How to Choose Among Interleukin-23 Inhibitors for Inflammatory Bowel Disease

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Abstract: Interleukin (IL)-23 plays a central role in the immunopathogenesis of Crohn's disease (CD) and ulcerative colitis (UC). Recent evidence has shown that intestinal inflammation may be predominantly driven by IL-23, prompting the development of selective IL-23p19 monoclonal antibodies that more precisely target this pathway compared with ustekinumab, a p40 inhibitor that blocks both IL-23 and IL-12. Currently, 3 IL-23p19 inhibitors—risankizumab, mirikizumab, and guselkumab—have shown efficacy in phase 3 trials in CD and UC. Comparative studies show superiority of risankizumab and guselkumab over ustekinumab for key endpoints in CD. Mirikizumab has shown noninferiority with ustekinumab with numerically higher remission in biologic-experienced subgroups. Safety profiles have been favorable across all agents in this drug class. No comparative studies currently exist that match up these 3 agents; therefore, selection in clinical practice will likely be based on practical differences, including induction route (intravenous or subcutaneous), maintenance dose frequency, device type, manufacturer support, and insurance programs. With ongoing utilization, real-world evidence may clarify optimal sequencing and comparative effectiveness, as well as long-term safety. Overall, IL-23 inhibitors represent a major advance in IBD management, offering a highly effective and well-tolerated treatment. This article summarizes these individual clinical trial data, available comparative data, and practical real-world considerations.

Keywords
Ulcerative colitis, Crohn's disease, inflammatory bowel disease, interleukin-23, biologics

Crohn's disease (CD) and ulcerative colitis (UC) are idiopathic inflammatory diseases of the digestive tract with rising incidence and prevalence. Inflammatory bowel disease (IBD) is associated with substantial morbidity and reduced quality of life. Disease pathogenesis in CD and UC is multifactorial, with complex interactions between genetic susceptibility, environmental exposures, and immune dysregulation. Variants in the interleukin (IL)-23 signaling pathway are genetic risk factors for IBD.[1] IL-23 is a regulator of downstream inflammatory responses directed toward the IL-17 pathway, which is present in the gut. IL-23 inhibition is less systemic and more tissue specific than anti–tumor necrosis factor (TNF) therapies, a separate class of medications effective in the management of IBD.[2] Ustekinumab was the first US

Table 1. Primary Endpoints and Outcomes in Phase 3 Trials of IL-23 and IL-12/23 Inhibitors in IBD

Trial	Indication	Phase/design	Time to endpoint	Primary endpoint	Results (*P* value)
Ustekinumab					
UNITI-1 2016	CD (anti-TNF failure)	Phase 3, DB, PC	6 weeks	Clinical response	34.3% (UST 130 mg) vs 21.5% (PBO) (*P*≤.003)
UNITI-2 2016	CD (conventional Tx failure)	Phase 3, DB, PC	6 weeks	Clinical response	51.7% (UST 130 mg) vs 28.7% (PBO) (*P*≤.001)
IM-UNITI 2016	CD (maintenance)	Phase 3, DB, withdrawal	44 weeks	Clinical remission	53.1% (UST Q8W), 48.8% (UST Q12W) vs 35.9% (PBO) (*P*=.005 and *P*=.04)
UNIFI 2019	UC (induction + maintenance)	Phase 3, DB, PC	8 weeks 44 weeks	• Induction: Clinical remission • Maintenance remission	• 15.5% (UST) vs 5.3% (PBO) (*P*<.001) • 43.8% (UST Q8W) vs 24.0% (PBO) (*P*<.001)
Risankizumab					
ADVANCE 2022	CD (induction)	Phase 3, DB, PC	12 weeks	• Clinical remission • Endoscopic response	• 45% (RIS 600 mg), 42% (RIS 1200 mg) vs 25% (PBO) • 40% (RIS 600 mg), 32% (RIS 1200 mg) vs 12% (PBO) (*P*≤.0001)
MOTIVATE 2022	CD (bio-IR induction)	Phase 3, DB, PC	12 weeks	• Clinical remission • Endoscopic response	• 42% and 40% (RIS 600 mg and 1200 mg) vs 20% (PBO) • 29% and 34% (RIS 600 mg and 1200 mg) vs 11% (PBO) (*P*≤.0001)
FORTIFY 2022	CD (maintenance)	Phase 3, DB, withdrawal	52 weeks	• Clinical remission • Endoscopic response	• 52% (RIS 360 mg), 55% (RIS 180 mg) vs 41% (PBO) (*P*<.05, *P*<.05) • 47% (RIS) vs 22% (PBO)
INSPIRE / COMMAND 2024	UC (induction & maintenance)	Phase 3, DB, PC	12 weeks 52 weeks	• Induction: Clinical remission • Maintenance: Clinical remission	• 20.3% (RIS) vs 6.2% (PBO) (Δ14%, *P*<.001) • 40.2% (RIS 180 mg), 37.6% (RIS 360 mg) vs 25.1% (PBO) (*P*<.001, *P*<.01)
Mirikizumab					
LUCENT-1 / LUCENT-2 2023	UC (induction & maintenance)	Phase 3, DB, PC	12 weeks 40 weeks	• Induction remission • Maintenance remission	• 24.2% (MIR) vs 13.3% (PBO) • 49.9% (MIR) vs 25.1% (PBO) (*P*<.001)
VIVID-1 2025	CD (induction & maintenance)	Phase 3, DB, active vs UST and PBO	12 weeks 52 weeks	• Week 52 CDAI clinical remission-composite • Week 52 endoscopic response-composite	• CDAI composite 45.4% (MIR) vs 19.6% (PBO) (*P*<.0001) • Endoscopic composite 38% (MIR) vs 9% (PBO) (*P*<.0001); noninferior to UST
Guselkumab					
GALAXI-2 / GALAXI-3 2024	CD	Phase 3, DB, PC, treat-through	12 weeks 48 weeks	Clinical response + remission/endoscopic response composites	Met both coprimary endpoints; superior to UST (*P*<.001)
GRAVITI 2025	CD	Phase 3, DB, PC, SC treat-through	12 weeks	• Clinical remission • Endoscopic response	• 56.1% (GUS) vs 21.4% (PBO) • 41.3% (GUS) vs 21.4% (PBO) (*P*<.001)
QUASAR 2025	UC	Phase 3, DB, PC	12 weeks 44 weeks	• Induction clinical remission • Maintenance clinical remission	• 22.6% (GUS) vs 7.9% (PBO) • 50% (GUS Q4W), 45% (GUS Q8W) vs 19% (PBO) (*P*<.001)
ASTRO 2025	UC	Phase 3, DB, PC, SC treat-through	12 weeks	Induction clinical remission	27.6% (GUS) vs 6.5% (PBO) (*P*<.001)

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Table 1. *(Continued)* Primary Endpoints and Outcomes in Phase 3 Trials of IL-23 and IL-12/23 Inhibitors in IBD

Trial	Indication	Phase/design	Time to endpoint	Primary endpoint	Results (*P* value)
Risankizumab vs ustekinumab					
SEQUENCE 2024	CD (head-to-head)	Phase 3b, open-label, active-controlled	24 weeks 48 weeks	• Clinical remission • Endoscopic remission	• 58.6% (RIS) vs 39.5% (UST) (noninferior) • 31.8% (RIS) vs 16.2% (UST) (superior, *P*<.001)

Bio-IR, biologic-inadequate responder; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; DB, double-blind; GUS, guselkumab; IBD, inflammatory bowel disease; IL, interleukin; MIR, mirikizumab; PBO, placebo; PC, placebo-controlled; PRO, patient-reported outcome; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; RIS, risankizumab; SC, subcutaneous; TNF, tumor necrosis factor; Tx, treatment; UC, ulcerative colitis; UST, ustekinumab.

Food and Drug Administration (FDA)–approved drug that targeted the IL-23 signaling pathway; this human monoclonal antibody inhibits the p40 subunit of both IL-12 and IL-23 from binding to the IL-12RB1 receptors, which are expressed on the surface of immune cells.[3] Blocking the p40 subunit also inhibits the T-helper (Th) 1 and Th17 cytokine pathways, which may be involved in inflammation in CD and UC.[4]

Given increasing evidence of IL-23 as a key upstream cytokine in the Th17-mediated intestinal inflammation, selective inhibition of the p19 subunit provides a more targeted blockade of IL-23 alone. This is hypothesized to be more effective at modulating inflammation than inhibiting the p40 subunit.[5] Such mechanistic insights have led to the development of several human monoclonal antibodies that target only the p19 subunit and thereby selectively inhibit IL-23. These include risankizumab (Skyrizi, AbbVie), a humanized immunoglobulin (Ig) G1 monoclonal antibody; mirikizumab (Omvoh, Eli Lilly), a humanized IgG4 monoclonal antibody; and guselkumab (Tremfya, Janssen), a fully human IgG1-λ monoclonal antibody. Guselkumab additionally binds to cluster of differentiation 64 (CD64), a receptor highly expressed on myeloid cells found in the inflamed colonic tissue of IBD patients. Binding CD64 is theorized to allow guselkumab to block IL-23 at its source; however, the clinical significance of this remains unclear.[6] The availability of multiple drugs with the same mechanism poses new questions of how to choose between them. This article focuses on IL-23 inhibitor therapies, summarizing individual clinical trial data, available comparative data, and practical real-world considerations.

Clinical Trials

Ustekinumab

Ustekinumab was FDA-approved in 2016 for moderate-to-severe CD based on the UNITI-1 and UNITI-2 trials.[3] These were double-blind, placebo-controlled phase 3 studies of patients in whom anti-TNF therapies (UNITI-1) and conventional therapies, including azathioprine, mercaptopurine, methotrexate, and glucocorticoids (UNITI-2), had previously failed. Patients received a single dose of 130 mg intravenous (IV) ustekinumab, 6 mg/kg IV ustekinumab, or placebo. Clinical response rates at week 6 (primary outcome) were significantly higher in the IV ustekinumab groups than in patients receiving placebo (34.3% and 33.7% compared with 21.5%, respectively, in UNITI-1, and 51.7% and 55.5% compared with 28.7%, respectively, in UNITI-2). For all clinical trials discussed, corresponding *P* values and statistical comparisons are reported in Table 1.

Patients who completed the induction trial were then enrolled in IM-UNITI, where they were randomly assigned to receive maintenance with either subcutaneous (SC) injections of 90 mg of ustekinumab (at 8- and 12-week intervals) or placebo. The primary outcome of the maintenance trial was clinical remission at week 44, which was achieved by 53.1% and 48.8% of patients receiving ustekinumab every 8 and 12 weeks, respectively, compared with 35.9% on placebo. Every-8-week dosing was more effective; therefore, the current recommended dosing of ustekinumab in the United States is a single 6 mg/kg IV induction dose followed by 90 mg SC every 8 weeks, or every 12 weeks in the European Union and Japan.

Ustekinumab was FDA-approved in 2019 for moderate-to-severe UC based on the UNIFI clinical trial.[7] Patients were randomly assigned to a single induction dose of IV ustekinumab (130 kg or 6 mg/kg) or placebo. Those who had clinical response to induction therapy after 8 weeks were randomly assigned to SC maintenance 90 mg ustekinumab every 12 or 8 weeks or placebo. Approximately 50% of patients had a history of failure with biologics. Primary endpoints of both induction and maintenance trials were clinical remission. The patients who received ustekinumab 6 mg/kg had significantly higher rates of clinical remission at week 8 than placebo (15.5% compared with 5.3%). Approximately, 54% of

patients with clinical response entered the maintenance trial, where clinical remission rates at week 44 were significantly higher with ustekinumab at every 12 weeks (38.4%) and 8 weeks (43.8%) than placebo (24.0%). Endoscopic improvement was seen in 51.1% of patients on ustekinumab every 8 weeks compared with 28.6% receiving placebo at week 44. Notably, 7 patients receiving ustekinumab developed cancer (3 cases of nonmelanoma skin cancer) and 1 patient receiving placebo. Additionally, there were 4 cases of opportunistic infections in the ustekinumab-treated group. Overall, there were similar incidences of serious adverse events (SAEs) with ustekinumab 6 mg/kg compared with placebo (3.4% compared with 6.9%); the most common SAE was worsening UC. Based on these results, the recommended dosing of ustekinumab for UC is the same as for CD: 6 mg/kg IV induction dose followed by 90 mg SC every 8 weeks in the United States, or every 12 weeks in the European Union and Japan.

Risankizumab

Risankizumab was the first selective IL-23 inhibitor therapy that was FDA-approved for CD in 2022. ADVANCE and MOTIVATE were randomized, double-blind, placebo-controlled studies in adults with moderate-to-severe CD, which compared the efficacy and safety of risankizumab with placebo for induction.[8] Patients previously had inadequate response or intolerance to biologics (MOTIVATE) or conventional therapy (ADVANCE) and were randomized to receive IV risankizumab (600 mg or 1200 mg) or placebo at weeks 0, 4, and 8. Primary endpoints examined were clinical remission and endoscopic response at week 12.

In ADVANCE, Crohn's Disease Activity Index (CDAI) clinical remission rates were significantly increased with risankizumab at 600 mg and 1200 mg both compared with placebo (45% and 42% vs 25%, respectively). Risankizumab at both doses had higher rates of endoscopic response at week 12 as well. In the MOTIVATE arm (patients previously exposed to biologics), there was also statistically significantly higher clinical remission and endoscopic response rates with both 600 mg and 1200 mg risankizumab dosing compared with placebo. In both studies, the 1200-mg dose yielded no additional efficacy compared with the 600-mg dose; additionally, there were no dose-dependent safety findings.

Patients who had clinical response to risankizumab in the prior trials were then enrolled in the FORTIFY trial and received either SC risankizumab (180 mg or 360 mg) or placebo.[9] Both the 180 mg and 360 mg doses demonstrated statistically significant higher rates of clinical remission and endoscopic response at week 52. There were numerically higher rates of clinical remission and endoscopic response with the higher dose of risankizumab in patients who had prior biologic exposure. AEs were similar across groups, including placebo, with the most common reported events being worsening CD, arthralgia, and headaches.

Subsequently, real-world long-term data showed similar corticosteroid-free clinical remission rates at 12 and 52 weeks at 58% and 50%, respectively.[10] Notably, remission rates in ustekinumab-experienced patients were not statistically lower compared with naive patients.

Risankizumab was subsequently evaluated for use in UC in the INSPIRE and COMMAND studies, which led to its FDA approval for UC in 2024. Adults with moderate-to-severe active UC who had previous exposure to 1 or more conventional therapies, advanced therapies, or both were included in these studies.[11] In the induction trial, patients received 1200 mg of IV risankizumab at weeks 0, 4, and 8 or placebo. Patients with clinical response were rerandomized to receive 180 mg or 360 mg of SC risankizumab or placebo every 8 weeks for 52 weeks. Clinical remission rates were the primary outcomes for both trials. Clinical remission rates at week 12 were statistically significantly higher for risankizumab at 20.3% vs 6.2% for placebo. Approximately half of the patients had a clinical response and proceeded to the maintenance trial, in which clinical remission rates at week 52 were 40.2% for 180 mg, 37.6% for 360 mg, and 25.1% for placebo. Notably, post-hoc analyses of these trials showed that clinical remission rates were higher in the biologic-naive group (29.7% vs 8.4% in the placebo group) compared with biologic-experienced (11.4% vs 4.3% placebo).[12] There were no new safety risks detected within the treatment groups compared with clinical trials in CD.

Mirikizumab

Mirikizumab was the first selective IL-23 agent that was FDA-approved for UC in 2023. Adult patients with moderate-to-severe active UC who had previous inadequate response to conventional treatment, biologic therapy, or tofacitinib were enrolled in the LUCENT-1 and LUCENT-2 phase 3 clinical trials. Patients were allowed to receive oral 5-aminosalicylic acid (5-ASA), glucocorticoids, or immunomodulators during the trial. Those who had previous exposure to IL-12/23 or IL-23 or had failure with more than 3 biologic therapies were excluded. Patients were randomly assigned to receive 300 mg IV mirikizumab or placebo every 4 weeks for 12 weeks for induction.[13] Those who had clinical response during the induction trial were then randomized to 200 mg SC mirikizumab or placebo every 4 weeks for an additional 40 weeks. Primary endpoints for both trials were clinical remission. Patients who received mirikizumab had significantly higher rates of clinical remission at the end of

the induction period at week 12 compared with placebo (24.2% vs 13.3%, respectively). Endoscopic remission (Mayo score of 0 or 1, excluding friability) was achieved by 36.3% of patients on mirikizumab compared with 21.1% on placebo. Of those in the induction trial, approximately 42% had clinical response and underwent randomization again into the maintenance trial. At week 40, patients who received mirikizumab had statistically significantly higher rates of clinical remission than those who received placebo (49.9% vs 25.1%, respectively); endoscopic remission was achieved in 36.8% vs 9.2%, respectively. The most frequent AEs were nasopharyngitis and arthralgias, which were more common in the mirikizumab group than in the placebo group.

Subsequently, mirikizumab was evaluated in the VIVID-1 phase 3, randomized, double-blind, placebo-controlled treat-through study for CD leading to its FDA approval for CD in 2025.[14] Adult patients with moderate-to-severe CD and previous exposure to biologic or conventional therapies were randomly assigned to mirikizumab 900 mg IV at weeks 0, 4, and 8 and then 300 mg SC every 4 weeks until week 52, ustekinumab 6 mg/kg IV at week 0 and then 90 mg SC every 8 weeks until week 52, or placebo. The coprimary endpoints were composite endpoints of patient-reported outcome (PRO) clinical response at week 12 and endoscopic response at week 51 (endoscopic response–composite) and PRO clinical response at week 12 and CDAI clinical remission at week 52 (CDAI clinical remission-composite). Mirikizumab was superior to placebo in both coprimary endpoints: the endoscopic response–composite was reached in 38% on mirikizumab compared with 9% on placebo, and CDAI clinical remission–composite was reached in 45.4% compared with 19.6%, respectively. Additionally, mirikizumab was shown to be noninferior to ustekinumab with a noninferiority margin of 10% for clinical remission by week 52 but did not achieve statistical superiority for endoscopic response. Rates of clinical remission and endoscopic response were numerically higher compared with ustekinumab in the patients who were biologic-exposed (51% vs 40% and 45% vs 40%, respectively). The overall AEs and discontinuations were lower in the mirikizumab group compared with placebo.

Guselkumab

Guselkumab was approved for the treatment of both moderate-to-severe active UC in 2024 and CD in 2025. The phase 3 QUASAR trials were two randomized, double-blind, placebo-controlled studies that evaluated guselkumab in patients with moderate-to-severe UC.[15] All patients had previous inadequate response or intolerance to conventional or advanced therapies. They were randomly assigned to receive guselkumab 200 mg IV or placebo at weeks 0, 4, and 8. Those with clinical response at week 12 were then randomly assigned to maintenance therapy with guselkumab 200 mg every 4 weeks or 100 mg every 8 weeks or placebo for 44 weeks. Primary endpoints were clinical remission at induction at week 12 and maintenance at week 44; 22.6% of patients had clinical remission at induction week 12 on guselkumab, compared with 7.9% of patients on placebo. Similarly, clinical remission at maintenance week 44 was achieved by 50% and 45% of guselkumab-treated patients (200 mg every 4 weeks and 100 mg every 8 weeks, respectively) compared with 19% of placebo-treated patients.

ASTRO was a subsequent phase 3 study that investigated the efficacy and safety of fully SC induction and maintenance guselkumab therapy for patients with moderate-to-severe UC who had an inadequate response or intolerance to conventional therapy, prior biologics and/or ozanimod (Zeposia, Bristol Myers Squibb), or Janus kinase inhibitor (JAKi).[16] Patients were randomized to receive guselkumab 400 mg at weeks 0, 4, and 8 for induction followed by guselkumab 200 mg every 4 weeks or guselkumab 100 mg every 8 weeks, or placebo for 48 weeks. The primary endpoint was clinical remission at induction week 12, which was achieved by 27.6% of patients on guselkumab compared with 6.5% of patients on placebo. At week 48 in the maintenance trial, guselkumab at both doses had higher rates of clinical remission when compared with placebo.[17] Additionally, 47.1% and 44.6% of patients had endoscopic improvement (endoscopic subscore of 1, or 1 with no friability) at week 48 on the 200-mg and 100-mg dosing, respectively, compared with placebo at 11.5%. Notably, these results were also seen in the advanced therapy–experienced group (prior biologic, JAKi, or sphingosine-1 phosphate receptor modulator), with 32.7% achieving clinical remission at week 48.

Guselkumab was investigated for CD in the phase 3 GALAXI-2 and GALAXI-3 trials, which were 48-week double-blind, placebo-controlled, triple-dummy, treat-through design studies. In these studies, IV guselkumab was evaluated as induction therapy followed by a SC maintenance phase.[18] Patients were randomized to 200 mg IV guselkumab at weeks 0, 4, and 8 with subsequent SC guselkumab at 200 mg every 4 weeks or 100 mg every 8 weeks, standard dosing ustekinumab, and IV placebo for weeks 0, 4, and 8. At week 12, patients who did not have a clinical response to placebo were then given ustekinumab. Both regimens of guselkumab were superior to placebo for the coprimary composite endpoints of clinical response at week 12 and clinical remission at week 48, and clinical response at week 12 and endoscopic response at week 48. There were no clinically meaningful differences between the maintenance doses of 100 mg every 8 weeks and 200 mg every 4 weeks despite differences in

Table 2. IL-23 Inhibitor Dosing and Route of Administration

Therapy (indication)	Week 0 (route)	Week 4 (route)	Week 8 (route)	Week 12 (route)	Week 16 (route)	Ongoing
Risankizumab (CD)	600 mg (IV)	600 mg (IV)	600 mg (IV)	180 mg or 360 mg (SC) [1 device]		Every 8 weeks
Risankizumab (UC)	1200 mg (IV)	1200 mg (IV)	1200 mg (IV)	180 mg or 360 mg (SC) [1 device]		Every 8 weeks
Mirikizumab (CD)	900 mg (IV)	900 mg (IV)	900 mg (IV)	300 mg (SC) [2 devices]		Every 4 weeks
Mirikizumab (UC)	300 mg (IV)	300 mg (IV)	300 mg (IV)	200 mg (SC) [1 device]		Every 4 weeks
Guselkumab (CD/UC)	200 mg (IV) or 400 mg (SC) [2 devices]	200 mg (IV) or 400 mg (SC) [2 devices]	200 mg (IV) or 400 mg (SC) [2 devices]	200 mg (SC) [1 device]		Every 4 weeks
					100 mg (SC) [1 device]	Every 8 weeks

CD, Crohn's disease; IL, interleukin; IV, intravenous; SC, subcutaneous; UC, ulcerative colitis.

steady-state serum trough concentrations of guselkumab. Additionally, both guselkumab dose regimens were superior to ustekinumab at week 48 in analyses of pooled data for the clinical and endoscopic composite endpoints. AEs were equivalent between the treatment groups, and SAEs were lower in the guselkumab group than in the ustekinumab and placebo groups.

GRAVITI was a phase 3 study that investigated the efficacy of a fully SC induction and maintenance guselkumab therapy. This double-blind, placebo-controlled, treat-through study randomized adults with moderate-to-severe CD to guselkumab 400 mg SC every 4 weeks for induction and then either 200 mg SC every 4 weeks or 100 mg SC every 8 weeks for maintenance, or placebo.[19] Coprimary endpoints were clinical remission and endoscopic response at week 12. At week 12, guselkumab had both statistically significantly increased rates of clinical remission (56.1% vs 21.4%) and endoscopic response (41.3% vs 21.4%) compared with placebo. Therefore, based on these studies, both IV and SC induction with guselkumab were deemed to be effective therapeutic options and were approved for use in CD. Because of these approvals, guselkumab is now also available for both IV and SC induction for the treatment of UC.

FUZION was a phase 3, randomized, double-blind, placebo-controlled multicenter study of CD patients with 1 or more draining perianal fistulae, confirmed by centrally read magnetic resonance imaging.[20] Participants were randomly assigned (2:2:1) to receive guselkumab 200 mg IV at weeks 0 and 4, followed by 100 mg SC every 8 weeks, 200 mg every 4 weeks, or placebo induction and maintenance. The week-24 outcomes were impressive, with higher rates of combined fistula remission in 28.3%, 27.0%, and 10.3%, respectively. This study represented the first such large, randomized, placebo-controlled trial of a CD therapy since the 1999 landmark and the 2004 ACCENT II infliximab trials and suggested that this therapy (or class) may have a role in the treatment of perianal fistulous CD.[21,22]

Comparative Studies

There are currently no head-to-head trials that compare the different IL-23–specific agents. A few studies have compared IL-23–specific agents with the IL-12/23 agent ustekinumab in CD, but there are no studies in UC currently.

In the industry-sponsored, phase 3b, open-label SEQUENCE study, patients with previous failure of an anti-TNF agent were randomized to receive either risankizumab or ustekinumab at standard doses for 48 weeks.[23] The coprimary endpoints were clinical remission (defined as a decrease in CDAI score <150) at week 24 and endoscopic remission (defined as Simple Endoscopic Score for Crohn's Disease ≤4 and at least a 2-point reduction from baseline and no subscore >1 in any individual variable)

Table 3. Patient Support Programs

	First dose program[a]	Bridge program[a]	Patient assistance program	Copay card[a]	Nursing support
Risankizumab		Yes	Yes	$0	Yes
Mirikizumab		Yes	Yes	$5	Yes (virtual only)
Guselkumab	Yes (CD or UC)	Yes	Yes	$0	Yes

CD, Crohn's disease; UC, ulcerative colitis.

[a]Commercial insurance only.

at week 48. Clinical remission rates were 58.6% in the risankizumab arm compared with 39.5% in the ustekinumab arm, showing noninferiority with a margin of 10%. Endoscopic remission rates were 32% in the risankizumab arm compared with 16% in the ustekinumab arm, showing superiority. Based on these trial results, the American College of Gastroenterology CD guidelines now recommend the use of risankizumab over ustekinumab in patients with moderate-to-severe CD with prior anti-TNF exposure.[24] Incidence of AEs was similar between both groups, and no new safety signals were observed.

Within the GALAXI 2/3 trials previously mentioned, SC guselkumab was superior to ustekinumab in the composite endpoint of clinical remission and endoscopic response. This was consistent even in the subgroup of biologic-experienced patients.[18] Within the VIVID-1 trial, mirikizumab was noninferior to ustekinumab for clinical remission (54.1% vs 48.4%) but did not achieve endoscopic response superiority based on the trial design.[14] In the subgroup of biologic-experienced patients, there was a numerically higher proportion of clinical remission and endoscopic response in the mirikizumab group compared with the ustekinumab group, although this was not statistically significant.

Safety

Across the pivotal trials, the IL-23p19 inhibitors have demonstrated a favorable safety profile in both UC and CD.[7-9,11,14-19] The most frequently reported AEs are nasopharyngitis, upper respiratory tract infections, headaches, arthralgias, and injection-site reactions; the majority of these are mild and rarely lead to discontinuation. Rates of serious infection, opportunistic infections, tuberculosis reactivation, and malignancy have not been increased relative to placebo in any phase 3 study, and no major adverse cardiovascular signal has emerged. Although no head-to-head trials have directly compared the IL-23p19 agents with one another, AE rates in the ustekinumab-controlled trials were comparable to or lower than those for ustekinumab, with no new safety signals. Overall, the IL-23 inhibitors are distinguished as a class by their favorable safety profile.

Practical Considerations

All three IL-23 agents have different SC administration devices. The SC formulation (ie, on-body injector cartridge, auto-injector pen, or prefilled syringe) may be important for patients in terms of comfort and ease of injection. Patients may also prefer one agent based on the frequency of self-injection and the number of injections needed (Table 2). Among the 3 agents, mirikizumab is the only agent that requires 2 injection pens for a standard maintenance dose in patients with CD.

Currently (at the time of this publication), all IL-23 agents are available with an IV induction in the United States; however, only guselkumab is available as an SC induction agent for both UC and CD. This may be an important consideration with regards to ease of initiating therapy and allowing for a single insurance approval. A multicenter study evaluating delays to advanced IBD therapies found that IV vs SC/oral administration was associated with more delays.[25,26]

In the United States, patient support programs are important to ensure patients can successfully initiate and maintain therapy. Currently, all IL-23 agents have the availability of a bridge program (commercial insurance only) that requires proof of a prior authorization and appeal denial. Through the bridge program, patients will receive medication from the manufacturer at no cost. Guselkumab for UC or CD offers a first dose program (commercial insurance only) in which patients can obtain medication as fast as 1 day if they qualify (≥18 years of age, commercially insured, diagnosis of UC or CD). All manufacturers provide copay card support (commercial insurance only) to ensure patients' out-of-pocket cost is $0 for guselkumab, $0 for risankizumab, and $5 for mirikizumab (Table 3). Nursing support through the manufacturer is offered with guselkumab (in-person or virtual),

risankizumab (in-person or virtual), and mirikizumab (virtual only) to assist with administration education. It remains to be seen what the impact of ustekinumab biosimilars, which have recently been approved, may be on insurance formularies with respect to IL-23 agents.

Conclusion

IL-23 therapies represent an exciting expansion to our current armamentarium of IBD therapies that are both safe and effective in both biologic-naive and biologic-experienced patients. Head-to-head clinical trial data show superiority of guselkumab and risankizumab over ustekinumab, and noninferiority of mirikizumab vs ustekinumab in CD. Guselkumab and risankizumab also have indications for moderate-to-severe plaque psoriasis and active psoriatic arthritis, which may be an additional consideration when tailoring treatment plans. Use of guselkumab in perianal CD may signify the first therapy since infliximab with a large, placebo-controlled trial showing efficacy in these patients with a challenging phenotype. Although no current direct comparative data are available among the IL-23 agents, some differences, including mode of administration, dosing frequency, and delivery systems, may affect patient preference. Ongoing real-world studies may further define optimal positioning of these agents within IBD management.

Disclosures

Dr Choden has no relevant conflicts of interest to disclose. Dr Choi has served on the speakers bureau for Janssen, AbbVie, and Eli Lilly; and has served as a consultant for Bristol Myers Squibb (BMS), Boehringer Ingelheim, AbbVie, Eli Lilly, Janssen, and Pfizer. Dr Cohen has served as a consultant and as an advisory or scientific advisory board member for AbbVie, Bausch Health, BMS/Celgene, Eli Lilly, Genentech, Gilead Sciences, Johnson & Johnson, Pfizer, and Takeda; and as a data and safety monitoring board member for Reistone Biopharma.

References

1. Sewell GW, Kaser A. Interleukin-23 in the pathogenesis of inflammatory bowel disease and implications for therapeutic intervention. *J Crohns Colitis*. 2022;16(suppl 2):ii3-ii19.
2. Verstockt B, Salas A, Sands BE, et al; Alimentiv Translational Research Consortium (ATRC). IL-12 and IL-23 pathway inhibition in inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol*. 2023;20(7):433-446.
3. Feagan BG, Sandborn WJ, Gasink C, et al; UNITI–IM-UNITI Study Group. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2016;375(20):1946-1960.
4. Deepak P, Loftus EV Jr. Ustekinumab in treatment of Crohn's disease: design, development, and potential place in therapy. *Drug Des Devel Ther*. 2016;10:3685-3698.
5. Korta A, Kula J, Gomułka K. The Role of IL-23 in the pathogenesis and therapy of inflammatory bowel disease. *Int J Mol Sci*. 2023;24(12):10172.
6. Sachen KL, Hammaker D, Sarabia I, et al. Guselkumab binding to $CD64^+$ IL-23-producing myeloid cells enhances potency for neutralizing IL-23 signaling. *Front Immunol*. 2025;16:1532852.
7. Sands BE, Sandborn WJ, Panaccione R, et al; UNIFI Study Group. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2019;381(13):1201-1214.
8. D'Haens G, Panaccione R, Baert F, et al. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. *Lancet*. 2022;399(10340):2015-2030.
9. Ferrante M, Panaccione R, Baert F, et al. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. *Lancet*. 2022;399(10340):2031-2046.
10. Zinger A, Choi D, Choi N, et al. Long-term effectiveness and safety of risankizumab in patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2025;23(10):1817-1823.
11. Louis E, Schreiber S, Panaccione R, et al; INSPIRE and COMMAND Study Group. Risankizumab for ulcerative colitis: two randomized clinical trials. *JAMA*. 2024;332(11):881-897.
12. Panaccione R, Louis E, Colombel JF, et al. Risankizumab efficacy and safety based on prior inadequate response or intolerance to advanced therapy: post hoc analysis of the INSPIRE and COMMAND phase 3 studies. *J Crohns Colitis*. 2025;19(1):jjaf005.
13. D'Haens G, Dubinsky M, Kobayashi T, et al; LUCENT Study Group. Mirikizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2023;388(26):2444-2455.
14. Ferrante M, D'Haens G, Jairath V, et al; VIVID Study Group. Efficacy and safety of mirikizumab in patients with moderately-to-severely active Crohn's disease: a phase 3, multicentre, randomised, double-blind, placebo-controlled and active-controlled, treat-through study. *Lancet*. 2024;404(10470):2423-2436.
15. Rubin DT, Allegretti JR, Panés J, et al; QUASAR Study Group. Guselkumab in patients with moderately to severely active ulcerative colitis (QUASAR): phase 3 double-blind, randomised, placebo-controlled induction and maintenance studies. *Lancet*. 2025;405(10472):33-49.
16. Peyrin-Biroulet L, Allegretti JR, Danese S, et al. OP10 Efficacy and safety of subcutaneous guselkumab induction therapy in patients with ulcerative colitis: results through week 12 from the phase 3 ASTRO study. *J Crohns Colitis*. 2025;19(suppl 1):i19-i20.
17. Allegretti JR, Peyrin-Biroulet L, Long M, et al. Efficacy and safety of subcutaneous guselkumab induction and maintenance therapy in participants with ulcerative colitis: results through week 48 from the phase 3 ASTRO study. Presented at: United European Gastroenterology Week; October 7, 2025; Berlin, Germany. Abstract OP203.
18. Panaccione R, Feagan BG, Afzali A, et al; GALAXI 2 & 3 Study Group. Efficacy and safety of intravenous induction and subcutaneous maintenance therapy with guselkumab for patients with Crohn's disease (GALAXI-2 and GALAXI-3): 48-week results from two phase 3, randomised, placebo and active comparator-controlled, double-blind, triple-dummy trials. *Lancet*. 2025;406(10501):358-375.
19. Hart A, Panaccione R, Steinwurz F, et al; GRAVITI Study Group. Efficacy and safety of guselkumab subcutaneous induction and maintenance in participants with moderately to severely active Crohn's disease: results from the phase 3 GRAVITI study. *Gastroenterology*. 2025;169(2):308-325.
20. Peyrin-Biroulet L. Guselkumab for perianal fistulizing Crohn's disease: week 24 results from the phase 3, randomized, double-blind, placebo-controlled multicenter FUZION study. Presented at: Digestive Disease Week; May 5, 2026; Chicago, IL. Abstract 1058b.
21. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med*. 1999;340(18):1398-1405.
22. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*. 2004;350(9):876-885.
23. Peyrin-Biroulet L, Chapman JC, Colombel JF, et al; SEQUENCE Study Group. Risankizumab versus ustekinumab for moderate-to-severe Crohn's disease. *N Engl J Med*. 2024;391(3):213-223.
24. Lichtenstein GR, Loftus EV, Afzali A, et al. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol*. 2025;120(6):1225-1264.
25. Gottesman S, Xiao K, Nguyen HP, et al. Higher rates of delay in starting advanced inflammatory bowel disease therapies linked to insurance delays, intravenous infusions, and lack of pharmacy support. *Clin Transl Gastroenterol*. 2025;16(3):e00808.
26. Choi D, Kametas M, Gianni J, Han J, Rubin DT. Leveraging interprofessional team-based care in an IBD clinic to transition patients from intravenous to subcutaneous risankizumab-rzaa. *JACCP J Am Coll Clin Pharm*. 2025;8(8):682-687.