

# IL-23p19 Antagonists vs Ustekinumab for Treatment of Crohn's Disease: A Meta-Analysis of Randomized Controlled Trials

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**INTRODUCTION:** We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing interleukin (IL)-23p19 antagonists with ustekinumab, stratified by prior biologic exposure, in patients with moderate-to-severe Crohn's disease (CD).

**METHODS:** Through a systematic review through August 17, 2024, we identified phase 2 and 3 RCTs comparing IL-23p19 antagonists vs ustekinumab in adults with moderate-to-severe CD. The primary outcome was achieving clinical remission at ~1 year, and secondary outcomes were achieving endoscopic remission and serious adverse events. We performed subgroup analyses based on prior exposure to biologic therapy, primarily tumor necrosis factor antagonists. Certainty of evidence was appraised using the Grading of Recommendations Assessment, Development, and Evaluation approach.

**RESULTS:** We included 5 head-to-head RCTs with a treat-through design (n = 2,506), of which 1 was conducted exclusively in patients with prior tumor necrosis factor antagonist exposure. On meta-analysis, patients treated with IL-23p19 inhibitors may be more likely to achieve clinical remission (relative risk [RR], 1.18 95% confidence interval [CI] 1.02–1.36) (low certainty of evidence) and endoscopic remission (RR 1.53, 95% CI 1.07–2.20) compared with ustekinumab. On subgroup analysis, IL-23p19 antagonists are probably more efficacious than ustekinumab in patients with prior biologic exposure (clinical remission: RR 1.31, 95% CI 1.16–1.48; endoscopic remission: RR 1.61, 95% CI 1.27–2.05) (moderate to high certainty), but not in biologic-naïve patients (clinical remission: RR 0.99, 95% CI 0.90–1.08; endoscopic remission: RR 1.16, 95% CI 0.82–1.65). IL-23p19 antagonists may be associated with a lower risk of serious adverse events as compared with ustekinumab (RR 0.79, 95% CI 0.61–1.02).

**DISCUSSION:** IL-23p19 antagonists are probably more efficacious and safer than ustekinumab in patients with moderate-to-severe CD in patients with prior biologic exposure, but not in biologic-naïve patients.

**KEYWORDS:** inflammatory bowel disease; head-to-head trials; risankizumab; guselkumab; comparative efficacy

**SUPPLEMENTARY MATERIAL** accompanies this paper at <http://links.lww.com/AJG/D597>

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## INTRODUCTION

Treatment options for patients with moderate-to-severe Crohn's disease (CD) have increased in the past decade, with multiple different classes of medications targeting different pathways of inflammation. Interleukin (IL)-23 has emerged as a critical cytokine that is responsible for the differentiation of proinflammatory CD4<sup>+</sup> Th17 cells and stimulation of other type 17 immune cells including  $\gamma\delta$  T cells, natural killer T cells, mucosal-invariant T cells, and IL-17-secreting innate lymphoid cells. IL-23 is a heterodimeric cytokine with a p40 and p19 subunit, of which p40 is shared with IL-12 (1,2). Ustekinumab, a biologic that targets the p40 subunit and therefore both IL-12 and IL-23, has been approved for treatment of CD since 2016 (3). Subsequently, monoclonal antibodies targeting the p19 subunit and selectively blocking IL-23 have been shown to have greater efficacy in several immune-mediated conditions such as psoriasis compared to ustekinumab (4,5). Recently, several IL-23p19 antagonists have been approved or at advanced stages of approval for treatment of moderate-to-severe CD including risankizumab, mirikizumab, and guselkumab (6).

With availability of both IL-12/23 antagonists and more selective IL-23 antagonists, it is critical to understand the comparative efficacy and safety of these agents to inform their positioning in the treatment algorithm for CD. In the SEQUENCE trial of patients with moderate-to-severe CD with prior tumor necrosis factor (TNF)- $\alpha$  antagonist exposure, a higher proportion of patients treated with risankizumab compared with ustekinumab achieved clinical and endoscopic remission (7). Since then, several trials comparing IL-23p19 antagonists with ustekinumab in broader populations of biologic-naive and biologic-exposed patients have been conducted showing variable results. Hence, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) in adults with moderate-to-severe CD comparing IL-23p19 antagonists vs ustekinumab, stratified by prior biologic exposure.

## METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guideline (8).

### Study selection

We identified phase 2 or 3 RCTs that met the following inclusion criteria: (i) Patients: adults (age  $\geq 18$  years) with moderately to severely active CD who were either TNF antagonist-naive or previously exposed to TNF antagonist therapy; (ii) Intervention: IL-23p19 antagonists either approved or at advanced stages of development (risankizumab, mirikizumab, guselkumab); (iii) Comparator: ustekinumab as an active comparator, with or without an alternative placebo arm; (iv) Outcome: clinical remission and/or endoscopic remission at 48–52 weeks.

We excluded trials of alternative anti-IL-23p19 (e.g., brazikumab, tildrakizumab) or anti-IL12/23p40 (e.g., briakinumab, apilimod mesylate) that are not being pursued for regulatory approval and pediatric studies.

### Search strategy, data abstraction, and risk of bias assessment

We conducted a comprehensive search of multiple electronic databases through August 17, 2024. The databases included MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (via Ovid), as well as clinical trial registries. The

search strategy was designed and implemented by an experienced medical librarian, using controlled vocabular as well as text words, for RCTs of biologic therapy and small molecules in patients with CD. Details of the search strategy are shown in Supplementary Table 1 (see Supplementary Digital Content 1, <http://links.lww.com/AJG/D597>). We searched the bibliographies of these selected articles, systematic reviews, and clinical trial registries ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) to identify any additional studies. We reviewed abstracts from major gastroenterology conferences (Digestive Disease Week, American College of Gastroenterology annual meeting, European Crohn's and Colitis Organization annual meeting, and United European Gastroenterology Week) from 2022 to 2024 to identify additional abstracts on the topic. Finally, we contacted experts in the field to identify other unpublished studies.

Two sets of investigators independently reviewed the title and abstract of studies identified in the search to exclude studies that did not address the research question of interest based on pre-specified inclusion and exclusion criteria. The full text of the remaining articles was examined to determine whether it contained relevant information. Conflicts in study selection at this stage were resolved by consensus.

Data on study, participant, disease, and treatment-related characteristics were abstracted onto a standardized form, by 2 sets of investigators independently, and discrepancies were resolved by consensus. Two sets of study investigators independently rated the quality of included trials using the Cochrane Risk of Bias Tool version 2.0, found in Supplementary Table 2 (see Supplementary Digital Content 1, <http://links.lww.com/AJG/D597>) (9).

### Outcomes

The primary outcome was achieving or maintaining clinical remission at the study end point (CD Activity Index  $< 150$ ). Secondary outcomes of interest were endoscopic remission based on the trial definition, typically Simple Endoscopic Score [SES]-CD  $\leq 4$  or  $\leq 2$  (GALAXI-1), deep remission (combination of clinical remission and endoscopic remission or response), serious adverse events, serious infections, and tolerability (discontinuation of treatment because of adverse events). The timing of outcome assessment was typically 48–52 weeks. When data for multiple doses of the same medication were available, for agents that have received regulatory approval for CD (i.e., risankizumab, ustekinumab), only data for the approved dose and administration was considered, whereas for agents that have not received regulatory approval (guselkumab), all doses were combined; for mirikizumab, only 1 dosing regimen was studied in the head-to-head phase III trial. The denominator used in all trials was based on intention-to-treat analysis, and all dropouts were assumed to be treatment failures for the primary outcome of clinical remission.

### Statistical analysis

We calculated risk ratios (RRs) and corresponding 95% confidence intervals (CIs) using the DerSimonian and Laird random-effects model. Our primary *a priori* defined subgroup analysis was based on prior treatment exposure status (biologic-naive vs biologic-exposed patients, typically TNF antagonist exposure). In this analysis, a *P* value for differences between subgroups of  $< 0.10$  was considered statistically significant. In all RCTs, biologic exposure status was a stratification variable, preserving randomization. We assessed heterogeneity between study-specific

estimates using the inconsistency index ( $I^2$ ) and used cutoffs of 0%–30%, 31%–60%, 61%–75%, and 76%–100% to suggest minimal, moderate, substantial, and considerable heterogeneity, respectively. Owing to the small number of included studies, we did not perform statistical assessment for publication bias. All analyses were performed using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).

### Certainty of evidence

The quality of evidence was judged using the Grading of Recommendations Assessment, Development, and Evaluation framework (10). Using this approach, evidence from RCTs starts at high quality. This evidence can be further rated down for risk of bias in evidence, indirectness, inconsistency, imprecision, and publication bias.

## RESULTS

Our search strategy yielded 4,038 unique studies, updating a prior systematic review from June 2020. From this, we included 5 RCTs with a treat-through design and a total of 2,506 adult patients with moderate-to-severe CD, comparing risankizumab (SEQUENCE) (7), mirikizumab (VIVID-1) (11), and guselkumab (GALAXI 1, GALAXI 2 and 3) (12,13) with ustekinumab. Two trials of guselkumab were only published as conference proceedings. Baseline characteristics are listed in Table 1. One RCT (SEQUENCE) included only patients with prior exposure to TNF antagonists, whereas others included ~50% patients with prior biologic exposure; of patients with prior biologic exposure, >90% had prior exposure to TNF antagonists. Four trials assessed primary and secondary outcomes at week 48, except VIVID-1, which assessed week 52 outcomes. Deep remission was defined as a combination of clinical remission and endoscopic remission in all trials, except VIVID-1, in which deep remission was defined as a combination of clinical remission and endoscopic response ( $\geq 50\%$  improvement from baseline in SES-CD or SES-CD  $\leq 2$  for isolated ileal disease); GALAXI-1 did not report deep remission outcome. Four trials were deemed to be at low risk of bias, whereas 1 RCT (SEQUENCE), an open-label trial was deemed to be at high risk of bias for the clinical remission outcome. Overall rate of efficacy and safety outcomes in selected trials is presented in Table 2.

### Overall efficacy and safety

**Clinical remission.** On meta-analysis of 5 RCTs, patients treated with IL-23p19 antagonists were 18% more likely to achieve clinical remission compared with ustekinumab (983/1,600 [61%] vs 467/906 [52%]; RR 1.18, 95% CI 1.02–1.36;  $I^2 = 70\%$ ) (Figure 1). The overall body of evidence was rated as low certainty, being rated down for risk of bias and inconsistency. On *post hoc* sensitivity analysis, after exclusion of mirikizumab, overall results were unchanged.

**Endoscopic remission.** Patients treated with IL-23p19 inhibitors were 53% more likely to achieve endoscopic remission compared with ustekinumab (493/1,600 [31%] vs 199/906 [22%]; RR 1.53, 95% CI 1.07–2.20;  $I^2 = 80\%$ ). The overall body of evidence was rated as moderate certainty, being rated down for inconsistency. On *post hoc* sensitivity analysis, after exclusion of mirikizumab, overall results were unchanged.

**Deep remission.** Patients treated with IL-23p19 antagonists were 46% more likely to achieve deep remission (442/1,416 [31%] vs 174/843 [21%]; RR 1.46, 95% CI 1.14–1.88;  $I^2 = 59\%$ ). On *post hoc*

sensitivity analysis, after exclusion of mirikizumab, overall results were unchanged.

**Safety.** IL-23p19 antagonists were associated with a numerically 21% lower risk of serious adverse events compared with ustekinumab (171/1,707 [10%] vs 123/945 [13%]; RR 0.79, 95% CI 0.61–1.02), although the difference did not achieve statistical significance ( $I^2 = 19\%$ ) (Figure 2). There was no significant difference in the risk of serious infections (31/1,707 [1.8%] vs 33/945 [3.5%]; RR 0.56, 95% CI 0.25–1.24;  $I^2 = 52\%$ ) and treatment discontinuation because of adverse events (95/1,707 [5.6%] vs 49/945 [5.2%]; RR 1.01, 95% CI 0.66–1.53;  $I^2 = 26\%$ ) between IL-23p19 antagonists and ustekinumab (Figure 2). On *post hoc* sensitivity analysis, after exclusion of mirikizumab, overall results were unchanged. There was limited data on what proportion of serious adverse events were related to worsening of underlying CD.

### Subgroup analysis

Prior biologic exposure (almost uniformly prior TNF antagonist exposure, with or without other biologics) was a significant treatment effect modifier, with higher efficacy of IL-23p19 antagonists vs ustekinumab observed only in patients with prior biologic exposure but not in biologic-naïve patients.

**Clinical remission.** Rates of achieving clinical remission were significantly higher with IL-23p19 antagonists vs ustekinumab among biologic-exposed patients (542/937 [58%] vs 263/597 [44%]; RR 1.31, 95% CI 1.16–1.48;  $I^2 = 19\%$ ), compared with biologic-naïve patients (416/626 [66%] vs 194/295 [66%]; RR 0.99, 95% CI 0.90–1.08;  $I^2 = 0\%$ ), with  $P$  value for interaction  $< 0.01$  (Figure 3). The overall body of evidence supporting the higher efficacy of IL-23p19 antagonists compared with ustekinumab for achieving clinical remission in biologic-exposed patients was rated as moderate certainty, being rated down for risk of bias. On *post hoc* sensitivity analysis, after exclusion of mirikizumab, overall results were unchanged.

**Endoscopic remission.** Rates of achieving endoscopic remission were significantly higher with IL-23p19 antagonists vs ustekinumab in biologic-exposed patients (272/937 [29%] vs 108/604 [18%]; RR 1.61, 95% CI 1.27–2.05;  $I^2 = 27\%$ ) but not in biologic-naïve patients (252/626 [40%] vs 102/295 [35%]; RR 1.16, 95% CI 0.82–1.65,  $I^2 = 68\%$ ), with  $P$  value for interaction = 0.13 (Figure 4). The overall body of evidence supporting the higher efficacy of IL-23p19 antagonists compared with ustekinumab for achieving endoscopic remission in biologic-exposed patients was rated as high certainty. On *post hoc* sensitivity analysis, after exclusion of mirikizumab, IL-23p19 antagonists (guselkumab) was superior to ustekinumab in achieving endoscopic remission even in biologic-naïve patients.

## DISCUSSION

As the treatment landscape for CD evolves, there is a pressing need to inform positioning of different therapies. In this systematic review and meta-analysis comparing 2 classes of therapies for treatment of moderate-to-severe CD, we observed that IL-23p19 antagonists may be more efficacious in achieving clinical, endoscopic, and deep remission compared with ustekinumab with low-to-moderate certainty of evidence and may be associated with lower risk of serious adverse events. Importantly, this benefit of IL-23p19 antagonists apparent only in a subset of patients with prior biologic exposure (mostly prior TNF antagonist exposure with or without other advanced therapies) but not

**Table 1. Baseline study and patient characteristics in selected trials**

Study ID	No. of participants	Trial phase	Age (yr) Mean (SD) or median (IQR)	Sex (% male)	Disease duration (yr) Mean (SD) or median (IQR)	Disease location (% IC/IC)	Prior steroid use (%)	Prior biologic failure/TNF failure/anti-integrin failure (%)
Peyrin-Biroulet 2024 (SEQUENCE)	RIS: 255 UST: 265 Total: 520	IIIb	RIS: 38.0 (13.1) UST: 38.3 (13.8)	RIS: 53 UST: 49	RIS: 7.3 (0.3–40.6) UST: 7.3 (0.3–51.9)	RIS: 44/17/40 UST: 43/17/40	RIS: 23 UST: 27	RIS: 100/100/0 UST: 100/100/0
Jairath 2024 (VIVID 1)	MIR: 579 UST: 287 PBO: 199 Total: 1,150	III	MIR: 36.0 (13.2) UST: 36.6 (12.7) PBO: 36.3 (12.7)	MIR: 57 UST: 48 PBO: 59	MIR: 7.4 (8.2) UST: 7.2 (7.7) PBO: 7.8 (7.4)	MIR: 50/11/39 UST: 48/10/42 PBO: 52/10/39	MIR: 31 UST: 31 PBO: 29	MIR: 49/46/12 UST: 48/46/11 PBO: 49/45/12
Danese 2024 (GALAXI 1)	GUS (I) 200–>100 mg: 61 GUS (II) 600–>200 mg: 63 GUS (III) 1,200–>200 mg: 61 UST: 63 PBO: 61 Total: 309	II	GUS (I): 39 (29–49) GUS (II): 37 (26–50) GUS (III): 35 (30–51) UST: 36 (26–42) PBO: 36 (29–47)	GUS (I): 62 GUS (II): 57 GUS (III): 51 UST: 65 PBO: 61	GUS (I): 6.1 (2.3–14.3) GUS (II): 7.6 (2.9–16.2) GUS (III): 4.6 (2.1–9.7) UST: 5.9 (2.1–10.6) PBO: 7.3 (3.5–12.4)	GUS (I): 28/28/44 GUS (II): 37/35/29 GUS (III): 28/21/51 UST: 37/17/46 PBO: 39/18/43	GUS (I): 39 GUS (II): 30 GUS (III): 33 UST: 41 PBO: 39	GUS (I): 52/50/10 GUS (II): 56/56/13 GUS (III): 56/54/5 UST: 59/59/8 PBO: 49/48/8
Panaccione 2024 <sup>a</sup> (GALAXI 2 and 3)	GUS (I) 200–>100: 286 GUS (II) 200–>200: 296 UST: 291 PBO: 148 Total: 1,021	III	GUS (I): 36.0 (12.2) GUS (II): 36.9 (13.3) UST: 37.4 (13.2) PBO: 34.8 (12.2)	GUS (I) 54 GUS (II) 60 UST: 58 PBO: 60	GUS (I): 7.1 (6.7) GUS (II): 7.1 (7.2) UST: 7.3 (7.5) PBO: 7.1 (7.5)	GUS (I): 40/21/40 GUS (II): 35/27/38 UST: 41/19/40 PBO: 37/21/42	GUS (I): 38 GUS (II): 36 UST: 38 PBO: 35	GUS (I): 54/52/9 GUS (II): 50/48/6 UST: 54/51/11 PBO: 53/51/9

C, colonic; GUS, guselkumab; I, ileal; IC, ileocolonic; IQR, interquartile range; MIR, mirikizumab; PBO, placebo; RIS, risankizumab; TNF, tumor necrosis factor antagonist; UST, ustekinumab.

<sup>a</sup>Pooled GALAXI 2 and 3 data.

**Table 2. Efficacy and safety outcomes in selected trials**

Study ID	Clinical remission, %	Endoscopic remission, %	Deep remission, %	Serious AEs, %	Serious infections, %	Treatment discontinuation due to AEs, %
Peyrin-Biroulet 2024 (SEQUENCE)	RIS: 61 UST: 41	RIS: 32 UST: 16	RIS: 23 UST: 11	RIS: 10 UST: 17	RIS: 3 UST: 4	RIS: 4 UST: 5
Ferrante 2024 (VIVID 1)	MIR: 54 UST: 48 PBO: 20	MIR: 29 UST: 28 PBO: 4	MIR: 34 UST: 28 PBO: 6	MIR: 10 UST: 11 PBO: 17	MIR: 2 UST: 3 PBO: 3	MIR: 5 UST: 3 PBO: 10
Danese 2024 (GALAXI 1)	GUS (I): 64 GUS (II): 73 GUS (III): 57 UST: 59	GUS (I): 18 GUS (II): 17 GUS (III): 33 UST: 6	Not available	GUS (I): 8 GUS (II): 7 GUS (III): 7 UST: 13	GUS (I): 3 GUS (II): 3 GUS (III): 1 UST: 1	GUS (I): 7 GUS (II): 3 GUS (III): 8 UST: 8
Panaccione 2024 <sup>a</sup> (GALAXI 2 and 3)	GUS (I): 65 GUS (II): 70 UST: 63	GUS (I): 33 GUS (II): 37 UST: 25	GUS (I): 30 GUS (II): 34 UST: 22	GUS (I): 11 GUS (II): 7 UST: 12	GUS (I): 0 GUS (II): 1 UST: 4	GUS (I): 7 GUS (II): 6 UST: 7

AE, adverse event; C, colonic; GUS, guselkumab; I, ileal; IC, ileocolonic; IQR, interquartile range; MIR, mirikizumab; PBO, placebo; RIS, risankizumab; UST, ustekinumab.

<sup>a</sup>Pooled GALAXI 2 and 3 data.

### IL-23p19 Antagonists vs. Ustekinumab – All patients

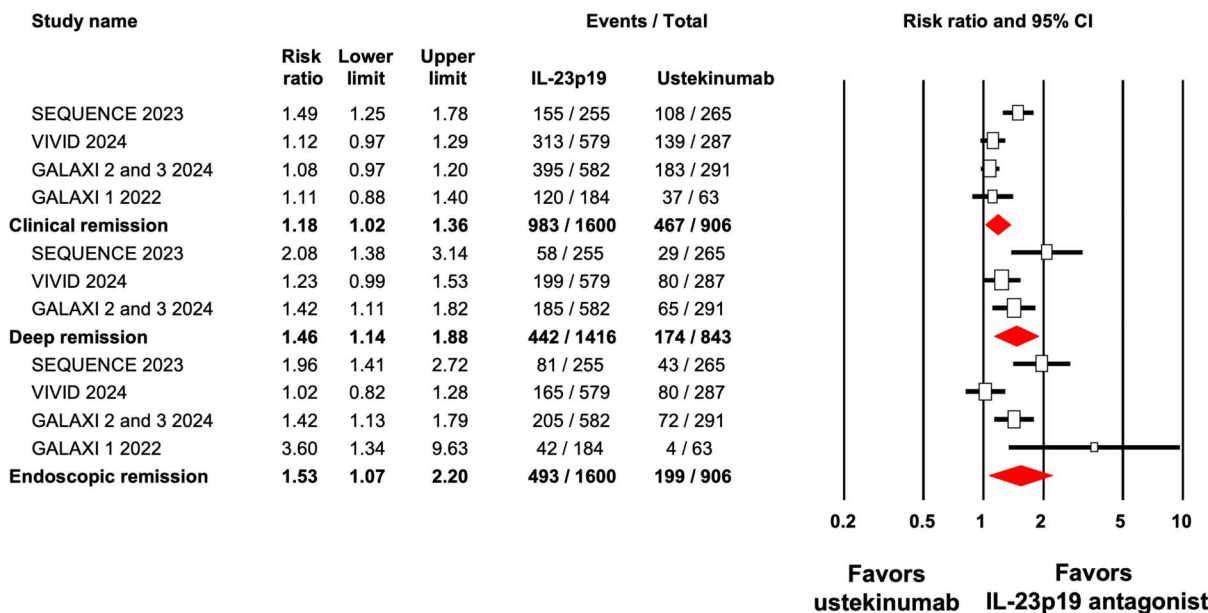


Figure 1. Efficacy of IL-23p19 antagonists vs ustekinumab in patients with moderate-to-severe Crohn's disease on meta-analysis of head-to-head trials. CI, confidence interval; IL, interleukin.

in biologic-naive patients. These findings suggest that IL-23p19 antagonists may be preferred over ustekinumab in patients with moderate-to-severe CD, particularly in patients with prior TNF-antagonist exposure.

These findings are similar to those observed in other immune-mediated diseases such as psoriasis in which treatments targeting

p19 have been shown to have superior efficacy compared with those targeting p40 (14). Although both classes of drugs inhibit IL-23, targeting p19 has more selective and greater affinity binding, potentially leading to a greater reduction of IL-23 levels (15,16). Our findings of higher efficacy of IL-23p19 antagonists only in patients with prior TNF-antagonist exposure but not in

### IL-23p19 Antagonists vs. Ustekinumab – Adverse Events

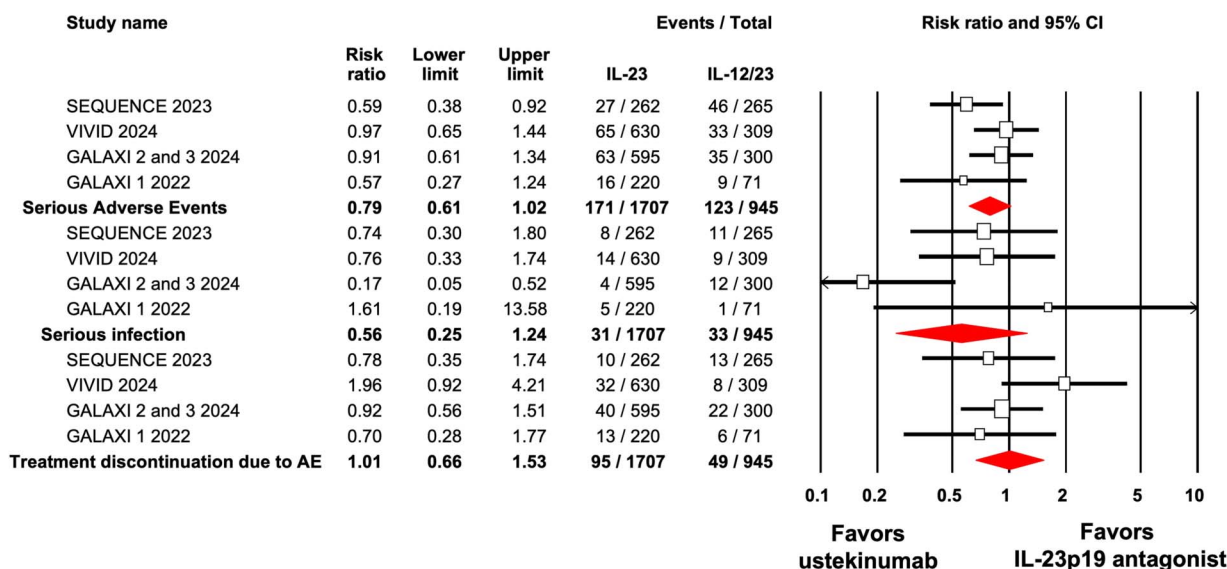
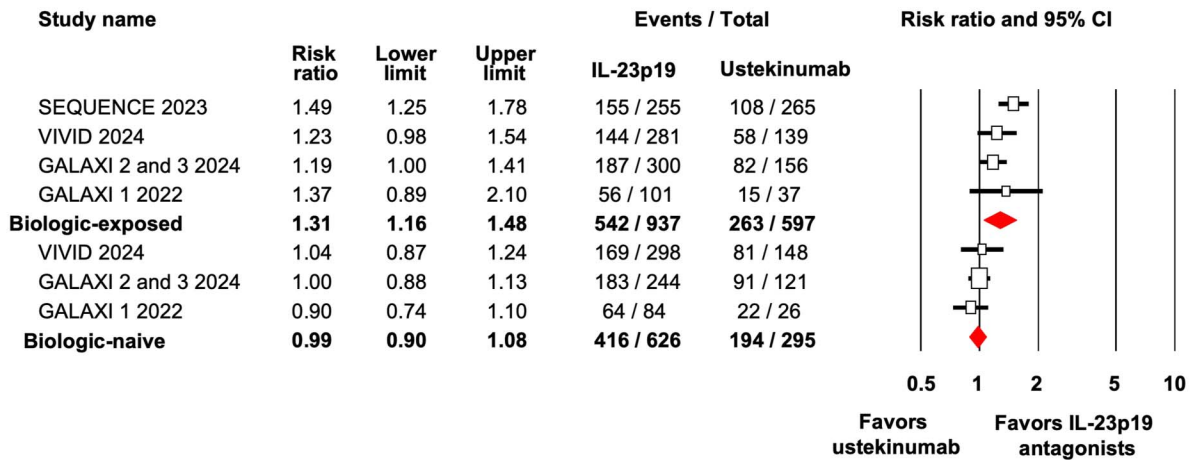


Figure 2. Safety of IL-23p19 antagonists vs ustekinumab in patients with moderate-to-severe Crohn's disease on meta-analysis of head-to-head trials. CI, confidence interval; IL, interleukin.

## IL-23p19 antagonists vs. Ustekinumab – Clinical Remission



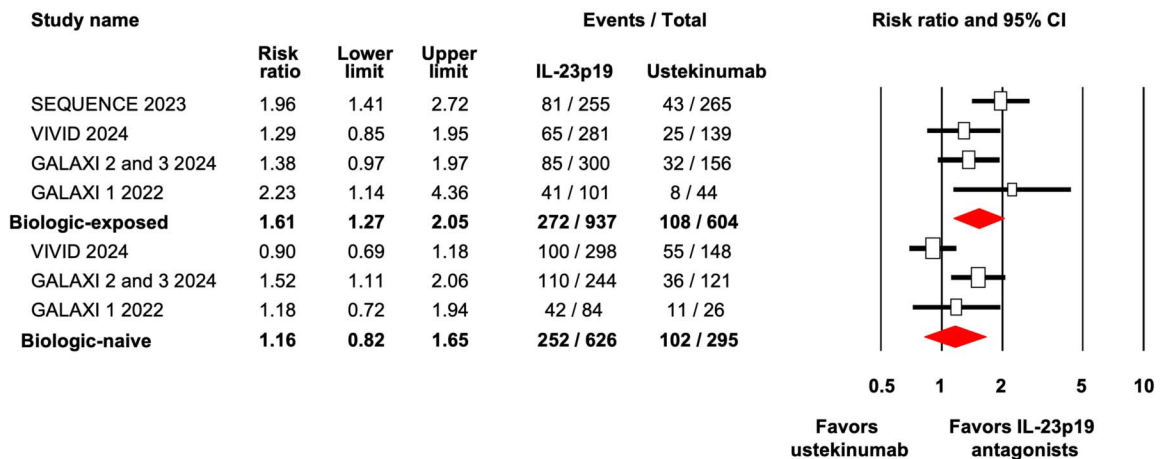
**Figure 3.** Efficacy of IL-23p19 antagonists vs ustekinumab in achieving clinical remission, stratified by prior biologic exposure. CI, confidence interval; IL, interleukin.

TNF-antagonist-naïve patients are intriguing. A recent network meta-analysis further supports the role of anti-IL-23p19 agents in patients with prior biologic failure (17). Intestinal biopsies from patients refractory to TNF antagonists exhibited upregulation of IL-23 receptor by T cells along with increased IL-23p19 but not IL-12p40 expression, indicating molecular resistance to TNF antagonist therapy in these patients and providing a rationale for targeting IL-23 specifically in this population (18). By contrast, in biologic-naïve patients, it has been postulated that initial inflammation may be driven by IL-12 during early disease, whereas chronic inflammation in later stages of disease may be more dependent on IL-23 (19). Hence, ustekinumab may be as effective as IL-23p19 antagonists in patients with CD naïve to advanced therapy, whereas IL-23p19 antagonists may be more efficacious in later, more refractory stages (20). Interestingly, an opposite

finding has been suggested in patients with ulcerative colitis (UC). On analyzing trials of IL-23p19 antagonists and ustekinumab in UC, there was no difference in the magnitude of benefit with IL-23p19 antagonists over placebo in biologic-naïve vs biologic-exposed patients, whereas the magnitude of benefit with ustekinumab over placebo may be higher in patients with prior biologic exposure vs biologic-naïve patients (21).

An alternative explanation for these observed differences in biologic-naïve and biologic-exposed patients may be due to intrinsic differences in the efficacy of different IL-23p19 antagonists, which may have subtle differences in mechanisms of action. For example, mirikizumab was noninferior but not superior to ustekinumab in the VIVID-1 trial, whereas guselkumab was demonstrated to be superior to ustekinumab in phase III trials including all patients with moderate-to-severe CD. By contrast,

## IL-23p19 antagonists vs. Ustekinumab – Endoscopic Remission



**Figure 4.** Efficacy of IL-23p19 antagonists vs ustekinumab in achieving endoscopic remission, stratified by prior biologic exposure. CI, confidence interval; IL, interleukin.

risankizumab has only been compared with ustekinumab in TNF-antagonist-exposed patients (7,11–13). In our analysis, after exclusion of the VIVID-1 trial of mirikizumab, guselkumab was associated with a higher rate of endoscopic remission, but not clinical remission, compared with ustekinumab even in biologic-naïve patients. In patients with UC, risankizumab and guselkumab may also be more efficacious than mirikizumab based on indirect treatment comparison (22,23). However, any inferences regarding differences in the efficacy of individual IL-23 antagonists should be made with caution given the nuances in trial design for each agent and the varying efficacy of ustekinumab in these trials. Further studies evaluating different IL-23p19 antagonists vs ustekinumab and against each other, stratified by type and number of biologic failures and disease duration, will be required to understand the role of these treatments in the management of CD.

We observed a favorable safety profile of IL-23p19 antagonists compared with ustekinumab, with a trend toward lower incidence of serious adverse events, although no differences were observed in the risk of serious infections or tolerability. Although we do not have details of the nature of adverse events, one of the most common serious adverse events in RCTs of CD is worsening of underlying IBD (24). Hence, these findings may reflect higher efficacy of IL-23p19 antagonists, rather than a true difference in drug-related safety, although this is speculative at this point. Long-term safety data for IL-23p19 antagonists in CD are not yet available. However, data in psoriasis have not identified any concerning issues with IL-23p19 antagonists or ustekinumab, with the latter showing favorable safety profiles with over 5 years of follow-up in CD (25–27).

Although our novel and rigorous synthesis provides actionable findings for clinical practice, we acknowledge several limitations. First, there is an inherent paucity of head-to-head trials in the field, and we included 5 RCTs in our synthesis. Second, there was considerable heterogeneity in the overall analysis. This was at least partly explained by prior biologic exposure status. Beyond biologic exposure status, inclusion of different IL-23p19 antagonists and subtle differences in outcome definition for endoscopic remission and deep remission may contribute to observed heterogeneity. Third, there were limited data on other potential treatment effect modifiers such as disease duration and disease location. Finally, data from pivotal phase III trials of guselkumab were obtained from conference proceedings, and the findings may occasionally change with updated analyses during peer review.

In summary, there is moderate-certainty evidence that IL-23p19 antagonists are probably more efficacious and maybe safer than ustekinumab in patients with moderate-to-severe CD with prior TNF antagonist exposure. These benefits were not observed in patients who were naïve to advanced therapies. Future clinical studies on how prior exposure to non-TNF-targeting advanced therapies modifies treatment efficacy of IL-23p19 antagonists over ustekinumab and future mechanistic studies on why TNF antagonist exposure potentiates the efficacy of IL-23p19 antagonists over ustekinumab are warranted.

#### CONFLICTS OF INTEREST

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**Specific author contributions:** S.S. and V.J.: study concept and design. Y.Y., S.K.V., V.J., and S.S.: acquisition, analysis and interpretation of data. C.D. and S.S.: drafting of the manuscript. Y.Y.,

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## Study Highlights

### WHAT IS KNOWN

- Both interleukin (IL)-12/23 antagonists such as ustekinumab and more selective IL-23p19 antagonists such as risankizumab, mirikizumab, and guselkumab are effective for the treatment of Crohn's disease.

### WHAT IS NEW HERE

- IL-23p19 antagonists are probably more efficacious than ustekinumab in achieving clinical and endoscopic remission in patients with prior TNF antagonist exposure.

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