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

The revised 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	High
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	High
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. The evidence supporting abrocitinib 200 mg is of higher certainty than that for 100 mg.*	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.	Conditional	Low

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.		
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. *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.*	Conditional	Low

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. Interim 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 focused and interim update processes.

An interim 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 an interim 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 an interim update dictate 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 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 an interim update is approved for development by the CGC, a guideline-interim 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. Interim updates are undertaken by an 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 these 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.

Interim 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.

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) leadership. 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 interim update considers new evidence and standardizes the analysis addressing the following clinical questions from the previously published guidelines for the management of atopic dermatitis (AD) in adults with topical and systemic therapies: 1) What is the efficacy and safety of biologic therapies for AD? and 2) What is the efficacy and safety of systemic JAKis for AD?[1,2] This 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 interim 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 the date of the previous search to December 2nd, 2025. 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.

Study Selection and Data Extraction

Studies identified 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 independently by two reviewers using predefined inclusion and exclusion criteria established during the original AD guideline development process. 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 by two independent reviewers, during which a final inclusion decision was made. Disagreements were resolved through discussion by the original pair of reviewers to reach a consensus or a third party was engaged to resolve the conflict.

A structured data table was used to extract relevant data from the included studies. Data extraction was initially performed independently by a reviewer with subsequent quality control via review by a second extractor. Discrepancies were resolved through discussion by the original data extractor and the reviewing party.

Risk of Bias Assessment

The risk of bias was assessed for all included studies using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials.[3]

Evidence Synthesis

Pairwise meta-analyses were conducted for all outcomes and comparisons of interest, provided at least two studies were available, using a random-effects model. The treatment effect for dichotomous outcomes was measured via risk ratios and 95% confidence intervals (CIs), calculated by Wald-type method. Continuous outcomes were reported as mean differences with 95% CIs.

Standardizing the Evidence Synthesis

This interim update standardized the evidence synthesis approach across all considered recommendations. The 2023 guideline derived effect estimates from network meta-analysis, reporting dichotomous outcomes as odds ratios and continuous outcomes as standardized mean differences.[2,4] To ensure methodological consistency with

the 2025 focused update and across JAKi and biologic recommendations, the present update instead employed pairwise meta-analysis, with effect estimates expressed as risk ratios and mean differences. Furthermore, whereas the 2023 guideline analyses pooled monotherapy trials with trials of systemic therapy combined with concomitant topical therapy, this interim update analyzed these trial types separately for all interventions, with the exception of those with FDA indications for use in combination with topical therapy.

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] For the imprecision domain, the guideline panel established minimally important differences (MIDs) for each critical and important outcome prior to evidence review. MIDs were defined as the smallest absolute difference in an outcome that a patient or clinician would consider meaningful when making a treatment decision. Imprecision was rated down when the 95% confidence interval around the pooled effect estimate crossed the MID threshold, indicating that the evidence was consistent with both a clinically important benefit and either no meaningful benefit or meaningful harm. MIDs were established on an outcome-by-outcome basis through panel consensus informed by published literature on patient-important thresholds, where available, and by clinical judgment regarding the magnitude of effect that would be expected to influence treatment decisions. See Table a. for the established MIDs. 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 A. Minimally Important Differences

Outcome Measure	**MID** (specific to absolute difference)
DLQI	3.3 points[6,7]
DLQI≥4	12%
EASI	6.6 points[8,9]
EASI 100	5%
EASI 90	10%
EASI 75	10%
IGA 0/1	12%
POEM	3.4 points[8]
PP-NRS4	10%
Discontinuations	10%

Serious adverse events	2%
Adverse events (non-serious)	10%
Treatment-related adverse events	5%

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.[10] Per the GRADE approach, recommendations are either "strong" or "conditional".[11] The implications of each strength of recommendation are summarized in **Table II**.

Manuscript Review and Currency Statement

This interim update has been developed following the AAD/AAD Association Administrative Regulations for Evidence-Based Clinical Practice Guidelines, which includes the opportunity for review and comment by the entire AAD membership and final review and comment by the AAD Board of Directors. The guidance issued by this interim update will be considered current for 5 years from the date of publication unless reaffirmed, updated, or retired before that time.

References

1. Davis DMR, Frazer-Green L, Alikhan A, Bercovitch L, Cohen DE, Darr JM et al. Focused update: Guidelines of care for the management of atopic dermatitis in adults. Journal of the American Academy of Dermatology 2025;93:745.e1-.e7.
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. J Am Acad Dermatol 2023;89:e1-e20.
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. Drucker AM, Morra DE, Prieto-Merino D, Ellis AG, Yiu ZZN, Rochwerg B et al. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. JAMA Dermatol 2022;158:523-32.
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. Basra MK, Salek MS, Camilleri L, Sturkey R , Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. Dermatology 2015;230:27-33.
7. Finlay AY , Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-6.

8. Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD , Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy 2012;67:99-106.
9. Silverberg JI, Lei D, Yousaf M, Janmohamed SR, Vakharia PP, Chopra R et al. What are the best endpoints for Eczema Area and Severity Index and Scoring Atopic Dermatitis in clinical practice? A prospective observational study. Br J Dermatol 2021;184:888-95.
10. 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.
11. 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.

e-Table 1. Dupilumab Monotherapy GRADE Summary of Findings (Short-term)

Dupilumab 600mg LD then 300mg every 2 weeks monotherapy for 16 weeks

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis
Intervention: Dupilumab 600mg LD then 300mg every 2 weeks monotherapy for 16 weeks
Comparison: placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with Dupilumab monotherapy**				
IGA (0,1) assessed with: IGA 0 or 1 with ≥2-point improvement from baseline follow-up: 16 weeks CRITICAL	88 per 1,000	**337 per 1,000** (241 to 472)	**RR 3.83** (2.74 to 5.36)	1340 (5 RCTs)[1-4]	⨁⨁⨁⨁ High	
EASI75 follow-up: 16 weeks CRITICAL	132 per 1,000	**494 per 1,000** (397 to 615)	**RR 3.73** (3.00 to 4.64)	1207 (4 RCTs)	⨁⨁⨁⨁ High	
Pruritus improvement assessed with: Pruritus NRS ≥ 4-point improvement in patients with baseline NRS score of 4+ follow-up: 16 weeks CRITICAL	101 per 1,000	**390 per 1,000** (304 to 501)	**RR 3.86** (3.01 to 4.96)	1294 (5 RCTs)[1-4]	⨁⨁⨁⨁ High	
Discontinuation due to AEs follow-up: 16 weeks CRITICAL	20 per 1,000	**23 per 1,000** (11 to 52)	**RR 1.17** (0.53 to 2.62)	1211 (4 RCTs)	⨁⨁⨁⨁ High	
POEM assessed with: mean change from baseline in POEM total score follow-up: 16 weeks CRITICAL	MD **7.52 lower** (8.71 lower to 6.32 lower)		-	1204 (4 RCTs)	⨁⨁⨁⨁ High	
Serious adverse events follow-up: 16 weeks CRITICAL	57 per 1,000	**31 per 1,000** (17 to 54)	**RR 0.54** (0.30 to 0.95)	1211 (4 RCTs)	⨁⨁⨁⨁ High	

Flare prevention assessed with: patients with exacerbation of AD follow-up: 16 weeks CRTICIAL	325 per 1,000	**133 per 1,000** (101 to 175)	**RR 0.41** (0.31 to 0.54)	921 (2 RCTs)	⊕⊕⊕⊕ High
Quality of Life assessed with: DLQI mean change from baseline follow-up: 16 weeks CRITICAL	MD **5.04 points fewer** (6 fewer to 4.07 fewer)		-	1207 (4 RCTs)	⊕⊕⊕⊕ High
EASI90 follow-up: 16 weeks INFORMATIVE	68 per 1,000	**329 per 1,000** (239 to 451)	**RR 4.84** (3.52 to 6.65)	1207 (4 RCTs)	⊕⊕⊕⊕ High
Adverse events follow-up: 16 weeks INFORMATIVE	715 per 1,000	**708 per 1,000** (636 to 779)	**RR 0.99** (0.89 to 1.09)	1211 (4 RCTs)	⊕⊕⊕⊕ High
Infections and infestations follow-up: 16 weeks INFORMATIVE	277 per 1,000	**293 per 1,000** (224 to 385)	**RR 1.06** (0.81 to 1.39)	1211 (4 RCTs)	⊕⊕⊕⊕ High
Conjunctivitis follow-up: 16 weeks INFORMATIVE	15 per 1,000	**45 per 1,000** (21 to 95)	**RR 2.97** (1.39 to 6.32)	1211 (4 RCTs)	⊕⊕⊕◯ Moderate[a]
Upper Respiratory Tract Infection follow-up: 16 weeks INFORMATIVE	45 per 1,000	**45 per 1,000** (27 to 77)	**RR 1.01** (0.60 to 1.70)	1211 (4 RCTs)	⊕⊕⊕⊕ High
Nasopharyngitis follow-up: 16 weeks INFORMATIVE	95 per 1,000	**102 per 1,000** (73 to 143)	**RR 1.07** (0.77 to 1.50)	1211 (4 RCTs)	⊕⊕⊕⊕ High
Any Herpes Viral Infection follow-up: 16 weeks INFORMATIVE	35 per 1,000	**55 per 1,000** (31 to 98)	**RR 1.57** (0.88 to 2.81)	1046 (3 RCTs)	⊕⊕⊕◯ Moderate[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; **MD:** mean difference; **RR:** risk ratio

Explanations

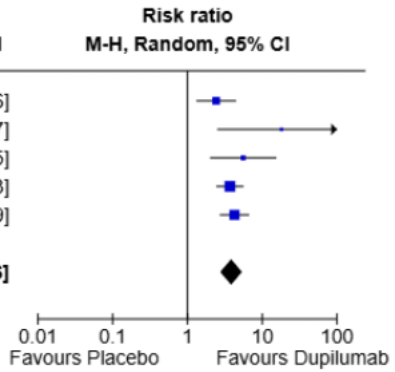
a. CI consistent with no meaningful difference and harm (based on MID of 2%)

b. CI consistent with benefit and harm (based on MID of 5%)

Analysis. IGA (0,1)

Study or Subgroup	Dupilumab Events	Dupilumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
LIBERTY-AD-HAFT	27	67	11	66	21.4%	2.42 [1.31 , 4.46]
NCT01859988	19	64	1	61	2.8%	18.11 [2.50 , 131.17]
NCT03912259	22	82	4	83	9.4%	5.57 [2.01 , 15.45]
SOLO 1	85	224	23	224	34.5%	3.70 [2.42 , 5.63]
SOLO 2	84	233	20	236	31.9%	4.25 [2.70 , 6.69]
Total (Wald[a])		**670**		**670**	**100.0%**	**3.83 [2.74 , 5.36]**
Total events:	237		59			

Test for overall effect: Z = 7.86 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.04; Chi² = 5.46, df = 4 (P = 0.24); I² = 27%

Footnotes

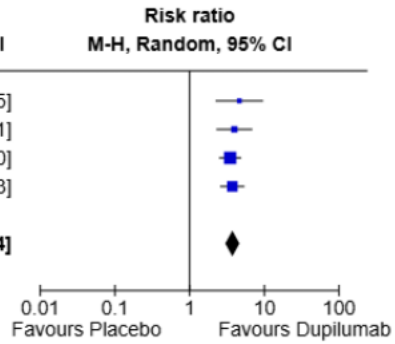
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. EASI75

Study or Subgroup	Dupilumab Events	Dupilumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
NCT01859988	34	64	7	61	8.9%	4.63 [2.22 , 9.65]
NCT03912259	47	82	12	83	15.6%	3.96 [2.27 , 6.91]
SOLO 1	115	224	33	224	41.6%	3.48 [2.48 , 4.90]
SOLO 2	103	233	28	236	33.9%	3.73 [2.56 , 5.43]
Total (Wald[a])		**603**		**604**	**100.0%**	**3.73 [3.00 , 4.64]**
Total events:	299		80			

Test for overall effect: Z = 11.77 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.53, df = 3 (P = 0.91); I² = 0%

Footnotes

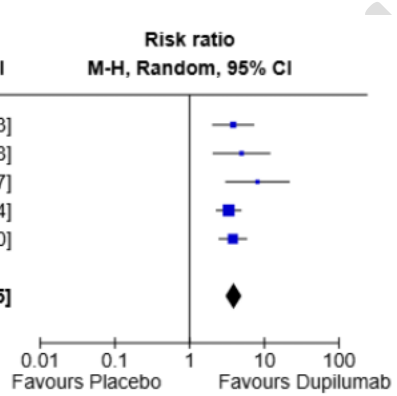
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. Pruritus improvement

Study or Subgroup	Dupilumab Events	Dupilumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
LIBERTY-AD-HAFT	35	67	9	66	14.7%	3.83 [2.00 , 7.33]
NCT01859988	26	64	5	61	7.8%	4.96 [2.03 , 12.08]
NCT03912259	32	82	4	83	6.3%	8.10 [3.00 , 21.87]
SOLO 1	87	213	26	212	39.7%	3.33 [2.24 , 4.94]
SOLO 2	81	225	21	221	31.6%	3.79 [2.43 , 5.90]
Total (Wald[a])		**651**		**643**	**100.0%**	**3.86 [3.01 , 4.95]**
Total events:	261		65			

Test for overall effect: Z = 10.65 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 3.03, df = 4 (P = 0.55); I² = 0%

Footnotes

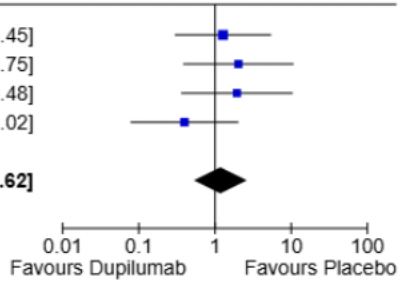
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. Discontinuation due to adverse events

Study or Subgroup	Dupilumab Events	Dupilumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
NCT01859988	4	64	3	61	30.3%	1.27 [0.30 , 5.45]
NCT03912259	4	82	2	83	23.0%	2.02 [0.38 , 10.75]
SOLO 1	4	229	2	222	22.5%	1.94 [0.36 , 10.48]
SOLO 2	2	236	5	234	24.2%	0.40 [0.08 , 2.02]
Total (Wald[a])		**611**		**600**	**100.0%**	**1.17 [0.53 , 2.62]**
Total events:	14		12			

Risk ratio M-H, Random, 95% CI



Test for overall effect: Z = 0.39 (P = 0.69)

Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 2.47, df = 3 (P = 0.48); I² = 0%

Footnotes

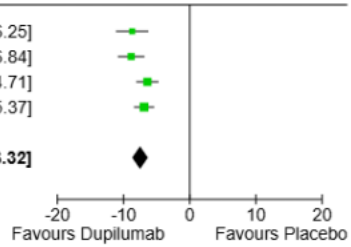
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. POEM

Study or Subgroup	Dupilumab Mean	Dupilumab SD	Dupilumab Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean difference IV, Random, 95% CI
NCT01859988	-9.8	6.905411	63	-1.1	6.913031	59	17.3%	-8.70 [-11.15 , -6.25]
NCT03912259	-12.89	5.958443	82	-4.04	7.179022	83	22.8%	-8.85 [-10.86 , -6.84]
SOLO 1	-11.5	7.483315	224	-5.1	10.476641	224	28.3%	-6.40 [-8.09 , -4.71]
SOLO 2	-10.2	7.632169	233	-3.3	9.217375	236	31.5%	-6.90 [-8.43 , -5.37]
Total (Wald[a])			**602**			**602**	**100.0%**	**-7.52 [-8.71 , -6.32]**

Mean difference IV, Random, 95% CI



Test for overall effect: Z = 12.37 (P < 0.00001)

Heterogeneity: Tau² (REML[b]) = 0.56; Chi² = 4.83, df = 3 (P = 0.18); I² = 38%

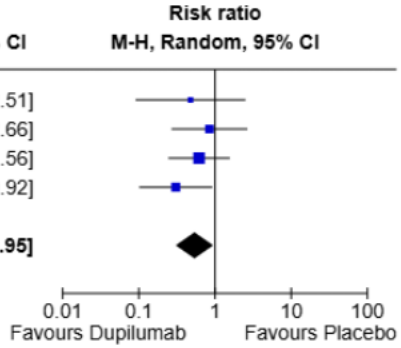
Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

Analysis. Serious adverse events

Study or Subgroup	Dupilumab Events	Dupilumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
NCT01859988	2	64	4	61	11.7%	0.48 [0.09 , 2.51]
NCT03912259	5	82	6	83	24.5%	0.84 [0.27 , 2.66]
SOLO 1	7	229	11	222	37.4%	0.62 [0.24 , 1.56]
SOLO 2	4	236	13	234	26.4%	0.31 [0.10 , 0.92]
Total (Wald[a])		**611**		**600**	**100.0%**	**0.54 [0.30 , 0.95]**
Total events:	18		34			



Test for overall effect: Z = 2.15 (P = 0.03)

Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 1.72, df = 3 (P = 0.63); I² = 0%

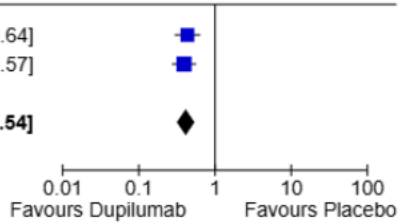
Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. Flare Prevention

Study or Subgroup	Dupilumab Events	Dupilumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
SOLO 1	30	229	67	222	47.1%	0.43 [0.29 , 0.64]
SOLO 2	32	236	81	234	52.9%	0.39 [0.27 , 0.57]
Total (Wald[a])		**465**		**456**	**100.0%**	**0.41 [0.31 , 0.54]**
Total events:	62		148			



Test for overall effect: Z = 6.53 (P < 0.00001)

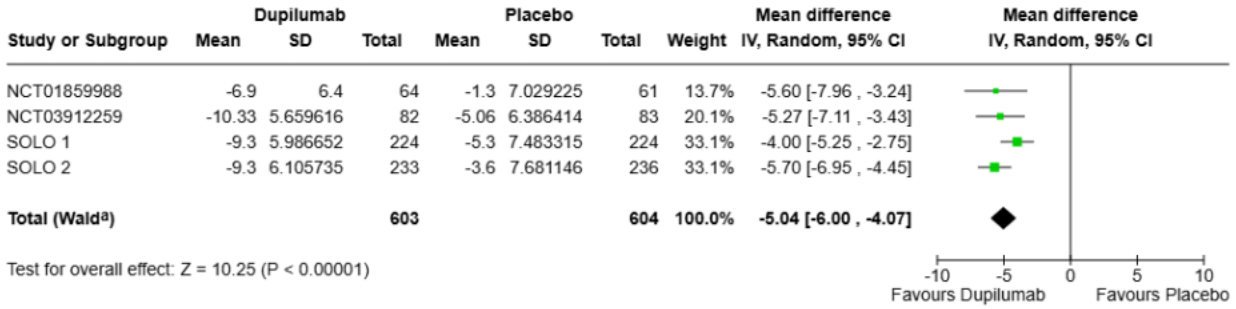
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. Quality of life



References

1. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. N Engl J Med 2016;375:2335-48.
2. Simpson EL, Silverberg JI, Worm M, Honari G, Masuda K, Syguła E et al. Dupilumab treatment improves signs, symptoms, quality of life, and work productivity in patients with atopic hand and foot dermatitis: Results from a phase 3, randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol 2024;90:1190-9.
3. Thaçi D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. Lancet 2016;387:40-52.
4. Zhao Y, Wu L, Lu Q, Gao X, Zhu X, Yao X et al. The efficacy and safety of dupilumab in Chinese patients with moderate-to-severe atopic dermatitis: a randomized, double-blind, placebo-controlled study. Br J Dermatol 2021.

e-Table 2. Dupilumab Combination Therapy GRADE Summary of Findings (Short-term)

Dupilumab 600mg LD then 300mg every 2 weeks + TCS for 12-16 weeks compared to Placebo + TCS

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis
Intervention: Dupilumab 600mg LD then 300mg every 2 weeks + TCS for 12 to 16 weeks
Comparison: Placebo + TCS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo + TCS	**Risk with Dupilumab + TCS**				
IGA (0,1) assessed with: IGA 0 or 1 with ≥2-point improvement from baseline follow-up: 16 weeks CRITICAL	124 per 1,000	**396 per 1,000** (312 to 504)	**RR 3.19** (2.51 to 4.06)	1186 (4 RCTs)	⨁⨁⨁⨁ High	
EASI75 follow-up: range 12 weeks to 16 weeks CRITICAL	254 per 1,000	**618 per 1,000** (524 to 730)	**RR 2.43** (2.06 to 2.87)	1343 (5 RCTs)[1-5]	⨁⨁⨁⨁ High	
Pruritus improvement assessed with: Pruritus NRS ≥ 4-point improvement in patients with baseline NRS score of 4+ follow-up: 16 weeks CRITICAL	173 per 1,000	**564 per 1,000** (453 to 701)	**RR 3.26** (2.62 to 4.05)	958 (3 RCTs)	⨁⨁⨁⨁ High	
Discontinuation due to AEs follow-up: range 12 weeks to 16 weeks CRITICAL	15 per 1,000	**23 per 1,000** (6 to 85)	**RR 1.52** (0.41 to 5.64)	969 (4 RCTs)	⨁⨁⨁⨁ High	
POEM assessed with: mean score, change from baseline follow-up: range 12 weeks to 16 weeks CRITICAL	MD **7.42 points lower** (8.51 lower to 6.32 lower)		-	1472 (5 RCTs)	⨁⨁⨁⨁ High	
Serious Adverse Events follow-up: range 12 weeks to 16 weeks CRITICAL	15 per 1,000	**13 per 1,000** (5 to 39)	**RR 0.89** (0.30 to 2.59)	969 (4 RCTs)	⨁⨁⨁⨁ High	
Quality of Life assessed with: DLQI mean score, change from baseline follow-up: range 12 weeks to 16 weeks	MD **4.62 points fewer** (5.28 fewer to 3.96 fewer)		-	1137 (4 RCTs)	⨁⨁⨁⨁ High	

CRITICAL					
EASI90 follow-up: range 12 weeks to 16 weeks INFORMATIVE	116 per 1,000	**402 per 1,000** (313 to 517)	**RR 3.46** (2.69 to 4.45)	1166 (4 RCTs)	⊕⊕⊕⊕ High
Treatment-emergent AEs follow-up: range 12 weeks to 16 weeks INFORMATIVE	356 per 1,000	**406 per 1,000** (288 to 570)	**RR 1.14** (0.81 to 1.60)	969 (4 RCTs)	⊕⊕⊕◯ Moderate[a]
Conjunctivitis follow-up: range 12 weeks to 16 weeks INFORMATIVE	45 per 1,000	**117 per 1,000** (72 to 192)	**RR 2.58** (1.58 to 4.23)	969 (4 RCTs)	⊕⊕⊕⊕ High[b]
Infections and infestations follow-up: range 12 weeks to 16 weeks INFORMATIVE	367 per 1,000	**378 per 1,000** (286 to 495)	**RR 1.03** (0.78 to 1.35)	403 (2 RCTs)	⊕⊕⊕◯ Moderate[c]
Upper Respiratory Tract Infection follow-up: range 12 weeks to 16 weeks INFORMATIVE	56 per 1,000	**43 per 1,000** (24 to 77)	**RR 0.78** (0.44 to 1.39)	969 (4 RCTs)	⊕⊕⊕⊕ High
Nasopharyngitis follow-up: range 12 weeks to 16 weeks INFORMATIVE	88 per 1,000	**100 per 1,000** (66 to 151)	**RR 1.13** (0.75 to 1.71)	969 (4 RCTs)	⊕⊕⊕⊕ High[d]
Herpes Infection follow-up: range 12 weeks to 16 weeks INFORMATIVE	7 per 1,000	**6 per 1,000** (0 to 100)	**RR 0.88** (0.05 to 14.99)	775 (3 RCTs)	⊕⊕⊕⊕ High[d]

*__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 consistent with benefit and harm (based on MID of 5%)

b. Results consistent with no effect and trivial benefit. Safety signal

c. CI consistent with benefit and harm (based on MID of 5%). Small sample is concerning for precision.

d. No difference between the absolute effects in the treatment group compared to placebo

References

1. Bieber T, Simpson EL, Silverberg JI, Thaçi D, Paul C, Pink AE et al. Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis. N Engl J Med 2021;384:1101-12.
2. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet 2017;389:2287-303.
3. Blauvelt A, Simpson EL, Tyring SK, Purcell LA, Shumel B, Petro CD et al. Dupilumab does not affect correlates of vaccine-induced immunity: A randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. J Am Acad Dermatol 2019;80:158-67.e1.
4. de Bruin-Weller M, Thaçi D, Smith CH, Reich K, Cork MJ, Radin A et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). British Journal of Dermatology 2018;178:1083-101.
5. Merola JF, Chiou AS, During E, Costanzo A, Foley P, Alfalasi A et al. Dupilumab significantly improves sleep in adults with atopic dermatitis: results from the 12-week placebo-controlled period of the 24-week phase IV randomized double-blinded placebo-controlled DUPISTAD study. Br J Dermatol 2023;189:685-94.

e-Table 3. Dupilumab GRADE Summary of Findings (Long-term)

Dupilumab 600mg LD then 300mg every 2 weeks + TCS for 52 weeks compared to Placebo + TCS [1]

Patient or population: Adolescents and adults aged 12+ with moderate to severe AD
Intervention: Dupilumab 600mg LD then 300mg every 2 weeks + TCS for 52 weeks
Comparison: Placebo + TCS

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo + TCS	**Risk with Dupilumab + TCS**				
IGA (0,1) assessed with: IGA 0 or 1 with ≥2-point improvement from baseline follow-up: 52 weeks CRITICAL	125 per 1,000	**360 per 1,000** (235 to 549)	**RR 2.88** (1.88 to 4.39)	353 (1 RCT)	⨁⨁⨁◯ Moderate[a]	

EASI75 follow-up: 52 weeks CRITICAL	216 per 1,000	**652 per 1,000** (494 to 859)	**RR 3.02** (2.29 to 3.98)	353 (1 RCT)	⊕⊕⊕◯ Moderate[b]
Pruritus improvement assessed with: Pruritus NRS ≥ 4-point improvement in patients with baseline NRS score of 4+ follow-up: 52 weeks CRITICAL	129 per 1,000	**511 per 1,000** (348 to 751)	**RR 3.98** (2.71 to 5.84)	335 (1 RCT)	⊕⊕⊕◯ Moderate[b]
Discontinuation due to AEs follow-up: 52 weeks CRITICAL	76 per 1,000	**18 per 1,000** (5 to 75)	**RR 0.24** (0.06 to 0.99)	425 (1 RCT)	⊕⊕⊕◯ Moderate[c]
POEM assessed with: mean score, change from baseline follow-up: 52 weeks CRITICAL	MD **8.4 points fewer** (10.12 fewer to 6.68 fewer)		-	353 (1 RCT)	⊕⊕⊕◯ Moderate[b]
Serious Adverse Events follow-up: 52 weeks CRITICAL	70 per 1,000	**45 per 1,000** (17 to 117)	**RR 0.65** (0.25 to 1.68)	425 (1 RCT)	⊕⊕⊕◯ Moderate[c]
Flares assessed with: proportion of patients with AD flares follow-up: 52 weeks CRITICAL	148 per 1,000	**169 per 1,000** (98 to 290)	**RR 1.14** (0.66 to 1.96)	359 (1 RCT)	⊕⊕⊕◯ Moderate[b]
Quality of Life assessed with: DLQI mean score, change from baseline follow-up: 52 weeks CRITICAL	MD **5.3 points fewer** (6.65 fewer to 3.95 fewer)		-	353 (1 RCT)	⊕⊕⊕◯ Moderate[b]
EASI90 follow-up: 52 weeks INFORMATIVE	155 per 1,000	**506 per 1,000** (357 to 716)	**RR 3.26** (2.30 to 4.61)	353 (1 RCT)	⊕⊕⊕◯ Moderate[b]
Treatment-emergent Adverse Events follow-up: 52 weeks INFORMATIVE	844 per 1,000	**878 per 1,000** (811 to 954)	**RR 1.04** (0.96 to 1.13)	425 (1 RCT)	⊕⊕⊕◯ Moderate[b]

Infections and infestations follow-up: 52 weeks INFORMATIVE	578 per 1,000	**572 per 1,000** (474 to 693)	**RR 0.99** (0.82 to 1.20)	425 (1 RCT)	⊕⊕⊕◯ Moderate[b]
Conjunctivitis follow-up: 52 weeks INFORMATIVE	79 per 1,000	**137 per 1,000** (75 to 249)	**RR 1.72** (0.94 to 3.14)	425 (1 RCT)	⊕⊕⊕◯ Moderate[b]
Herpes Infection follow-up: 52 weeks INFORMATIVE	79 per 1,000	**73 per 1,000** (34 to 156)	**RR 0.92** (0.43 to 1.97)	425 (1 RCT)	⊕⊕⊕◯ Moderate[b]
Upper Respiratory Tract Infection follow-up: 52 weeks INFORMATIVE	102 per 1,000	**100 per 1,000** (52 to 192)	**RR 0.98** (0.51 to 1.89)	425 (1 RCT)	⊕⊕⊕◯ Moderate[b]
Nasopharyngitis follow-up: 52 weeks	194 per 1,000	**227 per 1,000** (151 to 343)	**RR 1.17** (0.78 to 1.77)	425 (1 RCT)	⊕⊕◯◯ Low[d]

*__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 consistent with no meaningful difference and benefit (based on MID of 12%). Small sample is concerning for precision.

b. Small sample is concerning for precision.

c. Results consistent with less harm in the treatment group which indicates safety. Small sample is concerning for precision.

d. CI consistent with benefit and harm (based on MID of 5%). Small sample is concerning for precision.

References

1. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet 2017;389:2287-303.

e-Table 4. Tralokinumab Monotherapy GRADE Summary of Findings (Short-term)

Tralokinumab monotherapy 600 mg LD, 300 mg every 2 weeks for 16 weeks compared to Placebo
Patient or population: Adolescents and adults aged 12+ with moderate to severe AD

Intervention: Tralokinumab monotherapy 600 mg LD, 300 mg every 2 weeks for 16 weeks
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Tralokinumab monotherapy**				
IGA (0,1) assessed with: Patients with IGA score 0 or 1 follow-up: 16 weeks CRITICAL	113 per 1,000	**216 per 1,000** (164 to 284)	**RR 1.92** (1.46 to 2.52)	1805 (3 RCTs)[1, 2]	⨁⨁⨁◯ Moderate[a]	
EASI75 follow-up: 16 weeks CRITICAL	172 per 1,000	**337 per 1,000** (215 to 531)	**RR 1.96** (1.25 to 3.09)	1805 (3 RCTs)[1, 2]	⨁⨁⨁◯ Moderate[b]	
Pruritus Improvement assessed with: Pruritus NRS ≥ 4-point improvement in patients with baseline NRS score of 4+ follow-up: 16 weeks CRITICAL	99 per 1,000	**224 per 1,000** (163 to 307)	**RR 2.26** (1.65 to 3.10)	1563 (2 RCTs)	⨁⨁⨁◯ Moderate[c]	
Discontinuation due to AEs assessed with: AEs Leading to permanent discontinuation of IMP follow-up: 16 weeks CRITICAL	28 per 1,000	**23 per 1,000** (12 to 44)	**RR 0.84** (0.44 to 1.58)	1804 (3 RCTs)[1, 2]	⨁⨁⨁⨁ High	
POEM assessed with: mean score, change from baseline follow-up: 16 weeks CRITICAL	MD **4.85 points fewer** (5.88 fewer to 3.82 fewer)		-	1590 (2 RCTs)	⨁⨁⨁⨁ High	
Serious Adverse Events assessed with: Patients with at least 1 SAE follow-up: 16 weeks CRITICAL	28 per 1,000	**24 per 1,000** (13 to 45)	**RR 0.88** (0.48 to 1.63)	1804 (3 RCTs)[1, 2]	⨁⨁⨁⨁ High	
Flares assessed with: proportion of patients with AD flares follow-up: 16 weeks	455 per 1,000	**286 per 1,000** (191 to 427)	**RR 0.63** (0.42 to 0.94)	1590 (2 RCTs)	⨁⨁⨁⨁ High	

CRITICAL					
Quality of Life assessed with: DLQI mean score, change from baseline follow-up: 16 weeks CRITICAL	MD **3 points fewer** (4.76 fewer to 1.23 fewer)		-	1590 (2 RCTs)	⊕⊕⊕◯ Moderate[d]
EASI90 follow-up: 16 weeks INFORMATIVE	48 per 1,000	**164 per 1,000** (104 to 259)	**RR 3.43** (2.17 to 5.42)	1590 (2 RCTs)	⊕⊕⊕◯ Moderate[c]
Treatment-Related Adverse Events assessed with: patients with AE related to the treatment follow-up: 16 weeks INFORMATIVE	131 per 1,000	**122 per 1,000** (60 to 246)	**RR 0.93** (0.46 to 1.88)	214 (1 RCT)	⊕⊕◯◯ Low[e]
Conjunctivitis follow-up: 16 weeks INFORMATIVE	30 per 1,000	**75 per 1,000** (42 to 136)	**RR 2.49** (1.38 to 4.49)	1590 (2 RCTs)	⊕⊕⊕◯ Moderate[f]
Upper Respiratory Tract Infection assessed with: patients with URTI follow-up: 16 weeks INFORMATIVE	48 per 1,000	**58 per 1,000** (36 to 94)	**RR 1.20** (0.74 to 1.95)	1560 (2 RCTs)	⊕⊕⊕⊕ High
Viral Upper Respiratory Tract Infection follow-up: 16 weeks INFORMATIVE	119 per 1,000	**144 per 1,000** (88 to 236)	**RR 1.21** (0.74 to 1.98)	1804 (3 RCTs)[1, 2]	⊕⊕⊕◯ Moderate[f]

*__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

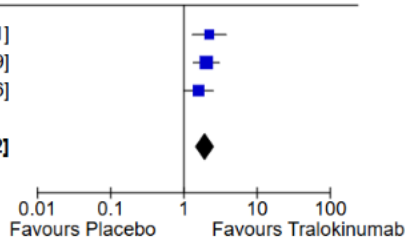
Explanations

a. CI consistent with no meaningful difference and benefit (based on MID of 12%)
b. CI consistent with no meaningful difference and benefit (based on MID of 5%)
c. CI consistent with no meaningful difference and benefit (based on MID of 10%)
d. CI consistent with no meaningful difference and benefit (based on MID of 3.3 points)
e. CI consistent with no meaningful difference and harm (based on MID of 5%). Small sample is concerning for precision.
f. CI consistent with no meaningful difference and harm (based on MID of 5%).

Analysis. IGA (0,1)

Study or Subgroup	Tralokinumab Events	Tralokinumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
ECZTRA 1	95	601	14	197	25.7%	2.22 [1.30 , 3.81]
ECZTRA 2	131	591	22	201	41.7%	2.03 [1.33 , 3.09]
ECZTRA 5	33	107	21	108	32.6%	1.59 [0.98 , 2.56]
Total (Wald[a])		**1299**		**506**	**100.0%**	**1.92 [1.46 , 2.52]**
Total events:	259		57			

Test for overall effect: Z = 4.67 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.99, df = 2 (P = 0.61); I² = 0%

Footnotes

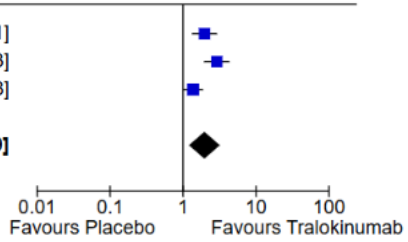
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. EASI75

Study or Subgroup	Tralokinumab Events	Tralokinumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
ECZTRA 1	150	601	25	197	32.5%	1.97 [1.33 , 2.91]
ECZTRA 2	196	591	23	201	32.1%	2.90 [1.94 , 4.33]
ECZTRA 5	53	107	39	108	35.5%	1.37 [1.00 , 1.88]
Total (Wald[a])		**1299**		**506**	**100.0%**	**1.96 [1.25 , 3.09]**
Total events:	399		87			

Test for overall effect: Z = 2.91 (P = 0.004)



Heterogeneity: Tau² (DL[b]) = 0.13; Chi² = 9.11, df = 2 (P = 0.01); I² = 78%

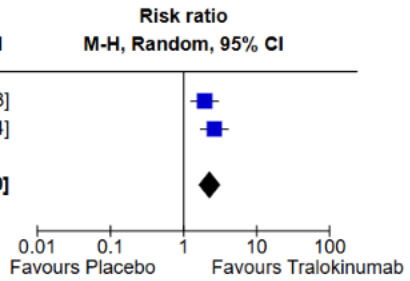
Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. Pruritus improvement

Study or Subgroup	Tralokinumab Events	Tralokinumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
ECZTRA 1	119	594	20	194	50.6%	1.94 [1.25 , 3.03]
ECZTRA 2	144	575	19	200	49.4%	2.64 [1.68 , 4.14]
Total (Wald[a])		**1169**		**394**	**100.0%**	**2.26 [1.65 , 3.10]**
Total events:	263		39			



Test for overall effect: Z = 5.04 (P < 0.00001)

Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.89, df = 1 (P = 0.34); I² = 0%

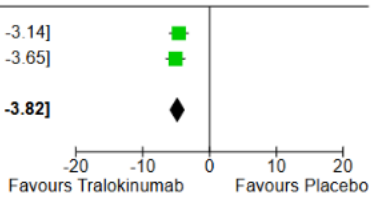
Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. POEM

Study or Subgroup	Tralokinumab Mean	Tralokinumab SD	Tralokinumab Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean difference IV, Random, 95% CI
ECZTRA 1	-7.6	8.580355	601	-3	9.263541	197	49.4%	-4.60 [-6.06 , -3.14]
ECZTRA 2	-8.8	8.022462	591	-3.7	9.357115	201	50.6%	-5.10 [-6.55 , -3.65]
Total (Wald[a])			**1192**			**398**	**100.0%**	**-4.85 [-5.88 , -3.82]**



Test for overall effect: Z = 9.24 (P < 0.00001)

Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%

Footnotes

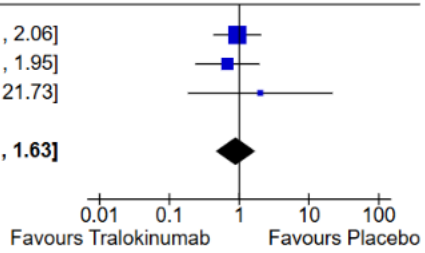
[a]CI calculated by Wald-type method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

Analysis. Serious adverse events

Study or Subgroup	Tralokinumab Events	Tralokinumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
ECZTRA 1	23	602	8	196	60.2%	0.94 [0.43 , 2.06]
ECZTRA 2	10	592	5	200	33.2%	0.68 [0.23 , 1.95]
ECZTRA 5	2	107	1	107	6.6%	2.00 [0.18 , 21.73]
Total (Wald[a])		**1301**		**503**	**100.0%**	**0.88 [0.48 , 1.63]**
Total events:	35		14			

Test for overall effect: Z = 0.40 (P = 0.69)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.72, df = 2 (P = 0.70); I² = 0%

Footnotes

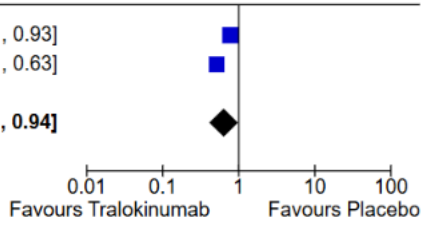
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. Flare prevention

Study or Subgroup	Tralokinumab Events	Tralokinumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
ECZTRA 1	216	602	91	196	50.9%	0.77 [0.64 , 0.93]
ECZTRA 2	135	592	89	200	49.1%	0.51 [0.41 , 0.63]
Total (Wald[a])		**1194**		**396**	**100.0%**	**0.63 [0.42 , 0.94]**
Total events:	351		180			

Test for overall effect: Z = 2.24 (P = 0.03)



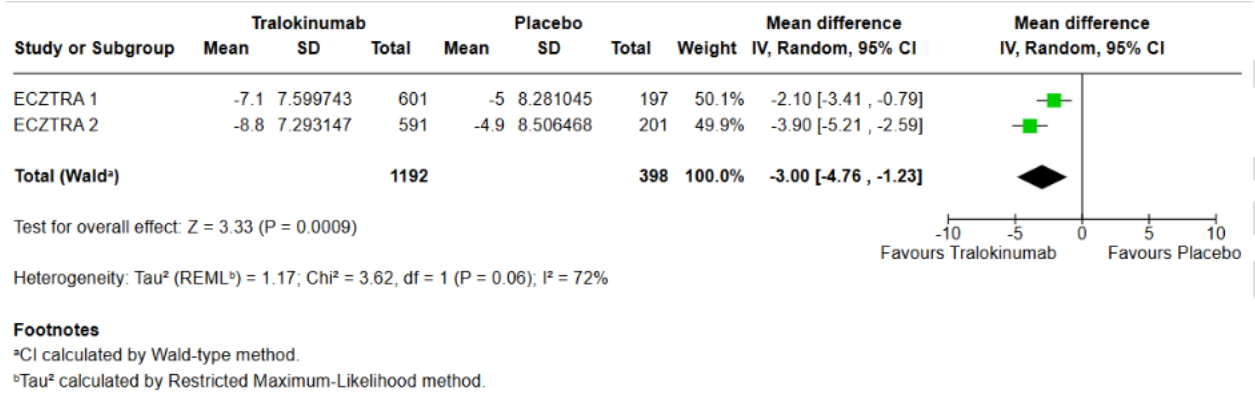
Heterogeneity: Tau² (DL[b]) = 0.07; Chi² = 8.12, df = 1 (P = 0.004); I² = 88%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. Quality of life



References

1. Merola JF, Bagel J, Almgren P, Røpke MA, Lophaven KW, Vest NS , Grewal P. Tralokinumab does not impact vaccine-induced immune responses: Results from a 30-week, randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. J Am Acad Dermatol 2021;85:71-8.
2. Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol 2021;184:437-49.

e-Table 5. Tralokinumab Combination Therapy GRADE Summary of Findings (Short-term)

Tralokinumab 600 mg LD, 300 mg + TCS every 2 weeks for 16 weeks compared to Placebo + TCS
Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis **Intervention:** Tralokinumab 600 mg LD, 300 mg + TCS every 2 weeks for 16 weeks **Comparison:** Placebo + TCS

Outcomes	Anticipated absolute effects* (95% CI) Risk with Placebo + TCS	Anticipated absolute effects* (95% CI) Risk with Tralokinumab + TCS	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
IGA (0,1) follow-up: 16 weeks CRITICAL	262 per 1,000	**388 per 1,000** (280 to 542)	**RR 1.48** (1.07 to 2.07)	378 (1 RCT)	⊕⊕⊕◯ Moderate[a]	
EASI75 follow-up: 16 weeks CRITICAL	433 per 1,000	**607 per 1,000** (494 to 737)	**RR 1.40** (1.14 to 1.70)	653 (2 RCTs)[1, 2]	⊕⊕⊕◯ Moderate[b]	
Pruritus improvement assessed with: ≥ 4-point improvement in patients with baseline NRS score of 4+ follow-up: 16 weeks CRITICAL	349 per 1,000	**457 per 1,000** (373 to 558)	**RR 1.31** (1.07 to 1.60)	644 (2 RCTs)	⊕⊕⊕◯ Moderate[b]	
Discontinuation due to AEs assessed with: AEs Leading to discontinuation of IMP follow-up: 16 weeks CRITICAL	8 per 1,000	**24 per 1,000** (3 to 196)	**RR 3.00** (0.37 to 24.65)	378 (1 RCT)	⊕⊕⊕◯ Moderate[c]	
POEM assessed with: mean score change from baseline follow-up: 16 weeks CRITICAL	MD **3.72 points fewer** (4.86 fewer to 2.57 fewer)		-	598 (2 RCTs)	⊕⊕⊕◯ Moderate[d]	
Serious adverse events assessed with: Patients with at least one SAE follow-up: 16 weeks CRITICAL	32 per 1,000	**8 per 1,000** (2 to 43)	**RR 0.25** (0.05 to 1.35)	378 (1 RCT)	⊕⊕⊕⊕ High[e]	
Flares assessed with: Proportion of patients with AD Flares follow-up: 16 weeks CRITICAL	139 per 1,000	**58 per 1,000** (26 to 128)	**RR 0.42** (0.19 to 0.92)	275 (1 RCT)	⊕⊕⊕⊕ High[e]	
Quality of Life assessed with: DLQI mean score change	MD **2.19 points fewer** (3.46 fewer to 0.92 fewer)		-	649 (2 RCTs)	⊕⊕⊕◯ Moderate[f]	

from baseline follow-up: 16 weeks CRITICAL					
EASI90 follow-up: 16 weeks INFORMATIVE	255 per 1,000	**374 per 1,000** (290 to 479)	**RR 1.47** (1.14 to 1.88)	653 (2 RCTs)	⊕⊕⊕◯ Moderate[c]
Conjunctivitis assessed with: Patients with conjunctivitis, conjunctivitis bacterial, conjunctivitis viral and conjunctivitis allergic AEs follow-up: 16 weeks INFORMATIVE	56 per 1,000	**131 per 1,000** (59 to 288)	**RR 2.36** (1.07 to 5.18)	378 (1 RCT)	⊕⊕⊕◯ Moderate[g]
Upper Respiratory Tract Infection assessed with: Patient with a URTI follow-up: 16 weeks INFORMATIVE	48 per 1,000	**75 per 1,000** (31 to 184)	**RR 1.58** (0.65 to 3.87)	378 (1 RCT)	⊕⊕⊕◯ Moderate[g]
Viral Upper Respiratory Tract Infection assessed with: Patients with viral URTI follow-up: 16 weeks INFORMATIVE	111 per 1,000	**194 per 1,000** (112 to 339)	**RR 1.75** (1.01 to 3.05)	378 (1 RCT)	⊕⊕⊕◯ Moderate[g]

*__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 consistent with no meaningful difference and benefit (based on MID of 12%)
b. CI consistent with no meaningful difference and benefit (based on MID of 15%)
c. CI consistent with benefit and harm (based on MID of 10%)
d. CI consistent with no meaningful difference and benefit (based on MID of 3.4 points)
e. Results consistent with no meaningful difference and benefit favoring the intervention over placebo. Safety signal
f. CI consistent with no meaningful difference and benefit (based on MID of 3.3)
g. CI consistent with no meaningful difference and harm (based on MID of 5%)

References

1. Merola JF, Bagel J, Almgren P, Røpke MA, Lophaven KW, Vest NS , Grewal P. Tralokinumab does not impact vaccine-induced immune responses: Results from a 30-week, randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. J Am Acad Dermatol 2021;85:71-8.
2. Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol 2021;184:437-49.

e-Table 6. Tralokinumab Monotherapy GRADE Summary of Findings (Long-term)

Tralokinumab monotherapy 600mg LD, 300 mg every 2 weeks for 52 weeks compared to Placebo[1]

Patient or population: Adolescents and adults aged 12+ with moderate to severe AD
Intervention: Tralokinumab monotherapy 600mg LD, 300 mg every 2 weeks for 52 weeks
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Tralokinumab monotherapy**				
IGA (0,1) follow-up: 52 weeks CRITICAL	340 per 1,000	**534 per 1,000** (242 to 1,000)	**RR 1.57** (0.71 to 3.45)	140 (2 RCTs)	⨁⨁◯◯ Low[a]	
EASI75 follow-up: 52 weeks CRITICAL	264 per 1,000	**559 per 1,000** (369 to 844)	**RR 2.12** (1.40 to 3.20)	196 (2 RCTs)	⨁⨁⨁◯ Moderate[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; **RR:** risk ratio

Explanations

a. CI consistent with benefit and harm (based on MID of 12%). Small sample is concerning for precision.

b. Small sample is concerning for precision.

References

1. Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol 2021;184:437-49.

e-Table 7. Lebrikizumab Monotherapy GRADE Summary of Findings (Short-term)

Lebrikizumab 500mg LD then 250mg every 2 weeks monotherapy compared to Placebo

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis short-term
Intervention: Lebrikizumab 500mg LD then 250mg every 2 weeks monotherapy
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Lebrikizumab monotherapy**				
IGA 0,1 follow-up: 16 weeks CRITICAL	134 per 1,000	**382 per 1,000** (297 to 491)	**RR 2.84** (2.21 to 3.65)	1225 (4 RCTs)[1-3]	⊕⊕⊕⊕ High	
EASI 75 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	
Pruritus improvement assessed with: ≥ 4-point improvement in patients with baseline NRS score of 4+ follow-up: 16 weeks	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	

CRITICAL					
Discontinuations due to AEs 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
POEM assessed with: mean score, change from baseline follow-up: 16 weeks CRITICAL	MD **5.68 lower** (7.66 lower to 3.7 lower)		-	852 (4 RCTs)[1-3]	⊕⊕⊕⊕ High
Serious AEs 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
Quality of Life assessed with: DLQI mean score, change from baseline follow-up: 16 weeks CRITICAL	MD **4.79 lower** (6.62 lower to 2.97 lower)		-	779 (3 RCTs)[1, 2]	⊕⊕⊕◯ Moderate[a]
Adverse Events follow-up: 16 weeks INFORMATIVE	622 per 1,000	**547 per 1,000** (466 to 640)	**RR 0.88** (0.75 to 1.03)	1194 (4 RCTs)[1-3]	⊕⊕⊕⊕ High
Infections and Infestations follow-up: 16 weeks INFORMATIVE	174 per 1,000	**209 per 1,000** (162 to 268)	**RR 1.20** (0.93 to 1.54)	1096 (3 RCTs)[2, 3]	⊕⊕⊕⊕ High
EASI 90 follow-up: 16 weeks INFORMATIVE	122 per 1,000	**359 per 1,000** (236 to 548)	**RR 2.94** (1.93 to 4.48)	1098 (3 RCTs)[2, 3]	⊕⊕⊕⊕ High
Conjunctivitis follow-up: 16 weeks INFORMATIVE	15 per 1,000	**50 per 1,000** (24 to 105)	**RR 3.31** (1.58 to 6.91)	1223 (4 RCTs)[1-3]	⊕⊕⊕⊕ High
Herpes Infection follow-up: 16 weeks INFORMATIVE	33 per 1,000	**22 per 1,000** (11 to 42)	**RR 0.67** (0.34 to 1.30)	1223 (4 RCTs)[1-3]	⊕⊕⊕⊕ High
Upper Respiratory Tract Infection follow-up: 16 weeks INFORMATIVE	58 per 1,000	**27 per 1,000** (5 to 154)	**RR 0.46** (0.08 to 2.67)	127 (1 RCT)[1]	⊕⊕⊕◯ Moderate[b]
Nasopharyngitis follow-up: 16 weeks	27 per 1,000	**41 per 1,000** (19 to 88)	**RR 1.53** (0.71 to 3.29)	976 (3 RCTs)[1, 2]	⊕⊕⊕⊕ High

INFORMATIVE

*__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

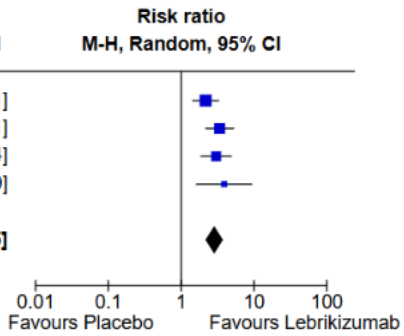
a. CI consistent with no important difference and meaningful benefit (based on MID 3.3 points)

b. Small sample is concerning for precision.

Analysis. IGA (0,1)

Study or Subgroup	Lebrikizumab Events	Lebrikizumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
ADopt-VA	51	125	23	122	35.0%	2.16 [1.42 , 3.31]
ADVOCATE 1	122	283	18	141	30.9%	3.38 [2.15 , 5.31]
ADVOCATE 2	93	281	16	146	26.1%	3.02 [1.85 , 4.94]
NCT03443024	28	75	5	52	8.1%	3.88 [1.60 , 9.39]
Total (Wald[a])		**764**		**461**	**100.0%**	**2.84 [2.21 , 3.65]**
Total events:	294		62			

Test for overall effect: Z = 8.15 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 2.75, df = 3 (P = 0.43); I² = 0%

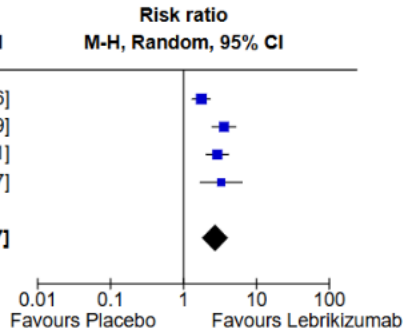
Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. EASI75

Study or Subgroup	Lebrikizumab Events	Total	Placebo Events	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]
NCT03443024	38	75	8	52	17.0%	3.29 [1.68 , 6.47]
Total (Wald[a])		**764**		**461**	**100.0%**	**2.71 [1.85 , 3.97]**
Total events:	422		97			



Test for overall effect: Z = 5.10 (P < 0.00001)

Heterogeneity: Tau² (DL[b]) = 0.11; Chi² = 10.88, df = 3 (P = 0.01); I² = 72%

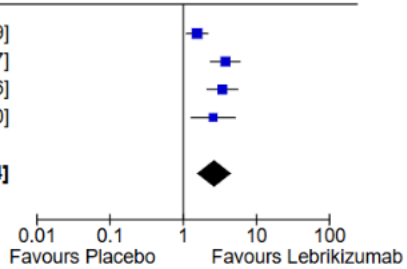
Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. Pruritus improvement

Study or Subgroup	Lebrikizumab Events	Total	Placebo Events	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]
NCT03443024	35	50	6	22	20.2%	2.57 [1.27 , 5.20]
Total (Wald[a])		**661**		**379**	**100.0%**	**2.63 [1.59 , 4.34]**
Total events:	303		68			



Test for overall effect: Z = 3.78 (P = 0.0002)

Heterogeneity: Tau² (DL[b]) = 0.19; Chi² = 12.63, df = 3 (P = 0.006); I² = 76%

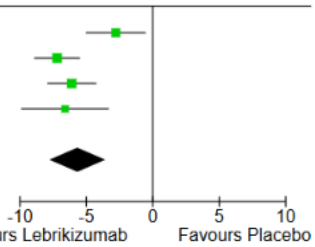
Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. POEM

Study or Subgroup	Lebrikizumab Mean	SD	Total	Placebo Mean	SD	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	-11.22	6.767708	203	-4.02	6.049052	70	28.9%	-7.20 [-8.90 , -5.50]
ADVOCATE 2	-9.55	7.121446	184	-3.45	6.232125	65	27.9%	-6.10 [-7.93 , -4.27]
NCT03443024	-12.4	6.9	59	-5.8	6.9	24	18.3%	-6.60 [-9.87 , -3.33]
Total (Wald[a])			**571**			**281**	**100.0%**	**-5.68 [-7.66 , -3.70]**



Test for overall effect: Z = 5.62 (P < 0.00001)

Heterogeneity: Tau² (REML[b]) = 2.79; Chi² = 9.97, df = 3 (P = 0.02); I² = 70%

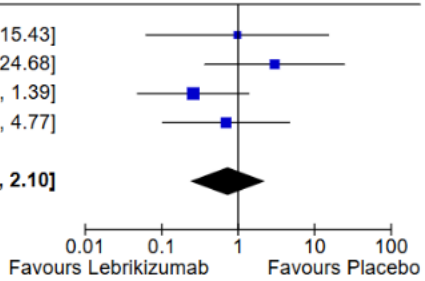
Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

Analysis. Serious adverse events

Study or Subgroup	Lebrikizumab Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Random, 95% CI
ADopt-VA	1	125	1	122	14.1%	0.98 [0.06 , 15.43]
ADVOCATE 1	6	282	1	141	23.4%	3.00 [0.36 , 24.68]
ADVOCATE 2	2	281	4	145	35.0%	0.26 [0.05 , 1.39]
NCT03443024	2	75	2	52	27.5%	0.69 [0.10 , 4.77]
Total (Wald[a])		**763**		**460**	**100.0%**	**0.73 [0.25 , 2.10]**
Total events:	11		8			



Test for overall effect: Z = 0.59 (P = 0.55)

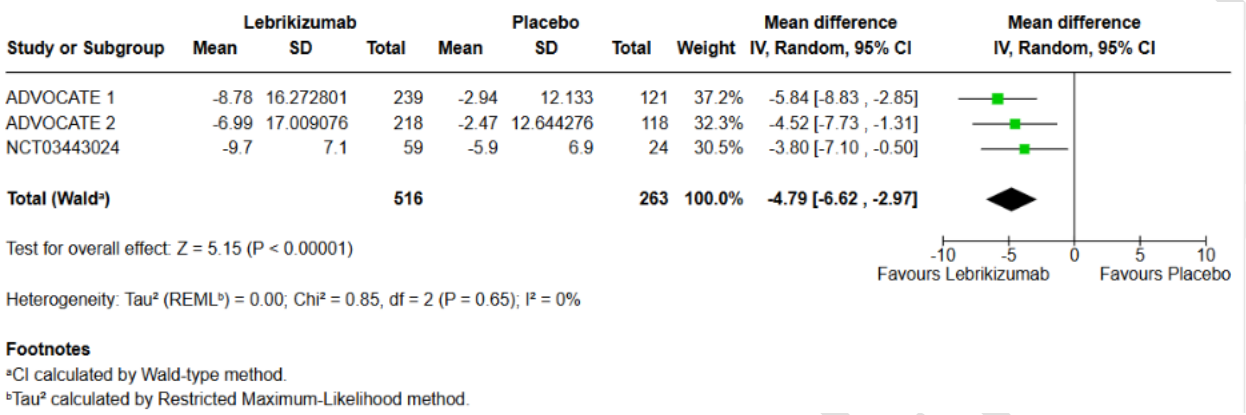
Heterogeneity: Tau² (DL[b]) = 0.10; Chi² = 3.28, df = 3 (P = 0.35); I² = 9%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. Quality of life



Study or Subgroup	Lebrikizumab Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
ADVOCATE 1	-8.78	16.272801	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]
NCT03443024	-9.7	7.1	59	-5.9	6.9	24	30.5%	-3.80 [-7.10 , -0.50]
Total (Wald[a])			**516**			**263**	**100.0%**	**-4.79 [-6.62 , -2.97]**

Test for overall effect: Z = 5.15 (P < 0.00001)

Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 0.85, df = 2 (P = 0.65); I² = 0%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

References

1. 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.
2. 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.
3. 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.

e-Table 8. Lebrikizumab Combination Therapy GRADE Summary of Findings (Short-term)

Lebrikizumab 500mg LD then 250mg every 2 weeks + TCS compared to Placebo + TCS

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis short-term
Intervention: Lebrikizumab 500mg LD then 250mg every 2 weeks + TCS
Comparison: Placebo + TCS

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo + TCS	**Risk with Lebrikizumab + TCS**				
IGA (0,1) follow-up: 16 weeks CRITICAL	181 per 1,000	**408 per 1,000** (240 to 700)	**RR 2.25** (1.32 to 3.86)	747 (3 RCTs)[1-4]	⊕⊕⊕◯ Moderate[a]	
EASI 75 follow-up: 16 weeks CRITICAL	324 per 1,000	**655 per 1,000** (444 to 966)	**RR 2.02** (1.37 to 2.98)	747 (3 RCTs)	⊕⊕⊕◯ Moderate[b]	
Pruritus improvement assessed with: ≥ 4-point improvement in patients with baseline NRS score of 4+ follow-up: 16 weeks CRITICAL	232 per 1,000	**472 per 1,000** (272 to 814)	**RR 2.03** (1.17 to 3.50)	652 (3 RCTs)	⊕⊕⊕◯ Moderate[c]	
Discontinuation due to AEs follow-up: 16 weeks CRITICAL	4 per 1,000	**6 per 1,000** (1 to 34)	**RR 1.64** (0.31 to 8.80)	747 (3 RCTs)	⊕⊕⊕⊕ High	
POEM assessed with: mean change from baseline follow-up: 16 weeks CRITICAL	MD **5.47 lower** (8.01 lower to 2.94 lower)		-	472 (2 RCTs)	⊕⊕⊕◯ Moderate[d]	
Serious Adverse Events follow-up: 16 weeks CRITICAL	15 per 1,000	**12 per 1,000** (3 to 47)	**RR 0.79** (0.21 to 3.05)	747 (3 RCTs)	⊕⊕⊕◯ Moderate[e]	
Quality of Life assessed with: DLQI mean score, change from baseline follow-up: 16 weeks CRITICAL	MD **1.6 lower** (3.23 lower to 0.03 higher)		-	491 (2 RCTs)	⊕⊕⊕⊕ High	

EASI 90 follow-up: 16 weeks	174 per 1,000	**384 per 1,000** (288 to 511)	**RR 2.21** (1.66 to 2.94)	747 (3 RCTs)	⊕⊕⊕⊕ High
Treatment related AEs follow-up: 16 weeks	367 per 1,000	**447 per 1,000** (378 to 528)	**RR 1.22** (1.03 to 1.44)	747 (3 RCTs)	⊕⊕⊕◯ Moderate[f]
URTIs follow-up: 16 weeks	63 per 1,000	**37 per 1,000** (13 to 98)	**RR 0.58** (0.21 to 1.55)	331 (1 RCT)	⊕⊕⊕⊕ High
Infections Assessed with: number of patients with opportunistic infection follow-up: 16 weeks	20 per 1,000	**17 per 1,000** (2 to 115)	**RR 0.82** (0.12 to 5.65)	425 (2 RCTs)	⊕⊕⊕⊕ High
Conjunctivitis follow-up: 16 weeks	15 per 1,000	**76 per 1,000** (29 to 198)	**RR 4.89** (1.87 to 12.83)	756 (3 RCTs)	⊕⊕⊕◯ Moderate[f]
Herpes Infection follow-up: 16 weeks	27 per 1,000	**47 per 1,000** (21 to 110)	**RR 1.75** (0.76 to 4.07)	747 (3 RCTs)	⊕⊕⊕⊕ High

*__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 consistent with no meaningful difference and benefit (based on MID of 12%)
b. CI consistent with no meaningful difference and benefit (based on MID of 15%)
c. CI consistent with no meaningful difference and benefit (based on MID of 10%)
d. CI consistent with no meaningful difference and benefit (based on MID of 3.4 points)
e. CI consistent with no meaningful difference and harm (based on MID of 2%)
f. CI consistent with no meaningful difference and harm (based on MID of 10%)

References

1. Katoh N, Tanaka A, Takahashi H, Shimizu R, Kataoka Y, Torisu-Itakura H et al. Efficacy and safety of lebrikizumab combined with topical corticosteroids in Japanese patients with moderate-to-severe atopic dermatitis: a phase 3, double-blind, placebo-controlled, randomized clinical trial (ADhere-J). Curr Med Res Opin 2025;41:1-12.
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. 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.
4. Warren RB, de Bruin-Weller M, Tsianakas A, Khemis A, Szepietowski JC, Hong HC et al. Efficacy and safety of lebrikizumab in adult and adolescent patients with moderate-to-severe atopic dermatitis inadequately controlled with or ineligible for ciclosporin A: a placebo-controlled, randomized phase IIIb clinical study (ADvantage). Br J Dermatol 2025;193:876-88.

e-Table 9. Lebrikizumab Monotherapy GRADE Summary of Findings (Long-term)

Lebrikizumab 250mg every 2 weeks monotherapy compared to Placebo[1]

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis who responded to therapy at 16 weeks
Intervention: Lebrikizumab 250mg every 2 weeks monotherapy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Lebrikizumab monotherapy**				
IGA (0,1) follow-up: 52 weeks CRITICAL	474 per 1,000	**711 per 1,000** (493 to 1,000)	**RR 1.50** (1.04 to 2.16)	115 (2 RCTs)	⊕⊕⊕◯ Moderate[a]	
EASI 75 follow-up: 52 weeks CRITICAL	649 per 1,000	**766 per 1,000** (617 to 948)	**RR 1.18** (0.95 to 1.46)	169 (2 RCTs)	⊕⊕⊕◯ Moderate[b]	
Pruritus improvement assessed with: 4-point improvement in patients with baseline NRS score of 4+ follow-up: 52 weeks CRITICAL	643 per 1,000	**855 per 1,000** (636 to 1,000)	**RR 1.33** (0.99 to 1.78)	89 (2 RCTs)	⊕⊕⊕◯ Moderate[c]	
Discontinuation due to AEs follow-up: 52 weeks CRITICAL	0 per 1,000	**-- per 1,000** (0 to 0)	**RR 1.61** (0.07 to 38.81)	173 (2 RCTs)	⊕⊕⊕◯ Moderate[d]	Event rate: 1/113 with LEB vs 0/60 with placebo
POEM assessed with: mean change in score	MD **2.26 lower** (4.37 lower to 0.14 lower)		-	173 (2 RCTs)	⊕⊕⊕◯ Moderate[e]	

from baseline follow-up: 52 weeks CRITICAL						
Serious AEs follow-up: 52 weeks CRITICAL	17 per 1,000	**18 per 1,000** (2 to 191)	**RR 1.06** (0.10 to 11.47)	173 (2 RCTs)	⊕⊕⊕◯ Moderate[f]	
Quality of Life assessed with: mean change in score from baseline follow-up: 52 weeks CRITICAL	MD **0.9 lower** (2.4 lower to 0.6 higher)		-	173 (2 RCTs)	⊕⊕⊕◯ Moderate[g]	
EASI 90 follow-up: 52 weeks INFORMATIVE	421 per 1,000	**627 per 1,000** (451 to 876)	**RR 1.49** (1.07 to 2.08)	169 (2 RCTs)	⊕⊕⊕◯ Moderate[c]	
Nasopharyngitis follow-up: 52 weeks INFORMATIVE	50 per 1,000	**36 per 1,000** (8 to 153)	**RR 0.71** (0.16 to 3.06)	173 (2 RCTs)	⊕⊕⊕◯ Moderate[h]	
Conjunctivitis follow-up: 52 weeks INFORMATIVE	50 per 1,000	**4 per 1,000** (73 to --)	**RR 0.08** (0.00 to 1.46)	173 (2 RCTs)	⊕⊕⊕◯ Moderate[d]	
Herpes infections follow-up: 52 weeks INFORMATIVE	33 per 1,000	**27 per 1,000** (5 to 155)	**RR 0.80** (0.14 to 4.64)	173 (2 RCTs)	⊕⊕⊕◯ Moderate[h]	
Potential opportunistic infections follow-up: 52 weeks INFORMATIVE	17 per 1,000	**3 per 1,000** (0 to 72)	**RR 0.18** (0.01 to 4.31)	173 (2 RCTs)	⊕⊕⊕◯ Moderate[g]	
Parasitic infections follow-up: 52 weeks INFORMATIVE	not pooled	not pooled	not pooled	173 (2 RCTs)	⊕⊕⊕◯ Moderate[g]	No events in either arm.

*__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 consistent with no meaningful difference and benefit (based on MID of 12%)
b. CI consistent with no meaningful difference and benefit (based on MID of 15%)
c. CI consistent with no meaningful difference and benefit (based on MID of 10%)
d. Very low event rate in a small sample is concerning for precision (leading to a very wide CI)
e. CI consistent with no meaningful difference and benefit (based on MID of 3.4 points)

f. CI consistent with no meaningful difference and harm (based on MID of 2%)
g. Small sample is concerning for precision
h. CI consistent with no meaningful difference and harm (based on MID of 10%)

References

1. Silverberg JI, Wollenberg A, Stein Gold L, Del Rosso J, Yosipovitch G, Lio P et al. Patients with Moderate-to-Severe Atopic Dermatitis Maintain Stable Response with No or Minimal Fluctuations with 1 Year of Lebrikizumab Treatment. Dermatol Ther (Heidelb) 2024;14:2249-60.

e-Table 10. Nemolizumab Combination Therapy GRADE Summary of Findings (Short-term)

Nemolizumab 30mg every 4 weeks + TCS and/or TCI for 16 weeks to 24 weeks compared to placebo +TCS/TCI

Patient or population: Adolescents and adults aged 12+ with moderate to severe AD
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)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo +TCS/TCI	**Risk with nemolizumab + TCS and/or TCI**				
IGA Success (0,1) follow-up: 16 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]	⨁⨁⨁◯ Moderate[a]	
EASI 75 follow-up: 16 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]	⨁⨁⨁◯ Moderate[b]	

Pruritus improvement assessed with: ≥4-point improvement from baseline in PP-NRS score follow-up: 16 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
Discontinuation due to Adverse Event follow-up: 16 to 24 weeks CRITICAL	31 per 1,000	**27 per 1,000** (15 to 47)	**RR 0.86** (0.49 to 1.52)	1833 (3 RCTs)[1, 2]	⨁⨁⨁⨁ High
POEM assessed with: mean score change from baseline follow-up: 16 weeks CRITICAL	MD **3.95 points lower** (4.84 lower to 3.06 lower)		-	1702 (2 RCTs)[2]	⨁⨁⨁◯ Moderate[c]
Serious Adverse Events follow-up: 16 to 24 weeks CRITICAL	22 per 1,000	**25 per 1,000** (13 to 49)	**RR 1.16** (0.60 to 2.25)	1833 (3 RCTs)[1, 2]	⨁⨁⨁⨁ High
Flare prevention assessed with: proportion of patients with AD flares follow-up: 16 to 24 weeks CRITICAL	78 per 1,000	**51 per 1,000** (35 to 73)	**RR 0.65** (0.45 to 0.94)	1842 (3 RCTs)[1, 2]	⨁⨁⨁⨁ High
Quality of life assessed with: DLQI, change from baseline follow-up: 16 to 24 weeks CRITICAL	MD **2.5 points lower** (3.39 lower to 1.61 lower)		-	1601 (3 RCTs)[1, 2]	⨁⨁⨁◯ Moderate[d]
EASI 90 follow-up: 16 to 24 weeks INFORMATIVE	170 per 1,000	**259 per 1,000** (202 to 334)	**RR 1.53** (1.19 to 1.97)	1842 (3 RCTs)[1, 2]	⨁⨁⨁◯ Moderate[f]
Treatment-related Adverse Events assessed with: Participants with AE related to the treatment follow-up: 16 weeks INFORMATIVE	122 per 1,000	**168 per 1,000** (130 to 216)	**RR 1.38** (1.07 to 1.78)	1719 (2 RCTs)[2]	⨁⨁⨁◯ Moderate[e]

Treatment-emergent Adverse Events Assessed with: participants with any AE follow-up: 16 to 24 weeks INFORMATIVE	478 per 1,000	**492 per 1,000** (449 to 545)	**RR 1.03** (0.94 to 1.14)	1832 (3 RCTs)[1, 2]	⊕⊕⊕⊕ High
Serious Infections follow-up: 16 weeks INFORMATIVE	2 per 1,000	**1 per 1,000** (0 to 28)	**RR 0.84** (0.04 to 16.29)	1719 (2 RCTs)[2]	⊕⊕⊕⊕ High
Infections Assessed with: participants with any infection follow-up: 16 to 24 weeks INFORMATIVE	70 per 1,000	**86 per 1,000** (62 to 120)	**RR 1.22** (0.88 to 1.70)	1832 (3 RCTs)[1, 2]	⊕⊕⊕⊕ High

*__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

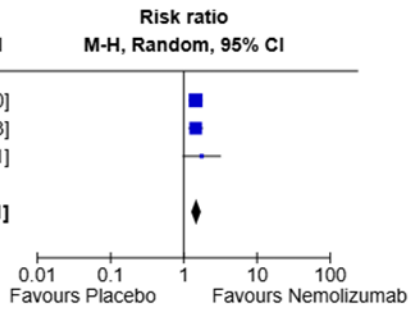
Explanations

a. Imprecision due to the 95% CI crossing the MCID of 12%
b. Imprecision due to the 95% CI crossing the MCID of 15%
c. Imprecision due to the 95% CI crossing the MCID of 3.4
d. Imprecision due to the 95% CI crossing the MID of 3.3 points
e. Imprecision due to the 95% CI crossing the MCID of 5%
f. Imprecision due to the 95% CI crossing the MCID of 10%

Analysis. IGA (0,1)

Study or Subgroup	Nemolizumab Events	Nemolizumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
ARCADIA 1	221	620	79	321	49.3%	1.45 [1.16 , 1.80]
ARCADIA 2	197	522	69	265	44.3%	1.45 [1.15 , 1.83]
Silverberg 2020	21	57	12	57	6.4%	1.75 [0.95 , 3.21]
Total (Wald[a])		**1199**		**643**	**100.0%**	**1.47 [1.26 , 1.71]**
Total events:	439		160			

Test for overall effect: Z = 4.88 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.35, df = 2 (P = 0.84); I² = 0%

Footnotes

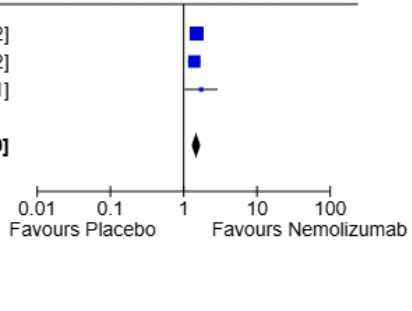
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. EASI75

Study or Subgroup	Nemolizumab Events	Nemolizumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
ARCADIA 1	270	620	93	321	50.1%	1.50 [1.24 , 1.82]
ARCADIA 2	220	522	80	265	42.9%	1.40 [1.13 , 1.72]
Silverberg 2020	26	57	15	57	7.0%	1.73 [1.03 , 2.91]
Total (Wald[a])		**1199**		**643**	**100.0%**	**1.47 [1.28 , 1.69]**
Total events:	516		188			

Test for overall effect: Z = 5.52 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.67, df = 2 (P = 0.71); I² = 0%

Footnotes

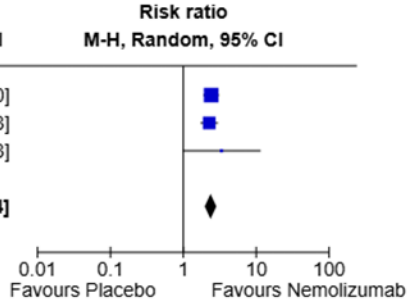
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. Pruritus improvement

Study or Subgroup	Nemolizumab Events	Nemolizumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
ARCADIA 1	265	620	57	321	53.2%	2.41 [1.87 , 3.10]
ARCADIA 2	214	522	48	265	44.6%	2.26 [1.72 , 2.98]
Silverberg 2020	10	57	3	57	2.2%	3.33 [0.97 , 11.48]
Total (Wald[a])		**1199**		**643**	**100.0%**	**2.36 [1.96 , 2.84]**
Total events:	489		108			

Test for overall effect: Z = 9.13 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.41, df = 2 (P = 0.81); I² = 0%

Footnotes

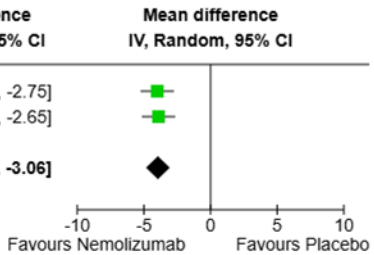
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. POEM

Study or Subgroup	Nemolizumab Mean	Nemolizumab SD	Nemolizumab Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean difference IV, Random, 95% CI
ARCADIA 1	-9	9.895454	612	-5	8.888194	316	50.0%	-4.00 [-5.25 , -2.75]
ARCADIA 2	-8.9	9.077445	515	-5	8.046738	259	50.0%	-3.90 [-5.15 , -2.65]
Total (Wald[a])			**1127**			**575**	**100.0%**	**-3.95 [-4.84 , -3.06]**

Test for overall effect: Z = 8.72 (P < 0.00001)



Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%

Footnotes

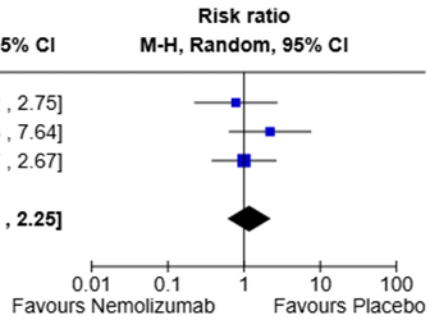
[a]CI calculated by Wald-type method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

Analysis. Serious adverse events

Study or Subgroup	Nemolizumab Events	Nemolizumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
ARCADIA 1	6	616	4	321	27.3%	0.78 [0.22 , 2.75]
ARCADIA 2	13	519	3	263	27.8%	2.20 [0.63 , 7.64]
Silverberg 2020	7	57	7	57	44.9%	1.00 [0.37 , 2.67]
Total (Wald[a])		**1192**		**641**	**100.0%**	**1.16 [0.60 , 2.25]**
Total events:	26		14			

Test for overall effect: Z = 0.45 (P = 0.65)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 1.49, df = 2 (P = 0.47); I² = 0%

Footnotes

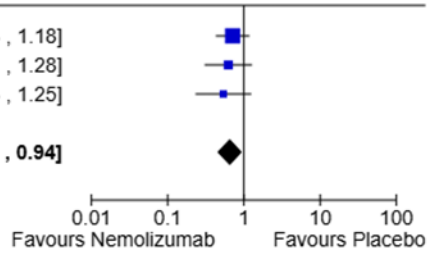
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. Flare prevention

Study or Subgroup	Nemolizumab Events	Nemolizumab Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
ARCADIA 1	33	620	24	321	53.6%	0.71 [0.43 , 1.18]
ARCADIA 2	16	522	13	265	26.9%	0.62 [0.31 , 1.28]
Silverberg 2020	7	57	13	57	19.5%	0.54 [0.23 , 1.25]
Total (Wald[a])		**1199**		**643**	**100.0%**	**0.65 [0.45 , 0.94]**
Total events:	56		50			

Test for overall effect: Z = 2.26 (P = 0.02)



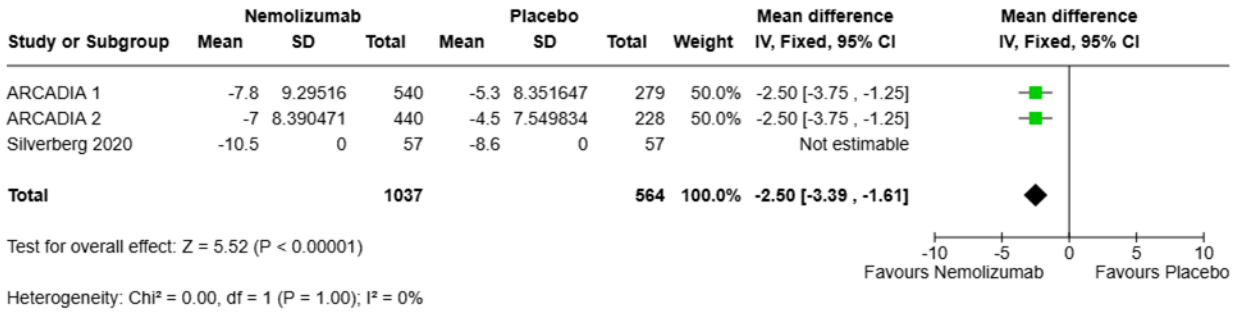
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.33, df = 2 (P = 0.85); I² = 0%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. Quality of life



References

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.