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Interleukin 12/23 and interleukin 23 inhibitors for moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis

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Abstract

Background Ulcerative colitis (UC) is a chronic inflammatory disease affecting ~1.5 million individuals, causing significant impairment in quality of life, psychological well-being, and healthcare burden. Using indirect meta-analysis, this study compared the efficacy and safety of anti-interleukin (IL)-12/23 and IL-23 agents vs. placebo and each other, during induction and maintenance in moderate-to-severe UC.

Methods A systematic search of PubMed, Cochrane, Scopus, Web of Science, and ClinicalTrials.gov was conducted on October 1, 2024. The randomized controlled trials (RCTs) included evaluated ustekinumab, mirikizumab, risankizumab, and guselkumab. The primary outcomes were clinical remission and endoscopic improvement at both induction and maintenance endpoints. Odds ratios (ORs) with 95% confidence intervals (CIs) and surface under the cumulative ranking (SUCRA) values were used to rank treatment efficacy.

Results Six RCTs (n=3808) were analyzed for induction and 5 RCTs (n=1697) for maintenance. During induction, risankizumab demonstrated the highest clinical remission rates (OR 3.89, 95%CI 2.24-6.75; SUCRA 80.7%) and endoscopic improvement rates (OR 4.21, 95%CI 2.12-8.35; SUCRA 87.6%) compared to placebo. In maintenance, guselkumab showed the highest clinical remission (OR 4.28, 95%CI 1.58-11.59; SUCRA 81.6%) and endoscopic improvement (OR 4.21, 95%CI 2.12-8.35; SUCRA 93.1%), and was superior to risankizumab (OR 2.05, 95%CI 1.09-3.84) for endoscopic outcomes.

Conclusions Risankizumab was most effective in induction, while guselkumab was more effective in maintenance. Head-to-head trials are warranted.

Keywords Ulcerative colitis, interleukin-12/23 inhibitors, interleukin-23 inhibitors, systematic review, network meta-analysis

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory illness that presents with mucosal inflammation in the colon and rectum, with standard symptoms of rectal bleeding, diarrhea and urgency [1]. It affects about 1.5 million people and has a prevalence of 0.4% in North America [1]. UC symptoms are associated with a lower quality of life, decreased social and psychological function, and higher healthcare costs [1,2]. Medical therapy aims to reduce symptoms by controlling mucosal inflammation and, in the long term, to avoid

disability, colectomy and colon cancer. [3]. Tumor necrosis factor inhibitors (TNF), such as infliximab and adalimumab, are first-line treatments for UC; however, about one third of patients fail to respond to the initial therapy with a TNF inhibitor [4].

Interleukin (IL)-23 is linked to intestinal inflammation and UC pathophysiology [5]. IL-23 consists of 2 components: the p40 subunit, which is also found in IL-12, and the p19 subunit, which is unique to IL-23. IL-23 plays a key role in maintaining and amplifying T helper 17 cells and stimulating various innate immune cells, which are important in the pathogenesis of chronic inflammatory diseases, especially UC [6-9]. Therefore, several phase II and III trials were conducted to evaluate the efficacy and safety of IL-12/23 p40 and IL-23 p19 inhibitors compared to placebo in patients with moderate-to-severe UC. One trial demonstrated the efficacy and safety of ustekinumab, which targets the IL-12/23 p40 subunit, in both the induction and maintenance phases [10], while other trials demonstrated the efficacy of risankizumab, guselkumab, and mirikizumab, which target IL-23 p19, in both the induction and maintenance phases [11-15].

Despite demonstrating efficacy in both the induction and maintenance phases, direct comparative studies evaluating anti-IL-12/23 and IL-23 therapies in patients with UC are lacking, resulting in a significant gap in our understanding of their relative efficacy and safety. Accordingly, we sought to conduct a network meta-analysis to compare the efficacy of all anti-IL-12/23 and IL-23 drugs in terms of efficacy and safety at the end of the induction and maintenance phases in patients with moderate-to-severe UC.

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Conflict of Interest: None

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Materials and methods

Study design

This systematic review and network meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the study protocol was prospectively registered in PROSPERO (CRD42024618036).

Search strategy

We performed a comprehensive literature search on October 1, 2024, across PubMed, Scopus, Cochrane Central Register of Controlled Trials, Web of Science and ClinicalTrials.gov. Reference lists of included articles were also screened, and an updated search was conducted on August 3, 2025. Keywords included "IL-23 inhibitors", "IL-12/23 inhibitors" and "ulcerative colitis". Detailed search strategies for each database are shown in Supplementary Table 1.

Study selection

Screening was conducted in 2 stages: titles/abstracts, followed by full-text review. Two reviewers (RHS, MSB) independently screened all studies, and disagreements were resolved by a third reviewer (BS). Inclusion criteria were randomized controlled trials (RCTs) evaluating IL-23 or IL-12/23 inhibitors vs. placebo in patients with moderate-to-severe UC. Exclusion criteria included RCTs comparing IL-23/IL-12/23 inhibitors with non-placebo comparators, RCTs that included mixed inflammatory bowel disease populations without separate data on UC, ongoing or duplicate studies, overlapping datasets, non-human or preclinical studies, and non-randomized designs. No restrictions were applied regarding language, country, year, or sex of participants.

Data extraction

Two reviewers independently extracted data using a standardized form. Extracted information was categorized into: (1) study characteristics (author, year, design, sample size), patient demographics, and treatment regimens; and (2) efficacy and safety outcomes at the end of the induction and maintenance phases.

Outcome definitions

The primary outcomes were clinical remission and endoscopic improvement at the end of both induction and maintenance phases. Secondary outcomes included clinical

response, endoscopic remission, histological–endoscopic mucosal improvement (HEMI), corticosteroid-free clinical remission, and safety outcomes (including any adverse events and serious infections at the maintenance stage). Definitions for all outcomes are provided in the Supplementary material. Outcomes were also assessed in subgroups stratified by prior inadequate response to advanced therapy.

Risk of bias assessment

Risk of bias was independently assessed by 2 reviewers using the Cochrane Risk of Bias 2.0 tool for RCTs [16]. Domains included randomization, deviations from intended interventions, missing data, outcome measurement and selective reporting. Discrepancies were resolved by consensus or by consultation with a third reviewer.

Data synthesis and statistical analysis

Categorical outcomes were expressed as counts and proportions, and continuous outcomes as means and standard deviations. A random-effects model was used to account for between-study heterogeneity. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes. A P-value <0.05 was considered statistically significant. Network meta-analysis was performed for the overall UC population and stratified by treatment history: (1) prior inadequate response to advanced therapy; and (2) no prior inadequate response. Treatment ranking was determined using the surface under the cumulative ranking (SUCRA) index, which estimates the likelihood of each treatment being the most effective or safest. Higher SUCRA values indicate superior relative performance [17]. Publication bias was assessed using the Egger test, supplemented by visual inspection of funnel plots. The quality of evidence was graded using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework, with outcomes rated as high, moderate, low or very low certainty. Downgrading criteria included risk of bias, inconsistency, indirectness, imprecision and publication bias [18].

Results

Study characteristics and risk of bias assessment

Our search yielded 11,887 articles from the database. We selected 62 studies for full-text screening and deemed only 6 appropriate for data extraction and analysis. Fig. 1 depicts the details of our selection process. Six double-blind RCTs were included: 2 were Phase II and 4 were Phase III.

A total of 3808 patients from 6 studies were included in the induction phase [10-15], with 2422 (63.6%) in the intervention group and 1386 (36.4%) in the control group. For the maintenance phase, 5 studies were included [10-13,15], involving a total of 1697 patients. Of these, 957 (56.4%) were in the intervention group, and 740 (43.6%) were in the control group. Table 1 presents an overview of the baseline characteristics of the patients at the beginning of the induction and maintenance phases. Fig. 2 and 3 present the drugs included in each outcome.

All trials demonstrated a low risk of bias, as assessed by the Cochrane Risk of Bias tool. The results of the bias assessment are shown in Supplementary Table 2.

Overall patients

Induction phase

Risankizumab achieved the highest rate of clinical remission (OR 3.89, 95%CI 2.24-6.75) compared to placebo (Fig. 4). Based on SUCRA, risankizumab ranked first (80.7%) (Supplementary Fig. 1). For clinical response, guselkumab demonstrated the greatest benefit (OR 4.15, 95%CI 2.53-6.82) vs. placebo (Supplementary Fig. 2). SUCRA confirmed guselkumab as the highest ranked (86.4%) (Supplementary Fig. 1).

Endoscopic outcomes were consistent. Risankizumab provided the largest increase in endoscopic improvement (OR 4.21, 95%CI 2.12-8.35) (Fig. 4), with a SUCRA ranking of 87.6% (Supplementary Fig. 1). For endoscopic remission, risankizumab had the highest rate (OR 3.39, 95%CI 1.77-6.50) compared to placebo (Supplementary Fig. 3), with SUCRA ranking risankizumab highest (73%) (Supplementary Fig. 1). Risankizumab also showed the highest statistically significant increase of HEMI (OR 3.87, 95%CI 2.49-6.07) compared to placebo, with SUCRA ranking risankizumab highest (87%).

Maintenance phase

Guselkumab achieved the highest rate of clinical remission (OR 4.28, 95%CI 1.58-11.59) (Fig. 5), ranking first by SUCRA (81.6%) (eFig. S4). For corticosteroid-free clinical remission, guselkumab had the highest increasing rate (OR 4.25, 95%CI 2.67-6.75) compared to placebo, and was superior to risankizumab directly (OR 2.17, 95%CI 1.14-4.14) (Supplementary Fig. 5). SUCRA ranked guselkumab first (95.8%) (Supplementary Fig. 4).

Guselkumab demonstrated the highest endoscopic improvement (OR 4.56, 95%CI 2.87-7.23) compared to placebo, and also outperformed risankizumab (OR 2.05, 95%CI 1.09-3.84) (Fig. 5). SUCRA ranked guselkumab highest (93.1%) (Supplementary Fig. 4). Mirikizumab achieved the greatest clinical response (OR 4.01, 95%CI 2.76-5.84), with superiority over risankizumab (OR 2.02, 95%CI 1.15-3.57) (Supplementary Fig. 6), and ranked first by SUCRA (98%) (Supplementary Fig. 4).

For HEMI, guselkumab demonstrated the highest increase (OR 4.54, 95%CI 2.82-7.30) compared to placebo (Supplementary Fig. 5), and ranked first by SUCRA (98.3%) (Supplementary Fig. 4). Regarding endoscopic remission,

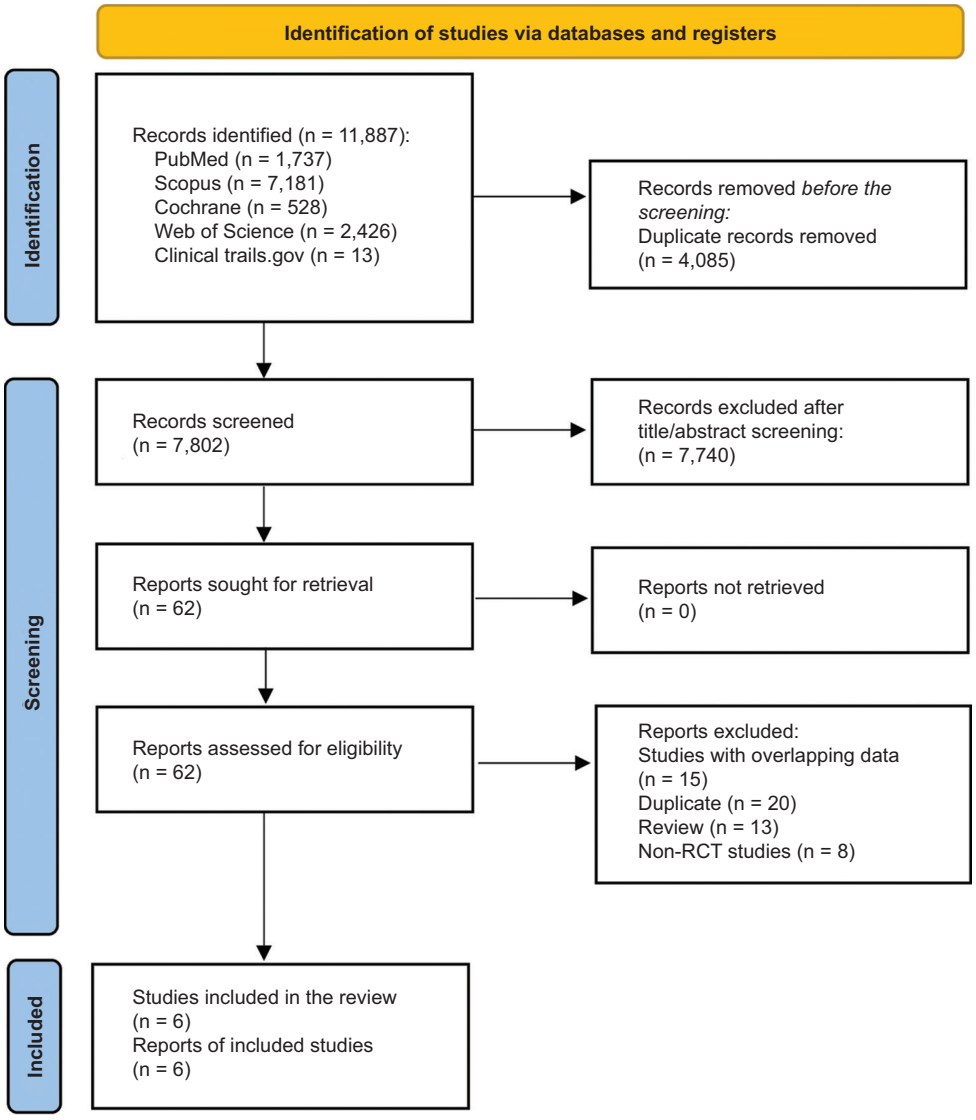

Figure 1 Study selection PRISMA flow diagram
RCT, randomized controlled trial

guselkumab showed the highest increase (OR 2.82, 95%CI 1.72-4.64) compared to placebo (Supplementary Fig. 6), and ranked first by SUCRA (83.7%) Supplementary Fig. 4). Across all agents, no significant differences were observed in adverse events or serious infections (Supplementary Fig. 7).

Patients without a history of inadequate response to advanced therapy

Induction phase

Risankizumab demonstrated the greatest efficacy in achieving clinical remission compared with placebo (OR 4.60, 95%CI 2.48-8.53) (Fig. 4). Based on SUCRA rankings, risankizumab had the highest probability of being most effective (90.1%) (Supplementary Fig. 1). For clinical response, guselkumab demonstrated the highest effect compared to placebo (OR 4.67, 95%CI 3.12-6.99). In addition, guselkumab was superior to mirikizumab (OR 2.01, 95%CI 1.18-3.45) and ustekinumab (OR 1.88, 95%CI 1.02-3.46), while mirikizumab was inferior to risankizumab (OR 0.56, 95%CI 0.33-0.97) (Supplementary Fig. 2). SUCRA analysis ranked guselkumab highest (91%) for clinical response (Supplementary Fig. 1).

For endoscopic improvement, risankizumab showed the largest benefit vs. placebo (OR 5.50, 95%CI 3.33-9.09). Risankizumab was superior to ustekinumab (OR 2.74, 95%CI 1.35-5.55), while mirikizumab was inferior to risankizumab (OR 0.40, 95%CI 0.21-0.74) (Fig. 4). SUCRA ranking again favored risankizumab (98.6%)(Supplementary Fig. 1). Risankizumab also achieved the highest rate of endoscopic remission (OR 4.99, 95%CI 2.09-11.87) (Supplementary Fig. 3), with SUCRA favoring risankizumab (87.3%) (Supplementary Fig. 1).

For HEMI, risankizumab showed the greatest effect compared to placebo (OR 5.49, 95%CI 2.97-10.14).

Table 1 Baseline characteristics for the studies and patients in the induction and maintenance phase

Study [ref.]	Phase	Blindness	Follow up	Countries /centers	Study arms	Total patients (M/F)	Age, mean (SD)	Disease duration, mean (SD)	Patients with/without a history of inadequate response to advanced therapy
Louis *et al* 2024 [11]	III	Double-blinded	Induction: 12 weeks	41 countries/261 centers	Induction: Intervention: Risankizumab 1200 mg IV every 4 weeks Control: Placebo IV every 4 weeks	Induction: Intervention: 650 (385/265) Control: 325 (201/124)	Induction: Intervention: 41.8 (13.5) Control: 42.8 (14.3)	Induction: Intervention: 7.7 (6.9) Control: 8.1 (7.0)	Induction: Intervention: (333/317) Control: (170/155)
			Maintenance: 52 weeks		Maintenance: Intervention: Risankizumab 160 mg SC every 8 weeks Control: Placebo SC every 8 weeks	Maintenance: Intervention: 179 (105/74) Control: 183 (101/82)	Maintenance: Intervention: 40.9 (14.7) Control: 39.2 (14.2)	Maintenance: Intervention: 8.5 (7.4) Control: 8.2 (7.2)	Maintenance: Intervention: (134/45) Control: (138/45)
Sandborn *et al* 2020 [13]	II	Double-blinded	Induction: 12 weeks	14 countries/75 centers	Induction: Intervention: Mirikizumab 200 mg IV every 4 weeks Control: Placebo IV every 4 weeks	Induction: Intervention: 62 (37/25) Control: 63 (36/37)	Induction: Intervention: 43.4 (14.7) Control: 42.6 (13.5)	Induction: Intervention: 9.0 (9.0) Control: 9.5 (9.6)	Induction: Intervention: NA Control: NA
			Maintenance: 40 weeks		Maintenance: Intervention: Mirikizumab 200 mg SC every 4 weeks Control: Placebo SC every 4 weeks	Maintenance: Intervention: 47 (NA/NA) Control: 13 1NA/NA)	Maintenance: Intervention: NA Control: NA	Maintenance: Intervention: NA Control: NA	Maintenance: Intervention: NA Control: NA
D'Haens *et al* 2023 [12]	III	Double-blinded	Induction: 12 weeks	34 countries/383 centers	Induction: Intervention: Mirikizumab 300 mg IV every 4 weeks Control: Placebo IV every 4 weeks	Induction: Intervention: 868 (530/338) Control: 294 (165/129)	Induction: Intervention: 42.9 (13.9) Control: 41.3 (13.8)	Induction: Intervention: 7.2 (6.7) Control: 6.9 (7.0)	Induction: Intervention: (361/507) Control: (118/176)
			Maintenance: 40 weeks		Maintenance: Intervention: Mirikizumab 200 mg SC every 4 weeks Control: Placebo SC every 4 weeks	Maintenance: Intervention: 365 (214/151) Control: 179 (104/75)	Maintenance: Intervention: 43.4 (14.2) Control: 41.2 (12.8)	Maintenance: Intervention: 6.9 (7.1) Control: 6.7 (5.6)	Maintenance: Intervention: (128/237) Control: (64/115)

(*Contd...*)

Table 1 (*Continued*)

Study [ref.]	Phase	Blindness	Follow up	Countries /centers	Study arms	Total patients (M/F)	Age, mean (SD)	Disease duration, mean (SD)	Patients with/without a history of inadequate response to advanced therapy
Peyrin-Biroulet *et al* 2023 [14]	IIb	Double-blinded	Induction: 12 weeks	27 countries/141 centers	Induction: Intervention: Guselkumab 200 mg IV every 4 weeks Control: Placebo IV every 4 weeks	Induction: Intervention: 101 (60/41) Control: 105 (66/39)	Induction: Intervention: 43.3 (14.3) Control: 41.2 (15.1)	Induction: Intervention: 7.0 (6.0) Control: 7.7 (7.2)	Induction: Intervention: (46/55) Control: (51/54)
Rubin *et al* 2024 [15]	III	Double-blinded	Induction: 12 weeks	32 countries/254 centers	Induction: Intervention: Guselkumab 200 mg IV every 4 weeks Control: Placebo IV every 4 weeks	Induction: Intervention: 421 (238/183) Control: 280 (161/119)	Induction: Intervention: 41 (13.9) Control: 39.8 (13.4)	Induction: Intervention: 7·8 (7·7) Control: 7·1 (6·5)	Induction: Intervention: (208/213) Control: (136/144)
			Maintenance: 44 weeks		Maintenance: Intervention: Guselkumab 200mg SC every 4 weeks Control: Placebo SC every 4 weeks	Maintenance: Intervention: 190 (100/90) Control: 190 (109/81)	Maintenance: Intervention: 41 (13.9) Control: 39.8 (13.4)	Maintenance: Intervention: 7·8 (7·7) Control: 7·1 (6·5)	Maintenance: Intervention: (88/102) Control: (75/115)
Sands *et al* 2019 [10]	III	Double-blinded	Induction: 8 weeks	24 countries/244 centers	Induction: Intervention: Ustekinumab 130 mg IV at week 0 Control: Placebo at week 0	Induction: Intervention: 320 (190/130) Control: 319 (197/22)	Induction: Intervention: 42.2 (13.9) Control: 41.2 (13.5)	Induction: Intervention: 8.1 (7.2) Control: 8.0 (7.2)	Induction: Intervention: (164/156) Control: (161/158)
			Maintenance: 44 weeks		Maintenance: Intervention: Ustekinumab 90 mg SC every 8 weeks Control: Placebo SC every 8 weeks	Maintenance: Intervention: 176 (94/82) Control: 175 (107/68)	Maintenance: Intervention: 39.5 (13.3) Control: 42.0 (13.9)	Maintenance: Intervention: 8.1 (6.6) Control: 7.5 (6.8)	Maintenance: Intervention: (91/85) Control: (88/87)

SD, standard deviation; SC, subcutaneous; NA, not applicable

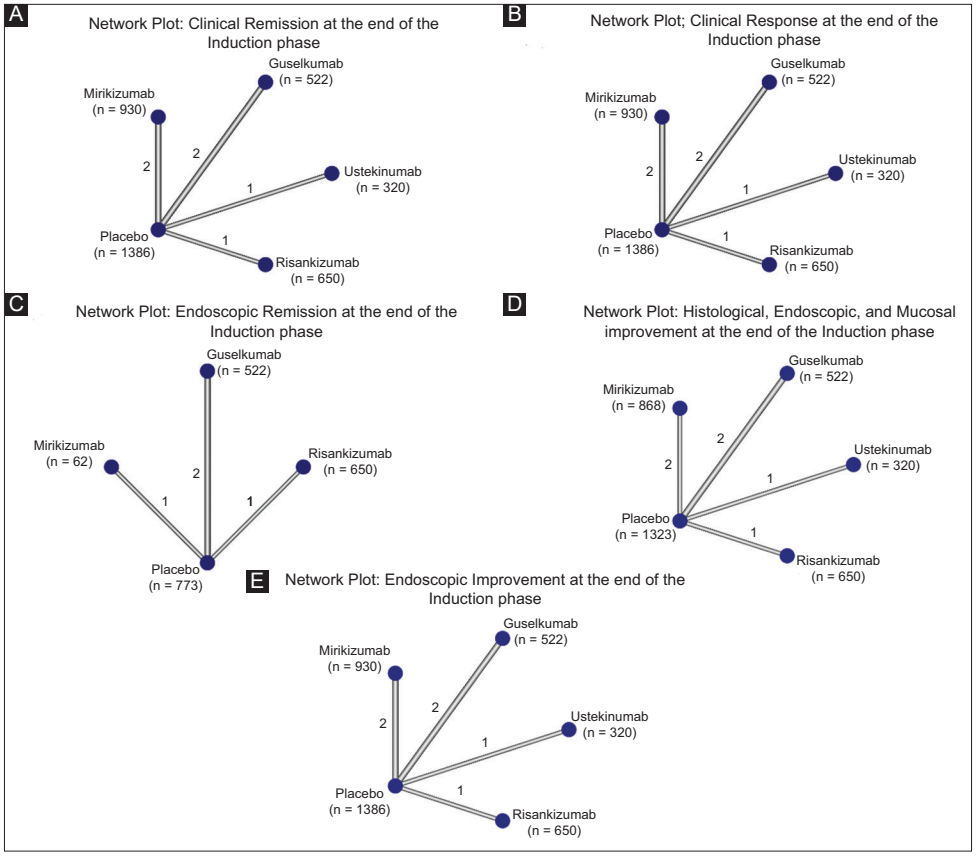

Figure 2 (A-E) Network plots for different outcomes at the end of the induction phase

Risankizumab was superior to ustekinumab (OR 2.41, 95%CI 1.04-5.58), while mirikizumab was inferior to risankizumab (OR 0.44, 95%CI 0.21-0.93) (Supplementary Fig. 2). SUCRA analysis supported risankizumab (95%) (Supplementary Fig. 1).

Maintenance phase

Guselkumab demonstrated the highest efficacy for achieving clinical remission (OR 4.00, 95%CI 2.21-7.23) (Fig. 5), with a SUCRA ranking of 92.2% (Supplementary Fig. 4). For corticosteroid-free remission, guselkumab was also superior (OR 3.67, 95%CI 2.04-6.63) and ranked highest (89.4%) (Fig. 5; Supplementary Fig. 4). Only mirikizumab was superior to placebo for clinical response (OR 4.65, 95%CI 2.78-7.78), ranking highest by SUCRA (97.1%) (Supplementary Fig. 4).

Guselkumab achieved the greatest effect in endoscopic improvement (OR 4.18, 95%CI 2.31-7.55) (Fig. 5), ranking highest by SUCRA (85.3%) (Supplementary Fig. 4). For HEMI, guselkumab showed the strongest effect (OR 4.27, 95%CI 2.34-7.79), followed by risankizumab, with SUCRA favoring guselkumab (86.4%) (Supplementary Fig. 5). Guselkumab was the only agent superior to placebo for endoscopic remission (OR 2.79, 95%CI 1.50-5.19) (Supplementary Fig. 6), ranking highest by SUCRA (82.9%) (Supplementary Fig. 4).

Patients with a history of inadequate response to advanced therapy

Induction phase

Ustekinumab achieved the highest statistically significant increase in clinical remission (OR 10.42, 95%CI 2.39-45.50) compared to placebo, whereas mirikizumab demonstrated a lower remission rate than ustekinumab (OR 0.19, 95%CI 0.04-0.96) (Fig. 4). Based on SUCRA, ustekinumab ranked highest (95.5%) (Supplementary Fig. 1). For clinical response, guselkumab showed the greatest increase (OR 4.06, 95%CI 2.63-6.25) compared with placebo (Supplementary Fig. 2). SUCRA ranked guselkumab highest (93.7%) (Supplementary Fig. 1).

Regarding endoscopic improvement, risankizumab demonstrated the highest efficacy (OR 3.13, 95%CI 1.79-5.48) compared to placebo (Fig. 4). SUCRA ranked risankizumab highest (66.5%) (Supplementary Fig. 1). Guselkumab also had the highest improved endoscopic remission rate compared to placebo (OR 3.07, 95%CI 1.81-5.97) and ranked highest by SUCRA (89.7%) (Fig. 3; Supplementary Fig. 1). For HEMI, ustekinumab was most effective (OR 4.00, 95%CI 1.58-10.15) compared to placebo (Supplementary Fig. 2). SUCRA ranked ustekinumab highest (80.8%) (Supplementary Fig. 1).

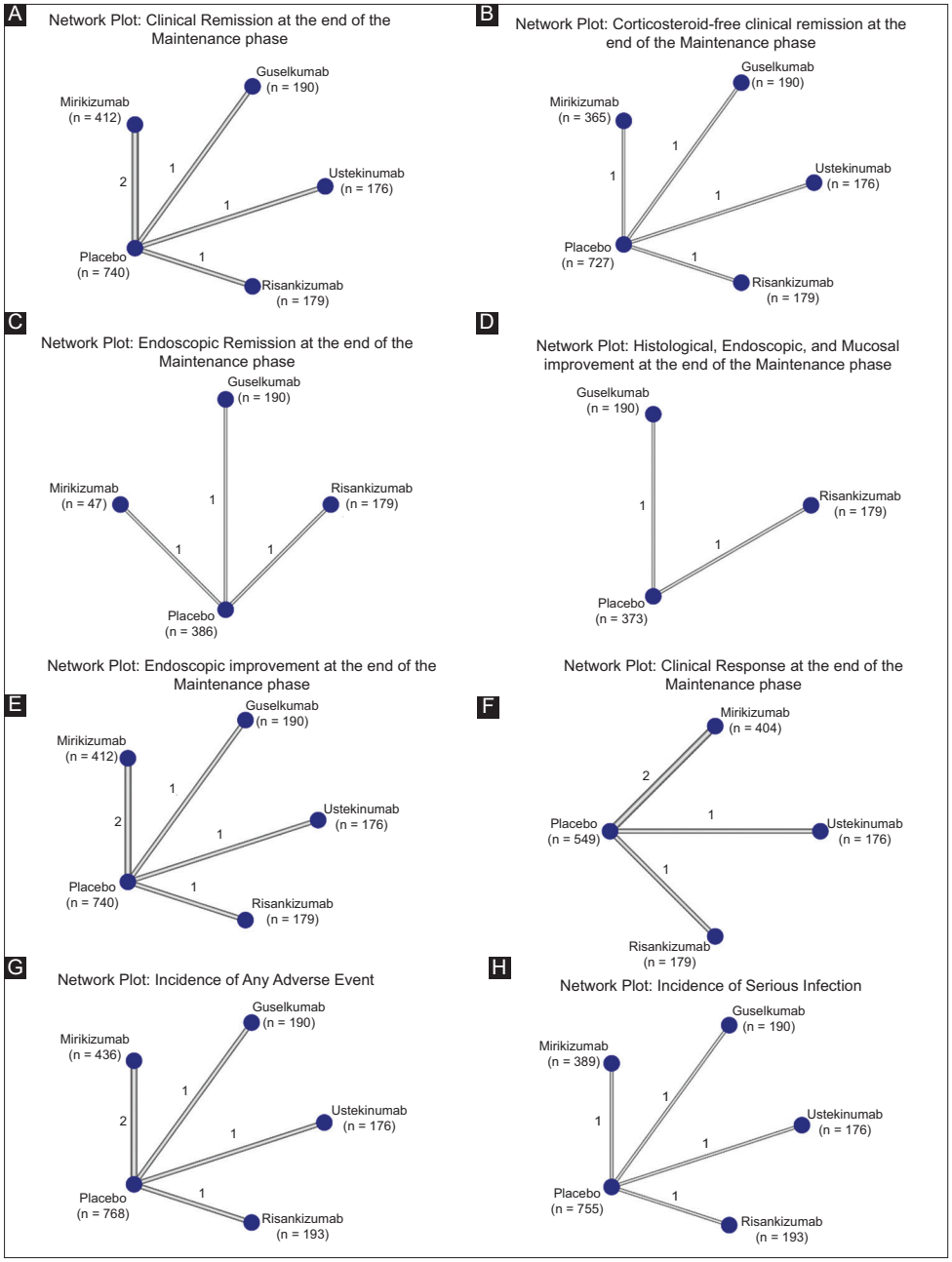

Figure 3 (A-H) Network plots for different outcomes at the end of the maintenance phase

Maintenance phase

Guselkumab demonstrated the highest rate of clinical remission (OR 7.59, 95%CI 2.98-19.30) compared to placebo and was also superior to risankizumab (OR 3.98, 95%CI 1.36-11.67) (Fig. 5). SUCRA ranked guselkumab highest (92.8%) (eFig. S4). For corticosteroid-free clinical remission, guselkumab was most effective (OR 9.25, 95%CI 3.39-25.20) compared to placebo, and was superior to risankizumab (OR 5.00, 95%CI 1.61-15.55) (Fig. 5). SUCRA ranked guselkumab highest (96.1%) (Supplementary Fig. 4).

Mirikizumab achieved the highest clinical response (OR 3.60, 95%CI 1.92-6.74), compared to placebo (Fig. 5), with SUCRA ranking mirikizumab highest (95.7%) (Supplementary Fig. 4). Guselkumab showed the greatest endoscopic improvement (OR 8.34, 95%CI 3.27-21.26) compared to placebo, and was superior to risankizumab (OR 3.99, 95%CI 1.39-11.51) (Fig. 5). SUCRA ranked guselkumab highest (96.3%) (Supplementary Fig. 4).

For HEMI, guselkumab was most effective (OR 7.24, 95%CI 2.83-18.50) compared to placebo, and was superior to risankizumab (OR 3.17, 95%CI 1.08-9.33) (Fig. 5). SUCRA ranked guselkumab highest (99.1%) (Supplementary Fig. 4). Only guselkumab demonstrated superiority in endoscopic

Patients without a history of Inadequate response to advanced therapy

Induction of endoscopic improvement	Induction of clinical remission				
	Guselkumab	1.511 [0.76,3.005]	0.782 [0.35,1.75]	1.524 [0.658,3.528]	3.602 [2.149,6.04]
	1.428 [0.787,2.591]	Mirikizumab	0.518 [0.241,1.114]	1.008 [0.452,2.249]	2.384 [1.515,3.752]
	0.565 [0.286,1.117]	0.396 [0.211,0.742]	Risankizumab	1.947 [0.788,4.812]	4.604 [2.484,8.533]
	1.55 [0.782,3.073]	1.086 [0.577,2.041]	2.742 [1.345,5.593]	Ustekinumab	2.364 [1.22,4.581]
	3.109 [1.961,4.928]	2.177 [1.492,3.176]	5.499 [3.329,9.085]	2.005 [1.209,3.326]	Placebo

Patients with a history of inadequate response to advanced therapy

Induction of endoscopic improvement	Induction of clinical remission				
	Guselkumab	1.652 [0.577,4.733]	1.069 [0.343,3.332]	0.308 [0.058,1.631]	3.207 [1.473,6.984]
	1.141 [0.446,2.918]	Mirikizumab	0.647 [0.218,1.925]	0.186 [0.036,0.957]	1.941 [0.956,3.943]
	0.99 [0.41,2.392]	0.868 [0.37,2.036]	Risankizumab	0.288 [0.053,1.562]	3.00 [1.31,6.869]
	1.017 [0.374,2.761]	0.891 [0.337,2.358]	1.026 [0.41,2.571]	Ustekinumab	10.417 [2.385,45.502]
	3.104 [1.568,6.145]	2.72 [1.428,5.183]	3.14 [1.794,5.475]	3.053 [1.473,6.329]	Placebo

Overall patients

Induction of endoscopic improvement	Induction of clinical remission				
	Guselkumab	1.457 [0.779,2.726]	0.869 [0.424,1.784]	1.027 [0.472,2.235]	3.379 [2.133,5.351]
	1.123 [0.498,2.534]	Mirikizumab	0.597 [0.297,1.198]	0.705 [0.33,1.504]	2.319 [1.516,3.547]
	0.717 [0.295,1.743]	0.638 [0.26,1.569]	Risankizumab	1.181 [0.512,2.724]	3.886 [2.237,6.75]
	1.356 [0.55,3.346]	1.207 [0.484,3.01]	1.892 [0.709,5.048]	Ustekinumab	3.29 [1.757,6.16]
	3.016 [1.711,5.317]	2.685 [1.498,4.812]	4.208 [2.122,8.346]	2.225 [1.101,4.495]	Placebo

Figure 4 Comparative efficacy of anti-interleukin [IL]-12/23 and anti-IL-23 for clinical remission and endoscopic improvement at the end of the induction phase in patients with and without a history of inadequate response to advanced therapy, as well as in all patients with moderate-to-severe ulcerative colitis. Comparisons are read from left to right; odds ratios with 95% confidence intervals were used. Blue boxes indicate a statistically significant difference in clinical remission, while green boxes indicate a statistically significant difference in endoscopic improvement

remission vs. placebo (OR 3.60, 95%CI 1.37-9.49) (Fig. 6), with SUCRA ranking it highest (96%) (Supplementary Fig. 4).

GRADE ratings summary

High certainty was assigned to clinical remission, endoscopic improvement, clinical response and HEMI during the induction phase, and to corticosteroid-free clinical remission and HEMI during the maintenance phase. In contrast, the evidence for clinical remission, clinical response and endoscopic remission during the maintenance phase was graded as low to very low. Adverse events and serious infections also received low certainty ratings, reflecting the limited event rates and potential underreporting. GRADE framework is demonstrated in Supplementary Table 3.

Discussion

TNF inhibitors have been the first-line treatment for UC for a long time. However, about one third of patients fail to respond to initial therapy, highlighting the need for alternatives [4]. Recent trials have demonstrated the efficacy and safety of anti-IL-12/23 and IL-23 inhibitors in both the induction and maintenance phases of UC treatment [10-15]. In this network meta-analysis, we combined data to evaluate the efficacy and safety of anti-IL-12/23 and anti-IL-23 medications, from 6 RCTs during the induction phase and 5 RCTs during the maintenance phase. We also examined outcomes in a cohort of moderate-to-severe UC patients, including subgroup analysis for those with or without a history of inadequate response.

The central therapeutic goal in UC is to achieve and sustain clinical remission while minimizing corticosteroid exposure [19-21]. In our analysis, risankizumab demonstrated the highest rates of clinical remission during induction, both in the overall population and in the subgroup of patients without a history of inadequate response to advanced therapy. Conversely, among the subgroup of patients with a history of inadequate response to advanced therapy, ustekinumab produced the greatest induction-phase gains in clinical remission. At the end of maintenance, guselkumab was the most effective across key outcomes, showing the highest rates of clinical remission and corticosteroid-free remission in both

Patients without a history of inadequate response to advanced therapy

Endoscopic improvement at the end of maintenance	Clinical remission at the end of maintenance				
	Guselkumab	1.667 [0.781,3.559]	1.728 [0.608,4.908]	1.932 [0.819,4.558]	4 [2.214,7.227]
	1.306 [0.613,2.783]	Mirikizumab	1.037 [0.388,2.769]	1.159 [0.53,2.535]	2.399 [1.492,3.858]
	1.536 [0.543,4.341]	1.176 [0.444,3.116]	Risankizumab	1.118 [0.387,3.232]	2.315 [0.979,5.472]
	1.615 [0.686,3.798]	1.236 [0.569,2.686]	1.051 [0.367,3.013]	Ustekinumab	2.071 [1.111,3.858]
	4.176 [2.309,7.552]	3.198 [1.998,5.118]	2.719 [1.158,6.382]	2.586 [1.396,4.792]	Placebo

Patients with a history of inadequate response to advanced therapy

Endoscopic improvement at the end of maintenance	Clinical remission at the end of maintenance				
	Guselkumab	1.645 [0.492,5.493]	3.977 [1.356,11.666]	2.384 [0.742,7.663]	7.594 [2.975,19.385]
	2.061 [0.641,6.633]	Mirikizumab	2.418 [0.959,6.099]	1.45 [0.517,4.061]	4.617 [2.162,9.863]
	3.992 [1.385,11.512]	1.937 [0.821,4.571]	Risankizumab	0.599 [0.25,1.438]	1.91 [1.125,3.241]
	2.993 [0.959,9.335]	1.452 [0.559,3.769]	0.75 [0.332,1.695]	Ustekinumab	3.185 [1.587,6.393]
	8.343 [3.274,21.261]	4.048 [2.009,8.156]	2.09 [1.272,3.433]	2.788 [1.459,5.327]	Placebo

Overall patients

Endoscopic improvement at the end of maintenance	Clinical remission at the end of maintenance				
	Guselkumab	1.192 [0.313,4.544]	2.135 [0.523,8.708]	1.877 [0.459,7.674]	4.278 [1.578,11.594]
	1.264 [0.693,2.288]	Mirikizumab	1.791 (0.472,6.795]	1.574 [0.414,5.989]	3.588 [1.47,8.758]
	2.045 [1.09,3.835]	1.618 [0.917,2.855]	Risankizumab	0.879 [0.216,3.58]	2.004 [0.744,5.4]
	1.742 [0.92,3.298]	1.378 [0.773,2.458]	0.852 [0.461,1.575]	Ustekinumab	2.28 [0.843,6.163)
	4.557 [2.873,7.226]	3.606 [2.482,5.239]	2.229 [1.453,3.418]	2.616 [1.682,4.068]	Placebo

Figure 5 Comparative efficacy of anti-interleukin [IL]-12/23 and anti-IL-23 for clinical remission and endoscopic improvement at the end of the maintenance phase in patients with and without a history of inadequate response to advanced therapy, as well as in the overall patients with moderate-to-severe ulcerative colitis. Comparisons are read from left to right; odds ratios with 95% confidence intervals were used. Blue boxes indicate a statistically significant difference in clinical remission, while green boxes indicate a statistically significant difference in endoscopic improvement

the overall patient population, and in the subgroups with or without a history of inadequate response to advanced therapy. These findings are concordant with a prior network meta-analysis comparing IL-12/23 and IL-23 in Crohn's disease, where guselkumab achieved the highest rates of clinical remission at the end of the induction and maintenance phases, as well as the highest corticosteroid-free remission rates at the end of the maintenance phase [22].

Mirikizumab also demonstrated strong maintenance-phase efficacy, emerging as the most effective therapy at the end of maintenance across all patient subgroups, irrespective of prior treatment history. During induction, guselkumab outperformed mirikizumab and ustekinumab in terms of clinical response among patients without a history of inadequate response to advanced therapy, while risankizumab demonstrated superiority over mirikizumab. In the subgroup of patients with a history of inadequate response to advanced therapy, ustekinumab yielded higher remission rates than mirikizumab during induction. During maintenance, guselkumab surpassed risankizumab for both clinical remission and corticosteroid-free remission in patients with a history of inadequate response to advanced therapy. Mirikizumab also outperformed risankizumab in clinical response at the end of maintenance in the overall population.

Discrepancies were observed between the rankings for clinical response and clinical remission within the same phase. These endpoints reflect distinct thresholds: response captures partial symptomatic improvement (including reductions in rectal bleeding), while remission requires more comprehensive disease control, typically including endoscopic healing. This divergence highlights the complexity of interpreting treatment effects, and underscores the importance of clearly defined endpoints. Mechanistic and pharmacologic distinctions probably contributed to these differences. Ustekinumab targets the shared p40 subunit of IL-12 and IL-23, while guselkumab, risankizumab and mirikizumab selectively inhibit the p19 subunit of IL-23. Selective p19 inhibition may preserve IL-12–mediated host defense while more precisely suppressing Th17-driven inflammation [20]. Structural and biophysical studies further demonstrate differences in p19 binding

epitopes and affinities; risankizumab and guselkumab exhibit higher IL-23 affinity and *in vitro* potency compared with ustekinumab and tildrakizumab, while crystallizable fragment (Fc) modifications and epitope features may influence mucosal penetration and receptor blockade [23]. Pharmacokinetics, pharmacodynamics, and dosing schedules also vary. For example, risankizumab for UC induction is administered as 1200 mg IV at weeks 0, 4 and 8 [24], whereas guselkumab is administered as 200 mg IV at the same intervals [15]. Such variations in exposure may account for differential early mucosal healing and long-term durability. Moreover, heterogeneity in trial populations—including the proportion of patients with or without a history of inadequate response to advanced therapy, corticosteroid tapering protocols, and central vs. local endoscopic reads—probably amplifies apparent efficacy differences beyond drug mechanisms alone.

Endoscopic and histological endpoints are key UC targets, given their association with reduced steroid use, hospitalization and colectomy risk [20,25]. HEMI is particularly predictive of favorable outcomes. During induction, risankizumab achieved the highest rates of endoscopic remission, HEMI, and endoscopic improvement overall, while guselkumab was most effective across these outcomes during maintenance, both overall and in the subgroup of patients without prior inadequate response. In patients with such a history, guselkumab maintained superiority for endoscopic remission, ustekinumab led in induction of HEMI, and risankizumab outperformed mirikizumab and ustekinumab for induction of HEMI and endoscopic improvement.

UC therapies are limited by non-response, waning efficacy, and adverse events [26-29]. In our analysis, there were no statistically significant differences between IL-23 pathway agents (risankizumab, ustekinumab, guselkumab, mirikizumab) and placebo regarding overall adverse events or serious infections during maintenance. These findings suggest a favorable safety profile that is consistent across agents.

Our results align with broader evidence supporting IL-23 inhibition as a safe and effective treatment for moderate-to-severe UC. Meta-analyses have consistently shown that IL-23 and IL-12/23 blockade improves clinical, endoscopic and histological outcomes relative to placebo [30]. Our network meta-analysis extends this evidence by enabling indirect comparisons between individual IL-23–targeting drugs, thereby offering more granular insights into comparative efficacy and safety.

The 2024 American Gastroenterological Association (AGA) Evidence Synthesis provides an important comparator [31]. The AGA ranked risankizumab and guselkumab among the most effective induction agents in the subgroup of patients without a history of inadequate response to advanced therapy, consistently with our findings. For the subgroup of patients with a history of inadequate response to advanced therapy, ustekinumab, tofacitinib and upadacitinib ranked higher, with risankizumab and guselkumab showing intermediate efficacy. Taken together, these results suggest that risankizumab or guselkumab may be optimal for patients without a history of inadequate response to advanced therapy, whereas ustekinumab may be preferable for patients with a history of inadequate response to advanced therapy.

Therapeutic selection among IL-23 inhibitors may depend on clinical priorities. Risankizumab ranked highest for rapid induction of endoscopic improvement and remission, particularly in patients without a history of inadequate response to advanced therapy. For maintenance, guselkumab consistently outperformed comparators in remission, corticosteroid-free remission, HEMI and endoscopic outcomes. In the subgroup of patients with prior inadequate response, ustekinumab was superior for induction, while guselkumab provided the most durable maintenance, with comparable safety.

This study has several strengths. It is the first network meta-analysis to evaluate IL-23–selective and IL-12/23 inhibitors in moderate-to-severe UC, stratified according to the patients' history of inadequate response to advanced therapy. It included both induction and maintenance phases, prioritizing clinically relevant endpoints (corticosteroid-free remission, HEMI), and all trials had a low risk of bias. While SEQUENCE compared risankizumab and ustekinumab in Crohn's disease [32], no head-to-head UC trials exist; our indirect analysis addresses this gap.

However, important limitations must be acknowledged. Induction phase durations varied slightly, with 12 weeks for all trials except the ustekinumab trial, while maintenance ranged from 40 weeks (mirikizumab) to 52 weeks (risankizumab). This variability may affect cross-trial comparisons. Endoscopic remission definitions were not uniform: for example, the Phase III mirikizumab trial defined remission as a subscore ≤1 without friability, which is equivalent to "endoscopic improvement" in other studies, necessitating reclassification. Two of the included studies were phase II, which may have reduced the robustness of the pooled estimates. Safety analyses were restricted to adverse events and serious infections, with limited long-term follow-up. Lastly, the number of trials per agent was small, reducing statistical power for indirect comparisons. These factors mandate cautious interpretation until validated by additional trials.

In conclusion, selecting optimal therapy for moderate-to-severe UC remains challenging, particularly for subgroups of patients with a history of inadequate response to advanced therapy. Our network meta-analysis demonstrated that guselkumab provided the most consistent maintenance-phase benefits across clinical and endoscopic endpoints, whereas risankizumab and ustekinumab were particularly effective during induction in patients without and with a history of inadequate response to advanced therapy, respectively. Mirikizumab also showed strong efficacy at the end of maintenance. All agents demonstrated favorable safety profiles compared with placebo. Future head-to-head RCTs are essential to definitively establish the comparative efficacy and safety of these IL-23 pathway inhibitors in UC.

Summary Box

What is already known:

- Tumor necrosis factor (TNF) inhibitors are commonly used as first-line biologic therapy for moderate-to-severe ulcerative colitis (UC), but approximately one third of patients do not respond adequately
- Anti-interleukin [IL]-12/23 (e.g., ustekinumab) and anti-IL-23 agents (e.g., risankizumab, guselkumab, mirikizumab) have recently emerged as promising treatment options for UC
- No direct head-to-head trials exist comparing these IL-12/23 and IL-23 agents for induction and maintenance therapy in UC

What the new findings are:

- Risankizumab demonstrated the highest induction-phase clinical remission rates in patients without prior inadequate response to advanced therapy, while ustekinumab achieved the highest rates in those with a prior inadequate response
- Guselkumab showed the highest clinical remission, corticosteroid-free remission, and endoscopic improvement rates during the maintenance phase compared to placebo in patients with moderate-to-severe UC, across all patients, and in subgroups of patients either with or without a history of inadequate response to advanced therapy
- No significant safety differences (in terms of adverse events or serious infections) were observed between IL-12/23 and IL-23 agents and the placebo

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Supplementary material

Supplementary Table 1 Search term results on 1st October 2024 for each database

Data Base		Search Term	Result
PubMed No filters applied	#1	"Colitis, Ulcerative" OR "Colitis Gravis" OR "Idiopathic Proctocolitis" OR "Inflammatory Bowel Disease" OR "Ulcerative Colitis" OR "Colitis, Ulcerative"[Mesh]	104,572
	#2	"Anti-IL-12/23" OR "Anti-IL 12/23" OR "Anti IL 12/23" OR "Ustekinumab" OR "stelara" OR "CNTO 1275" OR "Briakinumab" OR "ABT-874" OR "ABT874" OR "ABT 874" OR "Anti-IL-23" OR "Anti IL 23" OR "Risankizumab" OR "BI 655066" OR "BI-655066" OR "skyrizi" OR "risankizumab-rzaa" OR "ABBV-066" OR "Mirikizumab" OR "LY-3074828" OR "LY3074828" OR "Guselkumab" OR "Tremfya" OR "CNTO 1959" OR "CNTO-1959" OR "Tildrakizumab" OR "SCH 900222" OR "SCH-900222" OR "MK-3222" OR "Ilumya" OR "Interleukin-12" OR "Interleukin 12" OR "Interleukin-23" OR "Interleukin 23"	26,043
	#3	1# AND #2	1,737
Scopus Title Abstract Keyword Filter: Title	#1	"Colitis, Ulcerative" OR "Colitis Gravis" OR "Idiopathic Proctocolitis" OR "Inflammatory Bowel Disease" OR "Ulcerative Colitis"	154,525
	#2	"Anti-IL-12/23" OR "Anti-IL 12/23" OR "Anti IL 12/23" OR "Ustekinumab" OR "Briakinumab" OR "Anti-IL-23" OR "Anti IL 23" OR "Risankizumab" OR "Mirikizumab" OR "Guselkumab" OR "Tildrakizumab" OR "Interleukin-12" OR "Interleukin 12" OR "Interleukin-23" OR "Interleukin 23"	78,421
	#3	1# AND #2	7,181
Cochrane Library Title Abstract Keyword Filter: Trails	#1	"Colitis, Ulcerative" OR "Colitis Gravis" OR "Idiopathic Proctocolitis" OR "Inflammatory Bowel Disease" OR "Ulcerative Colitis"	9,238
	#2	"Anti-IL-12/23" OR "Anti-IL 12/23" OR "Anti IL 12/23" OR "Ustekinumab" OR "Briakinumab" OR "Anti-IL-23" OR "Anti IL 23" OR "Risankizumab" OR "Mirikizumab" OR "Guselkumab" OR "Tildrakizumab" OR "Interleukin-12" OR "Interleukin 12" OR "Interleukin-23" OR "Interleukin 23"	3,063
	#3	1# AND #2	528
Web of Science Filter: Title	#1	"Colitis, Ulcerative" OR "Colitis Gravis" OR "Idiopathic Proctocolitis" OR "Inflammatory Bowel Disease" OR "Ulcerative Colitis"	152,309
	#2	"Anti-IL-12/23" OR "Anti-IL 12/23" OR "Anti IL 12/23" OR "Ustekinumab" OR "Briakinumab" OR "Anti-IL-23" OR "Anti IL 23" OR "Risankizumab" OR "Mirikizumab" OR "Guselkumab" OR "Tildrakizumab" OR "Interleukin-12" OR "Interleukin 12" OR "Interleukin-23" OR "Interleukin 23"	22,620
	#3	1# AND #2	2,426
Clinical trials.gov Filter: Complete	Condition/Disease: Ulcerative Colitis Intervention: Ustekinumab – Guselkumab – Risankizumab - Mirikizumab		15

Total N = 11,887. After duplicate removal = 7802

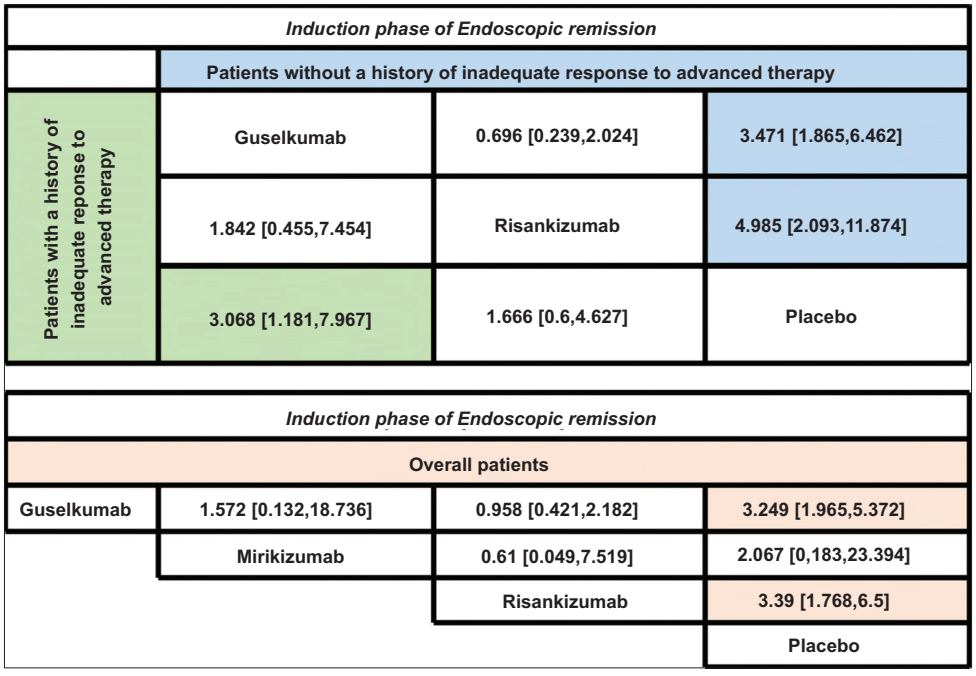
Supplementary Table 2 Risk of bias result

Study [ref.]	D1	D2	D3	D4	D5	Overall
Louis *et al*, 2024 [11]	Low	Low	Low	Low	Low	Low
Sandborn *et al*, 2020 [13]	Low	Low	Low	Low	Low	Low
D'Haens *et al*, 2023 [12]	Low	Low	Low	Low	Low	Low
Peyrin-Biroulet *et al*, 2023 [14]	Low	Low	Low	Low	Low	Low
Rubin *et al*, 2024 [15]	Low	Low	Low	Low	Low	Low
Sands *et al*, 2019 [10]	Low	Low	Low	Low	Low	Low

Supplementary Table 3 GRADE (Grading of Recommendations Assessment, Development, and Evaluation)

Outcome	Final GRADE Rating
Clinical Remission (Induction Phase)	HIGH
Clinical Remission (Maintenance Phase)	LOW
Endoscopic Improvement (Induction Phase)	HIGH
Endoscopic Improvement (Maintenance Phase)	MODERATE
Clinical Response (Induction Phase)	HIGH
Clinical Response (Maintenance Phase)	LOW
Endoscopic Remission (Induction Phase)	LOW
Endoscopic Remission (Maintenance Phase)	VERY LOW
HEMI (Induction Phase)	HIGH
HEMI (Maintenance Phase)	HIGH
Corticosteroid-Free Clinical Remission (Maintenance Phase)	HIGH
Adverse Events (Maintenance Phase)	LOW
Serious Infections (Maintenance Phase)	LOW

HEMI, Histological, Endoscopic, and Mucosal Improvement



Supplementary Figure 1 Endoscopic remission at the end of the induction phase
Comparisons are read from left to right; odds ratios with 95% confidence intervals were used. Blue boxes indicate a statistically significant difference in clinical remission among patients without a history of inadequate response to advanced therapy, green boxes indicate a statistically significant difference in endoscopic remission among patients with a history of inadequate response to advanced therapy, and beige boxes indicate a statistically significant difference in endoscopic remission among overall patients

Patients without a history of inadequate response to advanced therapy					
	Induction of histologic, endoscopic, mucosal improvement				
Induction of clinical response	Guselkumab	1.52 [0.772,2.992]	0.67 [0.298,1.504]	1.614 [0.741,3.515]	3.677 [2.172,6.225]
	2.014 [1.175,3.45]	Mirikizumab	0.441 [0.209,0.931]	1.062 [0.52,2.169]	2.419 [1.58,3.705]
	1.134 [0.64,2.012]	0.563 [0.328,0.968]	Risankizumab	2.409 [1.041,5.579]	5.487 [2.97,10.14]
	1.881 [1.024,3.455]	0.934 [0.524,1.665]	1.658 [0.9,3.052]	Ustekinumab	2.278 [1.284,4.038]
	4.671 [3.12,6.991]	2.32 [1.624,3.313]	4.117 [2.741,6.183]	2.484 [1.576,3.915]	Placebo

Patients with a history of inadequate response to advanced therapy					
	Induction of histologic, endoscopic, mucosal improvement				
Induction of clinical response	Guselkumab	1.213 [0.407,3.61]	1.228 [0.446,3.38]	0.765 [0.228,2.561]	3.061 [1.417,6.616]
	1.424 [0.765,2.652)	Mirikizumab	1.013 [0.368,2.791]	0.631 [0.188,2.114]	2.525 [1.166,5.465]
	1.488 [0.831,2.665)	1.045 [0.578,1.89]	Risankizumab	0.623 [0.199,1.945]	2.492 [1.293,4.804]
	1.856 [0.984,3.498]	1.303 [0.685,2.479	1.247 [0.68,2.285]	Ustekinumab	4.002 [1.578,10.154]
	4.057 [2.632,6.254]	2.849 [1.824,4.45]	2.726 [1.846,4.026]	2.186 [1.376,3.475]	Placebo

Overall patients					
	Induction of histologic, endoscopic, mucosal improvement				
Induction of clinical response	Guselkumab	1.529 [0.872,2.678]	0.901 [0.486,1.671]	1.348 [0.711,2.554]	3.502 [2.282,5.373]
	1.36 [10.666,2.775]	Mirikizumab	0.59 [0.332,1.047]	0.882 [0.485,1.602]	2,291 [1.595,3.291]
	1.279 [0.582,2.806]	0.94 [0.424,2.086]	Risankizumab	1.496 [0.78,2.868]	3.886 [2.489,6.067)
	1.803 [0.808,4.024]	1.326 [0.588,2.99]	1.41 [0.586,3.391]	Ustekinumab	2.598 [1.616,4.177)
	4.15 [2.527,6.818]	3.052 [1.828,5.096]	3.246 [1.764,5.973]	2.302 [1.225,4.328]	Placebo

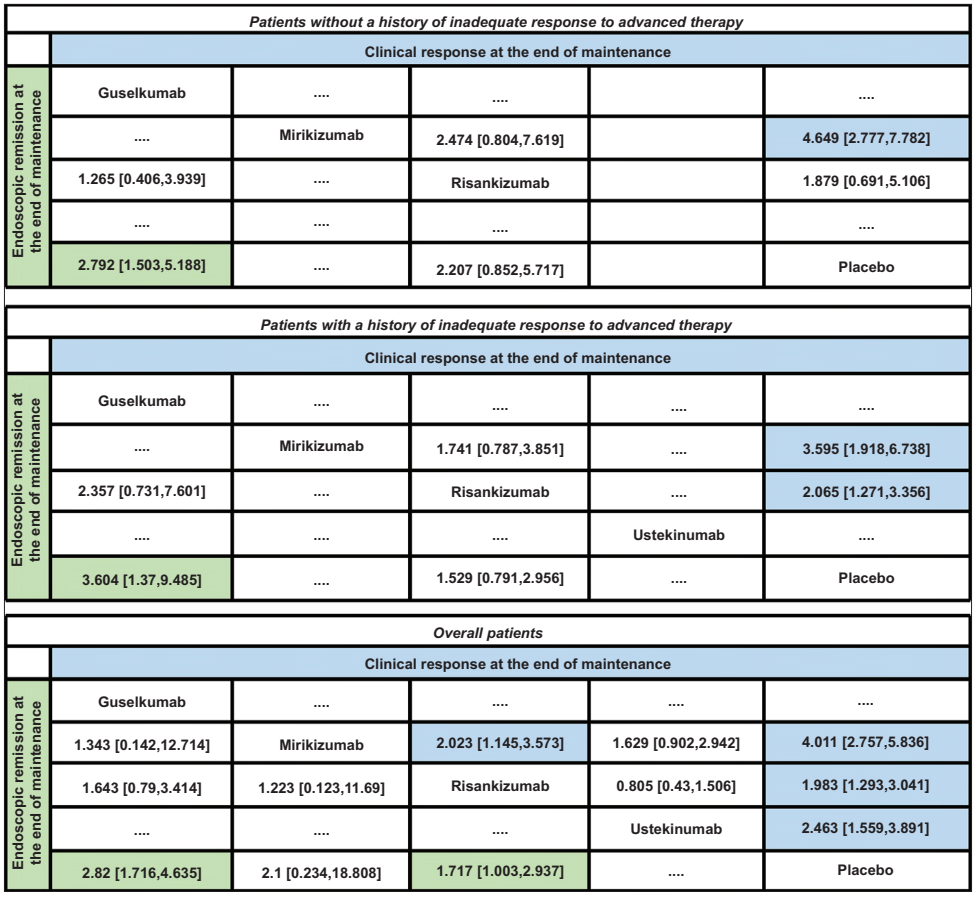
Supplementary Figure 2 Histological, endoscopic, mucosal improvement, and clinical response at the end of the induction phase in patients Comparisons are read from left to right; odds ratios with 95% confidence intervals were used. Blue boxes indicate a statistically significant difference in histological, endoscopic, mucosal improvement, while green boxes indicate a statistically significant difference in clinical response

Patients without a history of Inadequate response to advanced therapy					
	Histologic, endoscopic, mucosal improvement at the end of maintenance				
Corticosteroid-free clinical remission at the end of maintenance	Guselkumab	....	1.387 [0.481,4.005]	....	4.269 [2.338,7.794]
	1.495 [0.694,3.223]	Mirikizumab	....	....	....
	1.587 [0.559,4.503]	1.061 [0.394,2.856]	Risankizumab	....	3.077 [1.286,7.363]
	1.86 [0.789,4.384]	1.243 [0.563,2.748]	1.172 [0.405,3.389]	Ustekinumab	....
	3.673 [2.037,6.625]	2.456 [1.503,4.013]	2.315 [0.979,5.472]	1.975 [1.06,3.682]	Placebo

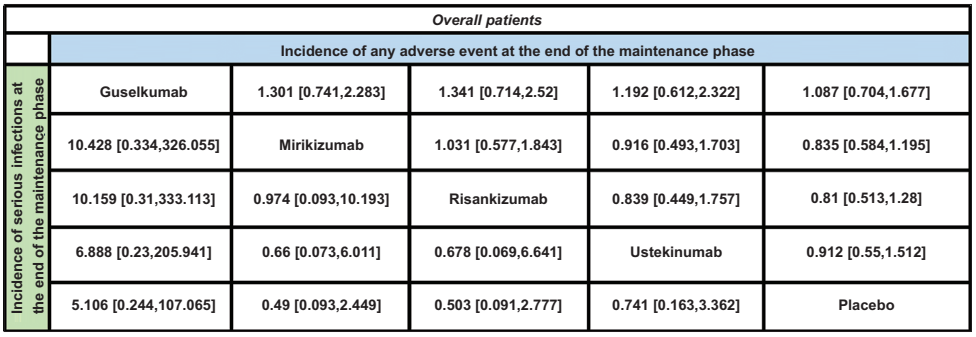
Patients with a history of inadequate response to advanced therapy					
	Histologic, endoscopic, mucosal improvement at the end of maintenance				
Corticosteroid-free clinical remission at the end of maintenance	Guselkumab	....	3.172 [1.078.9.331]	....	7.241 [2.834,18.501]
	2.211 [0.618,7.915]	Mirikizumab	....	....	....
	5.001 [1.609,15.545]	2.262 [0.875,5.846]	Risankizumab	....	2.283 [1.339,3.891]
	2.932 [0.857,10.029]	1.326 [0.459,3.835]	0.586 [0.241,1.424]	Ustekinumab	....
	9.245 [3.392,25.199]	4.181 [1.901,9.195]	1.849 [1.088,3.141]	3.153 [1.547,6.425]	Placebo

Overall patients					
	Histologic, endoscopic, mucosal Improvement at the end of maintenance				
Corticosteroid-free clinical remission at the end of maintenance	Guselkumab	....	1.847 [0.959,3.557]		4.539 [2.823,7.296]
	1.45 [0.78,2.694]	MIrIkIzumab	....	....	....
	2.169 [1.137,4.135]	1.496 [0.814,2.748]	Risankizumab	....	2.458 [1.564,3.862]
	1.791 [0.931,3.443]	1.235 [0.667,2.289]	0.826 [0.434,1.57]	Ustekinumab	....
	4.246 [2.669,6.754]	2.929 [1.943,4.415)	1.958 [1.25,3.066]	2.371 [1.496,3.757]	Placebo

Supplementary Figure 3 Histologic, endoscopic, mucosal, improvement and corticosteroid-free clinical remission at the end of the maintenance phase Comparisons are read from left to right; odds ratios with 95% confidence intervals were used. Blue boxes indicate a statistically significant difference in histologic, endoscopic, mucosal improvement, while green boxes indicate a statistically significant difference in corticosteroid-free clinical remission



Supplementary Figure 4 Clinical response and endoscopic remission at the end of the maintenance phase
Comparisons are read from left to right; odds ratios with 95% confidence intervals were used. Blue boxes indicate a statistically significant difference in clinical response, while green boxes indicate a statistically significant difference in endoscopic remission



Supplementary Figure 5 Incidence of any adverse event and incidence of serious infection at the end of the maintenance phase
Comparisons are read from left to right; odds ratios with 95% confidence intervals were used. Blue boxes indicate a statistically significant difference in the incidence of any adverse event, while green boxes indicate a statistically significant difference in the incidence of serious infection

Induction of Clinical Remission	
Patients without a history of inadequate response	
Intervention	SUCRA score
Risankizumab	0.901
Guselkumab	0.748
Ustekinumab	0.431
Mirikizumab	0.418
Placebo	0.001
Patients with a history of inadequate response	
Intervention	SUCRA score
Ustekinumab	0.955
Guselkumab	0.613
Risankizumab	0.577
Mirikizumab	0.345
Placebo	0.01
Overall patients	
Intervention	SUCRA score
Risankizumab	0.807
Guselkumab	0.69
Ustekinumab	0.66
Mirikizumab	0.344
Placebo	0

Induction of Clinical Response	
Patients without a history of inadequate response	
Intervention	SUCRA score
Guselkumab	0.91
Risankizumab	0.815
Ustekinumab	0.416
Mirikizumab	0.358
Placebo	0
Patients with a history of inadequate response	
Intervention	SUCRA score
Guselkumab	0.937
Mirikizumab	0.62
Risankizumab	0.574
Ustekinumab	0.369
Placebo	0
Overall patients	
Intervention	SUCRA score
Risankizumab	0.864
Guselkumab	0.652
Mirikizumab	0.598
Ustekinumab	0.385
Placebo	0.001

Induction of Endoscopic Improvement	
Patients without a history of inadequate response	
Intervention	SUCRA score
Risankizumab	0.986
Guselkumab	0.706
Mirikizumab	0.431
Ustekinumab	0.376
Placebo	0.001
Patients with a history of inadequate response	
Intervention	SUCRA score
Risankizumab	0.665
Guselkumab	0.653
Mirikizumab	0.639
Ustekinumab	0.543
Placebo	0.001
Overall patients	
Intervention	SUCRA score
Risankizumab	0.876
Guselkumab	0.647
Mirikizumab	0.552
Ustekinumab	0.422
Placebo	0.003

Induction of HEMI	
Patients without a history of inadequate response	
Intervention	SUCRA score
Risankizumab	0.95
Guselkumab	0.735
Mirikizumab	0.424
Ustekinumab	0.391
Placebo	0.001
Patients with a history of inadequate response	
Intervention	SUCRA score
Ustekinumab	0.808
Guselkumab	0.655
Risankizumab	0.523
Mirikizumab	0.51
Placebo	0.004
Overall patients	
Intervention	SUCRA score
Risankizumab	0.87
Guselkumab	0.78
Ustekinumab	0.488
Mirikizumab	0.361
Placebo	0

Induction of Endoscopic Remission	
Patients without a history of inadequate response	
Intervention	SUCRA score
Risankizumab	0.873
Guselkumab	0.627
Placebo	0
Patients with a history of inadequate response	
Intervention	SUCRA score
Guselkumab	0.897
Risankizumab	0.516
Placebo	0.087
Overall patients	
Intervention	SUCRA score
Risankizumab	0.73
Guselkumab	0.7
Mirikizumab	0.477
Placebo	0.093

Supplementary Figure 6 Surface Under the Cumulative Ranking (SUCRA) for the induction phase

Maintenance of Clinical Remission	
Patients without a history of inadequate response	
Intervention	SUCRA score
Guselkumab	0.922
Mirikizumab	0.566
Risankizumab	0.544
Ustekinumab	0.458
Placebo	0.01
Patients with a history of inadequate response	
Intervention	SUCRA score
Guselkumab	0.928
Mirikizumab	0.735
Ustekinumab	0.547
Risankizumab	0.289
Placebo	0.002
Overall patients	
Intervention	SUCRA score
Guselkumab	0.816
Mirikizumab	0.737
Ustekinumab	0.491
Risankizumab	0.421
Placebo	0.035

Maintenance of Corticosteroid-free Clinical Remission	
Patients without a history of inadequate response	
Intervention	SUCRA score
Guselkumab	0.894
Mirikizumab	0.601
Risankizumab	0.558
Ustekinumab	0.436
Placebo	0.011
Patients with a history of inadequate response	
Intervention	SUCRA score
Guselkumab	0.961
Mirikizumab	0.691
Ustekinumab	0.556
Risankizumab	0.289
Placebo	0.003
Overall patients	
Intervention	SUCRA score
Guselkumab	0.958
Mirikizumab	0.693
Ustekinumab	0.503
Risankizumab	0.346
Placebo	0

Maintenance of Endoscopic Improvement	
Patients without a history of inadequate response	
Intervention	SUCRA score
Guselkumab	0.853
Mirikizumab	0.644
Risankizumab	0.527
Ustekinumab	0.473
Placebo	0.003
Patients with a history of inadequate response	
Intervention	SUCRA score
Guselkumab	0.963
Mirikizumab	0.706
Ustekinumab	0.502
Risankizumab	0.328
Placebo	0.001
Overall patients	
Intervention	SUCRA score
Guselkumab	0.931
Mirikizumab	0.758
Ustekinumab	0.47
Risankizumab	0.341
Placebo	0

Maintenance of Clinical Remission	
Patients without a history of inadequate response	
Intervention	SUCRA score
Mirikizumab	0.971
Risankizumab	0.475
Placebo	0.054
Patients with a history of inadequate response	
Intervention	SUCRA score
Mirikizumab	0.957
Risankizumab	0.542
Placebo	0.001
Overall patients	
Intervention	SUCRA score
Mirikizumab	0.98
Ustekinumab	0.601
Risankizumab	0.418
Placebo	0

Maintenance of Endoscopic remission	
Patients without a history of inadequate response	
Intervention	SUCRA score
Guselkumab	0.829
Risankizumab	0.645
Placebo	0.026
Patients with a history of inadequate response	
Intervention	SUCRA score
Guselkumab	0.96
Risankizumab	0.486
Placebo	0.054
Overall patients	
Intervention	SUCRA score
Guselkumab	0.837
Mirikizumab	0.571
Risankizumab	0.499
Placebo	0.499

Maintenance of HEMI	
Patients without a history of inadequate response	
Intervention	SUCRA score
Guselkumab	0.864
Risankizumab	0.633
Placebo	0.003
Patients with a history of inadequate response	
Intervention	SUCRA score
Guselkumab	0.991
Risankizumab	0.508
Placebo	0.001
Overall patients	
Intervention	SUCRA score
Guselkumab	0.983
Risankizumab	0.517
Placebo	0

Incedence of any adverse events at the end of Maintenance	
Overall patients	
Intervention	SUCRA score
Guselkumab	0.746
Placebo	0.662
Ustekinumab	0.476
Mirikizumab	0.319
Risankizumab	0.297

Incedence of serious infection at the end of Maintenance	
Overall patients	
Intervention	SUCRA score
Guselkumab	0.883
Placebo	0.598
Ustekinumab	0.439
Mirikizumab	0.297
Risankizumab	0.283

Supplementary Figure 7 Surface under the cumulative ranking (SUCRA) for the maintenance phase