Lebrikizumab vs Other Systemic Monotherapies for Moderate-to-Severe Atopic Dermatitis: Network Meta-analysis of Efficacy

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SUPPLEMENTARY MATERIAL

Supplementary Methods

Systematic Literature Review (SLR)

To identify data from comparator studies for the network meta-analysis (NMA), a clinical SLR was conducted of randomized controlled trials (RCTs) in patients with moderate-to-severe atopic dermatitis (AD).

Sources Searched

A variety of sources were searched as part of the SLR, including the following electronic databases: The Cochrane Library (including The Cochrane Central Register of Controlled Trials [CENTRAL] and The Cochrane Database of Systematic Reviews), Embase (using the Elsevier Platform), and MEDLINE and MEDLINE In-Process (using the PubMed platform).

The following websites of professional organizations were searched to identify conference abstracts for the two most recent meetings: American Academy of Dermatology (AAD) annual meeting, Society for Investigative Dermatology (SID) annual meeting, European Academy of Dermatology and Venereology (EADV) congress, Revolutionizing Atopic Dermatitis (RAD), International Society of Atopic Dermatitis (ISAD), European Society for Pediatric Dermatology (ESPD), World Congress of Dermatology (WCD), World Congress of Pediatric Dermatology (WCPD).

To identify ongoing, discontinued, or completed clinical trials of lebrikizumab and comparators the following clinical trial registries were searched: ClinicalTrials.gov and International Clinical Trials Registry Platform.

In addition, the following key Health Technology Assessment (HTA) websites were searched for published assessments: National Institute for Health and Care Excellent (NICE), United States Food and Drugs Administration (FDA), European Medicines Agency (EMA), Pharmaceutical Benefits Advisory Committee (PBAC).

Reference lists of up to 25 relevant identified systematic reviews and meta-analyses were hand searched for further studies of interest.

SLR Eligibility Criteria

SLR eligibility criteria were specified in terms of patient population, intervention, comparator, outcome, time frame, and study design (PICOTS) (**Table S1)**. Search strategies for Embase, PubMed, and Cochrane databases are provided in **Table S2-4**. Only studies of European Medicines Agency-approved products evaluated in monotherapy trials were included in the feasibility assessment.

Study Selection and Data Extraction

Citations were downloaded using EndNote X20 and then exported into Microsoft Excel. Once all abstracts of potentially relevant published articles were identified, the study selection process was performed in the following two phases:

- Level 1 screen: Two researchers screened the titles and abstracts of studies identified from the electronic databases and internet searches, using the inclusion and exclusion criteria (**Table S1**). If disagreement about study relevance arose, consensus was reached through a third researcher.
- Level 2 screen: For the studies selected at level 1, full-texts were obtained and screened by 2 researchers, using the inclusion and exclusion criteria (**Table S1**). If disagreement about study relevance arose, consensus was reached through a third researcher.

Data were extracted from full-text publications, where available (i.e., abstracts and posters were not used unless an abstract or poster was the terminal source document). When a full-text journal publication was not available, the source used (e.g., abstract or poster) was noted. References to other publications within a study were traced to original sources, where appropriate. Data were extracted into an Excel spreadsheet. Any uncertainty about the data was checked by members of the research team not involved in the primary data extraction. Quality-control procedures included verification of all extracted data with original sources by a researcher who did not perform the primary data extraction.

If relevant data were reported in publications in graph form only, plot digitizer software (DigitizeIt) was used to extract numerical data [1]. The digitized plots were quality-control checked by a second researcher.

Network Meta-analysis

Assessment of Inconsistency

Network diagrams for all primary and secondary analysis results were investigated for presence of loops of evidence. A loop of evidence was identified in all monotherapy networks, since BREEZE-AD1 and BREEZE-AD2 were multi-arm trials investigating baricitinib 2 mg QD and baricitinib 4 mg QD versus placebo, but BREEZE-AD5 also investigated baricitinib 2 mg QD versus placebo. However, as the multi-arm trials are necessarily internally consistent, there was no concern with regard to conflict of indirect and direct evidence (i.e., loop inconsistency) in the monotherapy setting. It was therefore considered unnecessary to fit unrelated mean effects models as described in NICE DSU TSD 4, which would be highly complex given a large number of model parameters [2]. A recent publication also discusses the concept of design inconsistency,

which may be a possibility in these networks [3]. Design inconsistency amounts to a form of heterogeneity in study design, which was fully assessed in the feasibility assessment.

Simulation Parameters

Model parameters were estimated using a Markov Chain Monte Carlo (MCMC) method implemented in OpenBUGS, version 3.2.3 (revision 1012) [4]. For each analysis, three chains with different sets of initial values were used, and an initial 20,000 iterations were run as a burn-in period to achieve convergence. The burn-in was then discarded, and the analysis results were based on at least a further 40,000 iterations per chain with a thinning factor of 1 for a total of at least 120,000 iterations. Further iterations were conducted if there were concerns over convergence, and Monte Carlo standard errors (SEs) were checked to ensure sufficient accuracy [5].

Prior Distributions

Vague priors were specified for basic model parameters. The prior distribution for each parameter (μ_s, d_t, β) was Normal(0,100). The parameter $\boldsymbol{\mu}$ is indexed by study $\boldsymbol{s}$, and the parameter $\boldsymbol{d}$ is indexed by treatment $\boldsymbol{t}$. The parameter $\boldsymbol{\beta}$ refers to both the parameter for interaction between baseline risk and treatment in baseline risk model, and between baseline severity and treatment in network meta-regressions.

Informative priors were used to estimate the between-study standard deviation parameter τ^2 due to the lack of reliability in estimation of this parameter when specifying a vague (uniform) prior, based on inspection of auto-correlation and trace plots across parameters from this model. In particular, informative priors for τ^2 were specified as $\tau^2 \sim lognormal(-2.06, 1.51^2)$ based on the predictive distribution for between-study

heterogeneity given by Turner *et al*. for outcomes characterized as "signs/symptoms reflecting continuation/end of condition", which describes the outcomes assessed in this NMA [6].

Assessment of Convergence

Convergence was assessed using history trace plots, smoothed Kernel posterior density plots, and Brook–Gelman–Rubin (BGR) diagnostic plots for the primary analysis of Eczema Area and Severity Index (EASI) response, using the random effects (RE) model adjusted for baseline risk.

History trace plots of the parameters of interest display the evolution of the variables against iteration number and are a good tool to assess for non-convergence in the simulation. The plots must show all the characteristics of a random series: no trend over iteration number, values well-dispersed in space, and values which do not remain localized as iteration number increases.

The smoothed Kernel density plots were inspected and must show that the posterior density functions of each parameter of interest are approximately globally unimodal and symmetric. This will confirm whether convergence towards a sensible posterior distribution was achieved. In particular, convergence of the posterior distributions of the between-study standard deviations (SDs) were checked for all RE models.

Auto-correlation plots were used to assess the dependence between successive iterations of the Markov chains, and Monte Carlo SEs were checked to ensure sufficient information had been sampled. In particular, it was ensured that Monte Carlo SEs were less than 5% of the standard deviations of the basic model parameters [5].

Brook–Gelman–Rubin diagnostic plots were used to assess the within-chain and between-chain variability. Once the chains have converged, this variability should be approximately equal to one and should be stable across iterations.

Supplemental Tables and Figures

Table S1. SLR eligibility criteria/PICOTS

Study Characteristics	Eligible	Ineligible
Patient population	Adult or adolescent patients with moderate-to-severe AD Moderate-to-severe disease was defined by individual studies, defined by minimum requirements for baseline EASI scores (generally requiring a score of at least approximately 12), IGA scores (generally requiring a score of at least 3), as well as BSA involvement and occasionally pruritus NRS score at baseline	Patients with mild AD
Intervention[a]	Lebrikizumab	Interventions not listed within the inclusion criteria
Comparators	Upadacitinib, abrocitinib, baricitinib, dupilumab, lebrikizumab, and tralokinumab as part of a placebo-controlled monotherapy study	Comparators not listed within the inclusion criteria
Outcomes	Disease response: • Percentage of participants achieving IGA 0/1 response • Percentage of participants achieving 50% improvement on EASI (EASI 50) • Percentage of participants achieving 75% improvement on EASI (EASI 75) • Percentage of participants achieving 90% improvement on EASI (EASI 90) • Percent change from baseline in EASI score PROs: • Percentage change from baseline in pruritus/itch NRS • Percentage of participants who achieve a ≥4-point reduction from baseline in pruritus/itch NRS score • Percentage of participants who achieve a ≥4-point reduction from baseline in PP-NRS	Studies that do not report at least one of the outcomes of interest
Time Frame	No date limitations for full-text articles Conference abstracts published from 2019	Conference abstracts published before 2019
Study Design	Randomized, controlled, prospective clinical trials Systematic reviews, including meta-analyses	Non-randomized clinical trials and single-arm trials (pragmatic trials), phase I trials, observational studies, cohort studies, cross-sectional studies, case-control studies, epidemiological and/or ecological studies, prognostic studies, case reports, commentaries, letters, or editorials (publication type), consensus reports, non-systematic reviews, registry studies, retrospective studies, post hoc studies, surveys, preclinical studies, animal studies (not in humans), studies pooling moderate-to-severe ad results with other comorbidities and not presenting results separately, studies pooling results from several trials, post hoc analyses of entire study populations
Countries	All countries	No geographic limitations
Language	All languages	None

[a]To be included in the SLR, a study must have at least one of the interventions of interest in at least one study arm.

Abbreviations: AD, atopic dermatitis; AE, adverse event; BSA, body surface area; EASI, Eczema Area and Severity Instrument; IGA, investigator global assessment; NRS, numeric rating scale; PICOTS, patient population, intervention, comparator, outcome, time frame, and study design; PP-NRS, Peak Pruritus NRS score; PRO, patient-reported outcome; SLR, systematic literature review.

Table S2. Embase Search Strategy for the Systematic Literature Review

Search number	Search terms	Hits
Population		
#1	'atopic dermatitis'/exp OR ((atopic NEAR/1 dermatitis):ti,ab,de) OR 'atopic eczema':ti,ab,de OR 'coca sulzberger':ti,ab,de OR 'eczema atopica':ti,ab,de OR ((eczema NEAR/1 endogenous):ti,ab,de) OR ((eczema NEAR/1 infant*):ti,ab,de) OR ((neurodermatitis NEAR/1 constitutional*):ti,ab,de) OR 'neurodermatitis disseminata':ti,ab,de	54,611
Study type: RCTs		
#2	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	2,840,044
Exclusion terms		
#3	'animal'/exp NOT 'human'/exp	5,692,729
#4	comment*:ti OR 'letter':it OR 'editorial':it OR 'case report'/exp OR 'case stud*':ti OR 'case report*':ti OR 'case series':ti OR 'note':it OR 'short survey':it OR 'nonhuman'/exp OR 'animal experiment'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'animal model'/exp OR 'in vitro study'/exp OR 'in vitro':de,ab,ti OR 'in vitro studies':de,ab,ti OR 'in vitro technique':de,ab,ti OR 'in vitro techniques':de,ab,ti	15,703,139
All studies		
#5	#1 AND #2	7,365
#6	#5 NOT (#3 OR #4)	5,009
#7	#6 AND ([article]/lim OR [article in press]/lim OR [erratum]/lim OR [review]/lim)	3,650
#8	#6 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [1-1-2019]/sd NOT [31-12-2021]/sd	424
#9	#7 OR #8	**4,074**

RCT = randomized controlled trial.

Table S3. PubMed Search Strategy for the Systematic Literature Review

Search number	Search terms	Hits
Population		
#1	"Dermatitis, Atopic"[Mesh] OR "atopic dermatitis"[Text Word] OR "atopic eczema"[Text Word] OR "coca sulzberger"[Text Word] OR "eczema atopica"[Text Word] OR "endogenous eczema"[Text Word] OR "eczema infant*"[Text Word] OR "infant eczema"[Text Word] OR "infantile eczema"[Text Word] OR "infants eczema"[Text Word] OR "infants' eczema"[Text Word] OR "eczema infantum"[Text Word] OR "constitutional neurodermatitis"[Text Word] OR "neurodermatitis constitutionalis"[Text Word] OR "neurodermatitis disseminata"[Text Word]	31,525
Study type: RCTs		
#2	"randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms:noexp] OR "randomly"[Title/Abstract] OR "trial"[Title]	1,419,033
Exclusion terms		
#3	"Animals"[MeSH Terms] NOT "Humans"[MeSH Terms]	4,915,931
#4	"Comment"[Publication Type] OR "Letter"[Publication Type] OR "Editorial"[Publication Type] OR "Case Reports"[Publication Type] OR "case report*"[Title] OR "case stud*"[Title] OR "case series"[Title] OR "note"[Title] OR "Animal Experimentation"[Mesh] OR "Tissue Extracts"[Mesh] OR "Models, Animal"[Mesh] OR "In Vitro Techniques"[Mesh] OR "in vitro"[Text Word] OR "in vitro studies" OR "in vitro technique"[Text Word] OR "in vitro techniques"[Text Word]	6,404,762
All studies		
#5	#1 AND #2	3,102
#6	#5 NOT (#3 OR #4)	**2,674**

RCT = randomized controlled trial.

Table S4. Cochrane Search Strategy for the Systematic Literature Review

Search number	Search terms	Hits
Population		
#1	[mh "Dermatitis, Atopic"] OR (atopic NEAR/1 dermatitis):ti,ab,kw OR "atopic eczema":ti,ab,kw OR "coca sulzberger":ti,ab,kw OR "eczema atopica":ti,ab,kw OR (eczema NEAR/1 endogenous):ti,ab,kw OR (eczema NEAR/1 infant*):ti,ab,kw OR (neurodermatitis NEAR/1 constitutional*):ti,ab,kw OR "neurodermatitis disseminata":ti,ab,kw	5,181
Study type: RCTs		
#2	("randomized controlled trial" OR "controlled clinical trial"):pt OR (randomized OR placebo OR randomly OR trial OR groups):ti,ab,kw	1,448,320
Exclusion terms		
#3	[mh animals] NOT [mh humans]	59
#4	("Comment" OR "Letter" OR "Editorial" OR "Case Reports"):pt OR (case NEXT stud* OR case NEXT report* OR "case series" OR note):ti OR [mh "Animal Experimentation"] OR [mh "Tissue Extracts"] OR [mh "Models, Animal"] OR [mh "In Vitro Techniques"] OR "in vitro":ti,ab,kw OR "in vitro studies":ti,ab,kw OR "in vitro technique":ti,ab,kw OR "in vitro techniques":ti,ab,kw	43,343
All studies		
#5	#1 AND #2	4,224
#6	#5 NOT (#3 OR #4)	4,047
#7	#6 NOT "conference abstract":pt	3,254
#8	#6 AND "conference abstract":pt with Publication Year from 2019 to 2021, with Cochrane Library publication date from Jan 2019 to Dec 2021, in Trials	382
#9	#7 OR #8 **CDSR: 25** **CENTRAL: 3,610**	**3,635**

CDSR = Cochrane Database of Systematic Reviews; RCT = randomized controlled trial.

Table S5: Baseline demographic characteristics of patients in the 22 studies included in the NMA

Study (first author, year)	Treatment[a]	N	Age, (mean, SD)	Male, (N, %)	Race (%)		BMI, Mean (SD)
					White	Asian	
ADvocate1 (Silverberg JL, 2023) [7]	Lebrikizumab 250 mg Placebo	424	35.5 (17.4)	49.5	68.2	16.5	26.9 (6.3)
ADvocate2 (Silverberg JL, 2023) [7]	Lebrikizumab 250 mg Placebo	445	36.2 (16.9)	48.5	56.9	27.4	26.5 (6.5)
NCT03443024 (Guttman-Yassky E, 2020) [8]	Lebrikizumab 250 mg Placebo	207	40.2 (17.8)	42.0	52.2	9.2	28.9 (7.1)
LIBERTY AD ADOL (Simpson EL, 2020) [9]	Dupilumab 300mg Placebo	167	14.5 (1.8)	57.5	61.1	15.0	24.4 (7.0)
LIBERTY AD SOLO 1 (Simpson EL, 2016) [10]	Dupilumab 300 mg Placebo	448	39.6 (14.3)	55.4	67.2	24.6	26.3 (5.3)
LIBERTY AD SOLO 2 (Simpson EL, 2016) [10]	Dupilumab 300 mg Placebo	469	37.2 (14.0)	57.4	68.4	20.0	26.5 (5.8)
NCT03912259 (Zhao Y, 2022) [11]	Dupilumab 300 mg Placebo	165	30.6 (11.5)	71.5	0.0	100.0	-
NCT01859988 (Thaçi D, 2016) [12]	Dupilumab 300 mg Placebo	125	38.3 (12.6)	64.8	64.0	24.0	27.3 (6.8)
ECZTRA 1 (Wollenberg A, 2021) [13]	Tralokinumab 300 mg Placebo	802	38.8 (14.1)	59.1	70.3	20.0	-
ECZTRA 2 (Wollenberg A, 2021) [13]	Tralokinumab 300 mg Placebo	794	36.7 (14.6)	59.6	62.6	25.9	-
ECZTRA 5 (Merola JF, 2021) [14]	Tralokinumab 300 mg Placebo	215	34.2 (11.0)	41.4	54.9	15.8	-
ECZTRA 6 (Paller AS, 2023) [15]	Tralokinumab 300 mg Placebo	201	14.5 (1.7)	51.2	58.2	21.9	-
BREEZE-AD1 (Simpson EL, 2020) [16]	Baricitinib 4 mg Baricitinib 2 mg Placebo	497	35.5 (13.0)	63.0	58.8	30.0	25.0 (4.6)
BREEZE-AD2 (Simpson EL, 2020) [16]	Baricitinib 4 mg Baricitinib 2 mg Placebo	490	35.0 (13.4)	61.4	68.6	30.0	25.0 (4.5)

BREEZE-AD5 (Simpson EL, 2021) [17]	Baricitinib 4 mg Baricitinib 2 mg Placebo	293	39.3 (15.8)	50.9	56.3	18.8	-
NCT02780167 (2019) [18]	Abrocitinib 200 mg Abrocitinib 100 mg Placebo	167	40.8 (16.2)	47.9	70.1	10.2	27.9 (6.5)
JADE MOA (2023) [19]	Abrocitinib 200 mg Abrocitinib 100 mg Placebo	46	42.3 (17.7)	54.3	56.5	19.6	-
JADE MONO-1 (Simpson EL, 2020) [20]	Abrocitinib 200 mg Abrocitinib 100 mg Placebo	387	32.5 (16.1)	56.8	72.1	15.0	-
JADE MONO-2 (Silverberg JL, 2020) [21]	Abrocitinib 200 mg Abrocitinib 100 mg Placebo	391	35.1 (15.1)	58.6	59.3	33.0	-
NCT02925117 (Guttman-Yassky E, 2020) [22]	Upadacitinib 30 mg Upadacitinib 15 mg Placebo	125	39.4 (16.0)	60.8	57.6	23.2	27.0 (6.5)
Measure Up 1 (Guttman-Yassky E, 2021) [23]	Upadacitinib 30 mg Upadacitinib 15 mg Placebo	847	34.0 (15.7)	53.8	65.5	24.0	26.0 (6.1)
Measure Up 2 (Guttman-Yassky E, 2021) [23]	Upadacitinib 30 mg Upadacitinib 15 mg Placebo	836	33.6 (15.5)	56.3	69.0	21.9	26.0 (5.7)

[a]The JAK inhibitors abrocitinib, baricitinib, and upadacitinib were administered orally once daily. The monoclonal antibodies dupilumab, lebrikizumab, and tralokinumab were administered subcutaneously once every 2 weeks.
Abbreviations: AD, atopic dermatitis; BMI, body mass index; JAK, Janus kinase; NMA, network meta-analysis; SD, standard deviation.

Table S6: Baseline disease characteristics of patients in the 22 studies included in the NMA

Study (first author, year)	Treatment[a]	N	Years since diagnosis, (mean, SD)	EASI score (mean, SD)	IGA score of 4 (%)	SCORAD % (mean, SD)	POEM % (mean, SD)	DLQI (mean, SD)
ADvocate1 (Silverberg JL, 2023) [7]	Lebrikizumab 250 mg Placebo	424	22.6 (15.0)	29.5 (11.9)	40.3	66.1 (11.9)	-	15.4 (7.3)
ADvocate2 (Silverberg JL, 2023) [7]	Lebrikizumab 250 mg Placebo	445	20.6 (14.9)	29.7 (11.6)	35.3	66.4 (11.4)	-	15.6 (7.2)
NCT03443024 (Guttman-Yassky E, 2020) [8]	Lebrikizumab 250 mg Placebo	207	23.1 (17.1)	26.6 (11.0)	32.9	-	20.0 (6.4)	14.1 (7.3)
LIBERTY AD ADOL (Simpson EL, 2020) [9]	Dupilumab 300mg Placebo	167	12.4 (3.2)	35.4 (13.9)	53.3	70.5 (13.6)	21.1 (5.2)	13.1 (6.5)
LIBERTY AD SOLO 1 (Simpson EL, 2016) [10]	Dupilumab 300 mg Placebo	448	29.0 (15.3)	33.8 (14.0)	48.7	67.6 (14.0)	20.1 (6.1)	14.3 (7.3)
LIBERTY AD SOLO 2 (Simpson EL, 2016) [10]	Dupilumab 300 mg Placebo	469	27.7 (14.3)	32.7 (13.7)	49.0	68.2 (14.3)	20.9 (5.7)	15.4 (7.4)
NCT03912259 (Zhao Y, 2022) [11]	Dupilumab 300 mg Placebo	165	-	33.2 (13.1)	56.4	-	23.3 (4.4)	18.0 (6.2)
NCT01859988 (Thaçi D, 2016) [12]	Dupilumab 300 mg Placebo	125	30.2 (14.7)	33.4 (14.2)	47.2	67.8 (13.1)	-	13.7 (6.8)
ECZTRA 1 (Wollenberg A, 2021) [13]	Tralokinumab 300 mg Placebo	802	28.3 (14.7)	32.4 (13.8)	50.7	70.6 (12.9)	-	16.8 (7.0)
ECZTRA 2 (Wollenberg A, 2021) [13]	Tralokinumab 300 mg Placebo	794	28.1 (15.6)	32.2 (14.2)	48.7	70.1 (13.1)	-	17.7 (7.2)
ECZTRA 5 (Merola JF, 2021) [14]	Tralokinumab 300 mg Placebo	215	-	26.5 (11.0)	32.6	-	-	-
ECZTRA-6 (Paller AS, 2023) [15]	Tralokinumab 300 mg Placebo	201	12.1 (3.6)	31.6 (14.0)	46.3	68.1 (14.2)	-	-
BREEZE-AD1 (Simpson EL, 2020) [16]	Baricitinib 4 mg Baricitinib 2 mg Placebo	497	25.4 (15.1)	31.4 (12.6)	41.9	67.7 (13.5)	20.9 (5.6)	13.8 (7.4)
BREEZE-AD2 (Simpson EL, 2020) [16]	Baricitinib 4 mg Baricitinib 2 mg Placebo	490	24.3 (14.2)	33.6 (13.7)	50.2	68.4 (13.1)	20.5 (6.2)	14.3 (8.1)

BREEZE-AD5 (Simpson EL, 2021) [17]	Baricitinib 4 mg Baricitinib 2 mg Placebo	293	23.3 (16.4)	26.8 (11.1)	41.6	-	21.1 (6.0)	14.8 (7.4)
NCT02780167 (2019) [18]	Abrocitinib 200 mg Abrocitinib 100 mg Placebo	167	-	25.6 (12.8)	40.1	64.4 (13.3)	20.6 (6.0)	14.1 (7.6)
JADE MOA (2023) [19]	Abrocitinib 200 mg Abrocitinib 100 mg Placebo	46	-	26.6[b]	43.5[b]	-	-	-
JADE MONO-1 (Simpson EL, 2020) [20]	Abrocitinib 200 mg Abrocitinib 100 mg Placebo	387	23.5 (15.2)	30.5 (13.6)	40.8	65.5 (13.4)	19.6 (6.2)	14.5 (6.8)
JADE MONO-2 (Silverberg JL, 2020) [21]	Abrocitinib 200 mg Abrocitinib 100 mg Placebo	391	21.0 (14.7)	28.6 (11.5)	32.2	64.0 (12.3)	20.1 (5.7)	15.1 (6.8)
NCT02925117 (Guttman-Yassky E, 2020) [22]	Upadacitinib 30 mg Upadacitinib 15 mg Placebo	125	24.5 (16.3)	30.7 (13.0)	45.6	-	-	-
Measure Up 1 (Guttman-Yassky E, 2021) [23]	Upadacitinib 30 mg Upadacitinib 15 mg Placebo	847	20.7 (15.2)	29.5 (12.2)	45.2	67.2 (12.7)	21.4 (5.1)	16.5 (6.9)
Measure Up 2 (Guttman-Yassky E, 2021) [23]	Upadacitinib 30 mg Upadacitinib 15 mg Placebo	836	20.2 (13.8)	29.1 (12.0)	54.9	67.1 (12.6)	21.6 (5.0)	16.9 (7.0)

[a]The JAK inhibitors abrocitinib, baricitinib, and upadacitinib were administered orally once daily. The monoclonal antibodies dupilumab, lebrikizumab, and tralokinumab were administered subcutaneously once every 2 weeks.

[b]These study-level estimates were used in the network meta-regression.

Abbreviations: AD, atopic dermatitis; DLQI, dermatology orientated eczema measure; EASI, eczema are and severity index; IGA, Investigator Global Assessment; JAK, Janus kinase; NMA, network meta-analysis; POEM, patient orientated eczema measure; SCORAD, scoring atopic dermatitis; SD, standard deviation.

Table S7. Model fit statistic for EASI response at Week 16

Model	DIC	Dbar	Dhat	pD	Residual Deviance	Between-Trial SD	Beta (95% CrI)
FE unadjusted model	830.70	797.90	765.10	32.80	170.28	-	-
RE unadjusted model	834.20	794.80	755.40	39.41	167.16	0.101	-
FE BR model	834.20	800.20	766.20	33.99	172.51	-	-0.35 (-0.56, -0.09)
RE BR model	**837.00**	**795.10**	**753.20**	**41.90**	**167.42**	**0.100**	**-0.46 (-0.78, -0.14)**

Bold text indicates the selected model; residual deviance is to be interpreted with reference to 53 data points in this network. Abbreviations: BR, baseline risk; CrI, credible interval; Dbar, posterior mean residual deviance; Dhat, point estimate of the deviance; DIC, deviance information criterion; EASI, eczema area and severity index; FE, fixed effects; pD, effective number of parameters; RE, random effects; SD, standard deviation.

Table S8. Model fit statistics for IGA 0/1 response at Week 16

Model	DIC	Dbar	Dhat	pD	Residual Deviance	Between-Trial SD	Beta (95% CrI)
FE unadjusted model	316.30	285.30	254.30	31.02	48.32	-	-
RE unadjusted model	319.40	285.10	250.80	34.30	48.17	0.15	-
FE BR model	321.10	289.20	257.20	31.97	52.20	-	-0.57 (-0.76, -0.33)
RE BR model	**325.10**	**287.60**	**250.20**	**37.44**	**50.67**	**0.16**	**-0.68 (-0.97, -0.39)**

Bold text indicates the selected model; residual deviance is to be interpreted with reference to 53 data points in this network. Abbreviations: BR, baseline risk; CrI, credible interval; Dbar, posterior mean residual deviance; Dhat, point estimate of the deviance; DIC, deviance information criterion; FE, fixed effects; IGA, investigator global assessment; pD, effective number of parameters; RE, random effects; SD, standard deviation.

Table S9. Model fit statistics for pruritus/itch NRS response at Week 16

Model	DIC	Dbar	Dhat	pD	Residual Deviance	Between-Trial SD	Beta (95% CrI)
FE unadjusted model	321.60	291.50	261.40	30.06	57.00	NA	-
RE unadjusted model	321.60	285.90	250.10	35.75	51.37	0.213	-
FE BR model	329.00	298.30	267.50	30.77	63.76	NA	-0.64 (-0.91, -0.33)
RE BR model	**327.00**	**287.40**	**247.80**	**39.57**	**52.91**	**0.211**	**-0.79 (-1.09, -0.43)**

Bold text indicates the selected model; residual deviance is to be interpreted with reference to 48 data points in this network. Abbreviations: BR, baseline risk; CrI, credible interval; Dbar, posterior mean residual deviance; Dhat, point estimate of the deviance; DIC, deviance information criterion; FE, fixed effects; NRS, numeric rating scale; pD, effective number of parameters; RE, random effects; SD, standard deviation.

Table S10. Model fit statistics for pruritus/itch NRS response at Week 4

Model	DIC	Dbar	Dhat	pD	Residual Deviance	Between-Trial SD	Beta (95% CrI)
FE unadjusted model	252.20	226.30	200.30	25.96	42.78	NA	-
RE unadjusted model	254.50	225.50	196.50	29.01	41.97	0.191	-
FE BR model	255.00	228.00	201.10	26.92	44.53	NA	-0.52 (-0.74, -0.24)
RE BR model	**256.70**	**225.40**	**194.00**	**31.36**	**41.86**	**0.196**	**-0.60 (-0.90, -0.28)**

Bold text indicates the selected model; residual deviance is to be interpreted with reference to 39 data points in this network. Abbreviations: BR, baseline risk; CrI, credible interval; Dbar, posterior mean residual deviance; Dhat, point estimate of the deviance; DIC, deviance information criterion; FE, fixed effects; NRS, numeric rating scale; pD, effective number of parameters; RE, random effects; SD, standard deviation.

Table S11. NNT for clinical efficacy endpoints as estimated by a RE model adjusted for baseline risk

	NNT (95% CrI)					
	EASI 50	**EASI 75**	**EASI 90**	**IGA 0/1**	**PP NRS at week 4**	**PP NRS at week 12/16**
Upadacitinib 30 mg QD	1.57 (1.48, 1.69)	1.60 (1.47, 1.80)	1.91 (1.67, 2.25)	2.01 (1.74, 2.57)	1.75 (1.50, 2.22)	2.02 (1.74, 2.46)
Abrocitinib 200 mg QD	1.81 (1.64, 2.04)	1.97 (1.71, 2.33)	2.53 (2.08, 3.18)	3.04 (2.41, 4.05)	2.15 (1.77, 2.81)	2.31 (1.90, 2.93)
Upadacitinib 15 mg QD	1.86 (1.70, 2.10)	2.04 (1.79, 2.43)	2.66 (2.21, 3.35)	2.84 (2.30, 3.95)	2.25 (1.80, 3.08)	2.57 (2.09, 3.29)
Dupilumab 300 mg Q2W	2.26 (2.03, 2.59)	2.64 (2.27, 3.16)	3.69 (3.02, 4.67)	3.89 (3.11, 5.46)	7.43 (5.03, 12.20)	3.47 (2.78, 4.58)
Lebrikizumab 250 mg Q2W	2.38 (2.03, 2.93)	2.82 (2.28, 3.66)	4.01 (3.04, 5.56)	3.93 (3.04, 5.33)	4.95 (3.43, 7.74)	2.90 (2.26, 3.80)
Abrocitinib 100 mg QD	2.65 (2.22, 3.33)	3.22 (2.56, 4.27)	4.72 (3.51, 6.68)	5.42 (3.90, 8.12)	3.87 (2.81, 5.79)	3.50 (2.67, 4.91)
Tralokinumab 300 mg Q2W	3.84 (3.10, 4.96)	5.00 (3.85, 6.76)	7.92 (5.76, 11.32)	8.82 (6.36, 13.03)	16.67 (8.35, 47.44)	7.03 (4.81, 11.17)
Baricitinib 4 mg QD	4.38 (3.06, 7.40)	5.82 (3.80, 10.43)	9.43 (5.71, 18.15)	9.35 (5.28, 21.09)	5.27 (3.15, 10.71)	8.10 (4.42, 19.64)
Baricitinib 2 mg QD	5.52 (3.80, 9.61)	7.55 (4.91, 13.86)	12.63 (7.67, 24.70)	10.54 (6.49, 21.47)	10.04 (5.62, 23.10)	11.12 (6.11, 29.30)
Placebo	-	-	-	-	-	-

For each trial, endpoints were measured at the primary endpoint timepoint (i.e., week 12 for abrocitinib and week 16 for all other treatments).
An EASI response was defined as ≥50%, ≥75%, or ≥90% reduction in EASI score from baseline. An IGA 0/1 response was defined as ≥2-point improvement from baseline. For ΔNRS, the endpoint was ≥4- point reduction in pruritus itch score from baseline to weeks 4 and 16. The NNT was estimated relative to placebo, with lower NNT values indicating higher efficacy.
Abbreviations: CrI, credible interval; EASI, eczema area and severity index; IGA, Investigator Global Assessment; NNT, number needed to treat; NRS, numeric rating scale; PP, peak pruritus; QD, daily; Q2W, every 2 weeks; RE, random effects.

Table S12. Ranking table for IGA 0/1 response, RE model adjusted for baseline risk

Comparator	Probability Best	Mean SUCRA	Median Rank (95% CrI)
Lebrikizumab 250 mg Q2W	0.00	0.61	5.00 (3.00, 6.00)
Dupilumab 300 mg Q2W	0.00	0.62	4.00 (3.00, 6.00)
Baricitinib 2 mg QD	0.00	0.18	9.00 (7.00, 9.00)
Baricitinib 4 mg QD	0.00	0.24	8.00 (6.00, 9.00)
Abrocitinib 100 mg QD	0.00	0.45	6.00 (5.00, 7.00)
Abrocitinib 200 mg QD	0.00	0.80	3.00 (2.00, 4.00)
Tralokinumab 300 mg Q2W	0.00	0.26	8.00 (7.00, 9.00)
Upadacitinib 15 mg QD	0.00	0.84	2.00 (2.00, 4.00)
Upadacitinib 30 mg QD	1.00	1.00	1.00 (1.00, 1.00)
Placebo	0.00	0.00	10.00 (10.00, 10.00)

Abbreviations: CrI, credible interval; IGA, Investigator Global Assessment; QD, daily; Q2W, every 2 weeks; RE, random effects; SUCRA, surface under the cumulative ranking curve.

Table S13. Ranking table for pruritus/itch NRS response (Week 16), RE model adjusted for baseline risk

Comparator	Probability Best	Mean SUCRA	Median Rank (95% CrI)
Lebrikizumab 250 mg Q2W	0.01	0.67	4.00 (2.00, 6.00)
Dupilumab 300 mg Q2W	0.00	0.52	5.00 (4.00, 6.00)
Baricitinib 2 mg QD	0.00	0.15	9.00 (7.00, 9.00)
Baricitinib 4 mg QD	0.00	0.24	8.00 (7.00, 9.00)
Abrocitinib 100 mg QD	0.00	0.52	5.00 (4.00, 6.00)
Abrocitinib 200 mg QD	0.15	0.87	2.00 (1.00, 4.00)
Tralokinumab 300 mg Q2W	0.00	0.28	7.00 (7.00, 9.00)
Upadacitinib 15 mg QD	0.01	0.77	3.00 (2.00, 5.00)
Upadacitinib 30 mg QD	0.84	0.98	1.00 (1.00, 2.00)
Placebo	0.00	0.00	10.00 (10.00, 10.00)

Abbreviations: CrI, credible interval; NRS, numerical rating scale; QD, daily; Q2W, every 2 weeks; RE, random effects; SUCRA, surface under the cumulative ranking curve.

Table S14. Estimated differences in outcomes between comparators relative to lebrikizumab in phase 3 studies only

Outcome measurement	Dupilumab 300 mg Q2W	Baricitinib 2 mg QD	Baricitinib 4 mg QD	Abrocitinib 100 mg QD	Abrocitinib 200 mg QD	Tralokinumab 300 mg Q2W	Upadacitinib 15 mg QD	Upadacitinib 30 mg QD	Placebo
EASI	-0.17 (-0.48, 0.13)	0.34 (0.02, 0.67)	0.20 (-0.14, 0.55)	-0.04 (-0.42, 0.34)	-0.48 (-0.86, -0.10)	0.24 (-0.08, 0.54)	-0.45 (-0.78, -0.11)	-0.80 (-1.13, -0.47)	0.99 (0.75, 1.23)
IGA 0/1	1.07 (0.65, 1.80)	0.46 (0.25, 0.86)	0.52 (0.26, 1.09)	0.69 (0.39, 1.29)	1.36 (0.78, 2.51)	0.46 (0.28, 0.77)	1.73 (1.02, 3.05)	3.02 (1.78, 5.36)	0.15 (0.10, 0.24)
NRS at week 4	0.96 (0.50, 1.68)	0.61 (0.35, 1.03)	0.99 (0.56, 1.81)	1.71 (0.72, 3.36)	4.41 (1.87, 8.61)	0.45 (0.25, 0.76)	3.72 (2.13, 6.18)	6.25 (3.57, 10.37)	0.18 (0.11, 0.27)
NRS at week 12/16	0.92 (0.58, 1.47)	0.30 (0.16, 0.53)	0.36 (0.19, 0.70)	0.93 (0.55, 1.58)	1.67 (0.98, 2.83)	0.44 (0.28, 0.71)	1.32 (0.80, 2.15)	2.21 (1.35, 3.63)	0.13 (0.09, 0.19)

A Bayesian NMA using a baseline-risk adjusted RE model was conducted for EASI, IGA 0/1, and pruritus/itch NRS score. For EASI response, probit differences (95% CrI) are shown. For IGA 0/1 response, ORs (95% CrI) are shown. For pruritus/itch NRS score at weeks 4 and 12/16, ORs (95% CrI) are shown.

Abbreviations: CrI, credible interval; EASI, eczema area and severity index; IGA, investigator global assessment; NMA, network meta-analysis; NRS, numeric rating scale; OR, odds ratio; QD, daily; Q2W, every 2 weeks; RE, random effects.

Table S15. Model fit statistics: EASI response adjusted for baseline mean EASI in network meta-regression

Model	DIC	Dbar	Dhat	pD	Residual Deviance	Between-Trial SD	Beta (95% CrI)
FE model adjusted for baseline mean EASI score	832.70	798.90	765.00	33.83	171.20	-	-0.01 (-0.04, 0.03)
RE model adjusted for baseline mean EASI score	835.70	795.20	754.80	40.44	167.56	0.11	-0.01 (-0.05, 0.04)

The RE model adjusted for baseline mean EASI score was selected for analyses; residual deviance is to be interpreted with reference to 53 data points in this network. The beta (95% CrIs) relates to the adjustment for baseline EASI score.
Abbreviations: CrI, credible interval; Dbar, posterior mean residual deviance; Dhat, point estimate of the deviance; DIC, deviance information criterion; EASI, eczema area and severity index; FE, fixed effects; pD, effective number of parameters; RE, random effects; SD, standard deviation.

Table S16. Model fit statistics: IGA 0/1 response adjusted for baseline IGA severity in network meta-regression

Model	DIC	Dbar	Dhat	pD	Residual Deviance	Between-Trial SD	Beta (95% CrI)
FE model adjusted for baseline IGA severity	317.20	285.30	253.3	31.98	48.30	-	0.02 (-0.02, 0.05)
RE model adjusted for baseline IGA severity	320.60	285.40	250.10	35.28	48.40	0.15	0.02 (-0.02, 0.05)

The RE model adjusted for baseline IGA severity was the selected model for analyses; residual deviance is to be interpreted with reference to 53 data points in this network. The beta (95% CrIs) relates to the adjustment for proportion of patients with an IGA score of 4 at baseline.
Abbreviations: CrI, credible interval; Dbar, posterior mean residual deviance; Dhat, point estimate of the deviance; DIC, deviance information criterion; FE, fixed effects; IGA, investigator global assessment; pD, effective number of parameters; RE, random effects; SD, standard deviation.

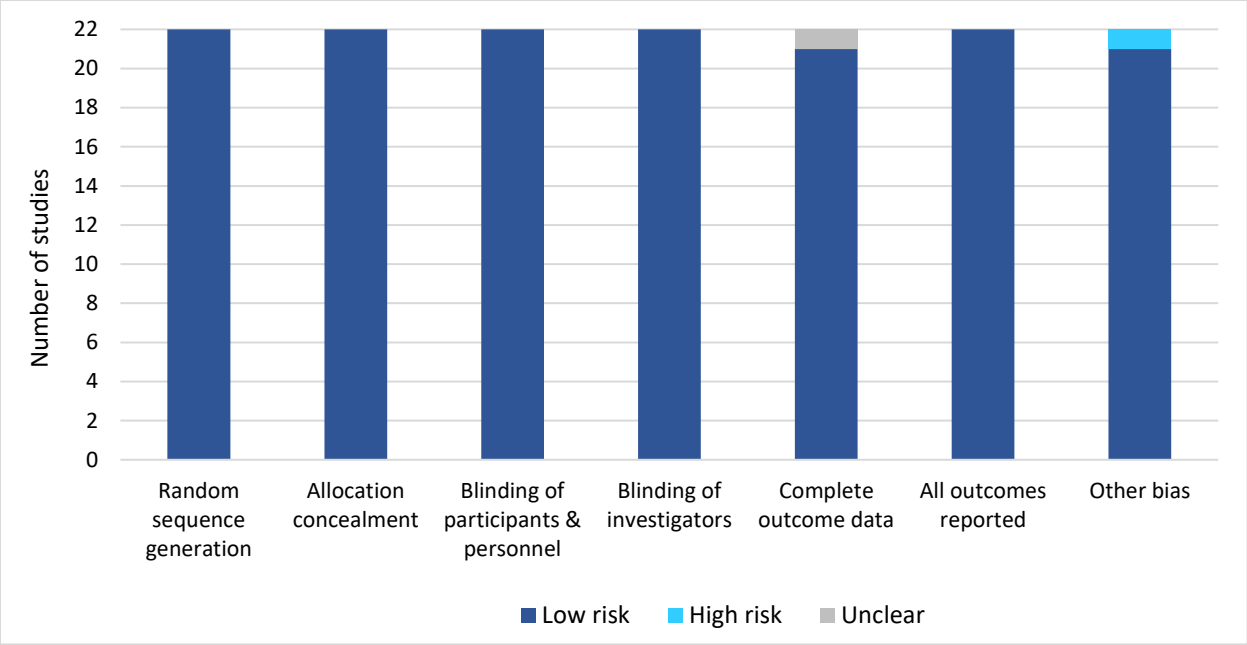

Figure S1. Overall risk of bias for studies included in the NMA (N=22)

Abbreviation: NMA, network meta-analysis.

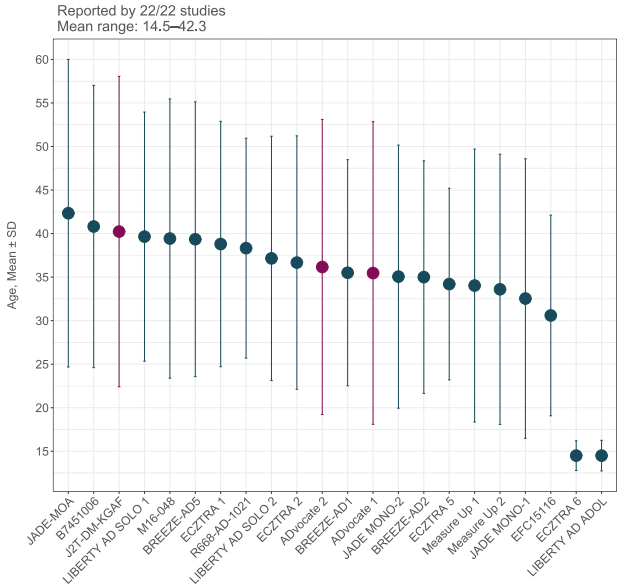

Figure S2. Heterogeneity assessment of age

Abbreviation: SD, standard deviation.

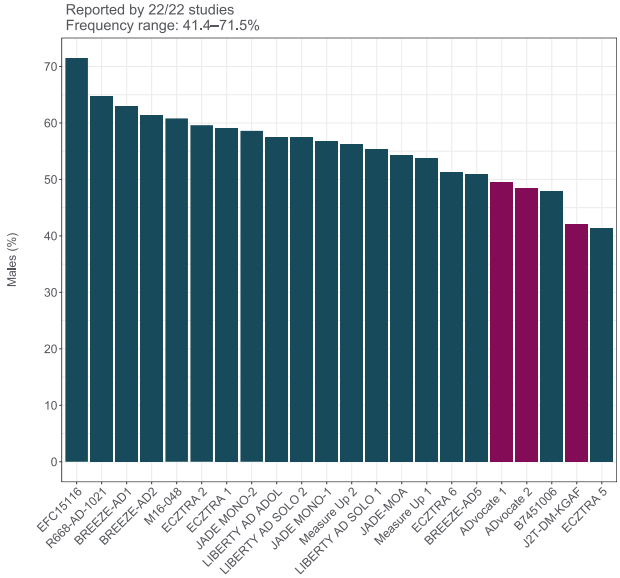

Figure S3. Heterogeneity assessment of sex

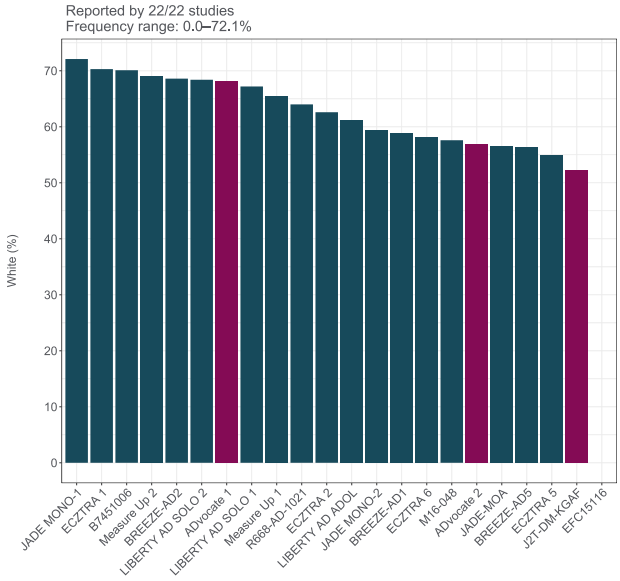

Figure S4. Heterogeneity assessment of White race

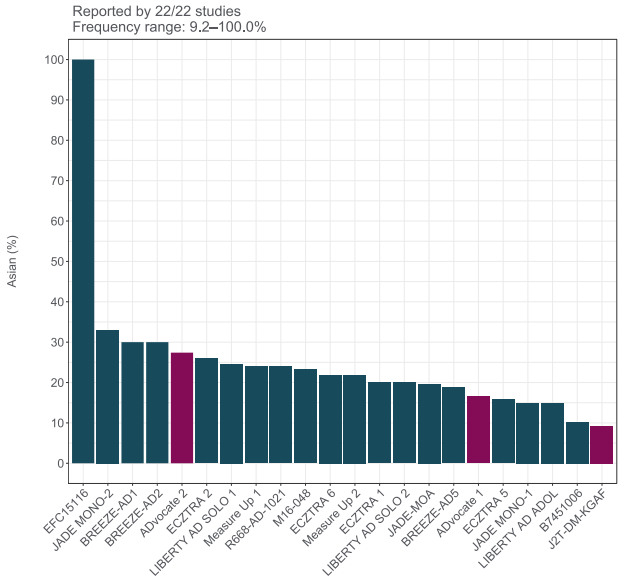

Figure S5. Heterogeneity assessment of Asian race

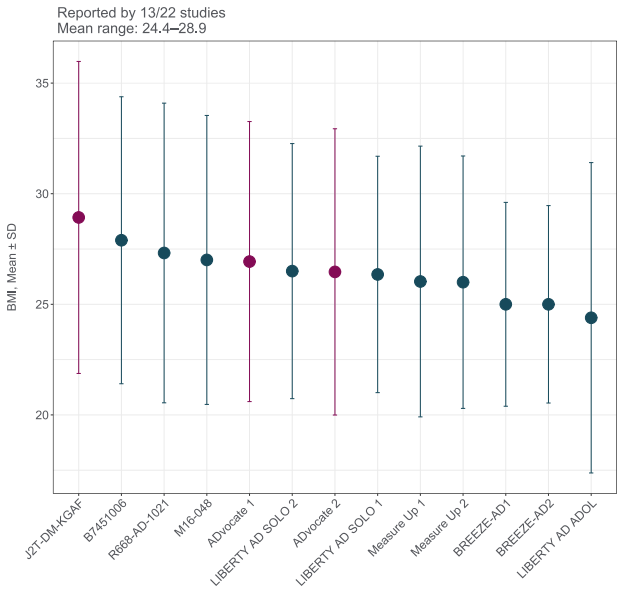

Figure S6. Heterogeneity assessment of BMI

Abbreviations: BMI, body mass index; SD, standard deviation.

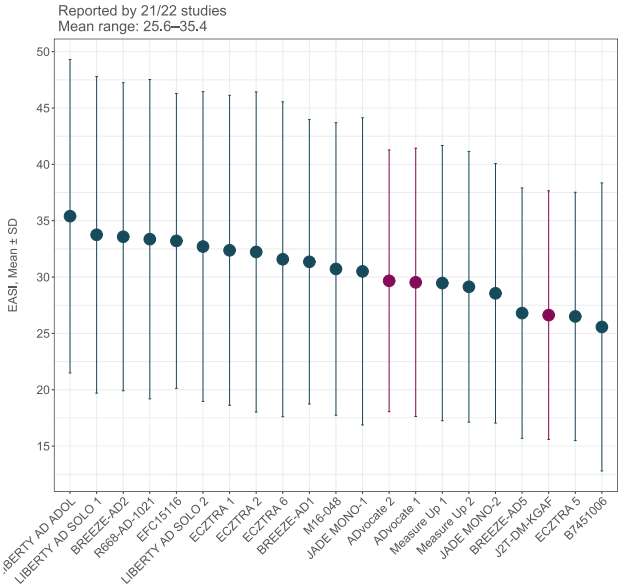

Figure S7. Heterogeneity assessment of baseline mean EASI

Abbreviations: EASI, eczema area and severity index; SD, standard deviation.

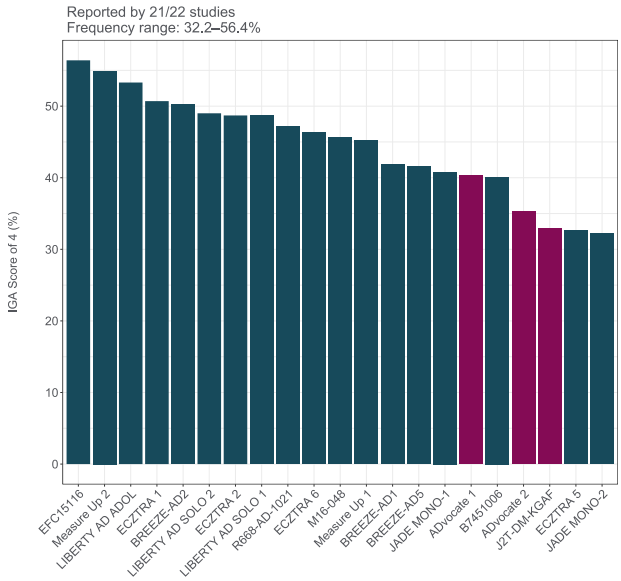

Figure S8. Heterogeneity assessment of baseline IGA of 4

Abbreviation: IGA, investigator global assessment.

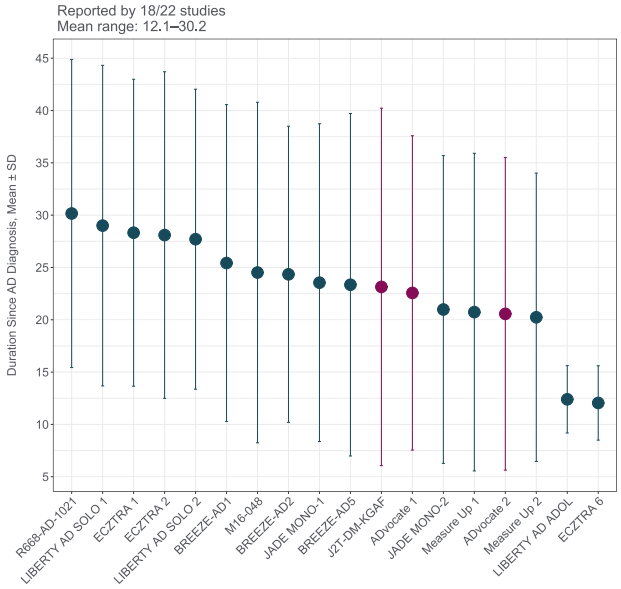

Figure S9. Heterogeneity assessment of time since AD diagnosis (years)

Abbreviation: AD, atopic dermatitis; SD, standard deviation.

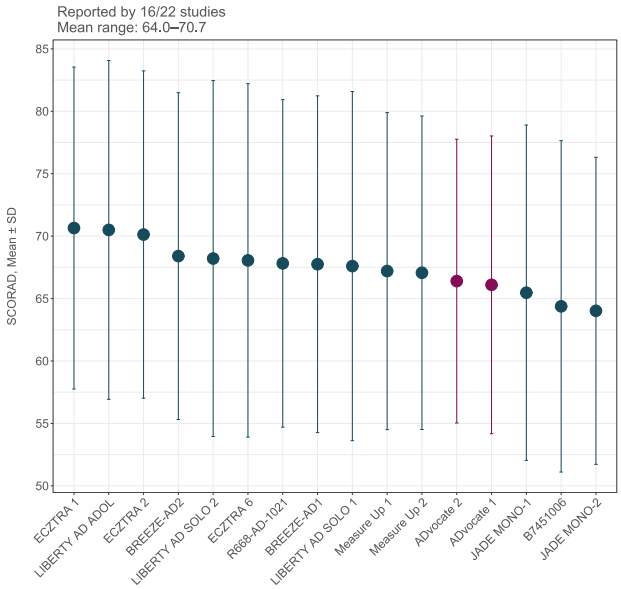

Figure S10. Heterogeneity assessment of SCORAD scores

Abbreviations: SCORAD, scoring atopic dermatitis; SD, standard deviation.

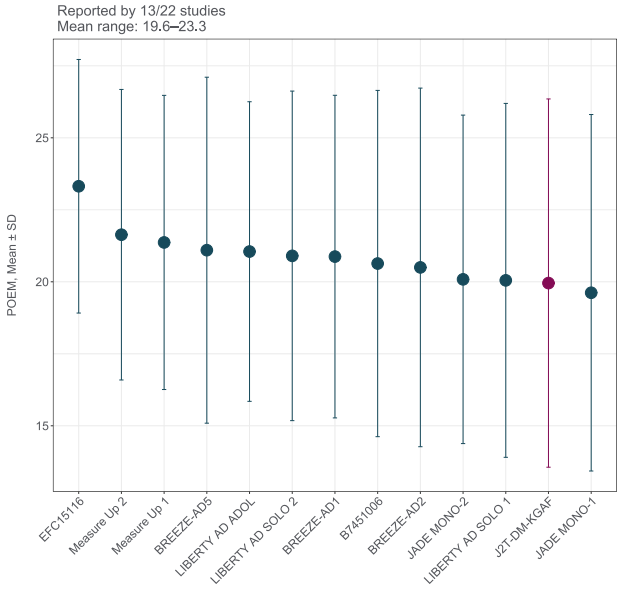

Figure S11. Heterogeneity assessment of POEM

Abbreviations: POEM, patient orientated eczema measure; SD, standard deviation.

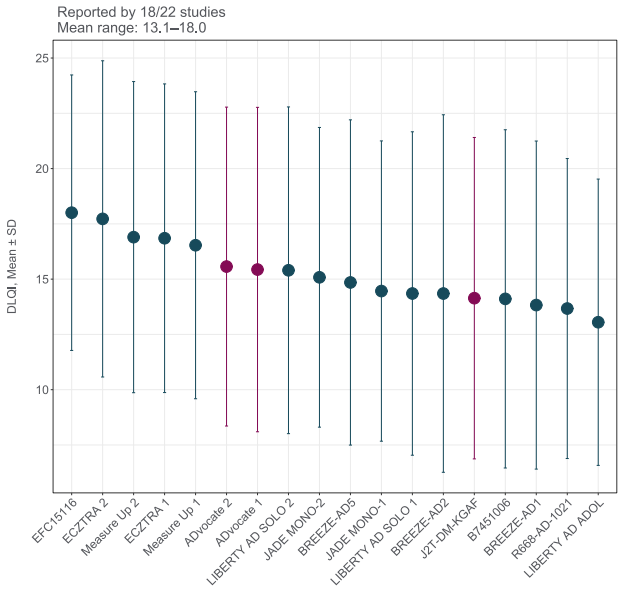

Figure S12. Heterogeneity assessment of DLQI

Abbreviations: DLQI, dermatology life quality index; SD, standard deviation.

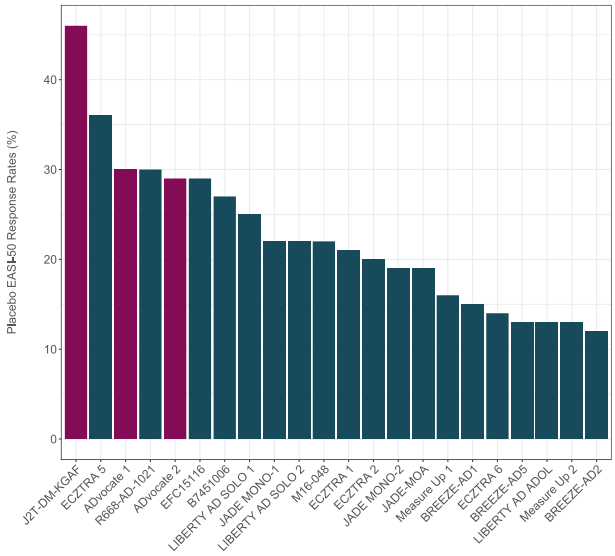

Figure S13. Placebo EASI 50 response: Monotherapy

Abbreviation: EASI, eczema area and severity index.

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