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REVIEW

One-Year Efficacy of Guselkumab Versus Advanced Therapies for the Treatment of Moderately to Severely Active Crohn's Disease: A Network Meta-Analysis

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ABSTRACT

Introduction: This study used network meta-analysis (NMA) to evaluate the comparative efficacy of available advanced therapies for moderately to severely active Crohn's disease (CD) versus the IL-23 inhibitor guselkumab.
Methods: A systematic literature review was conducted to identify randomized controlled trials (RCTs) of advanced therapies in moderately to severely active CD. Bayesian NMAs were conducted for outcomes of clinical response, clinical remission, endoscopic response, and a combined outcome of clinical remission with endoscopic response, at the end of the maintenance phase (up to 1 year). Primary analyses included patients with varied prior inadequate treatment responses, with additional analyses conducted for specific subgroups. Re-randomized trials were normalized in several cases to mimic a standard treat-through design, incorporating data from additional sources, when necessary, for patients who had an inadequate response or experienced a delayed response following induction.
Results: Of the 58 RCTs identified, 13 with maintenance endpoint data were ultimately included in the NMAs. Guselkumab 100 mg and 200 mg were more likely to be effective versus several comparators. Guselkumab 200 mg demonstrated significantly greater efficacy versus infliximab 10 mg/kg every 8 weeks and upadacitinib 30 mg daily for clinical response and clinical remission. For endoscopic response, guselkumab 200 mg showed significantly greater efficacy than ustekinumab, adalimumab, and upadacitinib. Significance was also noted versus ustekinumab on the combined outcome of clinical remission with endoscopic response. Similarly, guselkumab 100 mg demonstrated efficacy versus comparators across analyses. Guselkumab achieved higher rankings based on surface under the cumulative ranking curve. Findings of primary analyses within mixed populations

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were generally corroborated by subpopulation analyses.

***Conclusion*:** Results of this NMA in moderately to severely active CD indicate a higher likelihood of guselkumab achieving each clinical and endoscopic endpoint analyzed at the end of the maintenance phase versus other advanced therapies assessed.

PLAIN LANGUAGE SUMMARY

A network meta-analysis (NMA) was completed to compare the effectiveness of advanced treatments for Crohn's disease, a chronic inflammatory condition of the digestive tract. Our NMA focused on the drug guselkumab and how effective it is compared with other treatments for Crohn's disease. We looked at 4 outcomes related to efficacy that are common in trials: clinical response (improvement in symptoms), clinical remission (disappearance of symptoms), endoscopic response (seen in the digestive tract), and a combined outcome of clinical remission with endoscopic response. Data were analyzed from trials lasting up to 1 year. Patients who had not responded well to prior treatments were included in the analysis. Thirteen trials met all criteria and were included in the analysis. Guselkumab at doses of 100 mg and 200 mg was more effective than several treatments. Guselkumab 200 mg was significantly better than infliximab and upadacitinib for both clinical response and clinical remission. It also showed better results than ustekinumab, adalimumab, and upadacitinib for endoscopic response and was more effective than ustekinumab for the combined outcome of clinical remission with endoscopic response. Our analysis shows that guselkumab is likely to be more effective at achieving both symptom improvement and healing the digestive tract compared with other advanced treatments for moderate to severe Crohn's disease.

Keywords: Crohn's disease; Network meta-analysis; Biologics; Indirect treatment comparisons; Study design; Guselkumab

Key Summary Points

Why conduct this study?

Guselkumab has demonstrated superiority in 2 identically designed, 48-week, double-blind, placebo-controlled, treat-through, active-comparator (ustekinumab) studies. To better inform treatment decisions, network meta-analysis was performed to investigate comparative efficacy of guselkumab versus available therapies for patients with Crohn's disease.

What was learned from this study?

Results of this network meta-analysis suggest that guselkumab has a higher likelihood of achieving clinical and endoscopic outcomes versus several comparators and may be a preferred treatment option in patients with moderately to severely active Crohn's disease.

Guselkumab demonstrated significantly greater efficacy compared to several comparators, including vedolizumab, infliximab, and upadacitinib for clinical response and clinical remission.

For endoscopic response, guselkumab showed significantly greater efficacy than ustekinumab, adalimumab, and upadacitinib.

Findings of the primary analyses within mixed patient populations were generally corroborated by subgroup analyses focused on patients with and without inadequate response or intolerance to biologic therapy.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease characterized by transmural inflammation, which can occur throughout the entirety of the gastrointestinal tract, from the mouth to the anus [1–3]. Patients may experience symptoms such as diarrhea, abdominal pain, rectal bleeding, and fatigue [3], and chronic inflammation can lead to more serious

complications over time such as strictures, fistulas, and abscesses [4]. The prevalence and incidence of CD are generally highest in North America, Northern and Western Europe, and Australia [5], with the current prevalence of CD estimated at 165 per 100,000 individuals in the United States [6].

The management of CD may be challenging. Patients with higher severity disease or who have failed conventional therapies typically receive advanced therapies to induce remission or prevent relapse [7]. Several products are currently available or in development, with different anti-inflammatory mechanisms of action [7], including: tumor necrosis factor inhibition (e.g., infliximab and adalimumab), interleukin (IL)-12/23 inhibition (e.g., ustekinumab), IL-23 inhibition (e.g., risankizumab, mirikizumab, and guselkumab), integrin blockage (vedolizumab), and Janus kinase inhibition (upadacitinib). However, despite the availability of these advanced therapies, many patients fail to achieve adequate long-term disease control [8].

Guselkumab is an IL-23p19 subunit inhibitor that neutralizes IL-23, a key driver of CD pathogenesis, at its cellular source of production [9]. Guselkumab is currently approved in the United States and Europe for psoriasis and psoriatic arthritis, and is also approved in the United States for ulcerative colitis. In addition, guselkumab is currently under regulatory review for the treatment of moderately to severely active CD based on the results of the GALAXI program. The 2 double-blind GALAXI phase 3 studies independently established the short- and long-term efficacy of guselkumab compared with placebo in adult patients with moderately to severely active CD [10, 11]. In addition, statistical superiority to ustekinumab (Stelara®) was demonstrated across key endoscopic and composite outcomes in prespecified and multiplicity-controlled analyses of pooled data at Week 48, with relatively consistent results between the 2 studies. Both guselkumab subcutaneous maintenance doses [200 mg every 4 weeks (Q4W) and 100 mg every 8 weeks (Q8W)] were efficacious and had favorable safety profiles consistent with those of guselkumab in its approved indications. Although guselkumab has been directly compared with placebo and ustekinumab in the double-blind GALAXI trials, it has not been directly compared to other available advanced treatments indicated in CD.

The objective of this network meta-analysis (NMA) was to assess the comparative efficacy of guselkumab versus all available therapies at approximately 1 year (i.e., the typical follow-up period for maintenance therapy in clinical trials) based on outcomes of clinical response, clinical remission, endoscopic response, and a combined outcome of clinical remission with endoscopic response.

METHODS

A protocol for the systematic literature review (SLR) was registered with PROSPERO on September 19, 2023 (registration number CRD42023459494). The methods followed the guidance outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* [12], and reporting was conducted with guidance from the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [13]. A protocol for the NMAs was also developed a priori. This analysis and summary is based on previously completed/published trials and does not contain any new studies with human participants or animals performed by any of the authors.

The SLR was conducted to identify published records of phase 2-4 randomized controlled trials (RCTs), focused on adults or adolescents (≥ 16 years of age) with moderately to severely active CD. Eligible trials used an active- or placebo-controlled design to investigate key treatments such as: infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab, guselkumab, risankizumab, mirikizumab, tofacitinib, updacitinib, ozanimod, or etrasimod. However, trials were considered potentially eligible for quantitative synthesis if they investigated regimens approved in the United States, Canada, Europe, or Japan and if they investigated treatment efficacy in the maintenance phase (or fed into a maintenance trial). Detailed eligibility criteria are available in the Supplementary Material, Sect. 1.1.

EMBASE, MEDLINE, and Cochrane Central were searched on July 27, 2023. The search strategy (see Supplementary Material, Sect. 1.2) was developed by a medical information specialist and peer-reviewed using the Peer Review of Electronic Search Strategies (PRESS) checklist. Additional searching was conducted between July and October 2023 on the ClinicalTrials.gov website and of key clinical conferences held since 2022. The bibliographies of select published SLRs were also reviewed. Screening of retrieved citations was conducted by 2 independent reviewers in 2 stages (title and abstract review followed by full-text review), with discrepancies resolved through consensus or by a third reviewer. A list of citations excluded during full-text review is provided as Supplementary Material, Sect. 1.3. Extraction of trial characteristics and outcome data was conducted by 1 reviewer and validated by a second reviewer using a standardized spreadsheet, as were quality assessments that were conducted where full-text publications were available using guidance from the Centre for Reviews and Dissemination (University of York).

Additional trial data from gray literature sources such as health technology assessment and regulatory reports were identified through targeted literature review in some cases, particularly data among delayed responders or patients responding to placebo, or for subgroups of interest (reported throughout Supplementary Material).

The feasibility of conducting NMAs comparing guselkumab with comparator treatments was assessed, with particular focus on cross-trial heterogeneity in patient characteristics and study designs based on guidance from Tanaka et al. [14] and Cope et al. [15]. Trials demonstrating substantial heterogeneity based on the assessment, or which did not provide comparative data between 2 regimens of interest or against placebo (i.e., would not contribute to or connect to the network) could be deemed ineligible for inclusion in the NMAs.

Outcomes of interest were the following at the end of the maintenance phase of treatment (using the time point closest to 52 weeks), as defined in the GALAXI trials:

- Clinical remission: Crohn's Disease Activity Index (CDAI) score < 150.
- Clinical response: ≥ 100-point reduction from baseline in CDAI score or CDAI score < 150.
- Endoscopic response: ≥ 50% improvement from baseline in Simple Endoscopic ScoreCrohn's Disease (SES-CD) score or SES-CD score ≤ 2.
- Combined endoscopic response and clinical remission: ≥ 50% improvement from baseline in SES-CD score or SES-CD score ≤ 2 and a CDAI score < 150.

These definitions were preferred, but alternative definitions were permissible for inclusion in NMAs if it was deemed that they would have minimal impact on relative treatment effects.

Trial design was identified as a key source of heterogeneity. Broadly, trials could be of treat-through design, where continuation to maintenance was not conditional on induction response, or re-randomized design, in which only induction responders proceeded to maintenance where they were re-randomized to either active treatment or placebo. Trials employing re-randomization are more adaptive in nature, and can optimize clinical and ethical benefits; however, they are notably different from conventional treat-through trials and this heterogeneity should be accounted for upon conducting indirect comparisons [16]. Additional trial design variations were observed, underscoring this source of heterogeneity. In particular, trials could be of mixed variety, where active arms could follow a standard treat-through design, while patients who were initially randomized to placebo who did not respond at the end of induction could switch to open-label active therapy. Each trial design estimates a potentially different population (e.g., among induction responders versus among all patients randomized at induction) and if not dealt with would constitute a major source of bias in potential analyses.

Previous NMAs have used calculations in order to adjust outcome data from re-randomized trials to reflect treat-through designs,

therefore reducing cross-trial heterogeneity [16]. Randomized withdrawal trials were therefore normalized to mimic a standard treat-through design, where patients remain in the treatment sequence they were randomized to at the beginning of induction. Methods largely followed those from NICE TA633 [17]. Imputation (e.g., using data from other trials) or derivation with reported data was necessary for several trials, particularly for patients who did not respond or had a delayed response following induction (i.e., patients who would typically not be evaluated at the end of maintenance in a re-randomized study). Overall, imputation to facilitate normalization of trials, or the combination of distinct induction and maintenance phase trials, was minimized if more simplistic treat-through trials were available to incorporate a comparator of interest in the network without imputations (see details in results of feasibility assessment).

For the primary analysis, the population included a mixture of patients with various prior responses to treatment. The recent European Crohn's and Colitis Organisation (ECCO) clinical guidelines discourage the terminology "conventional therapy," as this has become outdated with biologic therapies being more accessible and increasingly viewed as a conventional part of CD treatment [18]. In accordance, subgroup analyses were planned for patients with inadequate response or intolerance to biologics (BIO-IR) and patients who had not previously had an inadequate response or intolerance to biologics (non-BIO-IR). Availability of subgroup data varied by trial, requiring conversion of subgroup data to mixed population data or conversion of mixed population data to subgroup data based on methods in NICE TA633 [17]. More details on normalization methods and calculation of subgroup or mixed population data are provided in the Supplementary Material, Sect. 3.1.

Bayesian NMAs were conducted using Just Another Gibbs Sampler (JAGS) software in R [19, 20]. Clinical remission and clinical response were analyzed together as an ordinal endpoint with 3 categories (no response/remission, response but not remission, and remission) using an inverse logit multivariate regression model for ordered categorical data, while a binomial likelihood model was used for the remaining outcomes. Random effects models were used given differences in trial designs, and log-normal informative prior distributions were used for the shared between-trial heterogeneity parameter to encourage convergence and prevent implausibly wide credible intervals (CrI) [21]. Median odds ratios (ORs) and 95% CrI for relative treatment effects were generated using Markov Chain Monte Carlo methods, and league tables were used to present analysis findings. CrI not including 1 were considered to represent high likelihood of efficacy advantage for a comparator, and this instance is briefly labeled as "significant" throughout this report. The surface under the cumulative ranking curve (SUCRA) and median ranks were used to support comparing the relative efficacy of therapeutics, where SUCRA values range from 0 to 1 and represent the percentage of efficacy that a treatment achieves relative to an ideal treatment [22].

RESULTS

SLR and NMA Feasibility Assessment

Across 6695 records identified in database searching and 1093 identified from other sources, 58 RCTs were identified in the SLR across 137 individual records. A total of 29 RCTs, of which 21 evaluated maintenance endpoints, were deemed potentially eligible for inclusion in the NMAs, and their high-level details are summarized in Table 1 (those included in the NMAs) and Table 2 (those excluded from the NMAs). A flow diagram summarizing the study selection process is provided in Fig. 1.

All identified trials were multicenter RCTs and were double-blind (with the exception of the open-label SEQUENCE trial). The majority of trials were also placebo-controlled, with the exception of SEAVUE, SEQUENCE, and SONIC. Eight of the RCTs used a treat-through design, whereas the remainder used responder re-randomization. All the prespecified advanced treatments of interest were investigated in more than 1 trial, with guselkumab investigated in the 3 GALAXI trials. All trials evaluated maintenance outcomes

at a minimum of 48 weeks, with the exception of CERTIFI, PRECISE-1, and PRECISE-2.

In general, the included RCTs were considered to be of good methodologic quality (see Table S1.4). Eligibility criteria were generally aligned across trials, though variation was noted for criteria related to prior treatment use and failure. With respect to baseline characteristics that were considered potential effect modifiers, broad homogeneity was noted across several traits: age, CDAI score at baseline, and concomitant steroid use.

Outcome definitions were broadly aligned across trials. In 3 trials (ENACT 1, ENACT 2, and ACCENT 1), the definition of clinical response based on CDAI was less stringent (requiring a minimum decrease in CDAI of 70 points rather than 100 points) versus the majority of trials. The definition of clinical remission was consistent across all trials reporting this outcome. Though endoscopic response was reported in fewer trials, homogeneity in definition was noted where definitions were available for review. It should be noted that, in the FORTIFY trial, endoscopic response was defined as > 50% improvement in SES-CD (or for patients with isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline), unlike the GALAXI trials that defined response as ≥ 50% improvement or SES-CD score ≤ 2.

Finally, heterogeneity was noted in placebo response rates in the maintenance phase of treatment, potentially driven by differences in study design (e.g., re-randomization) as well as differences in outcome definitions.

In summary, key sources of cross-trial heterogeneity included variation in trial designs (treat-through, re-randomized, and studies of only induction or maintenance), variation in patients' previous therapy exposures or failures, as well as variation in placebo response rates. Overall, these issues were not considered to preclude the conduct of valid NMAs, especially given the a priori plan to normalize trial designs as needed. SEQUENCE [23] was excluded from NMAs due to risks of bias introduced by its open-label design; however, sensitivity analyses to include this study while adjusting for bias associated with unblinded studies and accounting for differential drop-outs in treatment arms were conducted where feasible (see Supplementary Material, Sect. 2.3). SONIC was excluded due to only 1 of its treatment arms being eligible [24].

To minimize the use of imputation, where network connections are already established, 6 re-randomized trials were excluded from NMAs (as detailed in Table 2): SERENITY, EXTEND, CHARM, CLASSIC 1 and 2, and CERTIFI. In the case of IM-UNITI, this re-randomized trial was only leveraged in order to incorporate a unique regimen of ustekinumab 90 mg every 12 weeks, which was not investigated by the identified treat-through trials, and was connected to the network via ustekinumab 90 mg Q8W without the need to use and impute placebo arm data (see Supplementary Material, Sect. 3.2). PRECISE 2 and VISIBLE 2 were excluded due to having open-label induction phases, given the availability of studies with blinded induction regimens that investigated common agents. Overall, 13 trials with end of maintenance data were included in the NMA, and 9 required imputation or derivation in at least 1 outcome or treatment arm. The majority of imputations were for induction non-responders in re-randomized design studies, and particularly for placebo arms.

Network Meta-Analysis

Clinical response. Analyses informed by 11 trials (Fig. 2a) among 12 other treatment regimens (Fig. 2b) indicated that both guselkumab regimens (200 mg Q4W and 100 mg Q8W) were significantly more efficacious than the majority of the comparators, including certolizumab pegol, vedolizumab, natalizumab, upadacitinib, and infliximab. Guselkumab regimens were also non-significantly more efficacious than included IL-12/23– and IL-23–targeted agents and adalimumab. Guselkumab was also the only treatment which was significantly more efficacious than infliximab 10 mg/kg Q8W [for guselkumab 200 mg Q4W, OR 3.21, 95% CrI 1.32–8.24; for guselkumab 100 mg Q8W, OR 2.83, 95% CrI 1.17–6.99]. Guselkumab 200 mg Q4W and 100 mg Q8W had the first and second highest SUCRA values, respectively, among comparators (Fig. 3). SUCRA represents the

Table 1 Randomized controlled trials included in network meta-analyses

Trial Name	Phase	Blinding	Design	Trial Duration (weeks)	Trial Period	Treatment Arms	Number Randomized	Outcomes Reported			
								Clinical Response	Clinical Remission	Endoscopic Response	Combined Outcome[a]
GALAXI-1 (29)	2b	Double-Blind	TT	12 (induction), 48 (maintenance)	Induction	(1) Placebo	61	●	●	●	●
						(2) Guselkumab 200 mg Weeks 0, 4, 8	61				
						(3) Guselkumab 600 mg Weeks 0, 4, 8	63				
						(4) Guselkumab 1200 mg Weeks 0, 4, 8	61				
						(5) Ustekinumab 6 mg/kg single dose	63				
					Maintenance	From (2): Guselkumab 100 mg Q8W	61	●	●	●	●
						From (3): Guselkumab 200 mg Q4W	63				
						From (4): Guselkumab 200 mg Q4W	61				
						From (5): Ustekinumab 90 mg Q8W	63				
GALAXI-2 (30)	3	Double-Blind	TT	12 (induction), 48 (maintenance)	Induction	Placebo	76	●	●	●	●
						Guselkumab 200 mg Weeks 0, 4, 8	289				
						Ustekinumab 6 mg/kg single dose	143				
					Maintenance	Placebo	76	●	●	●	●
						Guselkumab 100 mg Q8W	143				
						Guselkumab 200 mg Q4W	146				
						Ustekinumab 90 mg Q8W	143				
GALAXI-3 (31)	3	Double-Blind	TT	12 (induction), 48 (maintenance)	Induction	Placebo	72	●	●	●	●
						Guselkumab 200 mg Q4W	293				
						Ustekinumab 6 mg/kg single dose	148				
					Maintenance	Placebo	72	●	●	●	●
						Guselkumab 100 mg Q8W	143				
						Guselkumab 200 mg Q4W	150				
						Ustekinumab 90 mg Q8W	148				
ACCENT I (32)	3	Double-Blind	RR	6 (induction), 54 (maintenance)	Induction	Placebo	188	●	●		
						Infliximab 5 mg/kg Weeks 0, 2, 6	192				
					Maintenance	Placebo	188	●	●		
						Infliximab 5 mg/kg Q8W	192				
ADVANCE (33)	3	Double-Blind	RR	12	Induction	Placebo	175	●	●	●	
						Risankizumab 600 mg Weeks 0, 4, 8	336				
MOTIVATE (33)				12	Induction	Placebo	187	●	●	●	●
						Risankizumab 600 mg Weeks 0, 4, 8	191				
FORTIFY (34)				64	Maintenance	Placebo	164	●	●	●	●
						Risankizumab 360 mg Q8W	141				
						Risankizumab 180 mg Q8W	157				
						Adalimumab 160/80 mg Weeks 0 and 2, then 40 mg Q2W	159				
EXTEND (35)	3	Double-Blind	RR	4 (induction), 48 (maintenance)	Induction/ Maintenance	Adalimumab 160/80 mg Weeks 0 and 2, then placebo	65	●	●		
						Adalimumab 160/80 mg Weeks 0 and 2, then 40 mg Q2W	64				
ENACT 1 (36)	3	Double-Blind	RR	12	Induction	Placebo	181	●	●		
						Natalizumab 300 mg Weeks 0, 4, 8	724				
ENACT 2 (36)				60	Maintenance	Placebo	170	●	●		
						Natalizumab 300 mg Q4W	168				
GEMINI 2 (37)	3	Double-Blind	RR	6 (induction), 52 (maintenance)	Induction	Placebo	148	●	●		
						Vedolizumab 300 mg Weeks 0, 2, 6	220				
					Maintenance	Placebo	153	●	●		
						Vedolizumab 300 mg Q8W	154				
						Vedolizumab 300 mg Weeks 0, 2, 6	209				
						Ustekinumab 90 mg Q8W	129				
PRECISE 1 (38)	3	Double-Blind	TT	6 (induction), 26 (maintenance)	Induction/ Maintenance	Placebo	328	●	●		
						Certolizumab pegol 400 mg Weeks 0, 2, 4, then Q4W	331				
SEAVUE (39)	3	Double-Blind	TT	8 (induction), 56 (maintenance)	Induction/ Maintenance	Adalimumab 160/80 mg Weeks 0 and 2, then 40 mg Q2W	195	●	●	●	●
						Ustekinumab 6 mg/kg single dose, then Q8W	191				
U-EXCEL (40)	3	Double-Blind	RR	12	Induction	Placebo QD	176	●	●	●	
						Upadacitinib 45 mg QD	350				
U-EXCEED (40)				12	Induction	Placebo	171	●	●	●	
						Upadacitinib 45 mg QD	324				
U-ENDURE (40)				52	Maintenance	Placebo	165	●	●	●	
						Upadacitinib 15 mg QD	169				
						Upadacitinib 30 mg QD	168				
UNITI-1 (41)	3	Double-Blind	RR	8	Induction	Placebo	247	●	●		
						Ustekinumab 6 mg/kg single dose	249				
UNITI-2 (41)				8	Induction	Placebo	209	●	●		
						Ustekinumab 6 mg/kg single dose	209				
IM-UNITI (41)				48	Maintenance	Placebo	131	●	●		
						Ustekinumab 90 mg Q8W	129				
VIVID I (42)	3	Double-Blind	TT	12 (induction), 40 (maintenance)	Induction/ Maintenance	Placebo	199		●	●	●
						Mirikizumab 900 mg Q4W to Week 12 then mirikizumab 300 mg Q4W	579				

Table 1 continued

Included patients varied from total randomized populations. Shading is used to distinguish unique trials or groups of trials linked by re-randomization. For some trials that included multiple induction regimens of the same agent, induction regimens are numbered and are referenced as applicable within maintenance regimen labels to denote treatment sequence. Trials were categorized as either treat-through TT or RR.

BID twice daily, *IV* intravenous, *NR* not reported, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q8W* every 8 weeks, *QD* once daily, *RCT* randomized controlled trial, *RR* responder re-randomization, *SC* subcutaneous, *TT* treat-through

[a]Combined outcome refers to endoscopic response and clinical remission

average probability that a drug outperforms its comparators. Guselkumab has an 87.5% probability of being better than other comparators on average, and this high SUCRA value suggests that guselkumab regimens may have the highest efficacy among all the treatment comparators.

Clinical remission. Analyses informed by 12 trials (Fig. 4a) among 13 other treatment regimens (Fig. 4b) indicated that both guselkumab regimens were significantly more efficacious than the majority of the comparators, including upadacitinib 15 mg daily (QD), infliximab, natalizumab, certolizumab pegol, and vedolizumab. Additionally, among all comparators, only guselkumab 200 mg Q4W was significantly more efficacious than upadacitinib 30 mg QD (OR 2.67, 95% CrI 1.19 to 6.07) and non-significantly more efficacious than IL-12/23– and IL-23–targeted agents and adalimumab. Guselkumab 200 mg Q4W and 100 mg Q8W had the first and third highest SUCRA values, respectively, among comparators (Fig. 3).

Endoscopic response. Analyses informed by seven trials (Fig. 5a) among seven other treatment regimens (Fig. 5b) indicated that both guselkumab regimens were significantly more efficacious than ustekinumab (for guselkumab 200 mg Q4W, OR 1.94, 95% CrI 1.23 to 3.10; for guselkumab 100 mg Q8W, OR 1.62, 95% CrI 1.07 to 2.51) and upadacitinib 15 mg (for guselkumab 200 mg Q4W, OR 3.85, 95% CrI 1.47 to 10.15; for guselkumab 100 mg Q8W, OR 3.22, 95% CrI 1.26 to 8.38), and non-significantly more efficacious than IL-12/23– and IL-23–targeted agents. Additionally, guselkumab 200 mg Q4W was also significantly more efficacious than adalimumab and upadacitinib 30 mg QD. Guselkumab 200 mg Q4W and 100 mg Q8W had the first and second highest SUCRA values, respectively, among comparators (Fig. 3).

Combined clinical remission with endoscopic response. Analyses were informed by 6 trials (Fig. 6a) among 5 other treatment regimens (Fig. 6b). Guselkumab regimens were non-significantly more efficacious than all agents; however, guselkumab 200 mg Q4W was significantly more efficacious than ustekinumab (OR 1.85, 95% CrI: 1.14 to 3.10). Guselkumab 200 mg Q4W and 100 mg Q8W had the first and second highest SUCRA values, respectively, among comparators (Fig. 3).

Subgroup Analyses

Clinical response. In the non-BIO-IR and BIO-IR subgroups, some regimens could not be incorporated (e.g., natalizumab and certolizumab pegol were absent in both subgroups; adalimumab and infliximab were absent in the BIO-IR subgroup only). In these subgroup analyses, both guselkumab regimens continued to demonstrate significant (i.e., CrI does not contain 1) efficacy advantages over infliximab (non-BIO-IR only), vedolizumab, and upadacitinib (Fig. 7).

Clinical remission. Findings from the main analysis were generally corroborated within BIO-IR and non-BIO-IR subgroup analyses, considering commonly included comparators (fewer comparators could be incorporated in subgroup analyses, aligned with analyses of clinical response; Fig. 7). However, the significant benefits of guselkumab regimens over upadacitinib regimens in the mixed population were not observed in the BIO-IR subgroup. Also, guselkumab 100 mg Q8W outranked

Table 2 Randomized controlled trials excluded from network meta-analyses

Trial Name	Phase	Blinding	Design	Trial Duration (weeks)	Trial Period	Treatment Arms	Number Randomized
SERENITY[a] (43)	2	Double-Blind	RR	12 (induction), 52 (maintenance)	Induction	(1) Placebo	64
						(2) Mirikizumab 200 mg Q4W	31
						(3) Mirikizumab 600 mg Q4W	32
						(4) Mirikizumab 1000 mg Q4W	64
					Maintenance	From (1): Mirikizumab 300 mg Q4W	46
						From (2): Mirikizumab 200 mg Q4W	9
						From (2): Mirikizumab 300 mg Q4W	10
						From (3): Mirikizumab 600 mg Q4W	9
						From (3): Mirikizumab 300 mg Q4W	11
						From (4): Mirikizumab 1000 mg Q4W	23
						From (4): Mirikizumab 300 mg Q4W	25
CERTIFI[b] (44)	3	Double-Blind	RR	8 (induction), 36 (maintenance)	Induction	Placebo	132
						Ustekinumab 6 mg/kg single dose	131
					Maintenance	Placebo	73
						Ustekinumab 90 mg Q8W	72
CHARM[c] (45)	3	Double-Blind	RR	4 (induction), 56 (maintenance)	Induction/ Maintenance	Adalimumab 160/80 mg Weeks 0 and 2, then Placebo	170
						Adalimumab 160/80 mg Weeks 0 and 2, then adalimumab 40 mg Q2W	172
						Adalimumab 160/80 mg Weeks 0 and 2, then 40 mg QW	157
CLASSIC 1[c] (46)	3	Double-Blind	RR	4	Induction	Placebo	74
						Adalimumab 160/80 mg Weeks 0 and 2, then 40 mg Q2W	76
CLASSIC 2[c] (47)				52	Maintenance	Placebo	18
						Adalimumab 40 mg Q2W	19
						Natalizumab 300 mg Weeks 0, 4, 8	259
						Natalizumab 300 mg Weeks 0, 4, 8	724
PRECISE 2[d] (48)	3	Double-Blind	TT	26	Induction/ Maintenance	Certolizumab pegol 400 mg Weeks 0, 2, 4, then Placebo	210
						Certolizumab pegol 400 mg Weeks 0, 2, 4, then Q4W	215
SEQUENCE[e] (49)	3	Open-label	TT	48	Induction	Risankizumab 600 mg Weeks 0, 4, 8	128
						Ustekinumab 6 mg/kg single dose	137
					Maintenance	Risankizumab 360 mg Q8W	255
						Ustekinumab 90 mg Q8W	265
SONIC[f] (24)	3	Double-Blind	TT	10 (induction), 50 (maintenance)	Induction/ Maintenance	Azathioprine 2.5 mg/kg + infliximab 5 mg/kg Weeks 0, 2, 6, then Q8W	169
						Infliximab 5 mg/kg Weeks 0, 2, 6, then Q8W	169
VISIBLE-2[g] (50)	3	Double-Blind	TT	2 (induction), 50 (maintenance)	Induction/ Maintenance	Vedolizumab 300 mg Weeks 0 and 2 then placebo	134
						Vedolizumab 300 mg Weeks 0 and 2 then vedolizumab 108 mg Q2W	275

Shading is used to distinguish unique trials or groups of trials linked by re-randomization. For some trials that included multiple induction regimens of the same agent, induction regimens are numbered and are referenced as applicable within maintenance regimen labels to denote treatment sequence. Trials were categorized as either TT or RR.

BID twice daily, *IV* intravenous, *NMA* network meta-analysis, *NR* not reported, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q8W* every 8 weeks, *QD* once daily, *RCT* randomized controlled trial, *RR* responder re-randomization, *SC* subcutaneous, *TT* treat-through

[a]SERENITY was excluded from NMAs to limit imputation methods related to normalization of RR trial designs given that the TT trial VIVID 1 investigated mirikizumab

[b]CERTIFI was excluded from NMAs to limit imputations related to normalization of RR trial designs given that several TT trials investigated ustekinumab (GALAXI 1, GALAXI 2, GALAXI 3,M-UNITI, and SEAVUE)

[c]EXTEND, CHARM, CLASSIC 1, and CLASSIC 2 were excluded from NMAs to limit imputations related to normalization of RR trial designs given that the TT trial SEAVUE investigated adalimumab

[d]PRECISE-2 was excluded from NMAs due to having an open-label induction in favor of PRECISE-1, which had a blinded induction phase

[e]SEQUENCE was excluded from NMAs based on risks of bias related to open-label design

[f]SONIC was excluded from NMAs given that only 1 treatment arm investigated a regimen of interest (other arms received azathioprine capsules)

[g]VISIBLE-2 was excluded from NMAs due to having an open-label induction and unapproved maintenance dose in favor of GEMINI-2

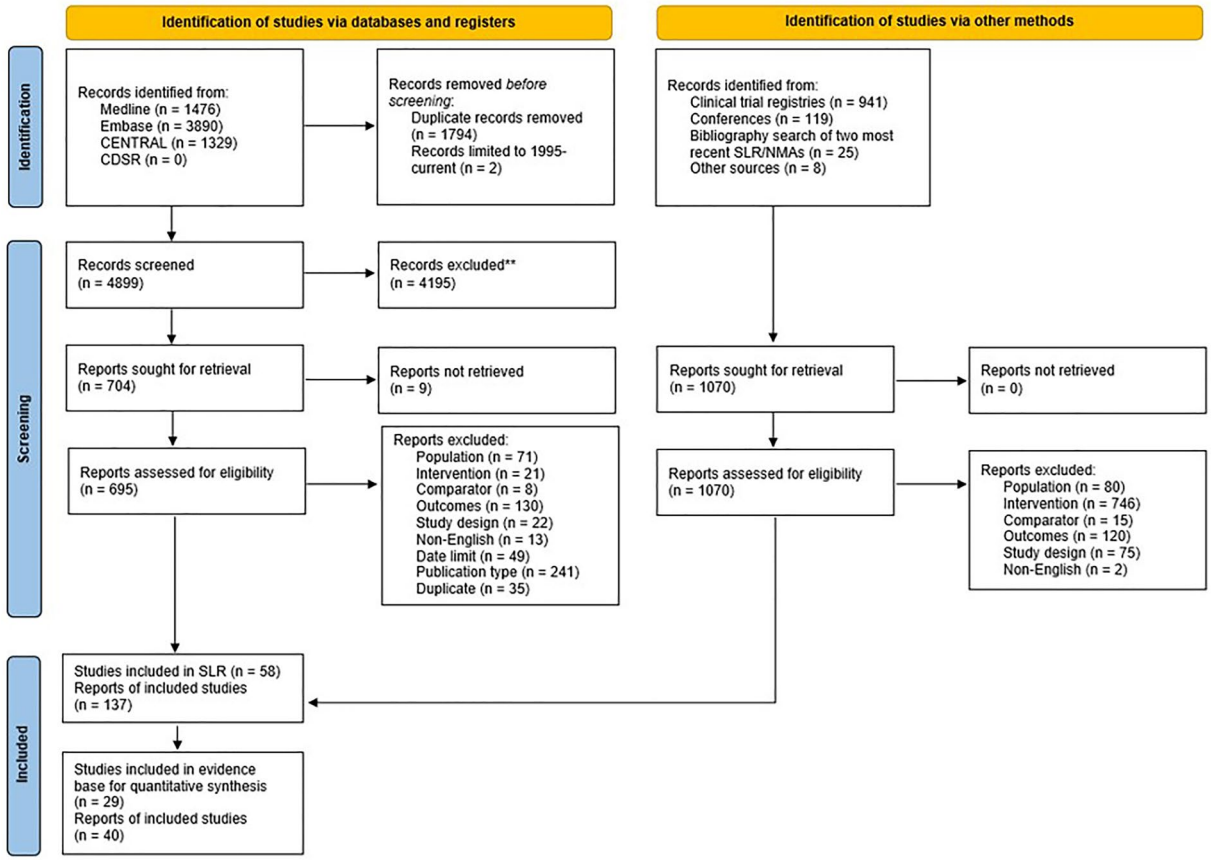


Fig. 1 Flow diagram of the study selection process. Qualitative synthesis refers to inclusion in the SLR, whereas quantitative synthesis refers to trials considered potentially eligible for NMA based on investigated treatment, regimen, and outcome reporting. *CDSR* Cochrane Database of Systematic Reviews, *CENTRAL* Cochrane Central Register of Controlled Trials, *NMA* network meta-analysis, *SLR* systematic literature review

mirikizumab in the BIO-IR subgroup, a finding not noted in analyses of other populations.

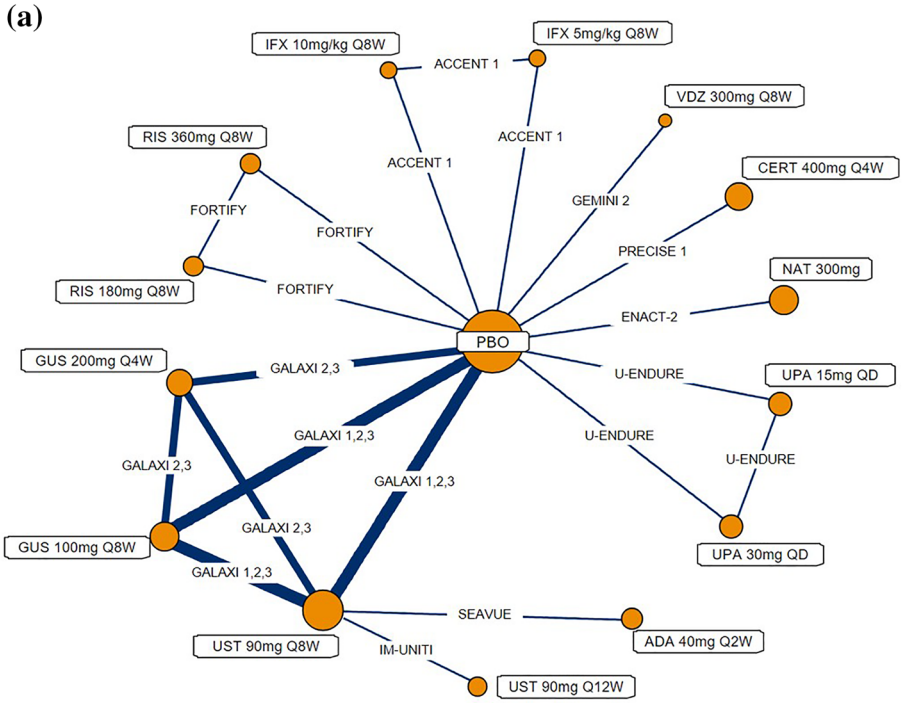
Endoscopic response. The BIO-IR and non-BIO-IR subgroup analyses had good consistency in the included list of comparators (Fig. 7), although fewer pairwise estimates favoring guselkumab regimens were significant.

Combined clinical remission with endoscopic response. Guselkumab regimens were non-significantly more efficacious than included comparators ustekinumab and adalimumab in the non-BIO-IR subgroup analysis and significantly more efficacious than the only available comparator, ustekinumab, in the BIO-IR subgroup. IL-12/23– and IL-23–targeted agents could not be included in subgroup analyses for this combined outcome, limiting the value of these analyses (Fig. 7).

DISCUSSION

The increasing approval and availability of targeted therapies for the treatment of CD provides more treatment choices for patients with CD. However, there is still an ongoing need to prioritize the selection of these treatments and to give guidance to physicians on how to select the most appropriate treatment option. Unfortunately, the lack of direct head-to-head comparisons in clinical trials, as well as variation in patient populations and clinical trial

(a)



(b)

GUS 200mg Q4W													
1.14 (0.71 to 1.84)	GUS 100mg Q8W												
1.41 (0.88 to 2.29)	1.23 (0.81 to 1.91)	UST 90mg Q8W											
1.46 (0.66 to 3.38)	1.28 (0.59 to 2.87)	1.03 (0.54 to 2.00)	UST 90mg Q12W										
1.78 (0.79 to 4.06)	1.57 (0.71 to 3.39)	1.26 (0.58 to 2.74)	1.22 (0.44 to 3.38)	RIS 360mg Q8W									
1.90 (0.86 to 4.28)	1.67 (0.78 to 3.65)	1.34 (0.72 to 2.58)	1.30 (0.52 to 3.27)	1.07 (0.39 to 2.95)	ADA 40mg Q2W								
2.04 (0.92 to 4.59)	1.79 (0.82 to 3.83)	1.45 (0.66 to 3.15)	1.40 (0.49 to 3.91)	1.15 (0.61 to 2.15)	1.07 (0.38 to 2.92)	RIS 180mg Q8W							
3.21 (1.32 to 8.24)	**2.83 (1.17 to 6.99)**	2.29 (0.96 to 5.63)	2.21 (0.74 to 6.71)	1.82 (0.68 to 4.92)	1.71 (0.57 to 5.14)	1.58 (0.61 to 4.28)	IFX 10mg/kg Q8W						
4.51 (2.06 to 9.98)	**3.93 (1.86 to 8.43)**	**3.19 (1.48 to 6.83)**	**3.08 (1.13 to 8.38)**	**2.54 (1.06 to 6.02)**	2.37 (0.88 to 6.39)	2.22 (0.93 to 5.24)	1.40 (0.52 to 3.64)	UPA 30mg QD					
4.89 (1.97 to 12.46)	**4.30 (1.73 to 10.47)**	**3.47 (1.42 to 8.42)**	**3.35 (1.09 to 10.19)**	**2.74 (1.03 to 7.29)**	2.56 (0.84 to 7.75)	2.40 (0.91 to 6.37)	1.50 (0.74 to 3.04)	1.08 (0.41 to 2.89)	IFX 5mg/kg Q8W				
5.66 (2.61 to 12.75)	**4.93 (2.32 to 10.81)**	**4.02 (1.86 to 8.65)**	**3.88 (1.40 to 10.69)**	**3.18 (1.33 to 7.65)**	**2.97 (1.11 to 8.25)**	**2.77 (1.16 to 6.64)**	1.75 (0.66 to 4.59)	1.25 (0.67 to 2.31)	1.16 (0.43 to 3.08)	UPA 15mg QD			
6.00 (2.75 to 13.49)	**5.25 (2.41 to 11.33)**	**4.26 (1.96 to 9.19)**	**4.12 (1.47 to 11.31)**	**3.37 (1.38 to 8.09)**	**3.16 (1.12 to 8.62)**	**2.95 (1.22 to 6.99)**	1.86 (0.70 to 4.85)	1.33 (0.56 to 3.16)	1.23 (0.47 to 3.24)	1.06 (0.44 to 2.55)	NAT 300mg Q4W		
6.92 (2.73 to 17.83)	**6.06 (2.45 to 15.13)**	**4.90 (2.03 to 12.23)**	**4.73 (1.53 to 14.50)**	**3.88 (1.45 to 10.39)**	**3.64 (1.21 to 11.20)**	**3.36 (1.30 to 9.15)**	2.13 (0.73 to 6.25)	1.52 (0.58 to 4.13)	1.41 (0.48 to 4.25)	1.21 (0.46 to 3.28)	1.15 (0.44 to 3.06)	VDZ 300mg Q8W	
8.06 (3.72 to 17.43)	**7.08 (3.35 to 14.67)**	**5.72 (2.72 to 11.82)**	**5.50 (2.07 to 14.60)**	**4.54 (1.94 to 10.48)**	**4.24 (1.58 to 11.10)**	**3.94 (1.68 to 9.11)**	2.49 (0.93 to 6.32)	1.78 (0.77 to 4.03)	1.65 (0.63 to 4.24)	1.42 (0.62 to 3.23)	1.34 (0.58 to 3.04)	1.17 (0.44 to 3.04)	CERT 400mg Q4W
12.75 (7.55 to 21.58)	**11.18 (6.90 to 18.00)**	**9.06 (5.59 to 14.52)**	**8.74 (3.81 to 19.59)**	**7.18 (3.84 to 13.31)**	**6.73 (2.99 to 15.02)**	**6.24 (3.38 to 11.44)**	**3.95 (1.82 to 8.39)**	**2.83 (1.54 to 5.21)**	**2.61 (1.21 to 5.60)**	**2.25 (1.21 to 4.21)**	**2.13 (1.15 to 3.90)**	1.85 (0.85 to 3.96)	1.58 (0.91 to 2.81)	PBO

Credible interval does not contain 1

Credible interval contains 1

Fig. 2 **a** Evidence network for primary analyses and **b** league table for random effects NMAs of clinical response. *Thickness of lines* connecting distinct regimens reflects the number of trials informing distinct connections, where induction trials are excluded from trial labels. *ADA* adalimumab, *CERT* certolizumab pegol, *GUS* guselkumab, *IFX* infliximab, *MIRI* mirikizumab, *NAT* natalizumab, *NMA* network meta-analysis, *PBO* placebo, *RIS* risankizumab, *UPA* upadacitinib, *UST* ustekinumab, *VDZ* vedolizumab

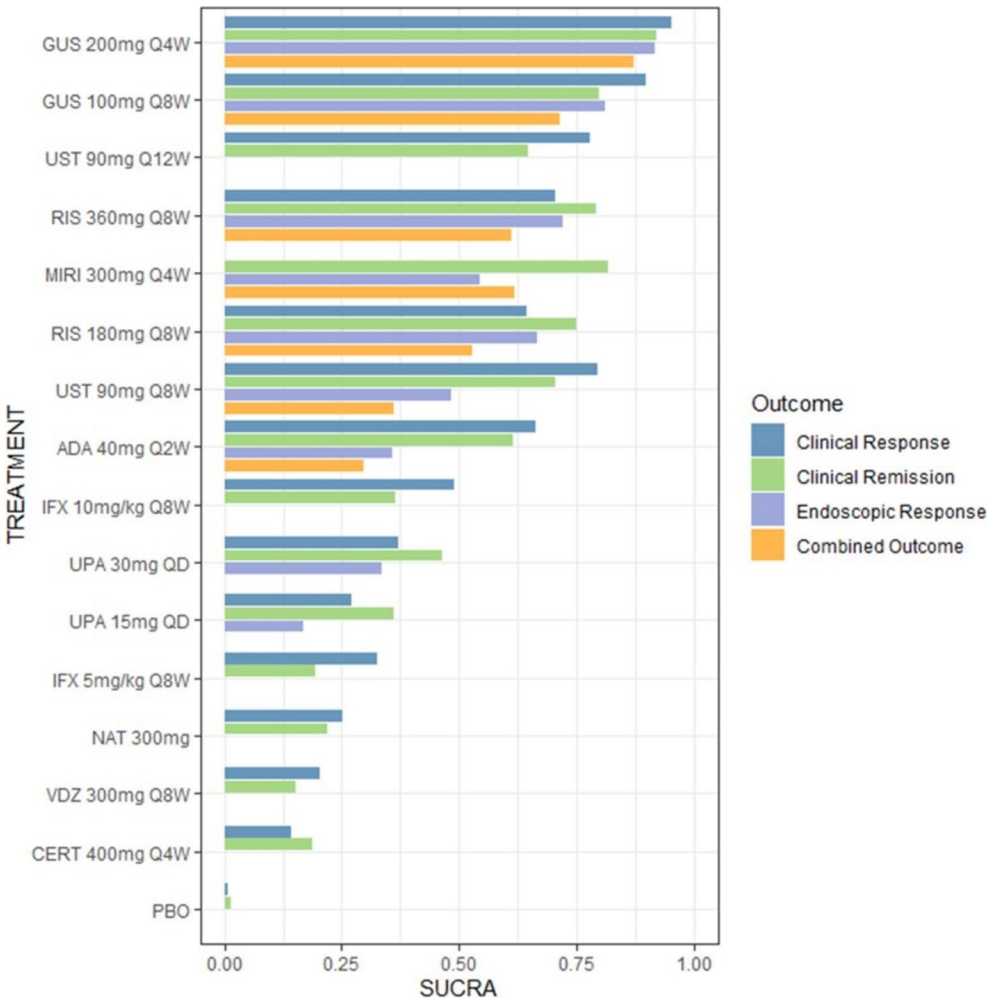
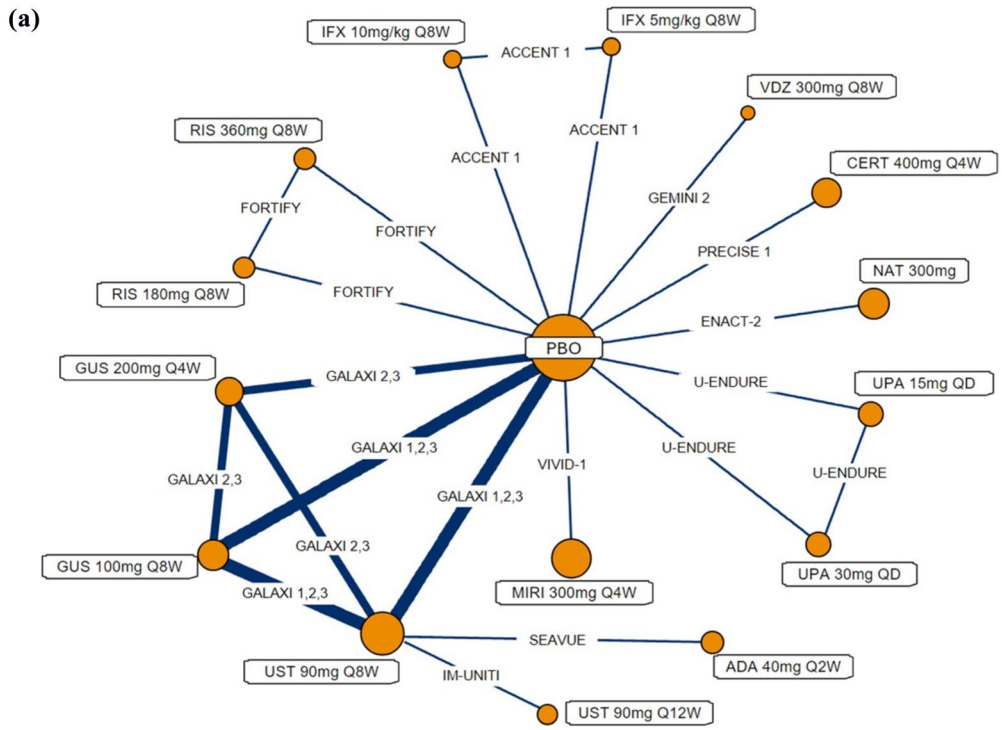


Fig. 3 Bar plot of SUCRA values for NMAs for all 4 outcomes across all treatments. Ordered by average of SUCRA values across outcomes. SUCRA values range from 0 to 1 and represent the percentage of efficacy that a treatment achieves relative to an ideal treatment. *ADA* adalimumab, *CERT* certolizumab pegol, *CRm* clinical remission, *ER* endoscopic response, *GUS* guselkumab, *IFX* infliximab, *MIRI* mirikizumab, *NMA* network meta-analysis, *PBO* placebo, *RIS* risankizumab, *SUCRA* surface under the cumulative ranking curve, *UPA* upadacitinib, *UST* ustekinumab, *VDZ* vedolizumab

designs (e.g., treat through vs. re-randomization trials), make cross-trial comparison very challenging for the practicing physician. Notably, patients in earlier CD trials had limited or no experience with biologics or small molecule drugs, whereas we have seen a high percentage of patients failing these drugs in more recent CD trials. Treating physicians are required to inform their patients appropriately about their treatment options to allow for reasonable shared decision-making. This is the case for starting the first-line treatment in a CD patient failing conventional therapy, but also for proceeding to second- or third-line treatment after failing biologic therapy. Given the lack of sufficient head-to-head trials in this disease, physicians look for other forms of evidence to guide treatment decisions and prioritize biologic therapies for the treatment of CD. NMAs provide an important additional tool for physicians and their patients and help to compare different treatment options, considering different clinically



(b)

GUS 200mg Q4W											
1.20 (0.59 to 2.50)	MIRI 300mg Q4W										
1.25 (0.79 to 1.99)	1.05 (0.51 to 2.08)	GUS 100mg Q8W									
1.25 (0.55 to 2.92)	1.04 (0.39 to 2.76)	1.00 (0.45 to 2.25)	RIS 360mg Q8W								
1.35 (0.59 to 3.19)	1.13 (0.43 to 2.96)	1.08 (0.49 to 2.42)	1.08 (0.59 to 2.02)	RIS 180mg Q8W							
1.45 (0.92 to 2.30)	1.21 (0.69 to 2.06)	1.15 (0.77 to 1.76)	1.16 (0.52 to 2.57)	1.08 (0.48 to 2.37)	UST 90mg Q8W						
1.65 (0.73 to 3.76)	1.37 (0.57 to 3.25)	1.31 (0.59 to 2.95)	1.32 (0.46 to 3.71)	1.22 (0.43 to 3.44)	1.13 (0.58 to 2.22)	UST 90mg Q12W					
1.74 (0.81 to 3.77)	1.45 (0.62 to 3.31)	1.39 (0.66 to 2.96)	1.40 (0.50 to 3.83)	1.30 (0.46 to 3.55)	1.20 (0.64 to 2.25)	1.06 (0.42 to 2.65)	ADA 40mg Q2W				
2.67 (1.19 to 6.07)	2.23 (0.82 to 5.78)	2.14 (0.96 tot 4.69)	2.15 (0.86 to 5.23)	1.98 (0.79 to 4.88)	1.85 (0.82 to 4.04)	1.63 (0.57 to 4.58)	1.54 (0.57 to 4.27)	UPA 30mg QD			
3.45 (1.51 to 7.94)	**2.88 (1.06 to 7.64)**	**2.76 (1.22 to 6.19)**	**2.75 (1.11 to 6.91)**	**2.55 (1.01 to 6.28)**	**2.39 (1.06 to 5.33)**	2.11 (0.73 to 5.90)	1.98 (0.72 to 5.57)	1.29 (0.69 to 2.37)	UPA 15mg QD		
3.51 (1.39 to 9.22)	**2.94 (1.02 to 8.45)**	**2.82 (1.14 to 7.10)**	**2.81 (1.02 to 7.73)**	2.60 (0.95 to 7.24)	2.43 (0.98 to 6.12)	2.14 (0.68 to 6.65)	2.02 (0.67 to 6.11)	1.31 (0.49 to 3.67)	1.02 (0.37 to 2.83)	IFX 10mg/kg Q8W	
5.20 (2.33 to 11.81)	**4.33 (1.68 to 11.09)**	**4.15 (1.91 to 9.14)**	**4.15 (1.68 to 10.33)**	**3.87 (1.57 to 9.30)**	**3.59 (1.66 to 7.85)**	**3.17 (1.11 to 8.92)**	**2.99 (1.10 to 8.08)**	1.94 (0.80 to 4.81)	1.50 (0.61 to 3.73)	1.48 (0.55 to 4.00)	NAT 300mg Q4W
5.61 (2.16 to 15.34)	**4.70 (1.61 to 13.87)**	**4.48 (1.76 to 11.84)**	**4.50 (1.59 to 12.65)**	**4.15 (1.48 to 11.70)**	**3.87 (1.54 to 10.10)**	**3.42 (1.09 to 11.19)**	**3.24 (1.04 to 9.93)**	2.11 (0.75 to 6.06)	1.63 (0.59 to 4.77)	1.60 (0.76 to 3.44)	1.08 (0.40 to 3.01)
5.71 (2.60 to 12.65)	**4.79 (1.86 to 12.00)**	**4.59 (2.13 to 9.71)**	**4.57 (1.93 to 11.02)**	**4.24 (1.74 to 10.02)**	**3.97 (1.84 to 8.39)**	**3.48 (1.27 to 9.46)**	**3.29 (1.20 to 8.69)**	2.14 (0.90 to 5.11)	1.65 (0.69 to 3.99)	1.63 (0.60 to 4.30)	1.10 (0.47 to 2.55)
6.61 (2.53 to 17.28	**5.55 (1.83 to 16.15)**	**5.25 (2.10 to 13.30)**	**5.24 (1.90 to 14.91)**	**4.84 (1.77 to 13.82)**	**4.56 (1.82 to 11.67)**	**4.00 (1.28 to 12.48)**	**3.80 (1.25 to 11.72)**	2.46 (0.89 to 6.94)	1.89 (0.69 to 5.39)	1.87 (0.62 to 5.70)	1.26 (0.47 to 3.48)
10.86 (6.40 to 18.60)	**9.09 (4.28 to 18.47)**	**8.70 (5.35 to 14.08)**	**8.70 (4.51 to 16.75)**	**8.08 (4.17 to 15.18)**	**7.51 (4.63 to 12.02)**	**6.62 (2.89 to 15.00)**	**6.27 (2.84 to 13.61)**	**4.07 (2.16 to 7.74)**	**3.14 (1.66 to 6.09)**	**3.10 (1.40 to 6.65)**	**2.10 (1.13 to 3.88)**

IFX 5mg/kg Q8W	VDZ 300mg Q8W	CERT 400mg Q4W	VDZ 300mg Q8W	PBO
1.17 (0.38 to 3.67)	1.14 (0.43 to 3.17)	**1.89 (1.05 to 3.42)**	1.66 (0.73 to 3.59)	
1.03 (0.36 to 2.78)	1.17 (0.38 to 3.67)	1.94 (0.85 to 4.35)	**2.10 (1.13 to 3.88)**	
1.10 (0.47 to 2.55)	1.26 (0.47 to 3.48)	**1.87 (0.62 to 5.70)**	**3.10 (1.40 to 6.65)**	
1.63 (0.60 to 4.30)	**1.87 (0.62 to 5.70)**	**1.89 (0.69 to 5.39)**	**3.14 (1.66 to 6.09)**	
3.29 (1.20 to 8.69)	**3.80 (1.25 to 11.72)**	**2.46 (0.89 to 6.94)**	**4.07 (2.16 to 7.74)**	
3.48 (1.27 to 9.46)	**4.00 (1.28 to 12.48)**	**4.56 (1.82 to 11.67)**	**6.62 (2.89 to 15.00)**	
3.97 (1.84 to 8.39)	**4.24 (1.74 to 10.02)**	**4.84 (1.77 to 13.82)**	**8.08 (4.17 to 15.18)**	
4.59 (2.13 to 9.71)	**4.57 (1.93 to 11.02)**	**5.24 (1.90 to 14.91)**	**8.70 (4.51 to 16.75)**	
4.48 (1.76 to 11.84)	**4.50 (1.59 to 12.65)**	**4.15 (1.48 to 11.70)**	**3.87 (1.54 to 10.10)**	
4.70 (1.61 to 13.87)	**4.48 (1.76 to 11.84)**	**4.59 (2.13 to 9.71)**	**4.79 (1.86 to 12.00)**	
4.33 (1.68 to 11.09)	**4.15 (1.91 to 9.14)**	**4.15 (1.68 to 10.33)**	**3.87 (1.57 to 9.30)**	
2.94 (1.02 to 8.45)	**2.82 (1.14 to 7.10)**	**2.81 (1.02 to 7.73)**	2.60 (0.95 to 7.24)	
2.88 (1.06 to 7.64)	**2.76 (1.22 to 6.19)**	**2.75 (1.11 to 6.91)**	**2.55 (1.01 to 6.28)**	
2.23 (0.82 to 5.78)	2.14 (0.96 tot 4.69)	2.15 (0.86 to 5.23)	1.98 (0.79 to 4.88)	
1.45 (0.62 to 3.31)	1.39 (0.66 to 2.96)	1.40 (0.50 to 3.83)	1.30 (0.46 to 3.55)	
1.37 (0.57 to 3.25)	1.31 (0.59 to 2.95)	1.32 (0.46 to 3.71)	1.22 (0.43 to 3.44)	
1.21 (0.69 to 2.06)	1.15 (0.77 to 1.76)	1.16 (0.52 to 2.57)	1.08 (0.48 to 2.37)	
1.13 (0.43 to 2.96)	1.08 (0.49 to 2.42)	1.08 (0.59 to 2.02)		
1.04 (0.39 to 2.76)	1.00 (0.45 to 2.25)			
1.05 (0.51 to 2.08)				
1.20 (0.59 to 2.50)				

Credible interval does not contain 1

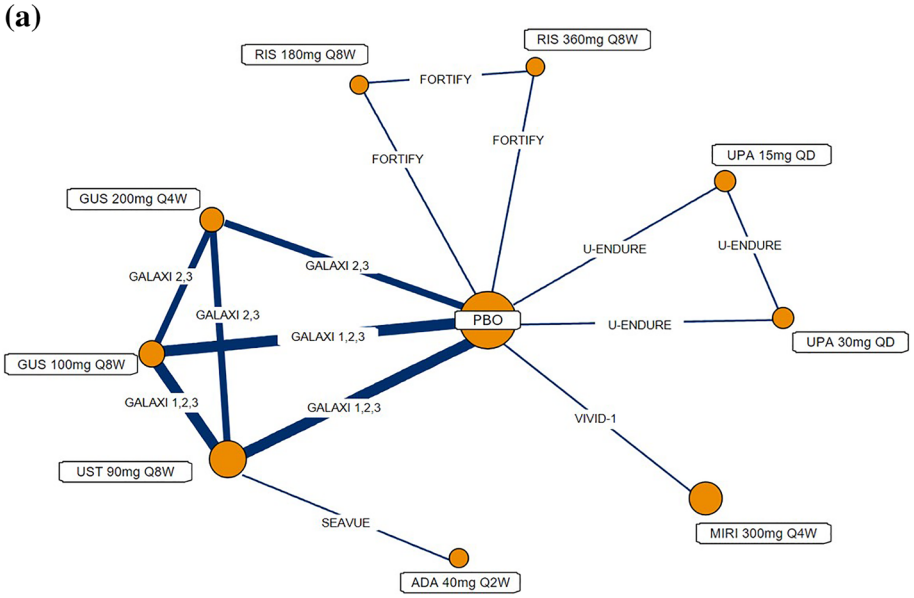
Credible interval contains 1

Fig. 4 **a** Evidence network for primary analyses and **b** league table for random effects NMAs of clinical remission. *ADA* adalimumab, *CERT* certolizumab pegol, *GUS* guselkumab, *IFX* infliximab, *MIRI* mirikizumab, *NAT* natalizumab, *NMA* network meta-analysis, *PBO* placebo, *RIS* risankizumab, *UPA* upadacitinib, *UST* ustekinumab, *VDZ* vedolizumab

relevant endpoints. This NMA may add relevant knowledge to inform clinical decision-making in various subgroups of patients with CD.

Guselkumab has been evaluated in long-term double-blind RCTs with active comparator ustekinumab and has demonstrated superiority

(a)



(b)

GUS 200mg Q4W									
1.19 (0.75 to 1.89)	GUS 100mg Q8W								
1.36 (0.53 to 3.51)	1.14 (0.45 to 2.88)	RIS 360mg Q8W							
1.47 (0.59 to 3.81)	1.23 (0.49 to 3.11)	1.08 (0.56 to 2.11)	RIS 180mg Q8W						
1.80 (0.88 to 3.87)	1.50 (0.75 to 3.11)	1.32 (0.44 to 3.93)	1.22 (0.42 to 3.61)	MIRI 300mg Q4W					
1.94 (1.23 to 3.10)	**1.62 (1.07 to 2.51)**	1.42 (0.56 to 3.64)	1.32 (0.53 to 3.28)	1.08 (0.60 to 1.91)	UST 90mg Q8W				
2.41 (1.10 to 5.29)	2.02 (0.95 to 4.40)	1.78 (0.58 to 5.46)	1.65 (0.54 to 5.04)	1.34 (0.55 to 3.18)	1.24 (0.65 to 2.38)	ADA 40mg Q2W			
2.67 (1.02 to 6.95)	2.24 (0.87 to 5.77)	1.97 (0.73 to 5.31)	1.83 (0.66 to 4.89)	1.49 (0.49 to 4.38)	1.37 (0.53 to 3.50)	1.11 (0.35 to 3.40)	UPA 30mg QD		
3.85 (1.47 to 10.15)	**3.22 (1.26 to 8.38)**	**2.83 (1.06 to 7.84)**	2.63 (0.97 to 7.11)	2.13 (0.71 to 6.42)	1.98 (0.78 to 5.07)	1.60 (0.51 to 4.95)	1.44 (0.75 to 2.79)	UPA 15mg QD	
12.71 (6.84 to 24.31)	**10.68 (5.83 to 20.01)**	**9.40 (4.65 to 19.10)**	**8.68 (4.27 to 17.28)**	**7.08 (3.05 to 16.22)**	**6.59 (3.56 to 12.19)**	**5.31 (2.15 to 12.75)**	**4.76 (2.37 to 9.76)**	**3.30 (1.62 to 6.73)**	PBO

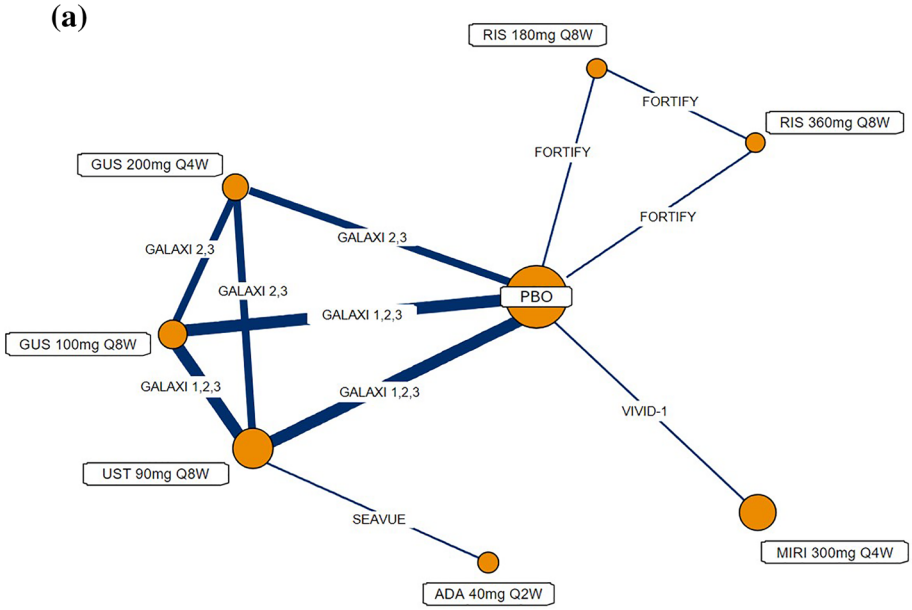
Credible interval does not contain 1

Credible interval contains 1

Fig. 5 **a** Evidence network for primary analyses and **b** league table for random effects NMAs of endoscopic response. *ADA* adalimumab, *GUS* guselkumab, *MIRI* mirikizumab, *NMA* network meta-analysis, *PBO* placebo, *RIS* risankizumab, *UPA* upadacitinib, *UST* ustekinumab

on stringent, long-term endpoints. In order to simultaneously compare guselkumab with other available advanced therapies for CD, a SLR was conducted to identify relevant RCTs and NMAs were performed for the outcomes of clinical response, clinical remission, endoscopic response, and a combination of clinical remission with endoscopic response. Results indicated that there was a higher likelihood of achieving clinical and endoscopic outcomes with guselkumab 100 mg Q8W and 200 mg Q4W compared with other advanced therapies. On clinical response and clinical remission, guselkumab 200 mg Q4W demonstrated greater efficacy versus several comparators, including infliximab 10 mg/kg Q8W, upadacitinib 30 mg

(a)



(b)

GUS 200mg Q4W							
1.22 (0.74 to 1.99)	**GUS 100mg Q8W**						
1.38 (0.63 to 3.21)	1.12 (0.53 to 2.54)	**MIRI 300mg Q4W**					
1.39 (0.48 to 4.24)	1.13 (0.40 to 3.40)	1.00 (0.30 to 3.51)	**RIS 360mg Q8W**				
1.54 (0.53 to 4.69)	1.25 (0.44 to 3.75)	1.12 (0.33 to 3.92)	1.11 (0.54 to 2.28)	**RIS 180mg Q8W**			
1.85 (1.14 to 3.10)	1.52 (0.97 to 2.43)	1.35 (0.70 to 2.53)	1.34 (0.45 to 3.83)	1.21 (0.41 to 3.49)	**UST 90mg Q8W**		
2.18 (0.94 to 5.25)	1.78 (0.78 to 4.22)	1.59 (0.60 to 4.12)	1.58 (0.43 to 5.61)	1.42 (0.39 to 5.11)	1.18 (0.58 to 2.39)	**ADA 40mg Q2W**	
12.90 (6.60 to 27.88)	**10.55 (5.53 to 22.10)**	**9.39 (3.72 to 24.52)**	**9.33 (4.20 to 20.70)**	**8.46 (3.83 to 18.74)**	**6.93 (3.59 to 14.68)**	**5.92 (2.22 to 16.31)**	**PBO**

Credible interval does not contain 1

Credible interval contains 1

Fig. 6 **a** Evidence network for primary analyses and **b** league table for random effects NMAs of combined clinical remission with endoscopic response outcome. *ADA* adalimumab, *GUS* guselkumab, *MIRI* mirikizumab, *NMA* network meta-analysis, PBO placebo, *RIS* risankizumab, *UST* ustekinumab

QD, and vedolizumab 300 mg Q8W. On endoscopic response, guselkumab 200 mg Q4W had significantly greater efficacy than most comparators. The comparative efficacy of guselkumab versus other agents was less clear in NMAs of the combined outcome (clinical remission with endoscopic response), where only 6 trials could be included; however, guselkumab regimens still outranked all included comparators. Throughout the analyses, guselkumab was generally non-significantly more effective than other IL-12/23– and IL-23–targeted agents. In general,

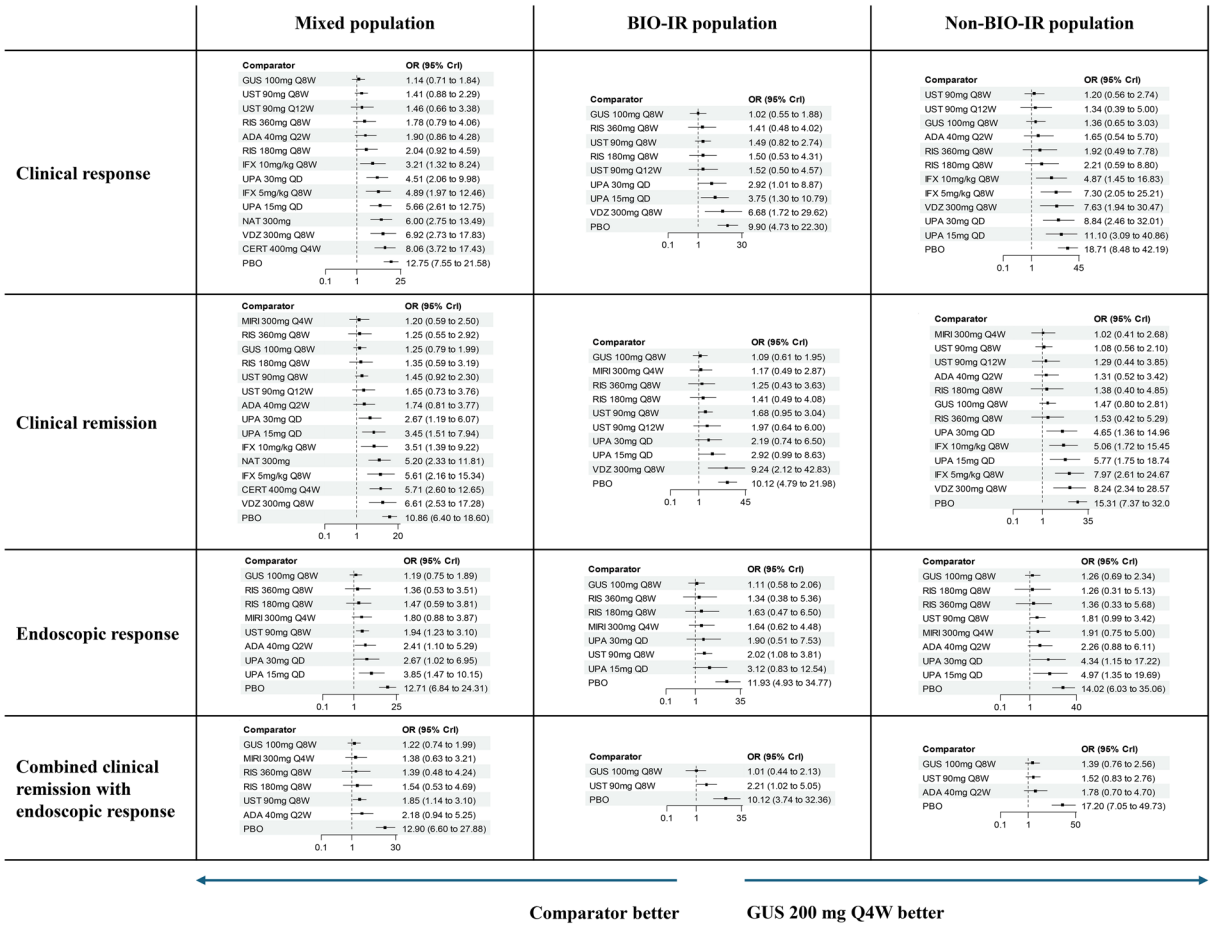


Fig. 7 Forest plots for random effects NMAs of efficacy outcomes in mixed, BIO-IR, and non-BIO-IR populations. *ADA* adalimumab, *BIO-IR* inadequate response or intolerance to biologics, *CERT* certolizumab pegol, *GUS* guselkumab, *IFX* infliximab, *MIRI* mirikizumab, *NAT* natalizumab, *NMA* network meta-analysis, *PBO* placebo, *Q4W* every 4 weeks, *RIS* risankizumab, *UPA* upadacitinib, *UST* ustekinumab, *VDZ* vedolizumab

the NMAs indicated that guselkumab regimens had a higher likelihood of achieving clinical and endoscopic outcomes, with consistently higher ranking compared with other treatments based on SUCRA. Primary analyses based on the mixed populations were supported by subgroup analyses in subpopulations with and without inadequate prior response (or intolerance) to biologics.

Accounting for heterogeneity in trial designs is important when undertaking NMAs in CD. A recent NMA by Singh et al. split the evidence base by trial design, which led to different sets of analyses based on separate sets of trials [25]. In their NMAs of CD treatments, Varu et al. used similar methods to those we employed for the normalization of CD trial designs, keeping the evidence base together [26]. These NMAs also yielded similar conclusions for commonly investigated comparators (e.g., ustekinumab ranked highly vs. older biologic agents). However, our analyses sought to limit the use of imputations unless required to incorporate a given comparator agent. As such, we expect that the risks of bias introduced by imputation are minimized. Importantly, the normalization of trial designs to mimic treat-through trials provides a way to view the patient journey more holistically

by avoiding isolated conclusions regarding the induction and maintenance treatment phases. Furthermore, treatment differences may not be apparent until well after brief induction periods, hence the inclusion of delayed responders in our analyses adds important information and improves the relevance of results to real-world clinical practice [27]. Overall, these methods ensure a complete and robust analysis of comparative efficacy that yields clinically relevant conclusions.

A key limitation across the NMAs is that several connections within every evidence network were informed by single studies (although the inclusion of multiple GALAXI studies mitigated this issue for guselkumab). Given the relatively sparse network geometry, baseline risk adjustment was not feasible to address cross-trial heterogeneity indicated by varied placebo response rates across trials. Cross-trial heterogeneity may increase the expected absolute error in NMAs and introduce inconsistency between direct and indirect estimates, impacting the validity of analysis conclusions as a result [28]. These limitations can only be resolved with the incorporation of additional data from clinical trials in CD, and which persist across previously published indirect treatment comparisons in this disease. The incorporation of additional head-to-head studies, as they emerge, could improve the robustness of analyses.

A limitation specific to treat-through trials should also be noted. Treat-through trials such as PRECISE-1 had substantial drop-out rates that may impact or bias results (e.g., when differential drop-out rates occur). However, since drop-out rates and response rates were largely similar across these trials and all trials used non-responder imputation, the impact and potential bias was judged to be minimal. Further, the normalization procedure may not fully replicate a treat-through for all trials, given treat-through trials condition on response by strict time point. Re-randomized trials with delayed response do not capture patients who had a response beyond the specified time point for evaluation of response. The normalization procedure further required the assumption that the probability of achieving final outcomes conditional on initial response/non-response was exchangeable across trials/doses for some treatments, in particular placebo. This assumption is unlikely to be exactly true, since variations in placebo response across trials would be expected to result in differences in populations of patients evaluated for subsequent response. Lastly, despite efforts to use consistent outcome definitions across trials, some variations remained relative to those described in the methods sections. The impact of these remaining differences on the relative treatment effects was assessed as being minimal and did not preclude the comparison of studies. For example, although a different threshold for change in CDAI (e.g., as used in older vs. newer studies) could influence the proportion of clinical response in a given treatment arm, it is less likely to impact relative treatment effects across treatment arms as used in NMAs.

CONCLUSION

The NMA results in a population with moderately to severely active CD indicate a higher likelihood of guselkumab achieving each clinical and endoscopic endpoint analyzed at the end of the maintenance phase versus other advanced therapies included in this study. Results of analyses conducted within subpopulations defined by prior inadequate treatment response were broadly in line with the overall population.

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Declarations

Conflicts of Interest. Tim Disher, Meaghan Bartlett, Becky Hooper, Jenna Ellis, and Ashley Bonner are current or former employees of EVERSANA. Myrlene Sanon, Dominik Naessen, and Zijiang Yang are employees of Johnson & Johnson and may hold stock/stock options in Johnson & Johnson. Drs. Axel Dignass and Jessica R. Allegretti have received personal compensation from Janssen for consultant fees. Axel Dignass reports fees for participation in clinical trials, review activities such as data monitoring boards, statistical analysis, and endpoint committees from Abivax, AbbVie, Bristol Myers Squibb, Dr Falk Pharma, Galapagos, Gilead, Janssen, and Pfizer; consultancy fees from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Dr Falk Foundation, Ferring Pharmaceuticals, Fresenius Kabi, Galapagos, J&J, Lilly, MSD, Pfizer, Pharmacosmos, Sandoz, Stada, Takeda, Tillotts, and Vifor Pharma; payment from lectures including service on speakers bureaus from AbbVie, Biogen, CED Service GmbH, Celltrion, Falk Foundation, Ferring, Galapagos, Gilead, High5MD, Janssen, Materia Prima, MedToday, MSD, Pfizer, Streamed-Up, Takeda, Tillotts, and Vifor Pharma; and payment for manuscript preparation from Falk Foundation, Takeda, Thieme, and UniMed Verlag. Preparation of this manuscript was funded by Janssen.

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