American Academy of Dermatology Association

Online Supplement

Focused update: Guidelines of Care for the Management of Atopic Dermatitis in Adults

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e-Appendix 1. Recommendations for the Management of Atopic Dermatitis in Adults with Topical and Systemic Therapies

The newly added recommendations appear in **bold font**. For evidence supporting recommendations from the previously published guidelines refer to the original publications[1, 2] and their online data supplements. *AD*, atopic dermatitis; *FDA*, Food and Drug Administration; *PUVA*, psoralen plus ultraviolet A

Recommendation	Strength	Certainty of Evidence
Topical Therapies		
Non-prescription therapies		
For adults with AD, we recommend the use of moisturizers. *Remark: The use of a particular moisturizer or active ingredient in an emollient cannot be recommended based on the limited available evidence.*	Strong	Moderate
For adults with AD, we conditionally recommend bathing for treatment and maintenance. *Remark: A standard for the frequency or duration of bathing appropriate for those with AD cannot be suggested based on the limited available evidence.*	Conditional	Low
For adults with moderate-to-severe AD experiencing a flare, we conditionally recommend the use of wet dressings.	Conditional	Low
Topical calcineurin inhibitors		
For adults with AD, we recommend the use of tacrolimus 0.03% or 0.1%.	Strong	High
For adults with mild-to-moderate AD, we recommend the use of pimecrolimus 1% cream.	Strong	High
Topical corticosteroids		
For adults with AD, we recommend topical corticosteroids.	Strong	High
For adults with AD, we recommend intermittent use of medium potency topical corticosteroids as maintenance therapy (2 times/week) to reduce disease flares and relapse.	Strong	High
Topical antimicrobials/antiseptics and antihistamines		
We conditionally recommend against the use of topical antimicrobials for AD in adults.	Conditional	Low
We conditionally recommend against the use of topical antihistamines for AD in adults.	Conditional	Low
We conditionally recommend against the use of topical antiseptics for AD in adults. *Remark: For patients with moderate to severe AD and clinical signs of secondary bacterial infection, bleach baths or the use of topical sodium hypochlorite may be suggested to reduce disease severity.*	Conditional	Very Low
Topical PDE-4 inhibitors		
For adults with mild to moderate AD, we recommend the use of crisaborole.	Strong	High
For adults with mild to moderate AD, we recommend the use of roflumilast 0.15% cream.	Strong	High
Topical JAK inhibitor		
For adults with mild to moderate AD, we recommend the use of ruxolitinib cream.	Strong	Moderate
Topical aryl hydrocarbon receptor agonist		

For adults with moderate to severe AD, we recommend tapinarof cream.	Strong	High
Phototherapy & Systemic Therapies		
Phototherapy		
For adults with AD, we conditionally recommend phototherapy. Remarks: Most current literature reports the efficacy and safety of narrow band UVB. Wherever possible, use a light source that minimizes the potential for harm under the supervision of a qualified clinician.	Conditional	Low
Monoclonal antibodies (biologics)		
For adults with moderate to severe AD, we recommend dupilumab.	Strong	Moderate
For adults with moderate to severe AD, we recommend tralokinumab.	Strong	Moderate
For adults with moderate to severe AD, we recommend lebrikizumab.	Strong	High
For adults with moderate to severe atopic dermatitis, we recommend nemolizumab with concomitant topical therapy.	Strong	High
JAK inhibitors		
For adults with moderate to severe AD, we recommend upadacitinib. Remarks: Upadacitinib is approved by the FDA in patients with AD who have failed other systemic therapies (pills or injections, including biologics) or when use of those therapies is inadvisable.	Strong	Moderate
For adults with moderate to severe AD, we recommend abrocitinib. Remarks: Abrocitinib is approved by the FDA in patients with AD who have failed other systemic therapies (pills or injections, including biologics) or when use of those therapies is inadvisable.	Strong	Moderate
For adults with moderate to severe AD, we recommend baricitinib. Remark: Baricitinib is not approved by the FDA for use in AD.	Strong	Moderate
Antimetabolites		
For adults with moderate to severe AD, we conditionally recommend methotrexate with proper monitoring. Remarks: Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients. In the US, the FDA has not approved methotrexate for use in AD.	Conditional	Low
Immunosuppressants		
For adults with AD, we conditionally recommend against systemic corticosteroids. Remarks: Their use should be reserved exclusively for acute, severe exacerbations and as a short-term bridge therapy to other systemic, corticosteroid-sparing therapy.	Conditional	Low
For adults with refractory moderate to severe AD, we conditionally recommend mycophenolate mofetil with proper monitoring. Remarks: Mycophenolate mofetil^ is not approved by the FDA for use in AD. Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients.	Conditional	Very Low
For adults with refractory moderate to severe AD, we conditionally recommend TPMT-dosed azathioprine with proper monitoring. Remarks: Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients.	Conditional	Low
For adults with refractory moderate to severe AD, we conditionally recommend limited-term use of cyclosporine with proper monitoring.	Conditional	Low

Remarks: Evidence suggests an initial dose of 3mg/kg/d to 5mg/kg/d is effective. The FDA has not approved cyclosporine for use in AD^^. The FDA has approved limited-term use (up to one year) in psoriasis. Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients.		

AD: atopic dermatitis; FDA: Food and Drug Administration; PUVA: psoralen plus ultraviolet A
^Mycophenolic acid can be used interchangeably depending on availability. Note that dosing differs for mycophenolic acid and mycophenolate mofetil.
^^While not approved by the US FDA for use in AD, cyclosporine is indicated for atopic dermatitis in other jurisdictions such as the European Union.

1. Davis DMR, Drucker AM, Alikhan A, Bercovitch L, Cohen DE, Darr JM et al. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies. Journal of the American Academy of Dermatology 2024;90:e43-e56.
2. Sidbury R, Alikhan A, Bercovitch L, Cohen DE, Darr JM, Drucker AM et al. Guidelines of care for the management of atopic dermatitis in adults with topical therapies. Journal of the American Academy of Dermatology 2023;89:e1-e20.

e-Appendix 2: Focused Update Process

Processes for updating the AAD's clinical practice guidelines are established and continue to develop under the direction of the AAD's Clinical Guidelines Committee (CGC). The standard comprehensive guideline updating process considers AAD guideline publications to be current up to five years post-publication with full updates, including consideration of all clinical questions addressed within a guideline publication, to be completed in alignment with the five-year currency cycle. Recognizing the need for timely updates to clinical guidance when novel evidence that has the potential to inform the revision or development of clinical practice recommendations within the scope of existing, recently published (< 5 years) AAD guidelines becomes available, the CGC oversaw the development of a focused update process.

A focused update is undertaken outside of the standard, comprehensive 5-year guideline updating process as necessitated by the availability of new evidence or a change in the clinical landscape that is likely to impact a subset of recommendations within the scope of an existing, current AAD guideline.

Initiation of a focused update is based on the identification of peer-reviewed publications of new, high-quality evidence that is considered likely to impact current clinical practice recommendations or support the development of new recommendations. Identification of the new evidence may be prompted by approval of new treatments by the U.S. Food and Drug Administration that impact the management of a dermatologic condition addressed in a current AAD guideline or identification of potentially impactful practice-changing evidence by AAD staff, guideline workgroup members, or CGC members.

CGC approval and prioritization of a focused update dictates that new evidence be critically reviewed by a guideline workgroup but does not indicate that a recommendation will be changed, or a new recommendation developed. Recommendations within the source guideline for the focused update that are not being considered directly during the update remain current. Recommendations revised or added by a focused update are considered current for the standard 5-year currency period or until superseded by another update or full guideline revision.

Once a focused update is approved for development by the CGC, a guideline-focused update workgroup of four to eight members is appointed by the CGC to ensure efficiency in the updating process. Workgroup empanelment adheres to all requirements of the AAD/AAD Association Administrative Regulations for Evidence-Based Clinical Practice Guidelines (March 2021).[1] Focused updates are undertaken by a

multidisciplinary expert workgroup supported by an AAD guidelines staff member with health research methodology expertise.

The evidence synthesis and assessment process as well as the process employed to revise or draft recommendations for focused updates adhere to the standard methodology for the development of AAD guidelines. Specifically, a systematic review of the literature relevant to the focused update is conducted and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach is employed to assess the certainty of the evidence and formulate and grade clinical recommendations.

Focused updates are subject to the standard AAD guideline multilevel review and approval process which includes the opportunity for review and comment by the entire AAD membership and final review and comment by the AAD Board of Directors.

1. American Academy of Dermatology. Administrative regulation–evidence-based clinical practice guidelines. Accessed October 15 AahsaoFPUAA-.

e-Appendix 3: Detailed Methodology

Expert Work Group Composition and Disclosures of Interest

Work Group members were reviewed for potential disclosures of interest (DOIs) and approved by the AAD's Clinical Guidelines Committee (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 update. 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 voting on 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 the guideline update development process and used to ensure management terms were observed.

Formulation of Questions and Outcomes of Interest

This focused update considers new evidence addressing the following clinical questions from the previously published guidelines for the management of atopic dermatitis in adults with topical and systemic therapies: What are the efficacy and safety of topically applied therapies for AD?[1] and what are the efficacy and safety of systemic therapies for AD?[2] This guidance updates the clinical questions by introducing two new topical and two new systemic therapies and does not update evidence of the topical or systemic therapies considered in the previous guidelines.

This focused update used the outcomes of interest that were identified and ranked as critical or important for clinical decision-making regarding the management of AD during the development of the original AD guidelines (see original guideline publications for outcome details).

Literature Searches

The literature search strategies employed for the original AD guidelines were revised and updated specifically to the clinical questions informing the focused update. AAD guidelines' staff (L.F.G) performed a systematic search of the literature for the clinical questions using MEDLINE (via PubMed) and Cochrane Library. Databases were searched from inception to December 9th, 2024. A combination of the National Library of Medicine's medical subject headings and other keywords specific to the clinical questions were used to identify studies. Searches were limited to English-language randomized controlled trials. The literature searches identified reports on 16 unique trials.

Study Selection and Data Extraction

Studies retrieved by the literature searches were reviewed for relevance over two rounds of study selection. During the first round of study selection, title and abstract screening was performed against predefined inclusion and exclusion criteria established during the original AD guideline development process by AAD guidelines staff. The full text of studies appearing to meet inclusion criteria during the title and abstract screening were retrieved and then underwent a second round of study selection, during which a final inclusion decision was made. Full-text screening inclusion decisions were made independently by AAD guidelines' staff with subsequent quality control by Work Group members. Disagreements were resolved through discussion by the original pair of reviewers to reach a consensus.

A structured data table was used to extract relevant data from the included studies. Data extraction was initially performed by AAD guidelines' staff with subsequent quality control via review and discussion by other Work Group members. Discrepancies were resolved through discussion by the original data extractor and the reviewing Work Group members.

Risk of Bias Assessment and Evidence Synthesis

The risk of bias was assessed in all included studies using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials.[3] Following risk of bias assessment, for dichotomous outcomes, when data were homogenous and poolable, the relative risk (RR) and its 95% confidence interval were calculated according to Altman 1991.[4] Continuous outcomes were reported as mean differences and their 95% confidence intervals.

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 for each critical or important outcome.[5] The GRADEPro Guideline Development Tool was used to create an evidence profile 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 I**).

Table I. *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 profile and considering the following: the balance of desirable and undesirable consequences of an intervention, the overall certainty of the evidence, patient values and preferences, resource use, acceptability, and feasibility.[6] Per the GRADE approach, recommendations are either "strong" or "conditional".[7] The implications of each strength of recommendation are summarized in **Table II**. Recommendations were also graded according to the GRADE approach.[7]

Table II. *Strength of Recommendation Implications*

Strength	Implication

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

Manuscript Review and Currency Statement

This focused update has been developed following 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.[8] The guidance issued by this focused update will be considered current for 5 years from the date of publication unless reaffirmed, updated, or retired before that time.

1. Sidbury R, Alikhan A, Bercovitch L, Cohen DE, Darr JM, Drucker AM et al. Guidelines of care for the management of atopic dermatitis in adults with topical therapies. Journal of the American Academy of Dermatology 2023;89:e1-e20.
2. Davis DMR, Drucker AM, Alikhan A, Bercovitch L, Cohen DE, Darr JM et al. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies. Journal of the American Academy of Dermatology 2024;90:e43-e56.
3. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
4. Altman DG. Practical statistics for medical research. London: Chapman and Hall; 1991.
5. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401-6.
6. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66:719-25.
7. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66:726-35.
8. American Academy of Dermatology. Administrative regulation–evidence-based clinical practice guidelines. Accessed October 15 AahsaoFPUAA-.

e-Table 1. Tapinarof Cream GRADE Summary of Findings

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: tapinarof 1% cream daily for 8 to 12 weeks
Comparison: vehicle daily 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.
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.

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

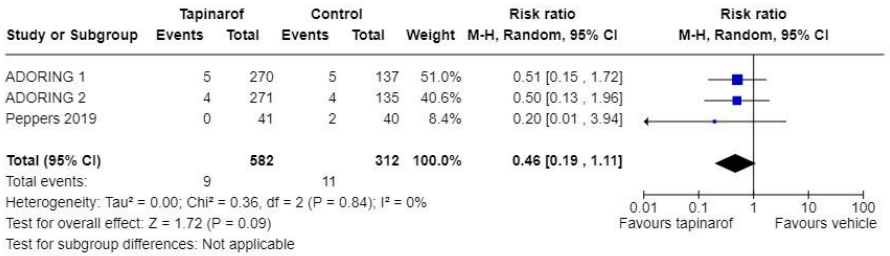
Patient or population: Children, adolescents, and adults aged 2+ years with moderate to severe atopic dermatitis
Intervention: tapinarof 1% cream daily for 8 to 12 weeks
Comparison: vehicle daily for 8 to 12 weeks

Outcome № of participants	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	Studies without poolable data	What happens
		vehicle	tapinarof	Difference			
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			

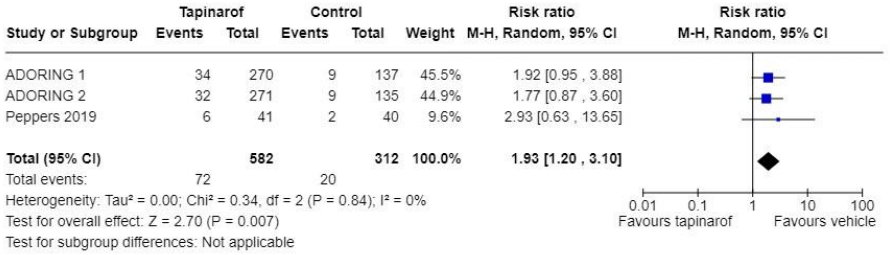
CI: confidence interval; **RR:** risk ratio

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.

Analysis. Withdrawal due to adverse event



Analysis. Treatment-related adverse events



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.

e-Table 2. Roflumilast Cream GRADE Summary of Findings

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 (54% of the INTEGUMENT study population is adults; 94.5% of the Gooderham study population is adults)
Intervention: roflumilast 0.15% cream daily for 28 days
Comparison: vehicle cream daily 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.
vIGA-AD 0 or 1 assessed with: patients achieving an IGA score of 0 or 1 follow-up: 4 weeks № of participants: 1427 (3 RCTs)[1-3] 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, 3] 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 clinically meaningful itch reduction.
Withdrawal due to adverse events assessed with: participants discontinuing treatment due to adverse event follow-up: 4 weeks № of participants: 1426 (3 RCTs)[2, 3] 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.

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

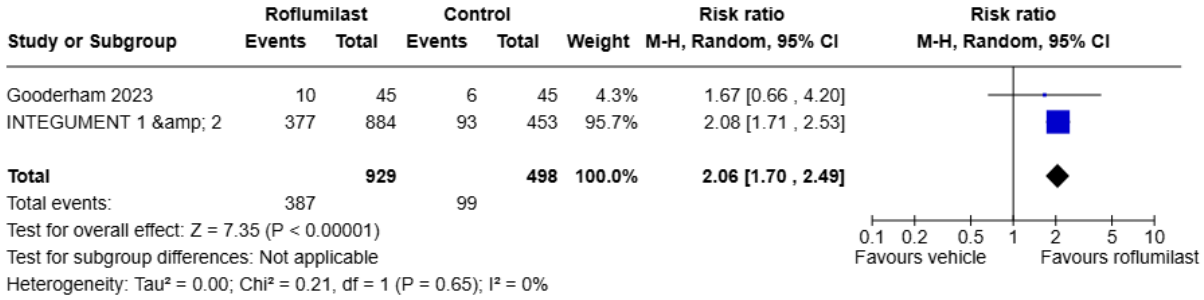
Patient or population: Children, adolescents, and adults with mild to moderate atopic dermatitis (54% of the INTEGUMENT study population is adults; 94.5% of the Gooderham study population is adults)
Intervention: roflumilast 0.15% cream daily for 28 days
Comparison: vehicle cream daily for 28 days

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		vehicle	**roflumilast 0.15%**	**Difference**		
Treatment-emergent adverse events of interest assessed with: adverse reactions reported in ≥1% of Subjects & reported more frequently with roflumilast in either trial follow-up: 4 weeks № of participants: (2 RCTs)[3]	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) Nasopharyngitis 8 (0.9) vs 3 (0.7) COVID-19 8 (0.9) vs 8 (1.8) Diarrhea 13 (1.5) vs 2 (0.4) Vomiting 13 (1.5) vs 2 (0.4) URTI 5 (0.6) 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.

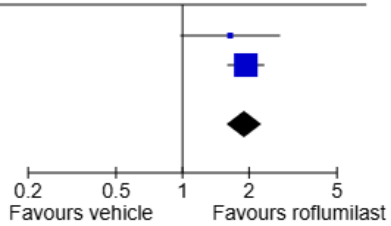
Analysis. EASI75



Analysis. vIGA-AD

Study or Subgroup	Roflumilast Events	Roflumilast Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95% CI
Gooderham 2023	23	45	14	45	12.1%	1.64 [0.98 , 2.76]
INTEGUMENT 1 & 2	366	884	97	453	87.9%	1.93 [1.59 , 2.35]
Total		**929**		**498**	**100.0%**	**1.90 [1.58 , 2.27]**
Total events:	389		111			

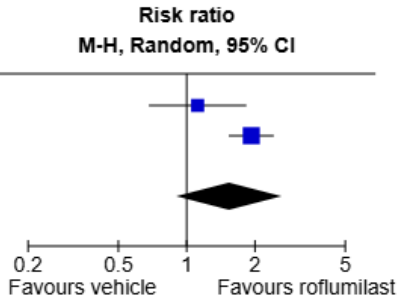
Test for overall effect: Z = 6.93 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.56); I² = 0%



Analysis. Itch

Study or Subgroup	Roflumilast Events	Roflumilast Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95% CI
Gooderham 2023	16	32	17	38	41.8%	1.12 [0.68 , 1.83]
INTEGUMENT 1 & 2	282	884	75	453	58.2%	1.93 [1.53 , 2.42]
Total		**916**		**491**	**100.0%**	**1.53 [0.90 , 2.62]**
Total events:	298		92			

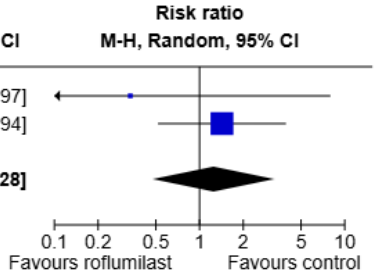
Test for overall effect: Z = 1.57 (P = 0.12)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.11; Chi² = 3.96, df = 1 (P = 0.05); I² = 75%



Analysis. Discontinuation

Study or Subgroup	Roflumilast Events	Roflumilast Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95% CI
Gooderham 2023	0	45	1	45	9.3%	0.33 [0.01 , 7.97]
INTEGUMENT 1 & 2	14	885	5	451	90.7%	1.43 [0.52 , 3.94]
Total		**930**		**496**	**100.0%**	**1.25 [0.47 , 3.28]**
Total events:	14		6			

Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%



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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.
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e-Table 3. Lebrikizumab Monotherapy GRADE Summary of Findings

Lebrikizumab monotherapy compared to placebo for adolescents & adults with AD

Patient or population: Adolescents and adults aged 12+ with moderate to severe AD
Intervention: lebrikizumab 500mg loading dose, then 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				
IGA 0 or 1 with ≥2-point improvement from baseline follow-up: 16 weeks CRITICAL	139 per 1,000	**386 per 1,000** (293 to 509)	**RR 2.77** (2.10 to 3.65)	1098 (3 RCTs)[1, 2]	⊕⊕⊕⊕ High	Lebrikizumab increases the number of patients achieving IGA 0 or 1 with ≥2-point improvement from baseline.
EASI75 follow-up: 16 weeks CRITICAL	210 per 1,000	**570 per 1,000** (389 to 835)	**RR 2.71** (1.85 to 3.97)	1225 (4 RCTs)[1-3]	⊕⊕⊕⊕ High	Lebrikizumab increases the number of patients achieving EASI75.
Pruritus improvement assessed with: NRS ≥4-point improvement in patients with NRS ≥4 at baseline follow-up: 16 weeks CRITICAL	179 per 1,000	**472 per 1,000** (285 to 779)	**RR 2.63** (1.59 to 4.34)	1040 (4 RCTs)[1-3]	⊕⊕⊕⊕ High	Lebrikizumab increases the number of patients achieving meaningful pruritus improvement.
POEM assessed with: mean change from baseline in POEM total score follow-up: 16 weeks CRITICAL	-	MD **5.7 lower** (7.68 lower to 3.71 lower)	-	852 (4 RCTs)[1-3]	⊕⊕⊕⊕ High	Lebrikizumab meaningfully reduces POEM scores compared to placebo.
Quality of life assessed with: DLQI mean change from baseline follow-up: 16 weeks CRITICAL	-	MD **4.79 lower** (6.62 lower to 2.97 lower)	-	779 (3 RCTs)[1, 3]	⊕⊕⊕◯ Moderate[a]	Lebrikizumab likely improves quality of life slightly.
Serious adverse events assessed with: patients experiencing an SAE follow-up: 16 weeks CRITICAL	17 per 1,000	**13 per 1,000** (4 to 37)	**RR 0.73** (0.25 to 2.10)	1223 (4 RCTs)[1-3]	⊕⊕⊕⊕ High[b]	Lebrikizumab results in little to no difference in serious adverse events.
Discontinuation due to AE assessed with: patients discontinuing treatment follow-up: 16 weeks CRITICAL	24 per 1,000	**25 per 1,000** (11 to 54)	**RR 1.04** (0.48 to 2.27)	1223 (4 RCTs)[1-3]	⊕⊕⊕⊕ High[c]	Lebrikizumab results in little to no difference in discontinuation due to AE.

Lebrikizumab monotherapy compared to placebo for adolescents & adults with AD

Patient or population: Adolescents and adults aged 12+ with moderate to severe AD
Intervention: lebrikizumab 500mg loading dose, then 250 mg every 2 weeks for 16 weeks
Comparison: placebo

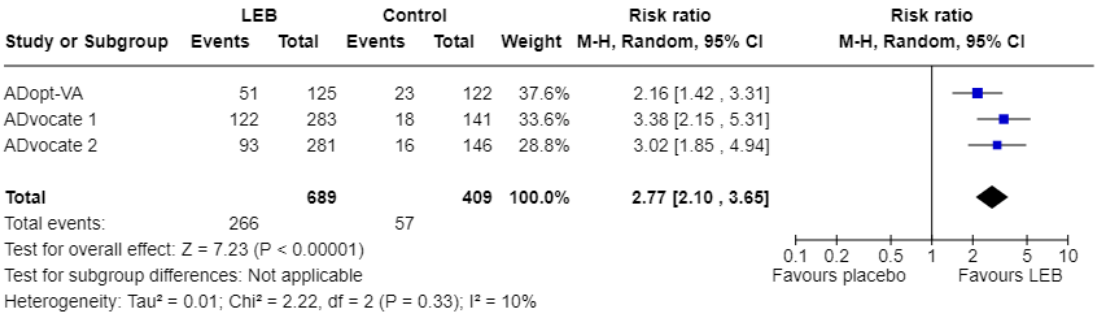
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with lebrikizumab**				
Treatment-emergent adverse events of interest follow-up: 52 weeks INFORMATIVE	The most common TEAEs across both studies throughout the entire 52-week treatment period in patients receiving at least one dose of LEB (n=806): AD (8.9%), conjunctivitis (8.2%), nasopharyngitis (8.2%) and allergic conjunctivitis (6.0%). The frequency of injection site reactions was low (2.4%), and no cases of anaphylaxis were reported. A small proportion of patients reported a TEAE of eosinophilia (1.5%); no eosinophil-related disorders were reported. The frequency of herpesvirus infection was 5.0%. A blinded medical review of potential opportunistic infections was completed and none were assessed to be opportunistic, based on the Winthrop criteria. No parasitic infections were reported. No clinically significant trends were observed in laboratory tests or vital signs.			806 (2 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; **MD:** mean difference; **RR:** risk ratio

Explanations

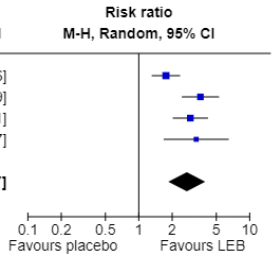
a. CI is consistent with a meaningful benefit and trivial difference.
b. Not downgraded for imprecision as the overall event rates are low and the rates in the intervention arm are comparable to placebo suggesting confidence in the safety of the intervention and confidence in the low rates of serious AE.
c. Not downgraded for imprecision as the overall event rates are low and the rates in the intervention arm are comparable to placebo suggesting confidence in the safety of the intervention and confidence in the low rates of discontinuation given the overall incidence of AEs.

Analysis. IGA 0/1



Analysis. EASI75

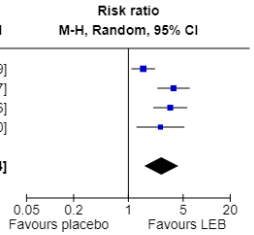
Study or Subgroup	LEB Events	LEB Total	placebo Events	placebo Total	Weight	Risk ratio M-H, Random, 95% CI
ADopt-VA	72	125	40	122	29.6%	1.76 [1.31 , 2.36]
ADvocate 1	166	283	23	141	26.3%	3.60 [2.44 , 5.29]
ADvocate 2	146	281	26	146	27.1%	2.92 [2.02 , 4.21]
Guttman-Yassky 2020	38	75	8	52	17.0%	3.29 [1.68 , 6.47]
Total		**764**		**461**	**100.0%**	**2.71 [1.85 , 3.97]**
Total events:	422		97			



Test for overall effect: Z = 5.10 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.11; Chi² = 10.88, df = 3 (P = 0.01); I² = 72%

Analysis. Pruritus improvement

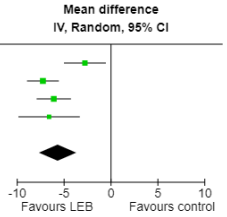
Study or Subgroup	LEB Events	LEB Total	placebo Events	placebo Total	Weight	Risk ratio M-H, Random, 95% CI
ADopt-VA	49	95	31	93	28.9%	1.55 [1.09 , 2.19]
ADvocate 1	122	263	16	130	25.8%	3.77 [2.34 , 6.07]
ADvocate 2	97	253	15	134	25.1%	3.43 [2.07 , 5.66]
Guttman-Yassky 2020	35	50	6	22	20.2%	2.57 [1.27 , 5.20]
Total		**661**		**379**	**100.0%**	**2.63 [1.59 , 4.34]**
Total events:	303		68			



Test for overall effect: Z = 3.78 (P = 0.0002)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.19; Chi² = 12.63, df = 3 (P = 0.006); I² = 76%

Analysis. POEM

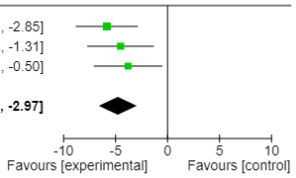
Study or Subgroup	LEB Mean	LEB SD	LEB Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, Random, 95% CI
ADopt-VA	-9.4	8.720665	125	-6.62	9.16765	122	25.0%	-2.78 [-5.01 , -0.55]
ADvocate 1	-11.28	6.767708	203	-4.02	6.049052	70	28.8%	-7.26 [-8.96 , -5.56]
ADvocate 2	-9.55	7.121446	184	-3.45	6.232125	65	27.9%	-6.10 [-7.93 , -4.27]
Guttman-Yassky 2020	-12.4	6.9	59	-5.8	6.9	24	18.3%	-6.60 [-9.87 , -3.33]
Total			**571**			**281**	**100.0%**	**-5.70 [-7.68 , -3.71]**



Test for overall effect: Z = 5.62 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 2.82; Chi² = 10.19, df = 3 (P = 0.02); I² = 71%

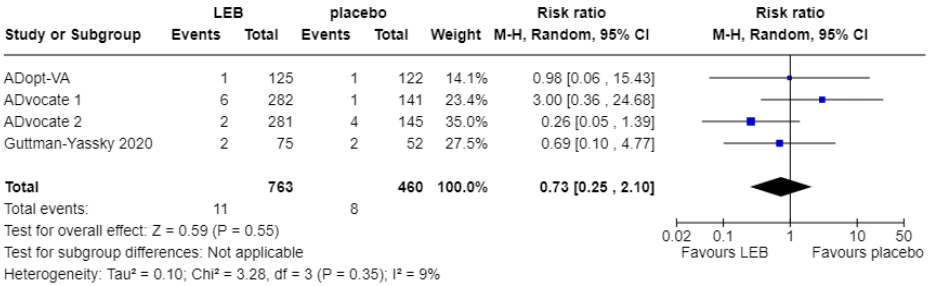
Analysis. Quality of life

Study or Subgroup	LEB Mean	LEB SD	LEB Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, Random, 95% CI
ADvocate 1	-8.78	16.325364	239	-2.94	12.133	121	37.2%	-5.84 [-8.83 , -2.85]
ADvocate 2	-6.99	17.009076	218	-2.47	12.644276	118	32.3%	-4.52 [-7.73 , -1.31]
Guttman-Yassky 2020	-9.7	7.1	59	-5.9	6.9	24	30.5%	-3.80 [-7.10 , -0.50]
Total			**516**			**263**	**100.0%**	**-4.79 [-6.62 , -2.97]**

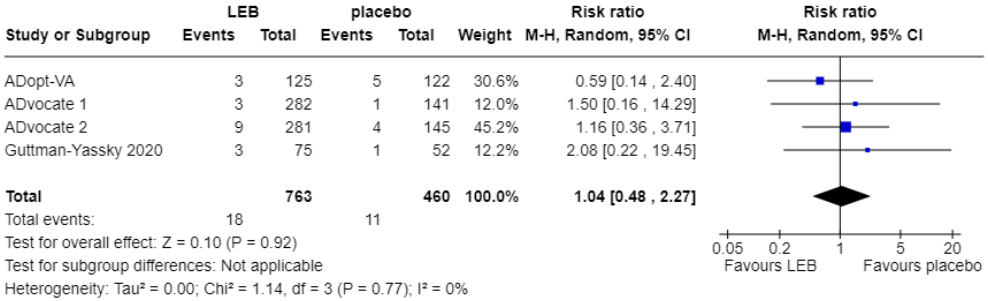


Test for overall effect: Z = 5.15 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 2 (P = 0.66); I² = 0%

Analysis. Serious adverse events



Analysis. Discontinuation due to adverse events



1. Silverberg JI, Guttman-Yassky E, Thaçi D, Irvine AD, Stein Gold L, Blauvelt A et al. Two Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis. N Engl J Med 2023;388:1080-91.
2. Soung J, Laquer V, Merola JF, Moore A, Elmaraghy H, Hu C et al. The Impact of Lebrikizumab on Vaccine-Induced Immune Responses: Results from a Phase 3 Study in Adult Patients with Moderate-to-Severe Atopic Dermatitis. Dermatol Ther (Heidelb) 2024;14:2181-93.
3. Guttman-Yassky E, Blauvelt A, Eichenfield LF, Paller AS, Armstrong AW, Drew J et al. Efficacy and Safety of Lebrikizumab, a High-Affinity Interleukin 13 Inhibitor, in Adults With Moderate to Severe Atopic Dermatitis: A Phase 2b Randomized Clinical Trial. JAMA Dermatol 2020;156:411-20.
4. Blauvelt A, Thyssen JP, Guttman-Yassky E, Bieber T, Serra-Baldrich E, Simpson E et al. Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: 52-week results of two randomized double-blinded placebo-controlled phase III trials. Br J Dermatol 2023;188:740-8.

e-Table 4. Lebrikizumab Combination Therapy Summary of Findings

Lebrikizumab + TCS compared to Placebo + TCS for **adolescents & adults** with AD

Patient or population: Adolescents and adults aged 12+ with moderate to severe AD
Intervention: lebrikizumab 500mg LD 250 mg every 2 weeks + TCS for 16 weeks
Comparison: placebo + TCS

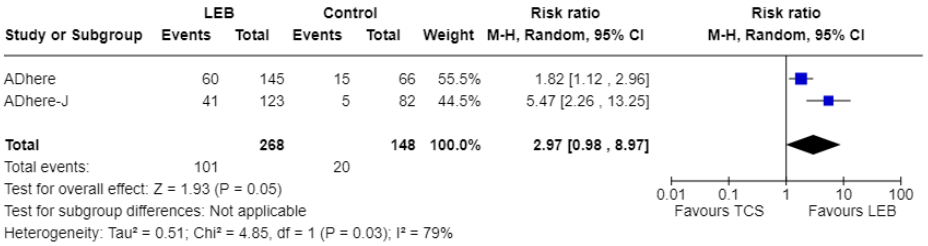
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo + TCS	**Risk with LEB + TCS**				
IGA 0 or 1 with ≥2-point improvement from baseline follow-up: 16 weeks CRITICAL	135 per 1,000	**401 per 1,000** (132 to 1,000)	**RR 2.97** (0.98 to 8.97)	416 (2 RCTs)[1, 2]	⊕⊕⊕◯ Moderate[a]	LEB likely results in a large increase in the number of patients achieving IGA 0 or 1 with ≥2-point improvement from baseline.
EASI75 follow-up: 16 weeks CRITICAL	264 per 1,000	**638 per 1,000** (269 to 1,000)	**RR 2.42** (1.02 to 5.75)	416 (2 RCTs)[1, 2]	⊕⊕⊕◯ Moderate[a]	LEB likely results in a large increase in the number of patients achieving EASI75.
Pruritus improvement assessed with: NRS ≥4-point improvement in patients with NRS ≥4 at baseline follow-up: 16 weeks CRITICAL	183 per 1,000	**643 per 1,000** (95 to 1,000)	**RR 3.52** (0.52 to 23.74)	351 (2 RCTs)[1, 2]	⊕⊕◯◯ Low[b]	LEB may result in a large increase in the number of patients achieving meaningful pruritus improvement.
POEM assessed with: Ls mean change from baseline follow-up: 16 weeks CRITICAL	The mean POEM was **0**	MD **3.99 lower** (6.47 lower to 1.51 lower)	-	141 (1 RCT)[1]	⊕⊕⊕◯ Moderate[c]	LEB likely reduces POEM.
Quality of life assessed with: Ls mean difference in DLQI from baseline follow-up: 16 weeks CRITICAL	The mean quality of life was **0**	MD **3.33 lower** (8.42 lower to 1.76 higher)	-	160 (1 RCT)[1]	⊕⊕⊕◯ Moderate[c]	LEB likely improves quality of life slightly.
Serious adverse events assessed with: patients experiencing SAEs follow-up: range 16 weeks to 28 weeks CRITICAL	13 per 1,000	**13 per 1,000** (2 to 84)	**RR 0.97** (0.15 to 6.48)	254 (2 RCTs)[1, 2]	⊕⊕⊕◯ Moderate[d]	LEB likely results in little to no difference in serious adverse events.
Discontinuation due to adverse event assessed with: patients discontinuing treatment follow-up: 16 weeks CRITICAL	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 3.21** (0.17 to 61.32)	211 (1 RCT)[1]	⊕⊕⊕◯ Moderate[d]	LEB likely results in little to no difference in discontinuation due to 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

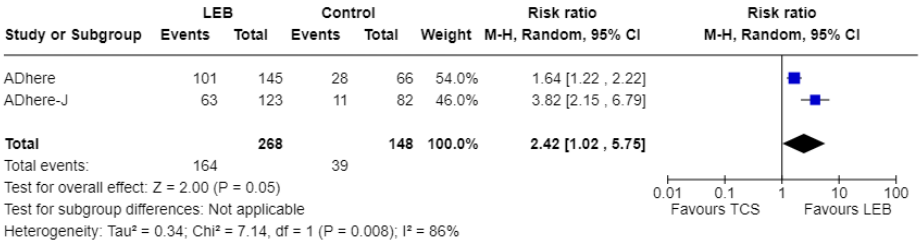
Explanations

a. Very wide CI consistent with trivial difference and large magnitude of benefit.
b. Very wide CI consistent with small harm and very large benefit.
c. CI consistent with meaningful benefit and trivial difference.
d. Overall sample is small

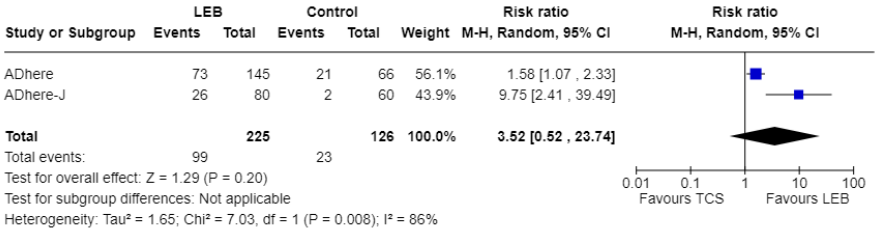
Analysis. IGA 0/1



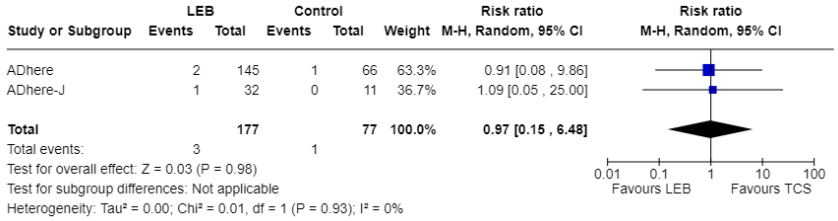
Analysis. EASI75



Analysis. Pruritus improvement



Analysis. Serious adverse events



1. 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.
2. Tanaka A, Igawa K, Takahashi H, Shimizu R, Kataoka Y, Torisu-Itakura H et al. Lebrikizumab Combined with Topical Corticosteroids Improves Patient-reported Outcomes in Japanese Patients with Moderate-to-severe Atopic Dermatitis. Acta Derm Venereol 2024;104:adv34375.

e-Table 5. Nemolizumab GRADE Summary of Findings

Nemolizumab + TCS/TCI compared to placebo +TCS/TCI for adolescents & adults with AD

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis
Intervention: nemolizumab 30mg every 4 weeks + TCS and/or TCI for 16 weeks to 24 weeks
Comparison: placebo +TCS/TCI

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: range 16 weeks to 24 weeks CRITICAL	168 per 1,000	**396 per 1,000** (329 to 477)	**RR 2.36** (1.96 to 2.84)	1842 (3 RCTs)[1, 2]	⊕⊕⊕⊕ 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: range 16 weeks to 24 weeks CRITICAL	292 per 1,000	**430 per 1,000** (374 to 494)	**RR 1.47** (1.28 to 1.69)	1842 (3 RCTs)[1, 2]	⊕⊕⊕⊕ High	Nemolizumab + TCS/TCI results in large increase in the number of patients achieving EASI75.
Quality of life assessed with: Change in DLQI score from baseline follow-up: range 16 weeks to 24 weeks CRITICAL	**Percentage change in DLQI from baseline:** -10.5% vs -8.6% (no measure of variance reported; n=114) **Mean change in DLQI score from baseline:** MD -2.45 (-3.25, -1.66); n=1487.			1856 (3 RCTs)[1, 2]	⊕⊕⊕⊕ High	Nemolizumab + TCS/TCI increases quality of life slightly.
IGA assessed with: IGA of 0 or 1 follow-up: range 16 weeks to 24 weeks CRITICAL	249 per 1,000	**366 per 1,000** (314 to 426)	**RR 1.47** (1.26 to 1.71)	1842 (3 RCTs)[1, 2]	⊕⊕⊕⊕ High	Nemolizumab + TCS/TCI increases the number of patients achieving meaningful IGA improvement.
POEM assessed with: Lsmean POEM change from baseline follow-up: 16 weeks CRITICAL	-	**MD 3.95 lower** (4.73 lower to 3.18 lower)		1702 (2 RCTs)[2]	⊕⊕⊕⊕ High	Nemolizumab + TCS/TCI meaningfully reduces POEM scores.
Serious adverse events assessed with: patients experiencing an SAE follow-up: range 16 weeks to 24 weeks CRITICAL	13 per 1,000	**17 per 1,000** (8 to 40)	**RR 1.38** (0.60 to 3.17)	1832 (3 RCTs)[1, 2]	⊕⊕⊕⊕ High[a]	Nemolizumab + TCS/TCI results in little to no difference in serious adverse events.
Discontinuation due to adverse event assessed with: patients discontinuing treatment due to AE follow-up: range 16 weeks to 24 weeks CRITICAL	25 per 1,000	**36 per 1,000** (7 to 192)	**RR 1.45** (0.27 to 7.69)	1833 (3 RCTs)[1, 2]	⊕⊕⊕⊕ High[b]	Nemolizumab + TCS/TCI increases discontinuation due to adverse events slightly.

Nemolizumab + TCS/TCI compared to placebo +TCS/TCI for adolescents & adults with AD

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis
Intervention: nemolizumab 30mg every 4 weeks + TCS and/or TCI for 16 weeks to 24 weeks
Comparison: placebo +TCS/TCI

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**				
Treatment-emergent adverse events of interest follow-up: range 16 weeks to 24 weeks INFORMATIVE	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. Another trial documented cytokine abnormalities only in the nemolizumab group leading to 2 discontinuations.			1842 (3 RCTs)[1, 2]	-	

***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 is consistent with trivial difference; not downgraded for the low, equitable event rates.
b. CI is consistent with trivial differences and a small unimportant increase. Not downgraded due to the rare event across the sizable sample.

1. Silverberg JI, Pinter A, Pulka G, Poulin Y, Bouaziz JD, Wollenberg A et al. Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. J Allergy Clin Immunol 2020;145:173-82.
2. 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.