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Original Research

## Safety Profile and Tolerability of Topical Phosphodiesterase 4 Inhibitors for the Treatment of Atopic Dermatitis: A Systematic Review and Meta-Analysis

Ana Martín-Santiago, MD<sup>1</sup>, Susana Puig, MD PhD<sup>2,3</sup>, Daniel Arumi, MD PhD<sup>4</sup>, Francisco Jose Rebollo Laserna, MD<sup>4,\*</sup>

<sup>1</sup>Hospital Universitari Son Espases, Palma de Mallorca, Spain

<sup>2</sup>Dermatology Department, Hospital Clinic of Barcelona, Universitat de Barcelona, Barcelona, Spain

<sup>3</sup>Centro de Investigación Biomédica en Red de Enfermedades Raras, Instituto de Salud Carlos III, Barcelona, Spain

<sup>4</sup>Pfizer SLU, Madrid, Spain

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## ABSTRACT

**Objective:** Evaluate the safety profile and tolerability of topical phosphodiesterase 4 (PDE4) inhibitors versus vehicle as treatment for atopic dermatitis in published studies.

**Methods:** A search was performed in Medline/PubMed, Web of Science, and Cochrane Library databases on September 27, 2021, by 1 evaluator, without restrictions on publication dates or languages. Terms such as *atopic dermatitis*, *phosphodiesterase 4 inhibitors*, *calcineurin inhibitors*, and *randomized controlled trials* were included. The database searches were carried out by 1 evaluator. The titles and abstracts were reviewed for the identification and evaluation of potentially eligible studies. Study selection was made by two reviewers, so there was no intra-examiner statistic at the study selection step. The full-text articles were reviewed to determine whether or not they would be included in the systematic review. Global analyses, which included studies with both unclear and low risk of bias and subanalyses of studies with a low risk of bias were performed.

**Results:** Out of 237 identified articles, 14 clinical trials were included in the meta-analysis. In global analyses of studies with low and unclear risk of bias, topical treatment with PDE4 inhibitors did not differ from vehicle treatment in global treatment emergent adverse events (relative risk = 0.99; 95% CI, 0.87–1.14;  $P = 0.94$ ) or in serious emergent adverse events appearance (relative risk = 0.92; 95% CI, 0.39–2.20;  $P = 0.86$ ). In subanalyses of studies with a low risk of bias, a reduced rate of atopic dermatitis exacerbation was observed in PDE4 inhibitors compared with the vehicle (relative risk = 0.62; 95% CI, 0.39–0.98;  $P = 0.04$ ) and risk of pain at the application site was confirmed (relative risk = 2.59; 95% CI, 1.27–5.28;  $P = 0.01$ ).

**Conclusions:** PDE4 inhibitors did not show differences from vehicle treatment in treatment emergent adverse events or serious emergent adverse events incidence. In studies with low risk of bias, PDE4 inhibitors had a statistically significant risk of producing pain and reduced occurrence of atopic dermatitis exacerbation.

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## Introduction

Atopic dermatitis (AD) is among the most common disorders in developed countries, with a prevalence of approximately 20% in

children and 3% to 10% in adults.<sup>1,2</sup> This pathology is characterized by intense itching and recurrent eczema lesions with a heterogeneous clinical presentation. The treatment of AD aims to improve symptoms and establish long-term control of the disease because chronic relapses are common.<sup>3</sup>

Therapeutic management of AD is based on disease activity, patient age, and anatomical location. Treatments for patients with mild to moderate AD focus on the administration of topical corti-

\* Address correspondence to: Francisco J. Rebollo Laserna, Pfizer SLU, Avenida Europa, 20 B, 28108, Alcobendas, Madrid, Spain.

E-mail address: [francisco.rebollo@pfizer.com](mailto:francisco.rebollo@pfizer.com) (F.J. Rebollo Laserna).

costeroids (TCSs), topical calcineurin inhibitors (TCIs), and topical phosphodiesterase 4 (PDE4) inhibitors.<sup>4,5</sup> The anti-inflammatory use of TCSs is the first line of pharmacological treatment, and the intermittent administration of these drugs carries little risk. However, improper use can cause local adverse effects.

TCIs, including tacrolimus and pimecrolimus, are restricted in their use due to their high cost and the adverse effects they produce. In 2005, the Pediatric Advisory Committee for the Food and Drug Administration recommended black box warnings due to a lack of long-term safety data and the potential risk of malignancies.<sup>6</sup>

PDE4 inhibitors are nonsteroidal anti-inflammatory drugs that not only modulate the inflammatory response but also prevent skin atrophy and deterioration of the epithelial barrier, which occur with the use of corticosteroid therapy.<sup>7</sup> Among the PDE4 inhibitors studied for the treatment of AD, we identified OPA-15406<sup>8,9</sup> (international common name, difamilast; also known as MM36); E6005<sup>10,11</sup>; cipamfylline<sup>12</sup>; and crisaborole 2% ointment, which was approved by the Food and Drug Administration in 2016.

Several systematic reviews have evaluated the efficacy,<sup>13,14</sup> adverse events,<sup>15</sup> and safety profile<sup>16</sup> of TCIs (such as tacrolimus and pimecrolimus) compared with TCSs<sup>13</sup> or other topical treatments,<sup>17</sup> finding that these calcineurin inhibitors present more adverse effects, such as burning of the skin or itching, than TCSs<sup>15,17</sup> or other topical treatments.

In 2 studies, Fishbein et al<sup>18</sup> and Yang et al<sup>19</sup> evaluated the safety profile and efficacy of topical treatment with corticosteroids and topical treatment with PDE4 inhibitors, respectively, compared with vehicle/placebo.<sup>18</sup> No differences were found in adverse events related to treatment or adverse events that required the interruption of treatment; therefore, there is little scientific evidence on the influence of the adverse events related to PDE4 inhibitors compared with those related to other topical treatments.<sup>19</sup>

Because the occurrence of harmful and unwanted responses to a drug is among the causes of drug discontinuation, the objective of this study was to evaluate the adverse effects and safety profile of topical PDE4 inhibitors compared with their vehicles in the treatment of AD.

## Materials and Methods

A systematic review was conducted following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.<sup>20</sup>

### Search strategy

A search was carried out in the following electronic databases on September 27, 2021: Medline/PubMed, Web of Science, and the Cochrane Library. The search strategies used are shown in **Table 1**. All references were saved in Mendeley 1.13.18 (Mendeley HQ: London, UK).

### Study selection

The database searches were carried out by 1 evaluator (R.R.). The titles and abstracts were reviewed for the identification and evaluation of potentially eligible studies. Study selection was made by 2 reviewers, with no intraexaminer statistic at step. The full-text articles were reviewed to determine whether or not they would be included in the systematic review.

### Inclusion criteria

The research question was formulated using the PICOS structure, as follows: Participants: patients with mild to moderate AD

lasting  $\geq 3$  months. Intervention: topical treatment with PDE4. Comparison: group 1, TCIs (ie, tacrolimus, FK 506; pimecrolimus, AMS 981); group 2, TCSs; and/or group 3, placebo/vehicle. Outcome: adverse events or safety. Study design: randomized controlled trials (RCTs). There were no restrictions on publication dates or language.

### Exclusion criteria

Observational studies, cost-effectiveness studies, studies with animals, systematic reviews, meta-analyses, and studies with routes of administration other than topical were excluded.

### Data extraction

Data from the retrieved trials were extracted and tabulated on a data extraction sheet by 2 independent assessors (R.R. and S.S.). The following data were extracted from each of the studies: reference, journal, country, intervention group, comparison group, single-center or multicenter design, clinical trial phase, protocol registry (database and registry number), blinding, intervention model, allocation ratio, number of arms in the study, sample size, number of patients per group, number of patients who completed the study, number of patients who due to adverse events led to withdrawal/interruption, AD diagnostic criteria, AD score, age, and sex.

The data extracted on adverse events and safety profile were as follows: treatment-emergent adverse events  $\geq 1$ , defined as an adverse event occurring at or after the first dose of the study drug; and treatment-emergent adverse events determined to be serious or greater, defined as an adverse event that occurred at or after the first dose of the study drug and motivated the interruption of the study. Treatment-related adverse events were defined as adverse events determined by the study investigator to be definitely, probably, or possibly related to treatment. Pain was defined as pain at the site of application, including sensations such as burning or stinging. Pruritus was defined as pruritus in general or at the site of application with the appearance of signs such as erythema, exudation, excoriation, induration/papulation, and lichenification. Skin and subcutaneous tissue disorders in general or as part of AD were defined as exacerbations of AD. Evaluation of AD was considered as an adverse event to the intervention/placebo, not in terms of efficacy. Investigations were defined as clinical laboratory test, radiologic test, physical parameters, and physiology test.

### Assessment of the risk of bias and methodological quality

The methodological quality assessment was carried out using the Cochrane risk-of-bias assessment tool and was performed by 2 independent evaluators (R.R. and S.S.). Any disagreements were resolved by discussion between the 2 evaluators until they reached a consensus. For the evaluation of losses that directly influenced the results of the study, 10% was set as an acceptable loss.<sup>21</sup> Studies were classified into the following categories: low risk of bias: low risk of bias for all key domains; unclear risk of bias: unclear risk of bias for 1 or more key domains; and high risk of bias: high risk of bias for 1 or more key domains.<sup>22</sup>

### Statistical analysis

Dichotomous data are summarized as relative risks (RRs) and were assessed using the Mantel-Haenszel method. Clinical trials with 0 events in the arms were included from the meta-analysis. We included the fixed 0.5 corrections. Only studies with low or unclear risk of bias were included in the meta-analysis. If no heterogeneity was found among the studies, a fixed-effects model was

**Table 1**  
Search strategies carried out in electronic databases.

Database	Search strategy	No. of references
Medline/PubMed	("Dermatitis, Atopic/therapy"[Majr] OR "Dermatitis, Atopic/therapy"[Mesh] OR "Eczema/therapy"[Mesh] OR Atopic dermatitis OR atopic eczema OR dermatitis) AND ("crisaborole" [Supplementary Concept] OR "Phosphodiesterase 4 Inhibitors"[Majr] OR "crisaborole" OR "Phosphodiesterase 4" OR "PDE4") AND ("Calcineurin Inhibitors" [Pharmacological Action] OR "Calcineurin Inhibitors"[Majr] OR "Tacrolimus"[Majr] OR "pimecrolimus" [Supplementary Concept] OR Calcineurin Inhibitor* OR "TCI"[TIAB] OR "FK 506"[TIAB] OR "FK-506"[TIAB] OR (topical AND ("Adrenal Cortex Hormones/therapeutic use"[Mesh] OR corticosteroid* OR "TCS"[TIAB])) OR placebo OR vehicle) AND (Randomized controlled trials OR RCT OR clinical trial* OR random*)	61
Web of Science	TS=(Atopic dermatitis OR atopic eczema OR dermatitis) AND TS=(crisaborole OR Phosphodiesterase 4 Inhibitors OR Phosphodiesterase 4 OR PDE4) AND TS=(Calcineurin Inhibitor* OR Tacrolimus OR pimecrolimus OR TCI OR FK 506 OR FK-506 OR (topical AND (corticosteroid* OR TCS)) OR placebo OR vehicle) AND TS=(Randomized controlled trials OR RCT OR clinical trial* OR random*)	96
Cochrane Library	Atopic dermatitis OR atopic eczema OR dermatitis [in Title Abstract Keyword] AND crisaborole OR Phosphodiesterase 4 Inhibitors OR Phosphodiesterase 4 OR PDE4 [in Title Abstract Keyword] AND Calcineurin Inhibitor* OR Tacrolimus OR pimecrolimus OR TCI OR FK 506 OR FK-506 OR (topical AND (corticosteroid* OR TCS)) OR placebo OR vehicle [in Title Abstract Keyword] AND Randomized controlled trials OR RCT OR clinical trial* OR random* [in Title Abstract Keyword]	80
Total references		237

used. Heterogeneity was assessed using the Cochran  $Q$  test ( $P < 0.10$ ) and quantified with the  $I^2$  statistic ( $<50\%$ ). The data are presented using forest plots in logarithmic scale. The results are presented with 95% CIs, and the tests were significant at  $P < 0.05$ . Data analysis was performed using Stata 16.1 (StataCorp, College Station, Texas).

## Results

The search strategy identified 237 articles, of which 155 were excluded based on the titles and abstracts. In the full-text evaluation, 7 articles were excluded. The flow chart in [Figure 1](#) shows the sequence of steps in the study selection process.

### Characteristics of the studies

Sixteen randomized clinical trials were included: 8 with crisaborole,<sup>4,23–29</sup> 4 with E6005,<sup>10,30,31,35</sup> 3 with OPA-15406,<sup>32–34</sup> and 1 with cipamfylline<sup>12</sup>; the characteristics of the studies are shown in [Table 2](#). Only studies with cipamfylline had a comparison group with corticosteroids and another with vehicle. The rest of the studies used vehicle as the comparison group.

Between 2002 and 2020, 4 single-center studies<sup>4,24,29,35</sup> and 11 multicenter studies<sup>10,12,23,25–28,30,32–34</sup> were reported; 1 study did not report if they used single- or multicenter designs.<sup>31</sup> The main countries where these clinical trials took place were Japan,<sup>10,24,30–33,35</sup> the United States,<sup>25–28</sup> Australia,<sup>23,29</sup> and Canada.<sup>4</sup> A study by Hanifin et al<sup>34</sup> was carried out in the United States, Poland, and Australia, and a study by Griffiths et al<sup>12</sup> was carried out in Canada, Denmark, the Netherlands, and the United Kingdom.

The clinical trial phases of the included studies covered the full range: Phase I,<sup>24,29</sup> Phase I/II,<sup>30,31,35</sup> Phase II,<sup>4,10,23,32–34</sup> and Phase III.<sup>25–28</sup> In 2 studies, the phase was not reported.<sup>12,31</sup> Only in the studies by Ono et al,<sup>24</sup> Yosipovitch et al,<sup>28</sup> Zane et al,<sup>29</sup> and Ohba et al<sup>31</sup> (in their study 001) was no clinical trial protocol reported. The intervention model was parallel and was performed within patients in three studies.<sup>4,23,24</sup> Most of the clinical trials had a double-blind design, with the exception of three studies.<sup>10,24,31</sup>

The total number of patients included in the studies with crisaborole 2% was 7739<sup>4,23–29</sup>; the trials with OPA-15406 included 394 patients,<sup>32–34</sup> those with E6005 included 216 patients,<sup>10,30,31,35</sup> and those with cipamfylline included 103 patients.<sup>12</sup> In more than half of the clinical trials, the percentage of patients who completed the study was high<sup>4,12,24–31,35</sup>; 7 studies had  $>10\%$  loss.<sup>10,12,23,24,32–34</sup>

### Characteristics of the patients

The most widely used diagnostic criteria for the inclusion of patients in clinical trials were based on the Hanifin and Rajka criteria,<sup>4,12,23–28,32–34</sup> and, to a lesser extent, the Japanese Dermatological Association's "Guidelines for the management of AD."<sup>10,30,31,35</sup>

The range of AD severity was mild to moderate in most studies<sup>4,23–28,30,32–35</sup>; only in the study of Ohba et al<sup>31</sup> did the severity range from mild to severe. In the study by Furue et al,<sup>10</sup> severe dermatitis was defined as eczema covering 5% to 30% of the body surface area, and in the study by Griffiths et al,<sup>12</sup> it was defined as symmetrical AD lesions on both arms with a minimum total severity score of 6. There were 3 studies<sup>24,29,31</sup> in which lesions were induced in healthy patients for drug evaluation.

The patients ranged in age from 2 to 79 years. There were 3 studies in which the mean age of the participants was younger than 18 years.<sup>25,30,32</sup> Fewer than half of the studies had more men than women in their samples,<sup>10,23,24,32,33</sup> and only the studies by Ohba et al<sup>31,35</sup> and Ono et al<sup>24</sup> had exclusively male patients.

### Assessment of methodological quality

The results obtained from the methodological evaluation are shown in [Supplemental Figure 1](#). Of the studies evaluated, 6 had a low risk of bias<sup>4,12,25,28,32,33</sup>; that is, all the domains had a low risk of bias. Ten studies had an unclear risk of bias: 2 studies with unclear risk in a single domain<sup>26,31</sup> and 6 with unclear risk in 2 domains.<sup>10,23,27,29,30,34</sup> Finally, 2 studies had a high risk of bias: 1 in the *sequence generation* domain<sup>24</sup> and 1 in the *selective outcome reporting* domain.<sup>35</sup>

### Meta-analysis

Studies were grouped according to outcomes of interest, and only those with low or unclear risk of bias were included in the global analysis. Sensitivity analyses were presented according to the type of PDE4 and risk of bias. [Figures 2](#) through [5](#) (and [Supplemental Figures 3, 4, 6, and 8–10](#)) show the forest plots of the analyses.

### Studies evaluating treatment-emergent adverse events $\geq 1$

A meta-analysis of 16 comparisons was performed (4 with low risk of bias and 12 with unclear risk of bias). Overall homogeneity between studies and studies with low risk of bias were excel-

**Table 2**  
Characteristics of the included studies.

Author, year	Intervention	Comparison	Center	Phase	Blinding	Intervention model	Allocation ratio	Arms	n	Intervention n	Comparison n	Patients completing the study	Diagnostic criteria for AD	No. of subjects who, due to adverse events, led to withdrawal/interruption
Bissonnette et al. <sup>4</sup>	Crisaborole 2%	Vehicle	Single-center	Ia	Double	Parallel (within patients)	1:1 (within patients)	2	40	40	40	38 (95.0%)	Hanifin and Rajka	2
Furue et al. <sup>10</sup>	E6005 2%	Vehicle	Multicenter	II	Single	Parallel	2:01	2	78	52	26	53 (67.9%)	Japanese Dermatological Association's "Guidelines for the management of AD"	Hydrocortisone 17-butyrate 0.1%; 2; Vehicle: NR
Griffiths CE et al. <sup>12</sup>	Cipamfylline	Vehicle or hydrocortisone 17-butyrate	Multicenter	NR	Double	Parallel	1:01	2	103	Vehicle: 54, hydrocortisone 17-butyrate: 49	Vehicle: 54, hydrocortisone 17-butyrate: 49	Vehicle: 49 (90.7%), hydrocortisone 17-butyrate: 44 (89.8%)	Hanifin and Rajka	2
Hanifin JM et al. <sup>34</sup>	OPA-15406 0.3% or 1%	Vehicle	Multicenter	II	Double	Parallel	NR	3	121	OPA-15406 0.3%: 41, 1%:43	OPA-15406 0.3%: 37	94 (77.7%)	Hanifin and Rajka; Rajka and Langeland	3
Murrell DF et al. <sup>23</sup>	Crisaborole 2%	Vehicle	Multicenter	Ia	Double	Parallel (within patients)	1:1 (within patients)	2	25	25	25	22 (88.0%)	Hanifin and Rajka	0
Nemoto O et al. <sup>30</sup>	E6005 0.05% or 0.2%	Vehicle	Multicenter	I and II	Double	Parallel	2:01	3	62	E6005 0.05%: 10, 0.2%: 32	20	61 (98.4%)	Japanese Dermatological Association's Guidelines for the management of AD	0
Ohba et al. <sup>31</sup>	E6005 0.01%, 0.03%, 0.1% or 0.2%	Vehicle	Single-center	I and II	Single	Parallel	4:01	4	40	E6005 0.01%: 8, 0.03%: 8, 0.1%: 8, 0.2%: 8	8 (2 of each cohort)	38 (95.0%)	Japanese Dermatological Association's Guidelines for the management of AD	2
Ohba et al. <sup>31</sup>	E6005 0.01% or 0.03% 0.1% or 0.2%	Study 001: vehicle/study 101: vehicle	NR	Study 001: NR/study 101: I and II	Single	Parallel	NR	2 (4 cohorts)	36	E6005 0.01%: 7, 0.03%: 7, 0.1%: 7, 0.2%: 7	8 (2 of each cohort)	Study 001: 33 (91.7%); study 101: 38 (95.0%)	Study 001: NR/study 101: Japanese Dermatological Association's Guidelines for the management of AD	Study 001: 2; Study 101: 2

(continued on next page)

Table 2 (continued)

Author, year	Intervention	Comparison	Center	Phase	Blinding	Intervention model	Allocation ratio	Arms	n	Intervention n	Comparison n	Patients completing the study	Diagnostic criteria for AD	No. of subjects who, due to adverse events, led to withdrawal/interruption
Ono et al. <sup>24</sup>	Crisaborole 2%	Vehicle	Single-center	I	Single	Parallel (within patients)	1:01	2 (within patients)	Cohort 1: 20; cohort 2: 12	Cohort 1: 20; cohort 2: 10	Cohort 1: 20; cohort 2: 2	Cohort 1: 20 (100%); cohort 2: 10 (83.3%)	NR and Hanifin and Rajka	Cohort 1: 0; cohort 2: 2
Paller et al. <sup>25</sup>	Crisaborole 2%	Vehicle	Multicenter	III	Double	Parallel	2:01	2	AD-301: 759; AD-302: 763	AD-301: 503; AD-302: 513	AD-301: 256; AD-302: 250	AD-301: 733 (99.6%); AD-302: 696 (98.6%)	Hanifin and Rajka	AD-301: 18; AD-302: NR
Saeki et al. <sup>33</sup>	OPA-15406 0.3% or 1%	Vehicle	Multicenter	II	Double	Parallel	1:01:01	3	73	OPA-15406 0.3%: 23, 1%:25	24	63 (86.3%)	Hanifin and Rajka	6
Saeki et al. <sup>33</sup>	OPA-15406 0.3% or 1%	Vehicle	Multicenter	II	Double	Parallel	1:01:01	3	200	OPA-15406 0.3%: 67, 1%:67	66	145 (72.5%)	Hanifin and Rajka	37
Silverberg et al. <sup>26</sup>	Crisaborole 2%	Vehicle	Multicenter	III (post hoc)	Double	Parallel	2:01	2	1522	1016	506	1522 (100.0%)	Hanifin and Rajka	NR
Simpson et al. <sup>27</sup>	Crisaborole 2%	Vehicle	Multicenter	III	Double	Parallel	2:01	2	1522	1016	506	1522 (100.0%)	Hanifin and Rajka	NR
Yosipovitch et al. <sup>28</sup>	Crisaborole 2%	Vehicle	Multicenter	III (post hoc)	Double	Parallel	2:01	2	1522	1016	506	1522 (100.0%)	Hanifin and Rajka	NR
Zane et al. <sup>29</sup>	Crisaborole 2%	Vehicle	Single-center	I	Double	Parallel	3:01	2	32	24	8	32 (100.0%)	NR	0

AD = atopic dermatitis; NR = not reported.

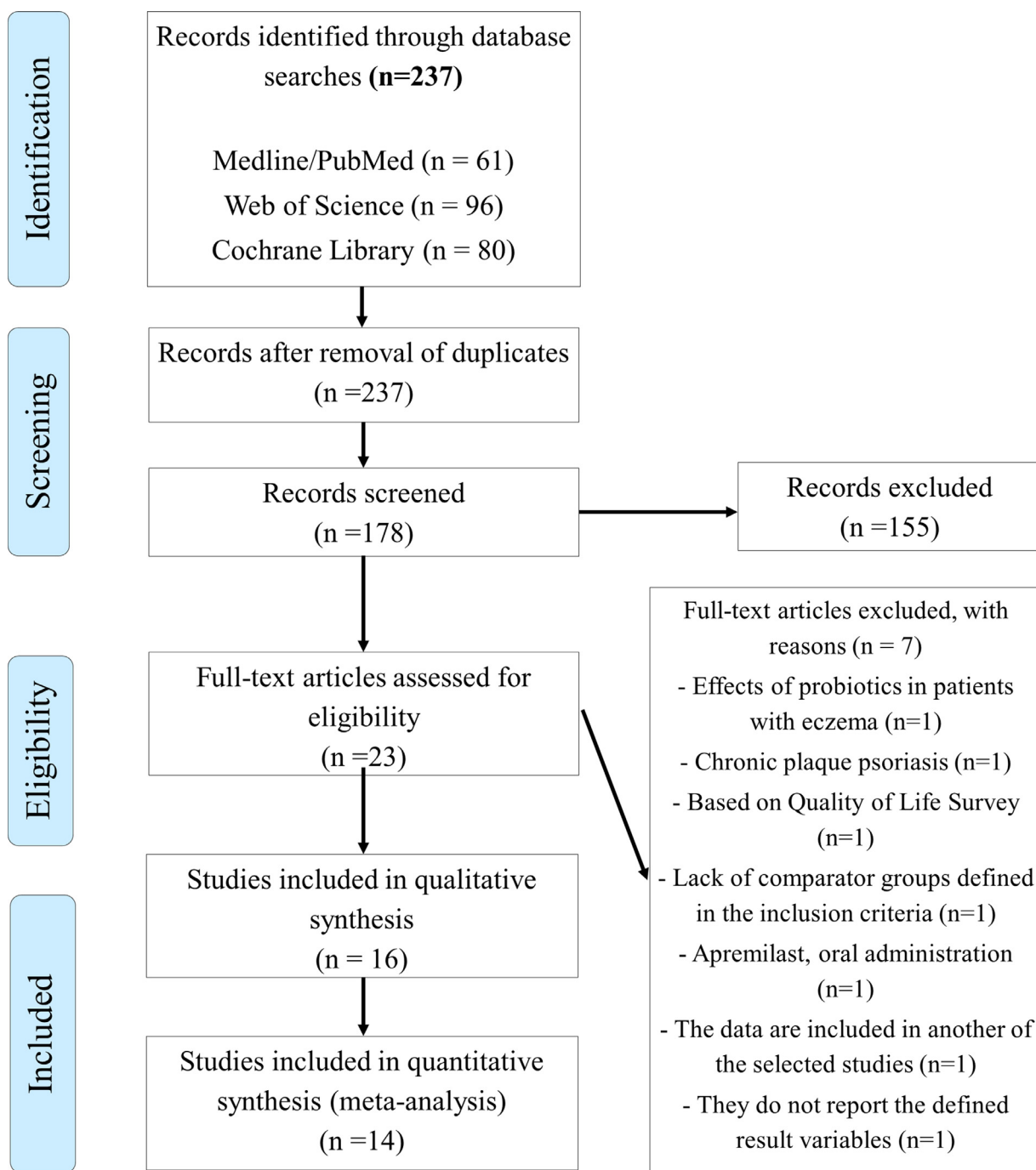


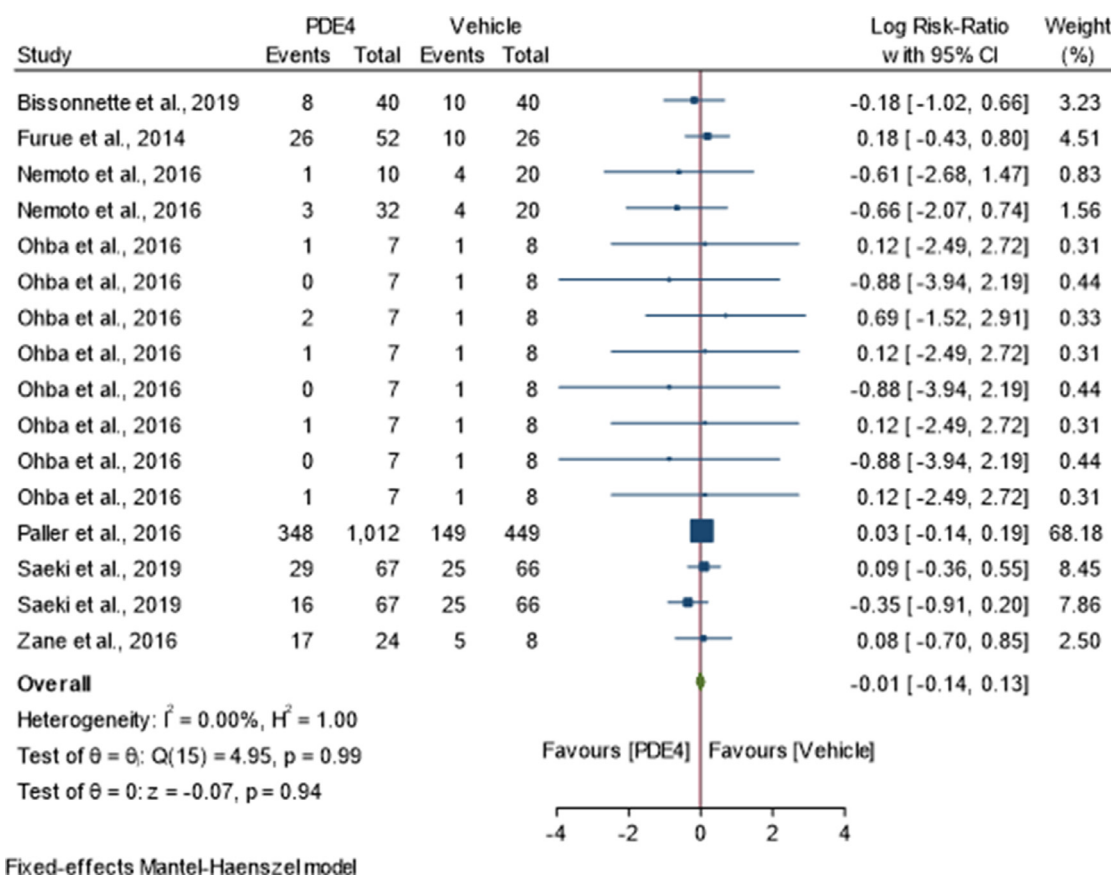
Figure 1. Study selection flow chart.

lent ( $I^2 = 0\%$ ). Topical treatment with PDE4 inhibitors did not show statistically significant differences from vehicle treatment either in the global treatment emergent adverse events (TEAEs) assessment (RR=0.99; 95% CI, 0.87–1.14;  $P=0.94$ ) (Figure 2) or in the case of the studies of low risk of bias (RR=1.00; 95% CI, 0.86–1.16;  $P=0.98$ ) (see Supplemental Figure 2).

A sensitivity analysis was also performed based on the type of PDE4 inhibitor (crisaborole, E6005, and OPA-15406) and did not find statistically significant differences from the vehicle regarding the occurrence of one or more TEAEs (see Supplemental Figure 3).

*Studies evaluating TEAE with a severity equal or higher than serious*

A meta-analysis of 19 comparisons was performed (4 with low risk of bias and 15 with unclear risk of bias). Overall homogeneity between studies and studies with low risk of bias were excellent ( $I^2 = 0\%$ ). Topical treatment with PDE4 inhibitors did not show statistically significant differences from vehicle treatment either in the global TEAE assessment (RR=0.92; 95% CI, 0.39–2.20;  $P=0.86$ ) (see Supplemental Figure 4) or in the case of the studies of low risk of bias (RR=0.82; 95% CI, 0.12–5.62;  $P=0.84$ ) (see Supplemental Figure 5).



**Figure 2.** Global analysis of phosphodiesterase 4 (PDE4) inhibitors versus vehicle for treatment-emergent adverse events  $\geq 1$ . The fixed-effects model shows excellent homogeneity ( $I^2 = 0\%$ ) and the overall result is not statistically significant ( $P = 0.94$ ).

A sensitivity analysis was also performed based on the type of PDE4 inhibitor (crisaborole, E6005, and OPA-15406) and did not find statistically significant differences from the vehicle regarding the occurrence of 1 or more treatment-emergent serious adverse events (crisaborole: RR = 0.65; 95% CI, 0.10–4.31;  $P = 0.65$ ; E6005: RR = 1.04; 95% CI, 0.33–3.26;  $P = 0.94$ ; and OPA-15406: RR = 0.93; 95% CI, 0.13–6.56;  $P = 0.94$  (see **Supplemental Figure 6**).

*Studies evaluating treatment-related adverse events*

A meta-analysis of 14 comparisons was performed (8 with low risk of bias and 6 with unclear risk of bias). The overall homogeneity among studies was excellent ( $I^2 = 0\%$ ), and the studies with a low risk of bias had low heterogeneity ( $I^2 = 16\%$ ). Topical treatment with PDE4 inhibitors did not show statistically significant differences from vehicle treatment either in the global TEAE assessment (RR = 1.22; 95% CI, 0.91–1.63;  $P = 0.18$ ) (**Figure 3**) or in the case of the studies of low risk of bias (RR = 1.35; 95% CI, 0.96–1.89;  $P = 0.74$ ) (see **Supplemental Figure 7**).

A sensitivity analysis was also performed based on the type of PDE4 inhibitor (crisaborole, E6005, and OPA-15406); this analysis found statistically significant differences compared with vehicle in the appearance of treatment-related adverse events in the crisaborole group (RR = 2.30; 95% CI, 1.20 to 4.40;  $P = 0.01$ ) (see **Supplemental Figure 8**).

*Studies evaluating pain at the application site*

A meta-analysis of 3 comparisons was performed (2 with low risk of bias and 1 with unclear risk of bias). Heterogeneity was high in the studies overall ( $I^2 = 52\%$ ) and in the studies with a low

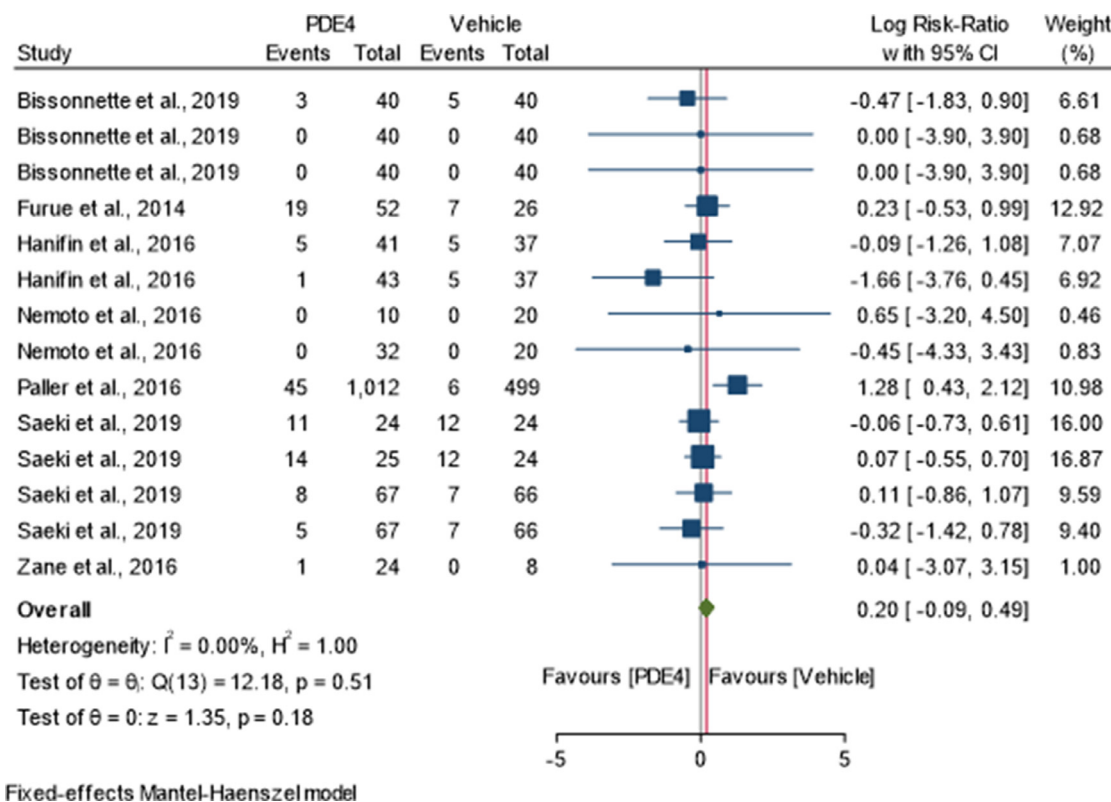
risk of bias ( $I^2 = 76\%$ ). Topical treatment with PDE4 inhibitors presented statistically significant differences from vehicle in the global analysis (RR = 2.59; 95% CI, 1.29–5.20;  $P = 0.01$ ) (**Figure 4**) as well as in studies with a low risk of bias (RR = 2.59; 95% CI, 1.27–5.28;  $P = 0.01$ ), behaving in both cases as a risk factor for the occurrence of burning or stinging in the area of application (see **Supplemental Figure 9**).

*Studies evaluating pruritus*

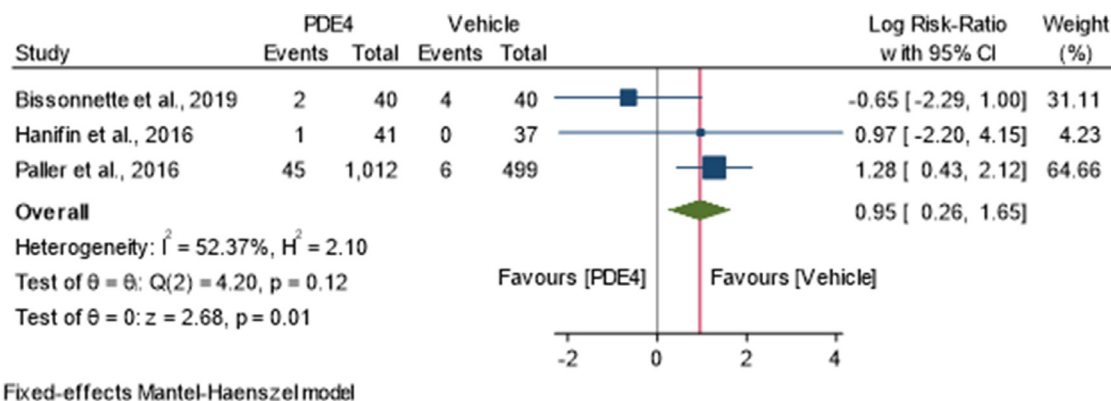
A meta-analysis of 4 comparisons was performed (1 with a low risk of bias and 3 with an unclear risk of bias). The overall homogeneity among studies was low ( $I^2 = 3\%$ ), and the studies with an unclear risk of bias had moderate heterogeneity ( $I^2 = 35\%$ ). Topical treatment with PDE4 inhibitors compared with vehicle did not show statistically significant differences either in the global TEAE assessment (RR = 0.68; 95% CI, 0.28–1.62;  $P = 0.38$ ) (**Figure 5**) or in the studies with an unclear risk of bias (RR = 0.61; 95% CI, 0.18–2.11;  $P = 0.44$ ). (see **Supplemental Figure 10**).

*Studies evaluating pruritus at the application site*

A meta-analysis of 4 comparisons was performed (2 with a low risk of bias and 2 with an unclear risk of bias). Overall homogeneity between studies and studies with low risk of bias were excellent ( $I^2 = 0\%$ ). Topical treatment with PDE4 inhibitors did not show statistically significant differences from vehicle in the global analysis (RR = 0.65; 95% CI, 0.31–1.34;  $P = 0.24$ ) (see **Supplemental Figure 11**) as well as in studies with a low risk of bias (RR = 0.43; 95% CI, 0.15–1.25;  $P = 0.12$ ) (see **Supplemental Figure 12**).



**Figure 3.** Global analysis of phosphodiesterase 4 (PDE4) inhibitors versus vehicle for treatment-related adverse events. The fixed-effects model shows excellent homogeneity ( $I^2 = 0\%$ ) and the overall result is not statistically significant ( $P = 0.18$ ).



**Figure 4.** Global analysis of the phosphodiesterase 4 (PDE4) inhibitors versus vehicle for pain at the application site. The fixed-effects model shows high heterogeneity ( $I^2 = 52.37\%$ ) and the overall result is statistically significant ( $P = 0.01$ ).

*Studies evaluating exacerbation of AD*

A meta-analysis of 17 comparisons was performed (6 with low risk of bias and 11 with unclear risk of bias). The included studies in general and the studies with a low risk of bias showed excellent homogeneity ( $I^2 = 0\%$ ). Topical treatment with PDE4 inhibitors did not show statistically significant differences from vehicle treatment in the global TEAE assessment when all studies are included in the analysis (RR = 0.75; 95% CI, 0.54–1.05;  $P = 0.10$ ) (see **Supplemental Figure 13**), although it did in the case of studies with a low risk of bias study analysis, in favor of PDE4 inhibitors (RR = 0.62; 95% CI, 0.39–0.98;  $P = 0.04$ ) (see **Supplemental Figure 14**).

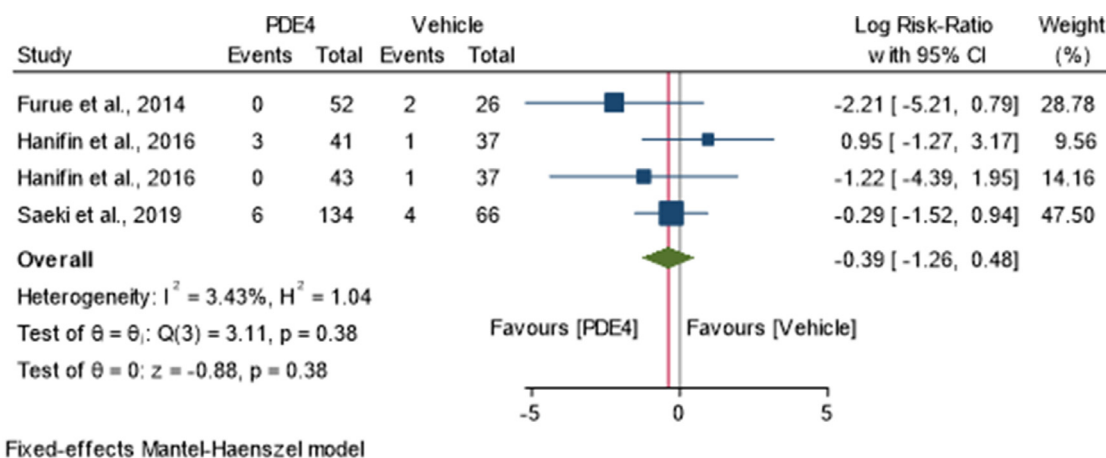
A sensitivity analysis was also performed based on the type of PDE4 inhibitor (crisaborole, E6005, and OPA-15406) and did not find statistically significant differences from the vehicle re-

garding the occurrence of exacerbation of the atopic dermatitis (**Figure 6**).

*Studies evaluating data extraction about investigations*

A meta-analysis of 13 comparisons was performed (5 with low risk of bias and 8 with unclear risk of bias) (see **Supplemental Figure 15**). The included studies in general and the studies with a low risk of bias showed excellent homogeneity ( $I^2 = 0\%$ ). Topical treatment with PDE4 inhibitors did not show statistically significant differences from vehicle in the global analysis (RR = 0.99; 95% CI, 0.49–1.99;  $P = 0.98$ ) (see **Supplemental Figure 15**) as well as in studies with a low risk of bias (RR = 0.95; 95% CI, 0.42–2.14;  $P = 0.90$ ), tended in both cases as a protector factor for the found data about investigations such as clinical laboratory test, radiologic





**Figure 5.** Global analysis of the phosphodiesterase 4 (PDE4) inhibitors versus vehicle for pruritus. The fixed-effects model shows slight heterogeneity ( $I^2 = 3.43\%$ ) and the overall result is not statistically significant ( $P = 0.38$ ).

test, physical parameters and physiology test (see **Supplemental Figure 16**).

**Discussion**

PDE4 inhibitors as a topical treatment for mild to moderate AD did not show statistically significant differences from vehicle in the occurrence of treatment-related adverse events or serious adverse events requiring discontinuation of treatment. In the studies with a low risk of bias, no statistically significant differences were found between topical treatment with PDE4 inhibitors and vehicle regarding the occurrence of adverse events related to treatment, pruritus, or skin and subcutaneous tissue disorders. Furthermore, these comparisons showed that PDE4 inhibitors had a protective tendency in the treatment of AD, in the sense that it produces less AD exacerbations than vehicle.

The study by Griffiths et al<sup>12</sup> included in the meta-analysis evaluated the appearance of skin and subcutaneous tissue disorders as an adverse event with cipamfylline 0.15% compared with TCS (ie, hydrocortisone 17-butyrate 0.1%), and the data did not show an association between cipamfylline and the occurrence of these adverse events. The rest of the studies included in this systematic review had a vehicle group as a comparator. The literature highlights the importance of not confusing the terms “placebo” and “vehicle” in RCTs because they are not the same. The difference is that a vehicle is a dermatological pharmaceutical product that improves the delivery and efficacy of the active compound, whereas a placebo is intended to mimic the active drug while having no actual efficacy. A topical vehicle is a safe product meant to be combined with active pharmacological substances, and a high concentration of the humectant glycerol confers therapeutic effects because of its inherent emollient properties. It should be noted that even the vehicle group undergoes molecular changes that promote the restoration of the epithelial barrier and improve dry skin; vehicles themselves demonstrate significant efficacy in RCTs.<sup>36-38</sup> Additionally, frequent application of emollients for long periods has been shown to reduce the risk of flare-ups in AD and improve the control of long-term adverse events.<sup>39,40</sup> Therefore, the vehicles used in RCTs have a good safety profile. Accordingly, the nonsignificant results found in this systematic review suggest that topical treatment with PDE4 inhibitors is safe for application in clinical settings.

Among the strengths of our study is that it focused on RCTs and incorporated a subgroup analysis based on quality criteria, where only studies with a low or unclear risk of bias were included. We believe that a systematic review providing clinical guidance on the safety profile of topical AD treatment with PDE4 inhibitors

should be based on RCTs and should restrict the inclusion of studies based on the quality of their design. Concerning RCTs, randomization is the only way to prevent systematic differences in the participants’ baseline characteristics between different intervention groups.

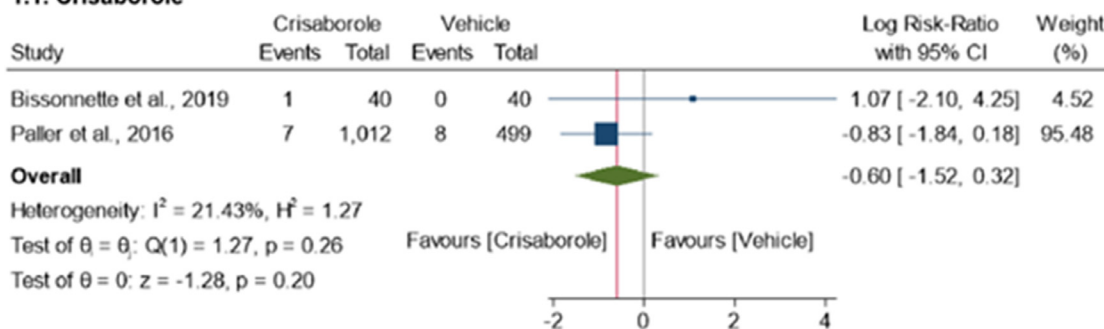
Regarding restrictions on study design, evaluating the risk of bias in each article is of particular importance for clinical decision making because the conclusions of a systematic review are valid only to the extent that the included studies are reliable. This criterion restricts the results because the included studies must show a low risk of bias in all the evaluated domains. An evaluation including only studies with a low risk of bias yields more reliable conclusions than an evaluation with no such restriction.<sup>22,41</sup> The sensitivity analysis highlights the importance of including studies with a low risk of bias to generate adequate scientific evidence.

Studies with a high risk of bias had selective outcome reporting<sup>35</sup> and no sequence generation.<sup>24</sup> A global analysis of the low-risk and unclear-risk studies was performed, but the sensitivity analysis reported only those studies that presented a correct design and bias-free methodology; these studies are considered to produce the most reliable results. The studies by Bissonnette et al,<sup>4</sup> Griffiths et al,<sup>42</sup> Paller et al,<sup>25</sup> Saeki et al,<sup>32,33</sup> and Yosipovitch et al<sup>28</sup> had a low risk of bias. These studies showed no statistically significant differences between the topical PDE4 inhibitor group and the vehicle group regarding TEAE, treatment-related adverse events, pruritus, or tissue disorders. Due to the safety profile of the vehicle, these results should be interpreted positively from a clinical point of view. Continuing with the same quality criteria, the studies showed that the use of topical PDE4 inhibitors was a risk factor for the occurrence of pain at the application site, with sensations such as burning or stinging. However, these drugs showed a beneficial profile, reducing exacerbation of AD.

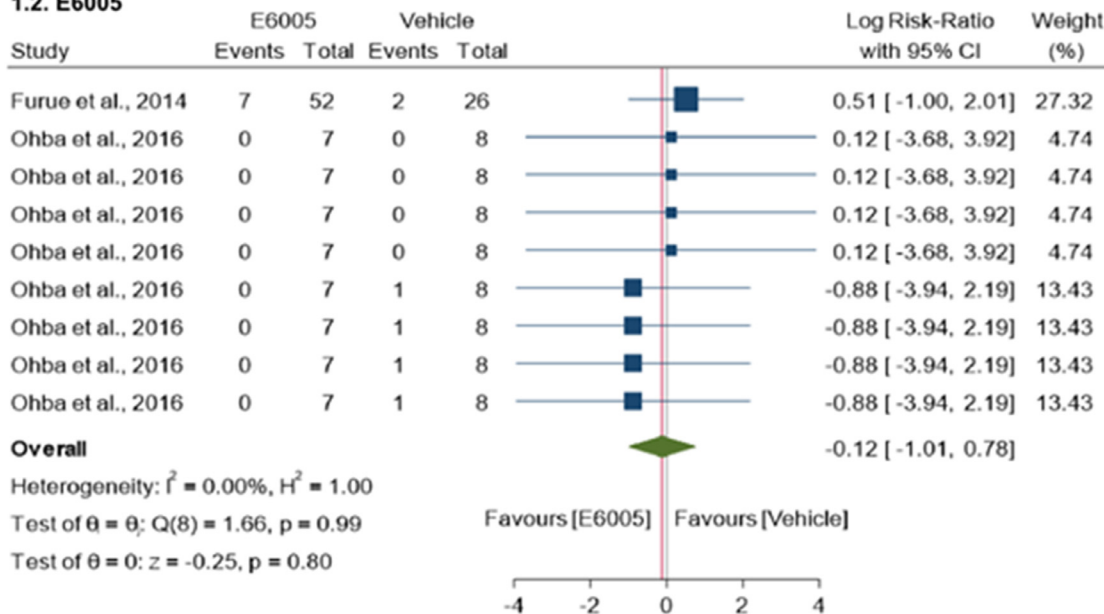
On the other hand, the sensitivity analysis based on the type of PDE4 inhibitor revealed that crisaborole 2% did not significantly differ from its vehicle in the appearance of adverse effects in general or pruritus in particular. In the latter case, it showed a protective tendency against pruritus in the treatment of AD.

Some PDE4 inhibitors, such as roflumilast<sup>43</sup> and apremilast,<sup>44</sup> have shown many adverse effects on systemic administration, but topical application has been found to decrease this exposure and minimize adverse effects. Scientific evidence on the adverse effects of treatment has been reported in systematic reviews by Broeders et al<sup>15</sup> and Ashcroft et al,<sup>17</sup> which describe burns on the skin. Additionally, articles such as those of Broeders et al<sup>15</sup> and Łabędź et al<sup>16</sup> reported pruritus; finally, Ashcroft et al<sup>17</sup> reported skin infections.

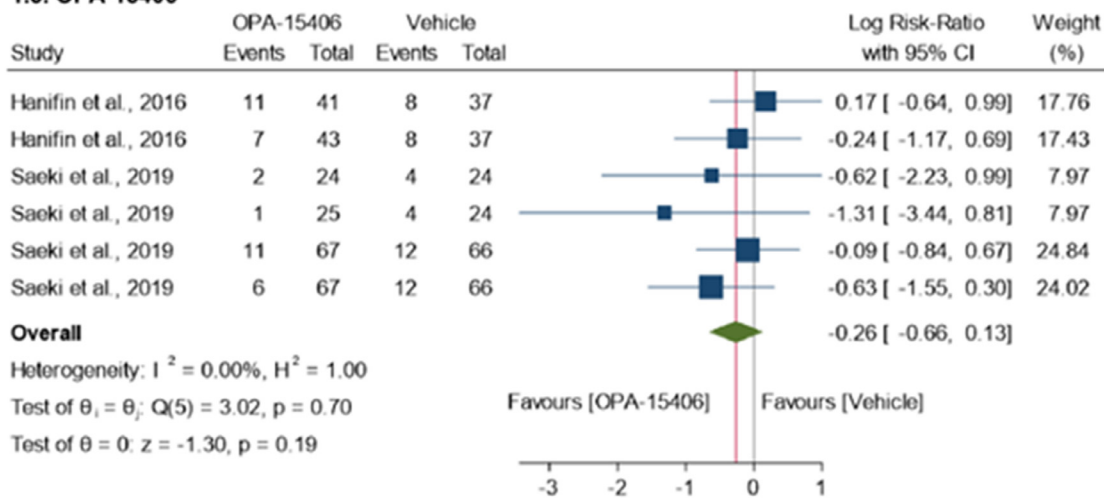
### 1.1. Crisaborole



### 1.2. E6005



### 1.3. OPA-15406



Fixed-effects Mantel-Haenszel model

**Figure 6.** Global analysis of phosphodiesterase 4 (PDE4) inhibitors versus vehicle, separated by PDE4 inhibitor type (crisaborole, E6005, and OPA-15406), for exacerbation of atopic dermatitis. The fixed-effects model shows excellent homogeneity ( $I^2=0\%$ ) for the sensitivity analysis of E6005 and OPA-15406, although the overall result in both cases is not statistically significant ( $P=0.80$  and  $P=0.19$ ). In the case of crisaborole, the result shows a slight heterogeneity ( $I^2=21.43\%$ ) with a nonsignificant global result ( $P=0.20$ ).

Only Yang et al<sup>19</sup> conducted a systematic review comparing topical PDE4 inhibitor treatment with vehicle treatment, and the only categories of adverse outcomes addressed in that study were treatment-related adverse events and adverse events that required discontinuation of treatment; instead, the study focused primarily

on efficacy. In our study, we analyzed 7 outcomes (TEAE  $\geq 1$ , TEAE serious or greater, treatment-related adverse events, pain, pruritus, skin and subcutaneous tissue disorders, and exacerbation of AD) that are relevant to clinicians because they monitor patients for possible treatment-related adverse events or sensations such as

burning or stinging at the application site. Our findings show that the application of these drugs can protect against the exacerbation of AD, pruritus, and skin and subcutaneous tissue disorders from the perspective of safety.

Our study evaluated the safety profile of crisaborole, E6005, OPA-15406, and cipamfylline. However, other systematic reviews with network meta-analyses have been carried out to assess the efficacy and safety profile of abrocitinib, baricitinib, and dupilumab, finding that the therapies did not show statistically significant differences in the appearance of TEAEs.<sup>45</sup>

It should also be noted that we found the following inconsistencies in data extraction. In the study by Furue et al.,<sup>10</sup> the number of TEAEs reported in the randomized phase was  $\geq 5\%$  of patients in either treatment group, which was not similar to the study by Paller et al.<sup>25</sup> where they were only reported in  $\geq 1\%$  of patients. Along the same lines, the TEAEs in the study by Saeki et al.<sup>33</sup> were observed in at least 5% of patients in any treatment group, which was not similar to the study by Paller et al.<sup>25</sup> On the other hand, some studies did not define the pain variable, which can be considered a subjective variable.<sup>33,34</sup> The method for measuring pain was only reported in 1 of the studies, which was performed using Dermatology Life Quality Index by responding to the question, "How itchy, scratchy, and painful has your skin been over the last week?"<sup>34</sup>

Among the limitations of our study is the shortage of RCTs in the indexed scientific literature that use TCIs or TCSs for the comparator group, these drugs being among the treatments of choice for AD.<sup>4,5</sup> In addition, because studies were searched by a single evaluator and then selected by 2 reviewers without the presence of an intraexaminer statistic at the study selection step, study selection was not performed according to the principles established for systematic reviews.

## Conclusions

Topical treatment with PDE4 inhibitors did not significantly differ from vehicle treatment regarding the incidence of adverse events, and in no case did it force the interruption of treatment. In particular, crisaborole 2% showed a lower rate of itching appearance in the treatment of AD when it was compared with the vehicle. Studies with a low risk of bias showed that PDE4 inhibitor treatment, compared with vehicle treatment, posed a significantly increased risk of pain at the application site. However, these drugs showed a positive protective effect against the exacerbation of AD and appearance of serious adverse events. These results have meaningful clinical implications because they suggest that topical PDE4 have a favorable safety profile, in the sense that they present a good safety profile compared with vehicle.

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D. Arumi and F. J. Rebollo Laserna had the idea for this study. A. Martín-Santiago, and S. Puig were actively involved in the design of the study. All authors actively revised data analysis and writing of the manuscript. All authors read and approved the final version of the manuscript before submission.

## Conflicts of Interest

A. Martín-Santiago has received consultancy honoraria from Abbvie, Leo Pharma, Lilly, Pfizer, and Sanofi, and speakers' honoraria from Leo Pharma, Leti, Pfizer, Pierre Fabre, and Sanofi. S. Puig has received consultancy honoraria from Almirall, Leo Pharma, Pfizer, Novartis, Sanofi, BMS, ISDIN, La Roche Posay, Regeneron, Sun Pharma, and Roche and speakers' honoraria from Almirall, Leo Pharma, Pfizer, BMS, ISDIN, La Roche Posay, Regeneron, Sanofi, Sun Pharma, and Roche. D. Arumi and F. J. Rebollo Laserna work for Pfizer SLU, Spain. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.curtheres.2022.100679](https://doi.org/10.1016/j.curtheres.2022.100679).

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