trials of patients with mild or mild-to-moderate disease that compared tacrolimus ointment (0.03\% or 01\%) with pimecrolimus 0.1\% cream (Table 8).\textsuperscript{19} These studies were published in 1 publication, 1 in children, all with mild disease, and 1 in adults with any level of disease. The majority of the adult patients had mild (32\%) or moderate (45\%) disease; a subgroup analysis of only those with moderate disease is included in the section above. All of the patients in these studies were enrolled with the purpose of short-term treatment of active disease, but neither required failure of topical corticosteroid treatment for enrollment nor
reported the proportion with lack of response to topical steroids. These studies were 6 weeks in duration and the investigators were blinded to treatment when conducting assessments. There were no head-to-head trials of crisaborole in this population.

Table 8. Head-to-Head RCTs in Patients with Mild-to-Moderate Atopic Dermatitis

<table>
<thead>
<tr>
<th>Author Year Quality</th>
<th>Population</th>
<th>N</th>
<th>Duration</th>
<th>Disease Severity</th>
<th>Tacrolimus Dosing</th>
<th>Pimecrolimus Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paller 2005</td>
<td>Children, 2 to 15 years</td>
<td>423</td>
<td>6 weeks</td>
<td>Mild</td>
<td>Tacrolimus 0.03% ointment twice daily</td>
<td>Pimecrolimus 1% cream twice daily</td>
</tr>
<tr>
<td>Paller 2005</td>
<td>Adults, &gt;16 years</td>
<td>413</td>
<td>6 weeks</td>
<td>Mild, Moderate, or Severe</td>
<td>Tacrolimus 0.1% ointment twice daily</td>
<td>Pimecrolimus 1% cream twice daily</td>
</tr>
</tbody>
</table>

*aSubgroup of Paller 2005-(c)*

**Response**
At 6 weeks, there was no difference between the drugs in children with mild AD; 46.9% of those using tacrolimus and 40.7% of those using pimecrolimus had response, based on the investigator’s assessment (Table 6). In adults with mild-to-moderate AD, response was significantly greater with tacrolimus (45.7%) than with pimecrolimus (27.1%; P=0.07).19

**Symptoms**
In children with mild AD, there was no difference between the drugs in the reduction in body surface area affects (an investigator assessed measure) (Table 9). Both patient-reported outcomes found tacrolimus to be significantly better than pimecrolimus. The difference in pruritus rating, however, was very small (0.7 cm on a 100 cm visual analog scale). The difference in EASI scores was larger (close to 10%).19

In adults with mild-to-moderate disease, tacrolimus was significantly better than pimecrolimus in symptom improvement measures in Table 7, although again the difference in improvement in pruritus was very small (0.7 cm on a 100 cm visual analog scale). There was a 16% difference in reduction in affected body surface area, and a 19% greater improvement in the EASI scale scores.19

Table 9. Response and Symptoms Improvement in Patients with Mild-to-Moderate Disease

<table>
<thead>
<tr>
<th>At 6 Weeks</th>
<th>Response (IGA 0 or 1)</th>
<th>Reduction in % BSA affected</th>
<th>Change in Pruritus</th>
<th>Percent Improvement in EASI Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tacrolimus Versus Pimecrolimus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paller, 2005</td>
<td>46.9% vs. 40.7%, P=NSD</td>
<td>57.1% vs. 50.2%, P=NSD</td>
<td>-2.0 cm vs. -2.7 cm (P≤0.01)</td>
<td>52.1% vs. 42.7%, P=0.07</td>
</tr>
<tr>
<td>Paller, 2005</td>
<td>45.7% (P≤0.0001) vs. 27.1%, P=0.07</td>
<td>50.2 vs 33.8; P&lt;0.001</td>
<td>-3.8 cm vs. -3.1 cm; P≤0.01</td>
<td>% 54.1% vs. 34.9%; P≤0.0001</td>
</tr>
</tbody>
</table>

BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator’s Global Assessment, NSD, no significant difference
Quality of Life
Neither of these trials measured quality of life.

Adverse Events
Adverse event outcomes differed somewhat across the 2 trials (Table 10). In children with only mild AD, there was a higher proportion withdrawing due to adverse events with pimecrolimus (EPC calculated relative risk 0.05, 95% CI 0.003 to 0.83; P=0.04). The study authors did not discuss possible reasons for this difference. The incidence of application site reactions, skin infections, acne and herpes simplex was not statistically different between the groups, although there was numerically greater incidence of burning with pimecrolimus (9.2%) than with tacrolimus (5.3%).

In adults with mild-to-moderate disease, there were not differences in withdrawals due to adverse events, but significantly more patients reported burning with tacrolimus than with pimecrolimus (8% more, P=0.02). Other application site reactions, or other adverse events occurred in similar proportions of patients with both drugs.

Table 10. Adverse Events: Tacrolimus and Pimecrolimus in Mild-to-Moderate Atopic Dermatitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Adverse Event Withdrawals</th>
<th>Application Site Reactions</th>
<th>Other Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paller, 2005</td>
<td>Children</td>
<td>0/209 (0%) vs 10/217 (4.6%)</td>
<td>Burning: 5.3% vs. 9.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pruritus: 5.3% vs. 6.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pain: 1.9% vs. 1.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Erythema: 1.0% vs. 1.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Skin infection: 0.0% vs. 0.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acne: 0.5% vs. 0.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Herpes simplex: 0.5% vs. 0.0%</td>
</tr>
<tr>
<td>Paller, 2005</td>
<td>Adults</td>
<td>6/210 (2.9%) vs 5/203 (2.5%)</td>
<td>Burning: 19.5% vs. 11.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pruritus: 9.5% vs. 6.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pain: 2.9% vs. 1.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Skin infection: 0% vs 1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acne 0.5% vs 1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Herpes Simplex: 0.5% vs. 0.5%</td>
</tr>
</tbody>
</table>

Serious Harms: Cancer
The risk of cancers in patients with AD has been studied in 9 cohort and 19 case-control studies. Many of these were included in a good-quality systematic review that specifically examined the risk of lymphoma with the use of topical calcineurin inhibitors.61

Lymphoma
The systematic review found that there is a small increased risk of lymphoma among patients with AD compared to the general population, based on 4 cohort studies (odds ratio 1.43, 95% CI 1.12 to 1.81). The mean age of patients in these studies was not reported. Among patients with AD, the risk of lymphoma was not significantly increased with either tacrolimus (2 studies, odds ratio 3.13, 95% CI 0.67 to 14.57) or pimecrolimus (2 studies, 1.58, 95% CI 0.83 to 3.00) use. Case control studies found no increased risk among patients with AD versus patients without AD, or with the topical calcineurin inhibitors. Evidence from cohort and case-control studies was conflicting for the risk with high-potency topical corticosteroids. A large fair-quality cohort study (N=953,064) conducted using data from Kaiser that was not included in the systematic review reported increased risk of T-cell lymphoma after covariate adjustment with tacrolimus (odds
ratio 3.13, 95% CI 1.41 to 6.94; P=0.005) compared with patients with AD not exposed to tacrolimus, but no increased risk with pimecrolimus (odds ratio 1.86, 95% CI 0.71 to 4.87; P=0.204). Follow-up was 6-months in this study, based on the reported timing of occurrence of cancers in the FDA’s review documents (range 90 to 159 days). In a fair-quality study of only children, conducted in the United States, using the Pediatric Eczema Elective Registry (N=7,457) there was not an increased risk of lymphoma with pimecrolimus compared with the general population (odds ratio 2.9, 95% CI 0.7 to 11.7). The study was developed with input from the FDA, and had 26,792 person-years of follow-up.56 Tacrolimus was not studied in this evaluation.

**Nonmelanoma Skin Cancer**
A poor-quality case-control study (N=2,821) of children found no increased risk of skin cancer with previous use of topical calcineurin inhibitors (adjusted odds ratio 0.50, 95% CI 0.25 to 0.98).57 This study relied on survey data, with the potential for recall bias.

**Any Cancer**
Three fair-quality cohort studies reported on the risk of any cancer with use of topical calcineurin inhibitors in patients with AD.54-56 In pediatric patients (described above), there was no increased risk found compared with the general population (odds ratio 1.2, 95% CI 0.5 to 2.8).56 The other 2 studies (Table 11) found the difference in risk for having used tacrolimus or pimecrolimus versus non-use to be not statistically significant, although the odds ratios favored tacrolimus (lower risk), with a potential small increased risk with pimecrolimus. Both studies had relatively short follow-up for studies of cancer development, based on the FDA’s analysis that cancers reported occurred at means of 90 to 159 days after treatment initiation.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Country</th>
<th>Tacrolimus Versus Non-Use</th>
<th>Pimecrolimus Versus Non-Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cai, 2016</td>
<td>66,176</td>
<td>Singapore</td>
<td>0.82 (0.44 to 1.39)</td>
<td>1.30 (0.59 to 2.45)</td>
</tr>
<tr>
<td>Hui, 2009</td>
<td>953,064</td>
<td>USA</td>
<td>0.93 (0.81 to 1.07)</td>
<td>1.15 (0.99 vs. 1.31)</td>
</tr>
</tbody>
</table>

**Network Meta-analysis: Crisaborole, Pimecrolimus, Tacrolimus and Placebo (Vehicle) Response**
We conducted a network meta-analysis of 2 head-to-head trials, 3 crisaborole versus placebo trials, and another 6 placebo-controlled trials of the topical calcineurin inhibitors in patients with mild-to-moderate AD for the outcome of response (Table 12, Figure 6).18,19,24,28,29,33,36,37,46 The network pools response outcomes from 4 different scales (IGA/IGADA, EASI, ISGA, and ADSI), but all of the studies were of similar durations. See Appendix B for a description of these scales. The diagram of the network for response in patients with moderate-to-severe AD is shown in Figure 4. In this network, pimecrolimus had the largest number of trials, and the comparison to placebo was the most frequent. The size of the nodes and lines reflect the numbers of trials for...
each comparison in the network. The results of this network analysis were found to be statistically consistent (an assessment of the model’s internal consistency). These results are more consistent with the findings of the head-to-head study in patients with either mild or moderate disease. In patients with mild disease only, there is less evidence to support a difference between the drugs, and the 3 trials of crisaborole were all in patients with mild disease only. Using network meta-analysis including, we found that tacrolimus had greater response than crisaborole, and that all 3 drugs were superior to placebo (vehicle). Other significant differences were not found.

Table 12. Network Meta-Analysis: Response in Moderate-to-Severe Atopic Dermatitis

<table>
<thead>
<tr>
<th></th>
<th>Crisaborole Versus Column on the Left</th>
<th>Tacrolimus Versus Left Column</th>
<th>Pimecrolimus Versus Left Column</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Crisaborole</td>
<td>-</td>
<td>1.57 (1.03,2.38)</td>
<td>1.22 (0.84,1.77)</td>
</tr>
<tr>
<td>Pimecrolimus</td>
<td>0.82 (0.57,1.19)</td>
<td>1.29 (0.98,1.69)</td>
<td>--</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>0.64 (0.42,0.97)</td>
<td>--</td>
<td>0.78 (0.59,1.02)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.48 (1.12,1.95)</td>
<td>2.32 (1.69,3.18)</td>
<td>1.80 (1.40,2.32)</td>
</tr>
</tbody>
</table>

*Bold = statistically significant difference*

Figure 6. Network Meta-Analysis: Response in Moderate-to-Severe Atopic Dermatitis

In this network meta-analysis of 11 trials in patients with mild-to-moderate AD, we found crisaborole to be superior to placebo (vehicle), inferior to tacrolimus, and not significantly different to pimecrolimus in treatment response (Table 12). A recent, good quality systematic review also reviewed the evidence on crisaborole. This review included only the 2 larger crisaborole trials (excluding a small pilot study), and conducted indirect comparison meta-analysis using a Bayesian approach that included only 2 additional studies of pimecrolimus versus placebo. Their findings were similar to ours in that crisaborole was not significantly different to pimecrolimus (RR 0.61, 95% CI 0.10 to 2.28). However, this Bayesian analysis found that neither crisaborole (RR 1.57, 95% CI 0.27 to 3.98), or pimecrolimus (RR 2.59, 95% CI 0.98 to 4.44) were superior to placebo in treatment response. The review also notes that they found
pimecrolimus to be inferior to tacrolimus and moderate potency corticosteroids, but data for these findings were not presented.

Key Question 3: Effectiveness and Harms in Subgroups of Patients with Atopic Dermatitis

Information on potential differences in effects of tacrolimus and pimecrolimus in subgroups of the population are very limited and inconclusive. In head-to-head studies, only location of affected skin was analyzed as subgroup analyses (in 2 trials). The remainder of the evidence on subgroups is indirect (i.e., from vehicle-controlled trials) and from analyses conducted post-hoc. This evidence is included here, from the previous version of this report for completeness.

Location of Affected Skin

A pooled analysis of the 3 trials published in 1 manuscript reported efficacy results for patients with head/neck involvement. Of 1060 patients across 3 trials, 710 patients with mild to severe disease had head/neck involvement. In this subgroup, a larger proportion of tacrolimus-treated patients experienced improvements in their EASI scores from baseline than pimecrolimus-treated patients at the end of 6 weeks (tacrolimus, 57% improvement compared with pimecrolimus 42%, P=0.01). Results for other body areas were not reported. In contrast to these findings, a smaller study of children with moderate-to-severe AD (N=139) found greater change in the body surface area affected with pimecrolimus (53.7%) than with tacrolimus (34.8%) in patients with head/neck involvement. The study also found that affected body surface area was improved more with tacrolimus (53.7%) than pimecrolimus (34.9%) in patients with lower limb involvement. While these differences are close to 19%, they were not statistically significant.

High Percentage of Body Surface Area with Atopic Dermatitis

In a small subset of adults with >75% body surface area affected by AD (N=82), patients receiving tacrolimus 0.1% ointment were more likely to achieve treatment success than patients receiving tacrolimus 0.03% ointment applied twice daily (30.2% vs. 5.1%, P=0.004) at the end of 12 weeks.

Baseline Disease Severity

Patients with mild disease who were randomized to tacrolimus 0.03% ointment exhibited greater treatment success (tacrolimus 56.7% vs. vehicle 32.3%, P=0.0007) than in patients with moderate disease (tacrolimus 41% vs. vehicle 15.9%, P=0.001). Another study showed little difference in the treatment effect of pimecrolimus 1% cream in patients with mild and moderate disease compared with patients with severe disease (estimated between-group difference in percent change in EASI score: 4.7%).

Age

In 1 pimecrolimus versus vehicle trial, infants 3 months to 1 year of age exhibited larger treatment effect in the proportion of patients with IGA score ≤1 than those who were 1 to 2 years of age (65.5% compared with 46.3%).
**Ethnicity**

A post-hoc analysis of a vehicle-controlled trial of tacrolimus and pimecrolimus (N=589) found no difference between white and multiracial patients in their response to pimecrolimus 1% cream (vehicle-corrected value in percent patients with IGA score ≤1: white 21.4% and multiracial 20.6%, P>0.5). The multiracial group included: 41.8% black, 11.6% Asian, and 46.6% Hispanic patients. Another post hoc analysis suggested that black adults (N=110) had better response in achieving >90% improvement of disease with tacrolimus 0.1% ointment (29.1% compared with vehicle, 7%, P=0.002) than with tacrolimus 0.03% ointment (16.4% compared with vehicle 7%, P=0.112) applied twice daily.

**Summary**

Comparative evidence was limited to the topical calcineurin inhibitors, tacrolimus, and pimecrolimus. While some measures favored tacrolimus, there was no consistent evidence of important differences between these drugs. Application site reactions were the most common adverse events experienced, with some indication that children have less with tacrolimus and adults have less with pimecrolimus. There is no comparative evidence for dupilumab or crisaborole. Dupilumab was superior to placebo with or without topical corticosteroids, in patients who had not responded to topical treatments. Long-term safety of dupilumab is unclear. Crisaborole was superior to placebo in mild-to-moderate atopic dermatitis, and was found to have similar response compared with pimecrolimus in network meta-analysis.

**References**


22. Bauer A, Lange N, Matterne U, Meurer M, Braeutigam M, Diepgen TL. Efficacy of pimecrolimus 1% cream in the long term management of atopic hand dermatitis. A


