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Research Article

Topical Administration of Crisaborole in Mild to Moderate Atopic Dermatitis: A Systematic Review and Meta-Analysis

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Background. Crisaborole has been considered a promising alternative for topical treatment of atopic dermatitis (AD), mainly supported by AD-301 and AD-302. However, critical insights into these two studies have previously been proposed. *Objective*. To make a comprehensive assessment of the application of crisaborole in mild to moderate AD. *Methods*. A systematic review and meta-analysis were conducted, in which only randomized controlled trials comparing the application of crisaborole twice daily to vehicle or other active treatment in patients with mild to moderate AD were included. The selection of outcomes was based on the recommendation of the HOME initiative. Patient-reported symptoms, clinician-reported signs, health-related quality of life, and the safety of crisaborole were all assessed using appropriate measurement instruments. *Results*. Eight RCTs with 2266 patients were included in the pooled analysis. Compared to those treated with vehicle, patients on crisaborole experienced a greater improvement in NRS (MD −0.70; 95% CI −0.94 to −0.47), POEM (MD −3.50; 95% CI −4.34 to −2.66), EASI (MD −14.49%; 95% CI −18.24% to −10.73%), ISGA (RR 1.45; 95% CI 1.28 to 1.63), DLQI (MD −1.54; 95% CI −2.17 to −0.92), and DFI (MD −1.16; 95% CI −1.72 to −0.59) during the 4-week treatment. More patients achieved EASI 75 (RR 1.71; 95% CI 1.43 to 2.04) with crisaborole administration. There was no significant difference between two interventions in the incidence of AEs (RR 1.12; 95% CI 0.98 to 1.29), SAEs (RR 1.89; 95% CI 0.47 to 7.60), or AE-related withdrawal (RR 0.87; 95% CI 0.47 to 1.60). One RCT also made comparison between crisaborole and pimecrolimus, suggesting that no significant difference was detected in the improvement of EASI or NRS at most time points. *Conclusion*. High-quality evidence was provided to demonstrate that the short-term application of crisaborole is safe and efficacious for the treatment of mild to moderate AD. The practical efficacy of crisaborole is similar to that of pimecrolimus.

1. Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a prevalent chronic inflammatory cutaneous disorder characterized by recurrent eczematous lesions and intense itching, which seriously affects patients' quality of life [1]. Globally, approximately 20% of children and 5% of adults have been diagnosed with AD [2, 3]. The demand for repeated medical treatment poses a tremendous burden on household expenditures and social health care. The pathophysiology of AD is fairly complex, involving the dysfunction of the epidermal barrier, the abnormality of the skin microbiome, and the dysregulation of immunity dominated by the Th2 immune responses [4–6]. With the advances in our understanding of the pathogenesis, considerable progress has been made in the treatment of AD in the past few years [7].

The overall goal of treatment of AD is symptom improvement and long-term control, which requires personalized management based on the severity of the disease [8]. Among the existing therapies, topical treatment is of great importance, especially in patients with mild to moderate AD [9]. However, the options of topical medication have been limited to topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCIs) for a long time. Although the efficacy of TCSs is satisfactory, the prevalence of corticosteroid phobia in the population results in poor adherence [10], significantly decreasing the likelihood of treatment success

in clinical practice. The dilemma of TCIs is located in the black-box warning that refers to the potential risk of causing malignant tumors, though data have not shown a concrete correlation between them. The situation was not rectified until 2016 when crisaborole was approved by the US Food and Drug Administration (FDA) for the treatment of patients aged 2 years or older with mild to moderate AD (the age limit was lowered to as young as 3 months in 2020). Since then, crisaborole has been considered a promising alternative for topical medication.

Crisaborole is a small molecule inhibitor targeted at phosphodiesterase 4 (PDE4), an intracellular enzyme that has been confirmed to facilitate the production of IL-4, IL-5, IL-13, and IFN-γ, thereby exacerbating the impaired skin barrier and the immune disorder in patients with AD [11]. The approval of crisaborole is largely supported by two phase 3 multicenter randomized controlled trials (RCTs) conducted in the US, AD-301 and AD-302 [12]. In fact, critical insights into the studies, such as the controversial selection of primary outcomes and the inappropriate combination of results, have previously been proposed [13]. Nevertheless, numerous literature works regarding crisaborole as a favorable treatment for AD still cite them as the main evidence.

The articles on the list include a meta-analysis of PDE4 inhibitors published in 2019 (data on crisaborole were extracted from AD-301 and AD-302) [14] and a network meta-analysis published in 2020 that indirectly compared crisaborole to TCI (data on crisaborole were extracted from AD-301, AD-302, and another RCT with only 25 participants) [15]. These two studies concluded, respectively, that crisaborole was superior to vehicle or pimecrolimus. In addition to the narrow sources of data, it is clearly not convincing enough to choose the Investigator's Static Global Assessment (ISGA) as the prime or even sole measurement instrument of AD [13, 16]. The limitations of these studies make it clear that a more rigorous evaluation is needed. Recently, several latest RCTs on the application of crisaborole in AD have been conducted in Canada, China, Japan, and Europe. We attempt to integrate the available data and assess crisaborole in multiple dimensions, which might provide meaningful reference for clinical practice.

2. Methods

This work was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17] and registered in advance via the PROSPERO database (CRD42022330034).

2.1. Search Strategy. A systematic literature search was performed in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov on May 3, 2022. The publication language was restricted to English, and the search strategy was constructed by the combination of the following medical terms: "atopic dermatitis or atopic eczema" and "crisaborole or eucrisa or AN2728" (eTable 1 in Supplementary Materials).

2.2. Study Selection. The titles and abstracts were independently screened by two investigators for potential eligibility. Disagreements were resolved by consensus. Subsequently, full text articles were independently reviewed by two investigators to assess their final eligibility. A third senior reviewer was available to make a professional judgement when any disagreement emerged. Our target studies were RCTs comparing the topical application of crisaborole twice daily to vehicle or other active treatment in patients with mild to moderate AD. Duplicate publications and uncompleted trials were excluded.

2.3. Data Extraction. The pivotal information was extracted from the eligible studies, including the ClinicalTrials.gov identifier, study design, characteristics of patients, diagnostic criteria, severity of AD, intervention details, duration, and outcomes. Data extraction was conducted by two independent investigators to ensure accuracy.

2.4. Study Outcomes. The outcomes were selected on the basis of the consensus reached by the Harmonising Outcome Measures for Eczema (HOME) initiative [18]. Considering the availability of data, the efficacy of crisaborole was evaluated in three core outcome domains, including patient-reported symptoms, clinician-reported signs, and health-related quality of life, with appropriate measurement instruments. In addition, the assessment of safety was also conducted.

2.5. Quality Assessment. Two investigators independently assessed the risk of bias for each included RCT using the Cochrane Collaboration's assessment tool as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias (eFig 1 in Supplementary Materials) [19]. Disagreements were resolved by discussion and consensus with a third investigator. The funnel plot was used to assess the publication bias (eFig 2 in Supplementary Materials).

2.6. Statistical Analysis. Meta-analysis was performed with Review Manager Software (Version 5.4). Relative risk (RR) and a 95% confidence interval (CI) were used to assess dichotomous outcomes, while continuous variables were described by the mean difference (MD) with a 95% CI. Heterogeneity was assessed with I^2 index. If I^2 value was no more than 50%, the heterogeneity between the studies was thought to be acceptable, and the fixed effect model was used. A value of I^2 over 50% was interpreted as high heterogeneity. Consequently, the random effect model was selected, and sensitivity analysis followed.

3. Results

In total, 675 records were retrieved by the systematic search (Figure 1). After duplicate publications were removed, title and abstract screening and full text reviewing were

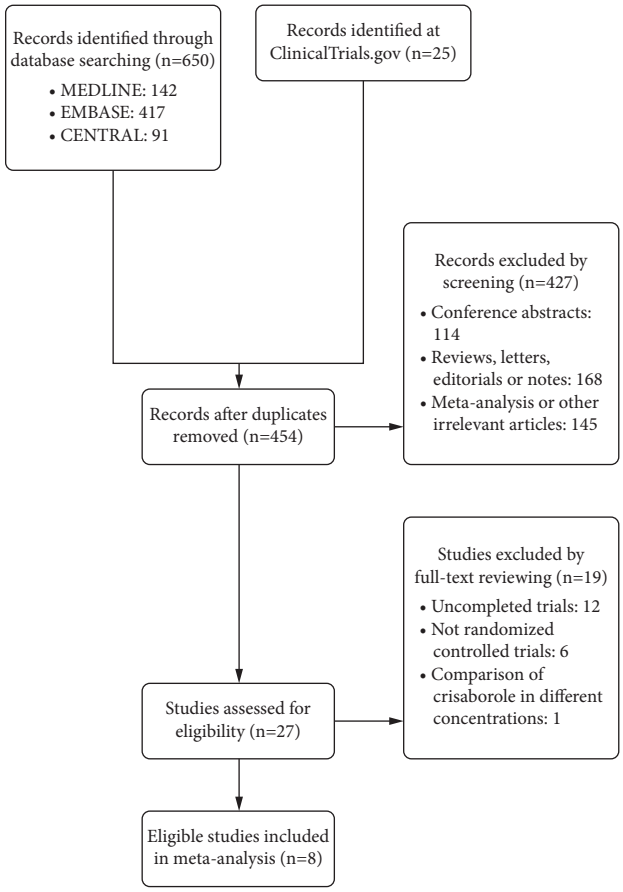

Figure 1: The flow diagram of inclusion and exclusion.

conducted as the planned strategy. Ultimately, eight studies met the selection criteria, including six RCTs published in five articles [12, 20–23] and two unpublished RCTs (NCT03539601 and NCT04360187) [24, 25] with outcomes available at ClinicalTrials.gov.

3.1. Characteristics of Included Studies. The primary details of the included studies have been presented in order (Table 1). Eight RCTs with 2266 patients evaluated the application of crisaborole 2% ointment versus vehicle twice daily for treatment of mild to moderate AD. The duration of the treatment ranged from 1 to 6 weeks. One study also made comparison between crisaborole and other active medications.

3.2. Evidence of Efficacy

3.2.1. Patient-Reported Symptoms. Pruritus Numerical Rating Scale (NRS): four RCTs included in the pooled analysis reported the change from the baseline in NRS during 4 weeks (Figure 2). Compared to vehicle treatment, topical administration of crisaborole twice daily significantly reduced the NRS value in patients with mild to moderate AD (MD −0.70; 95% CI −0.94 to −0.47). There was moderate heterogeneity detected between the studies ($I^2 = 32\%$; $P = 0.13$). Similar results were observed in the subgroup analysis at various time points. Furthermore, one RCT compared crisaborole with pimecrolimus, reporting that there was no significant difference between the NRS values of the two groups at most time points (Table 2). A comparative decrease in the NRS of patients on crisaborole was only observed at one week (MD −0.72; 95% CI −1.34 to −0.10).

Patient-oriented eczema measure (POEM): only one RCT assessed the symptoms of AD with this measurement instrument. The change from the baseline in POEM was reported at both 2 weeks and 4 weeks (eFig 3 in Supplementary Materials). Pooled data showed that patients on crisaborole experienced a significant improvement in POEM compared to those on vehicle (MD −3.50; 95% CI −4.34 to −2.66). No heterogeneity was detected ($I^2 = 0\%$; $P = 0.39$).

3.2.2. Clinician-Reported Signs. Eczema Area and Severity Index (EASI): the percentage change from the baseline in EASI and the number of patients achieving 75% improvement (EASI 75) was measured in two RCTs (Figure 3; eFig 4 in Supplementary Materials). A significant decrease in EASI value was reported in the crisaborole group versus the vehicle group (MD −14.49%; 95% CI −18.24% to −10.73%) with no heterogeneity detected ($I^2 = 0\%$; $P = 0.98$). Early improvement in EASI was observed in patients treated with crisaborole for a week (MD −14.12%; 95% CI −21.40% to −6.84%). In addition, the application of crisaborole contributed to a larger number of patients achieving EASI 75 than vehicle intervention (RR 1.71; 95% CI 1.43 to 2.04), and no heterogeneity was detected ($I^2 = 0\%$; $P = 0.92$). The comparison of crisaborole to pimecrolimus made in one RCT showed that no significant difference was detected between the two types of treatment in EASI improvement or the proportion of patients achieving EASI 75 at various time points (Table 2).

Investigator's Static Global Assessment (ISGA): four RCTs defined an ISGA score ranging from 0 to 4 as one of the primary outcomes (Figure 4). The pooled analysis indicated that patients on crisaborole were more likely to achieve ISGA 0 (clear) or 1 (almost clear) versus vehicle at 4 weeks (RR 1.45; 95% CI 1.28 to 1.63) with mild heterogeneity detected ($I^2 = 29\%$; $P = 0.24$). Similar results were observed in the proportion of patients achieving ISGA 0/1 with at least a 2-grade improvement from the baseline (RR 1.55; 95% CI 1.30 to 1.83), and mild heterogeneity was detected ($I^2 = 18\%$; $P = 0.30$).

3.2.3. Health-Related Quality of Life. Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI): DLQI was measured in four RCTs to assess the impact on quality of life, while CDLQI was used in three RCTs (Figure 5). Patients treated with crisaborole experienced a greater improvement in the DLQI score (MD −1.54; 95% CI −2.17 to −0.92) or CDLQI score (MD −1.19; 95% CI −1.91 to −0.46) at 4 weeks in comparison to those with vehicle treatment. The result of heterogeneity test for either one turned out to not be significant ($I^2 = 43\%$; $P = 0.16$ and $I^2 = 0\%$; $P = 0.46$, respectively).

Table 1: Characteristics of the included studies.

CT.gov identifier authors (year)	Phase	Design	Location	Participants (age)	Race	Diagnostic criteria	Severity of AD	Interventions	Duration (days)	Outcomes
NCT01301508 Murrell et al. (2015) [20]	2a	R, DB	Australia (multicenter)	25 (≥18 y)	Unavailable	Hanifin and Rajka criteria	Mild to moderate	Crisaborole 2% or vehicle BID	42	ASDI, AEs, and SAEs
NCT02118766 Paller et al. (2016) [12]	3	R, DB	USA (multicenter)	759 (≥2 y)	Available†	Hanifin and Rajka criteria	Mild to moderate	Crisaborole 2% or vehicle BID	28	ISGA, DLQI, AEs, and SAEs
NCT02118792 Paller et al. (2016) [12]	3	R, DB	USA (multicenter)	763 (≥2 y)	Available†	Hanifin and Rajka criteria	Mild to moderate	Crisaborole 2% or vehicle BID	28	ISGA, DLQI, CDLQI, DFI, AEs, and SAEs
NCT03233529 Bissonnette et al. (2019) [21]	2a	R, DB	Canada (single-center)	40 (≥18 y)	Available†	Hanifin and Rajka criteria	Mild to moderate	Crisaborole 2% or vehicle BID	14	TSS, NRS, ISGA, TEWL, AEs, SAEs, and Biomarkers
NCT03260595 Ono et al. (2020) [22]	1	R	Japan (single-center)	12 (≥18 y)	Asian	Hanifin and Rajka criteria	Mild to moderate	Crisaborole 2% or vehicle BID	7	AEs and SAEs
NCT03954158 Fujita et al. (2021) [23]	2b	R, DB	Japan (multicenter)	41 (≥2 y)	Asian	Hanifin and Rajka criteria	Mild to moderate	Crisaborole 2% or vehicle BID	14	TSS, NRS, ISGA, AEs, and SAEs
NCT03539601 (2022) [24]	3b/4	R, AB	Germany, Italy, Poland, Sweden, Switzerland, UK, USA (multicenter)	235 (≥2 y)	Available†	Hanifin and Rajka criteria	Mild to moderate	Crisaborole 2% or hydrocortisone butyrate 0.1% or pimecrolimus 1% or vehicle BID	28	EASI, NRS, ISGA, BSA, DLQI, CDLQI, DFI, AEs, and SAEs
NCT04360187 (2022) [25]	3	R, DB	China, Japan (multicenter)	391 (≥2 y)	Asian	Hanifin and Rajka criteria	Mild to moderate	Crisaborole 2% or vehicle BID	28	POEM, EASI, NRS, ISGA, BSA, DLQI, CDLQI, DFI, AEs, and SAEs

R: randomized; DB: double-blind; AB: assessor blinded; BID: twice daily; ASDI: atopic dermatitis severity index; AEs: adverse events; SAEs: serious adverse events; ISGA: investigator's static global assessment; DLQI: dermatology life quality index; CDLQI: children's dermatology life quality index; DFI: dermatitis family impact questionnaire; TSS: total sign score; NRS: Pruritus Numerical Rating Scale; TEWL: transepidermal water loss; EASI: Eczema Area and Severity Index; BSA: body surface area; POEM: patient-oriented eczema measure. †Available on Clinicaltrials.gov.

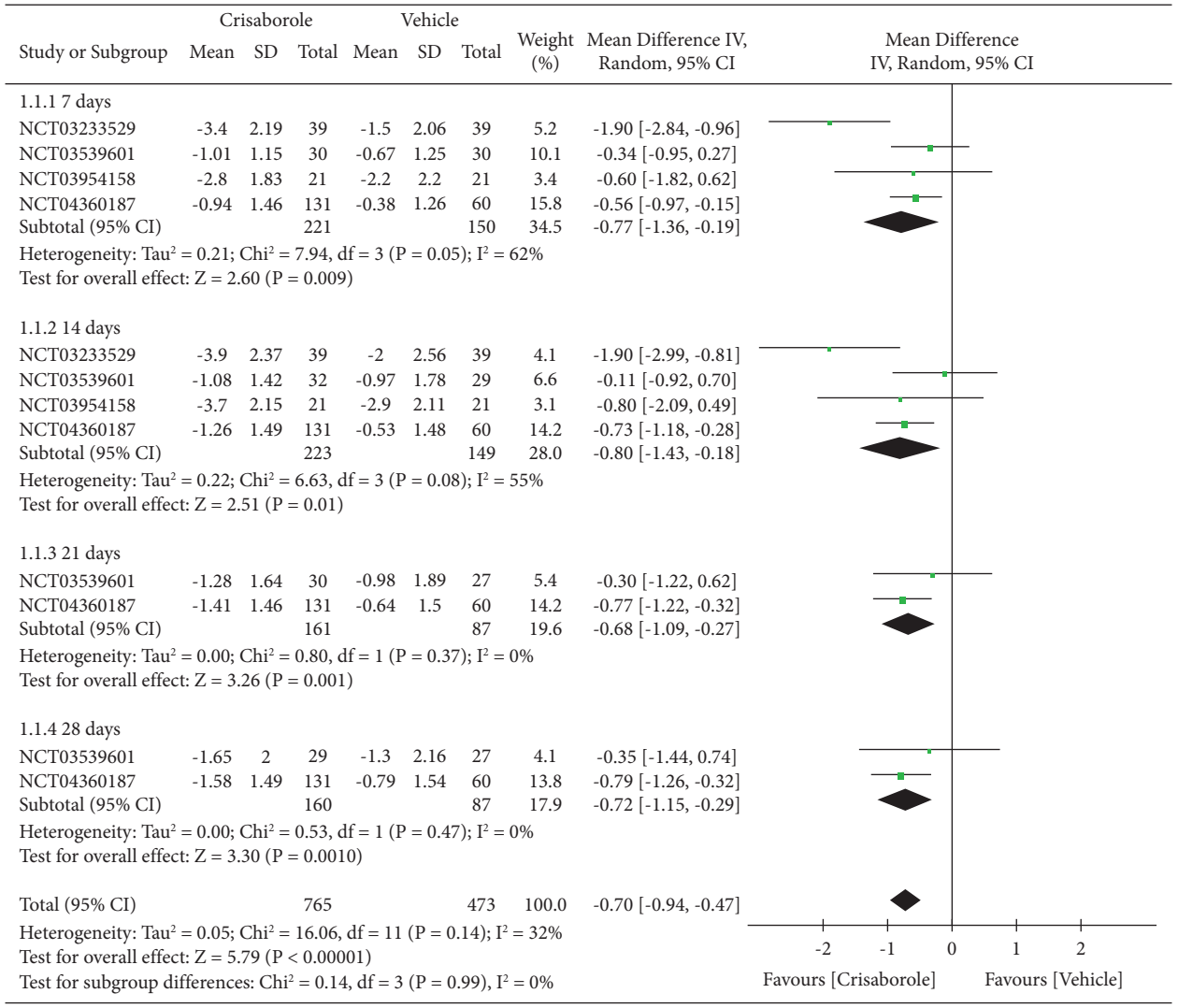

Figure 2: Pooled analysis of change from the baseline in the Pruritus Numerical Rating Scale of patients on crisaborole versus vehicle.

Table 2: A comparison of crisaborole to pimecrolimus.

Outcomes or subgroups	Participants	Effect estimate	*P* value
Change from the baseline in the Pruritus Numerical Rating Scale			
7 days	30/26	MD −0.72 (95% CI −1.34 to −0.10)	0.02
14 days	32/25	MD 0.27 (95% CI −0.56 to 1.10)	0.52
21 days	30/24	MD 0.38 (95% CI −0.54 to 1.30)	0.42
28 days	29/24	MD 0.02 (95% CI −1.05 to 1.09)	0.97
Percentage change from the baseline in the Eczema Area and Severity Index (EASI)			
7 days	54/45	MD 0.74 (95% CI −13.60 to 15.08)	0.92
14 days	53/44	MD −0.15 (95% CI −14.96 to 14.66)	0.98
21 days	50/41	MD 8.02 (95% CI −5.92 to 21.96)	0.26
28 days	50/43	MD 8.51 (95% CI −5.71 to 22.89)	0.24
Proportion of patients achieving EASI 75			
7 days	58/47	RR 2.84 (95% CI 0.62 to 13.02)	0.18
14 days	58/47	RR 1.01 (95% CI 0.43 to 2.36)	0.98
21 days	58/47	RR 0.96 (95% CI 0.47 to 1.94)	0.90
28 days	58/47	RR 0.81 (95% CI 0.47 to 1.41)	0.45

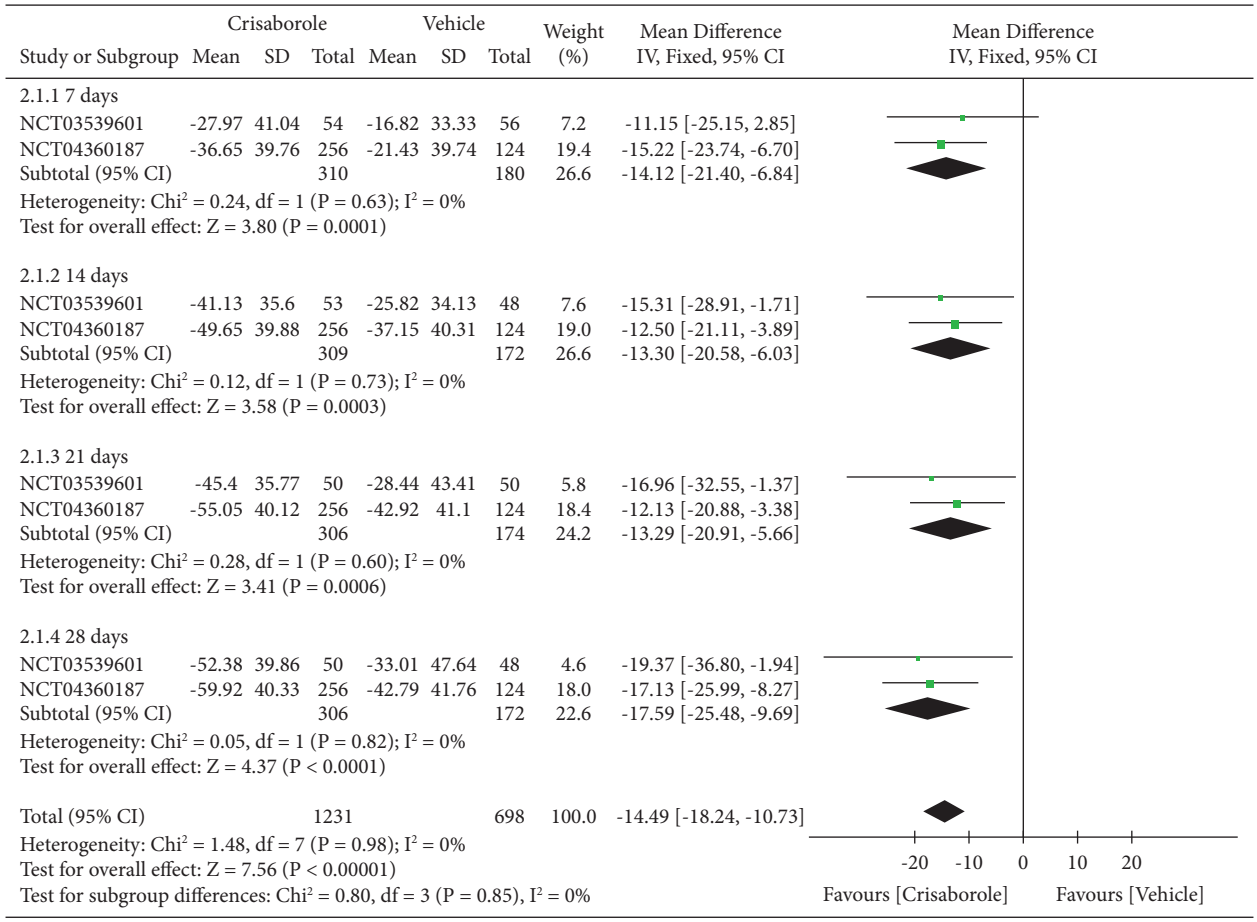

Figure 3: Pooled analysis of percentage change from the baseline in the Eczema Area and Severity Index of patients on crisaborole versus vehicle.

Dermatitis Family Impact Questionnaire (DFI): three RCTs reported this outcome to assess the impact on the lives of families that had children diagnosed with mild to moderate AD (eFig 5 in Supplementary Materials). The result showed that a greater improvement of DFI was observed in the crisaborole group versus the vehicle group during the 4-week treatment (MD −1.16; 95% CI −1.72 to −0.59). No heterogeneity was detected ($I^2 = 0\%$; $P = 0.59$).

3.3. Evidence of Safety. Adverse events (AEs): five RCTs were included in the pooled analysis (eFig 6 in Supplementary Materials). Data on AEs of different interventions were not available in the other three RCTs because crisaborole and vehicle were applied to the same patients. Results revealed that 33.66% (451/1340) of patients treated with crisaborole experienced treatment emergent AEs in 4 weeks, while the proportion in the vehicle group was 29.96% (207/691), in which no significant difference was detected (RR 1.12; 95% CI 0.98 to 1.29). There was moderate heterogeneity between the studies ($I^2 = 50\%$; $P = 0.09$).

Serious adverse events (SAEs): three RCTs reported the occurrence of SAEs during the treatment (eFig 7 in Supplementary Materials). 9 of 1272 patients treated with crisaborole and 2 of 630 with vehicle experienced SAEs, and the difference was confirmed to not be statistically significant (RR 1.89; 95% CI 0.47 to 7.60). No heterogeneity was detected between the studies ($I^2 = 0\%$; $P = 0.58$).

AE-related withdrawal: four RCTs reported AE-related withdrawal during the treatment (eFig 8 in Supplementary Materials). The pooled data suggested that the incidence of AE-related withdrawal was 1.87% (25/1340) in patients on crisaborole and 2.15% (15/697) in those on vehicle. There was no significant difference between the two groups (RR 0.87; 95% CI 0.47 to 1.60), and mild heterogeneity was detected ($I^2 = 1\%$; $P = 0.39$).

4. Discussion

This systematic review and meta-analysis focused on crisaborole 2% ointment for treatment of AD and included eight eligible RCTs. Our findings provided evidence for the short-term safety and efficacy of crisaborole in patients with mild to moderate AD. In comparison to vehicle intervention, crisaborole reduced the severity of AD, relieved pruritus symptoms, and improved quality of life during the 4-week treatment. Patients on crisaborole experienced early improvement in their EASI and NRS scores at the end of the first week. In terms of safety, the application of crisaborole did not increase the incidence of treatment-emergent AEs or SAEs.

Study or Subgroup	Crisaborole Events	Crisaborole Total	Vehicle Events	Vehicle Total	Weight (%)	Risk Ratio M-H, Fixed, 95% CI
2.3.1 ISGA 0/1 at 28 days						
NCT02118766	260	503	104	256	46.5	1.27 [1.07, 1.51]
NCT02118792	249	513	74	250	33.6	1.64 [1.33, 2.02]
NCT03539601	19	58	10	59	3.3	1.93 [0.98, 3.79]
NCT04360187	107	260	37	131	16.6	1.46 [1.07, 1.99]
Subtotal (95% CI)		1334		696	100.0	1.45 [1.28, 1.63]
Total events	635		225			
Heterogeneity: Chi² = 4.25, df = 3 (P = 0.24); I² = 29%						
Test for overall effect: Z = 6.03 (P < 0.00001)						
2.3.4 ISGA 0/1 with ≥2-grade improvement at 28 days						
NCT02118766	165	503	65	256	48.3	1.29 [1.01, 1.65]
NCT02118792	161	513	45	250	34.0	1.74 [1.30, 2.34]
NCT03539601	11	58	5	59	2.8	2.24 [0.83, 6.04]
NCT04360187	71	260	20	131	14.9	1.79 [1.14, 2.80]
Subtotal (95% CI)		1334		696	100.0	1.55 [1.30, 1.83]
Total events	408		135			
Heterogeneity: Chi² = 3.65, df = 3 (P = 0.30); I² = 18%						
Test for overall effect: Z = 4.99 (P < 0.00001)						

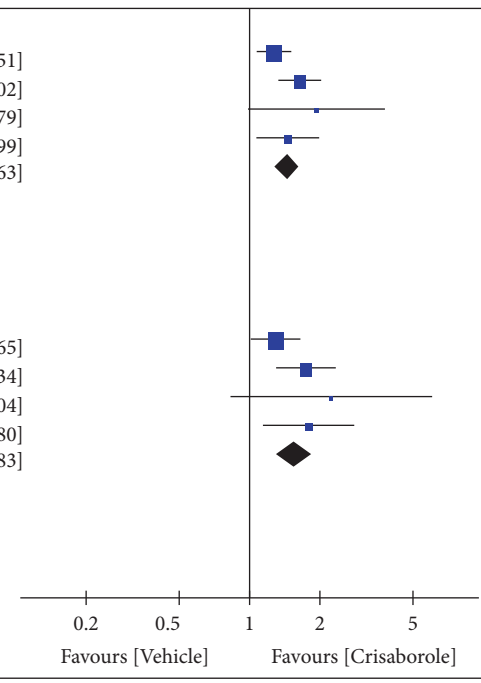

Figure 4: Pooled analysis of proportion of patients on crisaborole versus vehicle achieving the Investigator's Static Global Assessment (ISGA) 0/1 and ISGA 0/1 with ≥2-grade improvement.

Study or Subgroup	Crisaborole Mean	Crisaborole SD	Crisaborole Total	Vehicle Mean	Vehicle SD	Vehicle Total	Weight (%)	Mean Difference IV, Fixed, 95% CI
3.1.1 Change from baseline in DLQI at 28 days								
NCT02118766	-5.5	5.45	503	-3.6	4.6	256	71.2	-1.90 [-2.64, -1.16]
NCT02118792	-5	5.49	97	-3.4	4.75	40	11.5	-1.60 [-3.43, 0.23]
NCT03539601	-3.9	4.76	19	-4.9	5.6	18	3.4	1.00 [-2.36, 4.36]
NCT04360187	-1.8	4.11	110	-1.5	4.67	38	13.9	-0.30 [-1.97, 1.37]
Subtotal (95% CI)			729			352	100.0	-1.54 [-2.17, -0.92]
Heterogeneity: Chi² = 5.23, df = 3 (P = 0.16); I² = 43%								
Test for overall effect: Z = 4.86 (P < 0.00001)								
3.1.2 Change from baseline in CDLQI at 28 days								
NCT02118792	-4	4.92	404	-2.9	5.01	204	74.7	-1.10 [-1.94, -0.26]
NCT03539601	-3.4	4.85	21	-3.1	2.73	20	9.2	-0.30 [-2.69, 2.09]
NCT04360187	-3.9	5.37	121	-1.8	6	59	16.1	-2.10 [-3.91, -0.29]
Subtotal (95% CI)			546			283	100.0	-1.19 [-1.91, -0.46]
Heterogeneity: Chi² = 1.55, df = 2 (P = 0.46); I² = 0%								
Test for overall effect: Z = 3.21 (P = 0.001)								

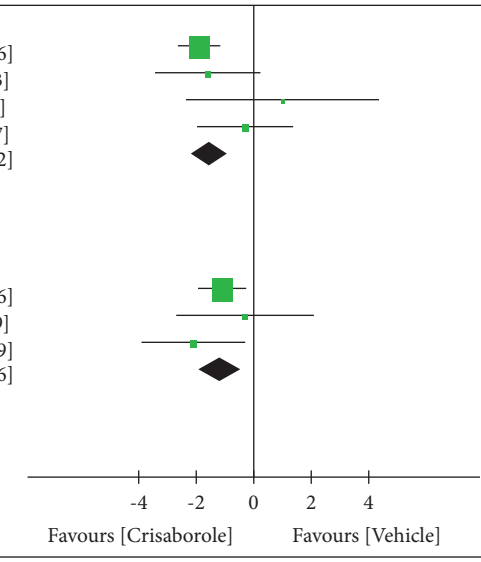

Figure 5: Pooled analysis of changes from the baseline in the Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI) of patients on crisaborole versus vehicle.

Numerically, the advantage of crisaborole versus vehicle appears to be limited in several assessments, which might raise concerns about the practical efficacy of crisaborole. However, the unexpectedly positive responses observed in patients treated with vehicle do deserve our attention, such as the significant reduction in the EASI score, which should be taken into consideration when the efficacy of crisaborole is challenged. According to the absolute improvements and the comparative results, we believe that crisaborole is a topical medication with moderate efficacy. The systematic search also identified an unpublished RCT that compared crisaborole to pimecrolimus, reporting that there was no

significant difference detected in EASI or NRS improvement between the two groups, which contradicts a prior network meta-analysis [15]. Undoubtedly, results supported by direct comparison in clinical trials must be more reliable, contributing to a tangible way of conceptualizing the efficacy of crisaborole.

The emergence of crisaborole enriches the armaments of dermatologists for treatment of AD, particularly under the circumstances where both TCSs and TCIs have their own shortcomings (presented in Introduction). Nevertheless, it worries us that crisaborole might still not meet patients' requirements for topical treatment. With regard to long-term safety, an open-label, 48-week study of AD-303 reported that 10.2% of 517 patients experienced treatment-related AEs, of which the most common were flares of AD, application site pain, and application site infection [26]. Despite few literature works reporting its use in the real world, it has been proposed that application site pain appears more frequently in clinical practice than in trials [27]. Once there are more detailed data in support of it, crisaborole will have trouble standing out in comparison with other nonsteroidal agents such as TCIs.

For the moment, the rapid development of small molecule drugs and biological agents has widely expanded the treatment options of AD [28], but topical medication remains an essential part. After the advent of crisaborole, delgocitinib 0.5% ointment (approved in Japan in 2020) and ruxolitinib 1.5% cream (approved by the FDA in 2021) entered the market in succession [29]. However, the practical application of new topical medications is proceeding slowly in part because of their high prices. Further investigations are encouraged to provide real-world data.

Compared to the previous meta-analysis involving crisaborole, there are several strengths in our study. On the one hand, a comprehensive search was performed, in which additional RCTs besides AD-301 and AD-302 were included. The earlier trials of crisaborole were conducted in the US and Australia (Table 1), and few Asians were recruited (data available at ClinicalTrials.gov). Our pooled analysis included three RCTs conducted among Asian population, which helps ensure representation and avoid race serving as an interference factor in the assessment [30, 31]. On the other hand, diverse measurement instruments were used to generate a rigorous evaluation. AD is a complicated and debilitating disease with heterogeneity, which definitely requires a reasonable assessment. In accordance with the study design, we took the recommendation of the HOME initiative as the main principle for the selection of outcome domains and their instruments. Appropriate modification was necessary, for instance, ISGA was introduced as the supplementary assessment for clinician-reported signs because the EASI score was reported in only two trials.

Limitations also exist in the study. It has been confirmed that the inconvenience of topical therapies easily impairs the adherence of patients. The crisaborole administration in trials received supervision of regular follow-up, and therefore, the results obtained might not be equivalent to that in clinical practice. Furthermore, only a 4-week treatment was assessed, leading to a lack of long-term data. Considering that crisaborole might play a potential role in the proactive treatment of AD, a scientific analysis is needed to assess the drug's long-term safety and efficacy.

In conclusion, a comprehensive and rigorous assessment of crisaborole for treatment of AD was eventually conducted, which provides high-quality evidence for clinical practice. According to the pooled analysis of short-term trials, crisaborole 2% ointment is a safe and efficacious topical medication for mild to moderate AD. Its practical efficacy is similar to pimecrolimus. However, further investigations are still required to shed light on its application in the real world (registration number: CRD42022330034).

Data Availability

The data that support the findings of the research are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Yufei He and Jia Liu equally contributed to the preparation, writing of the original draft, methodology, and investigation; Yulian Wang took the lead in validation, project administration, and supervision; Wenhao Kuai and Ran Liu equally carried out data curation, formal analysis, and visualization; Jianhua Wu took the lead in conceptualization, writing the review, and editing. Yufei He and Jia Liu contributed equally to this manuscript.

Supplementary Materials

The search strategy, the risk of bias, and the funnel plot have been presented in the supplementary files. There are also details of several other assessments such as POEM, EASI 75, DFI, AEs, SAEs, and AE-related withdrawal, which serve as additional evidence for efficacy and safety of crisaborole. eTable 1: search strategy. eFig 1: risk of bias of the included studies. eFig 2: the funnel plot of the studies included in the pooled analysis of AEs. eFig 3: change from the baseline in POEM. eFig 4: proportion of patients achieving EASI 75. eFig 5: change from the baseline in DFI. eFig 6: incidence of AEs. eFig 7: incidence of SAEs. eFig 8: incidence of AE-related withdrawal. (*Supplementary Materials*)

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