Comparative Efficacy and Relative Ranking of Biologics and Oral Therapies for Moderate-to-Severe Plaque Psoriasis: A Network Meta-analysis

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ABSTRACT

Introduction: The clinical benefits of biologic and oral treatments for moderate-to-severe plaque psoriasis are well-established, but efficacy outcomes can vary across therapies. Comparative efficacy analysis can be highly informative in clinical settings with multiple therapeutic options. This study assessed the short-term and long-term comparative efficacy of biologic and oral treatments for moderate-to-severe psoriasis. ***Methods***: A systematic literature review identified phase 2/3/4 randomized controlled trials (RCTs) through to 1 July 2020 for Food and Drug Administration- or European Medicines Agency-licensed treatments for moderate-to-severe psoriasis. Psoriasis Area and Severity Index (PASI) 75/90/100 response rates at the end of the primary response (short-term: 10–16 weeks from baseline) and maintenance periods (long-term: 48–52 weeks from baseline) were estimated using Bayesian network meta-analysis. Surfaces under the cumulative ranking curves (SUCRA) were estimated to present the relative ranking of treatments. ***Results***: In the short term ($N = 71$ RCTs), the PASI 90 response rates were highest for ixekizumab (72.9%, SUCRA 0.951), risankizumab (72.5%, 0.940), and brodalumab (72.0%, 0.930), which were significantly higher than those for guselkumab (65.0%, 0.795), secukinumab (65.0%, 0.794), infliximab (56.8%, 0.702), certolizumab (400 mg: 49.6%, 0.607; 200 mg: 42.2%, 0.389), ustekinumab (90 mg: 47.9%, 0.568; weight-based: 45.7%, 0.505; 45 mg: 44.6%, 0.460), adalimumab (43.0%, 0.410), tildrakizumab (200 mg: 39.7%, 0.327; 100 mg: 37.2%, 0.268), etanercept (18.0%, 0.171), apremilast (12.4%, 0.090), and dimethyl fumarate (12.2%, 0.092). The PASI 100 response rates were highest for ixekizumab (41.4%),

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risankizumab (40.8%), and brodalumab (40.3%). In the long term ($N = 11$ RCTs), the PASI 90 rate was highest for risankizumab (85.3%, SUCRA: 0.998), which were significantly higher than those for brodalumab (78.8%, 0.786), guselkumab (78.1%, 0.760), ixekizumab (72.1%, 0.577), secukinumab (67.0%, 0.450), ustekinumab (weight-based: 55.0%, 0.252), adalimumab (51.6%, 0.176), and etanercept (37.9%, 0.001). Risankizumab had the highest PASI 100 response rate (65.4%), followed by brodalumab (55.7%) and guselkumab (54.8%).

Conclusions: Ixekizumab, risankizumab, and brodalumab had the highest short-term efficacy, and risankizumab had the highest long-term efficacy.

Keywords: Biologic therapies; Network meta-analysis; Plaque psoriasis

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Key Summary Points

Why carry out this study?

A comparative efficacy analysis of the clinical benefits of biologic and oral treatments for moderate-to-severe plaque psoriasis can help inform treatment decisions when multiple therapeutic options are available.

This study assessed the short-term and long-term comparative efficacy of biologic and oral treatments for moderate-to-severe plaque psoriasis licensed by the US Food and Drug Administration or European Medicines Agency using data from their phase 2, 3, or 4 randomized controlled trials.

Psoriasis Area and Severity Index (PASI) 75/90/100 response rates at the end of the primary response period (short-term: 10–16 weeks from baseline) and the maintenance period (long-term: 48–52 weeks from baseline) were estimated using Bayesian network meta-analysis.

What was learned from the study?

In the short term ($N = 71$ trials), the PASI response rates were highest for ixekizumab, risankizumab, and brodalumab; in the long term ($N = 11$ trials), the PASI response rates were highest for risankizumab.

Ixekizumab, risankizumab, and brodalumab had the highest short-term efficacy, and risankizumab had the highest long-term efficacy.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14102903.

INTRODUCTION

Novel biologic therapies have shifted the treatment paradigm for moderate-to-severe plaque psoriasis [1–3]. Anti-tumor necrosis factor (TNF) agents (e.g., etanercept, infliximab, and adalimumab) and an anti-interleukin (IL) 12/23 agent (ustekinumab) were among the earliest biologic treatments licensed by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for psoriasis. In recent years, biologic drugs targeting IL-17 (ixekizumab, brodalumab, and secukinumab) and IL-23 (risankizumab, guselkumab, and tildrakizumab) have become available and expanded the therapeutic options for psoriasis.

To facilitate the selection of appropriate treatment regimens among the available candidates, it is important to evaluate multiple aspects of each treatment, including the efficacy, safety, treatment adherence, and health-related quality of life (HRQoL), and to consider the contraindications of the target patient population [4]. Specifically, the comparative efficacy data, particularly a high level of skin

clearance as an outcome (i.e., a 90 or 100% reduction in Psoriasis Area and Severity Index [PASI 90, PASI 100, respectively]), are of key interest. These efficacy outcomes have been associated with improvement in HRQoL, psoriasis symptoms, and work productivity. For example, Elewski et al. [5] reported that patients who achieved PASI 90–100 at week 12 in the ERASURE and FIXTURE trials were more likely to achieve a sustained response in HRQoL measured by the Dermatology Life Quality Index. Viswanathan et al. [6] showed that patients who achieved PASI 100 response at week 12 in a clinical trial had significantly lower psoriasis symptom severity [6]. Feldman et al. [7] showed that employed patients in the CLEAR trial who achieved at least PASI 90 had significantly lower work productivity loss and reduced annual indirect costs. Outcomes assessing a high level of skin clearance have also become increasingly used in clinical development programs [8–11], making it possible to conduct an indirect comparison of such outcomes associated with various treatments.

While several recent network meta-analyses (NMAs) have been conducted to compare the relative efficacy of treatments for moderate-to-severe plaque psoriasis, knowledge gaps still exist [12–19]. First, PASI 100 results were not available in some of the recent NMAs [13, 15]. Second, such NMAs may lack sufficient statistical power to detect potential differences between treatments with the highest PASI 90 and 100 response rates. Third, comparative evidence assessing the long-term efficacy of treatments is limited due to the dearth of head-to-head trials that did not implement crossover or re-randomization in the study design [14]. Expert opinions have stressed the importance of maintaining long-term skin clearance, even if short-term skin clearance is achieved [20]. Compared with the short-term PASI response, the long-term PASI response can additionally reflect the variation in response over time, accounting for the gradual loss of response among some patients.

Recently, several large head-to-head trials have been published that compare various novel treatments for psoriasis, including IXORA-R comparing ixekizumab with guselkumab [8], ECLIPSE comparing guselkumab with secukinumab [21], CLARITY comparing secukinumab with ustekinumab [22], and IMMerge comparing risankizumab with secukinumab [9]. Incorporating these studies in an indirect comparison of the PASI response rates may not only improve the statistical power to detect differences in both short- and long-term PASI response rates, but also enhance and inform the evidence network for comparisons of long-term treatment efficacy. To this end, this study updated the NMA conducted by Armstrong et al. [14] by incorporating recently published clinical trial data to provide a comprehensive assessment of the short-term and long-term PASI response rates, including PASI 90 and 100 as outcomes, associated with licensed treatments for moderate-to-severe plaque psoriasis.

METHODS

Data Source

A systematic literature review (SLR) was conducted to identify randomized controlled clinical trials of treatments for moderate-to-severe psoriasis through to 1 July 2020, which was an update of the SLR by Armstrong et al. [14]. The search strategy is detailed in the Methods section of the electronic supplementary material. Eligible trials were required to (1) be a phase 2, 3, or 4 randomized clinical trial (RCT) on treatments for moderate-to-severe plaque psoriasis among adults who were eligible for systemic therapies or phototherapy; (2) include treatments and dosages licensed by the US FDA or the EMA; and (3) report at least one of the efficacy outcomes of interest (PASI 75, 90, and 100; indicating the proportions of patients who achieved at least a 75, 90, or 100% reduction in PASI) by the end of the primary response period (short-term: 10–16 weeks from baseline) or the end of the maintenance period (long-term: 48–52 weeks from baseline). For the long-term NMA, trials were excluded if (1) patients switched to a different treatment during the post-induction period compared with the induction period; (2) patients received a different dosage

during the post-induction period compared with the induction period, such that the entire treatment regimen considering both the induction period and the post-induction period was not licensed; or (3) patients were re-randomized based on certain efficacy criteria, such as PASI 75, during the post-induction period.

As this is a post-hoc NMA of previously published results of clinical trial data, no institutional board review was required. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Comparators

The comparators in this study included anti-IL-23 agents (guselkumab 100 mg at weeks 0 and 4, then every 8 weeks; risankizumab 150 mg at weeks 0 and 4, then every 12 weeks; tildrakizumab 100 mg and 200 mg at weeks 0 and 4, then every 12 weeks), anti-IL-17 agents (brodalumab 210 mg at weeks 0, 1, and 2, then every 2 weeks; ixekizumab 160 mg at week 0, 80 mg every 2 weeks until week 12, then 80 mg every 4 weeks; secukinumab 300 mg at weeks 0, 1, 2, 3, and 4, then every 4 weeks), anti-TNF agents (adalimumab 80 mg at week 0, then 40 mg every 2 weeks starting at week 1; certolizumab 400 mg at weeks 0, 2, and 4, then 200 mg or 400 mg every 2 weeks; etanercept 25 mg twice-weekly/50 mg weekly; infliximab 5 mg/kg at weeks 0, 2 and 6, then every 8 weeks), an anti-phosphodiesterase type 4 inhibitor (PDE4) agent (apremilast 30 mg twice daily after the initial titration schedule), an anti-IL-12/23 agent (ustekinumab 45 mg, 90 mg, or with a weight-based dosage [45 mg ≤ 100 kg, 90 mg > 100 kg] at weeks 0 and 4, then every 12 weeks), as well as dimethyl fumarate uptitrated to a maximum daily dose of 720 mg for the treatment of moderate-to-severe plaque psoriasis.

Outcomes

The outcomes were the proportions of patients who achieved PASI 75, 90, and 100 response by the end of the pre-specified primary assessment period for the short-term NMA (weeks 10–16 after baseline) and the end of the pre-specified maintenance period for the long-term NMA (weeks 48–52 after baseline). The number needed to treat (NNT) for each treatment relative to placebo by the end of the primary assessment period was also calculated. These pre-specified periods for the primary assessment period and maintenance period were chosen because the studies for the various medications were designed and a priori powered for those time periods. Additionally, these time points often corresponded to the primary or secondary endpoints of the clinical trials.

Statistical Analyses

NMA Models

Bayesian probit NMAs [23] were implemented to jointly model the PASI 75, 90, and 100 response rates. Due to the rich set of clinical trials in the short-term network, a reference-arm adjustment was implemented to account for potential cross-trial heterogeneities in treatment effects associated with the placebo response rate of each trial [19, 24]. Additionally, a random-effects model was applied to the short-term NMA to account for the potential heterogeneities that cannot be explained by placebo response rates. For the long-term NMA, a fixed-effects NMA model was fit due to the relative sparsity of the network.

For each treatment, the posterior distributions of the PASI 75, 90, and 100 response rates in the short term (10–16 weeks after baseline) and the long term (48–52 weeks after baseline) were summarized using posterior medians and 95% credible intervals (CrI). As the response rates were correlated, an overlap in two CrIs did not rule out the possibility of a statistically significance difference between two treatments. Therefore, odds ratios (ORs) were used to formally compare the PASI response rates between each pair of treatments and were summarized using posterior medians and 95% CrIs. Additionally, the treatments were ranked using the surface under the cumulative ranking curve (SUCRA) and mean rank with 95% CrI [25].
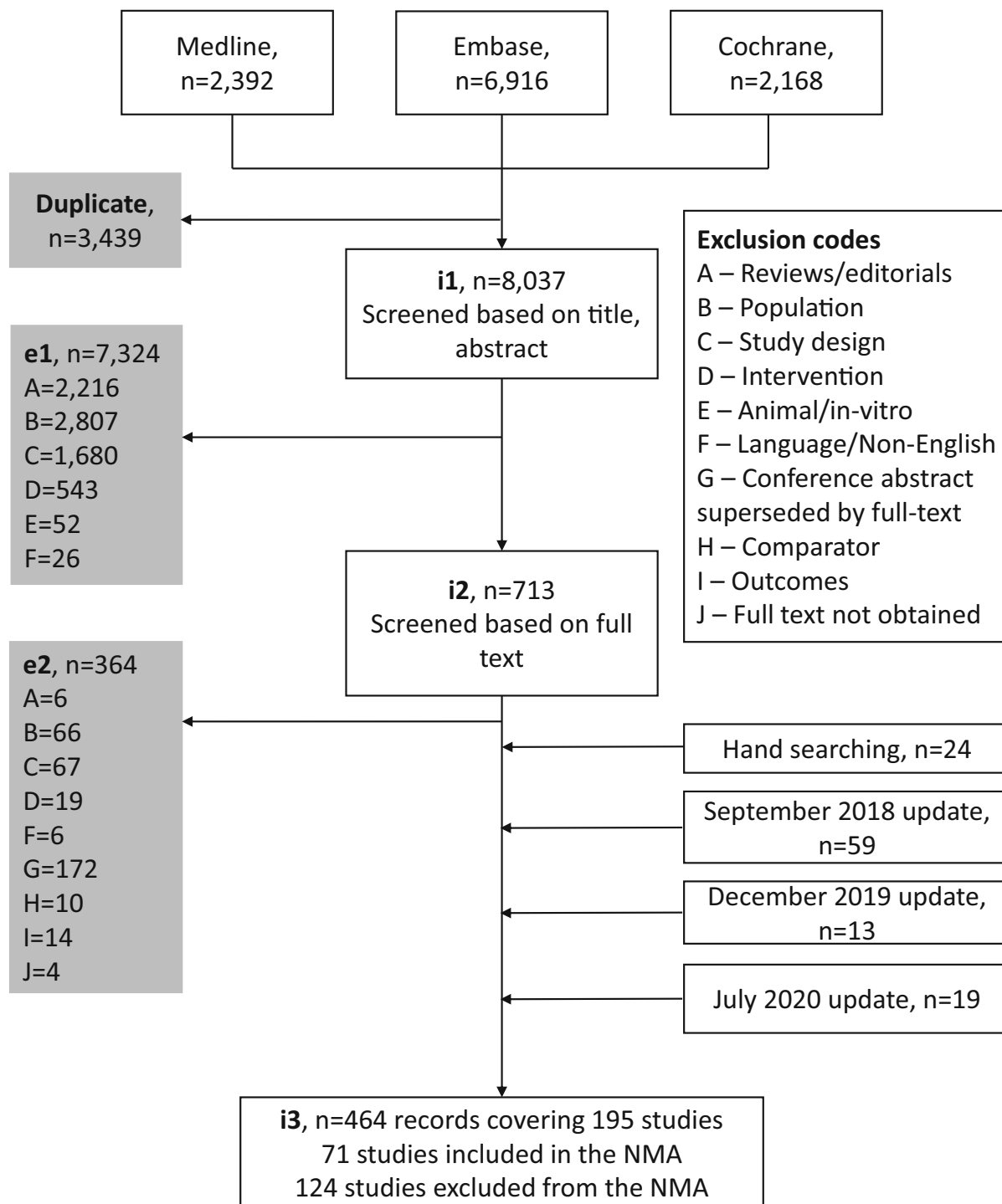
Fig. 1 Study screening and selection flow. *e1* exclusion 1, *e2* exclusion 2, *i1* inclusion 1, *i2* inclusion 2, *i3* inclusion 3, *NMA* network meta-analysis

For the short-term NMA, the NNT for each treatment relative to the placebo was calculated as the reciprocal of difference of a treatment in PASI 75, 90, and 100 response rates versus placebo.
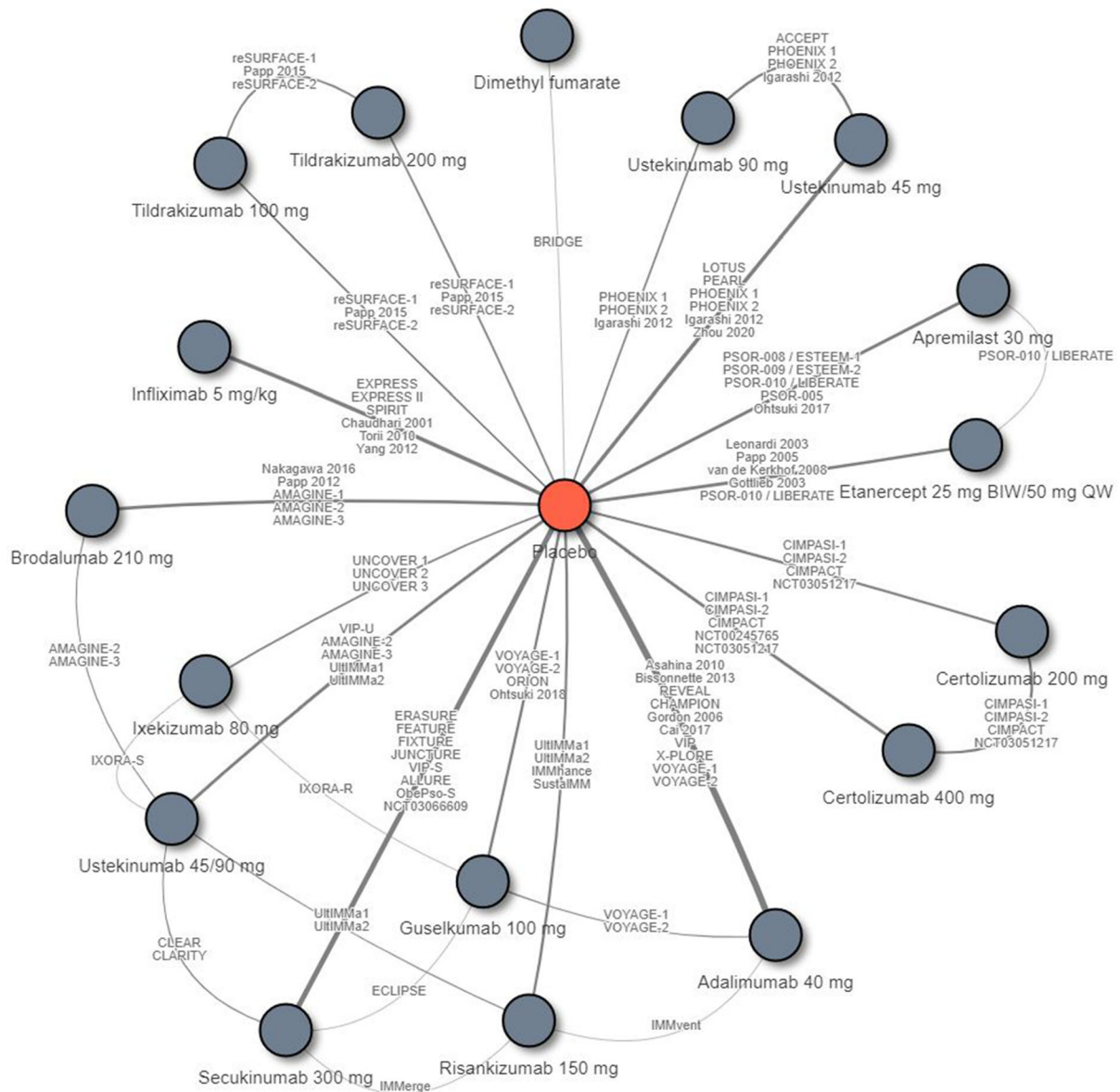
Fig. 2 Evidence network for the network meta-analysis (NMA) of the Psoriasis Area and Severity Index (PASI) response by the end of the primary response period (short-term; 10–16 weeks after baseline). The included trials were: Asahina et al. [27], Bissonnette et al. [28], REVEAL [29], CHAMPION [30], Gordon et al. [31], Cai et al. [32], VIP [33], Leonardi et al. [34], Papp et al. [35], van de Kerkhof et al. [36], Gottlieb et al. [37], EXPRESS [38], EXPRESS II [39], SPIRIT [40], Chaudhari et al. [41], Torii et al. [42], Yang et al. [43], UNCOVER 1 [44], UNCOVER 2 [45], UNCOVER 3 [45], IXORA-S [10], IXORA-R [8], ERASURE [46], FEATURE [47], FIXTURE [46], JUNCTURE [48], CLEAR [49], CLARITY [11], VIP-S [50], ALLURE [51], ObePso-S [52], NCT03066609 [53],

ACCEPT [54], LOTUS [55], PEARL [56], PHOENIX 1 [57], PHOENIX 2 [58], Igarashi et al. [59], VIP-U [60], Zhou et al. [61], X-PLORE [62], VOYAGE-1 [63], VOYAGE-2 [64], ORION [65], Ohtsuki et al. [66], ECLIPSE [21], Nakagawa et al. [67], Papp et al. [68], AMAGINE-1 [69], AMAGINE-2 [70], AMAGINE-3 [70], CIMPASI-1 [71], CIMPASI-2 [71], CIMPACT [72], NCT00245765 [73], NCT03051217 [74], reSURFACE-1 [75], Papp et al. [76], reSURFACE-2 [75], UltIMMa1 [77], IMMvent [78], IMMhance [79], SustalMM [80], IMMerge [9], BRIDGE [81], PSOR-008/ESTEEM-1 [82], PSOR-009/ESTEEM-2 [83], PSOR-010/LIBERATE [84], PSOR-005 [85], and Ohtsuki et al. [86]. *BIW* Twice weekly, *QW* once weekly

Additionally, the heterogeneity in treatment contrasts for the short-term NMA was summarized using (1) the posterior distribution measuring the effect of placebo response on treatment contrasts and (2) the posterior distribution measuring the residual cross-trial variance in treatment contrasts.

Computation

The posterior samples of the Bayesian NMA models were drawn using the Markov Chain Monte Carlo technique. Three parallel chains, each with 5000 adaptation iterations, 50,000 burn-in iterations, 50,000 posterior simulations, and a thinning factor of 10, were implemented. Vague prior distributions were applied for all parameters, such that the posterior distributions were driven primarily by the observed data. All analyses were conducted in R statistical software (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria) and JAGS 4.3.0 (Free Software Foundation, Inc., Boston, MA, USA)

RESULTS

Literature Search

A total of 464 publications covering 195 studies were identified in the SLR through to 1 July 2020, with 71 studies included in the NMAs and 124 studies excluded from the NMAs (Fig. 1). All 71 studies were included in the short-term NMA, and 11 of the 71 studies were included in the long-term NMA. Compared with the SLR conducted by Armstrong et al. [14], 52 additional records were identified, with 11 additional studies qualifying for the short-term NMA and four additional studies qualifying for the long-term NMA.

Short-term Efficacy

A total of 71 eligible RCTs connecting 18 treatment regimens were included in the NMA of short-term PASI response rates (10–16 weeks after baseline) (Fig. 2). A list of the trials included in the short-term NMA is included in

Table S1 in the electronic supplementary material.

The posterior medians of the PASI 90 response rates were highest for ixekizumab (median 72.9% [95% CrI 68.3%, 77.1%]), risankizumab (72.5% [68.1%, 76.7%]), and brodalumab (72.0% [67.3%, 76.7%]), followed by guselkumab (65.0% [60.3%, 69.7%]), secukinumab (65.0% [61.0%, 68.7%]), infliximab (56.8% [50.4%, 62.9%]), certolizumab 400 mg (49.6% [43.0%, 56.3%]), ustekinumab 90 mg (47.9% [41.4%, 54.2%]), ustekinumab weight-based dosage (45.7% [41.2%, 50.3%]), ustekinumab 45 mg (44.6% [39.2%, 49.8%]), adalimumab (43.0% [38.7%, 47.4%]), certolizumab 200 mg (42.2% [35.3%, 49.4%]), tildrakizumab 200 mg (39.7% [33.2%, 46.8%]), tildrakizumab 100 mg (37.2% [30.8%, 44.1%]), etanercept (18.0% [14.5%, 22.2%]), apremilast (12.4% [9.7%, 15.9%]), and dimethyl fumarate (12.2% [7.2%, 20.2%]) (Table 1). Similarly, the posterior medians of the PASI 100 response rates were highest for ixekizumab (median 41.4% [95% CrI 36.3%, 46.6%]), risankizumab (40.8% [36.1%, 46.0%]), and brodalumab (40.3% [35.2%, 46.1%]). SUCRA and mean rank suggested a similar ranking of treatments as the median PASI response rates. Ixekizumab, risankizumab, and brodalumab were associated with the highest SUCRA (0.951, 0.940, and 0.930, respectively) and mean rank (1.8, 2.0, and 2.2, respectively) (Table 1; and ESM Fig. S1).

The posterior distributions of the pairwise ORs suggested that the PASI response rates were comparable between ixekizumab, risankizumab, and brodalumab, which were significantly higher than those of all other treatments, including guselkumab and secukinumab, with 95% probability (Table 2 [PASI 90 and 100]; ESM Table S2 [PASI 75]). Guselkumab and secukinumab were associated with significantly higher PASI response rates compared with infliximab, certolizumab (200 and 400 mg), ustekinumab (45 mg, 90 mg, and weight-based), adalimumab, tildrakizumab (100 and 200 mg), etanercept, apremilast, and dimethyl fumarate, with 95% probability.

The NNTs to achieve PASI 75, 90, or 100 for each treatment relative to placebo are presented in Fig. 3. The NNTs to achieve one additional

Table 1 Estimated response rates, SUCRA, and mean rank from the NMA of short-term PASI response

Treatment	Posterior median, % (95% CrI)			SUCRA[a]	Mean rank (95% CrI)
	PASI 75	PASI 90	PASI 100		
Ixekizumab 160 mg at week 0, then 80 mg Q2W	89.9 (87.3, 92.0)	72.9 (68.3, 77.1)	41.4 (36.3, 46.6)	0.951	1.8 (1.0, 3.0)
Risankizumab 150 mg at weeks 0, and 4, then Q12W	89.6 (87.2, 91.8)	72.5 (68.1, 76.7)	40.8 (36.1, 46.0)	0.940	2.0 (1.0, 3.0)
Brodalumab 210 mg at weeks 0, 1, and 2, then Q2W	89.4 (86.7, 91.9)	72.0 (67.3, 76.7)	40.3 (35.2, 46.1)	0.930	2.2 (1.0, 3.0)
Guselkumab 100 mg at weeks 0, and 4, then Q8W	85.3 (82.3, 88.1)	65.0 (60.3, 69.7)	32.9 (28.5, 37.7)	0.795	4.5 (4.0, 5.0)
Secukinumab 300 mg at weeks 0, 1, 2, 3, and 4, then Q4W	85.3 (82.7, 87.6)	65.0 (61.0, 68.7)	32.9 (29.2, 36.7)	0.794	4.5 (4.0, 5.0)
Infliximab 5 mg/kg at weeks 0, 2, and 6, then Q8W	79.8 (75.0, 84.0)	56.8 (50.4, 62.9)	25.6 (20.7, 31.0)	0.702	6.1 (5.0, 7.0)
Certolizumab 400 mg Q2W	74.4 (68.7, 79.5)	49.6 (43.0, 56.3)	20.1 (15.7, 25.2)	0.607	7.7 (6.0, 11.0)
Ustekinumab 90 mg at weeks 0, and 4, then Q12W	73.0 (67.3, 77.9)	47.9 (41.4, 54.2)	18.9 (14.8, 23.5)	0.568	8.3 (7.0, 12.0)
Ustekinumab 45 mg ≤ 100 kg, 90 mg > 100 kg at weeks 0, and 4, then Q12W	71.1 (67.1, 74.9)	45.7 (41.2, 50.3)	17.4 (14.7, 20.6)	0.505	9.4 (7.0, 12.0)
Ustekinumab 45 mg at weeks 0, and 4, then Q12W	70.1 (65.3, 74.5)	44.6 (39.2, 49.8)	16.7 (13.5, 20.3)	0.460	10.2 (8.0, 13.0)
Adalimumab 80 mg at week 0, then 40 mg Q2W	68.7 (64.7, 72.5)	43.0 (38.7, 47.4)	15.7 (13.2, 18.6)	0.410	11.0 (8.0, 14.0)
Certolizumab 400 mg at weeks 0, 2, and 4, then 200 mg Q2W	68.0 (61.3, 74.2)	42.2 (35.3, 49.4)	15.3 (11.4, 20.0)	0.389	11.4 (8.0, 14.0)
Tildrakizumab 200 mg at weeks 0, and 4, then Q12W	65.7 (59.1, 72.1)	39.7 (33.2, 46.8)	13.8 (10.3, 18.2)	0.327	12.4 (9.0, 14.0)
Tildrakizumab 100 mg at weeks 0, and 4, then Q12W	63.3 (56.5, 69.7)	37.2 (30.8, 44.1)	12.4 (9.2, 16.5)	0.268	13.4 (11.0, 14.0)
Etanercept 25 mg BIW/50 mg QW	40.2 (34.7, 45.9)	18.0 (14.5, 22.2)	4.1 (2.9, 5.5)	0.171	15.1 (15.0, 16.0)

Table 1 continued

Treatment	Posterior median, % (95% CrI)			SUCRA[a]	Mean rank (95% CrI)
	PASI 75	PASI 90	PASI 100		
Apremilast 30 mg BID after initial titration schedule	31.3 (26.4, 36.8)	12.4 (9.7, 15.9)	2.4 (1.7, 3.4)	0.090	16.5 (16.0, 17.0)
Dimethyl fumarate (LAS 41008)	30.9 (21.4, 43.3)	12.2 (7.2, 20.2)	2.3 (1.1, 4.8)	0.092	16.4 (15.0, 17.0)
Placebo	5.3 (4.8, 5.8)	1.1 (1.0, 1.3)	0.1 (0.1, 0.1)	0.000	18.0 (18.0, 18.0)

BID twice daily, *BIW* twice weekly, *CrI* credible interval, *NMA* network meta-analysis, *PASI* Psoriasis Area and Severity Index, *PASI 75, 90, 100* 75, 90, or 100% decrease from baseline PASI, respectively, *QW* once weekly, *Q2W* once every 2 weeks, *Q4W* once every 4 weeks, *Q8W* once every 8 weeks, *Q12W* once every 12 weeks

[a] SUCRA (surfaces under the cumulative ranking curves) measures the probability of a treatment being in the top ranks

PASI 90 response were 1.39 (95% CrI 1.32, 1.49) for ixekizumab, 1.40 (1.32, 1.49) for risankizumab, and 1.41 (1.32, 1.51) for brodalumab. The NNTs to achieve one additional PASI 100 response were 2.42 (95% CrI 2.15, 2.76) for ixekizumab, 2.45 (2.18, 2.78) for risankizumab, and 2.49 (2.18, 2.84) for brodalumab.

The random-effects model with reference-arm adjustment revealed cross-trial heterogeneities in treatment contrasts. On the probit scale, each unit increase in the placebo PASI response rate was associated with a statistically significant decrease of 0.750 (95% CrI 0.534, 1.008) in the difference between the active treatment and placebo. The residual cross-trial variance of treatment contrasts on the probit scale was 0.014 (95% CrI 0.006, 0.028), which differs from zero with 95% probability.

Long-Term Efficacy

A total of 11 eligible RCTs connecting eight treatment regimens were included in the NMA of long-term PASI response rates (48–52 weeks after baseline) (Fig. 4). A list of the trials included in the long-term NMA is shown in ESM Table S3.

The posterior PASI 90 response rates were highest for risankizumab (median 85.3% [95% CrI 81.4%, 88.7%]), followed by brodalumab (78.8% [74.0%, 83.0%]), guselkumab (78.1% [72.5%, 83.0%]), ixekizumab (72.1% [62.7%, 80.1%]), secukinumab (67.0% [62.8%, 71.0%]), ustekinumab (weight-based 55.0% [52.7%, 57.3%]), adalimumab (51.6% [41.8%, 61.3%]), and etanercept (37.9% [30.4%, 45.8%]) (Table 2). Similarly, the posterior PASI 100 response rates were highest for risankizumab (median: 65.4% [95% CrI 59.3%, 71.1%]), followed by brodalumab (78.1% [72.5%, 83.0%]) and guselkumab (54.8% [47.6%, 61.9%]). SUCRA and mean rank suggested a consistent ranking of treatments as the PASI response rates, with risankizumab associated with a SUCRA of 0.998 and a mean rank of 1.0, followed by brodalumab and guselkumab (Table 3; ESM Fig. S2).

The posterior distributions of the pairwise odds ratios suggested that the PASI response rates associated with risankizumab were significantly higher than all other treatments, including brodalumab, guselkumab, ixekizumab, and secukinumab with 95% probability (Table 4 [PASI 90 and 100] and Table S4 [PASI 75] in the electronic supplementary material). Brodalumab and guselkumab were associated with significantly higher PASI response rates than ustekinumab, adalimumab, and etanercept with 95% probability.

Table 2 Pairwise odds ratio of achieving PASI 90 and 100 response in the short term

(a) PASI 90: posterior median (95% CrI)

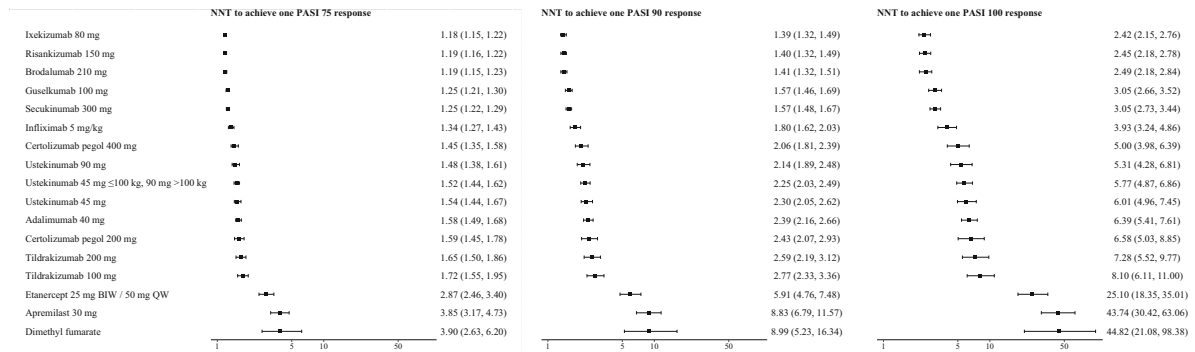| IXE	RIS	BRO	GUS	SEC	INF	CZP400	UST90	UST_W	UST45	ADA	CZP200	TIL200	TIL100	ETA	APR	DMF	PBO
IXE	1.02 (0.75, 1.42)	1.05 (0.75, 1.42)	1.45 (1.09, 1.90)*	1.45 (1.12, 1.89)*	2.05 (1.48, 2.86)*	2.74 (1.92, 3.87)*	2.93 (2.11, 4.11)*	3.21 (2.44, 4.18)*	3.35 (2.49, 4.56)*	3.58 (2.67, 4.74)*	3.69 (2.55, 5.34)*	4.09 (2.83, 5.85)*	4.54 (3.16, 6.52)*	12.23 (8.74, 17.19)*	18.96 (13.07, 27.06)*	19.32 (10.03, 36.18)*	237.65 (184.46, 305.82)*
0.98 (0.72, 1.34)	**RIS**	1.02 (0.75, 1.37)	1.42 (1.07, 1.88)*	1.42 (1.11, 1.86)*	2.00 (1.43, 2.85)*	2.68 (1.91, 3.74)*	2.86 (2.05, 4.08)*	3.13 (2.44, 4.50)*	3.27 (2.43, 4.46)*	3.49 (2.75, 4.46)*	3.61 (2.54, 5.15)*	3.99 (2.81, 5.67)*	4.44 (3.14, 6.32)*	11.96 (8.60, 16.86)*	18.51 (13.27, 25.82)*	18.84 (10.31, 34.33)*	232.00 (182.92, 298.99)*
0.96 (0.70, 1.33)	0.98 (0.73, 1.33)	**BRO**	1.39 (1.03, 1.88)*	1.39 (1.06, 1.87)*	1.96 (1.39, 2.84)*	2.62 (1.86, 3.72)*	2.80 (2.00, 4.06)*	3.06 (2.39, 3.99)*	3.20 (2.36, 4.49)*	3.41 (2.61, 4.57)*	3.53 (2.46, 5.13)*	3.90 (2.74, 5.63)*	4.34 (3.05, 6.29)*	11.69 (8.35, 16.77)*	18.10 (12.88, 25.81)*	18.44 (9.99, 34.08)*	227.01 (177.20, 298.73)*
0.69 (0.53, 0.91)*	0.71 (0.53, 0.93)*	0.72 (0.53, 0.97)*	**GUS**	1.00 (0.79, 1.29)	1.41 (1.01, 1.99)*	1.89 (1.35, 2.63)*	2.02 (1.46, 2.85)*	2.21 (1.71, 2.88)*	2.31 (1.72, 3.15)*	2.46 (1.94, 3.14)*	2.55 (1.79, 3.61)*	2.82 (1.99, 3.98)*	3.13 (2.22, 4.45)*	8.43 (6.11, 11.82)*	13.06 (9.36, 18.24)*	13.30 (7.19, 24.30)*	163.75 (129.80, 209.20)*
0.69 (0.53, 0.89)*	0.71 (0.54, 0.90)*	0.72 (0.54, 0.94)*	1.00 (0.78, 1.27)	**SEC**	1.41 (1.05, 1.90)*	1.88 (1.37, 2.58)*	2.01 (1.50, 2.74)*	2.21 (1.77, 2.72)*	2.31 (1.77, 3.02)*	2.46 (1.91, 3.13)*	2.54 (1.81, 3.56)*	2.81 (2.01, 3.91)*	3.12 (2.23, 4.35)*	8.42 (6.22, 11.46)*	13.06 (9.26, 18.04)*	13.30 (7.02, 24.50)*	163.55 (132.86, 200.72)*
0.49 (0.35, 0.68)*	0.50 (0.35, 0.70)*	0.51 (0.35, 0.72)*	0.71 (0.50, 0.99)*	0.71 (0.53, 0.95)*	**INF**	1.34 (0.91, 1.94)	1.43 (1.02, 2.02)*	1.56 (1.13, 2.15)*	1.64 (1.19, 2.25)*	1.74 (1.25, 2.41)*	1.80 (1.21, 2.66)*	1.99 (1.34, 2.93)*	2.21 (1.50, 3.26)*	5.97 (4.18, 8.54)*	9.26 (6.16, 13.69)*	9.43 (4.73, 18.26)*	115.96 (87.46, 153.58)*
0.37 (0.26, 0.52)*	0.37 (0.27, 0.52)*	0.38 (0.27, 0.54)*	0.53 (0.38, 0.74)*	0.53 (0.39, 0.73)*	0.75 (0.51, 1.10)	**CZP 400**	1.07 (0.74, 1.57)	1.17 (0.85, 1.62)	1.22 (0.87, 1.74)	1.30 (0.96, 1.79)	1.35 (0.99, 1.84)	1.49 (1.01, 2.20)*	1.66 (1.13, 2.45)*	4.47 (3.10, 6.52)*	6.91 (4.77, 10.10)*	7.04 (3.76, 13.28)*	86.87 (65.00, 116.86)*
0.34 (0.24, 0.47)*	0.35 (0.25, 0.49)*	0.36 (0.25, 0.50)*	0.50 (0.35, 0.69)*	0.50 (0.37, 0.67)*	0.70 (0.49, 0.99)*	0.93 (0.64, 1.35)	**UST 90**	1.10 (0.79, 1.49)	1.15 (0.89, 1.46)	1.22 (0.88, 1.67)	1.26 (0.85, 1.86)	1.39 (0.93, 2.04)	1.55 (1.04, 2.27)*	4.18 (2.91, 5.96)*	6.48 (4.32, 9.48)*	6.60 (3.33, 12.64)*	81.22 (60.78, 106.95)*
0.31 (0.24, 0.41)*	0.32 (0.25, 0.41)*	0.33 (0.25, 0.42)*	0.45 (0.35, 0.59)*	0.45 (0.37, 0.56)*	0.64 (0.47, 0.88)*	0.85 (0.62, 1.17)	0.91 (0.67, 1.27)	**UST_W**	1.04 (0.79, 1.40)	1.11 (0.88, 1.42)	1.15 (0.82, 1.62)	1.27 (0.91, 1.78)	1.42 (1.01, 1.98)*	3.82 (2.80, 5.25)*	5.91 (4.27, 8.13)*	6.02 (3.27, 10.96)*	74.07 (59.87, 92.48)*
0.30 (0.22, 0.40)*	0.31 (0.22, 0.41)*	0.31 (0.22, 0.42)*	0.43 (0.32, 0.58)*	0.43 (0.33, 0.56)*	0.61 (0.44, 0.84)*	0.82 (0.57, 1.15)	0.87 (0.69, 1.12)	0.96 (0.71, 1.26)	**UST45**	1.07 (0.80, 1.41)	1.10 (0.76, 1.58)	1.22 (0.84, 1.74)	1.35 (0.94, 1.93)	3.65 (2.62, 5.09)*	5.66 (3.91, 8.03)*	5.76 (3.00, 10.80)*	70.97 (55.29, 90.16)*
0.28 (0.21, 0.37)*	0.29 (0.22, 0.36)*	0.29 (0.22, 0.38)*	0.41 (0.32, 0.51)*	0.41 (0.32, 0.52)*	0.57 (0.41, 0.80)*	0.77 (0.56, 1.04)	0.82 (0.60, 1.14)	0.90 (0.70, 1.14)	0.94 (0.71, 1.25)	**ADA**	1.03 (0.74, 1.43)	1.14 (0.82, 1.58)	1.27 (0.91, 1.76)	3.42 (2.51, 4.71)*	5.30 (3.89, 7.17)*	5.40 (2.99, 9.64)*	66.46 (54.02, 82.44)*
0.27 (0.19, 0.39)*	0.28 (0.19, 0.39)*	0.28 (0.20, 0.41)*	0.39 (0.28, 0.56)*	0.39 (0.28, 0.55)*	0.56 (0.38, 0.82)*	0.74 (0.54, 1.01)	0.79 (0.54, 1.18)	0.87 (0.62, 1.22)	0.91 (0.63, 1.31)	0.97 (0.70, 1.35)	**CZP 200**	1.11 (0.74, 1.65)	1.23 (0.82, 1.84)	3.32 (2.25, 4.91)*	5.13 (3.48, 7.58)*	5.22 (2.76, 9.92)*	64.42 (47.10, 88.10)*
0.24 (0.17, 0.35)*	0.25 (0.18, 0.36)*	0.26 (0.18, 0.36)*	0.36 (0.25, 0.50)*	0.36 (0.26, 0.50)*	0.50 (0.34, 0.75)*	0.67 (0.45, 0.99)*	0.72 (0.49, 1.07)	0.78 (0.56, 1.10)	0.82 (0.58, 1.19)	0.87 (0.63, 1.22)	0.90 (0.61, 1.35)	**TIL 200**	1.11 (0.83, 1.50)	2.99 (2.05, 4.43)*	4.63 (3.15, 6.83)*	4.72 (2.49, 8.91)*	58.14 (42.90, 79.58)*
0.22 (0.15, 0.32)*	0.23 (0.16, 0.32)*	0.23 (0.16, 0.33)*	0.32 (0.22, 0.45)*	0.32 (0.23, 0.45)*	0.45 (0.31, 0.67)*	0.60 (0.41, 0.88)*	0.65 (0.44, 0.96)*	0.71 (0.50, 0.99)*	0.74 (0.52, 1.06)	0.79 (0.57, 1.09)	0.81 (0.54, 1.22)	0.90 (0.67, 1.21)	**TIL 100**	2.70 (1.84, 3.97)*	4.18 (2.82, 6.14)*	4.25 (2.23, 8.00)*	52.37 (38.46, 71.37)*
0.08 (0.06, 0.11)*	0.08 (0.06, 0.12)*	0.09 (0.06, 0.12)*	0.12 (0.08, 0.16)*	0.12 (0.09, 0.16)*	0.17 (0.12, 0.24)*	0.22 (0.15, 0.32)*	0.24 (0.17, 0.34)*	0.26 (0.19, 0.36)*	0.27 (0.20, 0.38)*	0.29 (0.21, 0.40)*	0.30 (0.20, 0.44)*	0.33 (0.23, 0.49)*	0.37 (0.25, 0.54)*	**ETA**	1.55 (1.06, 2.23)*	1.58 (0.82, 2.98)	19.42 (14.66, 25.63)*
0.05 (0.04, 0.08)*	0.05 (0.04, 0.08)*	0.06 (0.04, 0.08)*	0.08 (0.05, 0.11)*	0.08 (0.06, 0.11)*	0.11 (0.07, 0.16)*	0.14 (0.10, 0.21)*	0.15 (0.11, 0.23)*	0.17 (0.12, 0.23)*	0.18 (0.12, 0.26)*	0.19 (0.14, 0.26)*	0.20 (0.13, 0.29)*	0.22 (0.15, 0.32)*	0.24 (0.16, 0.35)*	0.65 (0.45, 0.94)*	**APR**	1.02 (0.55, 1.86)	12.53 (9.39, 16.95)*
0.05 (0.03, 0.10)*	0.05 (0.03, 0.10)*	0.05 (0.03, 0.10)*	0.08 (0.04, 0.14)*	0.08 (0.04, 0.14)*	0.11 (0.05, 0.21)*	0.14 (0.08, 0.27)*	0.15 (0.08, 0.30)*	0.17 (0.09, 0.31)*	0.17 (0.09, 0.33)*	0.19 (0.10, 0.33)*	0.19 (0.10, 0.36)*	0.21 (0.11, 0.40)*	0.24 (0.12, 0.45)*	0.63 (0.34, 1.23)	0.98 (0.54, 1.81)	**DMF**	12.31 (6.83, 22.58)*
0.00 (0.00, 0.01)*	0.00 (0.00, 0.01)*	0.00 (0.00, 0.01)*	0.01 (0.00, 0.01)*	0.01 (0.00, 0.01)*	0.01 (0.01, 0.01)*	0.01 (0.01, 0.02)*	0.01 (0.01, 0.02)*	0.01 (0.01, 0.02)*	0.01 (0.01, 0.02)*	0.02 (0.01, 0.02)*	0.02 (0.01, 0.02)*	0.02 (0.01, 0.03)*	0.02 (0.01, 0.07)*	0.05 (0.04, 0.07)*	0.08 (0.06, 0.11)*	0.08 (0.04, 0.15)*	**PBO**

Table 2 continued

(b) PASI 100: posterior median (95% CrI)

IXE	1.02 (0.75, 1.37)	1.04 (0.76, 1.40)	1.44 (1.09, 1.87)*	1.44 (1.12, 1.86)*	2.06 (1.48, 2.89)*	2.81 (1.95, 4.04)*	3.02 (2.15, 4.32)*	3.35 (2.52, 4.39)*	3.51 (2.58, 4.85)*	3.78 (2.80, 5.05)*	3.91 (2.65, 5.84)*	4.40 (2.96, 6.51)*	4.97 (3.35, 7.41)*	16.60 (11.31, 24.53)*	28.97 (18.81, 43.85)*	29.68 (13.28, 65.14)*	757.82 (577.18, 990.53)*
0.98 (0.73, 1.32)	**RIS**	1.02 (0.76, 1.35)	1.41 (1.07, 1.86)*	1.41 (1.10, 1.83)*	2.01 (1.43, 2.89)*	2.75 (1.93, 3.91)*	2.95 (2.09, 4.29)*	3.27 (2.53, 4.25)*	3.43 (2.52, 4.80)*	3.69 (2.89, 4.76)*	3.84 (2.63, 5.64)*	4.31 (2.95, 6.32)*	4.86 (3.33, 7.18)*	16.26 (11.13, 24.11)*	28.31 (19.11, 41.90)*	28.96 (13.64, 62.03)*	740.37 (571.56, 969.06)*
0.96 (0.71, 1.32)	0.98 (0.74, 1.31)	**BRO**	1.38 (1.03, 1.86)*	1.38 (1.06, 1.84)*	1.97 (1.39, 2.87)*	2.69 (1.88, 3.88)*	2.89 (2.04, 4.26)*	3.20 (2.48, 4.19)*	3.36 (2.45, 4.78)*	3.62 (2.74, 4.86)*	3.75 (2.55, 5.61)*	4.22 (2.88, 6.27)*	4.76 (3.24, 7.15)*	15.90 (10.83, 23.92)*	27.72 (18.59, 41.87)*	28.38 (13.25, 61.27)*	725.14 (554.07, 966.45)*
0.69 (0.53, 0.92)*	0.71 (0.54, 0.94)*	0.72 (0.54, 0.97)*	**GUS**	1.00 (0.79, 1.29)	1.43 (1.01, 2.04)*	1.95 (1.37, 2.78)*	2.10 (1.49, 3.04)*	2.32 (1.77, 3.06)*	2.44 (1.79, 3.40)*	2.62 (2.04, 3.39)*	2.72 (1.86, 4.01)*	3.05 (2.09, 4.48)*	3.45 (2.36, 5.11)*	11.54 (7.90, 17.12)*	20.10 (13.48, 29.95)*	20.57 (9.53, 44.18)*	525.70 (405.28, 687.95)*
0.69 (0.54, 0.90)*	0.71 (0.55, 0.91)*	0.73 (0.54, 0.94)*	1.00 (0.78, 1.27)	**SEC**	1.43 (1.05, 1.95)*	1.95 (1.38, 2.74)*	2.09 (1.53, 2.92)*	2.32 (1.84, 2.90)*	2.43 (1.83, 3.27)*	2.62 (2.00, 3.40)*	2.71 (1.88, 3.96)*	3.05 (2.10, 4.42)*	3.45 (2.37, 5.02)*	11.52 (8.03, 16.66)*	20.10 (13.28, 29.79)*	20.57 (9.29, 44.71)*	524.92 (413.98, 662.55)*
0.49 (0.35, 0.68)*	0.50 (0.35, 0.70)*	0.51 (0.35, 0.72)*	0.70 (0.49, 0.99)*	0.70 (0.51, 0.95)*	**INF**	1.36 (0.91, 2.04)	1.47 (1.02, 2.14)*	1.63 (1.14, 2.28)*	1.71 (1.20, 2.42)*	1.84 (1.28, 2.61)*	1.90 (1.24, 2.94)*	2.14 (1.38, 3.28)*	2.42 (1.56, 3.73)*	8.08 (5.33, 12.24)*	14.10 (8.72, 22.35)*	14.44 (6.18, 32.88)*	368.24 (268.17, 501.21)*
0.36 (0.25, 0.51)*	0.36 (0.26, 0.52)*	0.37 (0.26, 0.53)*	0.51 (0.36, 0.73)*	0.51 (0.37, 0.72)*	0.73 (0.49, 1.10)	**CZP 400**	1.08 (0.72, 1.64)	1.19 (0.84, 1.69)	1.25 (0.86, 1.84)	1.34 (0.95, 1.91)	1.40 (0.99, 1.98)	1.57 (1.02, 2.43)*	1.77 (1.15, 2.75)*	5.92 (3.84, 9.22)*	10.30 (6.59, 16.19)*	10.53 (4.81, 23.41)*	269.95 (193.32, 376.86)*
0.33 (0.23, 0.46)*	0.34 (0.23, 0.48)*	0.35 (0.23, 0.49)*	0.48 (0.33, 0.67)*	0.48 (0.34, 0.65)*	0.68 (0.47, 0.98)*	0.93 (0.61, 1.39)	**UST 90**	1.11 (0.77, 1.55)	1.16 (0.88, 1.52)	1.25 (0.86, 1.77)	1.29 (0.83, 2.00)	1.46 (0.93, 2.24)	1.64 (1.05, 2.54)*	5.49 (3.57, 8.38)*	9.58 (5.88, 15.16)*	9.81 (4.21, 22.26)*	250.71 (179.29, 343.10)*
0.30 (0.23, 0.40)*	0.31 (0.24, 0.40)*	0.31 (0.24, 0.40)*	0.43 (0.33, 0.57)*	0.43 (0.34, 0.54)*	0.61 (0.44, 0.87)*	0.84 (0.59, 1.19)	0.90 (0.64, 1.30)	**UST_W**	1.05 (0.77, 1.46)	1.13 (0.86, 1.48)	1.17 (0.80, 1.73)	1.32 (0.90, 1.93)	1.49 (1.02, 2.20)*	4.97 (3.41, 7.34)*	8.66 (5.80, 12.86)*	8.86 (4.11, 19.08)*	226.37 (175.40, 293.98)*
0.28 (0.21, 0.39)*	0.29 (0.21, 0.40)*	0.30 (0.21, 0.41)*	0.41 (0.29, 0.56)*	0.41 (0.31, 0.55)*	0.58 (0.41, 0.83)*	0.80 (0.54, 1.17)	0.86 (0.66, 1.13)	0.95 (0.68, 1.29)	**UST 45**	1.08 (0.77, 1.47)	1.11 (0.74, 1.68)	1.25 (0.82, 1.88)	1.42 (0.93, 2.14)	4.73 (3.17, 7.06)*	8.25 (5.25, 12.67)*	8.44 (3.73, 18.74)*	215.68 (160.56, 285.69)*
0.26 (0.20, 0.36)*	0.27 (0.21, 0.35)*	0.28 (0.21, 0.37)*	0.38 (0.29, 0.49)*	0.38 (0.29, 0.50)*	0.54 (0.38, 0.78)*	0.74 (0.52, 1.05)	0.80 (0.56, 1.16)	0.89 (0.67, 1.16)	0.93 (0.68, 1.29)	**ADA**	1.04 (0.71, 1.51)	1.17 (0.80, 1.69)	1.32 (0.90, 1.93)	4.40 (3.01, 6.49)*	7.67 (5.21, 11.17)*	7.85 (3.71, 16.52)*	200.31 (155.96, 259.16)*
0.26 (0.17, 0.38)*	0.26 (0.18, 0.38)*	0.27 (0.18, 0.39)*	0.37 (0.25, 0.54)*	0.37 (0.25, 0.53)*	0.53 (0.34, 0.81)*	0.72 (0.51, 1.01)	0.77 (0.50, 1.20)	0.85 (0.58, 1.25)	0.90 (0.60, 1.35)	0.96 (0.66, 1.40)	**CZP 200**	1.12 (0.71, 1.78)	1.27 (0.80, 2.02)	4.24 (2.67, 6.76)*	7.37 (4.60, 11.81)*	7.54 (3.40, 16.94)*	193.35 (133.71, 277.47)*
0.23 (0.15, 0.34)*	0.23 (0.16, 0.34)*	0.24 (0.16, 0.35)*	0.33 (0.22, 0.48)*	0.33 (0.23, 0.48)*	0.47 (0.30, 0.73)*	0.64 (0.41, 0.98)*	0.69 (0.45, 1.08)	0.76 (0.52, 1.11)	0.80 (0.53, 1.21)	0.86 (0.59, 1.25)	0.89 (0.56, 1.41)	**TIL 200**	1.13 (0.80, 1.60)	3.77 (2.38, 6.03)*	6.57 (4.10, 10.52)*	6.73 (3.02, 15.01)*	171.92 (119.74, 247.87)*
0.20 (0.13, 0.30)*	0.21 (0.14, 0.30)*	0.21 (0.14, 0.31)*	0.29 (0.20, 0.42)*	0.29 (0.20, 0.42)*	0.41 (0.27, 0.64)*	0.56 (0.36, 0.87)*	0.61 (0.39, 0.95)*	0.67 (0.45, 0.98)*	0.71 (0.47, 1.07)	0.76 (0.52, 1.11)	0.79 (0.49, 1.25)	0.89 (0.62, 1.25)	**TIL 100**	3.34 (2.10, 5.33)*	5.83 (3.60, 9.31)*	5.95 (2.65, 13.29)*	152.35 (105.19, 219.25)*
0.06 (0.04, 0.09)*	0.06 (0.04, 0.09)*	0.06 (0.04, 0.09)*	0.09 (0.06, 0.13)*	0.09 (0.06, 0.12)*	0.12 (0.08, 0.19)*	0.17 (0.11, 0.26)*	0.18 (0.12, 0.28)*	0.20 (0.14, 0.29)*	0.21 (0.14, 0.32)*	0.23 (0.15, 0.33)*	0.24 (0.17, 0.42)*	0.27 (0.19, 0.48)*	0.30 (0.19, 0.48)*	**ETA**	1.74 (1.08, 2.77)*	1.78 (0.77, 4.04)	45.59 (31.88, 64.62)*
0.03 (0.02, 0.05)*	0.04 (0.02, 0.05)*	0.04 (0.02, 0.05)*	0.05 (0.03, 0.07)*	0.05 (0.03, 0.08)*	0.07 (0.04, 0.11)*	0.10 (0.06, 0.15)*	0.10 (0.07, 0.17)*	0.12 (0.08, 0.17)*	0.12 (0.08, 0.19)*	0.13 (0.09, 0.19)*	0.14 (0.08, 0.22)*	0.15 (0.10, 0.24)*	0.17 (0.11, 0.28)*	0.57 (0.36, 0.93)*	**APR**	1.02 (0.47, 2.23)	26.13 (18.02, 38.41)*
0.03 (0.02, 0.08)*	0.03 (0.02, 0.07)*	0.04 (0.02, 0.08)*	0.05 (0.02, 0.10)*	0.05 (0.02, 0.11)*	0.07 (0.03, 0.16)*	0.09 (0.04, 0.21)*	0.10 (0.04, 0.24)*	0.11 (0.05, 0.24)*	0.12 (0.05, 0.27)*	0.13 (0.06, 0.27)*	0.13 (0.06, 0.29)*	0.15 (0.07, 0.33)*	0.17 (0.08, 0.38)*	0.56 (0.25, 1.29)	0.98 (0.45, 2.12)	**DMF**	25.54 (11.96, 55.12)*
0.00 (0.00, 0.00)*	0.00 (0.00, 0.00)*	0.00 (0.00, 0.00)*	0.00 (0.00, 0.00)*	0.00 (0.00, 0.00)*	0.00 (0.00, 0.00)*	0.00 (0.00, 0.01)*	0.00 (0.00, 0.01)*	0.00 (0.00, 0.01)*	0.00 (0.00, 0.01)*	0.00 (0.00, 0.01)*	0.01 (0.00, 0.01)*	0.01 (0.00, 0.01)*	0.01 (0.00, 0.01)*	0.02 (0.02, 0.03)*	0.04 (0.03, 0.06)*	0.04 (0.02, 0.08)*	**PBO**

Values in table are presented as the pairwise odds ratio with the 95% credible interval in parenthesis. An odds ratio > 1 indicates that the treatment in that row has a higher probability of achieving PASI response compared with the treatment in that column. An odds ratio < 1 indicates that the treatment in that row has a lower probability of achieving PASI response compared with the treatment in that column

ADA adalimumab, *APR* apremilast, *BRO* brodalumab, *CZP 200* certolizumab 200 mg, *CZP 400* certolizumab 400 mg, *DMF* dimethyl fumarate, *ETA* etanercept, *GUS* guselkumab, *INF* infliximab, *IXE* ixekizumab, *PBO* placebo, *RIS* risankizumab, *SEC* secukinumab, *TIL 100* tildrakizumab 100 mg, *TIL 200* tildrakizumab 200 mg, *UST_W* ustekinumab weight based, *UST 45* ustekinumab 45 mg, *UST 90* ustekinumab 90 mg

[a]Denotes that 95% CrI excludes 1

	NNT to achieve one PASI 75 response		NNT to achieve one PASI 90 response		NNT to achieve one PASI 100 response	
Ixekizumab 80 mg		1.18 (1.15, 1.22)		1.39 (1.32, 1.49)		2.42 (2.15, 2.76)
Risankizumab 150 mg		1.19 (1.16, 1.22)		1.40 (1.32, 1.49)		2.45 (2.18, 2.78)
Brodalumab 210 mg		1.19 (1.15, 1.23)		1.41 (1.32, 1.51)		2.49 (2.18, 2.84)
Guselkumab 100 mg		1.25 (1.21, 1.30)		1.57 (1.46, 1.69)		3.05 (2.66, 3.52)
Secukinumab 300 mg		1.25 (1.22, 1.29)		1.57 (1.48, 1.67)		3.05 (2.73, 3.44)
Infliximab 5 mg/kg		1.34 (1.27, 1.43)		1.80 (1.62, 2.03)		3.93 (3.24, 4.86)
Certolizumab pegol 400 mg		1.45 (1.35, 1.58)		2.06 (1.81, 2.39)		5.00 (3.98, 6.39)
Ustekinumab 90 mg		1.48 (1.38, 1.61)		2.14 (1.89, 2.48)		5.31 (4.28, 6.81)
Ustekinumab 45 mg ≤100 kg, 90 mg >100 kg		1.52 (1.44, 1.62)		2.25 (2.03, 2.49)		5.77 (4.87, 6.86)
Ustekinumab 45 mg		1.54 (1.44, 1.67)		2.30 (2.05, 2.62)		6.01 (4.96, 7.45)
Adalimumab 40 mg		1.58 (1.49, 1.68)		2.39 (2.16, 2.66)		6.39 (5.41, 7.61)
Certolizumab pegol 200 mg		1.59 (1.45, 1.78)		2.43 (2.07, 2.93)		6.58 (5.03, 8.85)
Tildrakizumab 200 mg		1.65 (1.50, 1.86)		2.59 (2.19, 3.12)		7.28 (5.52, 9.77)
Tildrakizumab 100 mg		1.72 (1.55, 1.95)		2.77 (2.33, 3.36)		8.10 (6.11, 11.00)
Etanercept 25 mg BIW / 50 mg QW		2.87 (2.46, 3.40)		5.91 (4.76, 7.48)		25.10 (18.35, 35.01)
Apremilast 30 mg		3.85 (3.17, 4.73)		8.83 (6.79, 11.57)		43.74 (30.42, 63.06)
Dimethyl fumarate		3.90 (2.63, 6.20)		8.99 (5.23, 16.34)		44.82 (21.08, 98.38)

Fig. 3 Estimated numbers needed to treat (*NNTs*) relative to placebo for short-term PASI response. Values are presented with the 95% credible interval (*CrI*) in parenthesis. *BIW* Twice weekly, *PASI 75, 90, 100* 75, 90, or 100% decrease from baseline PASI, respectively, *QW* once weekly

DISCUSSION

The results suggest that ixekizumab, risankizumab, and brodalumab were associated with significantly higher PASI response rates than the other licensed treatments in the short term, and that risankizumab was associated with significantly higher PASI response rates than the other licensed treatments in the long term. The results established the benefits of these treatments towards achieving a high level of skin clearance (PASI 100 and PASI 90).

Compared with the prior NMA by Armstrong et al. [14], this study identified 11 additional trials for the short-term PASI NMA and four additional trials for the long-term PASI NMA. These additions included several large head-to-head trials between active treatments reporting short-term PASI results, such as IXORA-R (*n* = 1027) and ECLIPSE (*n* = 1048) [8, 21]. The increase in statistical power made it possible to detect previously unidentified significant differences in PASI response rates between the treatments. Specifically, the present study found statistically significantly higher short-term PASI response rates associated with ixekizumab, risankizumab, and brodalumab compared with guselkumab following the addition of the 11 recent trials. Furthermore, the four newly added trials with long-term PASI results extended the long-term NMA conducted by Armstrong et al. [14] and further connected guselkumab and adalimumab to facilitate an

indirect comparison of eight active treatments. The large sample sizes of the newly included head-to-head trials, such as CLARITY (*n* = 1102) and ECLIPSE (*n* = 1048) [21, 22], also made it possible for the present long-term NMA to detect statistical differences between treatments.

In the short-term NMAs of this study, two anti-IL-17 agents (ixekizumab and brodalumab) and an anti-IL-23 agent (risankizumab) were associated with the most favorable efficacy outcomes, including achievement of a high level of skin clearance. This result is consistent with the findings of other recent NMAs for moderate-to-severe plaque psoriasis. For example, Sbidian et al. [15] suggested that anti-IL-17 agents (ixekizumab, secukinumab, bimekizumab, and brodalumab), anti-IL-23 agents (risankizumab and guselkumab), and infliximab were significantly more effective, in terms of PASI 90 response rates, than ustekinumab and other anti-TNF agents (adalimumab, certolizumab, and etanercept). Mahil et al. [13] showed that in terms of achieving clear/nearly clear skin status, ixekizumab was associated with the highest SUCRA value followed by risankizumab. Sawyer et al. [12] reported that the anti-IL-17 agents guselkumab and risankizumab were more efficacious than tildrakizumab, ustekinumab, anti-TNF agents, and non-biologic systemic treatments. Tada et al. [17] similarly reported that brodalumab, ixekizumab, and risankizumab were associated with
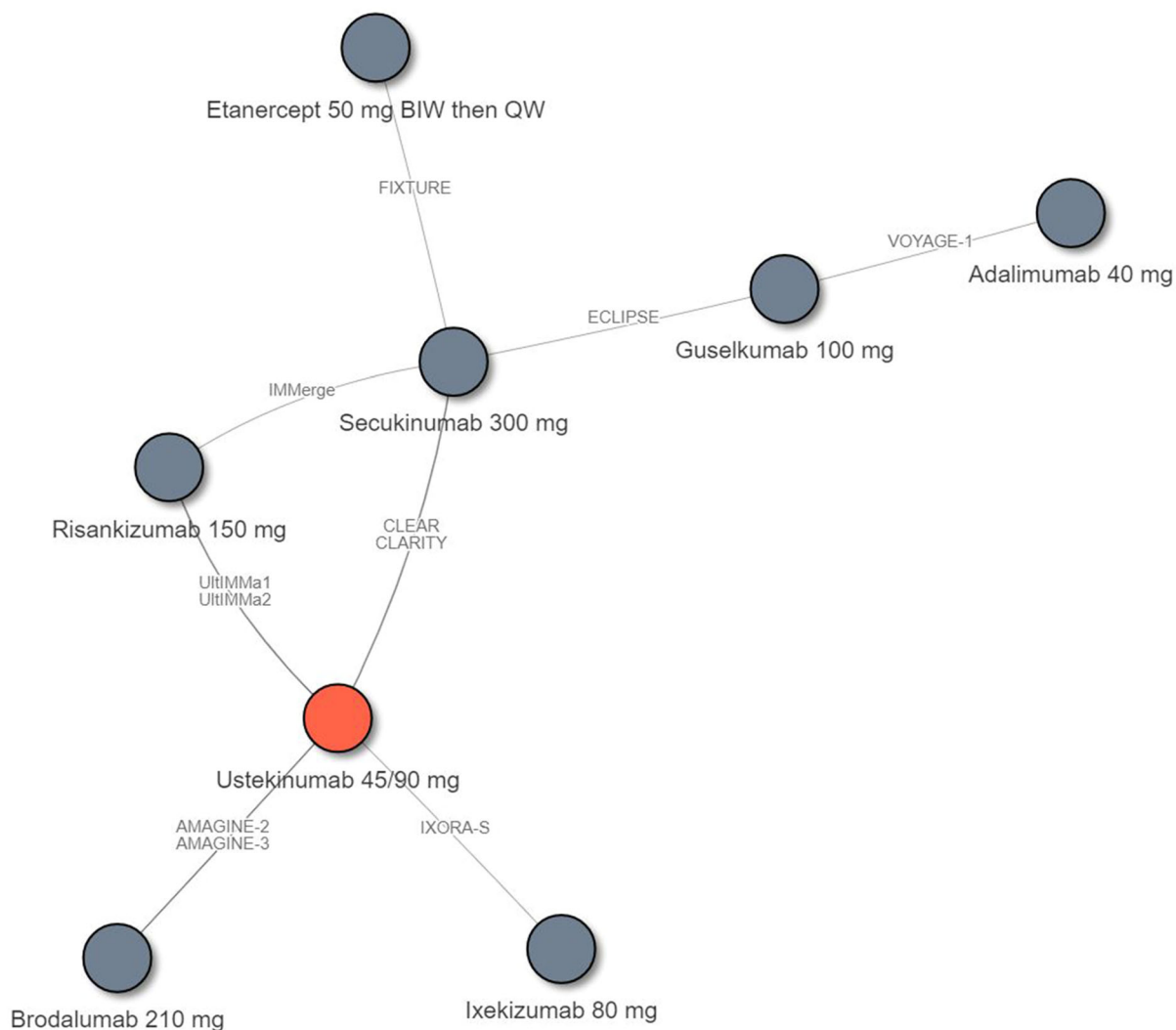
Fig. 4 Evidence network for the NMA of PASI response by the end of the maintenance period (long-term; 48–52 weeks after baseline). The included trials were: AMAGINE-2 [70], ECLIPSE [21], VOYAGE-1 [63], CLEAR [87], FIXTURE [46], CLARITY [22], IXORA-S [88], UltIMMa1 [77], and IMMerge [9]

the highest rates of PASI 90 and PASI 100 response and the highest SUCRA values.

The long-term NMA suggested that PASI 90 and 100 response rates were highest for risankizumab by the end of the maintenance period (PASI 90: 85.3%; PASI 100: 65.4%), followed by brodalumab and guselkumab. To date, few studies have attempted an NMA comparing the relative efficacy of treatments in the long term. Yasmeen et al. [16] found that risankizumab, brodalumab, and guselkumab were associated with a higher probability of achieving a PASI response than other biologics, but did not

detect statistically significant differences between the three treatments.

This study benefits from the following strengths. First, the inclusion of newly published clinical trials permitted the addition of guselkumab and adalimumab into the long-term NMA and increased the sample sizes and statistical power for detection of differences in PASI response rates between treatments in both the short-term and long-term NMAs. Second, the use of the random-effects model adjusted for reference-arm response for the short-term NMAs addressed the potential heterogeneities

Table 3 Estimated response rates, SUCRA, and mean rank from the NMA of long-term PASI response

Treatment	Posterior median, % (95% CrI)			SUCRA[a]	Mean rank (95% CrI)
	PASI 75	PASI 90	PASI 100		
Risankizumab 150 mg at weeks 0, and 4, then Q12W	93.6 (91.2, 95.4)	85.3 (81.4, 88.7)	65.4 (59.3, 71.1)	0.998	1.0 (1.0, 1.0)
Brodalumab 210 mg at weeks 0, 1, and 2, then Q2W	89.7 (86.6, 92.3)	78.8 (74.0, 83.0)	55.7 (49.4, 61.8)	0.786	2.5 (2.0, 4.0)
Guselkumab 100 mg at weeks 0, and 4, then Q8W	89.3 (85.6, 92.3)	78.1 (72.5, 83.0)	54.8 (47.6, 61.9)	0.760	2.7 (2.0, 4.0)
Ixekizumab 160 mg at week 0, 80 mg Q2W until week 12, then 80 mg Q4W	85.4 (78.5, 90.6)	72.1 (62.7, 80.1)	47.2 (37.0, 57.6)	0.577	4.0 (2.0, 5.0)
Secukinumab 300 mg at weeks 0, 1, 2, 3, and 4, then Q4W	81.8 (78.5, 84.7)	67.0 (62.8, 71.0)	41.5 (37.0, 46.1)	0.450	4.9 (4.0, 5.0)
Ustekinumab 45 mg ≤ 100 kg, 90 mg > 100 kg at weeks 0, and 4, then Q12W	72.4 (70.2, 74.4)	55.0 (52.7, 57.3)	29.8 (27.6, 32.1)	0.252	6.2 (6.0, 7.0)
Adalimumab 80 mg at week 0, then 40 mg Q2W	69.4 (60.2, 77.5)	51.6 (41.8, 61.3)	26.9 (19.3, 35.7)	0.176	6.8 (6.0, 7.0)
Etanercept 50 mg BIW until week 12, then QW	56.3 (48.1, 64.2)	37.9 (30.4, 45.8)	16.7 (12.1, 22.4)	0.001	8.0 (8.0, 8.0)

[a] SUCRA measures the probability of a treatment being in the top ranks

in treatment contrasts across trials, and insured the validity for the statistical inference for the short-term NMAs under a rich network.

Limitations

This study is subject to the following limitations. First, NMAs rely on the transitivity assumption, requiring that the study conduct and patient populations be comparable across trials. There may be observed or unobserved factors, such as differences in study design, patient characteristics, and concomitant treatments, that may modify the treatment efficacy and influence the comparability of the clinical trials in the NMAs. The assessment time points also varied across trials. However, as the included clinical trials were designed a priori for the assessments at these time points, these pre-specified time points were chosen for this analysis. Second, the potential differences between patients with moderate-to-severe plaque psoriasis in the clinical trials and the real world, such as patient characteristics, adherence, and persistence to treatments, may limit the generalizability of the study results [26]. Third, due to the relative dearth of available data, the long-term network is still sparse. Fourth, while the long-term NMA was able to assess the relative efficacy of treatments by 48–52 weeks after baseline, direct evidence comparing the PASI response rates beyond 1 year is lacking. Lastly, PASI may only represent one of the many aspects measuring the

Table 4 Pairwise odds ratio of achieving PASI 90 and 100 response in the long term

PASI 90 response: posterior median (95% CrI)

RIS	1.57 (1.08, 2.28)[a]	1.63 (1.12, 2.37)[a]	2.25 (1.35, 3.73)[a]	2.86 (2.16, 3.82)[a]	4.76 (3.64, 6.29)[a]	5.48 (3.49, 8.61)[a]	9.56 (6.46, 14.28)[a]
0.64 (0.44, 0.92)[a]	BRO	1.04 (0.71, 1.53)	1.44 (0.87, 2.34)	1.82 (1.36, 2.46)[a]	3.03 (2.37, 3.92)[a]	3.49 (2.21, 5.52)[a]	6.09 (4.07, 9.16)[a]
0.61 (0.42, 0.89)[a]	0.96 (0.66, 1.42)	GUS	1.38 (0.82, 2.31)	1.76 (1.39, 2.25)[a]	2.92 (2.19, 3.94)[a]	3.36 (2.56, 4.42)[a]	5.88 (4.08, 8.50)[a]
0.44 (0.27, 0.74)[a]	0.70 (0.43, 1.15)	0.72 (0.43, 1.22)	IXE	1.27 (0.81, 2.02)	2.11 (1.39, 3.26)[a]	2.43 (1.37, 4.33)[a]	4.24 (2.51, 7.26)[a]
0.35 (0.26, 0.46)[a]	0.55 (0.41, 0.74)[a]	0.57 (0.45, 0.72)[a]	0.79 (0.50, 1.23)	SEC	1.66 (1.42, 1.95)[a]	1.91 (1.35, 2.71)[a]	3.34 (2.54, 4.41)[a]
0.21 (0.16, 0.28)[a]	0.33 (0.26, 0.42)[a]	0.34 (0.25, 0.46)[a]	0.47 (0.31, 0.72)[a]	0.60 (0.51, 0.71)[a]	UST_W	1.15 (0.78, 1.69)	2.01 (1.47, 2.77)[a]
0.18 (0.12, 0.29)[a]	0.29 (0.18, 0.45)[a]	0.30 (0.23, 0.39)[a]	0.41 (0.23, 0.73)[a]	0.52 (0.37, 0.74)[a]	0.87 (0.59, 1.28)	ADA	1.75 (1.12, 2.73)[a]
0.10 (0.07, 0.15)[a]	0.16 (0.11, 0.25)[a]	0.17 (0.12, 0.25)[a]	0.24 (0.14, 0.40)[a]	0.30 (0.23, 0.39)[a]	0.50 (0.36, 0.68)[a]	0.57 (0.37, 0.89)[a]	ETA

PASI 100 response: posterior median (95% CrI)

RIS	1.50 (1.08, 2.10)[a]	1.56 (1.11, 2.19)[a]	2.11 (1.32, 3.40)[a]	2.66 (2.06, 3.45)[a]	4.44 (3.49, 5.68)[a]	5.14 (3.29, 8.13)[a]	9.40 (6.30, 14.23)[a]
0.67 (0.48, 0.93)[a]	BRO	1.03 (0.72, 1.48)	1.41 (0.88, 2.24)	1.77 (1.34, 2.34)[a]	2.96 (2.35, 3.73)[a]	3.42 (2.16, 5.49)[a]	6.26 (4.12, 9.60)[a]
0.64 (0.46, 0.90)[a]	0.97 (0.68, 1.38)	GUS	1.36 (0.83, 2.22)	1.71 (1.37, 2.14)[a]	2.86 (2.18, 3.75)[a]	3.31 (2.50, 4.42)[a]	6.05 (4.15, 8.89)[a]
0.47 (0.29, 0.76)[a]	0.71 (0.45, 1.14)	0.74 (0.45, 1.20)	IXE	1.26 (0.81, 1.95)	2.10 (1.40, 3.16)[a]	2.43 (1.37, 4.34)[a]	4.45 (2.60, 7.66)[a]
0.38 (0.29, 0.49)[a]	0.56 (0.43, 0.75)[a]	0.58 (0.47, 0.73)[a]	0.79 (0.51, 1.23)	SEC	1.67 (1.43, 1.95)[a]	1.93 (1.34, 2.81)[a]	3.53 (2.62, 4.84)[a]
0.23 (0.18, 0.29)[a]	0.34 (0.27, 0.43)[a]	0.35 (0.27, 0.46)[a]	0.48 (0.32, 0.71)[a]	0.60 (0.51, 0.70)[a]	UST_W	1.16 (0.78, 1.74)	2.11 (1.50, 3.04)[a]
0.19 (0.12, 0.30)[a]	0.29 (0.18, 0.46)[a]	0.30 (0.23, 0.40)[a]	0.41 (0.23, 0.73)[a]	0.52 (0.36, 0.74)[a]	0.86 (0.57, 1.29)	ADA	1.83 (1.13, 2.95)[a]
0.11 (0.07, 0.16)[a]	0.16 (0.10, 0.24)[a]	0.17 (0.11, 0.24)[a]	0.22 (0.13, 0.38)[a]	0.28 (0.21, 0.38)[a]	0.47 (0.33, 0.67)[a]	0.55 (0.34, 0.88)[a]	ETA

Values in table are presented as the pairwise odds ratio with the 95% CrI. An odds ratio > 1 indicates that the treatment in that row has a higher probability of achieving PASI response compared with the treatment in that column. An odds ratio < 1 indicates that the treatment in that row has a lower probability of achieving PASI response compared with the treatment in that column

ADA adalimumab, *BRO* brodalumab, *ETA* etanercept, *GUS* guselkumab, *IXE* ixekizumab, *RIS* risankizumab, *SEC* secukinumab, *UST_W* ustekinumab weight based

[a] Denoted that 95% CrI excludes 1

efficacy of treatments for moderate-to-severe plaque psoriasis. With additional data, future studies may consider comparisons of other measures of treatment efficacy, such as the resolution of itch, HRQoL, and treatment adherence.

CONCLUSIONS

This study provides an up-to-date, comprehensive indirect comparison of the relative efficacy of licensed treatments for moderate-to-severe plaque psoriasis. Ixekizumab, risankizumab, and brodalumab were associated with the highest PASI response rates by the end of the primary response period. Risankizumab was associated with the highest PASI response rates by the end of the maintenance period. Future research can take an integrative approach to assess multiple aspects of each treatment, including efficacy, safety, treatment adherence, and HRQoL, and identify subgroups of patients (using clinical, laboratory, and genomic data) who can benefit the most from each biologic and oral treatment for moderate-to-severe plaque psoriasis.

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