

# Application of Topical Phosphodiesterase 4 Inhibitors in Mild to Moderate Atopic Dermatitis

## A Systematic Review and Meta-analysis

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 Supplemental content

**IMPORTANCE** Topical medication is the central treatment for patients with atopic dermatitis (AD), but the options are limited. Phosphodiesterase 4 (PDE4) inhibitors are a new candidate for AD therapy.

**OBJECTIVE** To evaluate the efficacy and safety of topical PDE4 inhibitors in mild to moderate AD.

**DATA SOURCES** Clinical trials were identified from MEDLINE, Embase, Cochrane Controlled Register of Trials, Chinese medical databases (Wanfang, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database, and China Science and Technology Journal Database), ClinicalTrials.gov, and other trial registries from inception to August 15, 2018. No restrictions on languages were placed.

**STUDY SELECTION** Only double-blind randomized clinical trials with topical PDE4 inhibitors vs topical vehicle treatment for patients with mild to moderate AD were included.

**DATA EXTRACTION AND SYNTHESIS** Two reviewers independently extracted study features, intervention details, and outcomes. A meta-analysis was performed using the random-effects model. The Cochrane Collaboration's risk of bias assessment tool was used to assess the risk of bias. Funnel plots and Egger tests were used to assess the publication bias.

**MAIN OUTCOMES AND MEASURES** Changes from baseline in target lesion score were expressed in terms of standardized mean differences (SMDs) with 95% CIs. Outcomes of investigators' assessment and safety were expressed in terms of relative risk with 95% CIs.

**RESULTS** Seven studies were identified, which included 1869 patients with mild to moderate AD. Overall, compared with the topical vehicle control, topical application of PDE4 inhibitors was associated with a significant decrease in target lesion score (SMD  $-0.40$ ; 95% CI,  $-0.61$  to  $-0.18$ ;  $P < .001$ ) and a higher response rate in investigators' assessment of clear or almost clear skin (relative risk,  $1.50$ ; 95% CI,  $1.33$ - $1.70$ ;  $P < .001$ ). There was no difference in treatment-related adverse events or in adverse events that required discontinuation of therapy. Subgroup analyses indicated that after 14 and 28 days of therapy with PDE4 inhibitors, target lesion score was significantly decreased. However, these beneficial effects were displayed only for the PDE4 inhibitors crisaborole and AN2898 (crisaborole at day 14: SMD,  $-0.59$ ; 95% CI,  $-1.15$  to  $-0.02$ ;  $P = .04$ ; AN2898 at day 14: SMD,  $-0.76$ ; 95% CI,  $-1.38$  to  $-0.13$ ;  $P = .02$ ; crisaborole at day 28: SMD,  $-0.86$ ; 95% CI,  $-1.44$  to  $-0.28$ ;  $P = .004$ ; AN2898 at day 28: SMD,  $-0.68$ ; 95% CI,  $-1.30$  to  $-0.05$ ;  $P = .03$ ). Heterogeneity was not significant across studies.

**CONCLUSIONS AND RELEVANCE** This meta-analysis suggests that topical PDE4 inhibitors are a safe and effective treatment for mild to moderate AD. Current evidence supports the use of crisaborole or AN2898 as the choice of maintenance or sequential therapy for mild to moderate AD.

JAMA Dermatol. doi:10.1001/jamadermatol.2019.0008  
Published online March 27, 2019.

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Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, affecting approximately 20% of children and 3% of adults,<sup>1</sup> and it imposes a significant financial and societal burden because of the direct medical costs and decreased productivity of individuals with AD.<sup>2,3</sup> The burden of AD appears to be related mainly to the limited methods of treatment. Furthermore, according to the AD treatment guidelines,<sup>4</sup> there is no standard of care, and treatment should be tailored to an individual's needs.

Topical interventions are the mainstay of AD therapy. Until now, topical corticosteroids have been the first-line treatment. However, their use is limited by potential local and systemic adverse effects. Topical calcineurin inhibitors are classified as second-line anti-inflammatory therapy for AD, with advantages in long-term maintenance and application to special sites.<sup>5</sup> Topical calcineurin inhibitors inhibit calcineurin-dependent T-cell activation, suppress mast cell activation, and decrease the activation of epidermal dendritic cells.<sup>6</sup> However, the black box warning about potential for developing malignant neoplasms with the use of topical calcineurin inhibitors<sup>7</sup> reduces patients' adherence to treatment.

Therefore, novel topical therapies are needed to improve the risk-benefit profile of current treatments. Phosphodiesterase 4 (PDE4) inhibitors are the new nonsteroidal, anti-inflammatory agents being investigated for the treatment of AD and psoriasis.<sup>8</sup> Phosphodiesterase 4 is a key regulator of inflammatory cytokine production that converts the intracellular secondary messenger cyclic adenosine monophosphate into 5'-adenosine monophosphate, which promotes proinflammatory responses.<sup>8</sup> In patients with AD, PDE activity is increased, and inflammatory cytokines, such as interleukin (IL)-4, IL-13, and IL-31, are overexpressed.<sup>9,10</sup> Therefore, PDE is a therapeutic target in AD to increase intracellular levels of cyclic adenosine monophosphate and reduce the release of inflammatory cytokines.<sup>11</sup>

Recently, treatment of AD using different types and varied concentrations of PDE4 inhibitors has been evaluated in different populations. However, the effectiveness of the different types of PDE4 inhibitors is still under debate. Although Nemoto et al<sup>12</sup> did not find a significant difference between the PDE4 inhibitor E6005 and vehicle treatment in lowering severity score, a large sample clinical trial showed that more patients with AD achieved success in the Investigator's Static Global Assessment with crisaborole than with vehicle treatment.<sup>13</sup> In addition, although the US Food and Drug Administration approved crisaborole ointment in December 2016 for the treatment of mild to moderate eczema or AD in patients 2 years of age or older, until now, the efficacy and safety of topical PDE4 inhibitors for the treatment of AD have not yet been systematically analyzed using randomized clinical trials. Therefore, the aim of this study was to quantitatively synthesize current evidence on the efficacy and safety of topical PDE4 inhibitors in the treatment of mild to moderate AD using a meta-analysis, which may provide more details to facilitate clinical decision making.

## Key Points

**Questions** Are topical phosphodiesterase 4 inhibitors safe and effective as treatment of mild to moderate atopic dermatitis?

**Findings** In this meta-analysis, 7 double-blind randomized clinical trials of topical phosphodiesterase 4 inhibitors vs vehicle treatment for 1869 patients with mild to moderate atopic dermatitis were included. Topical application of phosphodiesterase 4 inhibitors was associated with a statistically significant improvement in both target lesion score and investigators' assessment of atopic dermatitis compared with the control vehicles.

**Meaning** Topical phosphodiesterase 4 inhibitors represent a new option for the management of atopic dermatitis.

## Methods

This meta-analysis was conducted and reported in accordance with the standard methodological guidelines for meta-analysis of randomized clinical trials<sup>14</sup> and the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (PRISMA).<sup>15</sup> It is also registered in PROSPERO (<https://www.crd.york.ac.uk/prosperto/>). The methods of this meta-analysis were prespecified in a previously published protocol (PROSPERO: registration number CRD42018107082). Modifications to that protocol are described in the eAppendix in the Supplement.

## Search Strategy

We searched electronic databases (Cochrane Controlled Register of Trials, MEDLINE, and Embase), Chinese medical databases (Wanfang, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database, and China Science and Technology Journal Database), and ClinicalTrials.gov from inception to August 15, 2018. We also searched unpublished trials on the US Food and Drug Administration website and the reference lists of all identified relevant studies.

The detailed search strategies used in Cochrane Controlled Register of Trials, MEDLINE, and Embase are described in eTable 1 in the Supplement. The search strategies were modified to meet the requirements of different databases.

## Study Selection

Two of us (H.Y. and J.W.) independently screened the records based on titles and abstracts using these search strategies to identify and assess potentially eligible studies. Disagreements were resolved by consensus. Full-text copies of potentially relevant articles were obtained and reviewed for eligibility. We included all randomized clinical trials that compared topical PDE4 inhibitors with vehicle treatment for patients with mild to moderate AD, regardless of age, sex, race/ethnicity, concentration, dose, and duration of treatment. We excluded duplicate publications, nonhuman studies, conference abstracts, and studies that did not report on outcomes of interest. There were no language restrictions.

## Data Extraction

We extracted the following information: ClinicalTrials.gov identifier, participant numbers and age, diagnosis criteria, severity of AD, intervention details, molecular formula, outcomes of different types of PDE 4 inhibitors, and timing of outcomes. Efficacy outcomes included change from baseline in target lesion scores and investigators' assessment of clear or almost clear skin. Safety outcomes included adverse events (AEs) leading to withdrawal, at least 1 AE, and treatment-related AEs. When studies presented the outcome data only in the figures, we used Image J software (National Institutes of Health; <https://imagej.nih.gov/ij/>) to measure distances on a graph.

## Assessment of Risk of Bias

Two of us (H.Y. and X.Z.) independently assessed the risk of bias of each included study using the Cochrane Collaboration's risk of bias assessment tool. Disagreements were resolved by discussion and consensus with another one of us (H.W.).

## Statistical Analysis

The statistical analysis was performed using Review Manager, version 5.3 software (The Cochrane Collaboration) and STATA, version 12.0 software (StataCorp). We calculated the standardized mean difference (SMD) with 95% CIs for changes in the target lesion score of topical PDE4 vs vehicle control because the scales of measurement of the target lesion score varied. We also calculated the relative risk (RR) with 95% CIs for dichotomous outcomes of investigators' assessment of clear or almost clear skin and the AEs. Random-effects meta-analyses were performed to pool the data. Heterogeneity was assessed using the Cochran Q test and quantified with the  $I^2$  statistic.  $I^2 > 50\%$  or  $P < .10$  was defined as substantial heterogeneity. The funnel plot, Egger test, and trim-and-fill method<sup>16</sup> were used to assess publication bias.

## Results

### Search Results and Characteristics of Included Studies

We initially identified 214 studies in 3 electronic databases and 2 additional unpublished trials from ClinicalTrials.gov. A total of 7 studies that met the selection criteria were identified. The flowchart for screening studies is shown in **Figure 1**.

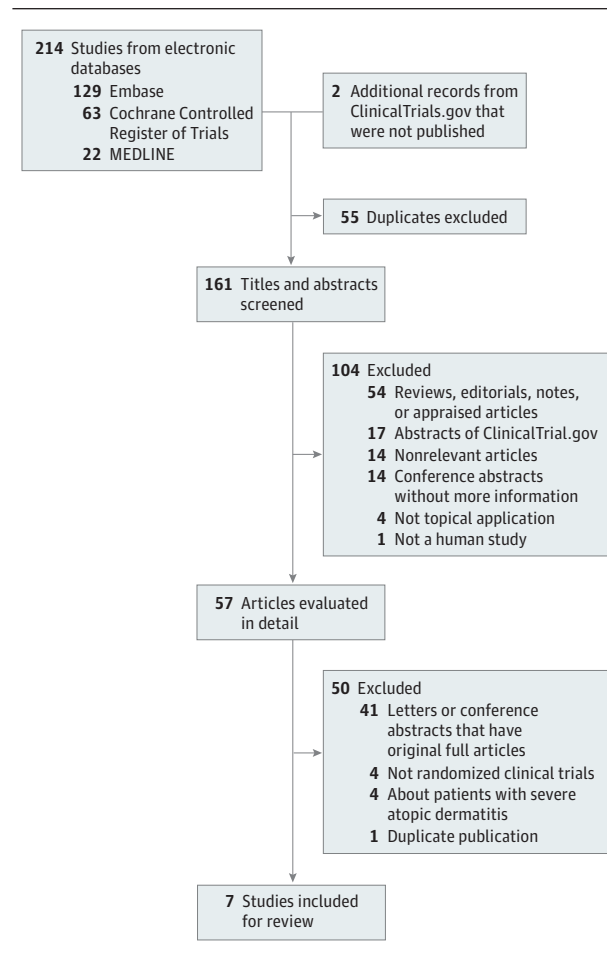
A total of 1869 patients were included in this meta-analysis. Five PDE4 inhibitors with distinct molecules were assessed. All of the included studies used topical vehicles as a control. There was variety in the treatment duration for the 7 included studies, ranging from 7 to 56 days. Two trials (NCT01301508<sup>17</sup> and Murrell et al<sup>18</sup>) were bilateral studies, which means that the drug and vehicle control treatments were performed for the same patients. The characteristics of the 7 included studies are summarized in **Table 1**.<sup>12,13,17-23</sup>

### Efficacy Outcomes

#### Overall Clinical Efficacy

**Change From Baseline in Target Lesion Score** | Four studies (including 186 patients) were analyzed. Three studies (Furue et al,<sup>19</sup>

**Figure 1. Flowchart of the Identification, Inclusion, and Exclusion of Studies**



Murrell et al,<sup>18</sup> and NCT01301508<sup>17</sup>) measured outcomes on a scale of 0 to 15 points, while 1 study (Nemoto et al<sup>12</sup>) measured outcomes on a scale of 0 to 16 points. Overall, a random-effects model meta-analysis showed that PDE4 inhibitors were associated with a statistically significant decrease in target lesion score compared with the vehicle group (SMD, -0.40; 95% CI, -0.61 to -0.18;  $P < .001$ ). Heterogeneity was not significant between studies ( $I^2 = 20\%$ ;  $P = .26$ ) (**Figure 2**).

**Investigators' Assessment of Clear or Almost Clear Skin** | Four studies (including 1720 patients) were analyzed. **Figure 3** shows that, overall, PDE4 inhibitors were associated with significantly higher scores in investigators' assessment of clear or almost clear skin (RR, 1.50; 95% CI, 1.33-1.70;  $P < .001$ ), and no heterogeneity was detected. ( $I^2 = 0\%$ ;  $P = .95$ ).

#### Clinical Efficacy According to Treatment Duration

A subgroup analysis was performed by pooling studies with the same treatment duration (**Figure 2**). The results revealed that, compared with the vehicle, PDE4 inhibitors were associated with a significant decrease in scores at day 14 (SMD, -0.45; 95% CI, -0.80 to -0.10;  $P = .01$ ) and day 28 (SMD, -0.57; 95% CI, -0.91 to -0.24;  $P < .001$ ). There was no significant

Table 1. Characteristics of the 7 Included Studies

| Source                            | Clinical Trials Identifier  | No. of Participants (Age) | Definition of AD                      | Severity of AD   | Interventions                                                  | PDE4 Inhibitor Molecular Formula                                                             | Bilateral Study | End Point               | Outcomes                                                                                          |
|-----------------------------------|-----------------------------|---------------------------|---------------------------------------|------------------|----------------------------------------------------------------|----------------------------------------------------------------------------------------------|-----------------|-------------------------|---------------------------------------------------------------------------------------------------|
| Furie et al, <sup>19</sup> 2014   | NCT01461941                 | 78 (20-64 y)              | Saeki et al <sup>20</sup>             | Mild to moderate | E6005, 0.2%, or topical control vehicle twice daily            | C <sub>26</sub> H <sub>24</sub> N <sub>4</sub> O <sub>5</sub>                                | No              | Weeks 4 and 12          | AEs, EASI, SCORAD, Itch Behavioral Rating Scale (0-8 points), targeted lesion score (0-15 points) |
| Nemoto et al, <sup>12</sup> 2016  | NCT02094235                 | 62 (2-15 y)               | Saeki et al <sup>20</sup>             | Mild to moderate | E6005, 0.2% and 0.05%, or topical control vehicle twice daily  | C <sub>26</sub> H <sub>24</sub> N <sub>4</sub> O <sub>5</sub>                                | No              | Weeks 1 and 2           | AEs, local IGA, total IGA, targeted lesion score (0-16 points)                                    |
| Murrell et al, <sup>18</sup> 2015 | NCT01301508                 | 25 (18-75 y)              | Hanifin and Rajka et al <sup>21</sup> | Mild to moderate | Crisaborole, 2%, or topical control vehicle twice daily        | C <sub>14</sub> H <sub>10</sub> BNO <sub>3</sub>                                             | Yes             | Weeks 2, 4, and 6       | AEs, ADSI (0-15 points), investigator assessment of target lesions score                          |
| Paller et al, <sup>13</sup> 2016  | NCT02118766 and NCT02118792 | 1522 (≥2 y)               | Hanifin and Rajka <sup>21</sup>       | Mild to moderate | Crisaborole, 2%, or topical control vehicle twice daily        | C <sub>14</sub> H <sub>10</sub> BNO <sub>3</sub>                                             | No              | Weeks 1, 2, 3, and 4    | AEs, ISGA, severity of pruritus (0-3 scale)                                                       |
| Hanifin et al, <sup>22</sup> 2016 | NCT02068352                 | 121 (10-70 y)             | Hanifin and Rajka <sup>21</sup>       | Mild to moderate | OPA-15406, 1% and 0.3%, or topical control vehicle twice daily | C <sub>23</sub> H <sub>24</sub> F <sub>2</sub> N <sub>2</sub> O <sub>5</sub>                 | No              | Weeks 1, 2, 4, 6, and 8 | AEs, IGA, EASI, severity of pruritus (100-mm visual analog scale), DLQI, CDLQI                    |
| NCT01856764, <sup>23</sup> 2017   | NCT01856764                 | 40 (18-65 y)              | Hanifin and Rajka <sup>21</sup>       | Moderate         | Roflumilast, 0.5%, or topical control vehicle twice daily      | C <sub>17</sub> H <sub>14</sub> Cl <sub>2</sub> F <sub>2</sub> N <sub>2</sub> O <sub>3</sub> | No              | Week 2                  | AEs, SCORAD, TEWL, severity of pruritus (100-mm visual analog scale)                              |
| NCT01301508, <sup>17</sup> 2017   | NCT01301508                 | 21 (18-75 y)              | Hanifin and Rajka <sup>21</sup>       | Mild to moderate | AN2898, 1%, or topical control vehicle twice daily             | C <sub>15</sub> H <sub>9</sub> BN <sub>2</sub> O <sub>3</sub>                                | Yes             | Weeks 2, 4, and 6       | AEs, ADSI (0-15 points)                                                                           |

Abbreviations: AD, atopic dermatitis; ADSI, Atopic Dermatitis Severity Index; AE, adverse event; CDLQI, Children's Dermatology Life Quality Index; C<sub>14</sub>H<sub>10</sub>BNO<sub>3</sub>, crisaborole; C<sub>15</sub>H<sub>9</sub>BN<sub>2</sub>O<sub>3</sub>, AN2898; C<sub>17</sub>H<sub>14</sub>Cl<sub>2</sub>F<sub>2</sub>N<sub>2</sub>O<sub>3</sub>, roflumilast; C<sub>23</sub>H<sub>24</sub>F<sub>2</sub>N<sub>2</sub>O<sub>5</sub>, CID 99456640 (OPA-15406); C<sub>26</sub>H<sub>24</sub>N<sub>4</sub>O<sub>5</sub>, deoxynortrypto-

quivalone (E6005); DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, investigators' assessment; ISGA, Investigator's Static Global Assessment; PDE4, phosphodiesterase 4; SCORAD, Scoring Atopic Dermatitis; TEWL, transepidermal water loss.

heterogeneity between studies in both of the subgroups. However, at day 7 and day 42, no significant differences in disease scores were found between the group treated with PDE4 inhibitors and the group that received the vehicle. In addition, mild heterogeneity in subgroups at day 7 ( $I^2 = 39\%$ ;  $P = .20$ ) and significant heterogeneity in subgroups at day 42 ( $I^2 = 57\%$ ;  $P = .13$ ) were detected (Figure 2).

The outcome of an investigator's assessment of clear or almost clear skin showed that PDE4 inhibitors were associated with significantly higher response rates at day 14 (RR, 2.14; 95% CI, 1.12-4.06;  $P = .02$ ), day 28 (RR, 1.77; 95% CI, 1.16-2.71;  $P = .008$ ), and day 42 (RR, 1.81; 95% CI, 1.05-3.11;  $P = .03$ ), while no significant differences were observed at day 7 and day 56 between the group treated with PDE4 inhibitors and the group that received the vehicle. Heterogeneity was not statistically significant between studies in all the treatment time point subgroups (Figure 3).

#### Clinical Efficacy According to Molecular Formula of PDE4 Inhibitors

A subgroup analysis was performed by pooling studies with the same type of PDE4 inhibitors based on molecule at the same treatment duration (Table 2). Change from baseline in target lesion

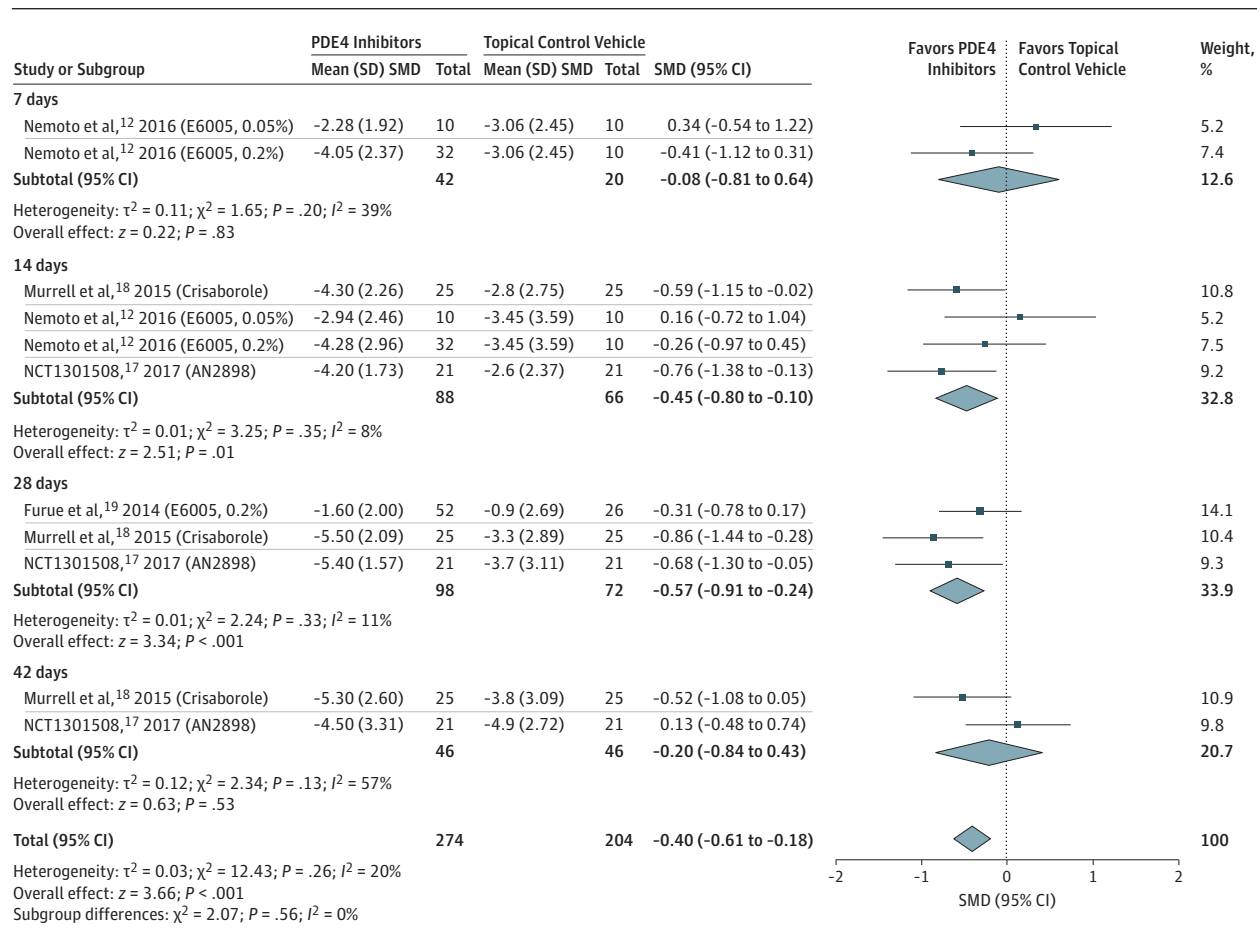
score was studied in 3 PDE4 inhibitors (E6005, AN2898, and crisaborole). Both AN2898 and crisaborole were associated with a significant decrease in target lesion score at day 14 (AN2898: SMD,  $-0.76$ ; 95% CI,  $-1.38$  to  $-0.13$ ;  $P = .02$ ; crisaborole: SMD,  $-0.59$ ; 95% CI,  $-1.15$  to  $-0.02$ ;  $P = .04$ ) and at day 28 (AN2898: SMD,  $-0.68$ ; 95% CI,  $-1.30$  to  $-0.05$ ;  $P = .03$ ; crisaborole: SMD,  $-0.86$ ; 95% CI,  $-1.44$  to  $-0.28$ ;  $P = .004$ ). However, no significant change in target lesion score was seen at day 42. E6005 was not associated with a significant change in target lesion score at each treatment time point. No significant heterogeneity was detected.

Investigators' assessment of clear or almost clear skin was measured for 3 PDE4 inhibitors (E6005, crisaborole, and OPA-15406). None of the 3 PDE4 inhibitors displayed a significant association in these measures. Statistically significant heterogeneity between crisaborole studies at day 28 was detected ( $I^2 = 63\%$ ;  $P = .10$ ).

#### Safety Outcomes

##### AEs Leading to Withdrawal

Adverse events led to study withdrawal of participants in 3 studies of 3 different PDE4 inhibitors (E6005, OPA-15406, and

**Figure 2. Meta-analysis of the Association of Phosphodiesterase 4 (PDE4) Inhibitors vs Topical Control Vehicle With Change From Baseline in Target Lesion Score by Treatment Duration**

Results based on inverse-variance random-effects meta-analyses. SMD indicates standardized mean difference.

crisaborole). The results were not statistically different between the PDE4 inhibitor and vehicle treatment (RR, 0.74; 95% CI, 0.37-1.48;  $P = .39$ ) for all 3 PDE4 inhibitors. Across these studies, 33 of 1680 patients withdrew because of AEs, with similar rates seen between the PDE4 group (19 of 1111 [1.7%]) and the vehicle group (14 of 569 [2.5%]). No heterogeneity was detected ( $I^2 = 0\%$ ;  $P = .65$ ) (eFigure 1A in the [Supplement](#)).

#### At Least 1 AE

Five studies with 4 PDE4 inhibitors (roflumilast, E6005, OPA-15406, and crisaborole) reported at least 1 AE. No significant differences were found between PDE4 inhibitors and vehicles (RR, 1.11; 95% CI, 0.94-1.31;  $P = .22$ ). There was no statistically significant heterogeneity between studies ( $I^2 = 0\%$ ;  $P = .47$ ) (eFigure 1B in the [Supplement](#)).

#### Treatment-Related AEs

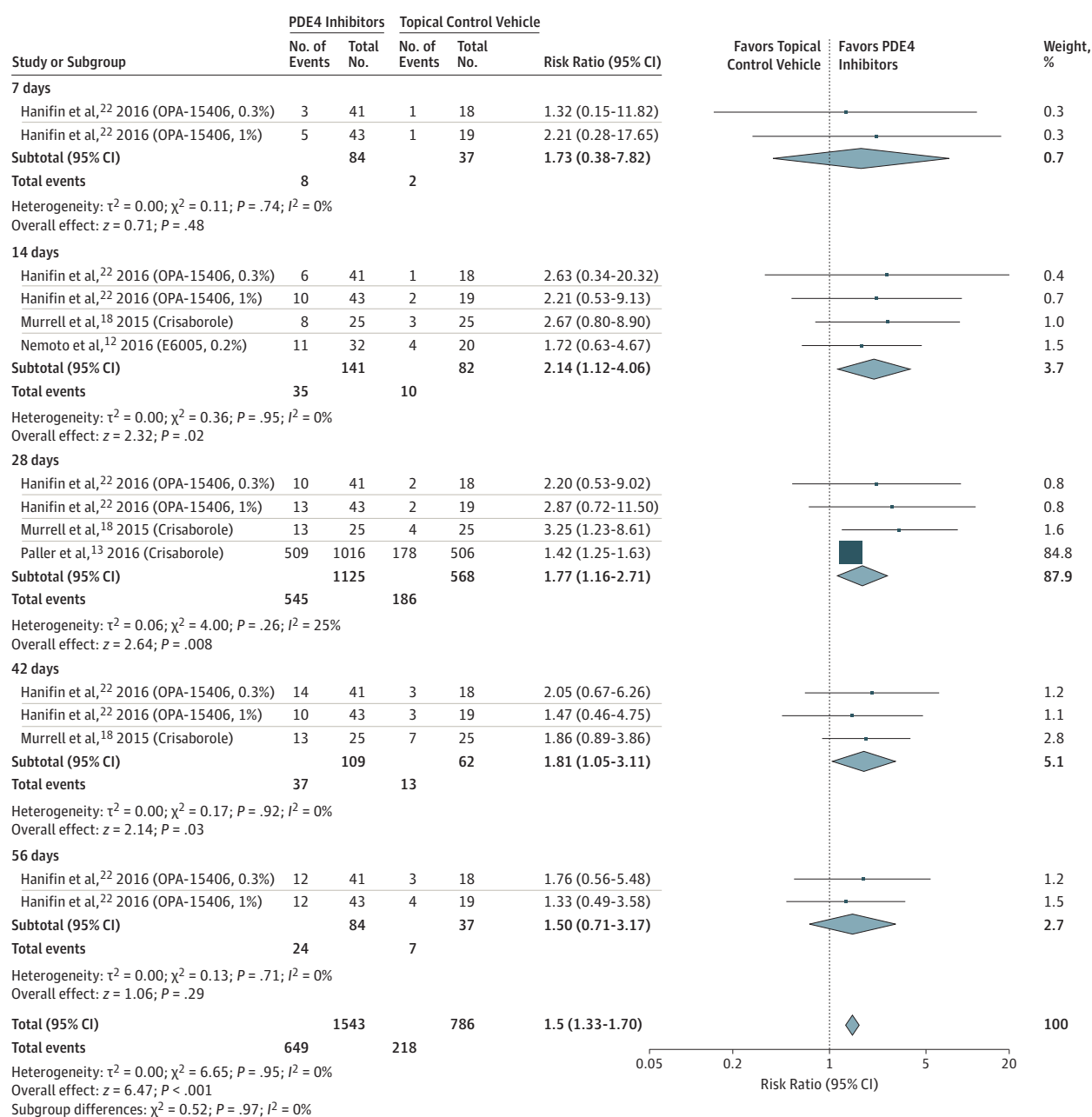
Treatment-related AEs included application site reactions (pain, burning, pruritus, stinging, and erythema), exacerbation of AD, and infection (including Kaposi varicelliform eruption, yeast infection, and nasopharyngitis). All treatment-related AEs were reported to be mild to moderate. Three

included studies (Furue et al,<sup>19</sup> Hanifin et al,<sup>22</sup> and Paller et al<sup>13</sup>) of 3 PDE4 inhibitors (E6005, OPA-15406, and crisaborole) including 88 patients reported on treatment-related AEs (eFigure 1C in the [Supplement](#)). However, the difference between groups treated with PDE4 inhibitors and those who received the vehicle was not statistically significant (RR, 1.45; 95% CI, 0.52-4.09;  $P = .48$ ). There was statistically significant heterogeneity between studies ( $I^2 = 76\%$ ;  $P = .02$ ). Crisaborole was associated with a significantly higher rate of treatment-related AEs than the vehicle (RR, 3.70; 95% CI, 1.59-8.61;  $P = .002$ ).

#### Risk of Bias and Publication Bias Assessment

The included studies were determined to have a low and unclear risk of bias (eFigure 2 in the [Supplement](#)). A detailed assessment of the risk of bias can be found in eTable 2 in the [Supplement](#).

For the efficacy outcome of change from baseline in target lesion score, no publication bias was detected by using a funnel plot (eFigure 3 in the [Supplement](#)) or Egger test (bias, 2.88; 95% CI, -1.33 to 7.08;  $P = .16$ ). However, the effect outcome of investigators' assessment of clear or almost clear skin

**Figure 3. Meta-analysis of the Association of Phosphodiesterase 4 (PDE4) Inhibitors vs Topical Control Vehicle With Investigators' Assessment of Clear or Almost Clear Skin by Treatment Duration**

Results based on Mantel-Haenszel random-effects meta-analyses.

displayed publication bias by using the Egger test (bias, 3.36; 95% CI, 2.34-4.37;  $P < .001$ ). In addition, no changes were noted after the use of the trim-and-fill method.

## Discussion

The present study is the first meta-analysis, to our knowledge, on the efficacy and safety of topical PDE4 inhibitors for the treatment of AD. Our results indicate that topical PDE4 in-

hibitors were effective for patients with mild to moderate AD, especially when using crisaborole and AN2898 for 14 to 28 days, and the patients had infrequent and mild AEs.

Because of the availability of sufficient data, we chose target lesion score and investigators' assessment of clear or almost clear skin as instruments to measure outcomes. Target lesion score is a measure of the basic characteristics of localized lesions that is objective, reliable, and consistent between investigators. Investigators' assessment of clear or almost clear skin is a measure of general physical signs, as well

Table 2. Subgroup Analyses of Different Topical PDE4 Inhibitors at Different Treatment Time Points

| Time Point and Type of Inhibitor                        | Comparison No. | Treatment/Control | SMD (95% CI)           | P Value | I <sup>2</sup> , % |
|---------------------------------------------------------|----------------|-------------------|------------------------|---------|--------------------|
| Change From Baseline in Target Lesion Score             |                |                   |                        |         |                    |
| At 7 d                                                  |                |                   |                        |         |                    |
| E6005                                                   | 2              | 42/20             | −0.08 (−0.81 to 0.64)  | .83     | 39                 |
| At 14 d                                                 |                |                   |                        |         |                    |
| E6005                                                   | 2              | 42/20             | −0.09 (−0.65 to 0.46)  | .74     | 0                  |
| AN2898                                                  | 1              | 21/21             | −0.76 (−1.38 to −0.13) | .02     | NA                 |
| Crisaborole                                             | 1              | 25/25             | −0.59 (−1.15 to −0.02) | .04     | NA                 |
| At 28 d                                                 |                |                   |                        |         |                    |
| E6005                                                   | 1              | 52/26             | −0.31 (−0.78 to 0.17)  | .20     | NA                 |
| AN2898                                                  | 1              | 21/21             | −0.68 (−1.30 to −0.05) | .03     | NA                 |
| Crisaborole                                             | 1              | 25/25             | −0.86 (−1.44 to −0.28) | .004    | NA                 |
| At 42 d                                                 |                |                   |                        |         |                    |
| AN2898                                                  | 1              | 21/21             | 0.13 (−0.48 to 0.74)   | .67     | NA                 |
| Crisaborole                                             | 1              | 25/25             | −0.52 (−1.08 to 0.05)  | .07     | NA                 |
| Investigators' Assessment of Clear or Almost Clear Skin |                |                   |                        |         |                    |
| Time Point and Type of Inhibitor                        | Comparison No. | Treatment/Control | RR (95% CI)            | P Value | I <sup>2</sup> , % |
| At 7 d                                                  |                |                   |                        |         |                    |
| OPA-15406                                               | 2              | 84/37             | 1.73 (0.38 to 7.82)    | .48     | 0                  |
| At 14 d                                                 |                |                   |                        |         |                    |
| OPA-15406                                               | 2              | 84/37             | 2.34 (0.73 to 7.50)    | .15     | 0                  |
| E6005                                                   | 1              | 32/20             | 1.72 (0.63 to 4.67)    | .29     | NA                 |
| Crisaborole                                             | 1              | 25/25             | 2.67 (0.80 to 8.90)    | .11     | NA                 |
| At 28 d                                                 |                |                   |                        |         |                    |
| OPA-15406                                               | 2              | 84/37             | 2.52 (0.94 to 6.77)    | .07     | 0                  |
| Crisaborole                                             | 2              | 1041/531          | 3.25 (1.63 to 8.21)    | .11     | 63                 |
| At 42 d                                                 |                |                   |                        |         |                    |
| OPA-15406                                               | 2              | 84/37             | 1.75 (0.78 to 3.93)    | .17     | 0                  |
| Crisaborole                                             | 1              | 25/25             | 1.86 (0.89 to 3.86)    | .10     | NA                 |
| At 56 d                                                 |                |                   |                        |         |                    |
| OPA-15406                                               | 2              | 84/37             | 1.5 (0.71 to 3.17)     | .29     | 0                  |

Abbreviations: NA, not applicable; RR, relative risk; SMD, standardized mean difference.

as localized lesions, and is also an objective measurement tool without patients' subjective experience. Across all the included studies, PDE4 inhibitors significantly improved local and general physical signs in patients with mild to moderate AD. In addition, no publishing bias was detected in the measurement of the target lesion score, and no significant heterogeneity was detected among studies in overall comparison between PDE4 inhibitors and vehicles regarding both treatment duration and types of PDE4 inhibitors. This finding suggests that the effectiveness of PDE4 inhibitors for the treatment of mild to moderate AD is robust and reproducible. Therefore, topical PDE4 inhibitors represent a new option for the treatment of mild to moderate AD.

Based on the treatment time point analyses, the optimal treatment duration for PDE4 inhibitors in improving both local and general physical signs of AD was 14 to 28 days. However, a discrepancy in improving general and local physical signs when used for more than 42 days was found. This discrepancy could be because of the limitations involved in the measurement tool of the target lesion score, one of which is its poor sensitivity to change for small areas of whole involvement.<sup>24</sup> This discrepancy could also be because avail-

able data are limited on the measurement of the target lesion score. There were only 2 studies with statistically significantly high heterogeneity ( $I^2 = 57\%$ ;  $P = .13$ ) at 42 days. Thus, more longer-duration studies using more validated measurement tools, such as Scoring Atopic Dermatitis and the Eczema Area and Severity Index,<sup>25</sup> are needed.

Furthermore, although several topical PDE4 inhibitors have been developed, in this study, only crisaborole and AN2898 showed advantages over the vehicles in improving local signs, while E6005, OPA-15406, and roflumilast had no such advantages regarding either local or general physical signs. In addition, the efficacy of crisaborole was found to be time dependent compared with the vehicle (day 14: SMD, −0.59; 95% CI, −1.15 to −0.02;  $P = .04$ ; day 28: SMD, −0.86; 95% CI, −1.44 to −0.28;  $P = .004$ ). However, the short-term efficacy of crisaborole and AN2898 within 7 days was not reported. Although a recent post hoc analysis based on the data from the study by Paller et al<sup>13</sup> suggested that crisaborole can rapidly relieve pruritus as early as the second day after the first topical application, it used the Children's Dermatology Life Quality Index and Dermatology Life Quality Index, which may not be the most favorable tools to evaluate pruritus.<sup>26</sup> In the future, a visual

analog scale or numerical rating scale should be used as a measure of the intensity of patient-reported pruritus according to recommendations from the International Forum for the Study of Itch.<sup>27</sup> The immediate and long-term (ie, >4 weeks) anti-inflammatory effects of crisaborole and AN2898 need to be addressed in further trials.

None of the 5 PDE4 inhibitors displayed efficacy in terms of investigators' assessment of clear or almost clear skin. There was high heterogeneity ( $I^2 = 63\%$ ;  $P = .10$ ) in the subgroup at 28 days for those who received crisaborole. The higher number of patients in the study by Paller et al<sup>13</sup> ( $N = 1522$ ) than in the study by Murrell et al<sup>18</sup> ( $N = 25$ ) may have contributed to the heterogeneity. Both the study by Murrell et al<sup>18</sup> and the study by Paller et al<sup>13</sup> revealed that crisaborole was significantly more effective than the vehicles at day 28. Therefore, we should reserve judgement on the clinical efficacy depending on subgroup analyses in terms of investigators' assessment of clear or almost clear skin. More trials evaluating investigators' assessment of clear or almost clear skin as an outcome need to be conducted.

Taken together, patients treated with topical PDE4 inhibitors demonstrated significant improvements in the severity of the disease. It seems that topical PDE4 inhibitors would be better used for maintenance or sequential therapy for mild to moderate AD.

The topical PDE4 inhibitors displayed a favorable safety profile. Although patients treated with crisaborole experienced significantly more treatment-related AEs, the most common AEs were application-site reactions, such as application-site pain, burning, and stinging, which were mild and tolerable. Serious AEs were rare and were not considered to be associated with treatment. Compared with topical corticosteroids and topical calcineurin inhibitors, PDE4 inhibitors are much safer

for the treatment of AD. Although AN2898 was effective in the treatment of AD, its safety evaluations are missing in this meta-analysis. The only included study of AN2898 (NCT01301508<sup>17</sup>) was a bilateral study in which the drug and vehicle treatments were performed for the same patients. No appropriate data on AEs were provided regarding the 2 treatment groups. Therefore, the safety of AN2898 remains to be further studied.

### Limitations

The available data are limited. In studies using the target lesion score, fewer than 200 patients were tested. The measurement tools used are also a limitation. Both the target lesion score and the investigators' assessment of clear or almost clear skin are the quantification or qualification of the lesions without report of the patient's experience, such as itching and sleeplessness. A simple assessment of the lesion is not a comprehensive evaluation of the severity of disease. The Scoring Atopic Dermatitis and the Eczema Area and Severity Index, which consider both objective physical signs and patient's subjective experience (such as the localized lesion score, affected surface areas, itching, and sleeplessness), are considered to be more validated measurement tools for the assessment of the severity of AD.

### Conclusions

The results of this meta-analysis support the favorable efficacy and safety of topical PDE4 inhibitors, especially crisaborole and AN2898, for the treatment of mild to moderate AD. Further trials with shorter and longer durations, using more comprehensive and effective instruments, such as the Eczema Area and Severity Index or the Scoring Atopic Dermatitis, are needed.

### ARTICLE INFORMATION

**Accepted for Publication:** December 31, 2018.

**Published Online:** March 27, 2019.  
doi:10.1001/jamadermatol.2019.0008

**Open Access:** This article is published under the JN-OA license and is free to read on the day of publication.

**Author Contributions:** Drs Wang and Luo had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Yang and J. Wang contributed equally to this work.  
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**Conflict of Interest Disclosures:** None reported.

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