Supplemental Material

Guidelines of care for the management of atopic dermatitis in pediatric patients

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Supplemental Appendix 1: Detailed Methodology

Expert Work Group Composition and Disclosures of Interest

The co-chairs of the Work Group (D.D. and R.S.) were reviewed for potential disclosures of interest (DOIs) and approved by the AAD's Clinical Guidelines Committee (CGC). Additional Work Group members were nominated by the co-chairs based on their expertise related to the clinical questions. All Work Group nominees were reviewed for potential DOIs by the CGC. The majority (at least 51%) of the Work Group was required to be free of financial DOIs relevant to the topic of the guideline. Nominees found to have no relevant financial DOIs were approved, whereas nominees found to have potentially relevant financial DOIs were approved with management. Work Group members approved with management were prohibited from discussions on and voting for recommendations in which they had relevant DOIs. Work Group members completed a DOI form that was periodically updated and reviewed for potential relevant DOIs throughout guideline development and used to ensure management terms were observed. The multidisciplinary Work Group consisted of the co-chairs, 10 members, an additional member serving as a methodologist, and a patient representative. The Work Group was supported by an AAD guidelines staff member (L.F.G) with health research methodology expertise.

Formulation of Questions and Rating the Importance of Outcomes

Based on the aim of the guideline to evaluate how effective and safe currently available and approved topical therapies, systemic therapies, and phototherapy are for the management of AD in pediatric patients, the expert Work Group developed three clinical questions, using the Population, Intervention, Comparator, Outcome (PICO) format (**Table I**).

Next, the Work Group identified outcomes considered important for making clinical decisions regarding the medical management of AD through discussion and review of the core outcome set for AD trials developed by the Harmonizing Outcome Measures for Eczema (HOME) initiative (**Table 1**).[1] The Work Group ranked the importance of each primary outcome for decision-making via anonymous online voting using a 9-point scale (a ranking of 7-9 was assigned to outcomes critical for decision-making, 4-6 for outcomes important for decision-making, and 1-3 for outcomes of limited importance for decision-making).[2] Results of voting were used to categorize outcomes as "critical", "important", or "not important".

Table 1. Primary Outcomes

Primary Outcome	Importance Ranking
Change in clinical signs/symptoms of disease as assessed by clinician	Critical
Prevention of flares	Critical
Serious adverse events	Critical
Withdrawal due to adverse events	Critical
Infection	Important
Change in patent-reported symptoms	Critical
Change in quality of life	Critical
Change in itch severity	Critical

Evidence Search and Review

A search of the literature for all PICO questions using MEDLINE (via PubMed), CENTRAL, and the Cochrane Database of Systematic Reviews was conducted starting April 15th, 2024, and periodically updated through January 5th, 2025. Existing systematic reviews published within the previous 10 years and meeting all eligibility criteria were identified (**Table 2**). If systematic reviews were not available or the identified systematic reviews did not include an intervention of interest a review was commissioned by an expert systematic review group or a de novo review was conducted by the

Work Group with the assistance of AAD staff. The evidence review workflow is detailed in **Table 3**. All systematic reviews supporting this analysis met or followed standard methodology including development of PICO questions, explicit inclusion criteria, systematic literature searches, and vetted risk of bias assessment procedures.

Table 2. Eligibility Criteria for systematic review questions by guideline section

Category	Criteria
Topical Therapies	
Population	Children and adolescents (<18 years old) with clinically diagnosed AD of any severity
Intervention	Nonpharmacologic and pharmacologic topical therapies available and approved for use (for any indication) in the US. Including one of the following or a combination of: moisturizers, prescription emollient devices, bathing practices, oils, wet wraps; topical immunosuppressive agents; topical corticosteroids; topical calcineurin inhibitors; topical PDE-4 inhibitors; aryl hydrocarbon receptor activators; topical JAK inhibitors; topical antimicrobials and antiseptics; topical antihistamines; other topical treatments
Comparator	Placebo/vehicle, no treatment
Outcomes	Change in clinical signs/symptoms of disease as assessed by clinician; Prevention of flares; Serious adverse events; Withdrawal due to adverse events Infection; Change in patient-reported symptoms; Change in quality of life; Change in itch severity
Study Design	Published RCTs, including parallel, cross-over, and cluster RCTs, randomizing different clusters, patients, or body sites for individual participants
Other	English language
Phototherapy	
Population	Children and adolescents (<18 years old) with clinically diagnosed AD of any severity
Intervention	Any phototherapy/photochemotherapy available for use in the US
Comparator	Placebo, no treatment, other active treatment
Outcomes	Change in clinical signs/symptoms of disease as assessed by clinician; Prevention of flares; Serious adverse events; Withdrawal due to adverse events Infection; Change in patient-reported symptoms; Change in quality of life; Change in itch severity
Study Design	Published RCTs, including parallel, cross-over, and cluster RCTs, randomizing different clusters, patients, or body sites for individual participants
Other	None
Systemic Therapies	
Population	Children and adolescents (<18 years old) with clinically diagnosed AD of any severity
Intervention	Systemic therapies available and approved for use (for any indication) in the US. Including, but not limited to, one of the following or a combination of: abrocitinib, apremilast, azathioprine, baricitinib, cyclosporine, dupilumab, omalizumab, tralokinumab, upadacitinib, ustekinumab, interferon-gamma, intravenous immunoglobins, leukotriene inhibitors, mepolizumab, methotrexate, mycophenolate mofetil, oral antibiotic or antihistamines, systemic calcineurin inhibitors or corticosteroids, tumor necrosis factor-alpha inhibitors.
Comparator	Placebo, no treatment, other systemic intervention
Outcomes	Change in clinical signs/symptoms of disease as assessed by clinician; Prevention of flares; Serious adverse events; Withdrawal due to adverse events Infection; Change in patent-reported symptoms; Change in quality of life; Change in itch severity
Study Design	Published RCTs, including parallel, cross-over, and cluster RCTs, randomizing different clusters, patients, or body sites for individual participants
Other	English language studies

For de novo reviews, studies retrieved by the literature searches were reviewed for relevance over two rounds of study selection. Two reviewers independently screened citations. All citations deemed relevant by one or both reviewers were obtained as full text. Two independent reviewers screened full text citations against a priori established eligibility criteria (**Table 2**); discrepancies were resolved through discussion. Data extraction using structured data extraction spreadsheets was initially performed by an independent reviewer with subsequent quality control performed by a second reviewer. Risk of bias was assessed for all included studies using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (ROB2),the Newcastle Ottawa Scale for assessing the quality of nonrandomized studies in meta-analyses[3], or a modified Newcastle Ottawa Scale for assessing the quality of cross-sectional studies[4] based on study design.[5]

Table 3. Evidence Review Workflow

Clinical Topic Area	Evidence Review Workflow

Comorbidities	Updated a de novo systematic review conducted in May 2020 to support the development of the AAD's guidelines on comorbidities of adult atopic dermatitis.[6] Searches updated specific to pediatric AD through May 2024.
Primary prevention	For skincare interventions human milk consumption existing high quality systematic reviews by Kelleher 2022[7] and Gungor 2019[8] were updated with searches through June 2024; For microbiome, dietary (excluding human milk consumption), environmental, and other interventions, a de novo systematic review was conducted with a literature searches run from inception through June 2024.
Phototherapy	Previously contracted Cochrane systematic review was updated[9]; Search updated specific to pediatrics through July 2024, identifying no new trials.
Topical Therapies	Two existing high-quality systematic reviews[10,11] were used to identify pediatric data; Search were updated through June 2024.
Bleach bathing	Used existing high-quality systematic review by Bakaa 2022[12]; Updated searches through August 2024
Systemic Therapies: Abrocitinib Apremilast Azathioprine Baricitinib Cyclosporine Dupilumab Lebrikizumab Omalizumab Mepolizumab Tralokinumab Upadacitinib Ustekinumab	Used existing high quality Bayesian network meta-analysis by Drucker, et al.[13,14]; Searches updated through December 2024.
Mycophenolate mofetil Oral Antibiotics Systemic antivirals for eczema herpeticum Systemic calcineurin inhibitors Tumor necrosis factor-alpha inhibitors	De novo systematic reviews conduct between August 2024 and September 2024; No direct, relevant evidence identified
Interferon-gamma Intravenous immunoglobins Methotrexate	Updated an existing high quality systematic review & meta-analysis[15]; Searches update through August 2024
Leukotriene inhibitors	Used existing high quality Cochrane systematic review[16] Review search updated through July 2024 (no additional trials identified)
Oral antihistamines	Used existing high quality Cochrane review of oral H1 antihistamines as monotherapy[17]; Updated through September 2024 (no direct evidence was identified); Systematic review of oral H4 antihistamines as monotherapy was conducted in October 2024 (no direct evidence identified)
Systemic corticosteroids	Adapted an existing high quality systematic review and updated the search thorough January 2024.[15]

Assessing the Overall Certainty of the Body of Evidence

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach was used to assess the overall certainty of the evidence from systematic reviews for each critical or important outcome.[18] The GRADEPro Guideline Development Tool was used to create evidence profiles that categorized the overall certainty of the body of evidence for each outcome into one of four categories: high, moderate, low, or very low. Each category represents the confidence in the estimate of effect for an outcome (**Table 4**).

Table 4. Certainty of Evidence Ratings

Certainty of the Evidence	Confidence in the Estimate of Effect
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect

Very Low	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Formulating and Grading Recommendations

The Work Group drafted recommendations using the evidence profiles and considering the following: the balance of desirable and undesirable consequences of an intervention, the overall certainty of the evidence, patient values and preferences, and feasibility.[19] GRADE evidence-to-decision (EtD) frameworks were compiled for each clinical question to facilitate recommendation drafting. Structured searches were conducted for evidence of patient values and preferences, resource use, and feasibility to inform the EtD process. The workgroup also included a patient representative to provide input on preferences and values.

In accordance with the GRADE approach, recommendations were either “strong” or “conditional”.[20] The implications of each strength of recommendation are summarized in **Table 5**. Recommendations were also graded according to the GRADE approach.[20] In situations in which the supporting evidence for a recommendation was indirect only, but the certainty surrounding an intervention’s impact was high and the benefits of the intervention clearly outweigh the harms (or vice versa), a Good Practice Statement was developed.[21] Good Practice Statements are strong recommendations as the certainty surrounding the impact of the recommended intervention is high.

Table 5. Strength of Recommendation Implications

Strength	Implication
Strong	Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh the benefits
Conditional	Benefits finely balanced with risks and burden

Manuscript Review and Currency Statement

This guideline was developed in accordance with the AAD/AAD Association Administrative Regulations for Evidence-Based Clinical Practice Guidelines (March 2021), which includes the opportunity for review and comment by the entire AAD membership and final review and comment by the AAD Board of Directors.[22] This guideline will be considered current for a period of 5 years from the date of publication unless reaffirmed, updated, or retired before that time.

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Tables 1. Moisturizers

Moisturizers compared to control (vehicle, placebo, or no treatment) for children & adolescents with atopic dermatitis

Patient or population: Children from birth to 18 years with atopic dermatitis of any severity
Intervention: all moisturizers
Comparison: control (vehicle, placebo, or no treatment)

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Included studies with no poolable data	What happens
		Without moisturizer	With moisturizer	Difference			
Change in disease severity as assessed by investigators assessed with: EASI, SCORAD, TSS follow-up: range 4 weeks to 24 weeks № of participants: 1260 (9 RCTs)[1-9] CRITICAL	-			SMD **0.77 lower** (1.08 lower to 0.46 lower)	⊕⊕⊕⊕ High	Alexopoulos 2023[10]: MD (95%CI) in SCORAD change from baseline was **-6.74** (-8.36, -5.12; n=70) in favor of moisturizer (n=35) vs vehicle (n=35). Draelos 2019[11]: Moisturizer use (n=26) resulted in a **57.0%** improvement in SCORAD vs **56.6%** improvement with vehicle (n=13). Tripodi 2009[12]: The number of children with a ≥20% reduction in SCORAD with furfuryl palmitate-enriched moisturizer use was **14/48** vs **38/54** with vehicle. Wang 2020[13]: Median [IQR] EASI score after 4 weeks of treatment was 1.0 [0.4-4.7] with moisturizer use (n=115) vs 3.9 [1-6.8] without moisturizer (n=107).	Moisturizers are more beneficial than controls in reducing disease severity. All included studies demonstrate reduction in severity with moisturizer use, with 3 studies suggesting a clinically meaningful reduction.
IGA 0 or 1 assessed with: Participants with an IGA score of clear (0) or almost clear (1) follow-up: range 3 weeks to 6 weeks № of participants: 216 (3 RCTs)[2, 8, 11] CRITICAL	**RR 3.54** (0.99 to 12.70)	147 per 1000	**521 per 1000** (146 to 1000)	**374 more per 1000** (1 fewer to 1,000 more)	⊕⊕⊕◯ Moderate[a]	Alexopoulos 2023[10]: MD (95%CI) in IGA score change from baseline was -0.35 (-0.63, -0.07) in favor of moisturizer use compared to vehicle.	Moisturizers likely result in an increase in the number of participants cleared or almost cleared.
PO-SCORAD assessed with: mean change from baseline follow-up: 24 weeks № of participants: 127 (1 RCT)[4] CRITICAL	-	mean change in Po-SCORAD: **-1.4 (-4.05, 1.25)** points	-	MD **4.3 points lower** (8.27 lower to 0.33 lower)	⊕⊕⊕◯ Moderate[a]	Tiplica 2018[9]: PO-SCORAD score was reduced by 4.88 and 2.67 points in the two emollient groups (n=227) but increased by 2.90 points in the no emollient group (n=108) (P < 0.001).	Moisturizers likely result in no meaningful difference in change in disease severity as assessed by participants.
Itch response assessed with: mean change in VAS, P-VAS, NRS Pruritis Score, Itch Intensity Score follow-up: range 4 weeks to 6 weeks № of participants: 483 (4 RCTs)[1-3, 8] CRITICAL	-		-	SMD **1.38 lower** (2.52 lower to 0.24 lower)	⊕⊕⊕◯ Moderate[b,c]		Moisturizers likely result in a reduction from baseline in itch. All included studies demonstrate reduction in itch with moisturizer use, with 2/4 studies suggesting a clinically meaningful reduction.
Number of participants experiencing a flare follow-up: range 6 weeks to 24 weeks № of participants: 746 (6 RCTs)[2, 4, 8, 9, 14, 15] CRITICAL	**RR 0.57** (0.42 to 0.78)	511 per 1000	**291 per 1000** (215 to 399)	**220 fewer per 1000** (296 fewer to 112 fewer)	⊕⊕⊕◯ Moderate[d]	Wang 2020[13]: The HR for flares in the moisturizer group compared with the no moisturizer group was **0.38** (95% CI 0.25, 0.57) in the Cox regression model adjusted for age and sex.	Moisturizers likely reduce the number of participants experiencing a flare.
Change from baseline in quality of life assessed with: IDQOL, DFI, CDLQI follow-up: range 6 weeks to 24 weeks № of participants: 300 (3 RCTs)[4-6] CRITICAL	-	-	-	**SMD 0.39 lower** (0.9 lower to 0.12 higher)	⊕⊕⊕◯ Moderate[e]	Wang 2020[13]: Median [IQR] IDQL score after 4 weeks of treatment was 2 [1-5] with moisturizer use vs 5 [2-8] without moisturizer.	Moisturizers likely improve quality of life. Magnitude of improvement is unclear.

Moisturizers compared to control (vehicle, placebo, or no treatment) for children & adolescents with atopic dermatitis

Patient or population: Children from birth to 18 years with atopic dermatitis of any severity
Intervention: all moisturizers
Comparison: control (vehicle, placebo, or no treatment)

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Included studies with no poolable data	What happens
		Without moisturizer	With moisturizer	Difference			
Serious adverse events follow-up: range 4 weeks to 12 weeks № of participants: 1046 (7 RCTs)[2, 3, 6, 8, 10, 13, 14] CRITICAL	No SAEs were reported with moisturizer use (n=528) and 1 SAE was reported across the control groups (n=518).				⊕⊕⊕⊕ High		Serious adverse events were rare across both arms.
Adverse events follow-up: range 4 weeks to 24 weeks № of participants: 938 (8 RCTs)[2-4, 6-8, 11, 14] IMPORTANT	**RR 0.86** (0.63 to 1.18)	204 per 1000	**175 per 1000** (128 to 241)	**29 fewer per 1000** (75 fewer to 37 more)	⊕⊕⊕⊕ High	Alexopoulos 2023[10]: During 4 weeks of treatment, 8 AEs were reported in the moisturizer group (n=34) vs 2 AEs reported in the vehicle group (n=35). Wang 2020[13]: During 4 weeks of treatment, 48 AEs were reported in the moisturizer group (n=155) vs 46 AEs reported in the no moisturizer group (n=154).	Moisturizers result in little to no difference in the number of participants experiencing an adverse event.
Withdrawal due to adverse event follow-up: range 4 weeks to 24 weeks № of participants: 620 (4 RCTs)[2-4, 7] CRITICAL	**RR 0.64** (0.30 to 1.37)	49 per 1000	**31 per 1000** (15 to 67)	**18 fewer per 1000** (34 fewer to 18 more)	⊕⊕⊕⊕ High		Moisturizers result in little to no difference in the number of participants discontinuing treatment due to adverse event.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **SMD:** standardized mean difference; **HR**: Hazard ratio; **AE**: Adverse event

Explanations
a. Downgraded once for imprecision: small sample.
b. Not downgraded for borderline inconsistency as two trials suggest a large benefit and two trials suggest no benefit.
c. Downgraded once for imprecision: CI consistent with small unimportant effect and large effect.
d. Downgraded once for imprecision: CI consistent with moderate to large benefits and small potentially unimportant difference.
e. Downgraded once for imprecision: CI consistent with moderate to large benefit and no difference.

Table. Characteristics of included studies.

Study	Trial design	Follow up (weeks)	N randomized	Age (range included)	AD severity	Intervention	Comparator	Co-interventions allowed
Alexopoulos 2023	parallel	4	70	2-18yo	Mild to moderate	1% ectoine and 0.1% hyaluronic acid containing cream bid 28 days	Vehicle cream bid 28 days	None
Bianchi 2016	parallel	4	54	1-4yo	Mild	Oil-in-water emulsion bid 28 days + emollient cleansing gel for bathing od	emollient cleansing gel for bathing od	None
Boguniewicz 2008	parallel	6	142	6-12yo	Mild to moderate	Atopiclair tid for 43 days	Vehicle tid for 43 days	TCS for rescue only
Boralevi 2014	parallel	4	251	2-6yo	Mild	Glycerol and paraffin moisturizer bid 28 days	Vehicle bid 28 days	TCS for rescue only
Draelos 2019	parallel	4	39	3-18yo	Mild to moderate	Kamedis Eczema Therapy Cream Or "Leading OTC cream" bid for 28 days	Vehicle bid 28 days	Body wash
Gayraud 2015	parallel	24	130	6mo-15yo	Mild to moderate	Vitamin B3 (SBT complex) emollient bid 168 days	Vehicle bid 168 days	TCS or TCIs
Giordano-Labadie 2006	parallel	8	76	6mo-12yo	Mild to moderate	Oat emollient bid 56 days	No treatment for 56 days	TCS
Grimalt 2007	parallel	6	173	<12mo	Moderate to severe	Oat emollient bid 42 days	No emollient for 42 days	TCS for inflamed lesions
Korting 2010	parallel	4	99	0-12yo	Mild to moderate	Pale sulfonated shale oil tid 28 days	Vehicle tid 28 days	None

Ma 2017	parallel	12	64	2-12yo	Mild to moderate	Ceramide moisturizer bid 84 days	No moisturizer for 84 days	None
Patritzi 2008	parallel	6	60	2-17yo	Mild to moderate	Atopiclair tid 43 days	Vehicle tid 43 days	Rescue medication
Tiplica 2018	parallel	12	335	<18yo	Mild to moderate	Atopiclair tid or glycerol+paraffin moisturizer bid 84 days	No moisturizer for 84 days	TCS for rescue only
Tripodi 2009	parallel	2	117	3mo-14yo	Any	Furfuryl palmitate-enriched moisturizer bid 14 days	Vehicle bid 14 days	None
Wang 2020	parallel	12	309	0-2yo	Moderate	Prinsepia utilis Royle emollients bid 84 days	No emollients	None
Weber 2015	parallel	6	45	7mo-11yo	Any	Oat moisturizer for 24 weeks	No moisturizer for 24 weeks	Body cleanser & Eucerin Eczema relief instant for flare

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Table 2. Moisturizer with TCS

Active topical treatment in combination with moisturizer compared to active topical treatment only for children & adolescents with atopic dermatitis

Patient or population: Children & adolescents aged 4 months to 16 years with mild to moderate atopic dermatitis
Intervention: Moisturizer in combination with TCS bid for 21 days
Comparison: TCS alone bid for 21 days

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)** **Difference**	Certainty	Included studies with no poolable data	What happens
SCORAD assessed with: mean change from baseline follow-up: 3 weeks № of participants: 67 (1 RCT)[1] CRITICAL	-	MD **5 lower** (8.66 lower to 1.35 lower)	⨁⨁◯◯ Low[a,b]	Lucky 1997[2]: Mean Global Condition Scores (0-12; higher score indicates greater severity) after 3 weeks of treatment were 0.72 (0.61) in the lesions treated with moisturizer in combination with TCS vs 0.52 (0.51) with TCS treatment alone (n= 25 intraindividual).	Moisturizer in combination with a TCS may result in little to no difference in change in disease severity.
IDQOL assessed with: mean change from baseline follow-up: 3 weeks № of participants: 67 (1 RCT)[1] CRITICAL	-	MD **1.31 lower** (2.7 lower to 0.09 higher)	⨁⨁◯◯ Low[a,b]		Moisturizer in combination with a TCS may result in little to no difference in quality of life.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **TCS:** Topical corticosteroids

Explanations
a. Downgraded once for risk of bias: some concerns or high risk judgments for most domains; specific concerns with unmasked outcome assessment.
b. Downgraded once for imprecision: small sample.

Table. Characteristics of included studies.

Study	Trial design	Follow up (weeks)	N randomized	Age (range included)	AD severity	Intervention	Comparator	Co-interventions allowed
Lucky 1997	intraindividual	3	25	3-16yo	Mild to moderate	2.5% hydrocortisone od + oil-in-water moisturizer od for 21 days	2.5% hydrocortisone bid for 21 days	None
Msika 2008a	parallel	3	35	4-48mo	Mild to moderate	0.05% desonide bid + sunflower oil emollient bid for 21 days	0.05% desonide bid for 21 days	None
Msika 2008b	parallel	3	32	4-48mo	Mild to moderate	0.05% desonide od + sunflower oil emollient bid for 21 days	0.05% desonide od for 21 days	None

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2. Lucky AW, Leach AD, Laskarzewski P , Wenck H. Use of an Emollient As a Steroid-Sparing Agent in the Treatment of Mild to Moderate Atopic Dermatitis in Children. Pediatric Dermatology 1997;14:321-4.

Table 3. Moisturizer vs TCS

Moisturizer alone compared to active topical (TCS) for children & adolescents with atopic dermatitis

Patient or population: Children & adolescents aged 3 months to 18 years with atopic dermatitis of any severity
Intervention: moisturizer alone
Comparison: TCS

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	Included studies with no poolable data	What happens
		Risk with active topical (TCS)	Risk with moisturizer alone	Difference			
SCORAD assessed with: mean score follow-up: 4 weeks No. of participants: 210 (3 RCTs)[1-3] CRITICAL	–	MD **1.5 points lower** (4.17 lower to 1.16 higher)			⊕⊕⊕◯ Moderate[a]	Jirabundansuk 2014[4]: Mean SCORAD score decreased significantly in week 4 compared to baseline in both the moisturizer and TCS groups (p<0.001). Sugarman 2009[5]: There were no significant differences in SCORAD change from baseline at 4 weeks between the moisturizer and TCS groups. Udompataikul 2011[6]: The MD of SCORAD change from baseline was **2.57 (0.59, 4.55)** for moisturizer compared to TCS at 4 weeks.	Use of moisturizer alone likely results in little to no difference.
IGA 0 or 1 follow-up: 2 weeks No. of participants: 29 (1 RCT)[7] CRITICAL	**RR 0.79** (0.39 to 1.58)	600 per 1000	474 per 1,000 (163 to 810)	**126 fewer per 1000** (366 fewer to 348 more)	⊕⊕◯◯ Low[b,c]		Moisturizer alone may result in a reduction in the number of participants clear or almost clear.
Number of participants experiencing a flare follow-up: range 4 weeks to 20 weeks No. of participants: 199 (3 RCTs)[2, 6, 8] CRITICAL	**RR 1.79** (0.22 to 14.44)	110 per 1000	**218 per 1,000** (19 to 799)	**87 more per 1,000** (86 fewer to 1,000 more)	⊕⊕◯◯ Low[d]		Moisturizer alone may increase the number of participants experiencing a flare.
POEM assessed with: mean score follow-up: 4 weeks No of participants: 13 (1 RCT)[2] CRITICAL		The mean POEM was **5.27 (SD 4.94)** points	MD **1.19 points higher** (2.697 lower to 5.07 higher)		⊕⊕◯◯ Low[e]		There may be little to no difference in POEM with moisturizer use. Mean POEM scores at the end of treatment suggest mild disease in both treatment groups.
Itch response assessed with: mean VAS 10cm scores follow-up: 4 weeks No of participants: 121 (1 RCT)[5] CRITICAL		One trial reported a mean reduction in VAS score of **3.3** with moisturizer use (n=59) vs **3.7** with TCS (n=62) at 4 weeks.			⊕⊕◯◯ Low[a,b]		Moisturizer alone may result in similar change from baseline in itch as TCS. Both treatments resulted in clinically meaningful reduction in itch.
Quality of life assessed with: mean change in IDQOL & CDLQI follow-up: 20 weeks No of participants: 107 (1 RCT)[8] CRITICAL		The mean change from baseline in QoL was **-0.4 (4.4)** points	MD **2.6 points higher** (0.86 higher to 4.35 higher)		⊕⊕◯◯ Low[a,b]	De Belilovsky 2011[1]: **MD** of mean IDQOL scores after 3 weeks of treatment was = **-0.13** (95%CI -1.62, 1.36) for moisturizer vs TCS.	Moisturizer may result in a similar change from baseline in QoL. Change in quality of life with both moisturizer & TCS did not meet clinically meaningful thresholds.

Moisturizer alone compared to active topical (TCS) for children & adolescents with atopic dermatitis

Patient or population: Children & adolescents aged 3 months to 18 years with atopic dermatitis of any severity
Intervention: moisturizer alone
Comparison: TCS

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	Included studies with no poolable data	What happens
		Risk with active topical (TCS)	Risk with moisturizer alone	Difference			
Adverse events No of participants: 352 (6 RCT)[1, 2, 4, 6-8] IMPORTANT	**RR 1.08** (0.48 to 2.42)	53 per 1000	**57 per 1,000** (25 to 127)	**4 more per 1,000** (27 fewer to 75 more)	⊕⊕⊕◯ Moderate[a]		Adverse events were rare and equitable across the moisturizer and TCS groups. 4/6 studies report no adverse events.
Withdrawal due to adverse event No of participants: 110 (2 RCT)[1, 7] CRITICAL		Across 2 studies (n=110), only 1 discontinuation was reported in a participant treated with moisturizer.			⊕⊕⊕◯ Moderate[a]		Discontinuation was rare across both treatment groups.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations
a. Downgraded once for imprecision: small sample.
b. Downgraded once for risk of bias: high risk judgements for some domains; specific concerns with unmasked outcome assessment.
c. Downgraded once for imprecision: CI consistent with moderate harm and moderate benefit.
d. Downgraded twice for imprecision: CI consistent with small unimportant benefit and very large magnitude of harm.
e. Downgrade twice for imprecision: very small, intraindividual sample.

Table. Characteristics of included studies.

Study	Trial design	Follow up (weeks)	N randomized	Age (range included)	AD severity	Intervention	Comparator	Co-interventions allowed
De Belilovsky 2011	parallel	3	80	4mo-4yo	Mild to moderate	sunflower oil moisturizer bid 21 days	hydrocortisone propionate cream bid 21 days	Oil bath product
Horev 2022	parallel	2	30	2-18yo	Mild to moderate	honey & coconut oil emollient 14 days	hydrocortisone 1% cream 14 days	None
Jirabundansuk 2014	intraindividual	4	31	2-12yo	Mild to moderate	linoleic acid moisturizer bid 56 days	hydrocortisone 1% cream bid 28 days	None
Liu 2018	parallel	20	107	1-17yo	Mild to moderate	oil-in-water emollient bid 28 days	fluticasone propionate 0.05% cream (od 2x per week) + emollient (bid 28 days)	None
Sivapiromrat 2021	intraindividual	4	26	2-14yo	Mild to moderate	shea butter + ceramide moisturizer bid 56 days	Hydrocortisone 1% cream bid 28 days	Mild to moderate
Sugarman 2009	parallel	4	121	6mo-18yo	Moderate to severe	ceramide moisturizer bid 28 days	fluticasone 0.5% cream bid 28 days	None
Udompataikul 2011	intraindividual	6	30	2-15yo	Mild to moderate	licochalcone A lotion bid 42 days	hydrocortisone acetate 1% lotion bid 28 days	None
Wananukul 2013	intraindividual	4	55	3mo-14yo	Mild to moderate	0.025% licochalcone A moisturizer bid 28 days	Hydrocortisone 1% cream bid 28 days	None

References

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Table 4. Bathing with Soap

Washing with soap compared to washing with water for **children** with atopic dermatitis

Patient or population: Children aged 1-9 years with atopic dermatitis controlled by the use of regular application of TCS or tacrolimus 2 days per week
Intervention: Washing the upper and lower limbs on one side of the body with water alone
Comparison: Washing the upper and lower limbs on one side of the body with water and soap

Outcome № of participants (studies)	Anticipated absolute effects (95% CI)			Certainty	What happens
	Washing with water	Washing with soap	Difference		
EASI assessed with: Mean change in EASI score follow-up: 8 ± 3 weeks № of participants: 58 (1 RCT)[1] CRITICAL	MD **0.02 lower** (0.11 lower to 0.08 higher)			⨁⨁◯◯ Low[a]	Washing with soap may result in little to no difference in Eczema Area and Severity Index (EASI) score.
POEM assessed with: Mean change in POEM score follow-up: 8 ± 3 weeks № of participants: 58 (1 RCT)[1] CRITICAL	MD **0.05 higher** (0.85 lower to 0.95 higher)			⨁⨁◯◯ Low[a]	Washing with soap may result in little to no difference in Patient-Oriented Eczema Measure (POEM) score.
Adverse events № of participants: (1 RCT)[1] CRITICAL	No adverse events were reported.			⨁⨁◯◯ Low[a]	Washing with soap may result in little to no difference in adverse events.

CI: confidence interval; **MD:** mean difference

Explanations
a. Downgraded twice for imprecision due to very small sample.

References

1. Inuzuka Y, Natsume O, Matsunaga M, Monna Y, Okada E, Kato Y , Taguchi T. Washing with water alone versus soap in maintaining remission of eczema. Pediatr Int 2020;62:663-8.

Table 5. Bathing Frequency

Daily bathing compared to twice weekly bathing for **children** with atopic dermatitis

Patient or population: Children aged 6 months to 10 years with atopic dermatitis of any severity using standard care
Intervention: Bathe once a day
Comparison: Bathe once a day on Mondays and Thursdays

Outcome № of participants (studies)	Anticipated absolute effects (95% CI)			Certainty	What happens
	Twice weekly bathing	Daily bathing	Difference		
SCORAD assessed with: mean change from baseline follow-up: 2 weeks № of participants: 28 (1 RCT)[1] CRITICAL	The mean change in SCORAD was **-5.69 (SD 7.46)**	The mean change in SCORAD was **-4.50 (SD 5.63)**	MD **1.09 lower** (5.98 lower to 3.79 higher)	⨁⨁◯◯ Low[a,b]	Daily bathing may result in little to no difference in SCORAD.

CI: confidence interval; **MD:** mean difference

Explanations
a. Downgraded once for risk of bias: some concerns with minimal methods reporting.
b. Downgraded once for imprecision: small sample size.

References

1. Koutroulis I, Petrova K, Kratimenos P , Gaughan J. Frequency of bathing in the management of atopic dermatitis: to bathe or not to bathe? Clin Pediatr (Phila) 2014;53:677-81.

Table 6. Emollient Bathing

Emollient bath additives compared to no bath additives for **children** with atopic dermatitis

Patient or population: Children aged 1-11 years with atopic dermatitis of any severity
Intervention: emollient bath additives (Oilatum [Glaxo SmithKline; 63% light liquid paraffin], Balneum [Allmarall; 85% soya oil, or Aveeno [Johnson & Johnson]) for 12 months
Comparison: no bath additives for 12 months

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		No bath additives	With bath additives	Difference		
POEM (short-term) assessed with: mean score follow-up: 16 weeks № of participants: 461 (1 RCT)[1] CRITICAL	-	mean POEM was **8.4 (SD 6.0)**	7.5 (SD 6.0)	aMD[a] **0.41 lower** (1.1 lower to 0.27 higher)	⨁⨁⨁⨁ High	Bath additives result in little to no difference in POEM score.
POEM (long term) assessed with: mean repeated score over 52 weeks follow-up: 52 weeks № of participants: 461 (1 RCT)[1] CRITICAL	-	mean POEM **8.4 (SD 6.4)**	7.3 (SD 6.3)	aMD[a] **0.75 lower** (0.05 lower to 1.55 higher)	⨁⨁⨁⨁ High	Bath additives result in little to no difference in POEM score.

Emollient bath additives compared to no bath additives for children with atopic dermatitis

Patient or population: Children aged 1-11 years with atopic dermatitis of any severity
Intervention: emollient bath additives (Oilatum [Glaxo SmithKline; 63% light liquid paraffin], Balneum [Allmarall; 85% soya oil, or Aveeno [Johnson & Johnson]) for 12 months
Comparison: no bath additives for 12 months

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		No bath additives	With bath additives	Difference		
Quality of life (short-term) assessed with: Disease specific quality of life follow-up: 16 weeks № of participants: 461 (1 RCT)[1] CRITICAL	-	The median quality of life was **2 (IQR 0-5)**	The median quality of life was **3 (IQR 1-7)**	aMD[a] **0.29 higher** (0.57 lower to 1.14 higher)	⨁⨁⨁⨁ High	Bath additives result in little to no difference in quality of life.
Quality of life (long-term) assessed with: Disease specific quality of life via dermatitis family impact score follow-up: 52 weeks № of participants: 461 (1 RCT)[1] CRITICAL	-	The median quality of life was **2 (IQR 0-5)**	The median quality of life was **2 (IQR 0-6)**	aMD[a] **0.29 lower** (1.36 lower to 0.79 higher)	⨁⨁⨁⨁ High	Bath additives result in little to no difference in quality of life.
Exacerbation follow-up: 52 weeks № of participants: 461 (1 RCT)[1] CRITICAL	**aRR[a] 1.24** (0.96 to 1.60)	median 1 [IQR 0-3]	median 1 [IQR 0-3]	Not estimable	⨁⨁⨁⨁ High[b]	Bath additives result in little to no difference in exacerbations.
Any AE № of participants: 461 (1 RCT)[1] IMPORTANT	**OR 1.40** (0.79 to 2.47)	349 per 1000 Adverse effects were similar in both groups, despite slips in the bath, stinging, or redness being common side effects reported in the summary of product characteristics for emollient bath additives	429 per 1000 (298 to 570)	**80 more per 1000** (52 fewer to 221 more)	⨁⨁⨁◯ Moderate[c]	Bath additives likely increase any AE slightly.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

Explanations
a. Adjusted for ethnic group, topical corticosteroid use, and soap substitute use.
b. Did not downgrade for imprecision due rare event in a robust sample.
c. Downgrade once for imprecision: failed to meet optimal information size.

References

1. Santer M, Ridd MJ, Francis NA, Stuart B, Rumsby K, Chorozoglou M et al. Emollient bath additives for the treatment of childhood eczema (BATHE): multicentre pragmatic parallel group randomised controlled trial of clinical and cost effectiveness. Bmj 2018;361:k1332.

Table 7. Soak and Seal Bathing

Twice daily soak-and-seal baths vs twice weekly soak and seal baths for **children** with atopic dermatitis

Patient or population: Children aged 6 months to 11.5 years with moderate to severe atopic dermatitis
Intervention: wet method (twice-daily soak-and-seal [SS] baths for 15-20 minutes)
Comparison: dry method (twice-weekly SS baths for 10 minutes or less)

Outcome № of participants (studies)	Anticipated absolute effects (95% CI)			Certainty	What happens
	Dry method	Wet method	Difference		
SCORAD assessed with: mean score follow-up: 2 weeks № of participants: 84 (1 RCT)[1] CRITICAL			MD **21.2 lower** (27.6 lower to 14.9 lower) [a]	⨁⨁◯◯ Low[a,b]	Wet method (twice-daily SS baths for 15-20 minutes) may result in a large reduction in SCORAD.
Quality of life as assessed by parents (age 5+) assessed with: Dermatitis Family Impact follow-up: 2 weeks № of participants: (1 RCT)[1] CRITICAL	A repeated measure analysis of variance (ANOVA) model estimate of the Dermatitis Family Impact treatment effect between frequent bathing and infrequent bathing was -0.15 (p=0.9074) [a].			⨁⨁◯◯ Low[a,b]	Wet method (twice-daily SS baths for 15-20 minutes) may result in little to no difference in quality of life (for those 5 years and up) as assessed by parents.
Quality of life as assessed by patients (age 5+) assessed with: Children's Dermatology Life Quality Index follow-up: 2 weeks № of participants: (1 RCT)[1] CRITICAL	A repeated measure analysis of variance (ANOVA) model estimate of the Children's Dermatology Life Quality Index treatment effect between frequent bathing and infrequent bathing was 0.04 (p=0.9704) [a].			⨁⨁◯◯ Low[a,b]	Wet method (twice-daily SS baths for 15-20 minutes) may result in little to no difference in quality of life (for those 5 years and up) as assessed by patients.

CI: confidence interval; **MD:** mean difference

Explanations
a. Downgraded once for risk of bias: Cardona 2020 is a cross-over RCT that randomized patients to receive (i) twice weekly soak-and-seal (SS) bath for 2 weeks, followed by twice-daily SS baths for 2 weeks or (ii) twice-daily SS baths for 2 weeks, followed by twice weekly SS bath for 2 weeks. They reported effect estimates obtained from a repeated measure analysis of variance (ANOVA) model using the data from both phases. Therefore, there are some concerns with residual effects from the first intervention phase.
b. Downgraded once for imprecision: small intraindividual sample size.

References

1. Cardona ID, Kempe EE, Lary C, Ginder JH , Jain N. Frequent Versus Infrequent Bathing in Pediatric Atopic Dermatitis: A Randomized Clinical Trial. J Allergy Clin Immunol Pract 2020;8:1014-21.

Table 8. Bleach Baths

Adapted from: Bakaa L, Pernica JM, Couban RJ, Tackett KJ, Burkhart CN, Leins L, Smart J, Garcia-Romero MT, Elizalde-Jiménez IG, Herd M, Asiniwasis RN, Boguniewicz M, De Benedetto A, Chen L, Ellison K, Frazier W, Greenhawt M, Huynh J, LeBovidge J, Lind ML, Lio P, O'Brien M, Ong PY, Silverberg JI, Spergel JM, Wang J, Begolka WS, Schneider L, Chu DK. Bleach baths for atopic dermatitis: A systematic review and meta-analysis including unpublished data, Bayesian interpretation, and GRADE. Ann Allergy Asthma Immunol. 2022 Jun;128(6):660-668.e9. doi: 10.1016/j.anai.2022.03.024. Epub 2022 Mar 30. PMID: 35367346.

*Analysis includes two studies enrolling adult patients, but the majority of data are from children and adolescents.

Dilute bleach bathing compared to no bleach bathing for **children & adults** with atopic dermatitis

Patient or population: Children & adults aged 3mos to 65 years with atopic dermatitis or any severity
Intervention: dilute bleach bathing
Comparison: no bleach bathing

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		No bleach bath	Bleach bath	Difference		
EASI assessed with: Mean; Scale 0-72, lower better follow-up: range 4 weeks to 12 weeks № of participants: 257 (8 RCTs)[1-8] CRITICAL	-	Mean **27.6**	Mean **21.5**	MD **6.06 lower** (11.3 lower to 0.28 lower)	⊕⊕⊕◯ Moderate[a]	Dilute bleach bathing probably improves clinician-reported severity.
POEM assessed with: Mean; Scale 0-28; lower better follow-up: 4 weeks № of participants: 89 (2 RCTs)[9, 10] CRITICAL	-	Mean **15.40**	Mean **14.41**	MD **0.99 higher** (6.16 lower to 8.15 higher)	⊕⊕◯◯ Low[b]	Dilute bleach bathing may have little to no impact on patient-reported signs.
Itch response assessed with: VAS Scale 0-10; lower better follow-up: range 4 weeks to 12 weeks № of participants: 144 (3 RCTs)[4, 6, 10] CRITICAL	-	Mean **5.78**	Mean **5.39**	MD **0.39 lower** (1.85 lower to 1.08 higher)	⊕⊕◯◯ Low[b]	Dilute bleach bathing may have little to no impact on patient-reported itch.
Quality of life assessed with: Mean CDLQI Scale 0-30; lower better follow-up: 4 weeks № of participants: 80 (1 RCT)[4] CRITICAL	-	Mean **10.07**	Mean **8.47**	MD **1.6 lower** (4.21 lower to 1.01 higher)	⊕⊕◯◯ Low[c]	Dilute bleach bathing may slightly improve the quality of life.
Adverse events assessed with: total adverse events follow-up: range 60 min to 12 weeks № of participants: 230 (7 RCTs)[1, 2, 4-7, 10] IMPORTANT	**RR 0.98** (0.61 to 1.64)	18 per 100	17 per 100	**1 fewer per 100** (6.9 fewer to 11.4 more)	⊕⊕◯◯ Low[a]	Dilute bleach bathing may have little to no impact on adverse events.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Imprecision: serious. small sample (< 400).
b. Imprecision: very serious. small sample (<400) and wide CI.
c. Imprecision: very small, single study sample (<400).

Table. Characteristics of included studies.

Study	Trial design	Follow up (weeks)	N randomized	Age (range included)	AD severity	Intervention	Comparator
ACTRN12610000215022	Parallel	6	41	6mo-18yo	Moderate to severe	0.005% bleach, tiw, cephalexin 15 mg/kg/d tid initial 10 d	Emollient baths (liquid paraffin 95% v/v) tiw, cephalexin 15 mg/kg/d tid initial 10 d
ACTRN12611000260921	Parallel	6	16	1-15yo	Mild to severe	0.0042% bleach, 5 min, biw (+ standard care)	Water bath (+ standard care)

Gonzalez 2016	Parallel	4	21	3mo-5y	Moderate to severe	0.005% bleach bath, biw (+ fluticasone propionate cream)	Water bath (+ fluticasone propionate cream)
Hon 2016	Intraindividual	4	40	4-18yo	Moderate to severe	0.005% bleach bath for 10 min, tiw (+TCS for rescue only)	Water bath (+ TCS for rescue only)
Huang 2009	Parallel	12	31	6mo-17yo	Moderate to severe with *clinical infection*	0.005% bleach, 5-10 min, biw, mupirocin intranasal bid 5 consecutive d/mo, cephalexin 50 mg/kg/d tid initial 10 d	Water bath, petrolatum intranasal, cephalexin 50 mg/kg/d tid initial 10 d
Khadka 2021	Parallel	12	28	5-18yo	Moderate to severe	0.006% bleach, biw, 10-15 min (+ emollients and TCS)	Water bath (+ emollients and TCS)
NCT03619161	Parallel	4	58	6mo-17yo	Mild to moderate	0.005% bleach, 5-10 min, biw (+ bathroom cleaning)	Water bath (+ bathroom cleaning)
Shi 2016	Intraindividual	60 minutes	10	12-45yo	Mild to severe	0.005% bleach, 10 min, once	Water bath, 10 min, once
Wong 2013	Parallel	8	36	2-30yo	Moderate to severe	0.005% bleach, 10 min, biw, rinse with water, aqueous cream	Water bath

References

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2. ANZCTR12611000260921. When Children with Eczema are treated with Dilute Bleach baths and they are compared with Children with Eczema who have Water baths is there a difference in the Eczema as measured by the Eczema Area and Severity Index (EASI)? https://wwwanzctrorgau/Trial/Registration/TrialReviewaspx?id=336645&isReview=true 2012.
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Table 9. Wet Wrap Therapy

Wet wrap therapy (WWT) compared to conventional AD treatment for **children** with atopic dermatitis

Patient or population: pediatric atopic dermatitis
Intervention: Wet wrap therapy (WWT); One week of wet wraps initially applied daily for 24 hours a day over 1% hydrocortisone ointment (and if necessary, more potent topical steroids) followed by wet wraps 12 or 24 hours a day depending on progress as assessed by the ''education nurse''. When wet wraps were used for 12 hours a day, 1% hydrocortisone and emollients were used as required during the non-wet wrap period.
Comparison: Conventional AD treatment; Regular use of emollients (applied at least three times daily and ''whenever skin is dry''), as required use of 1% hydrocortisone ointment (applied twice daily), and if necessary, use of more potent topical steroids.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Conventional AD treatment	**WWT**	**Difference**		
Disease severity as assessed by investigators (final measurement) assessed with: SCORAD follow-up: 4 weeks № of participants: 45 (1 RCT)[1] CRITICAL	-	The mean SCORAD score was **17.0 (SD 12.8)**	The mean SCORAD score was **24.0 (SD 15.3)**	MD **3.4 lower** (12.2 lower to 5.5 higher)	⨁⨁◯◯ Low[a,b]	Wet wrap therapy (WWT) may result in little to no difference in the mean SCORAD score.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **WWT**: wet wrap therapy

Explanations
a. Downgraded once for risk of bias: some concerns with selective reporting and high risk of bias due to missing outcome data
b. Downgraded once for imprecision: CI consistent with a moderate benefit and small unimportant harm.

References

1. Hindley D, Galloway G, Murray J , Gardener L. A randomised study of "wet wraps" versus conventional treatment for atopic eczema. Arch Dis Child 2006;91:164-8.

Table 9. Tacrolimus 0.1%

Tacrolimus 0.1% (short term) compared to vehicle for children & adolescents with atopic dermatitis

Patient or population: Children aged 2-16 years with moderate to severe atopic dermatitis
Intervention: tacrolimus 0.1% bid for 3 to 12 weeks
Comparison: vehicle bid for 3 to 12 weeks

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		w/o tacrolimus	tacrolimus	**Difference**		
PGE "excellent improvement" or "cleared" assessed with: Participants with a PGE rating of "cleared" or "excellent improvement" follow-up: range 3 weeks to 14 weeks № of participants: 322 (2 RCTs)[1, 2] CRITICAL	**RR 3.02** (0.79 to 11.55)	127 per 1000	**382** (100 to 1000)	**256 more per 1000** (27 fewer to 1000 more)	⊕⊕⊕◯ Moderate[a]	Tacrolimus 0.1% probably meaningfully increases the number of participants cleared or with excellent improvement.
Itch response assessed with: Mean VAS-10 score following treatment follow-up: 4 weeks № of participants: 93 (1 RCT)[1] CRITICAL	Following treatment, mean itch scores were 1.7 for participants using tacrolimus vs 3.6 for participants using the vehicle (-47.1% reduction from baseline vs -3.6%, respectively).				⊕⊕◯◯ Low[b,c]	Tacrolimus 0.01% may result in a clinically meaningful reduction in itch. While this direct evidence is minimal a network meta-analysis[3] rates tacrolimus 0.1% use as amongst the most effective for itch reduction (NRS 0-10) with a high level of certainty: -2.27 (-2.84 to -1.70).
Withdrawal due to adverse event follow-up: range 4 weeks to 12 weeks № of participants: 327 (2 RCTs)[1, 2] CRITICAL	**RR 0.35** (0.11 to 1.09)	69 per 1000	**24 per 1000** (8 to 75)	**45 fewer per 1000** (61 fewer to 6 more)	⊕⊕⊕◯ Moderate[a]	The discontinuation rate is probably lower with the use of tacrolimus 0.01%.
Cancer risk assessed with: probability of cancer in patients with AD exposed to tacrolimus follow-up: mean 11 months № of participants: (64 non-randomized studies) IMPORTANT	For all age groups of patients with AD and using data from observational studies and randomized controlled trials, the use of tacrolimus compared is likely to have had little to no association with cancer compared to no TCI exposure: OR 0.99 95% credible interval 0.89-1.09.				⊕⊕⊕◯ Moderate[d]	Among individuals with AD, tacrolimus use is unlikely to increase the risk of cancer. Sensitivity analyses suggest these findings are consistent for pediatric populations.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. CI consistent with minimal difference and benefit.
b. Outcome measure not fully reported.
c. Small sample concerning imprecision.
d. Per Devasenpathy 2023 risk of bias assessment.

Table 10. Tacrolimus 0.03%

Tacrolimus 0.03% (short term) compared to vehicle for children & adolescents with atopic dermatitis

Patient or population: Children aged 2-16 years with moderate to severe atopic dermatitis
Intervention: tacrolimus 0.03% bid for 3 to 12 weeks (short term)
Comparison: vehicle bid for 3 to 12 weeks

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		w/o tacrolimus	tacrolimus	**Difference**		
PGE "excellent improvement" or "cleared" assessed with: Participants rated as having "excellent improvement" or "cleared" via PGE follow-up: range 3 weeks to 14 weeks № of participants: 317 (2 RCTs)[1, 2] CRITICAL	**RR 3.20** (1.25 to 8.18)	127 per 1000	**405 per 1000** (158 to 1000)	**278 more per 1000** (32 more to 909 more)	⊕⊕⊕◯ Moderate[a]	Tacrolimus 0.03% likely increases the number of participants with excellent improvement or cleared. *Non-poolable data:* **Chapman 2005:** IGA 0 or 1: RR 1.96 (1.45, 2.66)
Itch response (following treatment) assessed with: Mean VAS-10 itch scores at the end of treatment follow-up: 4 weeks № of participants:404 (2 RCTs)[1, 2] CRITICAL	Two studies report average final itch scores of 1.95 following tacrolimus treatment vs 3.65 following treatment with a vehicle (measures of dispersion not reported)				⊕⊕⊕◯ Moderate[b]	Tacrolimus 0.03% likely meaningfully reduces itch.
Withdrawal due to adverse event follow-up: range 4 weeks to 12 weeks № of participants: 642 (3 RCTs)[1-3] CRITICAL	**RR 0.66** (0.34 to 1.27)	66 per 1000	**44 per 1000** (22 to 84)	**22 fewer per 1000** (44 fewer to 18 more)	⊕⊕⊕◯ Moderate[c]	Rates of treatment discontinuation due to AE were low and similar across groups but are likely lower with the use of tacrolimus.
Treatment-emergent AEs of interest assessed with: AEs identified by trials as of interest or commonly (as defined per study) occurring follow-up: range 6 weeks to 12 weeks № of participants: (3 RCTs)[2-4]	**Chapman 2005:** Herpes simplex was not reported in any pediatric patients. **Paller 2001:** Based on adjusted 12-week incidence rates, no adverse event occurred at a statistically higher incidence in the 0.03% tacrolimus ointment treatment group compared with vehicle. **Schachner 2005:** The incidence of skin burning or stinging between treatment groups was not significantly different, with 19.0% (30 of 158) of patients treated with tacrolimus ointment and 17.0% of patients (27 of 159) treated with vehicle ointment reporting this application-site event				-	Incidence of adverse events in general and events of interest like herpes simplex and stinging/burning are likely not increased with the use of tacrolimus 0.03%.
Cancer risk assessed with: probability of cancer in patients with AD exposed to TCIs follow-up: mean 11 months № of participants: (57 non-randomized studies)[5]	For all age groups and using data from observational studies and randomized controlled trials, the use of tacrolimus (OR 1·05 [95% credible interval 0·94–1·15]) is likely to have had little to no association with cancer compared with no topical calcineurin inhibitor exposure.				⊕⊕⊕◯ Moderate[d]	Among individuals with AD, tacrolimus use is unlikely to increase the risk of cancer. Sensitivity analyses suggest these findings are similar for pediatric populations.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. CI consistent with minimal difference and substantial benefit.
b. Outcome measure is not fully reported (no measure of dispersion reported).
c. Small event rate leading to a CI consistent with small benefit or harm.
d. Per risk of bias assessment in Devasenapathy 2023.

References

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Table 11. Tacrolimus 0.03% Maintenance Therapy

Tacrolimus 0.03% maintenance therapy compared to vehicle for children & adolescents with atopic dermatitis[1]

Patient or population: Children aged 2-15 years with mild to severe atopic dermatitis
Intervention: tacrolimus 0.03% twice-weekly proactive application for 12 months
Comparison: vehicle twice-weekly for 12 months

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Vehicle	Tacrolimus	**Difference**		
Flare assessed with: participants experiencing at least one AD exacerbation requiring therapeutic intervention follow-up: 52 weeks № of participants: 250 (1 RCT) CRITICAL	**RR 0.70** (0.57 to 0.87)	704 per 1000	**493 per 1000** (401 to 612)	**211 fewer per 1000** (303 fewer to 92 fewer)	⊕⊕⊕◯ Moderate[a]	Use of tacrolimus 0.03% for long-term maintenance therapy probably meaningfully reduces the number of individuals experiencing a flare.
Serious adverse events assessed with: participants experiencing a SAE follow-up: 52 weeks № of participants: 250 (1 RCT) CRITICAL	**RR 7.00** (0.87 to 56.06)	8 per 1000	**56 per 1000** (7 to 448)	**48 more per 1000** (1 fewer to 440 more)	⊕⊕⊕◯ Moderate[b]	Serious adverse events were rare across treatment group but are probably more common with the use of tacrolimus.
Treatment-emergent adverse events of interest assessed with: Number of participants with AEs identified by trials as of interest follow-up: 52 weeks № of participants: 250 (1 RCT)	Application site pruritus 9 vs 12 Nasopharyngitis 7 vs 6 Pruritus 10 vs 2 Impetigo 7 vs 3 Application site infection 5 vs 3 Herpes simplex 3 vs 4 Skin papilloma 2 vs 5 Infected eczema 2 vs 4				-	The adverse event profile is similar across treatment groups, with application site irritation and pruritis as the most commonly occurring treatment-related events. Pruritus and impetigo were reported more often in patients in the tacrolimus group than in the vehicle group, while herpes simplex rates were equitable.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

Explanations
a. CI consistent with minimal and moderate benefit.
b. Minimal number of events leading to a very wide CI consistent with little to no difference and substantial harm.

References

1. Thaçi D, Reitamo S, Gonzalez Ensenat MA, Moss C, Boccaletti V, Cainelli T et al. Proactive disease management with 0.03% tacrolimus ointment for children with atopic dermatitis: results of a randomized, multicentre, comparative study. Br J Dermatol 2008;159:1348-56.

Table 12. Pimecrolimus 1%

Pimecrolimus 1% compared to vehicle for children & adolescents with atopic dermatitis

Patient or population: Children aged 3 months to 17 years with mild to moderate atopic dermatitis
Intervention: pimecrolimus 1% bid for 2 to 14 weeks
Comparison: vehicle bid for 2 to 14 weeks

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Studies with no poolable data	What happens
		Vehicle	Pimecrolimus	**Difference**			
IGA 0 or 1 assessed with: proportion of patients with IGA score of 0 or 1 follow-up: range 4 weeks to 14 weeks № of participants: 2637 (8 RCTs)[1-8] CRITICAL	**RR 1.87** (1.33 to 2.61)	382 per 1000	**715 per 1000** (509 to 998)	**333 more per 1000** (126 more to 616 more)	⊕⊕⊕⊕ High	Fowler 2007[9]: The risk of an IGA improvement of ≥ 1 point following treatment is significantly higher with the use of pimecrolimus: RR 1.32 (1.01 to 1.71) (n=153) (Low risk of bias).	Significantly more patients in the pimecrolimus group compared to the placebo group achieved IGA 0 or 1. The results are consistent for children (aged 3 months to 11 years): RR 1.78 (1.23 to 2.58).
Itch response assessed with: proportion of patients reporting no or mild itch in the 24 hours before assessment follow-up: 6 weeks № of participants: 1037 (4 RCTs)[2-5] CRITICAL	**RR 1.53** (1.26 to 1.86)	472 per 1000	**723 per 1000** (595 to 879)	**250 more per 1000** (123 more to 406 more)	⊕⊕⊕⊕ High	Fowler 2007[9]: The risk of at least a 2-point improvement in pruritus severity score (0[absent]-3[severe]) based on the previous 24-hours was significantly greater with pimecrolimus use: RR 2.02 (1.3 to 3.14) (n=153) (Low risk of bias). Kaufmann 2004[10]: Mean VAS 0-10 itch scores following treatment were significantly lower with pimecrolimus use: 2.1±2.3 vs 5.2±3.3 p<0.01 (n= 196) (High risk of bias).	Significantly more patients achieved no to mild itch following pimecrolimus treatment than placebo treatment.
CDLQI assessed with: mean change from baseline/final score follow-up: 4 weeks № of participants: 55 (2 RCT)[11, 12] CRITICAL	-	-	**MD 1.18 lower** (2.4 lower to 0.01 higher)		⊕⊕⊕◯ Moderate[c]		Neither treatment group experienced a clinically meaningful change in QoL from baseline. Pimecrolimus probably results in little to no diffrence in CDLQI.
Serious adverse events assessed with: patients with an SAE follow-up: range 6 weeks to 14 weeks № of participants: 1287 (2 RCTs)[4, 7] CRITICAL	**RR 1.13** (0.74 to 1.73)	59 per 1000	**67 per 1000** (44 to 102)	**8 more per 1000** (15 fewer to 43 more)	⊕⊕⊕⊕ High[d]		Pimecrolimus results in little to no difference in SAEs

Pimecrolimus 1% compared to vehicle for children & adolescents with atopic dermatitis

Patient or population: Children aged 3 months to 17 years with mild to moderate atopic dermatitis
Intervention: pimecrolimus 1% bid for 2 to 14 weeks
Comparison: vehicle bid for 2 to 14 weeks

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Studies with no poolable data	What happens
		Vehicle	Pimecrolimus	**Difference**			
Withdrawal due to adverse event assessed with: proportion of participants discontinuing treatment due to AE follow-up: range 1 weeks to 6 weeks № of participants: 773 (3 RCTs)[2, 9, 10] CRITICAL	**RR 0.65** (0.22 to 1.91)	21 per 1000	**13 per 1000** (5 to 40)	**7 fewer per 1000** (16 fewer to 19 more)	⨁⨁⨁⨁ High[d]		Withdrawals due to AE were rare and equitable across treatment groups. Pimecrolimus results in little to no difference in discontinuation.
Treatment-emergent adverse events of interest follow-up: 14 weeks № of participants: (6 RCTs)	The most common TEAEs across studies were: URTI: 38% vs 39% Nasopharyngitis: 24% vs 24% Application site burning was rare and occurred at similar rates across treatment groups: 5% vs 6% There is a low risk of skin infection or herpes as neither condition was documented as commonly occurring (in 5-10% of participants) across the 6 studies.						

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. One study is of a high risk of bias due to missing outcome data.
b. CI consistent with a clinically meaningful difference and a small difference of uncertain importance.
c. Very small sample is concerning for precision.
d. Small event rate suggests safety as the total small size is robust; Not downgraded.

References

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Table 13. Pimecrolimus 1% Long-Term

Pimecrolimus (long term) compared to vehicle for children & adolescents with atopic dermatitis

Patient or population: Children aged 3 months to 17 years with mild to severe atopic dermatitis
Intervention: pimecrolimus 1% bid upon signs and symptoms of AD for 24 to 52 weeks
Comparison: vehicle bid upon signs and symptoms of AD for 24 to 52 weeks

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Vehicle	Pimecrolimus	**Difference**		
Flare assessed with: proportion of patients not experiencing a flare follow-up: range 24 weeks to 26 weeks № of participants: 1689 (4 RCTs)[1-4] CRITICAL	**RR 1.65** (1.47 to 1.85)	369 per 1000	**609 per 1000** (542 to 683)	**240 more per 1000** (173 more to 314 more)	⊕⊕⊕⊕ High	Long-term use of pimecrolimus reduces AD exacerbations.
EASI (final score) assessed with: mean score following treatment follow-up: 24 weeks № of participants: 89 (1 RCT)[5] IMPORTANT	-	mean EASI (final score) was 9	7	MD **2 lower** (4.99 lower to 0.99 higher)	⊕⊕⊕◯ Moderate[a]	Long-term use of pimecrolimus probably does not result in a meaningful difference in EASI score following long-term treatment.
IGA 0 or 1 assessed with: proportion of patients with a score of 0 or 1 following treatment follow-up: range 24 weeks to 52 weeks № of participants: 2026 (3 RCTs)[1, 4, 6] IMPORTANT	**RR 1.05** (0.96 to 1.15)	487 per 1000	**511 per 1000** (468 to 560)	**24 more per 1000** (19 fewer to 73 more)	⊕⊕⊕◯ Moderate[b]	Long-term use of pimecrolimus probably results in a slight increase in the rate of patients achieving IGA 0 or 1.
Itch response assessed with: proportion of patients reporting no or mild itch in the 24 hours before assessment follow-up: 52 weeks № of participants: 250 (1 RCT)[1] CRITICAL	**RR 1.22** (0.97 to 1.54)	630 per 1000	**769 per 1000** (612 to 971)	**139 more per 1000** (19 fewer to 340 more)	⊕⊕⊕◯ Moderate[c]	Pimecrolimus long-term probably moderately increases the proportion of patients achieving no or mild itch.
CDLQI (final score) assessed with: mean score following treatment follow-up: 24 weeks № of participants: 104 (1 RCT)[5] CRITICAL	-	mean CDLQI (final score) was 4.6	3.6	MD **1 lower** (2.63 lower to 0.63 higher)	⊕⊕⊕◯ Moderate[a]	Long-term use of pimecrolimus likely results in little to no difference in CDLQI score following treatment.

Pimecrolimus (long term) compared to vehicle for children & adolescents with atopic dermatitis

Patient or population: Children aged 3 months to 17 years with mild to severe atopic dermatitis
Intervention: pimecrolimus 1% bid upon signs and symptoms of AD for 24 to 52 weeks
Comparison: vehicle bid upon signs and symptoms of AD for 24 to 52 weeks

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Vehicle	Pimecrolimus	**Difference**		
Serious adverse events assessed with: proportion of patients experiencing a serious adverse event follow-up: range 24 weeks to 52 weeks № of participants: 986 (2 RCTs)[2, 4] CRITICAL	**RR 0.45** (0.30 to 0.66)	143 per 1000	**64 per 1000** (43 to 94)	**79 fewer per 1000** (100 fewer to 49 fewer)	⊕⊕⊕⊕ High	Long-term use of pimecrolimus reduces serious adverse events slightly.
Withdrawal due to adverse event assessed with: proportion of patients discontinuing treatment due to AE follow-up: range 24 weeks to 26 weeks № of participants: 851 (3 RCTs)[3, 5, 7] CRITICAL	**RR 0.72** (0.17 to 3.07)	59 per 1000	**42 per 1000** (10 to 180)	**16 fewer per 1000** (49 fewer to 121 more)	⊕⊕⊕⊕ High[d]	Long-term pimecrolimus use reduces withdrawal due to adverse events slightly.
Treatment-emergent adverse events of interest follow-up: range 24 weeks to 52 weeks № of participants: (5 RCTs)[2-5, 7]	The most commonly reported TEAE was nasopharyngitis: 23% vs 19%. Application site burning/reaction was rare and equitable across treatment groups: 6% vs 4%					

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Very small sample
b. CI consistent with little to no difference and small possibly meaningful benefit.
c. CI consistent with little to no difference and moderate benefit.
d. Minimal events in the robust sample suggest safety.

Table 14. Long-term (uncontrolled) efficacy & safety data

Study (n)	Design	Efficacy	Safety
Langley 2008[8] N=335 2-17 years old	20-week open label phase following 6-week controlled trials	Improvement in mean EASI observed in the pimecrolimus group was sustained over the 20-week OL phase and remained at approximately 50% below the baseline level. The mean EASI scores for the vehicle the group also improved after these patients were switched to pimecrolimus cream 1%.	No treatment-related serious adverse events were reported. Discontinuation rates: (pimecrolimus / pimecrolimus group: 1.7% [4 / 233] vs vehicle / pimecrolimus: 1.0% [1 /102]) By the end of the OL phase, the rate of application site burning was 2.6% in the pimecrolimus / pimecrolimus group and 2.0% in the vehicle / pimecrolimus group, and symptoms were almost entirely mild in nature. No significant differences in the overall rate of infections were observed between groups during either phase of the study.

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Table 15. TCI Use in Children Under 2 Years

Study	Study Design	Population Age (n)	Outcome
Ho 2002[1]	RCT, followed by OLE for 20 weeks	3-23 months (186)	PIM 1% resulted in a greater reduction in the EASI score & itch improvement vs vehicle with sustained efficacy & favorable safety profile.
Kaufmann 2004[2] & Staab 2005[3]	RCT, followed by OLE for 12 weeks	3-23 months (195)	PIM 1% was effective & well tolerated with rapid onset of action.
Papp 2005[4] & McKenna 2006[5]	1 yr OLE	3-23 months (76)	PIM 1% resulted in a substantial reduction in flares & improved AD control with a favorable safety profile.
PETITE trial[6]	5-year OL, randomized, parallel group	3-11 months (2418)	PIM 1% similar to TCS efficacy, resulted in IGA of 0 or 1 at 3 weeks for 61% of treated infants, increasing 97% by 5 years; Favorable safety profile with substantial corticosteroid-sparing effect.
Salava 2022[7]	Prospective	1-3 years (152)	TAC 0.03% and 0.1% had comparable efficacy and safety profiles and mild and moderate potency TCS.
Study of the Atopic March[8, 9]	OL to age 3 yr	3-18 months (1091)	PIM 1% was effective in infants with a favorable safety profile, but high discontinuation rate after implementation of FDA black box warning

OL= Open label; OLE: Open label extension; PIM: Pimecrolimus; TAC: Tacrolimus

References

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Table 16. Very high potency TCS

Very high potency TCSs compared to vehicle for **adolescent** atopic dermatitis[1]

Patient or population: Adolescents (aged 12-17y) with moderate to severe AD
Intervention: clobetasol emulsion foam 0.05% bid for 2 weeks
Comparison: vehicle foam bid for 2 weeks

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Without TCS	With TCS	**Difference**		
IGA 0 or 1 assessed with: proportion of patients achieving IGA 0 or 1 follow-up: 2 weeks № of participants: 101 (1 RCT) CRITICAL	**RR 5.87** (1.96 to 17.61)	94 per 1000	**550 per 1000** (184 to 1000)	**457 more per 1000** (90 more to 1000 more)	⊕⊕⊕◯ Moderate[a]	Very high potency TCS probably results in a large increase in the proportion of patients achieving an IGA of 0 or 1.
Treatment-emergent adverse events assessed with: proportion of patients experiencing a TEAE follow-up: 2 weeks № of participants: 101 (1 RCT) IMPORTANT	**RR 1.39** (0.30 to 6.52)	6.3%	**8.7%** (1.9 to 40.8)	**24 more per 1000** (44 fewer to 345 more)	⊕⊕⊕◯ Moderate[b]	Very high potency TCSs probably increase treatment-emergent adverse events slightly.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. Very small sample.
b. Very small number of events leading to wide CI consistent with meaningful benefit and harm.

References

1. Kimball AB, Gold MH, Zib B , Davis MW. Clobetasol propionate emulsion formulation foam 0.05%: review of phase II open-label and phase III randomized controlled trials in steroid-responsive dermatoses in adults and adolescents. J Am Acad Dermatol 2008;59:448-54, 54.e1.

Table 17. Medium potency TCS in children

Medium potency TCSs compared to vehicle for **children** with atopic dermatitis[1]

Patient or population: Children aged 1 to 12 months with any infantile facial atopic dermatitis
Intervention: mometasone furoate 0.1% cream bid for 10 days
Comparison: vehicle cream bid for 10 days

Outcome	Relative	**Anticipated absolute effects (95% CI)**	Certainty	What happens

№ of participants (studies)	effect (95% CI)	Without TCS	With TCS	Difference		
EASI (post-intervention) assessed with: Mean score using a 7-point modified EASI scale (0=clear; 6=worse than baseline) follow-up: 17 days № of participants: 36 (1 RCT) CRITICAL	-	Mean mEASI (post-intervention) treatment was 4.48	1.1	MD **3.38 lower** (4.01 lower to 2.75 lower)	⊕⊕◯◯ Low[a,b]	TCS use may result in little to no difference in modified EASI score.
Itch response assessed with: Mean SSS score (0=no itch; 4=extremely severe) following treatment follow-up: 17 days № of participants: 36 (1 RCT) CRITICAL	-	Mean itch (post-intervention) was 1.95	0.25	MD **1.7 lower** (2.03 lower to 1.37 lower)	⊕⊕◯◯ Low[a,b]	High-potency TCSs may reduce itch in a clinically meaningful manner.
IDLQ (post-intervention) assessed with: Mean score following treatment follow-up: 17 days № of participants: 36 (1 RCT) CRITCIAL	-	Mean IDLQ (post-intervention) was 14.51	5.44	MD **9.07 lower** (12.62 lower to 5.52 lower)	⊕⊕◯◯ Low[a,b]	High-potency TCSs may improve QoL slightly.
Treatment-emergent adverse events assessed with: patients experiencing a TEAE follow-up: 10 days № of participants: 36 (1 RCT) IMPORTANT	No treatment-emergent adverse events were reported in either group.				⊕⊕◯◯ Low[a,b]	No TEAEs may suggest safety but the evidence is of low certainty given the small sample.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference

Explanations
a. Concerns about deviation from the intended intervention and lack of ITT analysis with the removal of 10% of randomized participants.
b. Very small sample.

References

1. Wu SH, Chen XQ, Liu B, Wu HJ , Dong L. Efficacy and safety of 15(R/S)-methyl-lipoxin A(4) in topical treatment of infantile eczema. Br J Dermatol 2013;168:172-8.

Table 18. Medium Potency TCS in Children & Adolescents

Medium potency TCSs (**short term**) compared to vehicle for **children & adolescents** atopic dermatitis[1]

Patient or population: Children & adolescents (aged 6 months to 18 years) with moderate to severe atopic dermatitis
Intervention: fluticasone propionate 0.05% bid for 4 weeks
Comparison: vehicle bid for 4 weeks

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Impact

Medium potency TCSs (**short term**) compared to vehicle for **children & adolescents** atopic dermatitis[1]

Patient or population: Children & adolescents (aged 6 months to 18 years) with moderate to severe atopic dermatitis
Intervention: fluticasone propionate 0.05% bid for 4 weeks
Comparison: vehicle bid for 4 weeks

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Impact
SCORAD assessed with: mean change from baseline follow-up: 4 weeks CRITICAL	(1 RCT)	⨁⨁◯◯ Low[a,b]	Both the use of TCS (n=69) and emollient (n=59) for 4 weeks resulted in a clinically meaningful mean reduction in SCORAD from baseline of -22.2 vs -18.7, respectively.
Itch response assessed with: mean change in VAS 10 score from baseline follow-up: 4 weeks CRITICAL	(1 RCT)	⨁⨁◯◯ Low[a,b]	Both the use of TCS (n=69) and emollient (n=59) for 4 weeks resulted in a clinically meaningful mean reduction in VAS10 itch score from baseline of -3.7 vs -3.3, respectively.
Serious adverse events assessed with: proportion of participants experiencing an SAE follow-up: 4 weeks CRITICAL	(1 RCT)	⨁⨁◯◯ Low[c,d]	No serious adverse events were reported with the use of TCS or emollient for 4 weeks.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval

Explanations
a. Study is of a high risk of bias due to deviations from the intended intervention & does not fully report the outcome measure.
b. Small sample suggests imprecision; incomplete outcome reporting prevents complete assessment.
c. Study is of a high risk of bias due to deviations from the intended intervention.
d. Small sample suggests imprecision.

References

1. Sugarman JL , Parish LC. Efficacy of a lipid-based barrier repair formulation in moderate-to-severe pediatric atopic dermatitis. J Drugs Dermatol 2009;8:1106-11.

Table 19. Medium Potency TCS Maintenance Therapy

Medium potency TCS (**maintenance therapy**) compared to vehicle for **children & adolescents** with atopic dermatitis

Patient or population: Children & adolescents (aged 1 to 17 years) with mild to severe atopic dermatitis
Intervention: fluticasone propionate 0.05% qd 2x per week with emollients for 16 to 20 weeks
Comparison: emollient bid for 16 to 20 weeks

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Without TCS	With TCS	**Difference**		

Medium potency TCS (**maintenance therapy**) compared to vehicle for **children & adolescents** with atopic dermatitis

Patient or population: Children & adolescents (aged 1 to 17 years) with mild to severe atopic dermatitis
Intervention: fluticasone propionate 0.05% qd 2x per week with emollients for 16 to 20 weeks
Comparison: emollient bid for 16 to 20 weeks

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Without TCS	With TCS	**Difference**		
SCORAD assessed with: mean change from baseline follow-up: 16 weeks № of participants: 49 (1 RCT)[1] IMPORTANT	-	mean change in SCORAD was NR	NR	MD **9.3 lower** (0.49 lower to 18.15 lower)	⊕⊕⊕◯ Moderate[a]	Medium potency TCS (long term) likely reduces SCORAD compared to emollient alone.
Flare assessed with: proportion of participants experiencing a disease exacerbation follow-up: range 16 weeks to 20 weeks № of participants: 224 (3 RCTs)[1-3] CRITICAL	**RR 0.36** (0.12 to 1.15)	562 per 1000	**202 per 1000** (67 to 646)	**360 fewer per 1000** (494 fewer to 84 more)	⊕⊕⊕◯ Moderate[b]	Medium potency TCS (long term) likely reduces the rate of disease exacerbations.
Quality of life assessed with: Mean change from baseline in IDQOL/CDLQI follow-up: 20 weeks № of participants: 107 (1 RCT)[3] CRITICAL	-	mean quality of life change was +2.2	-0.4	MD **2.6 lower** (4.33 lower to 0.87 lower)	⊕⊕⊕◯ Moderate[c]	Medium potency TCS (long term) likely results in little to no difference in quality of life.
Withdrawal due to adverse event assessed with: participants discontinuing treatment due to AE № of participants: 75 (1 RCT)[2] CRITICAL	One study reports no withdrawals from either treatment group.				⊕⊕⊕◯ Moderate[c]	Discontinuation is likely not a concern with the long-term use of medium potency TCS.
Treatment-emergent adverse events assessed with: proportion of participants with a TEAE follow-up: range 16 weeks to 20 weeks № of participants: 230 (3 RCTs)[1-3] IMPORTANT	**RR 1.30** (0.53 to 3.21)	223 per 1000	**290 per 1000** (118 to 717)	**67 more per 1000** (105 fewer to 493 more)	⊕⊕⊕◯ Moderate[d]	TEAE rates were similar across treatment groups but are likely higher with TCS use.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Small sample; CI consistent with minimal to no difference & substantial benefit.
b. Small event rate leading to CI consistent with substantial benefit and small harm.
c. Small sample
d. Small event rate leading to CI consistent with some benefit and substantial harm.

References

1. Rubio-Gomis E, Martinez-Mir I, Morales-Olivas FJ, Martorell-Aragones A, Palop-Larrea V, Bernalte-Sesé A et al. Fluticasone in mild to moderate atopic dermatitis relapse: A randomized controlled trial. Allergol Immunopathol (Madr) 2018;46:378-84.
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Table 20. Lower medium potency TCS

Lower medium potency TCS compared to vehicle for **children & adolescents** with atopic dermatitis

Patient or population: Children & adolescents (aged 3 months to 18 years) with mild to severe atopic dermatitis
Intervention: Hydrocortisone butyrate cream 0.1% bid for 4 weeks (short term); fluticasone propionate 0.05% bid 4x per week for 4wks stepped down to qd 2x per week for 16wks + emollient qd (maintenance therapy)
Comparison: vehicle bid for 4 weeks (short term); vehicle bid stepped down to qd + emollient for 20 weeks (maintenance therapy)

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Studies without poolable data	What happens
		Without TCS	With TCS	**Difference**			
EASI assessed with: mean % change from baseline follow-up: 4 weeks № of participants: 351 (2 RCTs)[1, 2] CRITICAL	-	MD **38.9% lower** (53.9 lower to 23 lower)			⊕⊕⊕◯ Moderate[a]	**Abramovits 2010:** Significantly more participants achieved treatment success^ with use of TCS (n=131) vs vehicle (133): **RR 2.25 (1.66, 3.05)[3]**	Lower medium potency TCS likely reduces EASI slightly.
Itch response assessed with: mean change from baseline in intensity of pruritus over the previous 24-hour period using a 4-point scale (0=none to 3=severe) follow-up: 4 weeks № of participants: 284 (1 RCT)[1] CRITICAL	-	mean itch change: -0.7	-1.4	MD **0.7 lower** (0.93 lower to 0.47 lower)	⊕⊕⊕⊕ High	**Abramovits 2010:** Significantly more participants achieved itch improvement* with TCS use (n=131) vs vehicle (n=133**): RR 1.48 (1.24, 1.77)[3]**	Lower medium potency TCS reduces itch slightly.
Flare (with long term use) assessed with: proportion of participants experiencing disease relapse follow-up: 20 weeks № of participants: 231 (1 RCT)[4] CRITICAL	**RR 0.19** (0.11 to 0.35)	662 per 1000	**126 per 1000** (73 to 232)	**536 fewer per 1000** (589 fewer to 431 fewer)	⊕⊕⊕⊕ High		Maintenance therapy with lower medium potency TCS reduces disease exacerbations.
CDLQI assessed with: mean change from baseline follow-up: 4 weeks № of participants: 48 (1 RCT)[2] CRITICAL	-	mean CDLQI change: -3.1	-6.4	MD **3.3 lower** (5.66 lower to 0.94 lower)	⊕⊕⊕◯ Moderate[a]		Lower medium potency TCS likely results in little to no difference in CDLQI.
Serious adverse events assessed with: proportion of participants experiencing an AE follow-up: 4 weeks № of participants: 548 (2 RCTs)[1, 3] CRITICAL	Two studies report no SAEs with TCS use (n=270) vs 2 SAEs with vehicle use (n=278).				⊕⊕⊕⊕ High		SAEs were rare but are less likely with TCS use.
Withdrawal due to adverse event assessed with: proportion of participants discontinuing treatment due to AE follow-up: 4 weeks № of participants: 284 (1 RCT)[1] CRITICAL	**RR 0.09** (0.01 to 1.67)	34 per 1000	**3 per 1000** (0 to 5.8)	**31 fewer 1000** (34 fewer to 23 more)	⊕⊕⊕◯ Moderate[b]		Lower medium potency TCS probably reduces withdrawal slightly.

Lower medium potency TCS compared to vehicle for **children & adolescents** with atopic dermatitis

Patient or population: Children & adolescents (aged 3 months to 18 years) with mild to severe atopic dermatitis
Intervention: Hydrocortisone butyrate cream 0.1% bid for 4 weeks (short term); fluticasone propionate 0.05% bid 4x per week for 4wks stepped down to qd 2x per week for 16wks + emollient qd (maintenance therapy)
Comparison: vehicle bid for 4 weeks (short term); vehicle bid stepped down to qd + emollient for 20 weeks (maintenance therapy)

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Studies without poolable data	What happens
		Without TCS	With TCS	**Difference**			

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio
^ Participants with a final PGA score of 0 or 1 who had a 2-point or more reduction in PGA from baseline (Using 5-point physician GA - clear, almost clear, mild, moderate and severe)
* Participants with at least a 1-point improvement in NRS itch score (0=none to 3=severe) from baseline

Explanations
a. Small sample
b. Small event rate leading to wide CI consistent with important benefit and harm.

References

1. Matheson R, Kempers S, Breneman D, Draelos Z, Johnson CE, Loss R et al. Hydrocortisone butyrate 0.1% lotion in the treatment of atopic dermatitis in pediatric subjects. J Drugs Dermatol 2008;7:266-71.
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years, with mild-moderate AD2018.
3. Abramovits W , Oquendo M. Hydrocortisone butyrate 0.1% lipocream in pediatric patients with atopic dermatitis. Skinmed 2010;8:72-9.
4. Hanifin J, Gupta AK , Rajagopalan R. Intermittent dosing of fluticasone propionate cream for reducing the risk of relapse in atopic dermatitis patients. Br J Dermatol 2002;147:528-37.

Table 21. Low/least potent TCS

Least potent TCS compared to vehicle for **children & adolescents** with atopic dermatitis

Patient or population: Children & adolescents (aged 3 months to 18 years) with mild to severe atopic dermatitis
Intervention: Low or least potent TCS bid for 1 to 6 weeks
Comparison: Vehicle bid for 1 to 6 weeks

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Studies without poolable data	What happens
		Without TCS	With TCS	**Difference**			
SCORAD (post-treatment) assessed with: mean score following treatment follow-up: range 1 weeks to 2 weeks № of participants: 75 (2 RCTs)[1, 2] CRITICAL	-	MD **10.28 lower** (24.56 lower to 4 higher)			⨁⨁◯◯ Low[a,b]	NCT00828412: Mean change from baseline in three item severity score was slightly lower with TCS use (n=48) vs vehicle (n=41): **MD -1.00 (-1.80, -0.20)**[3] Paller 2003: Significantly more TCS users (n=46) had excellent improvement^ from baseline vs vehicle (n=41): **RR 4.46 (1.88, 10.56)**[4] Hebert 2007: Significantly more TCS users (n=425) achieved treatment success* vs vehicle (n=157): **RR 3.61 (2.27, 5.74)**[5]	Least potent TCS use may meaningfully reduce SCORAD.

Least potent TCS compared to vehicle for **children & adolescents** with atopic dermatitis

Patient or population: Children & adolescents (aged 3 months to 18 years) with mild to severe atopic dermatitis
Intervention: Low or least potent TCS bid for 1 to 6 weeks
Comparison: Vehicle bid for 1 to 6 weeks

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Studies without poolable data	What happens
		Without TCS	With TCS	**Difference**			
Itch response assessed with: mean VAS 10 mm score following treatment follow-up: 2 weeks № of participants: 29 (1 RCT)[1] CRITICAL	-	mean itch: 5.66	2.35	MD **3.31 lower** (5.12 lower to 1.5 lower)	⨁⨁◯◯ Low[c,d]	**Hebert 2007:** Significantly fewer TCS users (425) had moderate to severe itch following treatment vs vehicle (n=157): **RR 0.28 (0.21, 0.39)**[5]	Least potent TCS may meaningfully reduce itch.
Flare assessed with: proportion of participants experiencing AD relapse follow-up: 6 weeks № of participants: 100 (1 RCT)[3] CRITICAL	**RR 0.08** (0.00 to 1.33)	120 per 1000	**10 per 1000** (0 to 160)	**110 fewer per 1000** (0 fewer to 40 more)	⨁⨁⨁◯ Moderate[e]		Least potent TCS probably reduces the rate of flares.
Serious adverse event assessed with: participants experiencing a SAE follow-up: range 2 weeks to 6 weeks № of participants: 769 (3 RCTs)[3-5] CRITICAL	Across 3 trials no SAEs were reported with short-term use of low potency TCSs (n=521) and 1 SAE was reported with vehicle(n=248) use.				⨁⨁⨁⨁ High		SAEs were rare across study arms suggesting safety.
Withdrawal due to adverse event assessed with: participants discontinuing treatment due to AE № of participants: 582 (1 RCT)[5] CRITICAL	**RR 0.25** (0.04 to 1.46)	1.9%	**0.5%** (0.1 to 2.8)	**14 fewer per 1000** (18 fewer to 9 more)	⨁⨁⨁⨁ High		Discontinuation was rare but rates are slightly lower with use of TCS.
Treatment-emergent adverse events of interest assessed with: AEs identified by trials as of interest or commonly (as defined per study) occurring follow-up: range 5 weeks to 6 weeks	**Hebert 2007:** Most common local AEs with TCS (n=425) were application site burning (1%) and rash (1%). No skin atrophy AEs reported with TCS but 1 was reported with vehicle (n=157). **NCT00828412:** Nasopharyngitis was the most commonly occurring AE: 3/50 with TCS use vs 1/50 with vehicle use.						

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio
^ Participants rated via investigator Global Estimate as having excellent (>75% clearance) improvement from baseline; * Participants with IGSS score of clear(0) or almost clear (1) and at least a 2-point change from baseline

Explanations

a. Both studies are of a high risk of bias for methodologic concerns or selection of reported outcomes.
b. Very small sample leading to CI consistent with a large positive effect and a small negative effect of uncertain importance.
c. High risk of bias due to concerns with the selection of reported outcomes.
d. Very small sample; CI consistent with moderate benefit and small benefit of uncertain importance.
e. Small event rate and sample leading to wide CI consistent with substantial benefit and small harm.

References

1. Abbasi S, Kamalinejad M, Babaie D, Shams S, Sadr Z, Gheysari M et al. A new topical treatment of atopic dermatitis in pediatric patients based on Ficus carica L. (Fig): A randomized, placebo-controlled clinical trial. Complement Ther Med 2017;35:85-91.

2. Canpolat F, Erkoçoğlu M, Tezer H, Kocabaş CN , Kandi B. Hydrocortisone acetate alone or combined with mupirocin for atopic dermatitis in infants under two years of age - a randomized double blind pilot trial. Eur Rev Med Pharmacol Sci 2012;16:1989-93.
3. NCT00828412. Comparison of the Efficacy and Safety of Two Topical Creams for Pediatric Atopic Dermatitis2009.
4. Paller AS, Nimmagadda S, Schachner L, Mallory SB, Kahn T, Willis I , Eichenfield LF. Fluocinolone acetonide 0.01% in peanut oil: therapy for childhood atopic dermatitis, even in patients who are peanut sensitive. J Am Acad Dermatol 2003;48:569-77.
5. Hebert AA, Cook-Bolden FE, Basu S, Calvarese B , Trancik RJ. Safety and efficacy of desonide hydrogel 0.05% in pediatric subjects with atopic dermatitis. J Drugs Dermatol 2007;6:175-81.

Table 22. Topical Antibiotics

There is no direct pediatric-specific evidence meeting inclusion criteria to assess the efficacy and safety of topical antibiotics for uninfected AD. The following indirect evidence was adapted from: Chu DK, et al. Topical treatments for atopic dermatitis (eczema): Systematic review and network meta-analysis of randomized trials. J Allergy Clin Immunol. 2023 Dec;152(6):1493-1519. doi: 10.1016/j.jaci.2023.08.030. Epub 2023 Sep 9. PMID: 37678572.

Topical antibiotics alone or in combination compared to vehicle/emollients or active therapy for uninfected atopic dermatitis[1]

Patient or population: Individuals of any age with uninfected atopic dermatitis of any severity
Intervention: topical antibiotics alone or in combination with active therapy
Comparison: vehicle/emollient or active therapy

Outcome № of participants (studies)	**Anticipated absolute effects (95% CI)** **Difference**	Certainty	What happens
SCORAD (post-treatment) assessed with: mean difference № of participants: 843 (12 RCTs) CRITICAL	MD **1.48 lower** (6.77 lower to 3.81 higher)	⨁⨁⨁◯ Moderate[a]	Antibiotic use likely results in no meaningful difference from control in SCORAD following treatment.
Itch response (post-treatment) assessed with: NRS 0-10 № of participants: 843 (12 RCTs) CRITICAL	MD **0.32 lower** (2.15 lower to 1.51 higher)	⨁◯◯◯ Very low[a]	Antibiotic use possibly results in no meaningful difference in itch score following treatment, but the evidence is very uncertain.
Flare assessed with: risk difference per 1000 № of participants: 843 (12 RCTs) CRITICAL	**RD -56** (-94 to 499)	⨁◯◯◯ Very low[a]	Antibiotic use possibly results is in no meaningful difference in rate of flares, but the evidence is very uncertain.
DLQI (post-treatment) assessed with: mean difference № of participants: 843 (12 RCTs) CRITICAL	MD **1.33 lower** (3.35 lower to 0.69 higher)	⨁◯◯◯ Very low[a]	Antibiotic use possibly results in no meaningful difference from control in quality of life following treatment, but the evidence is very uncertain.
Withdrawal due to adverse event assessed with: risk difference per 1000 № of participants: 84 (12 RCTs) CRITICAL	**RD 229** (-5 to 834)	⨁◯◯◯ Very low[a]	Antibiotic use possibly results in no meaningful difference in the rate of discontinuation of treatment, but the evidence is very uncertain.
Adverse events assessed with: risk difference per 1000 № of participants: 843 (12 RCTs) IMPORTANT	**RD 50** (-153 to 306)	⨁◯◯◯ Very low[a]	Antibiotic use possibly results in a slight difference in the occurrence of adverse events, but the evidence is very uncertain.

Topical antibiotics alone or in combination compared to vehicle/emollients or active therapy for uninfected atopic dermatitis[1]

Patient or population: Individuals of any age with uninfected atopic dermatitis of any severity
Intervention: topical antibiotics alone or in combination with active therapy
Comparison: vehicle/emollient or active therapy

Outcome № of participants (studies)	**Anticipated absolute effects (95% CI)** **Difference**	Certainty	What happens
NMA conclusions № of participants: 843 (12 RCTs)	Topical antibiotics alone or in combination with topical treatments were among the least effective and lowest in certainty across all outcomes.		

CI: confidence interval; **MD:** mean difference; **RD:** risk difference per 1000

Explanations

a. As assessed by Chu et al. 2023

References

1. Chu DK, Chu AWL, Rayner DG, Guyatt GH, Yepes-Nuñez JJ, Gomez-Escobar L et al. Topical treatments for atopic dermatitis (eczema): Systematic review and network meta-analysis of randomized trials. J Allergy Clin Immunol 2023;152:1493-519.

Table 23. Topical Antifungals

Topical antifungals compared to no topical antifungals for **children & adolescents** with atopic dermatitis[1]

Patient or population: Children & adolescents aged 5-14 years with atopic dermatitis of any severity
Intervention: hydrocortisone 1% plus miconazole cream bid for 2 weeks
Comparison: hydrocortisone 1% cream alone bid for 2 weeks

Outcomes	**Impact**	Certainty of the evidence (GRADE)
Investigator assessed response assessed with: Number of patients determined by 2 dermatologists to have better response with each intervention or no difference in response. follow-up: 2 weeks № of participants: 29 (1 RCT) CRITICAL	Following assessment of disease signs, 2 dermatologists were unable to distinguish between the two treatments (p=0.999)	⨁◯◯◯ Very low[a,b]
Participant assessed response assessed with: Number of patients noting a better response with each intervention or no difference follow-up: 2 weeks № of participants: 29 (1 RCT) CRITICAL	Ten participants reported a better response with adjuvant antifungal treatment, 15 reported a better response with TCS alone, and 4 reported no difference in response between the treatments (p=0.424).	⨁◯◯◯ Very low[a,b]

Adverse events assessed with: Number of participants experiencing adverse events (per treatment side) follow-up: 2 weeks № of participants: 29 (1 RCT) IMPORTANT	No adverse events reported.	⊕◯◯◯ Very low[a,b]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval

Explanations
a. Downgraded twice for risk of bias: some concerns and high-risk judgments for most domains; specific concerns with incomplete outcome data.
b. Downgraded twice for imprecision: due to very small sample from a single with-in participant trial.

References

1. Wong AW, Hon EK , Zee B. Is topical antimycotic treatment useful as adjuvant therapy for flexural atopic dermatitis: randomized, double-blind, controlled trial using one side of the elbow or knee as a control. Int J Dermatol 2008;47:187-91.

Table 24. Crisaborole

Crisaborole compared to vehicle for **children & adolescents** with atopic dermatitis

Patient or population: Children & adolescents (aged 3 months to 17 years) with mild to moderate atopic dermatitis
Intervention: crisaborole ointment 2% bid 2 to 4 weeks (short term); crisaborole ointment 2% qd for 52 weeks (long term)
Comparison: vehicle bid for 2 to 4 weeks (short term); vehicle qd for 52 weeks (long term)

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Studies without poolable data	What happens
		Vehicle	With crisaborole	**Difference**			
EASI assessed with: mean % change from baseline follow-up: 4 weeks № of participants: 62 (1 RCT)[1] CRITICAL	-	mean EASI % change was **-26.62**	MD **22.85% lower** (43.11 lower to 2.59 lower)		⊕⊕⊕◯ Moderate[a]	Fujita 2021[2]: MD in TSS^ score change from baseline: **-2.10 (-3.54, -0.66)** (Low risk of bias)	Crisaborole use probably results in a meaningful reduction in EASI.
IGA 0 or 1 assessed with: Participants who achieved success (ISGA score of clear[0] or almost clear[1] with ≥ 2 grade improvement from baseline follow-up: 4 weeks № of participants: 1388 (2 RCTs)[1, 3] CRITICAL	**RR 1.53** (1.25 to 1.87)	201 per 1,000	**308 per 1,000** (252 to 376)	**107 more** (50 more to 175 more)	⊕⊕⊕⊕ High		Significantly more participants using crisaborole achieved IGA 0 or 1.

Crisaborole compared to vehicle for **children & adolescents** with atopic dermatitis

Patient or population: Children & adolescents (aged 3 months to 17 years) with mild to moderate atopic dermatitis
Intervention: crisaborole ointment 2% bid 2 to 4 weeks (short term); crisaborole ointment 2% qd for 52 weeks (long term)
Comparison: vehicle bid for 2 to 4 weeks (short term); vehicle qd for 52 weeks (long term)

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Studies without poolable data	What happens
		Vehicle	With crisaborole	**Difference**			
POEM assessed with: Mean change in POEM score from baseline for participants aged 2-11 years old follow-up: 4 weeks № of participants: 178 (1 RCT)[4] CRITICAL	-	mean change in POEM was -3.8	-7.7	MD **3.9 lower** (5.57 lower to 2.23 lower)	⊕⊕⊕◯ Moderate[b]		Crisaborole use probably results in a clinically meaningful reduction in POEM.
Itch response assessed with: mean change from baseline follow-up: range 2 weeks to 4 weeks № of participants: 152 (2 RCTs)[2, 4] CRITICAL	-	-	SMD **0.51 SD lower** (0.85 lower to 0.17 lower)		⊕⊕⊕◯ Moderate[c]	**Eichenfield 2020[5]:** Significantly more participants achieved SPS* success with crisaborole: **RR 1.72 (1.40, 2.12)** (Low risk of bias)	Crisaborole probably reduces itch slightly.
Flare (maintenance therapy) assessed with: participants experiencing a disease exacerbation follow-up: 52 weeks № of participants: 107 (1 RCT)[6] CRITICAL	Median time of flare-free maintenance was longer for patients who received crisaborole (n=135) versus vehicle (n=135) (111 vs 30 days, respectively; p = 0.0034). The mean number of flare-free days was higher for patients who received crisaborole versus vehicle (234.0 vs 199.4 days, respectively; p = 0.0346). The mean number of flares was lower for patients who received crisaborole versus vehicle (0.95 vs 1.36, respectively; p = 0.0042).				⊕⊕⊕◯ Moderate[d]		Crisaborole maintenance therapy probably increases the time to flare and reduces the number of AD exacerbations.
CDLQI assessed with: Mean change in CDLQI score from baseline in participants aged 4-15y follow-up: 4 weeks № of participants: 233 (2 RCTs)[1, 4] CRITICAL	-	-	MD **1.29 lower** (3.05 lower to 0.46 higher)		⊕⊕⊕◯ Moderate[d]	**Simpson 2018[7]:** A non-statistically significant difference in change in CDLQI scores was reported with crisaborole vs vehicle: -4.5 vs -2.6, p=0.15 (n=911) (Some concerns for risk of bias) *dispersion not reported	Neither group experienced clinically meaningful reduction in CDLQI score and crisaborole probably results in little to no difference in CDLQI compared to vehicle.
Withdrawal due to adverse events assessed with: participants discontinuing treatment due to AEs follow-up: range 2 weeks to 4 weeks № of participants: 1353 (2 RCTs)[2, 3] CRITICAL	**RR 0.93** (0.37 to 2.32)	15 per 1,000	**14 per 1000** (6 to 35)	**1 fewer per 1000** (1 fewer to 2 more)	⊕⊕⊕⊕ High[e]		Crisaborole results in little to no difference in discontinuation.
Serious adverse events assessed with: participants experiencing an SAE follow-up: 2 weeks № of participants: 1353 (2 RCTs)[2, 3] CRITICAL	Fujita 2021 reported no SAEs in either treatment group (n=40). Luger 2022 reports 63/874 treatment-related AEs with crisaborole use vs 19/439 with vehicle use.				⊕⊕⊕◯ Moderate[d]		No SAEs were reported across groups. Treatment-related AEs are likely more common with crisaborole.

Crisaborole compared to vehicle for **children & adolescents** with atopic dermatitis

Patient or population: Children & adolescents (aged 3 months to 17 years) with mild to moderate atopic dermatitis
Intervention: crisaborole ointment 2% bid 2 to 4 weeks (short term); crisaborole ointment 2% qd for 52 weeks (long term)
Comparison: vehicle bid for 2 to 4 weeks (short term); vehicle qd for 52 weeks (long term)

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Studies without poolable data	What happens
		Vehicle	With crisaborole	**Difference**			
Treatment-emergent AE of interest assessed with: AEs identified by trials as of interest or commonly (as defined per study) occurring follow-up: 4 weeks № of participants: 1304 (1 RCT)[3]	Application site pain: 38/871 vs 4/433						

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardized mean difference
^Total Severity Score (TSS) calculated via severity of erythema, induration/papulation, excoriation, and lichenification using a 4-point severity scale; the sum of these ratings generated a total score on a 13-point scale (0–12 points).
*Severity or Pruritus Scale (SPS) success assessed via final SPS score ≤1 with ≥1-grade improvement from baseline); SPS=4-point rating scale (none [0], mild [1], moderate [2], severe [3])

Explanations
a. Very small sample leading to CI consistent with moderate and trivial benefit.
b. CI consistent with small benefit of uncertain importance and moderate benefit.
c. CI consistent with trivial and large effect.
d. Small number of events; concerning for precision.
e. Not downgraded for imprecision given the robust sample size despite low event rate as the low event rate suggests no harm with treatment.

Table. Long-term (uncontrolled) efficacy & safety data

Study (n)	Design	Efficacy	Safety
Geng 2021[8] N=418 *All ages*	open-label, 48-week study enrolled patients who completed a pivotal crisaborole trial without any drug-related safety issues that precluded further treatment with crisaborole.	After one to four initial consecutive treatment cycles, 77.6, 76.3, 59.4, and 43.1% of patients, respectively, achieved ISGA 0/1. Of these patients, 49.5, 37.8, 44.4, and 45.2%, respectively, maintained ISGA 0/1 at the end of a 28-day cycle off-treatment.	Incidence of TRAEs was 4.5, 4.7, 3.8, and 1.4% for patients. receiving one to four consecutive on-treatment cycles, respectively. One patient discontinued because of AEs.

References

1. NCT03539601. A study of crisaborole ointment 2%; crisaborole vehicle; TCS and TCI in subjects aged ≥ 2

years, with mild-moderate AD2018.
2. Fujita K, Yagi M, Moriwaki S, Yoshida M , Graham D. A phase 2b, randomized, double-blind, multicenter, vehicle-controlled study to assess the efficacy and safety of two crisaborole regimens in Japanese patients aged 2 years and older with mild-to-moderate atopic dermatitis. J Dermatol 2021;48:1640-51.
3. Luger TA, Hebert AA, Zaenglein AL, Silverberg JI, Tan H, Ports WC , Zielinski MA. Subgroup Analysis of Crisaborole for Mild-to-Moderate Atopic Dermatitis in Children Aged 2 to < 18 Years. Paediatr Drugs 2022;24:175-83.
4. Ma L, Zhang L, Kobayashi M, Tao X, Qian Q, Cheng H et al. Efficacy and safety of crisaborole ointment in Chinese and Japanese patients aged ≥2 years with mild-to-moderate atopic dermatitis. J Dermatol 2023;50:847-55.
5. Eichenfield LF, Yosipovitch G, Stein Gold LF, Kalabis M, Zang C, Vlahos B et al. Improvement in disease severity and pruritus outcomes with crisaborole ointment, 2%, by baseline atopic dermatitis severity in children and adolescents with mild-to-moderate atopic dermatitis. Pediatr Dermatol 2020;37:1030-7.

6. Eichenfield LF, Gower RG, Xu J, Alam MS, Su JC, Myers DE et al. Once-Daily Crisaborole Ointment, 2%, as a Long-Term Maintenance Treatment in Patients Aged ≥ 3 Months with Mild-to-Moderate Atopic Dermatitis: A 52-Week Clinical Study. Am J Clin Dermatol 2023;24:623-35.
7. Simpson EL, Paller AS, Boguniewicz M, Eichenfield LF, Feldman SR, Silverberg JI et al. Crisaborole Ointment Improves Quality of Life of Patients with Mild to Moderate Atopic Dermatitis and Their Families. Dermatol Ther (Heidelb) 2018;8:605-19.
8. Geng B, Hebert AA, Takiya L, Miller L, Werth JL, Zang C et al. Efficacy and Safety Trends with Continuous, Long-Term Crisaborole Use in Patients Aged ≥ 2 Years with Mild-to-Moderate Atopic Dermatitis. Dermatol Ther (Heidelb) 2021;11:1667-78.

Table 25. Roflumilast

*Pediatric-specific evidence aligned with our inclusion criteria is not available (awaiting INTEGUMENT-PED data). However, the INTEGUMENT 1 & 2 trials summarized below included participants aged 6 years + and 46% of the participants are pediatric. Data are additionally derived from a trial with a study population aged 12+ (5.5% of the study population was between the ages of 12 and 17 years).

Roflumilast 0.15% compared to vehicle for **children & adults** with atopic dermatitis

Patient or population: Children, adolescents, and adults with mild to moderate atopic dermatitis
Intervention: roflumilast 0.15 % cream QD for 28 days
Comparison: vehicle cream QD for 28 days

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		vehicle	roflumilast 0.15%	Difference		
EASI 75 assessed with: patients with a 75% or greater improvement in Eczema Area and Severity Index score from baseline. follow-up: 4 weeks № of participants: 1427 (3 RCTs)[1, 2] CRITICAL	**RR 2.06** (1.70 to 2.49)	19.9%	**41.0%** (33.8 to 49.5)	**211 more per 1000** (139 more to 296 more)	⊕⊕⊕⊕ High	Significantly more patients achieve EASI 75 with roflumilast.
IGA 0 or 1 assessed with: patients achieving an IGA score of 0 or 1 follow-up: 4 weeks № of participants: 1427 (3 RCTs)[1, 2] CRITICAL	**RR 1.90** (1.58 to 2.27)	22.3%	**42.3%** (35.2 to 50.6)	**201 more per 1000** (129 more to 283 more)	⊕⊕⊕⊕ High	Significantly more patients achieve IGA 0 or 1 with roflumilast.
Itch response assessed with: patients with ≥4-point improvement in Worst Itch Numerical score from baseline follow-up: 4 weeks № of participants: 1407 (3 RCTs)[1, 2] CRITICAL	**RR 1.53** (0.90 to 2.62)	18.7%	**28.7%** (16.9 to 49.1)	**99 more** (19 fewer to 304 more)	⊕⊕⊕⊕ High[a]	Roflumilast 0.15% results in an increase in patients achieving clinically meaningful itch reduction.

Roflumilast 0.15% compared to vehicle for **children & adults** with atopic dermatitis

Patient or population: Children, adolescents, and adults with mild to moderate atopic dermatitis
Intervention: roflumilast 0.15 % cream QD for 28 days
Comparison: vehicle cream QD for 28 days

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		vehicle	roflumilast 0.15%	Difference		
Withdrawal due to adverse events assessed with: participants discontinuing treatment due to adverse event follow-up: 4 weeks № of participants: 1426 (3 RCTs)[1, 2] CRITICAL	**RR 1.25** (0.47 to 3.28)	1.2%	**1.5%** (0.6 to 4)	**3 more per 1000** (6 fewer to 28 more)	⨁⨁⨁⨁ High[b]	Discontinuation was rare and similar between groups.
Treatment-emergent adverse events of interest assessed with: Adverse Reactions Reported in ≥1% of Subjects & reported more frequently with roflumilast follow-up: 4 weeks № of participants: (2 RCTs)[1]	Roflumilast n= 885 vs Vehicle n=451 Headache 26 (2.9) vs 4 (0.9) Nausea 17 (1.9) vs 2 (0.4) Application site pain 13 (1.5) vs 3 (0.7) Diarrhea 13 (1.5) vs 2 (0.4) Vomiting 13 (1.5) vs 2 (0.4)					

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. Not downgraded for borderline imprecision as the event rate is 390 and the imprecision is primarily driven by the small sample in the phase 2 trial.
b. The low event rate in a robust sample suggests safety. The evidence was not downgraded due to the rare event.

References

1. Eichenfield L, Boguniewicz M, Simpson E, Blauvelt A, Gooderham M, Lain E et al. ONCE-DAILY ROFLUMILAST CREAM 0.15% FOR ATOPIC DERMATITIS: POOLED Results: FROM INTEGUMENT-1/2 PHASE 3 TRIALS. Annals of Allergy, Asthma & Immunology 2023;131:S91.
2. Gooderham M, Kircik L, Zirwas M, Lee M, Kempers S, Draelos Z et al. The Safety and Efficacy of Roflumilast Cream 0.15% and 0.05% in Patients With Atopic Dermatitis: Randomized, Double-Blind, Phase 2 Proof of Concept Study. J Drugs Dermatol 2023;22:139-47.

Table 26. Ruxolitinib

*Pediatric-specific evidence aligned with our inclusion criteria is not available. The following evidence is derived from a population aged ≥ 12 years.

Ruxolitinib compared to vehicle for **adolescents & adults** with atopic dermatitis[1]

Patient or population: Individuals aged ≥ 12 years with mild to moderate atopic dermatitis
Intervention: 1.5% RUX cream bid for 8 weeks
Comparison: vehicle cream bid for 8 weeks

Outcome	Relative effect	Anticipated absolute effects (95% CI)	Certainty	What happens

№ of participants (studies)	(95% CI)	vehicle	ruxolitinib	Difference		
EASI assessed with: mean % change from baseline follow-up: 8 weeks № of participants: 652 (2 RCTs) CRITICAL	-		MD **42.67 lower** (49.37 lower to 35.97 lower)		⊕⊕⊕◯ Moderate[a]	Ruxolitinib likely reduces EASI slightly.
IGA 0 or 1 assessed with: patients achieving an IGA score of 0 to 1 who have an improvement of 2 or more points from baseline follow-up: 8 weeks № of participants: 725 (2 RCTs) CRITICAL	**RR 4.68** (2.50 to 8.75)	115 per 1000	**537 per 1000** (287 to 1000)	**422 more per 1000** (172 more to 889 more)	⊕⊕⊕◯ Moderate[a]	Ruxolitinib likely results in a large increase in the proportion of patients achieving IGA 0 or 1.
Itch response assessed with: patients with ≥ 4-point reduction in itch NRS score from baseline follow-up: 8 weeks № of participants: 465 (2 RCTs) CRITICAL	**RR 2.89** (2.03 to 4.11)	177 per 1000	**512 per 1000** (360 to 728)	**335 more per 1000** (183 more to 551 more)	⊕⊕⊕◯ Moderate[a]	Ruxolitinib likely meaningfully increases the number of patients achieving a meaningful itch response.
CDLQI assessed with: Mean change in CLDQI score from baseline follow-up: 8 weeks № of participants: 80 (2 RCTs) CRITICAL	-		MD **4.06 lower** (7.3 lower to 0.83 lower)		⊕⊕◯◯ Low[a,b]	Ruxolitinib may result in little to no difference in CDLQI.
Serious adverse events assessed with: participants experiencing a serious TEAE follow-up: 8 weeks № of participants: 749 (2 RCTs) CRITICAL	**RR 0.75** (0.13 to 4.47)	8 per 1000	**6 per 1000** (1 to 36)	**2 fewer per 1000** (7 fewer to 28 more)	⊕⊕⊕⊕ High[c]	Ruxolitinib results in little to no difference in serious adverse events.
Withdrawal due to adverse event assessed with: participants discontinuing treatment due to AE follow-up: 8 weeks № of participants: 749 (2 RCTs) CRITICAL	**RR 0.25** (0.08 to 0.82)	32 per 1000	**8 per 1000** (3 to 26)	**24 fewer per 1000** (29 fewer to 6 fewer)	⊕⊕⊕⊕ High[c]	Ruxolitinib results in little to no difference in withdrawal due to adverse event.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Some concerns about risk of bias due to missing outcome data likely related to the outcomes of interest.

b. CI consistent with clinically meaningful improvement and little to no difference.

c. A low event rate in a robust sample suggests safety and the CI is consistent with minimal difference.

Table. Long-term (uncontrolled) efficacy & safety data

Study (n)	Design	Efficacy	Safety
Papp 2023[2] N= 1072 *Aged 12-85*	Patients initially randomized to twice-daily 0.75%/1.5% ruxolitinib cream maintained their regimen during a 44-week open-label period (as-needed treatment). Patients on vehicle were rerandomized (1:1) at week 8 to either ruxolitinib cream strength.	Disease control was achieved throughout the 44-weeks; 74.1% to 77.8% of patients using 0.75% and 1.5%, respectively, had Investigator's Global	-TRAEs were reported in 2(2.0%) and 6 (6.1%) patients, using 0.75% and 1.5% respectively. -The most common TRAEs were neutropenia,

		Assessment 0/1 at week 52, and mean affected body surface area was low (1.4%-1.8%).	application site pain, and application site pruritus. -N=1 molar pregnancy was the only ruxolitinib-related serious adverse event reported. -Myocardial infarction was reported in 1 patient, and cerebrovascular accident (including stroke) was reported in 2 patients; all 3 patients had hypertension and other cardiovascular risk factors -Malignancies were reported in 6 patients but none were considered related to treatment.

References

1. Papp K, Szepietowski JC, Kircik L, Toth D, Eichenfield LF, Leung DYM et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: Results from 2 phase 3, randomized, double-blind studies. J Am Acad Dermatol 2021;85:863-72.
2. Papp K, Szepietowski JC, Kircik L, Toth D, Eichenfield LF, Forman SB et al. Long-term safety and disease control with ruxolitinib cream in atopic dermatitis: Results from two phase 3 studies. J Am Acad Dermatol 2023;88:1008-16.

Table 27. Tapinarof

*Pediatric-specific evidence aligned with our inclusion criteria is not available. However, the ADORING trials summarized below included participants aged 2 years + and >80% of the participants are pediatric. Data are additionally derived from a trial with a study population aged 12 to 65 years (13% of the study population was between the ages of 12 and 17 years).

Tapinarof compared to vehicle for **Children & adults** with atopic dermatitis

Patient or population: Children, adolescents, and adults aged 2+ years with moderate to severe atopic dermatitis
Intervention: 1% tapinarof qd for 8 to 12 weeks
Comparison: vehicle qd for 8 to 12 weeks

Outcome № of participants	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	Studies without poolable data	What happens
		vehicle	tapinarof	Difference			
EASI75 ≥75% improvement in EASI score from baseline Follow-up: 8 weeks № of participants: 813 (2 RCTs)[1] CRITICAL	**RR 2.60** (2.06 to 3.29)	221 per 1000	**574 per 1000** (454 to 726)	**353 more per 1,000** (from 234 more to 505 more)	⊕⊕⊕⊕ High	**Paller 2020:** tapinarof (n=41) resulted in a clinically meaningful reduction in EASI while vehicle (n=40) did not: -62% vs -28% (p=0.002).[2]	Tapinarof increases the number of patients achieving EASI75.
vIGA-AD response vIGA-AD score of 0 to 1 with an improvement of 2 or more points from baseline Follow-up: 8 weeks № of participants: 813 (2 RCTs)[1] CRITICAL	**RR 2.89** (2.16 to 3.86)	158 per 1000	**457 per 1000** (341 to 610)	**299 more per 1,000** (from 183 more to 452 more)	⊕⊕⊕⊕ High	**Paller 2020:** Tapinarof increases the number of patients achieving IGA 0 or 1 with 2+ point improvement: **RR 1.69** (0.92 to 3.07).[2]	Tapinarof increases the number of patients achieving a meaningful vIGA-AD response.

Tapinarof compared to vehicle for **Children & adults** with atopic dermatitis

Patient or population: Children, adolescents, and adults aged 2+ years with moderate to severe atopic dermatitis
Intervention: 1% tapinarof qd for 8 to 12 weeks
Comparison: vehicle qd for 8 to 12 weeks

Outcome № of participants	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	Studies without poolable data	What happens
		vehicle	tapinarof	Difference			
Itch response ≥4-point reduction in the average weekly PP-NRS total score from baseline Follow-up: 8 weeks № of participants: 614 (2 RCTs)[1] CRITICAL	**RR 1.77** (1.43 to 2.19)	335 per 1000	**593 per 1000** (479 to 734)	**258 more per 1000** (from 144 more to 399 more)	⊕⊕⊕⊕ High	**Paller 2020:** Tapinarof increases the number of patients achieving with ≥ 3-point reduction in weekly average NRS score from baseline: **RR 2.11** (0.89 to 5.01).[2]	Tapinarof increases the number of patients achieving a meaningful itch response.
Serious treatment-related adverse events AE considered serious & related to treatment by investigators Follow-up: range 8 to 12 weeks № of participants: 894 (3 RCTs)[1, 3] CRITICAL	No serious treatment-related adverse events were reported in either treatment arm across 3 RCTs.				⊕⊕⊕⊕ High		Serious adverse events are rare and tapinarof results in no difference in serious treatment-related adverse events.
Withdrawal due to adverse event participants discontinuing treatment due to AE Follow-up: range 8 to 12 weeks № of participants: 894 (3 RCTs)[1, 3] CRITICAL	**RR 0.46** (0.19 to 1.11)	35 per 1,000	**16 per 1,000** (7 to 39)	**19 fewer per 1,000** (from 29 fewer to 4 more)	⊕⊕⊕⊕ High[a]		Tapinarof results in little to no difference in withdrawal due to adverse event.
Treatment-related adverse events AE determined by investigators to be treatment-related Follow-up: range 8 to 12 weeks № of participants: 894 (3 RCTs)[1, 3] CRITICAL	**RR 1.93** (1.20 to 3.10)	64 per 1,000	**124 per 1,000** (77 to 199)	**60 more per 1,000** (from 13 more to 135 more)	⊕⊕⊕⊕ High[b]		Tapinarof increases treatment-related adverse events slightly.
Treatment-related AEs of interest AEs in >5% of patients & investigator determined AEs of interest Follow-up: range 8 to 12 weeks № of participants: 894 (3 RCTs)[1, 3] CRITICAL	**Most common:** Nasopharyngitis 22/582 vs 11/312 Folliculitis 52/582 vs 3/312 Impetigo 0/41 vs 3/40 Headache 23/541 vs 3/272			**Of interest:** Contact dermatitis 7/541 vs 5/272 Follicular event 51/541 vs 3/272 Headache 23/541 vs 3/272			

CI: confidence interval; **RR:** risk ratio

Explanations
a. Low event rate in robust sample; CI consistent with little to no difference so not downgraded for imprecision.
b. CI consistent with little to no difference & slight increase in harm.

References

1. Silverberg JI, Eichenfield LF, Hebert AA, Simpson EL, Stein Gold L, Bissonnette R et al. Tapinarof Cream 1% Once Daily: Significant Efficacy in the Treatment of Moderate to Severe Atopic Dermatitis in Adults and Children Down to 2 Years of Age in the Pivotal Phase 3 ADORING Trials. J Am Acad Dermatol 2024.
2. Paller AS, Stein Gold L, Soung J, Tallman AM, Rubenstein DS , Gooderham M. Efficacy and patient-reported outcomes from a phase 2b, randomized clinical trial of tapinarof cream for the treatment of adolescents and adults with atopic dermatitis. J Am Acad Dermatol 2021;84:632-8.
3. Peppers J, Paller AS, Maeda-Chubachi T, Wu S, Robbins K, Gallagher K , Kraus JE. A phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of atopic dermatitis. J Am Acad Dermatol 2019;80:89-98.e3.

Table 28. Dupilumab

Dupilumab compared to placebo for adolescent AD[1]

Patient or population: Adolescents aged ≥12 and <18 with moderate to severe AD inadequately controlled by topical treatment or for whom topical treatment was medically inadvisable
Intervention: dupilumab 200/300 mg every 2 weeks for 16 weeks (weight-based regimen)
Comparison: placebo every 2 weeks for 16 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with dupilumab				
IGA 0 or 1 assessed with: patients with a score of 0 or 1 follow-up: 16 weeks CRITICAL	24 per 1,000	**244 per 1,000** (59 to 1,000)	**RR 10.37** (2.50 to 42.95)	167 (1 RCT)	⊕⊕⊕⊕ High	Significantly more patients in the dupilumab group had IGA 0 or 1 than in the placebo group.
SCORAD assessed with: LS mean % change from baseline follow-up: 16 weeks CRITICAL	The mean change in SCORAD was **-17.6** %	MD **34 % lower** (43.4 lower to 24.6 lower)	-	167 (1 RCT)	⊕⊕⊕⊕ High	Dupilumab resulted in a clinically meaningful reduction in SCORAD at 16 weeks, while placebo did not.
Itch assessed with: improvement in peak score on NRS for pruritus ≥ 4 points follow-up: 16 weeks CRITICAL	48 per 1,000	**366 per 1,000** (135 to 992)	**RR 7.68** (2.83 to 20.84)	166 (1 RCT)	⊕⊕⊕⊕ High	Significantly more patients in the dupilumab group had meaningful itch reduction than in the placebo group
POEM assessed with: LS mean change from baseline follow-up: 16 weeks CRITICAL	The mean change in POEM was **-3.8**	MD **6.3 lower** (8.6 lower to 4 lower)	-	167 (1 RCT)	⊕⊕⊕◯ Moderate[a]	Dupilumab resulted in a significant and likely meaningful reduction in POEM compared to placebo.
Flare assessed with: participants with exacerbation of AD follow-up: 16 weeks CRITICAL	247 per 1,000	**183 per 1,000** (101 to 329)	**RR 0.74** (0.41 to 1.33)	167 (1 RCT)	⊕⊕⊕◯ Moderate[b]	Flares may be reduced with dupilumab, but the evidence is of lower certainty given the statistical inconsistency.
Quality of life-CDLQI assessed with: LS mean change from baseline follow-up: 16 weeks CRITICAL	The mean quality of life-CDLQI was **-5.1**	MD **3.4 lower** (5 lower to 1.8 lower)	-	167 (1 RCT)	⊕⊕⊕⊕ High	Dupilumab resulted in a clinically meaningful increase in QoL at 16 weeks, while placebo did not.
Serious treatment-emergent AEs assessed with: participants with a serious TEAE follow-up: 16 weeks CRITICAL	12 per 1,000	**4 per 1,000** (0 to 98)	**RR 0.35** (0.01 to 8.36)	167 (1 RCT)	⊕⊕⊕◯ Moderate[b]	Serious AEs may be reduced with dupilumab, but the evidence is of lower certainty given the minimal number of events leading to statistical inconsistency.
Withdrawal due to AE assessed with: participants with TEAEs leading to treatment discontinuation follow-up: 16 weeks CRITICAL	12 per 1,000	**4 per 1,000** (0 to 98)	**RR 0.35** (0.01 to 8.36)	167 (1 RCT)	⊕⊕⊕◯ Moderate[b]	Withdrawals due to AE were rare and equitable across treatment arms, but the evidence is of lower certainty given the minimal number of events leading to statistical inconsistency.

Dupilumab compared to placebo for adolescent AD[1]

Patient or population: Adolescents aged ≥12 and <18 with moderate to severe AD inadequately controlled by topical treatment or for whom topical treatment was medically inadvisable
Intervention: dupilumab 200/300 mg every 2 weeks for 16 weeks (weight-based regimen)
Comparison: placebo every 2 weeks for 16 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with dupilumab**				
Treatment-emergent AEs of interest follow-up: 16 weeks	Skin infections: 20.0% vs 11.0% Conjunctivitis: 4.7% vs 9.8% Upper RTI: 17.6% vs 12.2% Herpes viral infection: 3.5% vs 1.2%			167 (1 RCT)	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
Study was adequately powered so not downgraded for a small sample alone.
a. Downgraded once for imprecision as the CI is consistent with meaningful reduction and a small reduction of uncertain importance.
b. Downgraded once for imprecision as the event rate is very low providing limited AE information.

References:

1. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ et al. Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis: A Phase 3 Randomized Clinical Trial. JAMA Dermatol 2020;156:44-56.

Table 29. Dupilumab in Children Aged 6-11 Years

Dupilumab compared to standard care for children with AD[1]

Patient or population: Children aged 6-11 years with severe AD inadequately controlled with topical therapies
Intervention: Dupilumab 600 mg then 300 mg q4 weeks for 16 weeks (regardless of weight) + topical corticosteroids
Comparison: Placebo + topical corticosteroids

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	**Risk with dupilumab**				
IGA 0 or 1 assessed with: patients with a score of 0 or 1 follow-up: 16 weeks CRITICAL	114 per 1,000	**328 per 1,000** (188 to 571)	**RR 2.88** (1.65 to 5.02)	245 (1 RCT)	⊕⊕⊕⊕ High	Significantly more patients in the dupilumab group had IGA 0 or 1 than in the standard care group.
SCORAD assessed with: LS mean % change from baseline follow-up: 16 weeks CRITICAL	The mean change in SCORAD was **-29.8**	MD **32.6 lower** (38.7 lower to 26.5 lower)	-	245 (1 RCT)	⊕⊕⊕⊕ High	Dupilumab resulted in a clinically meaningful reduction in SCORAD at 16 weeks, while standard care did not.

Dupilumab compared to standard care for children with AD[1]

Patient or population: Children aged 6-11 years with severe AD inadequately controlled with topical therapies
Intervention: Dupilumab 600 mg then 300 mg q4 weeks for 16 weeks (regardless of weight) + topical corticosteroids
Comparison: Placebo + topical corticosteroids

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	**Risk with dupilumab**				
Itch assessed with: patients with >4-point reduction in weekly average of daily Peak Pruritus NRS follow-up: 16 weeks CRITICAL	123 per 1,000	**508 per 1,000** (306 to 842)	**RR 4.13** (2.49 to 6.85)	242 (1 RCT)	⊕⊕⊕⊕ High	Significantly more patients in the dupilumab group had meaningful itch reduction than in the standard care group.
POEM assessed with: LS mean change from baseline follow-up: 16 weeks CRITICAL	The mean change in POEM was **-5.3**	MD **8.3 lower** (10.24 lower to 6.36 lower)	-	245 (1 RCT)	⊕⊕⊕⊕ High	Dupilumab resulted in a clinically meaningful reduction in POEM at 16 weeks, while standard care did not.
Flare assessed with: patients with exacerbation of AD follow-up: 16 weeks CRITICAL	142 per 1,000	**67 per 1,000** (30 to 149)	**RR 0.47** (0.21 to 1.05)	240 (1 RCT)	⊕⊕⊕◯ Moderate[a]	Dupilumab may reduce AD flares but the evidence is of lower certainty given the minimal number of events.
Quality of Life-CDLQI assessed with: LS mean change from baseline follow-up: 16 weeks CRITICAL	The mean change in CDLQI was **-6.4**	MD **4.2 lower** (5.59 lower to 2.81 lower)	-	245 (1 RCT)	⊕⊕⊕⊕ High	Both treatments resulted in a possibly clinically meaningful increase in QoL at 16 weeks but dupilumab results in a slightly greater increase in QoL.
Serious treatment-emergent AEs assessed with: patients with a SAE follow-up: 16 weeks CRITICAL	17 per 1,000	**17 per 1,000** (2 to 116)	**RR 1.00** (0.14 to 6.98)	240 (1 RCT)	⊕⊕⊕◯ Moderate[a]	Dupilumab likely results in no difference in serious AEs.
Withdrawal due to AE assessed with: patients with a TEAE leading to treatment discontinuation follow-up: 16 weeks	17 per 1,000	**0 per 1,000** (0 to 0)	not estimable	240 (1 RCT)	⊕⊕⊕◯ Moderate[a]	Discontinuation was rare overall- only 2 patients in the standard care arm- and less likely with dupilumab.
Adverse events of interest follow-up: 16 weeks IMPORTANT	Conjunctivitis: 5/120 (4%) 8/120 (7%) Skin infection: 16/120 (13%) vs 7/120 (6%) Herpes viral infection: 6/120 (5%) vs 2/120 (2%)			240 (1 RCT)	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Downgraded one level for imprecision as small number of events led to statistical inconsistency.

References:

1. Paller AS, Siegfried EC, Thaçi D, Wollenberg A, Cork MJ, Arkwright PD et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial. J Am Acad Dermatol 2020;83:1282-93.

Table 30. Dupilumab in Children 6 Months to 6 Years

Dupilumab **weight-based dosing** compared to standard care for **children** with AD[1]

Patient or population: Children aged 6 months to < 6 years with moderate to severe AD and an inadequate response to topical corticosteroids
Intervention: Dupilumab 200 or 300 mg q4 weeks (weight-based) for 16 weeks + topical corticosteroids
Comparison: Placebo + topical corticosteroids

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	**Risk with dupilumab**				
IGA 0 or 1 assessed with: proportion of patients with score of 0 or 1 follow-up: 16 weeks CRITICAL	38 per 1,000	**277 per 1,000** (87 to 887)	**RR 7.30** (2.28 to 23.35)	162 (1 RCT)	⊕⊕⊕⊕ High	Significantly more patients in the dupilumab group had IGA 0 or 1 than in the standard care group.
SCORAD assessed with: LS mean % change from baseline follow-up: 16 weeks CRITICAL	The mean change in SCORAD was **-16.2%**	MD **38.4 lower** (46.7 lower to 30.2 lower)	-	162 (1 RCT)	⊕⊕⊕⊕ High	Dupilumab resulted in a clinically meaningful reduction in SCORAD at 16 weeks, while standard care did not.
Itch assessed with: improvement in peal score on NRS for pruritus >4 points follow-up: 16 weeks CRITICAL	90 per 1,000	**482 per 1,000** (230 to 1,000)	**RR 5.37** (2.56 to 11.27)	161 (1 RCT)	⊕⊕⊕⊕ High	Significantly more patients in the dupilumab group had meaningful itch reduction than in the standard care group.
POEM assessed with: LS mean % change from baseline follow-up: 16 weeks CRITICAL	The mean change in POEM was **-3.8**	MD **9.1 lower** (11.3 lower to 6.9 lower)	-	162 (1 RCT)	⊕⊕⊕⊕ High	Dupilumab resulted in a significant and likely meaningful reduction in POEM compared to standard care.
Flare assessed with: participants with exacerbation of AD follow-up: 16 weeks CRITICAL	321 per 1,000	**131 per 1,000** (71 to 250)	**RR 0.41** (0.22 to 0.78)	161 (1 RCT)	⊕⊕⊕⊕ High	Dupilumab reduces AD exacerbations compared to standard care.
Quality of Life- CDLQI assessed with: LS mean change from baseline follow-up: 16 weeks CRITICAL	The mean change in CDLQI was **-2.5**	MD **7.5 lower** (10.3 lower to 4.8 lower)	-	162 (1 RCT)	⊕⊕⊕◯ Moderate[a]	Dupilumab resulted in a clinically meaningful increase in QoL and likely increases QoL compared to standard care.
Severe or serious treatment-emergent AEs assessed with: patients with severe/serious TEAEs follow-up: 16 weeks CRITICAL	179 per 1,000	**23 per 1,000** (5 to 102)	**RR 0.13** (0.03 to 0.57)	161 (1 RCT)	⊕⊕⊕◯ Moderate[b]	Treatment-related severe/serious AEs may be reduced with dupilumab, but the evidence is of lower certainty given the minimal number of events leading to statistical inconsistency.

Dupilumab **weight-based dosing** compared to standard care for **children** with AD[1]

Patient or population: Children aged 6 months to < 6 years with moderate to severe AD and an inadequate response to topical corticosteroids
Intervention: Dupilumab 200 or 300 mg q4 weeks (weight-based) for 16 weeks + topical corticosteroids
Comparison: Placebo + topical corticosteroids

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	**Risk with dupilumab**				
Withdrawal due to AE assessed with: patients with TEAEs leading to treatment discontinuation follow-up: 16 weeks CRITICAL	13 per 1,000	**12 per 1,000** (1 to 189)	**RR 0.94** (0.06 to 14.77)	161 (1 RCT)	⨁⨁⨁◯ Moderate[b]	Withdrawals due to AE were rare and equitable across treatment arms, but the evidence is of lower certainty given the minimal number of events leading to statistical inconsistency.
Treatment-emergent AEs of interest follow-up: 16 weeks	Conjunctivitis: 0/78 vs 3/83 (4%) Skin infections, excluding herpes: 19/78 (24%) vs 10/83 (12%) Herpes viral infection: 4/78 (5%) vs 5/83 (6%)			161 (1 RCT)	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Downgraded one level for imprecision as the CI is consistent with a meaningful and unimportant increase in QoL.
b. Downgraded one level for imprecision due to the low number of events leading to statistical inconsistency.

References:

1. Paller AS, Simpson EL, Siegfried EC, Cork MJ, Wollenberg A, Arkwright PD et al. Dupilumab in children aged 6 months to younger than 6 years with uncontrolled atopic dermatitis: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2022;400:908-19.

Table. Dupilumab for pediatric AD- Uncontrolled Extension Data[1]

Treatment	Population (n)	Treatment Duration	Effectiveness	Safety
Dupilumab 300 mg every 4 weeks (q4w) irrespective of weight uptitrated to approved doses as needed	Children aged 12-17 (294)	52 weeks	IGA of 0/1: 43% EASI-75: 81% ≥ 6-point improvement in CDLQI: 86%	Safety profile consistent with original trials. Most AEs were mild or moderate. 5 most common AEs: Nasopharyngitis 20% AD 19% URTI 12% Headache 9% Conjunctivitis 9%

References:

1. Blauvelt A, Guttman-Yassky E, Paller AS, Simpson EL, Cork MJ, Weisman J et al. Long-Term Efficacy and Safety of Dupilumab in Adolescents with Moderate-to-Severe Atopic Dermatitis: Results Through Week 52 from a Phase III Open-Label Extension Trial (LIBERTY AD PED-OLE). Am J Clin Dermatol 2022;23:365-83.

Table 31. Tralokinumab

Tralokinumab compared to placebo for adolescents AD[1]

Patient or population: Adolescents aged 12-17 years with moderate to severe AD and a history of TCS/TCI treatment failure
Intervention: Tralokinumab 600 mg loading dose then 300 mg every 2 weeks for 16 weeks. Rescue medication was allowed.
Comparison: Placebo loading dose then every 2 weeks for 16 weeks. Rescue medication allowed.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Tralokinumab**				
IGA 0 or 1 assessed with: proportion of patients with score of 0 or 1 follow-up: 16 weeks CRITICAL	57 per 1,000	**210 per 1,000** (83 to 537)	**RR 3.66** (1.44 to 9.34)	182 (1 RCT)[1]	⊕⊕⊕◯ Moderate[a]	Significantly more patients in the tralokinumab group had IGA 0 or 1 than in the placebo group.
EASI assessed with: mean percentage change from baseline follow-up: 16 weeks CRITICAL	The mean % change in EASI was **-11.67**	MD **7.05 lower** (10.87 lower to 3.23 lower)	-	191 (1 RCT)[1]	⊕⊕⊕◯ Moderate[a]	Both groups experienced a clinically meaningful reduction in EASI at 16 weeks, but tralokinumab resulted in a significantly greater reduction in EASI.
SCORAD assessed with: adjusted mean change from baseline follow-up: 16 weeks CRITICAL	The mean change in SCORAD was **-9.5**	MD **19.7 lower** (27.1 lower to 12.2 lower)	-	191 (1 RCT)[1]	⊕⊕⊕◯ Moderate[a]	Both groups experienced a clinically meaningful reduction in SCORAD at 16 weeks, but tralokinumab resulted in a significantly greater reduction.
Itch assessed with: improvement in peak score on NRS for pruritus ≥4 points follow-up: 16 weeks CRITICAL	33 per 1,000	**247 per 1,000** (77 to 793)	**RR 7.50** (2.34 to 24.05)	187 (1 RCT)[1]	⊕⊕⊕◯ Moderate[a]	Significantly more patients in the tralokinumab group had meaningful itch reduction than in the standard care group.
Flare assessed with: patients with exacerbation of AD follow-up: 16 weeks CRITICAL	128 per 1,000	**73 per 1,000** (29 to 175)	**RR 0.57** (0.23 to 1.37)	191 (1 RCT)[1]	⊕⊕⊕◯ Moderate[b]	Tralokinumab may reduce AD flares but the evidence is of lower certainty given the minimal number of events .
CDLQI assessed with: adjusted mean change from baseline follow-up: 16 weeks CRITICAL	The mean change in CDLQI was **-6.7**	MD **2.6 lower** (4.5 lower to 0.7 lower)	-	191 (1 RCT)[1]	⊕⊕⊕◯ Moderate[c]	Tralokinumab resulted in a potentially meaningful increase in QoL at 16 weeks while placebo did not.

Tralokinumab compared to placebo for adolescents AD[1]

Patient or population: Adolescents aged 12-17 years with moderate to severe AD and a history of TCS/TCI treatment failure
Intervention: Tralokinumab 600 mg loading dose then 300 mg every 2 weeks for 16 weeks. Rescue medication was allowed.
Comparison: Placebo loading dose then every 2 weeks for 16 weeks. Rescue medication allowed.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Tralokinumab**				
Serious adverse events assessed with: patients with an SAE follow-up: 16 weeks CRITICAL	10 per 1,000	**53 per 1,000** (6 to 447)	**RR 5.16** (0.61 to 43.34)	191 (1 RCT)[1]	⊕⊕⊕◯ Moderate[d]	SAEs were rare across study groups but numerically lower with tralokinumab.
Withdrawal due to adverse events assessed with: patients discontinuing treatment follow-up: 16 weeks	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	191 (1 RCT)[1]	⊕⊕⊕◯ Moderate[e]	There were no withdrawals in either arm.
Treatment-emergent AEs of interest follow-up: 16 weeks IMPORTANT	Conjunctivitis: 2/94 (2.1%) vs 3/97 (3.1%) Keratitis: 0/94 (0%) vs 1/97 (1.0%) Eczema herpeticum: 1/94 (1.1%) vs 0/97 (0%) Malignant neoplasms: 0/94 (0%) vs 0/97 (0%) Skin infections requiring systemic treatment: 2/94 (2.1%) vs 2/97 (2.1%)			191 (1 RCT)[1]	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Downgraded once for imprecision: small sample. Sample was not adequately powered.
b. Downgraded once for imprecision: small sample size; CI consistent with a moderate benefit and small harm.
c. Downgraded once for imprecision: small sample; CI consistent with a moderate benefit and a small unimportant benefit.
d. Downgraded once for imprecision: small sample; CI consistent with trivial benefit and large harm.
e. Downgraded once for imprecision: small sample; no events in both groups.

Table. Tralokinumab for pediatric AD- Uncontrolled Extension Data[1]

Treatment	Population (n)	Treatment Duration	Effectiveness	Safety
Tralokinumab 300 mg every 2 weeks + optional use of TCS/TCI	70	52 weeks	IGA of 0 or 1: 22/70 (31.4%) EASI 75: 37/70 (52.9%)	Safety profile consistent with 16-week initial treatment phase. Most AEs mild or moderate.

References:

1. Paller AS, Flohr C, Cork M, Bewley A, Blauvelt A, Hong HC et al. Efficacy and Safety of Tralokinumab in Adolescents With Moderate to Severe Atopic Dermatitis: The Phase 3 ECZTRA 6 Randomized Clinical Trial. JAMA Dermatol 2023;159:596-605.

Table 32. Lebrikizumab

Lebrikizumab monotherapy compared to placebo for **adolescent** AD

Patient or population: Adolescents aged ≥12 to <18 years old, weighing ≥ 40 kg with moderate-to-severe AD
Intervention: lebrikizumab monotherapy (500 mg loading doses at baseline and Week 2 followed by 250 mg every 2 weeks) for 16 weeks
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with lebrikizumab monotherapy**				
IGA 0 or 1 with ≥2-point improvement from baseline follow-up: 16 weeks CRITICAL	143 per 1,000	**231 per 1,000** (97 to 551)	**RR 1.62** (0.68 to 3.86)	102 (2 RCTs)[1]	⊕⊕⊕◯ Moderate[a]	Lebrikizumab monotherapy likely increases the number of patients achieving IGA 0 or 1 with ≥2-point improvement from baseline.
EASI 75 follow-up: 16 weeks CRITICAL	171 per 1,000	**627 per 1,000** (295 to 1,000)	**RR 3.66** (1.72 to 7.75)	102 (2 RCTs)[1]	⊕⊕⊕◯ Moderate[a]	Lebrikizumab monotherapy likely increases the number of patients achieving EASI 75.
Pruritus improvement assessed with: NRS ≥4-point improvement in patients with NRS ≥4 at baseline follow-up: 16 weeks CRITICAL	133 per 1,000	**483 per 1,000** (187 to 1,000)	**RR 3.62** (1.40 to 9.37)	86 (2 RCTs)[1]	⊕⊕⊕◯ Moderate[a]	Lebrikizumab monotherapy likely increases the number of patients achieving meaningful pruritus Improvement .
Quality of life assessed with: mean change from baseline in DLQI or CLDQI follow-up: 16 weeks INFORMATIVE	For adolescent patients (N = 206) with moderate-to-severe AD on lebrikizumab 500mg_250mg_q2w mean change from baseline in: DLQI -6.9 (SE 0.9) CDLQI -6.1 (SE 0.4)			206 (1 non-randomised study)[2]	⊕◯◯◯ Very low[b]	Non-randomized, single cohort data suggest lebrikizumab results in clinically meaningful improvement in quality of life (MCID for DLQI of 4 points).
Adverse events assessed with: patients reporting AEs follow-up: 52 weeks INFORMATIVE	For adolescent patients, (N = 206): **Serious AEs:** 5/206 (AD, bile duct stone, cardiac arrest, conjunctivitis, multiple injuries, testicular torsion) No single SAE was reported by more than 1 patient and only conjunctivitis led to discontinuation. **Treatment-emergent AE**: 134/206; Most TEAEs were non-serious and mild (33.5%) or moderate (29.6%) in severity. **TEAEs that were most frequently reported (>5%):** AD (13.1%), nasopharyngitis (9.7%), COVID-19 infection (8.7%), upper respiratory tract infection (6.3%), headache (5.8%), and oral herpes (5.3%).			206 (1 non-randomised study)[2]	⊕◯◯◯ Very low[b]	Non-randomized, single cohort data suggest long-term safety and tolerability of lebrikizumab in adolescents.
Long-term efficacy follow-up: 52 weeks INFORMATIVE	For adolescent patients (N = 206) with moderate-to-severe AD on lebrikizumab 500mg_250mg_q2w at 52 weeks: **EASI-75** achieved 169/206 (81.9%) **IGA 0/1** achieved by 129/206 (62.6%) **DLQI** mean change from baseline -8.9 (SE 0.9) (n =35) **CDLQI** mean change from baseline -6.5 (SE 0.5) (n=168)			206 (1 non-randomised study)[2]	⊕◯◯◯ Very low[b]	Non-randomized, single cohort data suggest lebrikizumab results suggest robust long-term efficacy in adolescents.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. Very small event rate/sample size leading to imprecise estimate of effect.

b. Small sample is concerning for precision.

References:

1. Hebert AA, Flohr C, Hong HC, Irvine AD, Pierce E, Elmaraghy H et al. Efficacy of lebrikizumab in adolescent patients with moderate-to-severe atopic dermatitis: 16-week results from three randomized phase 3 clinical trials. J Dermatolog Treat 2024;35:2324833.
2. Paller AS, Flohr C, Eichenfield LF, Irvine AD, Weisman J, Soung J et al. Safety and Efficacy of Lebrikizumab in Adolescent Patients with Moderate-to-Severe Atopic Dermatitis: A 52-Week, Open-Label, Phase 3 Study. Dermatol Ther (Heidelb) 2023;13:1517-34.

Table 33. Lebrikizumab + TCS

Leb + TCS compared to Placebo + TCS for **adolescent** AD

Patient or population: Adolescents aged ≥12 to <18 years old, weighing ≥ 40 kg with moderate-to-severe AD
Intervention: lebrikizumab monotherapy (500 mg loading doses at baseline and Week 2 followed by 250 mg every 2 weeks) +TCS for 16 weeks
Comparison: Placebo + TCS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo + TCS	Risk with leb + TCS				
IGA 0 or 1 with ≥2-point improvement from baseline follow-up: 16 weeks CRITICAL	286 per 1,000	**563 per 1,000** (231 to 1,000)	**RR 1.97** (0.81 to 4.76)	46 (1 RCT)[1]	⨁⨁◯◯ Low[a]	Leb + TCS may result in a large increase in the number of patients achieving IGA 0 or 1 with ≥2-point improvement from baseline.
EASI 75 follow-up: 16 weeks CRITICAL	571 per 1,000	**874 per 1,000** (549 to 1,000)	**RR 1.53** (0.96 to 2.46)	46 (1 RCT)[1]	⨁⨁◯◯ Low[a]	Leb + TCS may result in a large increase in the number of patients achieving EASI 75.
Pruritus improvement assessed with: NRS ≥4-point improvement in patients with NRS ≥4 at baseline follow-up: 16 weeks CRITICAL	182 per 1,000	**458 per 1,000** (122 to 1,000)	**RR 2.52** (0.67 to 9.50)	35 (1 RCT)[1]	⨁⨁◯◯ Low[a]	Leb + TCS may result in a large increase in the number of patients experiencing meaningful pruritus improvement.
Quality of life assessed with: LS mean change from baseline in CLDQI follow-up: 16 weeks CRITICAL	The mean change quality of life was -4.7(SE 1.2)	LsMD **4.6 lower** (7.2 lower to 2 lower)	-	35 (1 RCT)[2]	⨁⨁◯◯ Low[b]	Leb + TCS likely results in little to no difference in quality of life.
Adverse events assessed with: patients experiencing AEs follow-up: 52 weeks INFORMATIVE	For adolescent patients, (N = 206): **Serious AEs:** 5/206 (AD, bile duct stone, cardiac arrest, conjunctivitis, multiple injuries, testicular torsion) No single SAE was reported by more than 1 patient and only conjunctivitis led to discontinuation. **Treatment-emergent AE**: 134/206; Most TEAEs were non-serious and mild (33.5%) or moderate (29.6%) in severity. **TEAEs that were most frequently reported (>5%):** AD (13.1%), nasopharyngitis (9.7%), COVID-19 infection (8.7%), upper respiratory tract infection (6.3%), headache (5.8%), and oral herpes (5.3%).			206 (1 non-randomised study)[3]	⨁◯◯◯ Very low[c]	Non-randomized, single cohort data suggest long-term safety and tolerability of lebrikizumab in adolescents.

Leb + TCS compared to Placebo + TCS for **adolescent** AD

Patient or population: Adolescents aged ≥12 to <18 years old, weighing ≥ 40 kg with moderate-to-severe AD
Intervention: lebrikizumab monotherapy (500 mg loading doses at baseline and Week 2 followed by 250 mg every 2 weeks) +TCS for 16 weeks
Comparison: Placebo + TCS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo + TCS	**Risk with leb + TCS**				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations

a. Very small sample/event rate leading to imprecise estimate of effect consistent with little to difference and large benefit.
b. CI consistent with meaningful benefit and no meaningful difference.
c. Small sample is concerning for precision.

References:

1. Hebert AA, Flohr C, Hong HC, Irvine AD, Pierce E, Elmaraghy H et al. Efficacy of lebrikizumab in adolescent patients with moderate-to-severe atopic dermatitis: 16-week results from three randomized phase 3 clinical trials. J Dermatolog Treat 2024;35:2324833.
2. Simpson EL, Gooderham M, Wollenberg A, Weidinger S, Armstrong A, Soung J et al. Efficacy and Safety of Lebrikizumab in Combination With Topical Corticosteroids in Adolescents and Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial (ADhere). JAMA Dermatol 2023;159:182-91.
3. Paller AS, Flohr C, Eichenfield LF, Irvine AD, Weisman J, Soung J et al. Safety and Efficacy of Lebrikizumab in Adolescent Patients with Moderate-to-Severe Atopic Dermatitis: A 52-Week, Open-Label, Phase 3 Study. Dermatol Ther (Heidelb) 2023;13:1517-34.

Table 34. Nemolizumab

Nemolizumab + TCS/TCI compared to placebo+TCS/TCI for adolescent AD[1]

Patient or population: Adolescents aged 12-17 years with moderate to severe atopic dermatitis
Intervention: nemolizumab 30mg every 4 weeks + TCS and/or TCI for 16 weeks
Comparison: placebo+ TCS/TCI for 16 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo+TCS/TCI	**Risk with nemolizumab + TCS/TCI**				
Itch improvement assessed with: patients with improvement in average PP-NRS scores of ≥4 from baseline follow-up: 16 weeks	178 per 1,000	**407 per 1,000** (252 to 656)	**RR 2.29** (1.42 to 3.69)	266 (2 RCTs)	⊕⊕⊕⊕ High	Nemolizumab + TCS/TCI results in a large increase in the number of patients achieving meaningful itch improvement.
EASI75 assessed with: patients with at least 75% improvement in EASI from baseline follow-up: 16 weeks	378 per 1,000	**518 per 1,000** (348 to 771)	**RR 1.37** (0.92 to 2.04)	266 (2 RCTs)	⊕⊕⊕◯ Moderate[a]	Nemolizumab + TCS/TCI likely results in large increase in the number of patients achieving EASI75.

Nemolizumab + TCS/TCI compared to placebo+TCS/TCI for adolescent AD[1]

Patient or population: Adolescents aged 12-17 years with moderate to severe atopic dermatitis
Intervention: nemolizumab 30mg every 4 weeks + TCS and/or TCI for 16 weeks
Comparison: placebo+ TCS/TCI for 16 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo+TCS/TCI	**Risk with nemolizumab + TCS/TCI**				
Quality of life assessed with: LS mean change in CDLQI follow-up: 16 weeks	-	MD **2.14 lower** (4.41 lower to 0.12 higher)	-	213 (2 RCTs)	⊕⊕⊕◯ Moderate[b]	Nemolizumab + TCS/TCI likely results in little to no difference in quality of life.
IGA success assessed with: IGA of 0 or 1 follow-up: 16 weeks	344 per 1,000	**489 per 1,000** (341 to 703)	**RR 1.42** (0.99 to 2.04)	266 (2 RCTs)	⊕⊕⊕◯ Moderate[c]	Nemolizumab + TCS/TCI likely increases the number of patients achieving meaningful IGA improvement.
Serious adverse events assessed with: patients experiencing an SAE follow-up: 16 weeks	12 per 1,000	**16 per 1,000** (6 to 43)	**RR 1.31** (0.48 to 3.62)	1409 (2 RCTs)	⊕⊕⊕◯ Moderate[d,e]	Nemolizumab + TCS/TCI likely results in little to no difference in serious adverse events.
Discontinuation due to adverse events assessed with: patients discontinuing treatment due to AE follow-up: 16 weeks	27 per 1,000	**30 per 1,000** (5 to 198)	**RR 1.09** (0.17 to 7.23)	1719 (2 RCTs)	⊕⊕⊕◯ Moderate[d,e]	Nemolizumab + TCS/TCI likely results in little to no difference in discontinuation due to adverse events.
Treatment-emergent adverse events of interest follow-up: 16 weeks	In the ARCADIA trials, no meaningful differences between the nemolizumab+ TCS-TCI group and placebo+TCS/TCI group were observed for the treatment-emergent adverse events of special interest of peripheral or facial edema, asthma (newly diagnosed or worsening of asthma), or infections.			1719 (2 RCTs)		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Downgraded one level for imprecision as CI consistent with meaningful benefit, no difference and trivial harm.
b. Downgraded one level for imprecision due to small sample despite CI consistent with no meaningful difference.
c. Downgraded one level for imprecision as CI consistent with a meaningful benefit (>25%), no difference, and trivial harm.
d. Sample includes adults & adolescents but the safety profile in adolescents is noted by the FDA as "consistent with the safety profile in adults", so was not downgraded for indirectness.
e. Downgraded one level for imprecision given the overall small sample of adolescents (n=176

References:

1. Silverberg JI, Wollenberg A, Reich A, Thaçi D, Legat FJ, Papp KA et al. Nemolizumab with concomitant topical therapy in adolescents and adults with moderate-to-severe atopic dermatitis (ARCADIA 1 and ARCADIA 2): results from two replicate, double-blind, randomised controlled phase 3 trials. Lancet 2024;404:445-60.

Table 35. Nemolizumab in children

Nemolizumab + TCS/TCI compared to placebo for children with AD[1]

Patient or population: children aged 6-12 years with AD and inadequately controlled moderate to severe itch
Intervention: nemolizumab 30mg every 4 weeks + TCS, TCIs, or systemic antihistamines for 16 weeks
Comparison: placebo + TCS, TCIs, or systemic antihistamines for 16 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with nemolizumab + TCS/TCI**				
Itch improvement assessed with: patients with improvement in average AP-NRS scores of ≥4 from baseline follow-up: 16 weeks	68 per 1,000	**419 per 1,000** (133 to 1,000)	**RR 6.14** (1.95 to 19.35)	87 (1 RCT)	⊕⊕◯◯ Low[a]	Nemolizumab + TCS/TCI may result in a large increase in the number of children with meaningful itch improvement.
EASI75 assessed with: patients with at least 75% improvement in EASI from baseline follow-up: 16 weeks	205 per 1,000	**311 per 1,000** (151 to 644)	**RR 1.52** (0.74 to 3.15)	89 (1 RCT)	⊕⊕◯◯ Low[a]	Nemolizumab + TCS/TCI may increase EASI75 slightly.
Quality of life assessed with: CDLQI total score: improvement of at least 2.5 points from baseline follow-up: 16 weeks	571 per 1,000	**834 per 1,000** (623 to 1,000)	**RR 1.46** (1.09 to 1.96)	84 (1 RCT)	⊕⊕⊕◯ Moderate[b]	Nemolizumab + TCS/TCI likely results in a large increase in the number of children with a 2.5+ point improvement in CDLQI.
IGA success assessed with: IGA 0 or 1 with 2+ level decrease from baseline follow-up: 16 weeks	91 per 1,000	**178 per 1,000** (57 to 548)	**RR 1.96** (0.63 to 6.03)	89 (1 RCT)	⊕⊕◯◯ Low[a]	Nemolizumab + TCS/TCI may result in a large increase in the number of patients achieving IGA success.
Serious adverse events assessed with: patients experiencing an SAE follow-up: 16 weeks	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 4.68** (0.23 to 94.82)	89 (1 RCT)	⊕⊕◯◯ Low[a]	Nemolizumab + TCS/TCI may result in little to no difference in serious adverse events.
Discontinuation due to adverse event assessed with: patients discontinuing treatment due to AE follow-up: 16 weeks	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	89 (1 RCT)	⊕⊕◯◯ Low[c]	Nemolizumab + TCS/TCI may result in little to no difference in discontinuation due to AEs.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations

a. Downgraded 2 levels for imprecision as ratio of upper and lower bound of the CI is >3.
b. Downgraded 1 level for imprecision as CI consistent with trivial difference and large magnitude of benefit.
c. Very small sample is concerning for precision.

References:

1. Igarashi A, Katsunuma T, Matsumura T , Komazaki H. Efficacy and safety of nemolizumab in paediatric patients aged 6-12 years with atopic dermatitis with moderate-to-severe pruritus: results from a phase III, randomized, double-blind, placebo-controlled, multicentre study. Br J Dermatol 2023;190:20-8.

Table 36. Omalizumab

Omalizumab + standard therapy compared to placebo + standard therapy for children & adolescents with AD[1]

Patient or population: Children adolescents aged 2-19 years with severe AD unresponsive to optimum therapy
Intervention: Omalizumab dosed by the manufacturer's specifications based on weight and total IgE plus standard therapy
Comparison: Placebo plus standard therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard therapy	**Risk with Omalizumab**				
EASI assessed with: adjusted change from baseline (serum IgE level & age < 10) follow-up: 24 weeks CRITICAL	The mean change in EASI was **-4.9**	MD **6.7 lower** (13.2 lower to 0.1 lower)	-	60 (1 RCT)[1]	⨁⨁◯◯ Low[a]	Omalizumab results in a clinically meaningful reduction in EASI, while placebo did not.
POEM assessed with: mean score follow-up: 24 weeks CRITICAL	The mean POEM was **16.0**	MD **1.1 lower** (4.6 lower to 2.4 higher)	-	60 (1 RCT)[1]	⨁⨁◯◯ Low[b]	POEM scores in both groups were in the "moderate eczema" range at 24 weeks. Omalizumab may result in a slight reduction in POEM.
Flare assessed with: patients with an AD exacerbation follow-up: 24 weeks CRITICAL	194 per 1,000	**166 per 1,000** (56 to 488)	**RR 0.86** (0.29 to 2.52)	61 (1 RCT)[1]	⨁⨁◯◯ Low[c]	Omalizumab may reduce AD exacerbations but the evidence is imprecise.
CDLQI/DLQI assessed with: mean score follow-up: 24 weeks ITICAL	The mean CDLQI/DLQI was **11.8**	MD **3.5 lower** (6.4 lower to 0.5 lower)	-	60 (1 RCT)[1]	⨁⨁◯◯ Low[a]	Omalizumab probably improves cDLQI/DLQI slightly.
Serious adverse events assessed with: patients with an AE follow-up: 24 weeks CRITICAL	194 per 1,000	**199 per 1,000** (72 to 552)	**RR 1.03** (0.37 to 2.85)	61 (1 RCT)[1]	⨁⨁◯◯ Low[c]	Rates of AEs were equitable across treatment arms.

Omalizumab + standard therapy compared to placebo + standard therapy for children & adolescents with AD[1]

Patient or population: Children adolescents aged 2-19 years with severe AD unresponsive to optimum therapy
Intervention: Omalizumab dosed by the manufacturer's specifications based on weight and total IgE plus standard therapy
Comparison: Placebo plus standard therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard therapy	Risk with Omalizumab				
Withdrawal due to adverse events assessed with: patients discontinuing treatment due to AE follow-up: 24 weeks CRITICAL	31 per 1,000	**32 per 1,000** (2 to 540)	**RR 1.03** (0.06 to 17.28)	63 (1 RCT)[1]	⨁⨁◯◯ Low[d]	Rates of withdrawal were low and equitable across treatment arms.
Treatment-emergent AEs of interest follow-up: 24 weeks	Infection: 8/32(25%) vs 6/30 (20%) Respiratory events: 25/32 (78%) vs 15/30 (50%) Dermatological events: 31/32 (97%) vs 23/13 (77%)			62 (1 RCT)[1]	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Downgraded once for imprecision: small sample.
b. Downgraded twice for imprecision: small sample; CI consistent with a moderate benefit and small unimportant harm.
c. Downgraded twice for imprecision: small sample; CI consistent with a moderate benefit and moderate harm.
d. Downgraded twice for imprecision: small sample; CI consistent with a small benefit and large harm.

References:

1. Chan S, Cornelius V, Cro S, Harper JI , Lack G. Treatment Effect of Omalizumab on Severe Pediatric Atopic Dermatitis: The ADAPT Randomized Clinical Trial. JAMA Pediatr 2020;174:29-37.

Table 37. Abrocitinib

Abrocitinib monotherapy compared to placebo for adolescent AD

Patient or population: Adolescents aged 12-17 with moderate to severe AD
Intervention: Once daily abrocitinib 100 mg for 12 weeks
Comparison: Once daily placebo form 12 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with abrocitinib				
IGA Response assessed with: patients with a score of 0 or 1 and a ≥ 2 grade improvement from baseline follow-up: 12 weeks CRITICAL	125 per 1,000	**265 per 1,000** (65 to 1,000)	**RR 2.12** (0.52 to 8.69)	50 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	Abrocitinib monotherapy likely increases IGA response. **Silverberg 2020**[2]: With abrocitinib 12.5% (0.0-28.7) of adolescents (n=17) achieved IGA response vs 0% (0.0-41.0) with placebo (n=8); MD 12.5% (-11.7-36.7)

Abrocitinib **monotherapy** compared to placebo for **adolescent** AD

Patient or population: Adolescents aged 12-17 with moderate to severe AD
Intervention: Once daily abrocitinib 100 mg for 12 weeks
Comparison: Once daily placebo form 12 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with abrocitinib**				
EASI 75 assessed with: patients who had achieved at least a 75% improvement in EASI score from baseline follow-up: 12 weeks CRITICAL	125 per 1,000	**441 per 1,000** (114 to 1,000)	**RR 3.53** (0.91 to 13.62)	50 (1 RCT)[1]	⊕⊕⊕◯ Moderate[b]	Abrocitinib monotherapy likely results in an increase in the proportion of patients achieving EASI 75. **Silverberg 2020**[2]: With abrocitinib 43.8% (19.4-68.1) of adolescents (n=17) achieved EASI 75 vs 0% (0.0-41.0) with placebo (n=8); MD 43.8% (13.5-74.0)
POEM assessed with: patients achieving a ≥4-point improvement from baseline follow-up: 12 weeks CRITICAL	600 per 1,000	**762 per 1,000** (534 to 1,000)	**RR 1.27** (0.89 to 1.82)	76 (2 RCTs)[3]	⊕⊕⊕◯ Moderate[c]	Abrocitinib may result in a meaningful improvement in POEM at 12 weeks compared to placebo.
Itch assessed with: patients with a ≥ 1 point improvement in PSAAD follow-up: 12 weeks CRITICAL	320 per 1,000	**666 per 1,000** (365 to 1,000)	**RR 2.08** (1.14 to 3.81)	76 (2 RCTs)[3]	⊕⊕⊕◯ Moderate[d]	Abrocitinib monotherapy likely results in a meaningful improvement in itch & other symptoms at 12 weeks.
Quality of Life-CDLQI assessed with: patients with ≥ 6-point improvement from baseline in CDLQI follow-up: 12 weeks CRITICAL	200 per 1,000	**568 per 1,000** (250 to 1,000)	**RR 2.84** (1.25 to 6.45)	76 (2 RCTs)[3]	⊕⊕⊕◯ Moderate[e]	Abrocitinib monotherapy likely results in a clinically meaningful increase in quality of life at 12 weeks.
Safety assessed with: Integrated safety analysis follow-up: 12 weeks	A safety analysis including adults & adolescents found people who were given abrocitinib were more likely to report nausea, headache, and acne than people given placebo. These adverse events were typically mild or moderate and did not require the participant to stop taking the study medicine. Herpes simplex infection was more common in people taking abrocitinib (about 4/100 participants for 200 mg and about 3 /100 participants for 100 mg) than in people who took placebo (about 2/100 participants)			1540 (5 RCTs)[4]	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. Downgraded once for imprecision as wide CI consistent with meaningful harm and benefit.
b. Downgraded once for imprecision as very wide CI is consistent with small harm and substantial benefit.
c. Downgraded once for imprecision as wide CI consistent with small harm and large benefit.
d. Downgraded once for imprecision as wide CI is consistent with a small unimportant benefit and substantial benefit.
e. Downgraded once for imprecision as the small sample is underpowered.

References:

1. Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet 2020;396:255-66.
2. Silverberg JI, Simpson EL, Thyssen JP, Gooderham M, Chan G, Feeney C et al. Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol 2020;156:863-73.
3. Cork MJ, McMichael A, Teng J, Valdez H, Rojo R, Chan G et al. Impact of oral abrocitinib on signs, symptoms and quality of life among adolescents with moderate-to-severe atopic dermatitis: an analysis of patient-reported outcomes. J Eur Acad Dermatol Venereol 2022;36:422-33.
4. Simpson EL, Silverberg JI, Nosbaum A, Winthrop KL, Guttman-Yassky E, Hoffmeister KM et al. Integrated Safety Analysis of Abrocitinib for the Treatment of Moderate-to-Severe Atopic Dermatitis From the Phase II and Phase III Clinical Trial Program. Am J Clin Dermatol 2021;22:693-707.

Table 38. Abrocitinib + TCS

Abrocitinib **+ topical therapy** compared to topical therapy for adolescent AD[1]

Patient or population: Adolescents aged 12-17 with moderate to severe AD and an inadequate response to topical medication or a need for systemic therapy
Intervention: Once daily **a**brocitinib 100mg plus medicated topical therapy
Comparison: placebo plus medicated topical therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with topical therapy	Risk with abrocitinib + topical therapy				
IGA Response Assessed with: patients with a score of 0 or 1 and a ≥ 2 grade improvement from baseline follow-up: 12 weeks CRITICAL	245 per 1,000	**416 per 1,000** (269 to 641)	**RR 1.70** (1.10 to 2.62)	183 (1 RCT)	⊕⊕⊕◯ Moderate[a]	Significantly more patients in the abrocitinib group had IGA 0 or 1 than in the placebo group
EASI assessed with: least square mean change from baseline follow-up: 12 weeks CRITICAL	The mean change in EASI was **-18.0**	MD **5 lower** (7.6 lower to 2.3 lower)	-	191 (1 RCT)	⊕⊕⊕◯ Moderate[a]	Both groups experienced a clinically meaningful reduction in EASI at 12 weeks, with a slightly greater reduction possible with abrocitinib.
POEM assessed with: least square mean change from baseline follow-up: 12 weeks CRITICAL	The mean change in POEM was **-6.9**	MD **4.1 lower** (6.1 lower to 2.2 lower)	-	190 (1 RCT)	⊕⊕⊕◯ Moderate[a]	Both groups experienced a clinically meaningful reduction in POEM at 12 weeks, with a slightly greater reduction possible with abrocitinib.
Itch assessed with: ≥ 4-point improvement in NRS follow-up: 12 weeks CRITICAL	298 per 1,000	**527 per 1,000** (357 to 780)	**RR 1.77** (1.20 to 2.62)	160 (1 RCT)	⊕⊕⊕◯ Moderate[a]	Significantly more patients in the abrocitinib group had meaningful itch reduction than in the placebo group.

Abrocitinib + topical therapy compared to topical therapy for adolescent AD[1]

Patient or population: Adolescents aged 12-17 with moderate to severe AD and an inadequate response to topical medication or a need for systemic therapy
Intervention: Once daily **a**brocitinib 100mg plus medicated topical therapy
Comparison: placebo plus medicated topical therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with topical therapy	**Risk with abrocitinib + topical therapy**				
CDLQI assessed with: least square mean change from baseline follow-up: 12 weeks CRITICAL	The mean change in CDLQI was **-6.3**	MD **2.3 lower** (3.7 lower to 0.8 lower)	-	191 (1 RCT)	⊕⊕⊕◯ Moderate[a]	Both groups experienced a potentially clinically meaningful increase in QoL at 12 weeks, but abrocitinib resulted in a greater increase.
Serious adverse events follow-up: 12 weeks CRITICAL	21 per 1,000	**4 per 1,000** (0 to 86)	**RR 0.20** (0.01 to 4.15)	191 (1 RCT)	⊕⊕⊕◯ Moderate[b]	Serious adverse events were rare in both arms and not considered treatment-related by investigators.
Withdrawal due to AE follow-up: 12 weeks CRITICAL	21 per 1,000	**11 per 1,000** (1 to 114)	**RR 0.51** (0.05 to 5.48)	191 (1 RCT)	⊕⊕⊕◯ Moderate[b]	Withdrawals due to AEs were rare in both arms.
Treatment-emergent AEs of interest follow-up: 12 weeks	Nausea: 1/96 (1.0%) vs 7/95 (7.4%) Acne: 1/96 (1.0%) vs 3/95 (3.2%) Headache: 7/96 (7.3%) vs 5/95 (5.3%) Herpes zoster: 0/96 (0%) vs 1/95 (1.1%) Herpes simplex: 0/96 (0%) vs 0/95 (0%) Oral herpes: 0/96 (0%) vs 1/95 (1.1%) Eczema herpeticum: 0/96 (0%) vs 1/95 (1.1%) Conjunctivitis: 1/96 (1.0%) vs 0/95 (0%)			(1 RCT)	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Downgraded once from imprecision: small sample.
b. Downgraded once from imprecision: small sample; CI consistent with a small benefit and small harm.

References:

1. Eichenfield LF, Flohr C, Sidbury R, Siegfried E, Szalai Z, Galus R et al. Efficacy and Safety of Abrocitinib in Combination With Topical Therapy in Adolescents With Moderate-to-Severe Atopic Dermatitis: The JADE TEEN Randomized Clinical Trial. JAMA Dermatol 2021;157:1165-73.

Table 39. Baricitinib 2mg

Baricitinib 2mg + TCS compared TCS for children & adolescents with AD[1]

Patient or population: Children aged 2-17 with moderate to severe AD and inadequate response to TCS in the past 6 months and inadequate response to or intolerance of TCNI or inadequate response to systemic treatments
Intervention: baricitinib 2mg equivalent plus low to moderate potency TCS
Comparison: placebo plus low to moderate potency TCS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low to moderate potency TCS	**Risk with baricitinib + TCS**				
vIGA-AD, 0-1 assessed with: proportion of patients with score of 0 or 1 follow-up: 16 weeks CRITICAL	164 per 1,000	**259 per 1,000** (156 to 426)	**RR 1.58** (0.95 to 2.60)	242 (1 RCT)[1]	⊕⊕⊕◯ Moderate[a]	Baricitinib + TCS may increase the proportion of patients achieving vIGA-AD 0/1 but the findings are imprecise.
EASI assessed with: mean change from baseline follow-up: 16 weeks CRITICAL	The mean change in EASI was **-14.16**	MD **1.67 lower** (1.92 lower to 1.42 lower)	-	242 (1 RCT)[1]	⊕⊕⊕◯ Moderate[b]	Baricitinib + TCS likely results in little to no difference in change in EASI.
POEM assessed with: mean score follow-up: 16 weeks CRITICAL	The mean POEM was **10.7**	MD **0.7 lower** (2.75 lower to 1.35 higher)	-	217 (1 RCT)[1]	⊕⊕⊕◯ Moderate[c]	Baricitinib likely results in little to no difference in POEM.
Itch assessed with: ≥ 4-point improvement follow-up: 16 weeks CRITICAL	164 per 1,000	**259 per 1,000** (124 to 537)	**RR 1.58** (0.76 to 3.28)	117 (1 RCT)[1]	⊕⊕⊕◯ Moderate[d]	Baricitinib may increase the proportion of patients with meaningful itch reduction but the findings are imprecise.
CDLQI assessed with: mean score follow-up: 16 weeks CRITICAL	The mean CDLQI was **5.4**	MD **3.3 lower** (4.64 lower to 1.96 lower)	-	209 (1 RCT)[1]	⊕⊕⊕◯ Moderate[b]	Baricitinib 2mg equivalent plus low to moderate potency TCS likely results in little to no difference in CDLQI.
Serious adverse events assessed with: participants experiencing an SAE follow-up: 16 weeks CRITICAL	41 per 1,000	**8 per 1,000** (1 to 70)	**RR 0.20** (0.02 to 1.71)	242 (1 RCT)[1]	⊕⊕⊕◯ Moderate[c]	Serious AEs were rare across both arms.
Withdrawal due to adverse events assessed with: participants discontinuing treatment due to AE follow-up: 16 weeks CRITICAL	16 per 1,000	**3 per 1,000** (0 to 69)	**RR 0.20** (0.01 to 4.19)	242 (1 RCT)[1]	⊕⊕⊕◯ Moderate[c]	Withdrawal due to AEs was rare across both arms.

Baricitinib 2mg + TCS compared TCS for children & adolescents with AD[1]

Patient or population: Children aged 2-17 with moderate to severe AD and inadequate response to TCS in the past 6 months and inadequate response to or intolerance of TCNI or inadequate response to systemic treatments
Intervention: baricitinib 2mg equivalent plus low to moderate potency TCS
Comparison: placebo plus low to moderate potency TCS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low to moderate potency TCS	**Risk with baricitinib + TCS**				
Treatment-emergent AEs of interest follow-up: 16 weeks	Abdominal pain: 3/122 (2.5%) vs 5/120 (4.2%) Acne: 5/122 (4.1%) s 4/120 (3.3%) Headache: 10/122 (8.2%) vs 11/120 (9.2%) Diarrhea: 2/122 (1.6%) 2/120 (1.7%) Nasopharyngitis: 6/122 (4.9%) vs 5/120 (4.2%) URTI: 1/122 (0.8) 4/120 (3.3%) Upper abdominal pain: 1/122 (0.8%) vs 2/120 (1.7%) Bronchitis: 1/122 (0.8%) vs 1/120 (0.8%) COVID-19: 4/122 (3.3%) vs 5/120 (4.2%) Decreased appetite: 0/122 (0%) vs 0/120 (0%) Gastroenteritis: 0/122 (0%) vs 2/120 (1.7%)			(1 RCT)[1]	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Downgraded once for imprecision: small sample size; CI consistent with a moderate benefit and trivial harm.
b. Downgraded once for imprecision: small sample size.
c. Downgraded once for imprecision: small sample size. CI consistent with a small benefit and small harm.
d. Downgraded once for imprecision: small sample size; CI consistent with a moderate benefit and small harm.

References:

1. Torrelo A, Rewerska B, Galimberti M, Paller A, Yang CY, Prakash A et al. Efficacy and safety of baricitinib in combination with topical corticosteroids in paediatric patients with moderate-to-severe atopic dermatitis with an inadequate response to topical corticosteroids: results from a phase III, randomized, double-blind, placebo-controlled study (BREEZE-AD PEDS). Br J Dermatol 2023;189:23-32.

Table 40. Baricitinib 4mg

Baricitinib 4mg + TCS compared to TCS for children & adolescents AD[1]

Patient or population: Children aged 2-17 with moderate to severe AD and inadequate response to TCS in the past 6 months and inadequate response to or intolerance of TCNI or inadequate response to systemic treatments
Intervention: baricitinib 4mg equivalent plus low to moderate potency TCS
Comparison: placebo plus low to moderate potency TCS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TCS	**Risk with baricitinib + TCS**				
vIGA-AD, 0-1 assessed with: proportion of patients with score of 0 or 1 follow-up: 16 weeks CRITICAL	164 per 1,000	**416 per 1,000** (266 to 656)	**RR 2.54** (1.62 to 4.00)	242 (1 RCT)[1]	⊕⊕⊕◯ Moderate[a]	Significantly more patients in the baricitinib group achieved vIGA-AD 0/1.
EASI assessed with: change from baseline follow-up: 16 weeks CRITICAL	The mean change in EASI was **-14.16**	MD **2.72 lower** (2.97 lower to 2.47 lower)	-	242 (1 RCT)[1]	⊕⊕⊕◯ Moderate[a]	Both groups had a clinically meaningful reduction in EASI but the reduction was slightly increased with baricitinib.
POEM assessed with: mean score follow-up: 16 weeks CRITICAL	The mean POEM was **10.7**	MD **0.8 lower** (2.75 lower to 1.15 higher)	-	219 (1 RCT)[1]	⊕⊕⊕◯ Moderate[b]	Baricitinib likely results in little to no difference in POEM at 16 weeks.
CDLQI assessed with: mean score follow-up: 16 weeks CRITICAL	The mean CDLQI was **5.4**	MD **0.3 lower** (1.68 lower to 1.08 higher)	-	211 (1 RCT)[1]	⊕⊕⊕◯ Moderate[b]	Baricitinib likely results in little to no difference in CDLQI at 16 weeks.
Itch assessed with: ≥ 4-point improvement from baseline follow-up: 16 weeks CRITICAL	164 per 1,000	**355 per 1,000** (178 to 704)	**RR 2.17** (1.09 to 4.30)	117 (1 RCT)[1]	⊕⊕⊕◯ Moderate[a]	Significantly more patients had a meaningful itch reduction with baricitinib.
Serious adverse events assessed with: patients with an AE follow-up: 16 weeks CRITICAL	41 per 1,000	**8 per 1,000** (1 to 70)	**RR 0.20** (0.02 to 1.71)	242 (1 RCT)[1]	⊕⊕⊕◯ Moderate[b]	Serious AEs were rare across both arms.
Withdrawal due to adverse events assessed with: patients discontinuing treatment due to AE follow-up: 16 weeks CRITICAL	16 per 1,000	**8 per 1,000** (1 to 91)	**RR 0.51** (0.05 to 5.53)	242 (1 RCT)[1]	⊕⊕⊕◯ Moderate[b]	Withdrawal due to AE was rare across both arms.

Baricitinib 4mg + TCS compared to TCS for children & adolescents AD[1]

Patient or population: Children aged 2-17 with moderate to severe AD and inadequate response to TCS in the past 6 months and inadequate response to or intolerance of TCNI or inadequate response to systemic treatments
Intervention: baricitinib 4mg equivalent plus low to moderate potency TCS
Comparison: placebo plus low to moderate potency TCS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TCS	Risk with baricitinib + TCS				
Treatment-emergent AEs of interest follow-up: 16 weeks	Abdominal pain: 3/122 (2.5%) vs 6/120 (5.0%) Acne: 5/122 (4.1%) vs 6/120 (5.0%) Headache: 10/122 (8.2%) vs 6/120 (5.0%) Diarrhea: 2/122 (1.6%) vs 5/120 (4.2%) Nasopharyngitis: 6/122 (4.9%) vs 5/120 (4.2%) URTI: 1/122 (0.8) vs 5/120 (4.2%) Upper abdominal pain: 1/122 (0.8%) vs 4/120 (3.3%) Bronchitis: 1/122 (0.8%) vs 3/120 (2.5%) COVID-19: 4/122 (3.3%) vs 3/120 (2.5%) Decreased appetite: 0/122 (0%) vs 3/120 (2.5%) Gastroenteritis: 0/122 (0%) vs 3/120 (2.5%)			(1 RCT)[1]	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Downgraded once for imprecision: small sample size.
b. Downgraded once for imprecision: small sample size. CI consistent with a small benefit and small harm.

References:

1. Torrelo A, Rewerska B, Galimberti M, Paller A, Yang CY, Prakash A et al. Efficacy and safety of baricitinib in combination with topical corticosteroids in paediatric patients with moderate-to-severe atopic dermatitis with an inadequate response to topical corticosteroids: results from a phase III, randomized, double-blind, placebo-controlled study (BREEZE-AD PEDS). Br J Dermatol 2023;189:23-32.

Table 41. Upadacitinib

Upadacitinib compared to placebo for adolescent AD

Patient or population: Adolescents aged 12-17 with moderate to severe AD who were candidates for systemic therapy (patients with a history of inadequate response to topical atopic dermatitis treatments, those who were using systemic treatment for atopic dermatitis, or those for whom topical treatments are otherwise medically inadvisable)
Intervention: Once daily upadacitinib 15mg
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo +/- TCS	Risk with upadacitinib				
EASI assessed with: LS mean change from baseline follow-up: 16 weeks CRITICAL		MD **12.33 lower** (14.76 lower to 9.91 lower)	-	177 (2 RCTs)[1]	⨁⨁⨁◯ Moderate[a,b]	Upadacitinib likely meaningfully reduces EASI. Katoh 2021: LSM % reduction in EASI from baseline was -23.9 with placebo vs -77.3 with upadacitinib.

Upadacitinib compared to placebo for adolescent AD

Patient or population: Adolescents aged 12-17 with moderate to severe AD who were candidates for systemic therapy (patients with a history of inadequate response to topical atopic dermatitis treatments, those who were using systemic treatment for atopic dermatitis, or those for whom topical treatments are otherwise medically inadvisable)
Intervention: Once daily upadacitinib 15mg
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo +/- TCS	Risk with upadacitinib				
NRS ≥ 4 assessed with: patients with ≥ 4-point improvement from baseline follow-up: 16 weeks CRITICAL	67 per 1,000	**280 per 1,000** (194 to 858)	**RR 4.17** (1.68 to 10.35)	236 (2 RCTs)[1]	⊕⊕⊕◯ Moderate[a,b]	Significantly more patients on upadacitinib had meaningful itch reduction.
POEM assessed with: LS mean change from baseline follow-up: 16 weeks CRITICAL		MD **6.47 lower** (8.53 lower to 4.41 lower)	-	171 (2 RCTs)[1]	⊕⊕⊕◯ Moderate[a,b]	Upadacitinib likely meaningfully reduces POEM.
DLQI (16-17 years old) assessed with: LS mean change from baseline follow-up: 16 weeks CRITICAL		MD **3.95 lower** (6.57 lower to 1.33 lower)	-	108 (3 RCTs)[1]	⊕⊕⊕◯ Moderate[a,b]	Upadacitinib probably reduces DLQI slightly.
CDLQI (12-15 years old) assessed with: LS mean change from baseline follow-up: 16 weeks CRITICAL		MD **4.51 lower** (6.3 lower to 2.72 lower)	-	101 (2 RCTs)[1]	⊕⊕⊕◯ Moderate[a,b]	Upadacitinib resulted in clinically meaningful reduction in CDLQI in both trials, while placebo did not.
Serious AE assessed with: participants with an SAE follow-up: 16 weeks CRITICAL	33 per 1,000	**25 per 1,000** (6 to 110)	**RR 0.76** (0.17 to 3.32)	243 (2 RCTs)[1]	⊕⊕⊕◯ Moderate[a,b]	The rate of SAEs was low in all study groups.
Withdrawal due to AE assessed with: patients discontinuing treatment due to AE follow-up: 16 weeks CRITICAL	17 per 1,000	**18 per 1,000** (3 to 117)	**RR 1.06** (0.16 to 7.10)	243 (2 RCTs)[1]	⊕⊕⊕◯ Moderate[a,b]	The rate of AEs leading to discontinuation was low and equitable across study arms.
Most common treatment-emergent AEs assessed with: patients with an AE follow-up: 16 weeks	The most common TEAEs in adolescents receiving upadacitinib were: Acne: 3/121 (2.5%) vs 14/122 (11.5%) Headache: 4/121 (3.3%) vs 8/122 (6.6%) URTI: 6/121 (5.0%) vs 11/122 (9.0%) Creatine phosphokinase level elevations:3 /121(2.5%) vs 8/122(6.6%) Nasopharyngitis: 3/121(2.5%) vs 5/122 (4.1%)			243 (2 RCTs)[2]	⊕⊕⊕◯ Moderate[b]	
Treatment-emergent AEs of interest assessed with: patients with an AE follow-up: 16 weeks	Serious infection: 1/121 (0.8%) vs 1/122 (0.8%) Herpes zoster: 0/121 (0%) vs 1/122 (0.8%) No opportunistic infections, active tuberculosis, malignant neoplasms (including nonmelanoma skin cancer), or any adjudicated MACEs, VTEs, or events of gastrointestinal perforation were reported in adolescents.			(3 RCTs)[2]	-	AEs of special interest were reported infrequently.

Upadacitinib compared to placebo for adolescent AD

Patient or population: Adolescents aged 12-17 with moderate to severe AD who were candidates for systemic therapy (patients with a history of inadequate response to topical atopic dermatitis treatments, those who were using systemic treatment for atopic dermatitis, or those for whom topical treatments are otherwise medically inadvisable)
Intervention: Once daily upadacitinib 15mg
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo +/- TCS	**Risk with upadacitinib**				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Two studies had a risk of selective reporting, but risk of bias was not downgraded.
b. Downgraded once for imprecision: small underpowered sample.

References:

1. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. Lancet 2021;397:2151-68.
2. Paller AS, Ladizinski B, Mendes-Bastos P, Siegfried E, Soong W, Prajapati VH et al. Efficacy and Safety of Upadacitinib Treatment in Adolescents With Moderate-to-Severe Atopic Dermatitis: Analysis of the Measure Up 1, Measure Up 2, and AD Up Randomized Clinical Trials. JAMA Dermatol 2023;159:526-35.

Table 42. Upadacitinib + TCS

Upadacitinib + TCS compared to placebo + TCS for adolescent AD

Patient or population: Adolescents aged 12-17 with moderate to severe AD
Intervention: Once daily upadacitinib 15mg plus TCS
Comparison: placebo plus TCS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo + TCS	**Risk with upadacitinib + TCS**				
EASI assessed with: LS mean change from baseline follow-up: 16 weeks CRITICAL	The mean change in EASI was **-15.2**	MD **8.3 lower** (11.68 lower to 4.92 lower)	-	103 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	Both arms experienced a clinically meaningful reduction in EASI with a greater reduction with the use of upadacitinib. **Katoh 2021**: LSM % reduction in EASI from baseline was -23.9 with placebo vs -77.3 with upadacitinib.

Upadacitinib + TCS compared to placebo + TCS for adolescent AD

Patient or population: Adolescents aged 12-17 with moderate to severe AD
Intervention: Once daily upadacitinib 15mg plus TCS
Comparison: placebo plus TCS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo + TCS	Risk with upadacitinib + TCS				
NRS ≥ 4 assessed with: patients with ≥ 4-point improvement from baseline follow-up: 16 weeks CRITICAL	213 per 1,000	**456 per 1,000** (260 to 797)	**RR 2.14** (1.22 to 3.74)	118 (1 RCT)[1]	⊕⊕⊕◯ Moderate[b]	Significantly more patients on upadacitinib had meaningful itch reduction.
POEM assessed with: LS mean change from baseline follow-up: 16 weeks CRITICAL	The mean change in POEM was **-5.8**	MD **5.6 lower** (8.01 lower to 3.19 lower)	-	100 (1 RCT)[1]	⊕⊕⊕◯ Moderate[a]	Both arms experienced a potentially meaningful reduction in POEM but the reduction was greater with upadacitinib.
DLQI (16-17 years old) assessed with: LS mean change from baseline follow-up: 16 weeks	The mean change in DLQI was **-6.3**	MD **2.6 lower** (5.61 lower to 0.41 higher)	-	35 (1 RCT)[1]	⊕⊕⊕◯ Moderate[a]	Upadacitinib probably reduces DLQI slightly.
CDLQI (12-15 years old) assessed with: LS mean change from baseline follow-up: 16 weeks	The mean change in CDLQI was **-5.0**	MD **4.3 lower** (6.48 lower to 2.12 lower)	-	65 (1 RCT)[1]	⊕⊕⊕◯ Moderate[b]	Upadacitinib resulted in a clinically meaningful reduction in CDLQI, while placebo did not.
Serious adverse events assessed with: participants with an SAE follow-up: 16 weeks CRITICAL	7 per 1,000	**11 per 1,000** (1 to 105)	**RR 1.61** (0.20 to 16.00)	303 (2 RCTs)[1, 2]	⊕⊕⊕◯ Moderate[b]	SAEs were rare and equitable across arms.
Withdrawal due to AE assessed with: patients discontinuing treatment due to AE follow-up: 16 weeks CRITICAL	One study reported 1 withdrawal in each arm (n=122) and another study reported no withdrawals (n=181).			303 (2 RCTs)[1, 2]	⊕⊕⊕◯ Moderate[b]	Withdrawals were rare and equitable across study groups.
Most common treatment-emergent AEs assessed with: patients with an AE follow-up: 16 weeks	The most common TEAEs in adolescents receiving upadacitinib were: Acne: 2/71 (2.8%) vs 11/70 (17%) Headache: 4/62 (6.5%) vs 5/60 (8.3%) URTI: 1/62(1.6%) vs 1/60 (1.7%) Creatine phosphokinase level elevations: 1/62 (1.6%) vs 1/60 (1.7%) Nasopharyngitis: 6/71 (8.5%) vs 7/70 (10.0%)			141 (2 RCTs)[2, 3]	-	
Treatment-emergent AEs of interest assessed with: patients with an AE follow-up: 16 weeks	Serious infections: 0/62 vs 0/60 Herpes zoster: 0/71 vs 0/70 No opportunistic infections, active tuberculosis, malignant neoplasms (including nonmelanoma skin cancer), or any adjudicated MACEs, VTEs, or events of gastrointestinal perforation were reported in adolescents.			141 (2 RCTs)[2, 3]	-	AEs of special interest were reported infrequently.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Downgraded once for imprecision due to underpowered sample and CI consistent with an unimportant and meaningful reduction.
b. Downgraded once for imprecision due to underpowered sample.

References:

1. Reich K, Teixeira HD, de Bruin-Weller M, Bieber T, Soong W, Kabashima K et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2021;397:2169-81.
2. Katoh N, Ohya Y, Murota H, Ikeda M, Hu X, Ikeda K et al. A phase 3 randomized, multicenter, double-blind study to evaluate the safety of upadacitinib in combination with topical corticosteroids in adolescent and adult patients with moderate-to-severe atopic dermatitis in Japan (Rising Up): An interim 24-week analysis. JAAD Int 2022;6:27-36.
3. Paller AS, Ladizinski B, Mendes-Bastos P, Siegfried E, Soong W, Prajapati VH et al. Efficacy and Safety of Upadacitinib Treatment in Adolescents With Moderate-to-Severe Atopic Dermatitis: Analysis of the Measure Up 1, Measure Up 2, and AD Up Randomized Clinical Trials. JAMA Dermatol 2023;159:526-35.

Table. Upadacitinib for pediatric AD- Uncontrolled Extension Data[1]

Treatment	Population (n)	Treatment Duration	Effectiveness	Safety
Upadacitinib 15 mg + TCS	19	112 weeks	Improvements in EASI, vIGA-AD, and NRS scores observed by 16 weeks of treatment were generally sustained through 112 weeks.	AEs of special interest were infrequent (< 3 cases). No new safety findings. Most common AEs at 112 weeks: Acne: 6/20.6 person years Nasopharyngitis: 4/24.5 person years Influenza: 2/27.0 person years URTI: 3/24.1 person years

References:

1. Katoh N, Ohya Y, Murota H, Ikeda M, Hu X, Ikeda K et al. Safety and Efficacy of Upadacitinib for Atopic Dermatitis in Japan: 2-Year Interim Results from the Phase 3 Rising Up Study. Dermatol Ther (Heidelb) 2023;13:221-34.

Table 43. Methotrexate

Methotrexate compared to low dose cyclosporin for children & adolescents with AD[1]

Patient or population: Children aged 8-14 years old with severe AD unresponsive to topical therapy and phototherapy (unresponsive or unfit)
Intervention: Methotrexate initial dose of 5mg then 7.5 mg weekly for 12 weeks
Comparison: Cyclosporine 2.5 mg/kg/day for 12 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Cyclosporin	**Risk with Methotrexate**				
SCORAD assessed with: change from baseline follow-up: 12 weeks CRITICAL	The mean change in SCORAD was **-25.01**	MD **1.24 lower** (5.98 lower to 3.5 higher)	-	40 (1 RCT)[1]	⊕⊕◯◯ Low[a,b]	Both treatments resulted in a clinically meaningful reduction in SCORAD. The reduction may be similar across treatments.
Relapse time assessed with: mean time to relapse ^ CRITICAL	Methotrexate showed a late relapse (average, 20 weeks), whereas cyclosporin showed a rapid relapse (average, 14 weeks). Relapse was considered for each patient when the SCORAD index increased by 50 % or more of the reduction after treatment.			40 (1 RCT)[1]	⊕⊕◯◯ Low[a,c]	Methotrexate may prolong time to relapse.
Serious adverse events assessed with: patients with an AE follow-up: 24 weeks CRITICAL	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	40 (1 RCT)[1]	⊕⊕◯◯ Low[a,d]	No SAEs were reported for either treatment.
Withdrawal due to adverse events assessed with: patients discontinuing treatment due to AE follow-up: 24 weeks CRITICAL	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	40 (1 RCT)[1]	⊕⊕◯◯ Low[a,d]	No withdrawals were reported for either treatment.
Treatment-emergent AEs of interest follow-up: 24 weeks	Nausea/vomiting: 2/20 (10%) vs 4/20 (20%) Abdominal pain: 0/20 (0%) vs 1/20 (5%) Anorexia: 1/20 (5%) vs 3/20 (15%) Glossitis/oral ulceration: 1/20 (5%) vs 4/20 (20%) Diarrhea: 3/20 (15%) vs 5/20 (25%) Pancytopenia: 3/20 (15%) vs 1/20 (5%) Anemia: 4/20 (20%) vs 6/20 (30%) Leukopenia: 7/20 (35%) vs 2/20 (10%) Thrombocytopenia: 2/20 (10%) vs 0/20 (0%) Elevated ESR: 2/20 (10%) vs 0/20 (0%) Abnormal liver function test: 2/20 (10%) vs 5/20 (25%) Abnormal renal function test: 3/20 (15%) vs 1/20 (5%) Fever: 3/20 (15%) vs 1/20 (5%) Fatigue: 9/20 (45%) vs 6/20 (30%) Headache: 5/20 (25%) vs 3/20 (15%) Hypertension: 1/20 (5%) vs 0/20 (0%) Flu-like symptoms: 4/20 (20%) vs 1/20 (5%)			40 (1 RCT)[1]	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference

Explanations
a. Downgraded once for risk of bias: limited methods reporting; open label study.
b. Downgraded once for imprecision: small sample; CI consistent with a small benefit and small harm.
c. Downgraded once for imprecision: small sample; failed to report the variances.
d. Downgraded once for imprecision: small sample; no events in both arms.

References:

1. El-Khalawany MA, Hassan H, Shaaban D, Ghonaim N , Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. Eur J Pediatr 2013;172:351-6.

Table 44. High Dose Cyclosporine vs Methotrexate

High dose cyclosporine compared to methotrexate for children & adolescents with AD[1]

Patient: Children aged 2-16 year old with severe recalcitrant AD and inadequate response to topical treatment
Intervention: Cyclosporine 4mg kg-1 qd for 36 weeks; At 12 weeks dose increases to 5mg kg-1 or decreases were permitted
Comparison: Methotrexate 0.1 mg kg_{-1} at week 0 and then 0.4 mg kg_{-1} weekly (maximum dose 25 mg PO weekly) until week 36

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with methotrexate	Risk with high dose cyclosporine				
EASI-50 (Short term) assessed with: participants with ≥50% improvement in EASI score from baseline follow-up: 12 weeks	529 per 1,000	**666 per 1,000** (509 to 794)	**OR 1.77** (0.92 to 3.42)	103 (1 RCT)	⨁⨁◯◯ Low[a]	High dose cyclosporine likely increases the number of participants achieving EASI-50 at 12 weeks.
EASI-50 (Long term) assessed with: participants with ≥50% improvement in EASI score from baseline follow-up: 36 weeks	870 per 1,000	**792 per 1,000** (659 to 881)	**OR 0.57** (0.29 to 1.11)	94 (1 RCT)	⨁⨁◯◯ Low[b]	High dose cyclosporine likely reduces the number of participants achieving EASI-50 at 36 weeks.
POEM (Short term) assessed with: Mean POEM scores follow-up: 12 weeks	mean POEM was **12.01**	MD **2.73 lower** (4.75 lower to 0.71 lower)	-	99 (1 RCT)	⨁⨁◯◯ Low[c]	High dose cyclosporine likely results in little to no clinically meaningful difference in POEM at 12 weeks.
POEM (Long term) assessed with: Mean POEM score follow-up: 36 weeks	mean POEM was **9.89**	MD **0.22 higher** (1.79 lower to 2.23 higher)	-	99 (1 RCT)	⨁⨁◯◯ Low[c]	High dose cyclosporine likely results in little to no clinically meaningful difference in POEM at 12 weeks.
Flare (Long term) assessed with: participants experiencing a flare follow-up: 36 weeks	368 per 1,000	**467 per 1,000** (266 to 679)	**OR 1.50** (0.62 to 3.62)	83 (1 RCT)	⨁⨁◯◯ Low[d]	High dose cyclosporine likely increases flare slightly.
CDLQI (Short term) assessed with: Mean CDLQI score follow-up: 12 weeks	mean CDLQI was **8.45**	MD **1.36 lower** (3.49 lower to 0.77 higher)	-	98 (1 RCT)	⨁⨁◯◯ Low[c]	High dose cyclosporine likely results in little to no difference in CDLQI 12 weeks.
CDLQI (Long term) assessed with: Mean CDLQI score follow-up: 36 weeks	mean CDLQI was **7.8**	MD **0.17 lower** (1.82 lower to 1.48 higher)	-	90 (1 RCT)	⨁⨁◯◯ Low[c]	High dose cyclosporine likely results in little to no difference in CDLQI at 36 weeks.

High dose cyclosporine compared to methotrexate for children & adolescents with AD[1]

Patient: Children aged 2-16 year old with severe recalcitrant AD and inadequate response to topical treatment
Intervention: Cyclosporine 4mg kg-1 qd for 36 weeks; At 12 weeks dose increases to 5mg kg-1 or decreases were permitted
Comparison: Methotrexate 0.1 mg kg_{-1} at week 0 and then 0.4 mg kg_{-1} weekly (maximum dose 25 mg PO weekly) until week 36

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with methotrexate	**Risk with high dose cyclosporine**				
Serious adverse events assessed with: participants experiencing a SAE follow-up: 60 weeks	137 per 1,000	**98 per 1,000** (31 to 269)	**OR 0.68** (0.20 to 2.31)	102 (1 RCT)	⨁⨁◯◯ Low[e]	2/5 SAEs reported in the CyA group were deemed possibly/probably treatment-related- bacterial lower respiratory tract infection of moderate severity, and eczema herpeticum of moderate severity, requiring hospital admission. 2/7 SAEs reported in the MTX group were deemed possibly/probably related to study treatment- herpes zoster shingles infection of mild severity and severe eczema herpetic.
Withdrawal due to AE assessed with: participants discontinuing treatment due to AE follow-up: 36 weeks	118 per 1,000	**82 per 1,000** (23 to 250)	**OR 0.67** (0.18 to 2.50)	102 (1 RCT)	⨁⨁◯◯ Low[e]	High dose cyclosporine may reduce withdrawal due to AE slightly.
Most common treatment-emergent AEs assessed with: rate of AEs follow-up: 36 weeks	The 5 most frequently reported AEs in the CyA group in descend ing order were AD flares (43%), headache (27%), abnormal (decrease of > 20% from baseline) estimated glomerular fil tration rate (GFR; 27.5%), upper abdominal pain (18%) and vomiting (18%). In the MTX group, the 5 most frequently reported AEs (in descending order) were nausea (43%), AD flares (29%), fatigue (23%), headache (22%) and vomiting (18%).			102 (1 RCT)	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations
a. Downgraded twice for imprecision due to wide CI consistent with no difference and large benefit due to very small sample.
b. Downgraded twice for imprecision due to wide CI consistent with no difference and moderate harm due to very small sample.
c. Downgraded twice for imprecision due to very small sample.
d. Downgraded twice for imprecision due to wide CI consistent with a small reduction and a large increase in odds due to very small sample.
e. Downgraded twice for imprecision due to wide CI consistent with important harm and benefit due to very small sample.

References:

1. Flohr C, Rosala-Hallas A, Jones AP, Beattie P, Baron S, Browne F et al. Efficacy and safety of ciclosporin versus methotrexate in the treatment of severe atopic dermatitis in children and young people (TREAT): a multicentre, parallel group, assessor-blinded clinical trial. Br J Dermatol 2023.

Table 45. Systemic corticosteroids

No direct evidence was identified for the use of systemic corticosteroids in management of children or adolescents with atopic dermatitis. The following indirect evidence is specific to adults with severe AD.

Adapted from: Siegels D, Heratizadeh A, Abraham S, Binnmyr J, Brockow K, Irvine AD, Halken S, Mortz CG, Flohr C, Schmid-Grendelmeier P, Van der Poel LA, Muraro A, Weidinger S, Werfel T, Schmitt J; European Academy of Allergy, Clinical Immunology Atopic Dermatitis Guideline group. Systemic treatments in the management of atopic dermatitis: A systematic review and meta-analysis. Allergy. 2021 Apr;76(4):1053-1076. doi: 10.1111/all.14631. Epub 2020 Nov 4. PMID: 33074565. *Search updated January 2024.*

Prednisolone compared to cyclosporine for adult AD[1]

Patient or population: Adults with severe AD
Intervention: Prednisolone initial dosage 0.5-0.8 mg/kg tapered to 0 over 2 weeks (adjunctive TCS and antihistamines allowed)
Comparison: Cyclosporine 2.7-4.0 mg/kg daily for 6 weeks (adjunctive TCS and antihistamines allowed)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with cyclosporine	**Risk with prednisolone**				
SCORAD assessed with: mean % change from baseline follow-up: 6 weeks CRITICAL	The mean % change in SCORAD was **-42.7%**	MD **11.8 lower** (27.98 lower to 4.38 higher)	-	20 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	Both treatments resulted in a clinically meaningful reduction in SCORAD at 6 weeks but the evidence is uncertain.
Flares assessed with: patients experiencing a relapse after initial response follow-up: 12 weeks CRITICAL	455 per 1,000	**891 per 1,000** (445 to 1,000)	**RR 1.96** (0.98 to 3.89)	20 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	Trial stopped early due to safety issues based on the high rate of relapse in the prednisolone group.
Serious adverse events assessed with: patients experiencing an SAE follow-up: 6 weeks CRITICAL	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 4.5** (0.2 to 100.0)	38 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	Serious adverse events were rare across the treatment arms.
Withdrawal assessed with: patients discontinuing treatment due to AE follow-up: 6 weeks CRITICAL	294 per 1,000	**547 per 1,000** (226 to 820)	**OR 2.9** (0.7 to 10.9)	38 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	Treatment discontinuation was common in both arms and numerically greater with prednisolone due to the high rate of relapse.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

Explanations
a. Downgraded once for risk of bias due to deviations from intended interventions (although ITT analysis was employed) and incomplete outcome reporting due to selection of reported outcomes
b. Downgraded once for indirectness as study population differs from the research question.
c. Downgraded once for imprecision as very small sample does not meet option information size.

References:

1. Schmitt J, Schäkel K, Fölster-Holst R, Bauer A, Oertel R, Augustin M et al. Prednisolone vs. ciclosporin for severe adult eczema. An investigator-initiated double-blind placebo-controlled multicentre trial. Br J Dermatol 2010;162:661-8.

Table 46. Mycophenolate mofetil

No direct evidence was identified for the use of mycophenolate mofetil in management of children or adolescents with atopic dermatitis.

Intervention	Evidence Summary	2014 Guideline Recommendations
Mycophenolate mofetil	No direct evidence matching inclusion criteria identified. *Limited clinical trial data:* A noninferiority trial compared enteric-coated mycophenolate sodium (EC-MPS) 1440mg/day (n=24) to cyclosporine A 3mg/kg/day (n=26) as maintenance therapy *after a 6-week run-in phase of CsA 5mg/kg/day* in adults with AD.[1] At 3 weeks after randomization to study treatments, increase in SCORAD was larger in the EC-MPS group with the mean difference between arms of 6.6 points (95%CI 1.5, 11.7). At 10 weeks, average SCORAD scores between the study arms were comparable: MD 0.8 (95%CI -4.4, 6.0) and SCORAD scores remained comparable at 33 weeks. No serious adverse events (requiring additional medication or discontinuation of study medication) were reported in either arm. The authors conclude EC-MPS is as effective as CsA for maintenance therapy. *Pooled individual patient data*: A systematic review and meta-analysis of individual patient data (primarily from low certainty case studies, and low certainty case series, cohort studies, and trials) reports that for patients with refractory AD (mean age 38.21±22.8) there was a clinical and statistically significant reduction in SCORAD scores following mycophenolate mofetil treatment: MD 18.01 (95%CI 8.54, 27.48, p=0.0002; n=37).[2] Across the 140 patients included in the review MMF was effective (complete or partial remission) in 77% with relapses occurring in 8.2%. The most common adverse effects reported across cases were headaches (10.7%), gastric discomfort (10.7%), herpes infection (9.3%), deranged liver function tests (7.9%), and other infections (6.4%).	Mycophenolate mofetil may be considered as an alternative, variably effective therapy for refractory AD. C III (Recommendation based on consensus, opinion, case studies, or disease-oriented evidence).

References:

1. Haeck IM, Knol MJ, Ten Berge O, van Velsen SG, de Bruin-Weller MS , Bruijnzeel-Koomen CA. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. J Am Acad Dermatol 2011;64:1074-84.
2. Phan K , Smith SD. Mycophenolate mofetil and atopic dermatitis: systematic review and meta-analysis. J Dermatolog Treat 2020;31:810-4.

Table 47. Azathioprine

All evidence on the use of azathioprine comes from mixed population studies including adolescents and adults.

Azathioprine compared to placebo for adolescents & adults with AD

Patient or population: Adolescents and adults aged ≥ 16 years with severe AD unresponsive to optimum topical therapy
Intervention: azathioprine dosed by thiopurine methyltransferase activity
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with azathioprine**				
SASSAD assessed with: mean change from baseline follow-up: 12 weeks CRITICAL	The mean SASSAD was **-6.6**	MD **5.4 lower** (9.3 lower to 1.4 lower)	-	61 (1 RCT)[1]	⊕◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of azathioprine on SASSAD.
Itch (patient reported) assessed with: mean change from baseline follow-up: 12 weeks CRITICAL	The mean itch (patient reported) was **-2.4**	MD **1.4 lower** (2.7 lower to 0.1 lower)	-	61 (1 RCT)[1]	⊕◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of azathioprine on itch (patient reported).
DLQI assessed with: mean change from baseline follow-up: 12 weeks CRITICAL	The mean DLQI was **-5.9**	MD **3.5 lower** (6.7 lower to 0.3 lower)	-	61 (1 RCT)[1]	⊕◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of azathioprine on DLQI.
Withdrawal due to AE assessed with: patients discontinuing treatment due to AE follow-up: 12 weeks CRITICAL	26 per 1,000	**101 per 1,000** (19 to 539)	**RR 3.85** (0.72 to 20.49)	98 (2 RCT)[1, 2]	⊕◯◯◯ Very low[a,b,d]	Withdrawals were numerically greater with azathioprine but the evidence is uncertain.
Treatment-emergent AEs of interest follow-up: 12 weeks	Nausea: 5/20 (25%) vs21/41 (51%) Headache: 3/20 (15%) vs 5/41 (21%) Abdominal pain: 2/20 (10%) vs 4/41 (10%) Lightheadedness: 1/20 (5%) vs 3/41 (7%) Malaise: 2/20 (10%) vs 1/41 (2%) Folliculitis: 2/20 (10%) vs 3/41 (7%) Lower respiratory tract infection: 0/20 (0%) vs 2/41 (5%) Upper respiratory tract infection: 1/20 (5%) vs 2/41 (5%)			61 (1 RCT)[1]	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Downgraded once for risk of bias: limited methods reporting (unclear allocation concealment and blinding of outcome assessors); unclear how missing data were handled; risk of selective reporting.
b. Downgraded once for indirectness: enrolled 16-65 years.
c. Downgraded once for imprecision: small sample size.
d. Downgraded once for imprecision: small sample size; CI consistent with a small benefit and large harm.

References:

1. Meggitt SJ, Gray JC , Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. Lancet 2006;367:839-46.
2. Berth-Jones J, Takwale A, Tan E, Barclay G, Agarwal S, Ahmed I et al. Azathioprine in severe adult atopic dermatitis: a double-blind, placebo-controlled, crossover trial. Br J Dermatol 2002;147:324-30.

Table 48. Cyclosporine

No direct evidence was identified to assess the management of AD in children or adolescents with cyclosporine. **See the methotrexate vs cyclosporine evidence above** and the indirect evidence below.

Table. Qualitative overview of systemic cyclosporine compared to other active treatments for AD

Comparison	Total n	Efficacy	Certainty of the evidence
CSA vs UVAB phototherapy[1]	72	*CSA superior to phototherapy*: Mean change in SCORAD at 8 weeks -54% vs -34%	Low
CSA vs Oral prednisolone[2]	38	CSA superior to oral prednisolone: Mean change in SCORAD at 6 weeks -55% vs -43%	Low
CSA vs Methotrexate[3]	97	CSA and methotrexate similarly effective: Mean change in SCORAD at 12 weeks -49% vs -28%; at 24 weeks -56% vs -48%	Low
CSA vs Extracorporeal photopheresis[4]	20	CSA and ECP were similarly effective: Mean change in SCORAD at 16 weeks -34% vs -46%	Low
CSA vs Tacrolimus ointment 0.1%[5]	30	CSA and topical tacrolimus were similarly effective^; Mean change in SCORAD at 6 weeks -88% vs -89%	Low

References:

1. Granlund H, Erkko P, Remitz A, Langeland T, Helsing P, Nuutinen M , Reitamo S. Comparison of cyclosporin and UVAB phototherapy for intermittent one-year treatment of atopic dermatitis. Acta dermato-venereologica 2001;81:22-7.
2. Schmitt J, Schäkel K, Fölster-Holst R, Bauer A, Oertel R, Augustin M et al. Prednisolone vs. ciclosporin for severe adult eczema. An investigator-initiated double-blind placebo-controlled multicentre trial. Br J Dermatol 2010;162:661-8.
3. Goujon C, Viguier M, Staumont-Salle D, Bernier C, Guillet G, Lahfa M et al. Methotrexate Versus Cyclosporine in Adults with Moderate-to-Severe Atopic Dermatitis: A Phase III Randomized Noninferiority Trial. J Allergy Clin Immunol Pract 2018;6:562-9 e3.
4. Koppelhus U, Poulsen J, Grunnet N, Deleuran MS , Obitz E. Cyclosporine and Extracorporeal Photopheresis are Equipotent in Treating Severe Atopic Dermatitis: A Randomized Cross-Over Study Comparing Two Efficient Treatment Modalities. Front Med (Lausanne) 2014;1:33.
5. Pacor ML, Di Lorenzo G, Martinelli N, Mansueto P, Rini GB , Corrocher R. Comparing tacrolimus ointment and oral cyclosporine in adult patients affected by atopic dermatitis: a randomized study. Clin Exp Allergy 2004;34:639-45.

Table 49. Interferon gamma

All evidence on the use of immunoglobulin comes from a mixed population study including children, adolescents, and adults.

Interferon gamma compared to placebo for children & adults with AD

Patient or population: Individuals aged 2-65 years with AD
Intervention: daily interferon gamma 50µg/m^2 injections for 12 weeks (TCS allowed)
Comparison: placebo (TCS allowed)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with interferon gamma**				
Physician global assessment assessed with: >50% improvement follow-up: 12 weeks CRITICAL	133 per 1,000	**667 per 1,000** (163 to 1,000)	**RR 5.00** (1.22 to 20.46)	21 (1 RCT)[1]	⨁⨁◯◯ Low[a,b]	Significantly more patients experienced PGA improvement with interferon gamma.
Itch (0-3 as none, mild, moderate, or severe) assessed with: , 50% improvement follow-up: 12 weeks	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 9.39** (0.61 to 144.15)	50 (1 RCT)[2]	⨁◯◯◯ Very low[b,c,d]	The evidence is very uncertain about the effect of interferon gamma on itch.
Flare assessed with: proportion of patients with flare follow-up: 12 weeks	23 per 1,000	**25 per 1,000** (2 to 387)	**RR 1.07** (0.07 to 16.62)	83 (1 RCT)[1]	⨁◯◯◯ Very low[a,e,f]	The evidence is very uncertain about the effect of interferon gamma on flare.
Withdrawal due to AE assessed with: patients discontinuing treatment due to AE follow-up: 12 weeks	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 3.22** (0.13 to 76.82)	83 (1 RCT)[1]	⨁◯◯◯ Very low[a,b,e]	Withdrawals were rare across both arms.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. Downgraded once for risk of bias: limited methods reporting (unclear allocation concealment and blinding); no intention to treat; risk of selective reporting.
b. Downgraded once for imprecision: small sample size.
c. Downgraded once for risk of bias: limited methods reporting (unclear random sequence generation, allocation concealment, and blinding of participants and outcome assessors); no information was provided as to how many patients dropped out.
d. Downgraded once for indirectness: enrolled >15 years.
e. Downgraded once for indirectness: enrolled 2-65 years.
f. Downgraded once for imprecision: small sample size; CI consistent with a small benefit and large harm

References:

1. Hanifin JM, Schneider LC, Leung DY, Ellis CN, Jaffe HS, Izu AE et al. Recombinant interferon gamma therapy for atopic dermatitis. J Am Acad Dermatol 1993;28:189-97.
2. Jang IG, Yang JK, Lee HJ, Yi JY, Kim HO, Kim CW , Kim TY. Clinical improvement and immunohistochemical findings in severe atopic dermatitis treated with interferon gamma. J Am Acad Dermatol 2000;42:1033-40.

Table 50. Immunoglobulin

All evidence on the use of immunoglobulin comes from a mixed population study including children, adolescents, and adults.

Immunoglobulin compared to placebo for children & adults AD[1]

Patient or population: Children > 2 years old with moderate to severe AD
Intervention: three injections of 2.0 g/kg IVIg at 1-month intervals over 3 months
Comparison: placebo + 1% hydrocortisone cream and oral antihistamines

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with immunoglobulin**				
SCORAD assessed with: mean score follow-up: 12 weeks CRITICAL	The mean SCORAD was **40.4**	MD **6.5 higher** (4.9 lower to 17.9 higher)	-	40 (1 RCT)[1]	⨁◯◯◯ Very low[a,b]	The evidence is very uncertain about the effect of immunoglobulin on SCORAD. Clinical improvement was seen within the IVIG group at 3 months but not 6 months but was higher than control at 3 months.
Serious adverse events assessed with: patients with an SAE follow-up: 6 months CRITICAL	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	40 (1 RCT)[1]	⨁◯◯◯ Very low[a,c]	No SAEs were reported in either arm.
Withdrawal due to adverse events assessed with: patients discontinuing treatment due to AE follow-up: 12 weeks CRITICAL	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 3.90** (0.23 to 64.97)	40 (1 RCT)[1]	⨁◯◯◯ Very low[a,b,]	5/30 children discontinued IVIg due to side effects including severe headache and nausea.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Downgraded twice for risk of bias: limited methods reporting (no information was provided as to how randomization/allocation concealment/blinding was performed); high dropout rate (12%); baseline imbalance in SCORAD (61.5 +- 13.3 vs. 42.1 +/- 9.9 in IVIg and placebo, respectively).
b. Downgraded once for imprecision: small sample.
c. Downgraded once for imprecision: small sample; no events in both arms.

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Table 51. Insufficient Evidence

Tumor necrosis factor-alpha inhibitors	No evidence for etanercept or infliximab for atopic dermatitis identified.
Systemic Calcineurin Inhibitors **(only systemic tacrolimus available in the US)**	No direct evidence matching inclusion criteria was identified for systemic tacrolimus to manage AD. *Indirect evidence:* An open-label pilot study of sequential therapy with oral tacrolimus and topical tacrolimus for severe AD in adults (n=12) reported clinically meaningful improvement in EASI score at 14 weeks (mean change 17.93) and improvement in average pruritis score (mean change 4.37). 5/12 patients had nausea and/or vomiting with oral tacrolimus and 4/12 had diarrhea.[1]

	A trial of oral pimecrolimus at 10, 20 and 30 mg bid compared to placebo for moderate-to-severe AD in adults found significant superiority of pimecrolimus at both weeks 7 and 13 to reduce EASI and found a dose response gradient among the pimecrolimus arms: Week 7 mean change -5.8, -8.4, -13.5 vs -5.0; Week 13 mean change -5.3, -7.3, -11.1 vs -4.8. At both week 7 and week 13, all the pimecrolimus-treated groups had a greater percentage of patients with pruritus scores ≤ 1, compared with the placebo-treated group (the difference was only significant for 20mg of pimecrolimus vs placebo at week 13). There were no differences between groups in overall incidence of AEs: total % of patients with AE 77%, 83%, 85% vs 92%.[2]
Systemic Antibiotics ***Noninfected AD***	No direct evidence matching inclusion criteria was identified. *Pediatric & mixed population data*: A crossover trial of cefuroxime axetil (dose not provided) and placebo bid for two weeks each with a one week washout in 20 patients (aged 6-58) with moderate-to-severe AD but no skin infection, reported "no difference were noted in the patients with respect to clinical severity" and no adverse events.[3] A trial of flucloxacillin 250 mg qid (n=25) for 4 weeks compared to placebo (n=25) in children with uninfected AD, reported a significantly lower rate of "good" or "excellent" global clinical outcomes in the flucloxacillin group (6/22 vs 17/24; RR 0.39, 95%CI 0.19, 0.8) and one withdrawal due to adverse event in each arm (RR 1 95%CI 0.07, 15.12).[4] The study also reported that the number of methicillin-resistant strains increased in the treatment group until 14 days after treatment. A trial of 74 AD patients (aged ≥12yo) with uninfected AD compared cefuroxime 500mg bid plus topical betamethasone dipropionate 0.05% bid for 2 weeks to betamethasone dipropionate alone.[5] Mean SCORAD reduction was clinically significant for both groups at weeks 1 and 2 and significantly greater in the oral antibiotic group: Week 1 -17.92 vs -10.05, p=0.003; Week 2 -28.0 vs -19.62, p<0.001. Adverse events were not discussed.
Infected AD	No direct evidence matching inclusion criteria was identified. *Pediatric & Mixed Population Data:* A trial of flucloxacillin 125mg-250mg qid for 7 days compared to placebo in 140 children with clinically infected AD reports no significant differences in mean change in EASI and POEM scores at two weeks: EASI MD 0.20 95%CI -0.12, 0.52; POEM MD 1.52 95%CI -1.35, 4.40.[6] No significant difference in change in POEM scores between groups was also reported at 3 months: MD -0.21 95%CI -3.12, 2.70. There were also no significant differences in change in QoL scores. There was one withdrawal due to worsening AD in each group and no difference in minor patient-reported adverse events between groups. A trial of cefadroxil 50mg/kg/day (n=16) for 2 weeks compared to placebo (n=17) in children with clinically infected AD (28/30 evaluable participants had infected AD) reports non-significant improvement in signs of AD in the antibiotic group compared to placebo: Global outcome of good or excellent 10/12 vs 9/17; RR 1.57 (95%CI 0.94, 2.63).[7] One withdrawal due to AE was reported in the antibiotic group. At 2 weeks, none of the participants in either the antibiotic or placebo group were found to have an antibiotic resistant organism. *Indirect Evidence:* A trial comparing two antibiotic agents (no control), mupirocin calcium cream tid (n=44) and cephalexin 250mg qid (n=38) for 10 days in patients (≥ 8yo) with secondarily infected AD found similar rates of clinical success (absence of exudate/pus, with or without complete resolution of other signs and symptoms of infection, a SIRS score of less than 8, and no use of additional antimicrobial): 89% vs 82%; p=0.29.[8] A non-significant difference in treatment-related adverse events was reported between the groups p=0.45.
TCS during oral antibiotic course in infected AD	A trial comparing two antibiotic agents (no control), retapamulin ointment 1% bid (n=363) for 5 days and cephalexin 500mg (n=183) bid for 10 days in patients (≥ 9months) with secondarily infected dermatitis (including AD, psoriasis, and allergic contact dermatitis) found similar rates of clinical success 7-9 days post-therapy (total resolution of all signs and symptoms of infection such that no additional antibiotic therapy was required): 85.9% vs 89.7%; difference -3.8 95%CI -9.9, 2.3.[8] Adverse events were reported by 22% of patients receiving retapamulin and 22% of patients taking cephalexin.

	No direct evidence matching inclusion criteria was identified. *Indirect evidence:* A trial comparing flucloxacillin and topical placebo (n=36), topical fusidic acid and oral placebo (n=37), and oral and topical placebos (control; n=40) for 1 week in children with non-severely infected AD reported at 2 weeks that neither oral or topical antibiotics produced a significant reduction in mean POEM scores compared to the placebo group : MD 1.5 (95%CI -1.4, 4.4) and 1.5 (95%CI -1.6, 4.5), respectively.[9] No serious adverse events were reported. A trial of 74 AD patients (aged ≥12yo) with uninfected AD compared cefuroxime 500mg bid plus topical betamethasone dipropionate 0.05% bid for 2 weeks to betamethasone dipropionate alone.[5] Mean SCORAD reduction was clinically significant for both groups at weeks 1 and 2 and significantly greater in the oral antibiotic group: Week 1 -17.92 vs -10.05, p=0.003; Week 2 -28.0 vs -19.62, p<0.001. Adverse events were not discussed.

Systemic antivirals for eczema herpeticum	No direct evidence matching inclusion criteria was identified. *Indirect evidence:* A systematic literature search identified one study that described participants as having "disseminated herpes simplex virus infections, such as eczema herpeticum"; 65% of the sample had AD.[10] For 32 patients randomized to 200mg acyclovir od for 5 days and 28 to placebo, treatment was "very effective" or "effective as assessed by investigators in 81.3% of the antiviral group compared to 42.9% if the placebo group ($p<0.01$). No adverse events were documented in the acyclovir group and 1 participant experienced an AE in the placebo group.

Oral antihistamines	No evidence for the use of oral H1 antihistamines as monotherapy for AD matching inclusion criteria was identified via updating the search conducted in support of a 2013 Cochrane review on the topic that also identified no trials (searches through 2012) that assessed the efficacy and safety of H1 antihistamines in adults or children with AD.[11] The majority of studies allow the use of concomitant therapies, so an assessment of the individual effects of oral H1 antihistamines on AD is not feasible.
Oral H1 antihistamines as monotherapy for AD	No evidence was identified for available FDA approved oral H4 antihistamines as monotherapy for AD in adults. *Investigational Data:* A trial compared an investigational oral H4 antihistamine 30mg qd (n=54 completed) for 8 weeks to placebo (n=24 completed) in adults with moderate-to-severe AD.[12] Concomitant therapy aside from emollients was not allowed but rescue therapy with topical steroids was permitted. Mean SCORAD scores were significantly reduced in the antihistamine group compared to placebo at weeks 4,6 and 8; MD at week 8 was 10.0 (p=0.004). Reduction in mean worst pruritus scores were not significantly different between the groups at week 8. The incidence of treatment-emergent adverse events was similar in both treatment groups: 66% in the antihistamine group and 64% in the placebo group.
Oral H4 antihistamines as monotherapy for AD	A trial compared two different doses of an investigational H4 antihistamine 100mg (n=27) or 300mg (n=27) to placebo (n=33) in adults with moderate AD.[13] No concomitant therapy was allowed but rescue therapy with topical steroid was permitted. The trial was stopped early by the sponsor, but 50 participants had evaluable 6-week data. Mean change in EASI score from baseline at 6 weeks was not significantly greater than placebo in either active arm (p=0.17 for 100 mg and 0.2 for 300 mg). Reduction in itch appeared to be dose-dependent with statistically significant reductions reported for the 300mg antihistamine group compared to placebo. Participants reporting adverse events were similar across the groups: 40.7%, 51.9%, and 54.5%, respectively. Two serious AEs were reported, both in the 300mg antihistamine group. A Cochrane systematic review of oral H1 antihistamines in combination with topical AD therapy concludes that based on low-to-moderate certainty evidence there is no consistent evidence that oral H1 antihistamine treatments are effective adjunctive therapy for AD when compared to placebo.[14] An update of the search identified no additional studies matching inclusion criteria. Key adult data from the review are presented below: One study assessed cetirizine 10 mg/d against placebo over four weeks in 84 adults. Results show no evidence of differences between groups in patient-assessed symptoms of eczema (pruritus measured as part of SCORAD; no numerical data given), numbers of adverse events (RR 1.11, 95% CI 0.50 to 2.45; mainly sedation, other skin-related problems, respiratory symptoms, or headache), or physician assessed changes in clinical signs, amount of local rescue therapy required, or number of applications as an indicator of eczema flares (nonnumerical data reported). Evidence for this comparison was of low quality. Compared with placebo, fexofenadine 120 mg/d taken in adults over one week (one study) probably leads to a small reduction in patient assessed symptoms of pruritus on a scale of 0 to 8 (mean difference (MD) -0.25, 95% CI -0.43 to -0.07; n = 400) and a greater reduction in the ratio of physician-assessed pruritus area to whole body surface area (P = 0.007; no further numerical data given); however, these reductions may not be clinically meaningful. Results suggest probably little or no difference in adverse events (mostly somnolence and headache) (RR 1.05, 95% CI 0.74 to 1.50; n = 411) nor in the amount of 0.1% hydrocortisone butyrate used (co-intervention in both groups) as an indicator of eczema flare, but no numerical data were given. Evidence for this comparison was of moderate quality.
Oral H1 antihistamines as add on therapy in AD	A study of 28 adults compared loratadine 10 mg/d taken over 4 weeks versus placebo. Researchers found no evidence of differences between groups in patient-assessed pruritus, measured by a 100-point visual analogue scale (MD -2.30, 95% CI -20.27 to 15.67); reduction in physician-assessed clinical signs (SCORAD) (MD -4.10, 95% CI -13.22 to 5.02); or adverse events. Study authors reported only one side effect (folliculitis with placebo) (RR 0.25, 95% CI 0.01 to 5.76). Evidence for this comparison was of low quality. Number of eczema flares was not measured for this comparison.

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Appendix 2. Systemic Interventions with Insufficient Evidence

Immunoglobulin

Evidence of the use of immunoglobulin comes from mixed population data including children, adolescents and adults. A single 40-patient study of patients greater than 2 years of age receiving three injections of 2.0 g/kg IVIG at 1-month intervals over 3 months found clinical improvement (on SCORAD) in the IVIG group at 3 months but not at 6 months.[1] Of note, 5/30 children discontinued IVIG due to side effects including severe headache and nausea.

Interferon Gamma

As was the case with immunoglobulin therapy above, evidence of the use of interferon gamma comes from mixed population data including children, adolescents and adults. Individuals aged 2-65 years with AD were treated with interferon gamma 50 $\mu g/m^2$ daily injections for 12 weeks – significantly more patients experienced physician global assessment improvement compared to placebo, but data on itch and flares was less clear.[2,3]

Systemic calcineurin inhibitors

No direct evidence matching inclusion criteria was identified for systemic tacrolimus to manage AD. An open-label pilot study of sequential therapy with oral tacrolimus and topical tacrolimus for severe AD in adults (n=12) reported clinically meaningful improvement in EASI score at 14 weeks (mean change 17.93) and improvement in average pruritus score (mean change 4.37). 5/12 patients had nausea and/or vomiting with oral tacrolimus and 4/12 had diarrhea.[4]

Systemic antibiotics

No direct evidence matching inclusion criteria was identified for systemic antibiotics in pediatric AD. For noninfected AD, the limited available data is mixed with two studies demonstrating no increased efficacy with oral antibiotics compared to placebo,[5,6] while one trial of 74 AD patients (aged 12 years and over) comparing cefuroxime 500 mg BID + topical betamethasone dipropionate 0.05% twice daily for 2 weeks to betamethasone dipropionate alone found significantly greater SCORAD reduction in the antibiotic group.[7]

Data for secondarily infected AD is also mixed. One study of 140 children receiving either flucloxacillin 125-250 mg four times per day for 7 days or placebo demonstrated no significant differences in mean change in EASI and POEM scores at two weeks;[8] a similar study with cefadroxil 50 mg/kg/day for 2 weeks reported non-significant improvement in signs of AD compared to placebo.[9] Two trials comparing two antibiotics (mupirocin calcium cream vs cephalexin 250 mg four times daily for 10 days, retapamulin 0.1% ointment for 5 days vs. cephalexin 500 mg twice daily for 10 days) but without placebo groups found clinical success in both groups.[10]

Systemic antivirals for eczema herpeticum

While no directive evidence was found for systemic antivirals for eczema herpeticum, a systematic literature search identified one study (indirect evidence) that described participants as having “disseminated herpes simplex virus infections, such as eczema herpeticum;” 65% of the sample had AD.[11] For 32 patients randomized to 200mg acyclovir four times a day for 5 days and 28 to placebo, treatment was “very effective” or “effective” as assessed by investigators in 81.3% of the antiviral group compared to 42.9% if the placebo group ($p < 0.01$). No adverse events were documented in the acyclovir group and 1 participant experienced an AE in the placebo group.

Oral antihistamines

H1 Antihistamines

No evidence for the use of oral H1 antihistamines as monotherapy for AD matching inclusion criteria was identified via updating the search conducted in support of a 2013 Cochrane review on the topic that also identified no trials (searches through 2012) that assessed the efficacy and safety of H1 antihistamines in adults or children with AD.[12] The majority of studies allow the use of concomitant therapies, so an assessment of the individual effects of oral H1 antihistamines on AD is not feasible.

A Cochrane systematic review of oral H1 antihistamines in combination with topical AD therapy concludes that based on low-to-moderate certainty evidence there is no consistent evidence that oral H1 antihistamine treatments are effective adjunctive therapy for AD when compared to placebo.[13] An update of the search identified no additional studies matching inclusion criteria. In adult studies, cetirizine and loratadine did not outperform placebo in eczema improvement or itch reduction. In one placebo-controlled study, fexofenadine 120 mg/d taken in adults over one week resulted in a small reduction in patient assessed symptoms of pruritus on a scale of 0 to 8 (MD -0.25, 95% CI -0.43 to -0.07; n = 400) and a greater reduction in the ratio of physician-assessed pruritus area to whole body surface area (P = 0.007); however, these reductions may not be clinically meaningful. Results suggest probably little or no difference in adverse events (mostly somnolence and headache) (RR 1.05, 95% CI 0.74 to 1.50; n = 411) nor in the amount of 0.1% hydrocortisone butyrate used (co-intervention in both groups) as an indicator of eczema flare.

H4 Antihistamines

No evidence was identified for available FDA approved oral H4 antihistamines as monotherapy for AD in adults. A trial compared an investigational oral H4 antihistamine 30mg daily (n = 54) for 8 weeks to placebo (n = 24) in adults with moderate-to-severe AD.[14] Concomitant therapy aside from emollients was not allowed but rescue therapy with topical steroids was permitted. Mean SCORAD scores were significantly reduced in the antihistamine group compared to placebo at weeks 4,6 and 8; MD at week 8 was 10.0 (p=0.004). Reduction in mean worst pruritus scores were not

significantly different between the groups at week 8. The incidence of treatment-emergent adverse events was similar in both treatment groups: 66% in the antihistamine group and 64% in the placebo group. Another trial of an investigational H4 antihistamine yielded less impressive results.[15]

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