




SYSTEMATIC REVIEW

Comparative efficacy and safety of systemic therapies used in moderate-to-severe atopic dermatitis: a systematic literature review and network meta-analysis

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Abstract

Given the lack of head-to-head studies of systemic therapies in moderate-to-severe atopic dermatitis (AD), network meta-analyses (NMAs) can provide comparative efficacy and safety data to inform clinical decision-making. In this NMA, eligible randomized controlled trials (RCTs) published before 24 October 2019 were identified by a systematic literature review. Short-term (12–16 weeks) efficacy (Investigator's Global Assessment [IGA] and Eczema Area and Severity Index [EASI] responses), patient-reported outcomes (PROs) and safety data from each trial were abstracted and analysed separately for monotherapy and combination therapy (systemic plus topical anti-inflammatory therapy). RCTs were analysed in fixed-effects and random-effects Bayesian NMA models. Overall, 19 phase 2 and phase 3 RCTs of abrocitinib, baricitinib, dupilumab, lebrikizumab, nemolizumab, tralokinumab and upadacitinib were included. In monotherapy RCTs, upadacitinib 30 mg once daily (QD) had the numerically highest efficacy (83.6% achieved $\geq 50\%$ improvement in EASI [EASI-50 response]), followed by abrocitinib 200 mg QD (74.6%), upadacitinib 15 mg QD (70.5%), dupilumab 300 mg every 2 weeks (Q2W) (63.4%) and abrocitinib 100 mg QD (56.7%). Similar trends in EASI-75 and EASI-90 response were observed. In combination therapy RCTs, abrocitinib 200 mg QD had the highest EASI-50 (86.6%), followed by dupilumab 300 mg Q2W (82.4%) and abrocitinib 100 mg QD (79.7%). Similar findings were observed for IGA response and PROs. In monotherapy and combination therapy RCTs, the probability of treatment-emergent adverse events (TEAEs) was higher among all active treatments than with placebo (except for dupilumab 300 mg Q2W [odds ratio (OR), 0.96; 95% credible interval (CrI), 0.45–2.18] and abrocitinib 100 mg QD [OR, 0.95; 95% CrI, 0.35–2.66] in combination therapy RCTs), although active treatments did not significantly differ from one another. Abrocitinib, dupilumab and upadacitinib were consistently the most effective systemic therapies in adult and adolescent patients with AD, with no significant TEAE differences in short-term RCTs.

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Conflict of interests

J.I. Silverberg has served as an investigator for Celgene, Eli Lilly, F. Hoffmann-LaRoche, Menlo Therapeutics, Realm Therapeutics, Regeneron and Sanofi; as a consultant for Pfizer Inc., AbbVie, Anacor, AnaptysBio, Arena Pharmaceuticals, Dermavant, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Glenmark, Incyte, Kiniksa, LEO Pharma, Menlo Therapeutics, Novartis, Realm Therapeutics, Regeneron and Sanofi; and as a speaker for Regeneron and Sanofi. J.P. Thyssen is an advisor/investigator or speaker for Pfizer Inc., AbbVie, Eli Lilly, LEO Pharma, Regeneron, and Sanofi Genzyme. K. Fahrbach and K. Mickle are employees of Evidera Inc., which received research funding from Pfizer Inc. J.C. Cappelleri, W. Romero, M.C. Cameron, D.E. Myers, C. Clibborn, and M. DiBonaventura are employees and shareholders of Pfizer Inc.

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^aAt time of analysis.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense pruritus and eczematous lesions.^{1,2} Affecting up to 20% of children and 10% of adults globally,^{3,4} AD is significantly associated with decreased levels of health-related quality of life (QoL),^{5,6} increased work-related impairment^{5,7} and high healthcare costs.^{8–10}

Few treatment options are approved for patients with moderate-to-severe AD who require systemic therapy.¹¹ Dupilumab, an interleukin (IL)-4 receptor antagonist that blocks both IL-4 and IL-13, is a subcutaneously administered biologic therapy available for children 6 years of age and older, adolescents, and adults with moderate-to-severe AD.^{12,13} In Europe, baricitinib is approved for use in adults with moderate-to-severe AD who are candidates for systemic therapy,¹⁴ and cyclosporine is approved only in certain countries for severe AD but is associated with dose-dependent nephrotoxicity.¹⁵ Systemic immunosuppressants (methotrexate, azathioprine and mycophenolate mofetil) are also used off-label to treat moderate-to-severe AD, although their use is also associated with end-organ toxicities.¹⁵

Treatments under the development for moderate-to-severe AD include oral Janus kinase (JAK) inhibitors (abrocitinib [JAK1], upadacitinib [JAK1] and baricitinib [JAK 1/2; outside of Europe]),^{16–18} IL-13 antagonists (lebrikizumab¹⁹ and tralokinumab²⁰) and an IL-31 antagonist (nemolizumab²¹). Evaluating efficacy and safety of new interventions in comparison with existing treatments is important to assist healthcare decision-makers and inform future clinical practice. Network meta-analyses (NMAs) can be used to synthesize available evidence on multiple treatments not been directly compared in a randomized controlled trial (RCT)^{22,23} and also allow indirect comparisons from sets of trials with a common treatment (e.g. placebo). NMA methodology combines all available comparative evidence while preserving within-trial randomized treatment comparisons.

A recent NMA including data up to October 2019 examined the efficacy of systemic therapies in moderate-to-severe AD, although monotherapy and combination therapy trials were pooled and more recent trials were not included.²⁴ Another recent NMA of systemic therapies reported robust evidence for baricitinib, dupilumab and ciclosporin-A.²⁵ The objective of this study was to provide an up-to-date analysis of the comparative efficacy and safety of systemic treatments for moderate-to-severe AD as monotherapy and in combination with topical therapies.

Methods

Eligibility criteria

Included RCTs were identified through a systematic literature review (SLR) in accordance with the guidelines and recommendations of The Cochrane Collaboration.²⁶ Reporting of the SLR adhered to the Preferred Reporting Items for Systematic Reviews

and Meta-Analyses²⁷ and A Measurement Tool to Assess Systematic Reviews²⁸ (Methods S1). The search was limited to RCTs in adolescents (aged 12–17 years) or adults (aged ≥ 18 years) with moderate-to-severe AD, included identified systemic monotherapy or systemic therapy with topical anti-inflammatory therapy (combination therapy) and reported efficacy and/or safety. Titles and abstracts of citations identified from searches and content of relevant full texts were evaluated. Screening was conducted by 2 investigators at each stage, with a third investigator resolving any disagreements (Tables S1–S4).

Data extraction and risk of bias assessment

Data on patient population, treatments, timepoints and available outcomes of interest were extracted by one investigator and validated for accuracy by a second, senior investigator. Risk of bias was evaluated using The Cochrane Collaboration's Risk of Bias Assessment Tool.²⁶

Outcomes of interest

Primary outcomes of interest included responder definitions of Eczema Area and Severity Index (EASI) and Investigator's Global Assessment (IGA) measures.^{29,30} Secondary outcomes included the SCORing Atopic Dermatitis (SCORAD) and the following patient-reported outcomes (PROs): Peak Pruritus Numerical Rating Scale (PP-NRS), Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), and Hospital Anxiety and Depression Scale (HADS).^{31–35} Rates of treatment-emergent adverse events (TEAEs) and discontinuations owing to AEs were analysed.

Feasibility assessment

An assessment was conducted to evaluate the feasibility of an NMA for each outcome of interest, which includes determining whether sufficient data were available for generating an evidence network and whether clinical heterogeneity existed across studies on factors that could preclude a comparison or impact the results of analyses. The time range of interest was 12–16 weeks, with data being used from the latest timepoint available. Baseline characteristics of each trial were considered similar enough for comparison (Table S5). Baseline disease severity showed a small degree of variation across trials but was considered minor and did not warrant exclusion of any trials.

Statistical analysis

Information leveraged from each trial was maximized with a 4-level efficacy variable based on the nested relationship among outcomes (e.g. a patient cannot achieve $\geq 90\%$ improvement from baseline in EASI score [EASI-90 response] without also achieving $\geq 75\%$ and $\geq 50\%$ improvement from baseline [EASI-75 and EASI-50 response, respectively]). The 4 response levels (no response, EASI-50, EASI-75, EASI-90) represented the highest level of response achieved and were analysed using a Bayesian

multinomial approach with methods from the National Institute for Health and Clinical Excellence Decision Support Unit and the literature.^{36,37} Base-case analysis assumed no treatment-by-threshold interaction effect (i.e. the pattern of results was assumed to be identical at each level of response). Model fit was not improved in analyses that relaxed this assumption; hence, the more parsimonious base-case model is presented. Other efficacy and safety outcomes that do not exhibit hierarchical relationships were examined as binary (e.g. IGA response) or continuous outcomes (e.g. POEM mean change) in Bayesian NMAs.

All models for EASI and IGA response were adjusted for the absolute level of placebo rates (i.e. baseline risk models) unless model fit based on deviance information criterion was poorer after accounting for baseline risk.³⁶ Additionally, the default

approach was to implement random-effects models, with prior for treatment heterogeneity selected to be vaguely informative (U [0,1] for the between-trial standard deviation of probit or logit differences and U[0,7] for POEM mean change differences; median standard deviation in POEM pre/post change was used as the upper end of the distribution as the estimate of between-study heterogeneity rarely exceeds the patient-level standard deviation). However, a fixed-effects alternative was used if the estimates of the random-effects models were unstable because of sparse data. All NMAs were performed using OpenBUGS 3.2.3 and involved a 100 000 run-in iteration phase and a 100 000-iteration phase for parameter estimation. Although traditional concepts of statistical significance and null hypothesis testing do not exist in a Bayesian framework, we considered 95% credible intervals that do not overlap zero to represent statistically conclusive differences

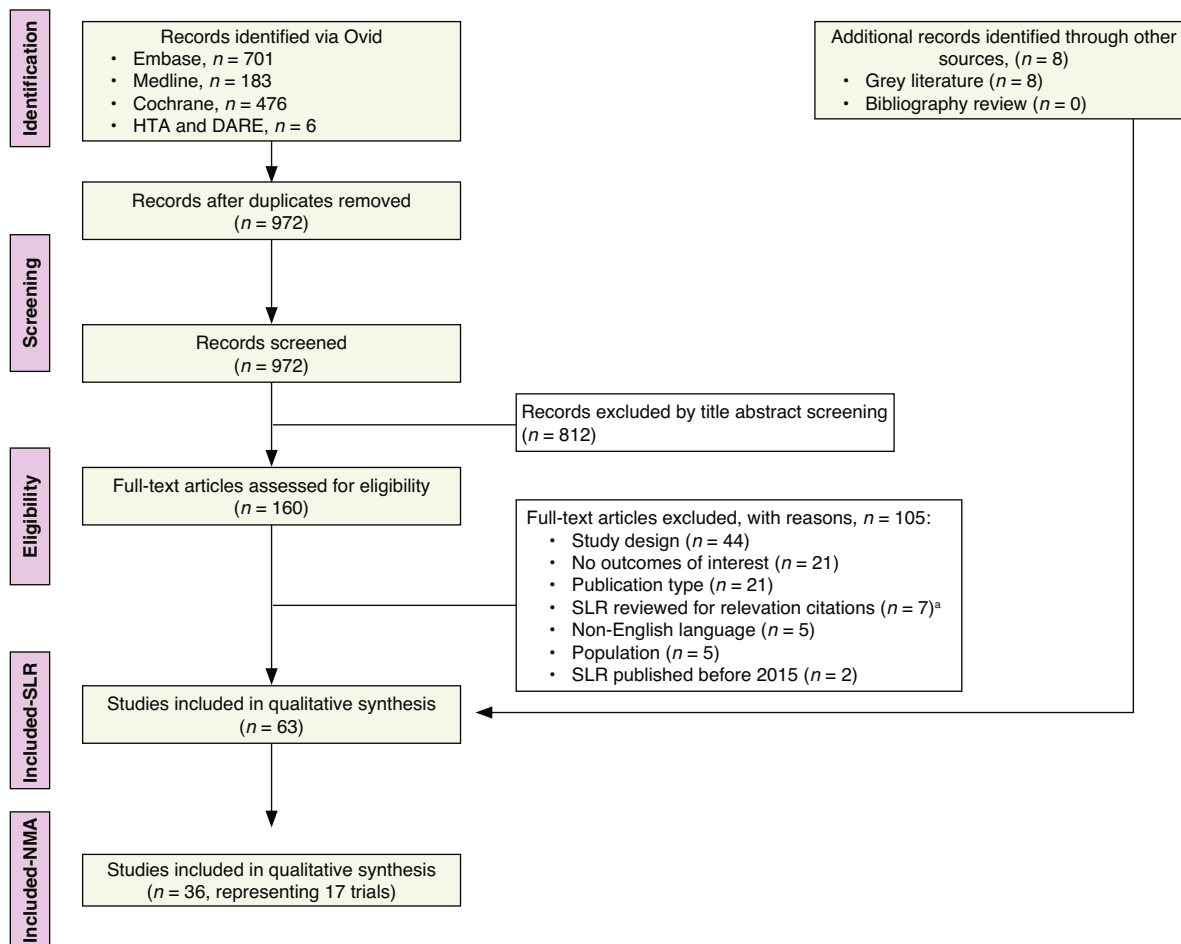


Figure 1 PRISMA study attrition diagram. ^aBibliographies were searched for relevant citations. DARE, database of abstracts of reviews of effects; HTA, health technology assessment; NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Table 1 Monotherapy and combination therapy trials included in the network meta-analysis

Trial name	Study phase	Study duration (weeks)	Interventions	Age (years)	EASI	IGA	PP-NRS	POEM	DLQI	HADS	TEAE	DAE
Monotherapy												
Abrocitinib phase 2b	2	12	Abrocitinib, placebo	Adults (18–75)	X	X	X					X
JADE MONO-1	3	12	Abrocitinib, placebo	Adolescents and adults (12+)	X	X	X	X	X	X	X	X
JADE MONO-2	3	13	Abrocitinib, placebo	Adolescents and adults (12+)	X	X	X	X	X	X	X	X
BREEZE-AD1	3	16	Baricitinib, placebo	Adults (unspecified)	X	X						
BREEZE-AD2	3	16	Baricitinib, placebo	Adults (unspecified)	X	X						
LIBERTY AD ADOL	3	16	Dupilumab, placebo	Adolescents (12–17)	X	X	X				X	X
LIBERTY AD SOLO 1	3	16	Dupilumab, placebo	Adults (18+)	X	X	X	X	X	X	X	X
LIBERTY AD SOLO 2	3	16	Dupilumab, placebo	Adults (18+)	X	X	X	X	X	X	X	X
Dupilumab phase 2b	2b	16	Dupilumab, placebo	Adults (18+)	X	X						X
XCIMA	2	12	Nemolizumab, placebo	Adults (18–65)	X							
Upadacitinib phase 2b	2b	16	Upadacitinib, placebo	Adults (18–75)	X			X				
Combination therapy												
JADE COMPARE	3	16	Abrocitinib, dupilumab placebo	Adults (18+)	X	X	X	X	X	X	X	X
BREEZE-AD7	3	16	Baricitinib, placebo	Adults (18+)	X	X	X	X	X	X	X	X
Baricitinib + TCS phase 2b	2	16	Baricitinib, placebo	Adults (18+)	X	X					X	X
LIBERTY AD CAFE	3	16	Dupilumab, placebo	Adults (18+)	X	X	X	X	X	X	X	X
LIBERTY AD CHRONOS	3	52	Dupilumab, placebo	Adults (18+)	X	X	X	X	X	X	X	X
TREBLE	2	12	Lebrikizumab, placebo	Adults (18–75)	X	X						
Nemolizumab phase 2b	2b	24	Nemolizumab, placebo	Adults (18+)	X	X	X					
Tralokinumab phase 2b	2b	12	Tralokinumab, placebo	Adults (18–75)	X	X	X				X	

DAE, discontinuation due to an adverse event; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; POEM, Patient-Oriented Eczema Measure; PP-NRS, Peak Pruritus-Numerical Rating Scale; TEAE, treatment-emergent adverse events.

between treatments; no overlap corresponds to roughly a $\geq 97.5\%$ probability that the better performing treatment has a superior effect relative to the worse performing treatment.

The networks included all doses investigated within each trial. However, to best inform healthcare decision-making, results do not focus on off-label dosing regimens of dupilumab or single administration of investigational biologic agents.

Results

Systematic review

972 unique records from electronic literature databases were identified. Following screening, 36 publications of 17 RCTs met inclusion criteria for the SLR and were considered eligible (Fig. 1).

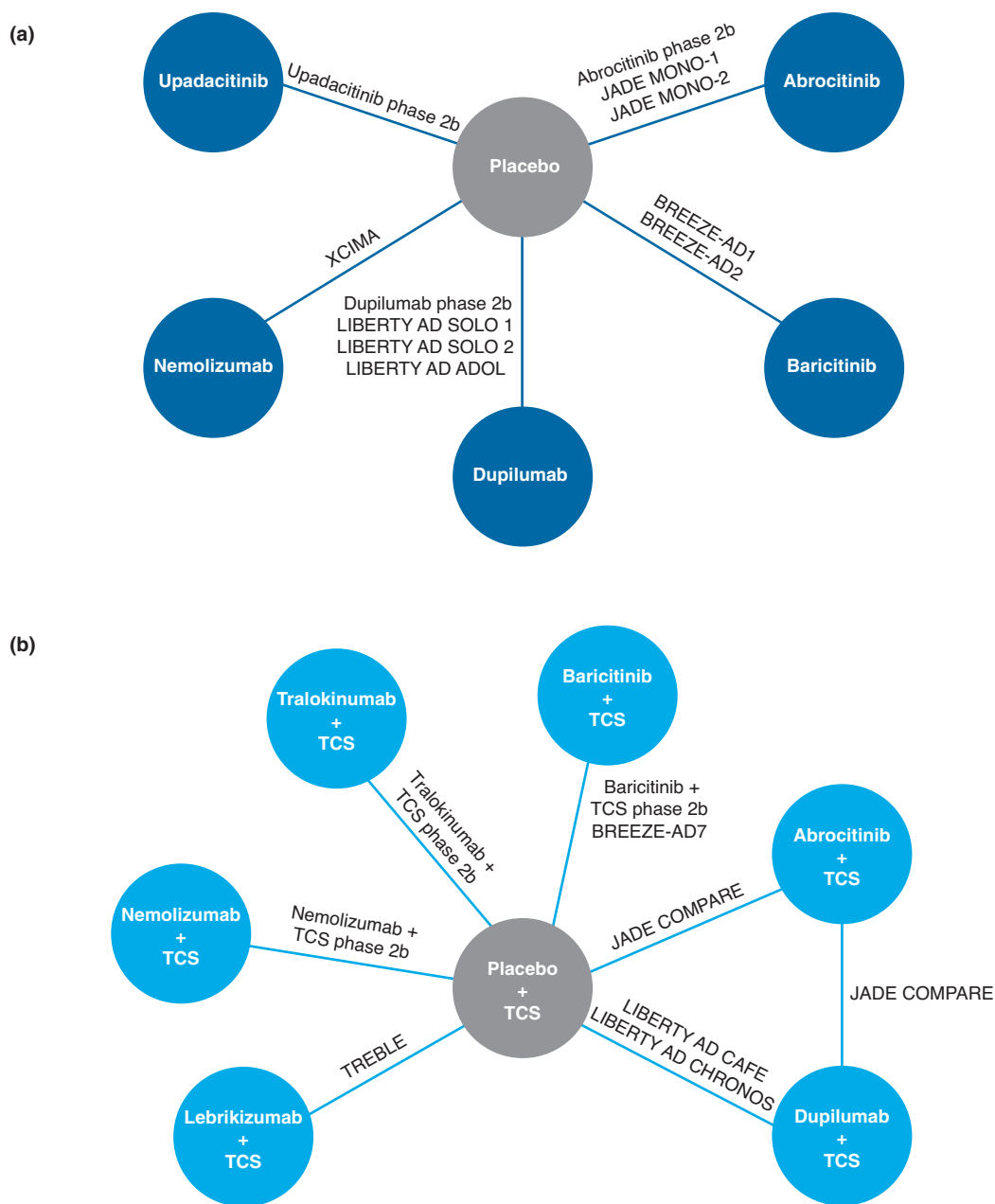


Figure 2 Network diagram for (a) monotherapy and (b) combination therapy trials. Not all outcomes were available for all trials. TCS, topical corticosteroids.

Study characteristics

Trials included present data on treatment with abrocitinib,^{16,38,39} baricitinib,^{17,40,41} dupilumab,^{42–46} lebrikizumab,⁴⁷ nemolizumab,^{21,48} tralokinumab²⁰ and upadacitinib⁴⁹ (Table 1 and Fig. 2). All JAK inhibitors were provided orally once daily; dupilumab and tralokinumab were provided by subcutaneous injection every 2 weeks; and lebrikizumab and nemolizumab were provided by subcutaneous injection every 4 weeks. Large phase 3 study results were available for abrocitinib, baricitinib and dupilumab. Phase 2 results were available for other treatments. Eligible trials assessing systemic immunosuppressants were identified but did not connect to the network and were not included. Not all trials included all outcomes; therefore, included comparisons represent the outcomes reported in all trials of a given network.

Risk of bias

Overall risk of bias was low, even when risk of blinding was unclear in most trials. All studies that met inclusion criteria were included in the NMA.

Statistical heterogeneity and inconsistency

Statistical heterogeneity, occurring when observed treatment effects vary more than expected due to sampling error, was calculated by examining I^2 values from direct, frequentist meta-analyses. There was little evidence of detectable heterogeneity. Inconsistency could not be assessed as there were no independent sources of indirect and direct evidence for the same comparison.

Network meta-analysis Monotherapy. Clinical efficacy—With respect to EASI response (11 studies, $N = 3339$), highest numerical efficacy in EASI-50 response was observed with upadacitinib 30 mg (84%), abrocitinib 200 mg (75%), upadacitinib 15 mg (70%), dupilumab 300 mg (63%) and abrocitinib 100 mg (57%). Both upadacitinib 30 mg and abrocitinib 200 mg exhibited a >97.5% probability of superiority over dupilumab 300 mg, both baricitinib doses and nemolizumab. Upadacitinib 30 mg was not statistically better than abrocitinib 200 mg (Table 2). Similar trends were observed with upadacitinib 30 mg, abrocitinib 200 mg, upadacitinib 15 mg, dupilumab 300 mg and abrocitinib 100 mg for EASI-75 (70%, 58%, 53%, 45% and 39%, respectively) and EASI-90 (52%, 39%, 34%, 28% and 22%, respectively) responses (Table 2).

For IGA response (9 studies, $N = 3188$), the baseline risk model was used given its better fit (deviance information criterion [DIC] = 144.5); all treatments exhibited $\geq 99\%$ probability of superiority to placebo (Fig. 3a). The greatest differentiation was observed for abrocitinib 200 mg (odds ratio [OR], 9.96; 95% credible interval [CrI], 7.77–12.59; >99.9% probability of superiority to placebo), dupilumab 300 mg (OR, 7.99; 95% CrI,

Table 2 Proportion of patients achieving each EASI threshold as estimated from the Bayesian network meta-analysis model

Treatment	Monotherapy (11 studies, $N = 3339$)		Combination therapy [†] (8 studies, $N = 2193$)	
	Median	95% CrI	Median	95% CrI
EASI-50 response				
Placebo	0.21	0.20–0.21	0.47	0.43–0.51
Baricitinib 2 mg QD	0.39	0.29–0.50	0.61	0.52–0.70
Baricitinib 4 mg QD	0.46	0.35–0.56	0.67	0.58–0.75
Dupilumab 200 mg Q2W	0.48	0.32–0.66	–	–
Dupilumab 200 or 300 mg Q2W	0.70	0.54–0.84	–	–
Dupilumab 300 mg Q2W	0.63	0.56–0.70	0.82	0.79–0.86
Lebrikizumab 125 mg Q4W	–	–	0.76	0.60–0.88
Nemolizumab 30 mg Q4W	–	–	0.78	0.66–0.87
Nemolizumab 0.5 mg/kg Q4W	0.36	0.18–0.57	–	–
Tralokinumab 300 mg Q2W	–	–	0.72	0.58–0.84
Upadacitinib 15 mg QD	0.70	0.45–0.89	–	–
Upadacitinib 30 mg QD	0.84	0.61–0.95	–	–
Abrocitinib 100 mg QD	0.57	0.47–0.66	0.80	0.74–0.85
Abrocitinib 200 mg QD	0.75	0.66–0.82	0.87	0.82–0.90
EASI-75 response				
Placebo	0.10	0.09–0.11	0.27	0.23–0.30
Baricitinib 2 mg QD	0.23	0.15–0.32	0.39	0.31–0.49
Baricitinib 4 mg QD	0.28	0.20–0.38	0.45	0.36–0.55
Dupilumab 200 mg Q2W	0.31	0.17–0.48	–	–
Dupilumab 200 or 300 mg Q2W	0.53	0.36–0.70	–	–
Dupilumab 300 mg Q2W	0.45	0.38–0.53	0.65	0.60–0.69
Lebrikizumab 125 mg Q4W	–	–	0.57	0.38–0.73
Nemolizumab 30 mg Q4W	–	–	0.59	0.45–0.72
Nemolizumab 0.5 mg/kg Q4W	0.20	0.09–0.39	–	–
Tralokinumab 300 mg Q2W	–	–	0.52	0.36–0.68
Upadacitinib 15 mg QD	0.53	0.28–0.78	–	–
Upadacitinib 30 mg QD	0.70	0.43–0.89	–	–
Abrocitinib 100 mg QD	0.39	0.29–0.48	0.61	0.54–0.68
Abrocitinib 200 mg QD	0.58	0.48–0.67	0.71	0.64–0.77
EASI-90 response				
Placebo	0.04	0.03–0.05	0.11	0.09–0.14
Baricitinib 2 mg QD	0.11	0.07–0.17	0.20	0.14–0.27
Baricitinib 4 mg QD	0.15	0.09–0.22	0.24	0.17–0.32
Dupilumab 200 mg Q2W	0.16	0.08–0.30	–	–
Dupilumab 200 or 300 mg Q2W	0.34	0.20–0.52	–	–
Dupilumab 300 mg Q2W	0.28	0.22–0.35	0.42	0.37–0.47
Lebrikizumab 125 mg Q4W	–	–	0.34	0.18–0.51
Nemolizumab 30 mg Q4W	–	–	0.36	0.24–0.50
Nemolizumab 0.5 mg/kg Q4W	0.10	0.03–0.22	–	–
Tralokinumab 300 mg Q2W	–	–	0.30	0.17–0.45
Upadacitinib 15 mg QD	0.34	0.14–0.62	–	–
Upadacitinib 30 mg QD	0.52	0.26–0.78	–	–
Abrocitinib 100 mg QD	0.22	0.15–0.30	0.38	0.31–0.45
Abrocitinib 200 mg QD	0.39	0.30–0.49	0.49	0.41–0.56

Not all treatments have been assessed in both monotherapy and combination therapy; missing data are denoted with –.

CrI, credible interval; EASI, Eczema Area and Severity Index; QD, once daily; Q2W, once every 2 weeks; Q4W, once every 4 weeks.

[†]In combination with topical therapy.

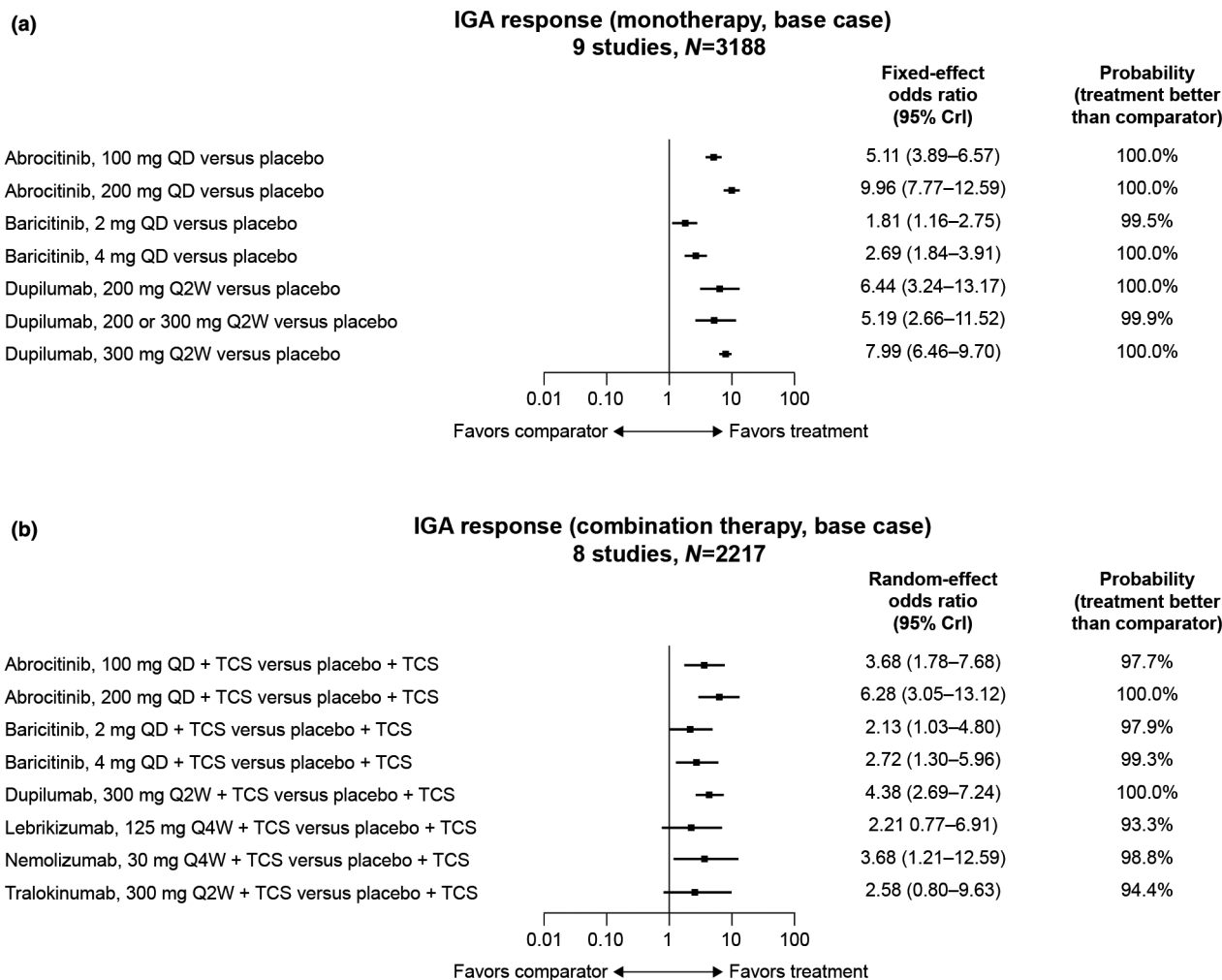


Figure 3 Odds ratios of achieving an IGA response compared with placebo in (a) monotherapy and (b) combination therapy. IGA response defined as clear (0) or almost clear (1) with ≥ 2 -point reduction from baseline. CrI, credible interval; IGA, Investigator’s Global Assessment; QD, once a day; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids.

6.46–9.70; >99.9% probability) and abrocitinib 100 mg (OR, 5.11; 95% CrI, 3.89–6.57; >99.9% probability; Table 3). Abrocitinib 200 mg had a 92.5% probability of superiority to dupilumab 300 mg and >99.9% probability of superiority to either baricitinib dose. The greatest SCORAD-50 responses ($\geq 50\%$ improvement from baseline; 4 studies, $N = 990$) were with upadacitinib 30 mg (OR, 24.34; 95% CrI, 5.50–144.75) and upadacitinib 15 mg (OR, 10.95; 95% CrI, 2.47–63.82; Table S6 and Fig. S4A).

Because efficacy evaluations were slightly different across included trials (12–16 weeks), post hoc sensitivity analyses limited to week 12 data were conducted to determine whether this would impact the results. Conclusions of week 12 results were similar to pooled results for weeks 12 to 16; therefore, the

remaining analyses leveraged pooled results (Fig. S1). Adjustment for baseline risk was explored for response outcomes and determined justified only for IGA response due to improvement in DIC.

Patient-reported outcomes—Abrocitinib and dupilumab had $\geq 99.9\%$ probability of achieving a better clinically meaningful PP-NRS4 response (≥ 4 -point improvement from baseline; 6 studies, $N = 1935$) than placebo (Fig. 4a). Abrocitinib 100 mg and 200 mg had 20.0% and 89.0% probability, respectively, of better PP-NRS4 response than dupilumab 300 mg. The upadacitinib and nemolizumab trials had not reported numerical PP-NRS4 response data at the time of our review. All treatments had $\geq 98.2\%$ probability of better symptom/QoL improvement

Table 3 League table comparing IGA response, PP-NRS4 response and safety outcomes among monotherapy treatments

Treatment	Odds ratio [95% CrI]					
	Placebo	Baricitinib 2 mg QD	Baricitinib 4 mg QD	Dupilumab 200 mg Q2W	Dupilumab 200 or 300 mg Q2W	Abrocitinib 100 mg QD
IGA response (9 studies, N = 3188)						
Baricitinib 2 mg QD	1.81 (1.16–2.75)					
Baricitinib 4 mg QD	2.69 (1.84–3.91)	1.49 (0.88–2.54)				
Dupilumab 200 mg Q2W	6.44 (3.24–13.17)	3.58 (1.65–7.89)	2.40 (1.14–5.20)			
Dupilumab 200 or 300 mg Q2W	5.19 (2.68–11.52)	2.89 (1.38–6.58)	1.94 (0.96–4.33)	0.81 (0.34–2.02)		
Dupilumab 300 mg Q2W	7.99 (6.46–9.70)	4.41 (2.69–7.25)	2.97 (1.88–4.61)	1.24 (0.59–2.57)	1.54 (0.64–3.14)	
Abrocitinib 100 mg QD	5.11 (3.89–6.57)	2.83 (1.69–4.73)	1.90 (1.18–3.03)	0.79 (0.36–1.68)	0.64 (0.47–0.88)	
Abrocitinib 200 mg QD	9.96 (7.77–12.59)	5.50 (3.33–9.16)	3.71 (2.31–5.85)	1.54 (0.71–3.24)	1.25 (0.92–1.70)	1.95 (1.42–2.67)
PP-NRS4 response (6 studies, N = 1935)						
Dupilumab 200 or 300 mg Q2W	12.48 (4.46–46.99)					
Dupilumab 300 mg Q2W	5.18 (3.63–7.49)			0.41 (0.11–1.24)		
Abrocitinib 100 mg QD	4.06 (2.65–6.39)			0.32 (0.08–1.00)	0.79 (0.45–1.39)	
Abrocitinib 200 mg QD	7.38 (4.81–11.68)			0.59 (0.15–1.83)	1.43 (0.81–2.52)	1.82 (1.35–2.46)
Treatment-emergent AEs (5 studies, N = 1866)						
Dupilumab 200 or 300 mg Q2W	1.13 (0.36–3.60)					
Dupilumab 300 mg Q2W	1.02 (0.49–2.15)			0.91 (0.23–3.51)		
Abrocitinib 100 mg QD	1.56 (0.72–3.39)			1.38 (0.34–5.54)	1.53 (0.52–4.41)	
Abrocitinib 200 mg QD	2.09 (0.96–4.54)			1.85 (0.46–7.44)	2.04 (0.69–5.94)	1.34 (0.63–2.85)
AEs leading to discontinuation (6 studies, N = 1748)						
Dupilumab 200 or 300 mg Q2W	0.20 (0.00–7.25)					
Dupilumab 300 mg Q2W	0.84 (0.21–3.38)			4.41 (0.09–2519.96)		
Nemolizumab 0.5 mg/kg Q4W	3.99 (0.32–109.95)			24.53 (0.24–17747.5)	4.76 (0.28–166.67)	
Abrocitinib 100 mg QD	0.52 (0.22–1.22)			2.63 (0.07–1464.11)	0.61 (0.12–3.17)	0.13 (0.00–1.81)
Abrocitinib 200 mg QD	0.52 (0.22–1.20)			2.64 (0.07–1578.14)	0.62 (0.12–3.14)	0.13 (0.00–1.79)

IGA response defined as clear (0) or almost clear (1) with ≥ 2 -point reduction from baseline. PP-NRS4 response defined as ≥ 4 -point improvement from baseline.

Cell numbers represent the odds ratio (95% CrI) of the row treatment meeting the response threshold (or experiencing the relevant AE) relative to the column treatment (e.g. baricitinib 2 mg QD has 1.81 the odds of achieving IGA response relative to placebo).

AE, adverse event; CrI, credible interval; IGA, Investigator's Global Assessment; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily; Q2W, once every 2 weeks; Q4W, once every 4 weeks.

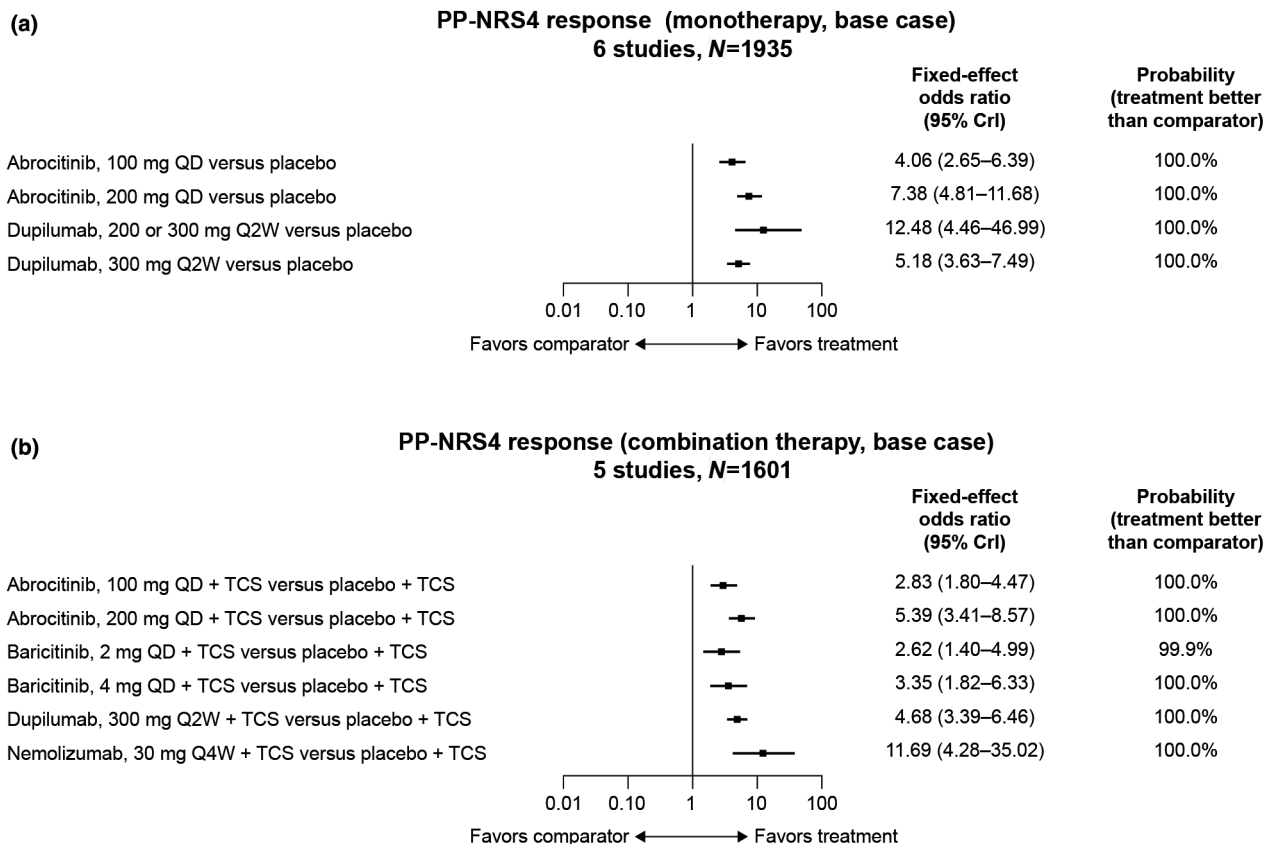


Figure 4 Odds ratios of achieving a PP-NRS4 response with (a) monotherapy and (b) combination therapy compared with placebo. PP-NRS4 response was defined as ≥ 4 -point improvement from baseline. CrI, credible interval; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once a day; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids.

than placebo. Greatest reductions in POEM scores (6 studies, $N = 1973$) versus placebo were with upadacitinib 30 mg (mean difference, -10.69 ; 95% CrI, -15.65 to -5.52) and abrocitinib 200 mg (mean difference, -7.16 ; 95% CrI, -9.85 to -4.46 ; Table S6 and Fig. S2A). The greatest reductions in DLQI scores (5 studies, $N = 1752$) were with dupilumab 200 mg (mean difference, -5.86 ; 95% CrI, -9.33 to -2.44) and abrocitinib 200 mg (mean difference, -5.46 ; 95% CrI, -7.87 to -2.94 ; Table S6 and Fig. S3A). The greatest reductions in HADS total scores (5 studies, $N = 1852$) versus placebo were with dupilumab 300 mg (mean difference, -3.48 ; 95% CrI, -5.16 to -1.05) and abrocitinib 200 mg (mean difference, -2.75 ; 95% CrI, -5.05 to -0.42 ; Table S6 and Fig. S5A).

Safety—Probability of TEAEs (5 studies, $N = 1866$) was numerically higher for all active treatments than placebo, ranging from an OR of 1.02 (95% CrI, 0.49–2.15) for dupilumab 300 mg to 2.09 (95% CrI, 0.96–4.54) for abrocitinib 200 mg (Fig. 5a).

Most active treatments had a numerically lower probability than placebo of having an AE leading to discontinuation (6 studies, $N = 1748$), including abrocitinib 100 mg (OR, 0.52; 95% CrI, 0.22–1.22), abrocitinib 200 mg (OR, 0.52; 95% CrI, 0.22–1.20) and dupilumab 300 mg (OR, 0.84; 95% CrI, 0.21–3.38; Fig. 6a). Patients treated with nemolizumab 0.5 mg/kg every 4 weeks were more likely to experience an AE leading to discontinuation (OR, 3.99; 95% CrI, 0.32–109.95; Table 3). No differences were statistically conclusive.

Combination therapy. Clinical efficacy—For EASI response (8 studies, $N = 2193$), the highest numerical efficacy in EASI-50 response was observed for abrocitinib 200 mg (87%), dupilumab 300 mg (82%), abrocitinib 100 mg (80%), nemolizumab 30 mg (78%) and lebrikizumab 125 mg (76%) (Table 2). Abrocitinib 200 mg exhibited a $>99\%$ probability of superiority over both baricitinib doses and 98.6% and 96% probability of superiority over tralokinumab 300 mg and dupilumab 300 mg,

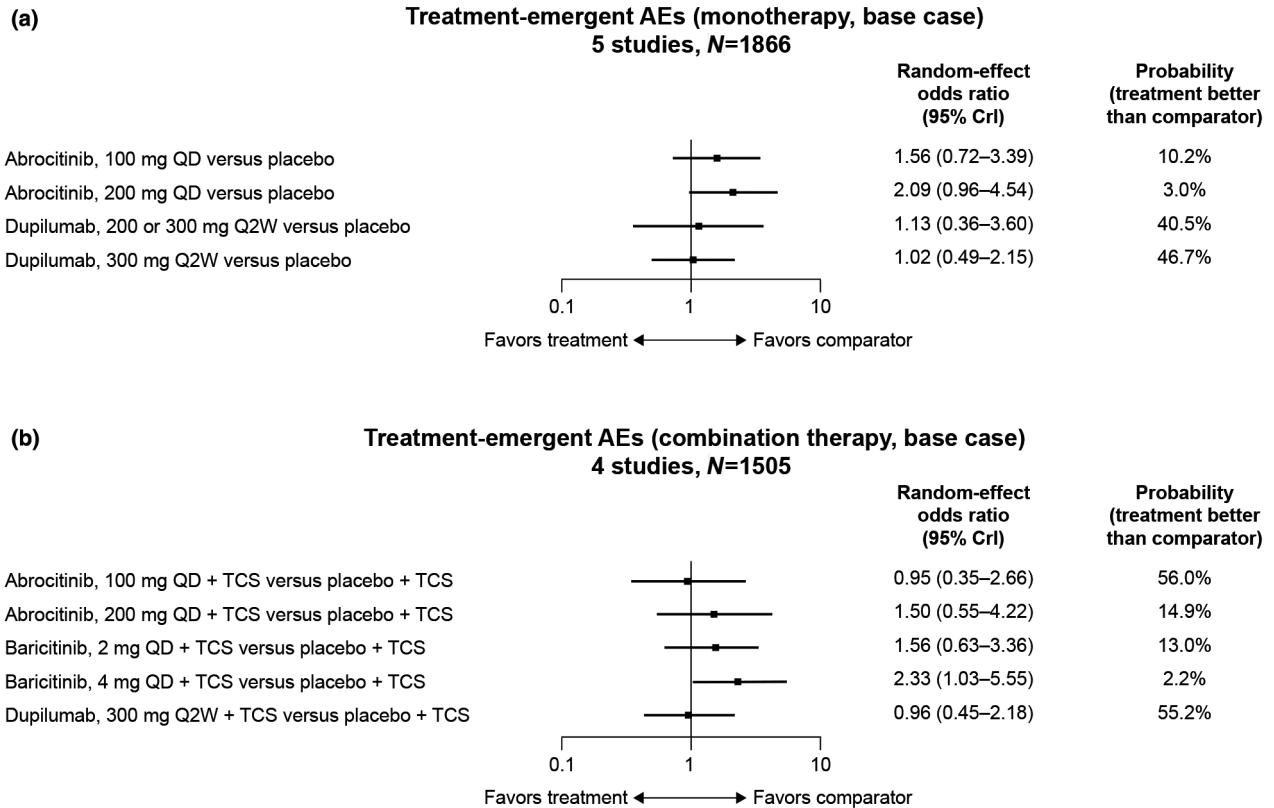


Figure 5 Odds ratios of experiencing a treatment-emergent AE with (a) monotherapy and (b) combination therapy compared with placebo. AE, adverse event; CrI, credible interval; QD, once a day; Q2W, every 2 weeks; TCS, topical corticosteroids.

respectively. Similar trends for abrocitinib 200 mg, dupilumab 300 mg, abrocitinib 100 mg, nemolizumab 30 mg and lebrikizumab 125 mg were observed for EASI-75 response (71%, 65%, 61%, 59% and 56%, respectively) and EASI-90 response (49%, 42%, 38%, 36% and 34%, respectively; Table 2).

All treatments exhibited $\geq 93\%$ probability of superiority to placebo in IGA response (8 studies, $N = 2217$; Fig. 3b). The greatest differentiation observed was for abrocitinib 200 mg (OR, 6.28; 95% CrI, 3.05–13.12; $>99.9\%$ probability of being more efficacious than placebo), dupilumab 300 mg (OR, 4.38; 95% CrI, 2.69–7.24; $>99.9\%$ probability), nemolizumab 30 mg (OR, 3.68; 95% CrI, 1.21–12.59, 98.8% probability) and abrocitinib 100 mg (OR, 3.68; 95% CrI, 1.78–7.68; 99.7% probability; Table 4). The greatest SCORAD-50 responses (4 studies, $N = 1225$) compared with placebo were with abrocitinib 200 mg (OR, 4.80; 95% CrI, 3.12–7.50) and dupilumab 300 mg (OR, 4.73; 95% CrI, 3.30–6.88; Table S7 and Fig. S4B).

Patient-reported outcomes—All treatments had $\geq 95\%$ probability of superiority to placebo in achieving PP-NRS4 response (5 studies, $N = 1601$; Fig. 4b), with the largest differences

observed for nemolizumab 30 mg (OR, 11.69; 95% CrI, 4.28–35.02; $>99.9\%$ probability of superiority to placebo), abrocitinib 200 mg (OR, 5.39; 95% CrI, 3.41–8.57; $>99.9\%$ probability) and dupilumab 300 mg (OR, 4.68; 95% CrI, 3.39–6.46; $>99.9\%$ probability; Table 4). All treatments had $\geq 99.9\%$ probability of greater symptom/QoL improvement than placebo. The greatest reductions in POEM scores (4 studies, $N = 1798$) were with abrocitinib 200 mg (mean difference, -8.21 ; 95% CrI, -13.15 to -3.06) and dupilumab 300 mg (mean difference, -7.04 ; 95% CrI, -10.25 to -3.81 ; Table S7 and Fig. S2B). The greatest reduction in DLQI scores (6 studies, $N = 2026$) was with abrocitinib 200 mg (mean difference, -5.52 ; 95% CrI, -7.35 to -3.75) and dupilumab 300 mg (mean difference, -4.62 ; 95% CrI, -5.84 to -3.46 ; Table S7 and Fig. S3B). The greatest reductions in HADS total scores (4 studies, $N = 1472$) were with abrocitinib 200 mg (mean difference, -3.06 ; 95% CrI, -7.53 to -1.47) and dupilumab 300 mg (mean difference, -2.30 ; 95% CrI, -5.23 – 0.54 ; Table S7 and Fig. S5B).

Safety—Numerically higher probabilities of TEAEs (4 studies, $N = 1505$) were observed with both baricitinib doses (2 mg;

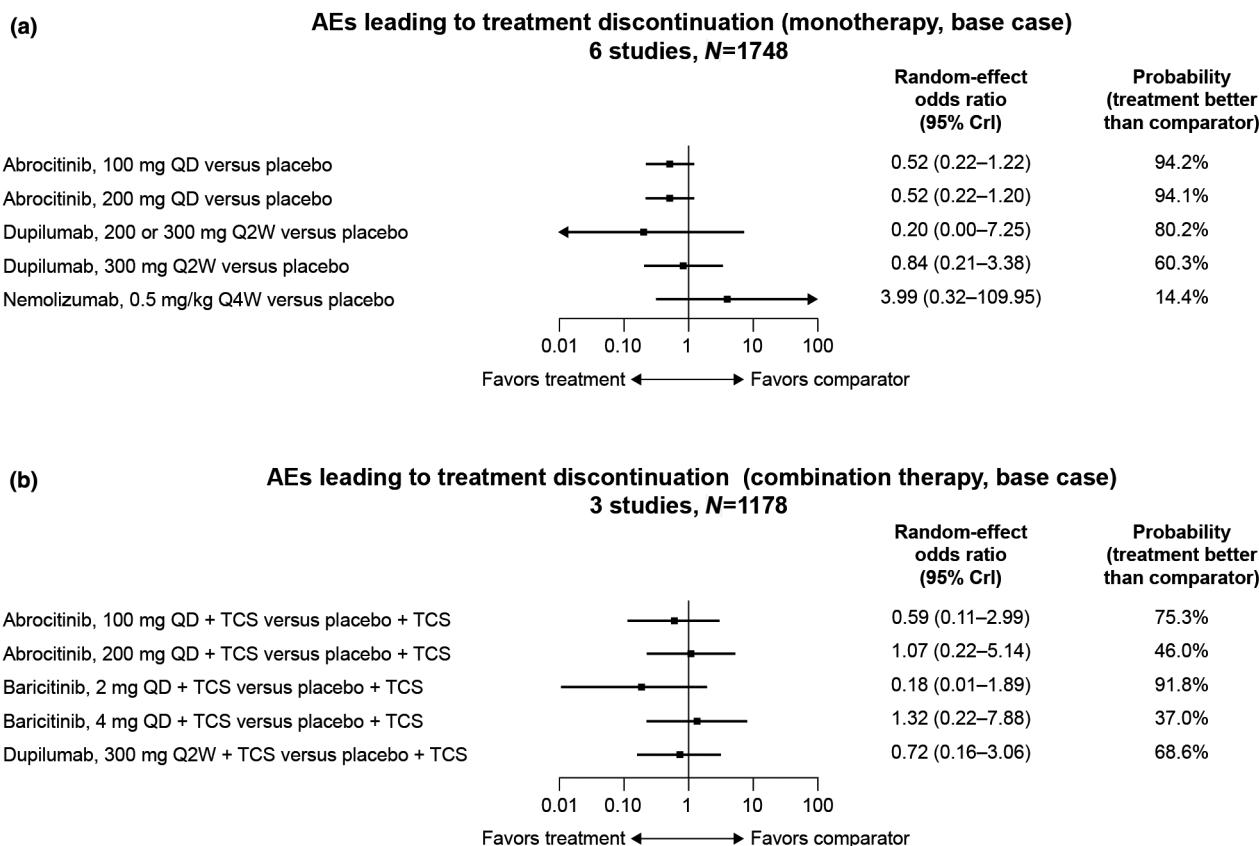


Figure 6 Odds ratios of experiencing an AE leading to discontinuation with (a) monotherapy and (b) combination therapy compared with placebo. AE, adverse event; CrI, credible interval; QD, once a day; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids.

OR, 1.56; 95% CrI, 0.63–3.36; 4 mg: OR, 2.33; 95% CrI, 1.03–5.55) and abrocitinib 200 mg (OR, 1.50; 95% CrI, 0.55–4.22) compared with placebo, but dupilumab 300 mg (OR, 0.96; 95% CrI, 0.45–2.18) and abrocitinib 100 mg (OR, 0.95; 95% CrI, 0.35–2.66) had numerically lower probabilities (Fig. 5b). A higher probability of AEs leading to discontinuation (3 studies, N = 1178) was observed with baricitinib 4 mg (OR, 1.32; 95% CrI, 0.22–7.88) and abrocitinib 200 mg (OR, 1.07; 95% CrI, 0.22–5.14) compared with placebo; other therapy/doses reported lower probabilities (Fig. 6b). These differences were not statistically conclusive (Table 4).

Discussion

Because direct head-to-head studies among systemic therapies in moderate-to-severe AD are not available, NMAs are an important means of examining comparative data of various treatments simultaneously. Although the focus and methods of this study vary from previous NMAs,^{24,25} the broad conclusions are similar. Results suggest that EASI response was highest for

abrocitinib 200 mg and upadacitinib 30 mg; although not statistically different from one another, EASI responses were meaningfully different (probability of superiority ≥97.5%) from all other treatments including dupilumab 300 mg and both baricitinib doses. Similar findings were observed for IGA.

Results of this NMA highlight the potential of JAK1 inhibition as a potent treatment for moderate-to-severe AD and suggest important clinical differentiation from other treatments. Clinical data on IL-13 inhibition are limited; however, results of this study also preliminarily suggest a trend towards a more efficacious profile for dual IL-4 and IL-13 inhibition by targeting IL-4 receptor alpha rather than IL-13 inhibition alone, although more research is needed.

The pattern of PROs was similar to that of clinical efficacy, yet the differentiation among treatments was reduced. The only meaningful separation at week 12/week 16 was between active treatments and placebo, in part because of inconsistent inclusion of PROs between trials. More research is needed to understand differences in PROs across treatments, but these results suggest

Table 4 League table comparing IGA response, PP-NRS4 response and safety outcomes among combination therapy

Treatment	Odds ratio [95% CrI]							
	Placebo	Baricitinib 2 mg QD	Baricitinib 4 mg QD	Dupilumab 300 mg Q2W	Lebrizumab 125 mg Q4W	Nemolizumab 30 mg Q4W	Tralokinumab 300 mg Q2W	Abrocitinib 100 mg QD
IGA response (8 studies, N = 2217)								
Baricitinib 2 mg QD	2.13 (1.03–4.80)							
Baricitinib 4 mg QD	2.72 (1.30–5.96)	1.27 (0.62–2.52)						
Dupilumab 300 mg Q2W	4.38 (2.69–7.24)	2.06 (0.79–4.94)	1.61 (0.63–3.94)					
Lebrizumab 125 mg Q4W	2.21 (0.77–6.91)	1.04 (0.26–4.04)	0.82 (0.21–3.21)	0.51 (0.16–1.74)				
Nemolizumab 30 mg Q4W	3.68 (1.21–12.59)	1.74 (0.44–7.03)	1.36 (0.35–5.61)	0.84 (0.25–3.11)	1.67 (0.33–8.26)			
Tralokinumab 300 mg Q2W	2.58 (0.80–9.63)	1.21 (0.29–5.47)	0.96 (0.23–4.22)	0.59 (0.16–2.37)	1.17 (0.22–6.32)	0.70 (0.13–4.00)		
Abrocitinib 100 mg QD	3.68 (1.78–7.68)	1.72 (0.58–4.85)	1.35 (0.47–3.82)	0.84 (0.42–1.66)	1.65 (0.44–6.03)	1.01 (0.24–3.76)	1.42 (0.32–5.79)	
Abrocitinib 200 mg QD	6.28 (3.05–13.12)	2.96 (0.98–8.18)	2.31 (0.80–6.44)	1.44 (0.72–2.84)	2.82 (0.73–10.25)	1.71 (0.41–6.39)	2.42 (0.55–9.79)	1.7 (0.82–3.58)
PP-NRS response (5 studies, N = 1601)								
Baricitinib 2 mg QD	2.62 (1.40–4.99)							
Baricitinib 4 mg QD	3.35 (1.82–6.33)	1.28 (0.72–2.27)						
Dupilumab 300 mg Q2W	4.68 (3.39–6.46)	1.79 (0.87–3.61)	1.4 (0.68–2.80)					
Nemolizumab 30 mg Q4W	11.69 (4.28–35.02)	4.46 (1.36–15.78)	3.49 (1.06–12.26)	2.5 (0.88–7.87)				
Abrocitinib 100 mg QD	2.83 (1.80–4.47)	1.08 (0.49–2.33)	0.84 (0.39–1.81)	0.6 (0.40–0.90)	0.24 (0.07–0.73)			
Abrocitinib 200 mg QD	5.39 (3.41–8.57)	2.06 (0.94–4.50)	1.61 (0.73–3.48)	1.15 (0.77–1.73)	0.46 (0.14–1.39)			1.91 (1.24–2.95)
Treatment-emergent AEs (4 studies, N = 1505)								
Baricitinib 2 mg QD	1.56 (0.63–3.36)							
Baricitinib 4 mg QD	2.33 (1.03–5.55)	1.50 (0.70–3.80)						
Dupilumab 300 mg Q2W	0.96 (0.45–2.18)	0.62 (0.21–2.13)	0.41 (0.13–1.31)					
Abrocitinib 100 mg QD	0.95 (0.35–2.66)	0.61 (0.18–2.45)	0.41 (0.11–1.50)	0.99 (0.36–2.64)				
Abrocitinib 200 mg QD	1.5 (0.55–4.22)	0.96 (0.28–3.88)	0.64 (0.17–2.39)	1.56 (0.56–4.18)				1.58 (0.55–4.59)
AEs leading to discontinuation (3 studies, N = 1178)								
Baricitinib 2 mg QD	0.18 (0.01–1.89)							
Baricitinib 4 mg QD	1.32 (0.22–7.88)	7.29 (0.67–245.67)						
Dupilumab 300 mg Q2W	0.72 (0.16–3.06)	3.97 (0.24–172.43)	0.55 (0.05–5.35)					
Abrocitinib 100 mg QD	0.59 (0.11–2.99)	3.29 (0.18–144.89)	0.44 (0.04–4.92)	0.81 (0.17–4.04)				
Abrocitinib 200 mg QD	1.07 (0.22–5.14)	5.94 (0.35–254.93)	0.82 (0.08–8.75)	1.49 (0.35–6.87)				1.83 (0.38–8.96)

IGA response defined as clear (0) or almost clear (1) with ≥ 2 -point reduction from baseline. PP-NRS4 response defined as ≥ 4 -point improvement from baseline.

Cell numbers represent the OR (95% CrI) of the row treatment meeting the response threshold (or experiencing the relevant AE) compared with the column treatment (e.g. baricitinib 2 mg QD in combination with topical therapy has 2.13 the odds of achieving IGA response compared with placebo in combination with topical therapy).

AE, adverse event; IGA, Investigator's Global Assessment; PP-NRS, Peak Pruritus-Numerical Rating Scale; QD, once daily; Q2W, once every 2 weeks; Q4W, once every 4 weeks.

that abrocitinib, upadacitinib and dupilumab consistently improved symptoms and disease-specific QoL in patients compared with placebo.

Assessing safety outcomes was challenging in this NMA because of the variability in types of information reported. Our analyses were limited to incidence of TEAEs and AEs that led to treatment discontinuation in short-term studies. No meaningful statistical differences were observed. Future research, including specific events of interest and trials that have longer follow-up times, is necessary to evaluate safety profiles of these treatments.

There are several limitations to this NMA. The analyses did not include change in EASI score; however, previous analyses showed that percentage change from baseline in EASI score is sensitive to outliers. EASI response thresholds are more stable, and thus, these were the focus of this analysis. In addition, since not all outcomes were consistently reported between trials, some treatment comparisons were not possible. It is possible that some between-trial differences could have influenced results, including abrocitinib monotherapy efficacy being assessed at 12 weeks rather than at 16 weeks for other treatments, differences in baseline characteristics in trials (e.g. HADS exclusion criteria) and differences in the use of background therapy in combination trials. Moreover, data for some treatments were available from only a single trial, thus potentially limiting the generalizability of findings. Finally, rapidity of response and long-term efficacy were beyond the scope of this NMA because of data availability limitations.

In conclusion, results of this NMA highlight that efficacy outcomes of JAK1 inhibitors (abrocitinib and upadacitinib) were consistently higher than those of dupilumab and baricitinib in moderate-to-severe AD. No meaningful statistical differences in safety-related outcomes were observed.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Material S1. Data sources and search strategy.

Table S1. Embase search strategies.

Table S2. MEDLINE search strategies.

Table S3. CENTRAL and CDSR search strategies.

Table S4. DARE and HTA database search strategies.

Table S5. Baseline demographic and clinical characteristics of studies included in the network meta-analysis.

Table S6. League table comparing mean differences of POEM, mean differences of DLQI, SCORAD-50 response, and mean differences of HADS among monotherapies.

Table S7. League table comparing mean differences of POEM, mean differences of DLQI, SCORAD-50 response, and mean differences of HADS among combination therapies.

Figure S1. Proportion of patients achieving each EASI threshold as estimated from the Bayesian network meta-analysis model at week 12.

Figure S2. Mean differences in POEM for (a) monotherapy (b) combination therapy.

Figure S3. Mean differences in DLQI for (a) monotherapy and (b) combination therapy.

Figure S4. Mean differences in SCORAD-50 response for (a) monotherapy and (b) combination therapy.

Figure S5. Mean differences in HADS for (a) monotherapy and (b) combination therapy.