Atopic Dermatitis (AD) ACE Clinical Guideline (ACG) Evidence-to-Recommendation Framework

This document outlines the underpinning evidence and rationale for the recommendation statements in the ACE Clinical Guideline (ACG) 'Mild and moderate atopic dermatitis (eczema) – A journey from flare to care'.

In ACGs, the strength of recommendation reflects the confidence that the desirable effects of the recommended practice outweigh undesirable effects across the range of patients for whom the recommendation applies, based on the best available evidence:

- A strong recommendation is usually made when benefits clearly outweigh the risks, based on at least moderate-certainty evidence.
- A weak or conditional recommendation may be needed when there is a closer balance between benefits and harms, evidence is of low certainty, there is significant variability in patients' values and preferences, or important concerns with resourcing and feasibility of the recommended practice.[1]

Recommendation 1:
Diagnose AD through history taking and clinical examination, focusing on key features such as skin itchiness, dryness, personal or family history of atopic diseases, disease chronicity, lesion morphology and distribution.

Strength of recommendation: **Strong** Conditional

Summary: A flexible diagnostic approach without mandating specific diagnostic criteria is strongly recommended, given varying sensitivity and specificity of existing criteria, particularly among Asians. This aligns with patients' preferences and current local practice, while avoiding unnecessary investigations in routine consultations.

Balance of benefits and harms

Key clinical features listed in the recommendation show high global prevalence rates: itch (94%), dry skin (73%) and personal or family history of atopic disease (53%).[2] Existing diagnostic criteria (Hanifin and Rajka [H&R], UK Working Party [UKWP] have limitations, including variable sensitivity (H&R: 48.2%-96%; UKWP: 10%-100%) and specificity (H&R: 77.6%-93.8%; UKWP: 77.6%-99.6%),[3-8] being too complex for routine use (H&R),[9] and having decreased sensitivity among Asians (UKWP) due to different AD morphology and distribution compared to Europeans and increased late-onset prevalence.[2, 10, 11] Although the Japan Dermatological Association criteria and Chinese Criteria for AD were developed for Asians, their validation remains limited to East Asia. Additional investigations like blood tests or skin biopsies are unnecessary in routine cases, as they add cost without providing significant diagnostic value in routine clinical settings.[12, 13] However, flexible diagnosis must be balanced against misdiagnosis risk, because conditions like psoriasis, seborrheic dermatitis and contact dermatitis can present similarly.[14] Therefore, careful clinical examination and history-taking are essential to exclude differential diagnoses.

Certainty of evidence	Values and preferences
In the absence of validation studies for established diagnostic criteria within a	Patients with uncomplicated AD may favour quick, non-invasive diagnostic processes integrated into routine consultations, based

Singaporean population, a flexible diagnostic approach is supported.	on indirect evidence suggesting less invasive procedures are preferred.[15]
Resources and feasibility	**Acceptability and other considerations**
The recommendation aligns with current standard practice for diagnosing AD without requiring additional resources.	Darker-skinned patients are under-represented in dermatology resources, contributing to underdiagnosis and misdiagnosis.[16-18]
Expert Group deliberation of above factors	
The Expert Group (EG) reached a strong recommendation for a flexible diagnostic approach after weighing evidence of varying sensitivity and specificity for existing criteria (particularly among Asians) against the low certainty of evidence due to limited validation studies, while considering the benefits of avoiding unnecessary investigations, aligning with patients' preferences, and ensuring feasibility in clinical practice.	

Recommendation 2:
Assess AD severity based on extent, frequency and intensity of clinical manifestations and patient- or caregiver-reported impact on quality of life.

Strength of recommendation: **Strong** Conditional

Summary: Descriptive assessment of AD severity without mandating specific scoring tools is strongly recommended, as it is practical for primary care, aligns with patients' values and ensures inclusive assessment across different skin types.

Balance of benefits and harms

The recommendation adapted the National Institute for Health and Care Excellence (NICE) severity classification system, which defines mild AD as infrequent episodes with minimal impact, moderate AD as frequent episodes with moderate impact on daily activities and psychological wellbeing, and severe AD as persistent episodes with severe functional impact.[19] The holistic approach evaluates signs, symptoms and impact on quality of life (aligning with reference guidelines),[19-21] and provides practical flexibility without mandatory scoring tools. While the Eczema Area and Severity Index (EASI) and SCORing Atopic Dermatitis (SCORAD) tools represent best practice, the Harmonising Outcome Measures for Eczema in Clinical Practice (HOME-CP) initiative acknowledges they were validated in controlled settings, not routine clinical practice, where time constraints, patient burden and clinician efforts need to be considered.[22-24] Further, subjective assessment and terms like "infrequent" or "frequent" may lead to clinician variability in categorising AD severity. Without quantitative measures such as scoring tools, clinicians may miss subtle changes in disease severity over time.

Certainty of evidence	**Values and preferences**
NICE severity definition was based on expert consensus which lacked formal validation, despite domains (e.g. erythema, excoriation) aligning with the clinical features listed in validated scoring tools like EASI and SCORAD.[19]	This holistic assessment approach aligns with patients' values. Local studies showed psychosocial aspects were most affected, with "self-consciousness due to appearance" ranked highest (38%) among AD challenges. This highlights the importance of quality of life in severity assessment.[25]
Resources and feasibility	**Acceptability and other considerations**
No additional training is required, unlike with scoring tools where clinician familiarity with calculation and interpretation of scores is needed.	Clinicians' acceptability is presumably high due to an inclusive and practical approach. The flexibility to assess "clinical manifestations" without mandating descriptors like "erythema" might benefit clinicians serving diverse populations, as erythema inadequately describes AD in patients with skin of colour who present with violaceous or dark brown lesions.[26, 27].

Expert Group deliberation of above factors

The EG reached a strong recommendation, recognising that while validated scoring tools represent best practice, they can be challenging for routine clinical use due to time constraints and training requirements. They concluded that this flexible approach better aligns with patients' values, offers practical feasibility without additional training, and maintains acceptability across diverse populations while acknowledging the trade-off of potential clinician variability in assessment.

Recommendation 3:
Review potential triggers for AD and advise on how to minimise exposure.

Strength of recommendation: **Strong** Conditional

Summary: Identifying triggers and providing feasible avoidance advice are strongly recommended based on alignment with patients' preferences for non-pharmacological management, minimal safety concerns and feasibility in routine care despite variable evidence certainty.

<table>
<tr><th colspan="2">Balance of benefits and harms</th></tr>
<tr><td colspan="2">Identifying and minimising AD triggers can reduce severity and flares, potentially decreasing need for topical treatments and improving quality of life.[19, 20, 28] Common triggers include aeroallergens (dust, animal dander, grass pollen), irritants (strong soaps, detergents), climate, pollutants, sweat, stress and smoking.[29-31] Avoidance measures are generally low-risk.[32]</td></tr>
<tr><th>Certainty of evidence</th><th>Values and preferences</th></tr>
<tr><td>Evidence certainty is generally low to moderate, varying by trigger type: climate and air pollutants have high certainty of association with AD;[30] smoking has moderate certainty from observational studies (upgraded due to dose-response relationship);[33, 34] avoidance measures such as dust mite control have low certainty, due to small, poorly blinded trials.[35]</td><td>The recommendation aligns with patients' values and preferences to start with non-pharmacological therapies and ensures minimal safety concerns.[36]</td></tr>
<tr><th>Resources and feasibility</th><th>Acceptability and other considerations</th></tr>
<tr><td>The recommendation is presumably feasible, as trigger identification is already incorporated into routine care through standard history taking, though patients may resist advice from clinicians that require major lifestyle changes like pet removal or significant environment modifications. Focus should be on realistic mitigation strategies suited to each patient's circumstances, recognising that complete trigger elimination is often impossible.</td><td>No significant concerns identified.</td></tr>
<tr><th colspan="2">Expert Group deliberation of above factors</th></tr>
<tr><td colspan="2">The EG reached a strong recommendation despite mixed evidence certainty because trigger identification represents a fundamental, low-risk approach aligning with current clinical practice and patients' preferences. The EG prioritised practical avoidance measures suited to patient's circumstances, recognising that complete trigger elimination is often impractical.</td></tr>
</table>

Recommendation 4:
For patients with mild or moderate AD, advise liberal moisturiser use as baseline therapy, and:

- **(A) Prescribe topical corticosteroids (TCS) as first-line anti-inflammatory treatment for active lesions.**
- **(B) If a non-steroidal alternative is required or preferred, consider topical calcineurin inhibitors (TCIs) (as second-line) or topical phosphodiesterase 4 inhibitors (PDE4i) (as third-line).**

Strength of recommendation (A): **Strong** Conditional

Strength of recommendation (B): Strong **Conditional**

Summary: The recommendation establishes moisturisers as universal baseline therapy and TCS as strong first-line therapy based on superior efficacy profile despite steroid phobia concerns. Non-steroidal alternatives (TCIs, PDE4i) received conditional second- and third-line recommendations as their efficacy profiles align more with mild-moderate potency TCS rather than high potency TCS, along with having higher costs and access barriers.

Balance of benefits and harms

Moisturisers offer modest but consistent benefits in reducing AD severity and prolonging time to flare with minimal adverse effects (stinging, folliculitis).[37, 38]

Compared to placebo, TCS demonstrate superior efficacy in reducing AD signs, symptoms and flares,[37, 39] with treatment response rates of 65% (95% confidence intervals [CI] 54%-74%) vs 32% (95% CI 8%-33%).[40] While inappropriate use may cause local adverse effects (skin thinning, striae, telangiectasia), evidence showed that when appropriately selected, short-term use (≤6 weeks) of even very potent TCS is not associated with significant local adverse effects.[41] Intermittent long-term use (3-5 years) of low to moderate potency TCS was not associated with significant local and systemic adverse effects (growth abnormalities, adrenal insufficiency, skin infection).[42]

Compared to placebo, TCIs demonstrate superior efficacy in reducing AD signs, symptoms and flares.[37, 39] In a 2023 network meta-analysis (NMA), tacrolimus 0.1%, tacrolimus 0.03% and pimecrolimus 1% demonstrated efficacy comparable to TCS group 4, group 5, and between groups 5 and 6, respectively.[37] Unlike TCS, they carry no risk of skin atrophy, making them valuable steroid-sparing alternatives with long-term safety data showing no convincing evidence of increased malignancy risk despite FDA black box warning.[43, 44] However, initial transient burning and stinging sensations occur more frequently than with TCS.

Topical PDE4i can improve mild-to-moderate AD severity, but their comparative efficacy against established therapies remains limited. Multiple NMAs identified them among the least effective treatments for reducing AD severity.[37, 41] Recent head-to-head trials comparing crisaborole 2% with TCS or TCIs, showed moderate potency TCS (group 5) had greater efficacy in reducing AD signs and symptoms compared to crisaborole, while differences between crisaborole and TCIs were not statistically significant (see evidence table in Appendix A).[45-49] Adverse effects include transient burning and stinging sensations similar to TCIs.[41]

Certainty of evidence	Values and preferences

Evidence certainty for moisturisers is low, downgraded by risk of bias and heterogeneity. Evidence certainty for TCS and TCIs is moderate, downgraded by risk of bias and heterogeneity respectively. Evidence certainty for PDE4i is low, downgraded by risk of bias and imprecision.	Most patients prefer starting with non-pharmacological options before topical anti-inflammatory treatments.[36] They favour non-fragrant, hypoallergenic formulations that are invisible with minimal impact on life.[36, 50, 51] Patients rated rapid relief of itch and burning sensations alongside skin clearance as important efficacy attributes.[36, 51] They demonstrate careful benefit-risk considerations, preferring minimal TCS duration,[36] and may favour TCIs and PDE4i as non-steroidal alternatives with minimal harm.[37]
Resources and feasibility	**Acceptability and other considerations**
Few moisturisers are subsidised (white soft paraffin, urea cream), while most are available over the counter. TCS are readily accessible in different healthcare settings, with various subsidised options available. Following recent inclusion of TCIs in local polyclinic formularies, access has improved, though they remain costly. PDE4i are limited in many public healthcare institutions and remain costly, creating significant access barriers for patients.	A local qualitative study revealed steroid phobia affects treatment acceptability.[52] Despite concerns, many patients continued TCS use due to lack of alternatives and perceived safety compared to systemic therapy.[52] TCIs and PDE4i were perceived to have higher acceptability among patients with steroid phobia seeking non-steroidal alternatives, though their initial burning and stinging sensations can affect early treatment adherence.
Expert Group deliberation of above factors	
The EG reached a strong recommendation for TCS as first-line therapy, recognising their superior efficacy and safety when used appropriately outweighs steroid phobia concerns in some patients. Their broad potency spectrum provides clinicians with the flexibility to match treatment intensity to AD severity, and allows for appropriate treatment escalation or de-escalation. TCIs, while demonstrating comparable efficacy to mild-moderate potency TCS, may provide insufficient anti-inflammatory activity for the more severe AD flares, hence their conditional second-line positioning as valuable steroid-sparing agents, especially for steroid-sensitive areas or patients with steroid phobia that cannot be easily resolved. They were limited by cost barriers and initial burning sensations, which affect treatment adherence. Given the limited evidence on PDE4i's efficacy versus TCS and TCIs; similar tolerability issues and cost concerns; and it being less accessible in primary care settings, PDE4i received a conditional third-line recommendation.	

Recommendation 5:
For patients with recurring AD flares (e.g. 2-3 flares/month), prescribe proactive therapy of topical anti-inflammatory to areas of skin prone to flare recurrences.

Strength of recommendation: **Strong** Conditional

Summary: Proactive therapy is strongly recommended for recurring AD, based on favourable benefit-risk profile and alignment with patients' values, recognising that patient suitability should be carefully assessed.

Balance of benefits and harms	
Proactive therapy prevents subclinical inflammation from progressing to clinical flares and prolongs remission in patients with recurring moderate-to-severe AD.[53] Proactive therapy with TCS or TCIs reduces flare incidence (15 RCTs, n=3058; RR 0.61, 95% CI 0.5-0.73, I^2=85%),[37] with little to no adverse effects (24% vs 27%), compared to reactive therapy (as-needed application when flare occurs).[28] Proactive therapy with once daily crisaborole showed lower mean flares versus vehicle (N=270; 0.95 vs 1.36; p=0.0042),[54] though more studies are needed to evaluate the effectiveness of twice weekly application.[55]	
Certainty of evidence	**Values and preferences**
Evidence certainty was moderate for TCS and TCIs due to heterogeneity[37] and low for PDE4i due to small number of studies and risk of bias.	Proactive therapy aligns with patients' values by preventing flares while minimising intensive treatment requirements.[28] Some patients prefer minimal TCS exposure due to concerns about prolonged use effects, highlighting the need for patient education.[36]
Resources and feasibility	**Acceptability and other considerations**
Proactive therapy requires less overall medication due to reduced flare frequency, potentially decreasing treatment costs in patients with recurring flares.[28] The EG acknowledged feasibility challenges including patient adherence, treatment acceptance in steroid phobia patients, and additional patient education time.	Patient acceptance may vary due to prolonged TCS use concerns. Clear benefit-risk communication is essential for optimal acceptance and adherence.
Expert Group deliberation of above factors	
The EG reached a strong recommendation due to substantial favourable benefit-risk ratio for appropriately selected patients, emphasising that proactive therapy targets those with recurring flares specifically. Despite feasibility challenges and variable patient preference and acceptability, the EG determined that comprehensive patient education could address concerns, justifying a strong recommendation for this targeted population.	

Recommendation 6:
For patients with inadequate treatment response, assess and address possible factors before modifying treatment.

Strength of recommendation: **Strong** Conditional

Summary: Systematic assessment of modifiable factors including diagnosis accuracy, secondary infections, treatment optimisation, and adherence issues before treatment escalation, is strongly recommended to avoid unnecessary therapeutic intensification and associated adverse effects.

Balance of benefits and harms	
Identifying modifiable factors improves current treatment effectiveness and prevents unnecessary escalation, by ensuring accurate diagnosis, and optimising existing topicals through proper potency selection and application technique. Addressing adherence barriers, steroid phobia and trigger factors resolves apparent treatment resistance without escalation.[19, 20, 28] Infection evaluation is important as it may cause or exacerbate AD flares.[19, 56] No significant harms identified as assessments represent routine care standards.	
Certainty of evidence	**Values and preferences**
Evidence certainty is likely low due to the nature of intervention (e.g. checking for adherence or infected AD), but the recommendation to address modifiable factors before modifying treatment, is consistent with reference guidelines[19, 20, 28] and routine clinical care based on clinical experience.	No significant concerns identified. Patients likely value thorough assessment before treatment escalation.
Resources and feasibility	**Acceptability and other considerations**
The recommendation is presumably feasible as assessments are incorporated in routine clinical follow-up. Specific components such as distinguishing infected from non-infected AD may challenge some clinicians.[57]	No significant concerns identified.
Expert Group deliberation of above factors	
The EG reached a strong recommendation, based on alignment with patient's preferences and current practice, despite evidence limitations.	

Recommendation 7:
Do not routinely give oral corticosteroids (OCS) for AD, except as a short course for:
- **Rescue therapy for acute, severe flares, or**
- **Bridging therapy to systemic treatment**

Strength of recommendation: Strong **Conditional**

Summary: Routine OCS should be discouraged due to unfavourable benefit-risk profile, including disease rebound upon discontinuation and higher risk of systemic side effects, though their rapid onset makes them acceptable for short-term rescue or bridging use.

<table>
<tr><th colspan="2">Balance of benefits and harms</th></tr>
<tr><td colspan="2">OCS provides transient AD improvement, with minimal improvement in symptoms and quality of life.[20, 28, 58] Studies demonstrated poorer outcomes versus ciclosporin (higher rebound discontinuations [46.6% vs 29.4%] and lower remission rates [4.8% vs 35.3%]);[59] and versus placebo (no difference in AD severity after 14 days despite initial 7-day improvement).[60] Short-term use of OCS significantly increases sepsis, venous thromboembolism, and fracture risks,[61] and potential growth stunting in children.[62]</td></tr>
<tr><th>Certainty of evidence</th><th>Values and preferences</th></tr>
<tr><td>Evidence certainty is low due to limited small trials and imprecision.[59, 60]</td><td>Patients value rapid symptom control but prefer safety.[36, 50, 51] OCS transient benefits partially aligned with this, but significant long-term harm concerns exist.</td></tr>
<tr><th>Resources and feasibility</th><th>Acceptability and other considerations</th></tr>
<tr><td>OCS are affordable and accessible but overprescribed due to poor stewardship – prescriptions rates are 24.4% internationally,[63] and 58.7% locally in moderate-to-severe AD patients.[64]</td><td>Due to rapid onset, short-term rescue or bridging use of OCS may be acceptable with detailed counselling on transient benefits, repeated use risks, adherence to prescribed duration and tapering schedules, and the need to seek more effective long-term therapy for recurrent or more severe flares.</td></tr>
<tr><th colspan="2">Expert Group deliberation of above factors</th></tr>
<tr><td colspan="2">The EG reached a conditional recommendation against routine OCS use due to transient benefits, significant risks and high rebound rates, while acknowledging its short-term rescue or bridging role. The recommendation emphasises the need for judicious prescribing and comprehensive patient counselling to balance rapid relief with long-term safety.</td></tr>
</table>

Recommendation 8:
For secondary infection of AD, continue patient's topical anti-inflammatory treatments alongside appropriate antimicrobial agents.

Strength of recommendation: **Strong** Conditional

Summary: Topical anti-inflammatories should be continued during secondary infection as they address underlying pathophysiology without causing harm.

Balance of benefits and harms	
Continuing topical anti-inflammatories during secondary infection addresses underlying AD inflammation, reduces scratching, decreases *Staphylococcus aureus* colonisation, and increases microbial diversity.[65] Studies showed TCS plus topical antibiotic is superior over topical antibiotic alone,[66, 67] as well as no harm from TCS use in infected AD[68]. Reference guidelines recommended continuing topical anti-inflammatories during infection.[20, 57] Despite theoretical concerns about TCS immunosuppression worsening infections,[65] TCS and TCIs are not associated with poorer outcomes even in severe viral infections like eczema herpeticum.[69] TCS plus topical antibiotics offer no significant advantage over TCS alone in terms of improving AD severity,[56] with added risk of antimicrobial resistance development.[20, 28, 57] A local audit showed higher fusidic acid resistance in patients with prior topical fusidic use.[70]	
Certainty of evidence	**Values and preferences**
Evidence certainty is low due to limited direct comparative studies, small sample sizes and high risk of bias.[66, 67] Most evidence derives from topical antibiotic studies rather than studies specifically comparing continuation of topical anti-inflammatory therapy with discontinuation.[56]	Patients value safe, effective therapies and prevention of complications.[36, 50, 51]
Resources and feasibility	**Acceptability and other considerations**
No concerns identified.	Expert experience suggests some clinicians may hesitate to continue topical anti-inflammatories during infection due to theoretical immunosuppression concerns, requiring education about safety evidence.
Expert Group deliberation of above factors	
The EG reached a strong recommendation based on clinical experience and alignment with international guidelines. They determined benefits clearly outweighed theoretical concerns despite low certainty direct evidence.	

Recommendation 9:
Avoid triple combination products of TCS, antibiotics and antifungals in AD patients with suspected or clinically evident bacterial infection.

Strength of recommendation: **Strong** Conditional

Summary: Triple combination products should be avoided due to inappropriately high-potency TCS, gentamicin having partial antimicrobial coverage against primary AD pathogens, unnecessary antifungal components, and risk of contact dermatitis, with no evidence supporting their use for infected AD.

<table>
<tr><th colspan="2">Balance of benefits and harms</th></tr>
<tr><td colspan="2">Evidence supporting triple combination products for AD severity improvement in patients with or without infected AD is limited. These products contain high-potency TCS (such as betamethasone dipropionate 0.05%) that may be inappropriately potent for AD management. They contain antibiotics like gentamicin, which only has partial efficacy against primary AD pathogens (S. aureus, Streptococcus pyogenes). Topical aminoglycosides (gentamicin[71, 72], neomycin[71]) commonly cause contact dermatitis, potentially worsening existing skin conditions. The antifungal component is unnecessary given the limited evidence supporting topical antifungals in AD patients.[73]</td></tr>
<tr><th>Certainty of evidence</th><th>Values and preferences</th></tr>
<tr><td>Evidence certainty is very low due to limited direct evidence on triple combination products for AD.</td><td>Patients value safe, effective therapies and prevention of complications.[36, 50, 51]</td></tr>
<tr><th>Resources and feasibility</th><th>Acceptability and other considerations</th></tr>
<tr><td>No concerns were identified; avoiding unnecessary medications may reduce costs.</td><td>Acceptability may be challenging due to widespread overprescription, and clinician diagnostic uncertainty between non-infected AD flares and infected AD.[57] Clinicians may feel apprehensive about potential negative outcomes if antibiotics were not prescribed.[74] Local surveys showed patients had high expectations for antibiotic treatment while showing less concern about antimicrobial resistance, often perceiving non-prescribing clinicians as providing inadequate care.[75]</td></tr>
<tr><th colspan="2">Expert Group deliberation of above factors</th></tr>
<tr><td colspan="2">The EG reached a strong recommendation against triple combination products recognising clear potential harm and widespread overprescription in suspected infected AD, justifying the strong stance to discourage their use.</td></tr>
</table>

Appendix A: Summary of findings

Evidence table for trials of crisaborole 2% ointment vs placebo

Certainty assessment						No. of participants		Effect	Certainty of evidence
No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Crisaborole	Placebo		
Outcome: Clinician-reported outcomes (binary) in terms of ISGA success (defined as achieving clear [0] or almost clear [1], together with a ≥2-grade improvement from baseline), after 4 weeks									
5 RCTs[45, 76-78]	Serious[a]	Not serious	Not serious	Not serious	Not serious	434/1374 (31.6%)	144/736 (19.6%)	Significantly more patients achieved ISGA success with crisaborole versus placebo (RR: 1.71, 95% CI 1.32 to 2.23, I2=48%).	⨁⨁⨁◯ MODERATE
Outcome: Clinician-reported outcomes (binary) in terms of ISGA improvement (achieving clear [0] or almost clear [1]), after 4 weeks									
4 RCTs[45, 76, 78]	Serious[a]	Not serious	Not serious	Not serious	Not serious	631/1334 (47.3%)	234/696 (33.6%)	Significantly more patients achieved ISGA improvement with crisaborole versus placebo (RR: 1.35, 95% CI 1.08 to 1.68, I2=68%).	⨁⨁⨁◯ MODERATE

ISGA: Investigator's Static Global Assessment

Explanations

[a]One study had high risk of bias, due to missing outcome data and selective reporting due to premature termination of study

Evidence table for head-to-head trials of crisaborole 2% ointment vs TCIs (pimecrolimus 1% cream, tacrolimus 0.03% ointment or tacrolimus 0.1% ointment)

Certainty assessment						No. of participants		Effect	Certainty of evidence
No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Crisaborole	TCIs		
Outcome: Clinician-reported outcomes (binary) in terms of ISGA success (defined as achieving clear [0] or almost clear [1], together with a ≥2-grade improvement from baseline), after 4 weeks									
2 RCTs[45, 49]	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	33/110 (30%)	**Pimecrolimus 1% cream:** 34/101 (33.7%)	Fewer patients, but not a statistically significant number, achieved ISGA success with crisaborole versus pimecrolimus (RR: 0.93, 95% CI 0.64 to 1.36, I2=0%)	⨁⨁◯◯ LOW
Outcome: Clinician-reported outcomes (binary) in terms of ISGA improvement (achieving clear [0] or almost clear [1]), between baseline to after 4 weeks									
2 RCTs[45, 49]	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	49/110 (44.5%)	**Pimecrolimus 1% cream:** 65/101 (64.4%)	Fewer patients, but not a statistically significant number, achieved ISGA improvement with crisaborole versus pimecrolimus (RR: 0.73, 95% CI 0.52 to 1.03, I2=37%).	⨁⨁◯◯ LOW
Outcome: Clinician-reported outcomes (continuous) in terms of change in EASI or ISGA scores, between baseline to after 4 weeks									

2 RCTs[45, 49]	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	50[c]	**Pimecrolimus 1% cream:** 43[c]	Crisaborole resulted in non-significant less EASI improvement than pimecrolimus (mean -49.47, SD 34.195 for crisaborole vs mean -60.08, SD 31.877 for pimecrolimus, p=0.1272).[45]	⊕⊕◯◯ LOW
						52	**Pimecrolimus 1% cream:** 54	Crisaborole versus pimecrolimus showed no significant difference in terms of EASI improvement (p>0.05).[49]	
1 RCT[46]	Serious[d]	Not serious	Not serious	Serious[b]	Not serious	19	**Tacrolimus 0.1% ointment**: 21	Crisaborole resulted in a non-significant delta ISGA (i.e. change from baseline to day 29) more than tacrolimus 0.1% ointment (-1.684 vs -1.476, p=0.499).[46]	⊕⊕◯◯ LOW
Outcomes: Patient-reported outcomes (continuous) in terms of symptoms like itch/sleep, and quality of life, after 4 to 12 weeks									
2 RCTs[45, 49]	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	40[c]	**Pimecrolimus 1% cream:** 33[c]	No significant differences between crisaborole and pimecrolimus 1% cream for changes in PP-NRS, DLQI, IDQI, CDLQI, DFI (all p>0.05).[45]	⊕⊕◯◯ LOW
						52	**Pimecrolimus 1% cream:** 54	No significant differences between crisaborole and pimecrolimus 1% cream for changes in pruritus-NRS, DLQI, IDLQI, CDLQI, DFI (p>0.05).[49]	
2 RCTs[46, 48]	Serious[f]	Not serious	Not serious	Serious[b]	Not serious	16	**Tacrolimus 0.03% ointment:** 20	No significant differences between crisaborole and tacrolimus 0.03% ointment across itch, pain interference, CDLQI, family DLQI, sleep habit, anxiety, depression and caregiver burden at the end of 12 weeks (all p>0.05).[48]	
						19	**Tacrolimus 0.1% ointment**: 21	No significant differences between crisaborole and tacrolimus 0.1% ointment for SPS and CDLQI after 4 weeks (all p>0.05).[46]	
Outcomes: Adverse events (in terms number of adverse events, treatment-emergent adverse events (TEAEs), or epidermal thinning) after 4 weeks to 12 weeks									
2 RCTs[45, 49]	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	24/52 (46.2%)	**Pimecrolimus 1% cream:** 20/54 (37.0%)	Crisaborole resulted in a non-significant higher incidence of adverse events than pimecrolimus (46.15% vs 37.04%, p=0.34).[49]	⊕⊕◯◯ LOW
						25/58[c] (43.1%)	**Pimecrolimus 1% cream:** 24/47 (51.1%)[c]	Crisaborole resulted in a non-significant lower incidence of TEAEs than pimecrolimus (43.1% vs 51.1%, p=0.438).[45]	
2 RCTs[46, 48]	Serious[e]	Not serious	Not serious	Serious[b]	Not serious	16	**Tacrolimus 0.03% ointment:** 20	Crisaborole resulted in non-significant higher incidence of adverse events than tacrolimus 0.03% ointment after 12 weeks (at 6 weeks: 25% for crisaborole vs 15% for tacrolimus, p=0.45; at 12 weeks: 37.5% for crisaborole vs 20% for tacrolimus, p=0.24).[48]	⊕⊕◯◯ LOW

						19	**Tacrolimus 0.1% ointment**: 21	Crisaborole resulted in less cases of pain and transient burning than tacrolimus 0.1% ointment, though the exact number of cases and statistical significance were not reported.[46]	

ISGA: Investigator's Static Global Assessment; **EASI**: Eczema Area and Severity Index; **SCORAD**: SCORing Atopic Dermatitis; **PP-NRS**: peak pruritus numerical rating scale; **DLQI**: Dermatology Life Quality Index; **IDQI**: Infants' Dermatitis Quality of Life Index: **CDLQI**: Children's Dermatology Life Quality Index; **DFI**: Dermatitis Family Impact; **SPS**: Severity of Pruritus Score; **TEAEs:** treatment-emergent adverse events

Explanations

[a]Both studies had high risk of bias due to premature termination with selective reporting and missing outcome data in one study, and open-label design with 12% attrition in the other study

[b]Using a minimally contextualised approach with a target of non-zero effect, evidence was downgraded once for imprecision due to small sample size (less than optimal information size)

[c]Study was terminated prematurely due to a business decision, and participant numbers varied slightly across outcomes as results were analysed at the point of trial termination

[d]Open-label single-blind (assessor) design (risk of performance bias)

[e]Both studies have high risk of bias due to open-label design (risk of performance bias); one study had 23% attrition rate due to difficulty retaining participants with "almost clear" AD at 6 weeks of the 12 weeks study period (risk of selection bias)

Evidence table for head-to-head trials of crisaborole 2% ointment vs TCS

Certainty assessment						No. of participants		Effect	Certainty of evidence
No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Crisaborole	TCS		
Outcome: Clinician-reported outcomes (binary) in terms of ISGA success (defined as achieving clear [0] or almost clear [1], together with a ≥2-grade improvement from baseline), after 4 weeks									
1 RCT[45]	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	11/58[c] (19.0%)	**Hydrocortisone butyrate 0.1% cream:** 33/71[c] (46.5%)	Significantly less patients achieved ISGA success with crisaborole than hydrocortisone butyrate 0.1% cream, a group 5 TCS (RR: 0.41, 95% CI 0.23 to 0.73)	⨁⨁◯◯ LOW
Outcome: Clinician-reported outcomes (binary) in terms of ISGA improvement (achieving clear [0] or almost clear [1]), after 4 weeks									
1 RCT[45]	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	14/58 (24.1%)	**Hydrocortisone butyrate 0.1% cream:** 35/71 (49.3%)	Significantly less patients achieved ISGA improvement with crisaborole than hydrocortisone butyrate 0.1% cream, a group 5 TCS (RR: 0.48, 95% CI 0.29 to 0.79)	⨁⨁◯◯ LOW
Outcome: Clinician-reported outcomes (continuous) in terms of change in EASI or ISGA scores, after 4 weeks									

1 RCT[45]	Serious [a]	Not serious	Not serious	Serious[b]	Not serious	50[c]	**Hydrocortisone butyrate 0.1% cream:** 65[c]	Crisaborole showed a significant less EASI improvement than hydrocortisone butyrate 0.1% cream (mean -49.47, SD 34.195 for crisaborole vs mean -75.50, SD 30.305 for hydrocortisone butyrate, p<0.001).	⊕⊕◯◯ LOW
Outcomes: Patient-reported outcomes (continuous) in terms of symptoms like itch/sleep, and quality of life, after 4 to 12 weeks									
1 RCT[45]	Serious [a]	Not serious	Not serious	Serious[b]	Not serious	40[c]	**Hydrocortisone butyrate 0.1% cream:** 56[c]	Crisaborole resulted in significant less improvement than hydrocortisone butyrate 0.1% cream in both PP-NRS (mean -1.65, SD 1.966 vs mean -4.02, SD 2.734; p=0.0002) and DFI (mean -3.6, SD 4.40 vs mean -6.4, SD 5.61; p=0.0346). No statistical differences for DLQI and CDLQI changes between crisaborole and hydrocortisone butyrate. (p>0.05).	⊕⊕◯◯ LOW
Outcomes: Adverse events (in terms number of TEAEs or epidermal thinning) after 4 weeks to 12 weeks									
1 RCT[45]	Serious [a]	Not serious	Not serious	Serious[b]	Not serious	25/58 (43.1%)	**Hydrocortisone butyrate 0.1% cream:** 12/71 (16.9%)	Crisaborole resulted in a significantly higher incidence of TEAEs than hydrocortisone butyrate 0.1% cream (43.1% vs 16.9%, p=0.00159).	⊕⊕◯◯ LOW
1 RCT[79]	Not serious	Not serious	Not serious	Not serious	Not serious	32 (on one forearm of each participant)	**Betamethasone valerate 0.1% cream:** 32 (on the other forearm of each participant)	Crisaborole resulted in less epidermal thinning than betamethasone valerate 0.1% cream (mean −13.76µm, 95% CI −17.42 to −10.10µm vs mean −31.66 µm, 95% CI −35.31 to −28.01µm), after 4 weeks (p<0.0001).	⊕⊕⊕⊕ HIGH

ISGA: Investigator's Static Global Assessment; **PP-NRS**: peak pruritus numerical rating scale; **DLQI**: Dermatology Life Quality Index; **IDQI**: Infants' Dermatitis Quality of Life Index: **CDLQI**: Children's Dermatology Life Quality Index; **DFI**: Dermatitis Family Impact; **TEAEs:** treatment-emergent adverse events

[a]Study had high risk of bias, due to missing outcome data and selective reporting due to premature termination of study

[b]Using a minimally contextualised approach with a target of non-zero effect, evidence was downgraded once for imprecision due to small sample size (less than optimal information size)

[c]Study was terminated prematurely due to a business decision, and participant numbers varied slightly across outcomes as results were analysed at the point of trial termination

Forest plot

Figure 1. Crisaborole vs comparator (placebo, TCS Group 5, pimecrolimus)
Outcome: Number of patients with ISGA success (defined as clear [0] or almost clear [1], combined with ≥ 2-grade improvement from baseline)

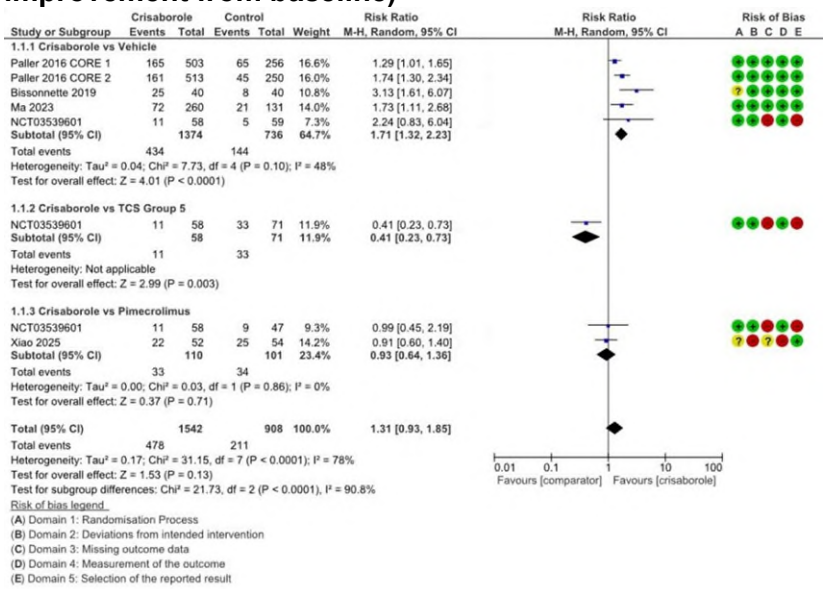
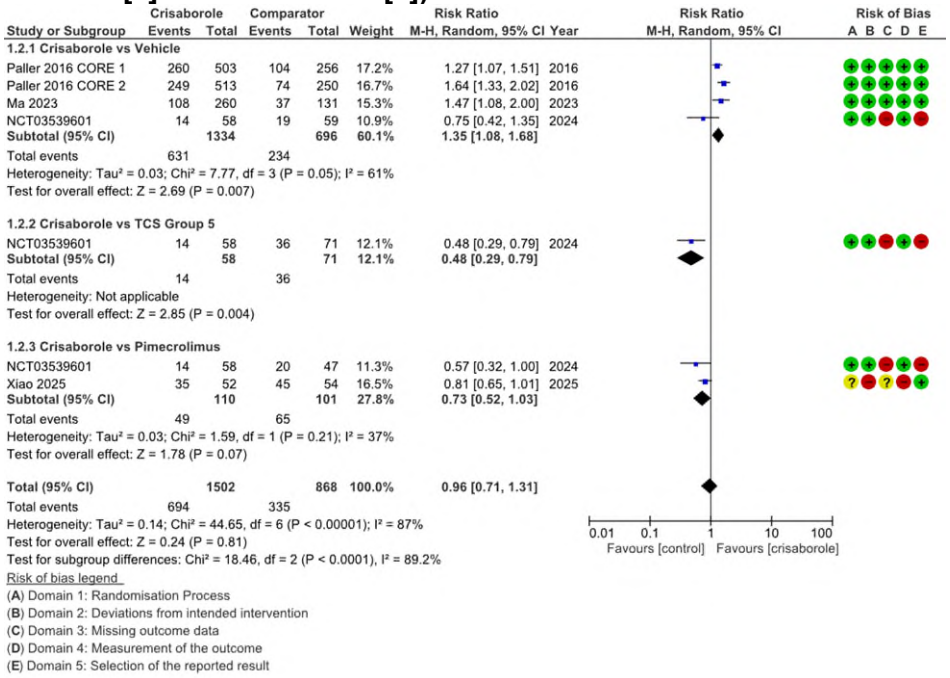


Figure 2. Crisaborole vs comparator (placebo, TCS Group 5, pimecrolimus)
Outcome: Number of patients with ISGA improvement (defined as clear [0] or almost clear [1])



Methods

A comprehensive search strategy was developed on 21 September 2025 in Embase (Elsevier), Medline (Ovid), PubMed and Cochrane Library for systematic review articles focusing on the effectiveness and safety of crisaborole in comparison with other topical anti-inflammatory agents, specifically TCS and TCIs. No language restrictions were applied. For systematic reviews, the search was restricted to those published in the recent 5 years published, i.e. from 2021 onwards. To minimise publication bias, searches were also conducted for grey literature (Google Scholar).

A second, targeted search was carried out, between 21 to 24 September 2025, to identify any randomised controlled trials (RCTs) in Embase (Elsevier), Medline (Ovid), Cochrane Library and in clinical trial registries (WHO ICTRP, ClinicalTrial.gov and Chinese Clinical Trial Registry), for head-to-head RCTs of crisaborole 2% ointment with TCS or TCIs. No year or language restrictions were applied, given the extremely limited number of head-to-head trials and to ensure capture of any studies potentially missed out by existing systematic reviews. Screening and selection of the potentially relevant articles were conducted based on relevant information detected from titles, abstracts, and full texts. Study information was extracted and analysed using Review Manager 5.4 (Cochrane Collaboration).[80] Risk of bias was assessed using the Cochrane Risk of Bias tool version 2 (RoB 2).[81] Analysis of results followed the GRADE guidance using a minimally contextualised framework with a target of certainty rating of a non-zero effect.[82]

Search strategy

Research question

1) What are the efficacy and safety of topical crisaborole compared to other topical anti-inflammatory agents (topical corticosteroids and topical calcineurin inhibitors) in patients with atopic dermatitis?

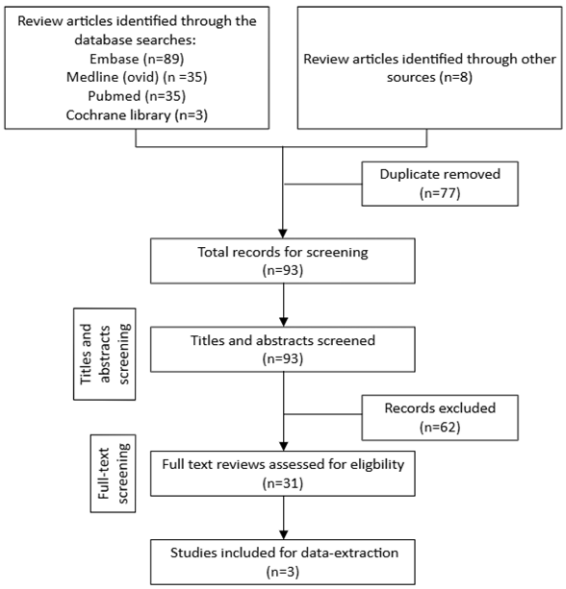
PICOs

Population	Patients of any age with clinically diagnosed active atopic dermatitis of any severity (not maintenance phase)
Intervention	Crisaborole 2% ointment
Comparator	Any TCS or TCIs
Outcome	Any outcomes (mainly focusing on efficacy and safety including clinician- or patient-reported outcomes)
Study design	RCTs (parallel or split body), Systematic Reviews
Year	• Any year of publications for RCTs • For systematic review (recently published, in the last 5 years)

Table 1. Searches for relevant systematic reviews and RCTs (Hits from Databases):

No	Name of database	Search date	Records (before deduplication)	Records (after deduplication)
1	Embase (Elsevier)	21 Sep 2025	89	87
2	Medline (Ovid)	21 Sep 2025	35	35
3	PubMed	21 Sep 2025	35	35
3	Cochrane Library	21 Sep 2025	3	3
4	Grey Literature Search (including relevant websites)	21 Sep 2025	8	8
	Total		170	168

Prisma diagram for Table 1



Search strategies used to identify systematic reviews

Database: Embase (Elsevier) Date of search: 21 September 2025 Search strategy: 1. 'crisaborole'/exp OR 'crisaborole'- 903 2. Eucrisa – 69 3. AN2728 – 62 4. Topical AND Phosphodies* AND (IV OR 4) AND Inhibitor$ - 1,632 5. 'Phosphodiesterase IV inhibitor' - 4,062 6. PDE*4 AND inhibitor$ - 3,994 7. PDE*IV AND inhibitor$ - 68 8. 1-7 – 8,093 9. Atopic dermatitis – 75,721 10. Eczema – 62,975 11. Neurodermatitis – 3,913 12. 9-11 – 121,983 13. 'systematic review*':ab,ti OR 'literature review*':ab,ti OR 'narrative review*':ab,ti OR 'scoping review*':ab,ti OR 'umbrella review*':ab,ti OR 'qualitative review*':ab,ti OR 'systematic meta-review*':ab,ti OR 'meta-analysis':ab,ti OR 'mapping review*':ab,ti OR 'integrated review*':ab,ti – 910,568 14. 8 AND 12 – 1,180 15. 13 AND 14 – 89
Database: Medline (ovid) Date of search: 21 September 2025 Search strategy: 1. (crisaborole or eucrisa or an2728).mp. - 272 2. exp Inhibitors, Phosphodiesterase 4/ - 2,870 3. Phosphodiesterase 4 inhibitors.mp. – 1,886 4. PDE?4 inhibitors.mp. - 920 5. Exp eczema/ - 13,217 6. Exp Dermatitis, Atopic/ - 27,649 7. Eczema.mp. – 27,292 8. Atopic dermatitis.mp. – 33,246 9. Neurodermatitis.mp. – 1,854 10. (systematic review* or literature review* or narrative review* or scoping review* or umbrella review* or qualitative review* or quantitative review* or systematic meta-

review* or meta-analysis* or mapping review* or integrated review*).ab,ti. – 744,574
11. 1 OR 2 OR 3 OR 4 – 3,605
12. 5 OR 6 OR 7 OR 8 OR 9 – 60,101
13. 11 AND 12 – 344
14. 13 AND 10 – 35

Database: Pubmed
Date of search: 21 September 2025
Search strategy:
1. crisaborole[tiab] OR eucrisa[tiab] OR an2728[tiab] – 258
2. "Phosphodiesterase 4 Inhibitors"[Mesh] OR "Phosphodiesterase 4 Inhibitor*"[tiab] OR "Phosphodiesterase IV Inhibitor*"[tiab] – 2,334
3. "atopic dermatitis" [tiab] OR "eczema"[tiab] OR "atopic eczema"[tiab] OR "neurodermatitis"[tiab] – 51,447
4. "systematic review*"[Tiab] OR "literature review*"[Tiab] OR "narrative review*"[Tiab] OR "scoping review*"[Tiab] OR "umbrella review*"[Tiab] OR "qualitative review*"[Tiab] OR "quantitative review*"[Tiab] OR "systematic meta review*"[Tiab] OR "meta analysis*"[Tiab] OR "mapping review*"[Tiab] OR "integrated review*"[Tiab] – 753,399
5. 1 OR 2 – 2,491
6. 5 AND 2 – 329
7. 6 AND 4 – 35

Database: Cochrane
Date of search: 21 September 2025
Search strategy:
1. Crisaborole:ab,ti – 136
2. Eucrisa:ab,ti – 55
3. AN2728:ab,ti – 22
4. MeSH descriptor: [Phosphodiesterase 4 inhibitors] explode all trees – 164
5. MeSH descriptor: [Dermatitis, Atopic] explode all trees – 2,782
6. MeSH descriptor: [Eczema] explode all trees – 1,551
7. 1 OR 2 OR 3 OR 4 – 316
8. 5 OR 6 – 3,397
9. 7 AND 8 – 61
10. Filter by review – 3

Grey Literature Searches (keyword searches) - Google Scholar
Date of search: 21 September 2025
Search strategy: "crisaborole" atopic dermatitis systematic review – 2,580
Filter since 2021 – 1,620, first 10 pages, filter to relevant – 8 articles

Included and excluded studies (from full-text screening)

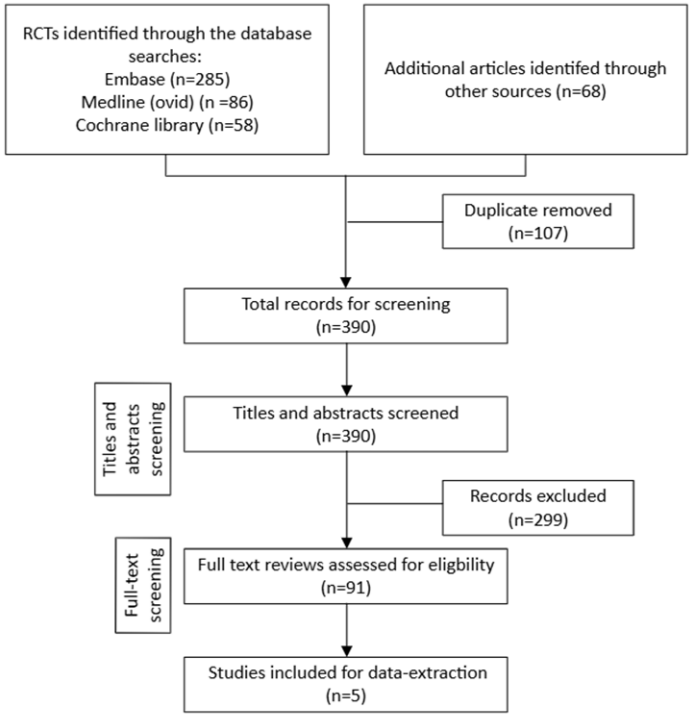
Included studies	Reasons for inclusion	Excluded studies	Reasons for exclusion
Lax 2024 (SR)	Comparison of crisaborole with other topical anti-inflammatories	Alkattan 2025 (SR)	No comparison of crisaborole with TCS or TCIs
Chu 2023 (SR)	Comparison of crisaborole with other topical anti-inflammatories	Begum 2025 (observational study)	Excluding observational study
Thom 2022 (SR)	Comparison of crisaborole with other	Carmona-Rocha 2025 (narrative review)	No comparison of crisaborole with TCS or TCIs

topical anti-inflammatories		
	Li 2025 (SR)	In Chinese, no comparison of crisaborole with TCS or TCIs
	Murai 2025 (SR)	No comparison of crisaborole with TCS or TCIs
	Wang 2025 (SR)	No comparison of crisaborole with TCS or TCIs
	Cui 2024 (SR)	No comparison of crisaborole with TCS or TCIs
	Chovatiya 2024 (SR)	No comparison of crisaborole with TCS or TCIs
	De 2024 (observational study)	Observational study, single arm (crisaborole only)
	Deva 2024 (SR)	Systematic review of guidelines, not particularly on treatment
	Ma 2024 (real world)	Single arm (crisaborole only)
	Blauvelt 2023 (narrative review)	No comparison of crisaborole with TCS or TCIs
	Chu 2024	Repeated study as Chu 2023 (already included)
	Farkouh 2023 (narrative review)	No comparison of crisaborole with TCS or TCIs
	Heinz 2023 (cost-effectiveness study)	Cost-effectiveness was contextualised to Canada and Australia, no specific details on efficacy/safety comparison of crisaborole with TCS/TCIs
	Zhao 2023 (SR)	No comparison of crisaborole with TCS or TCIs
	Rodriguez-Le 2022 (SR)	No comparison of crisaborole with TCS or TCIs
	Pinto 2022 (narrative review)	No comparison of crisaborole with TCS or TCIs
	Nusbaum 2022 (SR)	No mentioning of crisaborole within SR

Table 2. Searches on relevant RCTs and observational studies published from 2021 onwards (Hits from Databases)

No	Name of database	Search date	Records (before deduplication)	Records (after deduplication)
1	Embase (Elsevier)	21 Sep 2025	285	280
2	Medline (Ovid)	21 Sep 2025	86	18
3	Cochrane Library	22 Sep 2025	58	45
4	Grey literature (WHO ICTRP ClinicalTrial.gov, Chi Clinical Trial Registry)	22 and 24 Sept 2025	68	47
	Total		458	390

Prisma diagram for Table 2



Search strategies used to identify RCTs

Database: Embase (Elsevier)
Date of search: 21 September 2025
Search strategy:

1. 'crisaborole'/exp OR 'crisaborole'- 903
2. Eucrisa – 69
3. AN2728 – 62
4. Topical AND Phosphodies* AND (IV OR 4) AND Inhibitor$ - 1,632
5. ‘Phosphodiesterase IV inhibitor’ AND inhibitor$ - 4,062
6. PDE*4 AND inhibitor$ - 3,994
7. PDE*IV AND inhibitor$ - 68
8. 1-7 – 8,093
9. Atopic dermatitis – 75,721
10. Eczema – 62,975
11. Neurodermatitis – 3,913
12. 9-11 – 121,983
13. 'Randomised Controlled Trial*':ab,ti OR ‘Clinical Trial*':ab,ti OR ‘Multicenter stud*':ab,ti OR 'Phase 3 clinical trial*':ab,ti OR 'Phase 4 clinical trial*':ab,ti OR 'Randomisation*':ab,ti OR 'Single blind*':ab,ti OR ‘Double blind*':ab,ti OR 'Triple blind*':ab,ti – 1,349,614

14. 'humans'/exp – 30,218,668
15. 8 AND 12 – 1,180
16. 13 AND 14 AND 15– 285

Database: Medline (ovid)
Date of search: 21 September 2025
Search strategy:

1. (crisaborole or eucrisa or an2728).mp. - 272
2. exp Inhibitors, Phosphodiesterase 4/ - 2,870
3. Phosphodiesterase 4 inhibitors.mp. – 1,886
4. PDE?4 inhibitors.mp. - 920
5. Exp eczema/ - 13,217
6. Exp Dermatitis, Atopic/ - 27,649
7. Eczema.mp. – 27,292
8. Atopic dermatitis.mp. – 33,246
9. Neurodermatitis.mp. – 1,854
10. (Randomised Controlled Trial* or Clinical Trial* or Multicenter stud* or Phase 3 clinical trial* or Phase 4 clinical trial* or Randomisation* or Single blind* or Double blind* or Triple blind*).ab,ti. – 838,796
11. Humans/ - 22,962,981
12. 1 OR 2 OR 3 OR 4 – 3,605
13. 5 OR 6 OR 7 OR 8 OR 9 – 60,101
14. 12 AND 13 – 344
15. 14 AND 10 AND 11 – 86

Database: Cochrane
Date of search: 22 September 2025
Search strategy:

1. Crisaborole:ab,ti – 133
2. Eucrisa:ab,ti – 5
3. AN2728:ab,ti – 21
4. MeSH descriptor: [Phosphodiesterase 4 inhibitors] explode all trees – 164
5. MeSH descriptor: [Dermatitis, Atopic] explode all trees – 2,782
6. MeSH descriptor: [Eczema] explode all trees – 1,551
7. 1 OR 2 OR 3 OR 4 – 312
8. 5 OR 6 – 3,397
9. 7 AND 8 – 59
10. Filter by controlled trials – 58

Grey Literature Searches (keyword searches)
- ClinicalTrials.gov
Date of search: 21 September 2025
Search strategy: “Atopic dermatitis” as condition and “Crisaborole” as intervention – 26 trials registered
- Chinese Clinical Trial Registry
Date of search: 21 September 2025
Search strategy: “Crisaborole” – 3 trials registered; “AN2728” – 0 trial registered
- WHO ICTRP
Date of search: 24 September 2025
Search strategy: “Atopic dermatitis or eczema” as condition and “crisaborole” as intervention - 39

Included and excluded studies/trials that compares with TCS/TCIs (from full-text screening of 91 articles)

Included studies	Reasons for inclusion	Excluded studies	Reasons for exclusion
Chakraborty 2025	Crisaborole vs tacrolimus 0.1%	NCT04008784 2019	Observational prospective study, comparing crisaborole with combination therapy of crisaborole and TCS (triamcinolone acetonide 0.1% ointment)
Xiao 2025	Crisaborole vs pimecrolimus 1%	NCT03832010 2019	Not direct head-to-head comparison of crisaborole and TCS. 3-arm study - Group A: crisaborole (1st line), hydrocortisone or triamcinolone ointment (second-line), and Aquaphor moisturiser (baseline care). Group B: crisaborole-lookalike placebo (1st line), hydrocortisone or triamcinolone ointment (2nd line), and Aquaphor moisturiser (baseline care). Group C: hydrocortisone or triamcinolone ointment (first-line), Aquaphor moisturiser (baseline care), and Aquaphor-lookalike placebo
Wolf 2024	Crisaborole vs tacrolimus 0.03%	NCT07162896 2025	Crisaborole vs tacrolimus 0.1% (still recruiting)
Danby 2024 NCT04194814	Crisaborole vs betamethasone valerate 0.1% cream	NCT05016284 2022	Crisaborole vs JW-100, withdrawn
NCT03539601	Crisaborole vs Hydrocortisone butyrate 0.1% cream (TCS group 5) vs pimecrolimus 1%	CTRI/2025/09/ 094291	Crisaborole vs placebo (still recruiting)
		CTRI/2025/04/ 084122	Crisaborole vs tacrolimus 0.1% (still recruiting)
		CTRI/2025/03/ 083239	Crisaborole vs betamethasone valerate 0.1% cream (still recruiting)
		CTRI/2024/05/ 066965	Crisaborole vs age-appropriate tacrolimus vs mometasone 0.1% (still recruiting)
		ChiCTR210005 4340	Mometasone 0.1% applied for 2 weeks during active AD phase, then when flare resolved, apply crisaborole BD with emollient BD for 16 weeks

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