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# Efficacy and Safety of Guselkumab for Ulcerative Colitis

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## Abstract

**Introduction:** Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by relapsing–remitting colonic inflammation, where biologic therapies targeting tumor necrosis factor (TNF), integrins, and interleukin (IL) pathways are widely used. Despite available options, a substantial proportion of patients fail to achieve sustained disease remission. Guselkumab, a fully human monoclonal antibody targeting the IL-23p19 subunit, has recently emerged as a novel therapeutic option.

**Methods:** We reviewed available evidence from phase II/III clinical trials, real-world data, and indirect comparisons evaluating the efficacy, safety, and tolerability of guselkumab in patients

with moderate-to-severe UC. Outcomes of interest included clinical remission, endoscopic improvement, health-related quality of life, and incidence of adverse events. Comparisons with established biologics (e.g., infliximab, adalimumab, vedolizumab, ustekinumab, and golimumab) were summarized.

**Results:** The Phase IIb QUASAR study demonstrated significantly higher rates of clinical remission with guselkumab compared to placebo at week 12 (21% vs. 9%; $p<0.05$) and sustained efficacy through maintenance therapy (34% vs. 21% at week 44). Endoscopic improvement and histologic remission were also superior in the guselkumab arm. Safety analyses revealed a favorable profile, with low rates of serious infections, malignancies, and major adverse cardiovascular events. Indirect comparisons suggest that the efficacy and safety of this agent are comparable or superior to those of other IL-23 inhibitors and anti-TNF agents, including golimumab, although head-to-head studies are lacking.

**Conclusion:** Guselkumab is a promising addition to the therapeutic armamentarium for moderate-to-severe UC, offering durable efficacy and a favorable safety profile. Comparative analyses position guselkumab alongside established therapies such as anti-TNFs, anti-α4β7 integrin, and IL-12/23 inhibitors, offering a compelling option in the expanding IL-23 inhibitor class. Further long-term studies and direct comparative trials are warranted to better define its positioning relative to other advanced therapies.

**Keywords:** Ulcerative Colitis, Guselkumab, Interleukin-23, Biologics, Efficacy, Safety, Golimumab, Inflammatory Bowel Disease

## Introduction

Ulcerative colitis (UC) is a chronic, relapsing–remitting inflammatory bowel disease (IBD) characterized by diffuse mucosal inflammation of the colon and rectum. Its incidence and prevalence have been rising globally, contributing to significant morbidity and reduced quality of life [1]. Despite advances in medical therapy, a substantial proportion of patients experience inadequate response, loss of response on the long-term, or intolerance to conventional agents such as aminosalicylates, corticosteroids, thiopurines, and biologics [2]. This therapeutic gap underscores the need for novel treatment strategies targeting alternative pathways of inflammation.

As shown in Figure 1, a growing body of evidence demonstrates involvement of the interleukin (IL)-23/Th17 axis in the pathogenesis of UC. IL-23 promotes expansion and survival of pathogenic Th17 cells. This leads to sustained production of proinflammatory cytokines that perpetuate intestinal inflammation [3]. Consequently, selective blockade of IL-23 has emerged as a promising therapeutic approach. Guselkumab is a fully human monoclonal antibody that targets the p19 subunit of IL-23. It has demonstrated efficacy and safety in several immune-mediated diseases, including psoriasis and psoriatic arthritis [4,5].

Recently, clinical trials have evaluated guselkumab in patients with moderate-to-severe UC, showing encouraging results regarding induction and maintenance of remission [6]. However,

the currently available evidence has not yet been comprehensively synthesized, making it difficult for clinicians and researchers to draw firm conclusions about its place in therapy. A systematic review is therefore warranted to fill this gap by summarizing existing data on the efficacy and safety of guselkumab in UC and providing context for its role within evolving IBD treatment strategies.

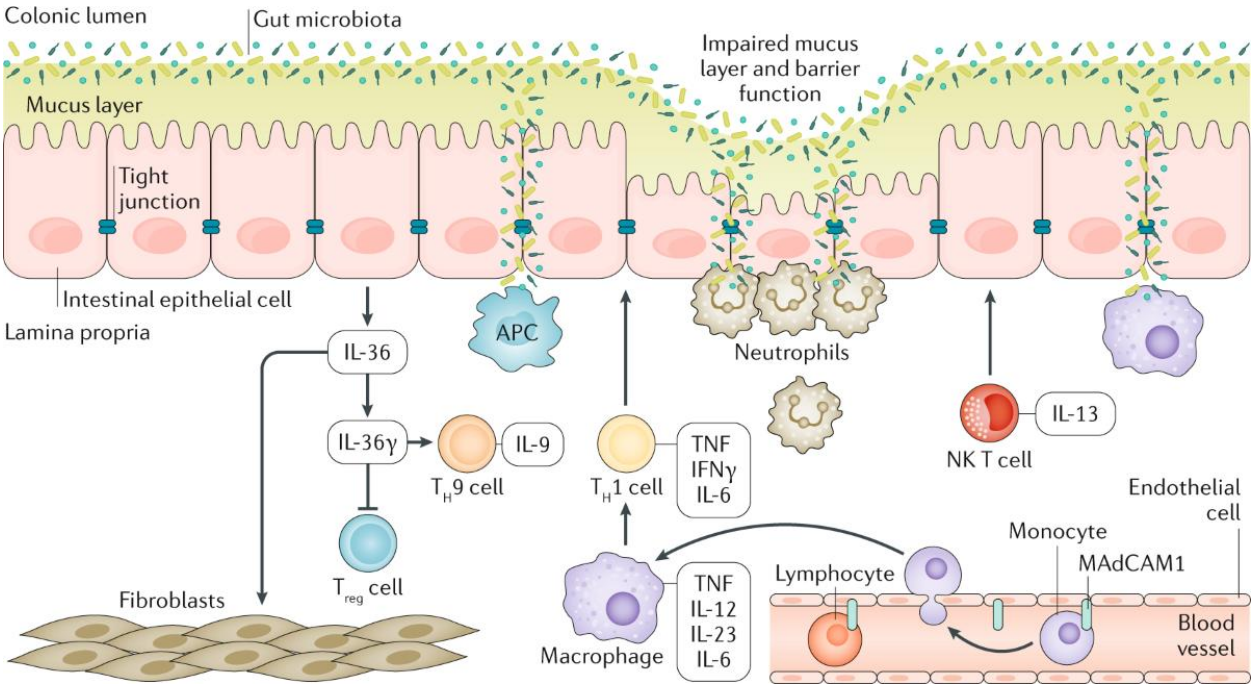


Figure 1: Reproduced from Kobayashi T. et al (2020). Pathogenesis of Ulcerative Colitis [6]

## Pharmacodynamics (PD) — mechanism of action and clinical biomarker effects

Guselkumab, a fully human IgG1λ monoclonal antibody, selectively binds to the p19 subunit of IL-23, preventing IL-23 from engaging the IL-23 receptor on target immune cells. As shown in Figure 1, guselkumab inhibits IL-23 signaling, reducing the expansion and survival of pathogenic Th17/Tc17 cells and downstream production of type-17 effector cytokines (IL-17A/F, IL-22) and related chemokines that drive neutrophil recruitment and mucosal inflammation. In contrast to p40 inhibitors, selective p19 blockade does not inhibit IL-12 signaling, which may contribute to a distinct immunomodulatory profile [7].

Mechanistic and tissue-level pharmacology

In vitro and ex vivo studies show that guselkumab binds IL-23 with high affinity (picomolar-range binding in comparative assays) and sterically prevents IL-23:IL-23R interaction, blocking downstream STAT3/Th17 transcriptional programs. Recent mechanistic work has shown that the native Fc of guselkumab can engage Fcγ receptors such as CD64 (FcγRI) on IL-23–producing myeloid cells, enabling capture/retention of the antibody at the cellular source of IL-23 and potentiating local neutralization in inflamed tissue, a tissue-level mechanism proposed to increase local potency beyond what plasma concentrations alone would predict[8]. This Fc-dependent myeloid-cell capture has been shown in laboratory models to increase neutralization potency compared with p19 antibodies that lack the same Fc interactions [8].

Time course of PD effects and clinical biomarker changes in UC

Within weeks of receiving therapeutic exposure, target engagement and downstream biomarker can be observed. In the QUASAR phase-2b induction study (intravenous induction at weeks 0,4, and 8), guselkumab produced early and clinically meaningful reductions in noninvasive inflammatory biomarkers: markers such as C-reactive protein (CRP) and fecal calprotectin showed significant improvement versus placebo as early as Week 4 and continued through Week 12 [9,10]. These biomarker improvements corresponded to higher rates of clinical response, symptomatic remission and endoscopic and histologic improvement at Week 12, indicating the mechanistic link between IL-23 blockade, biomarker normalization, and mucosal healing [9]. When synthesizing trials, compare the regimen (IV vs SC induction and maintenance dose) because induction exposure and biomarker kinetics differ depending on dosing strategy [9,10].

Biomarker nuance for interpretation

Fecal calprotectin and CRP are useful noninvasive surrogates of mucosal inflammation, but their sensitivity to histologic activity varies; in QUASAR, both noninvasive biomarkers and biopsy-based histology/endoscopy endpoints were included, so response interpretation should take into account both biomarker normalization and direct mucosal assessment [9]. In trials with histologic endpoints, histo-endoscopic mucosal improvement provides stronger evidence of tissue-level disease control than biomarkers alone [9].

## Pharmacokinetics (PK) — absorption, distribution, metabolism/elimination, immunogenicity, DDIs, and population PK

Its PK behavior is consistent with large IgG monoclonal antibodies: slow absorption from subcutaneous (SC) sites (lymphatic uptake), a small apparent volume of distribution primarily confined to plasma and interstitial fluid, catabolic elimination via proteolytic degradation in cells, and an FcRn-mediated salvage pathway that extends half-life. Clinical PK parameters vary slightly by indication and body weight; the numerical values below are based on pooled PopPK modeling and product-label estimates [7]. Table 1 summarizes the pharmacokinetic profile of guselkumab.

Absorption (SC) and formulation differences

Tmax following a single SC injection is usually several days (5–7 days). Absolute bioavailability after a 100-mg SC dose in healthy volunteers was measured to be between 40% and 60% (label reports 49% for some studies), which is consistent with lymphatic absorption and local degradation patterns seen with therapeutic antibodies. Systemic exposure (Cmax, AUC) rises approximately dose-proportionally across the clinical dose range. For ulcerative colitis regimens, higher early exposure is frequently achieved through intravenous (IV) induction dosing (used in some QUASAR arms) to accelerate mucosal exposure, followed by SC maintenance dosing [7].

Distribution

The apparent volume of distribution (steady state) (Vd) is small, with typical estimates of 10–15 L across indications (13.5 L reported in plaque psoriasis and 10.1 L reported in ulcerative colitis). This distribution supports confinement to vascular and interstitial compartments rather than extensive tissue sequestration. Tissue pharmacology (FcγR interactions, local IL-23 capture) may result in higher local potency in inflamed mucosa compared to plasma Vd [7].

Clearance and half-life

Guselkumab clearance is low and its terminal elimination half-life is moderate for an IgG1: population and label-derived estimates place the mean half-life around 15–18 days (label: ~17 days in UC populations; PopPK model-derived t½ 18.1 days). Apparent clearance (CL/F) estimates range from 0.5–0.57 L/day (0.516 L/day reported in psoriasis; 0.531 L/day reported in UC in label data). Standard regimens typically achieve steady-state concentrations in 12–14 weeks [11]. These values support clinical dosing intervals (every 4–8 weeks for maintenance and higher-exposure induction options) [11].

Dose linearity and PopPK model

The observed guselkumab concentrations were well described by a one-compartment linear PK model with first-order absorption and elimination in pooled PopPK analyses. Across the clinically studied range, exposure (Cmax and AUC) increases roughly proportionally to dose. After controlling for covariates, PopPK analyses (large pooled datasets from psoriasis, PsA, Crohn's disease, and UC) revealed broadly similar PK across indications. Although body weight is a key factor in determining exposure (higher weight leads to higher CL and V), weight-based dosing in registration programs [11].

Immunogenicity (anti-drug antibodies, ADA)

The incidence of ADA varies depending on the indication, assay methodology, and duration of follow-up. Pooled ADA analyses were uncommon in the registration program (low single-digit to low-teens percentiles), and the majority of ADAs detected were non-neutralizing. To date, ADA rates in UC trials have been low-to-moderate; high-titer neutralizing antibodies are uncommon, but they can lower trough concentrations in individual patients and lead to loss of response. When pooling ADA data from multiple studies, take into account differences in assay sensitivity and sample collection timing [7].

Metabolism / elimination mechanisms

Guselkumab is not metabolized by cytochrome P450 enzymes; instead, it is eliminated primarily via proteolytic catabolism to peptides and amino acids after cellular uptake (pinocytosis and receptor-mediated endocytosis), with FcRn-mediated recycling reducing catabolism. Target-mediated drug disposition (TMDD) may be important for some antibodies, but guselkumab PK at therapeutic exposures is well described by linear kinetics (TMDD does not dominate elimination at these doses) [7].

Drug–drug interactions (DDI) and CYP considerations

Monoclonal antibodies, such as guselkumab, are not CYP enzyme substrates, inhibitors or inducers; however, cytokine modulation can have indirect effect on hepatic CYP expression. The general clinical rule for cytokine modulators is to monitor narrow therapeutic index drugs metabolized by CYPs when starting or stopping therapy, because inflammation normalization can increase CYP activity and alter small-molecule clearance. Dedicated interaction studies with representative CYP probe substrates have revealed no consistent, clinically relevant direct interactions for guselkumab, so routine co-medication adjustments are not generally required; however clinical vigilance is advised for critical CYP substrates [7].

Exposure–response (ER) and regimen rationale in IBD

Exposure–response analyses from pooled programs show that higher maintained trough concentrations are associated with higher likelihood of clinical and endoscopic response in IBD populations. This supports strategies that use higher IV induction doses to achieve rapid high exposure followed by SC maintenance dosing to maintain troughs associated with a long-lasting response. The reported mean troughs for some UC regimens vary substantially by regimen (see PK Table 1). When comparing efficacy across studies, consider regimen-specific exposure (IV versus SC induction; maintenance dose and frequency) [12].

**Table 1: Pharmacokinetics summary table — (values from label / PopPK / trials)**

| Parameter | Typical value / range (source) |
|---|---|
| Molecular class | Human IgG1λ monoclonal antibody (anti-IL-23 p19) [7]. |
| SC Tmax | 5–7 days (after single SC dose) [7]. |
| SC bioavailability | 40–60% (100 mg SC 49% reported in early studies) [7]. |
| Apparent Vd (V/F) | 10–15 L (psoriasis ~13.5 L; UC ~10.1 L) [7]. |
| Apparent clearance (CL/F) | 0.516 L/day (psoriasis) to 0.531 L/day (UC) [7]. |
| Terminal t½ | 15–18 days (label: 17 days in UC) [7]. |
| Dose linearity | Approximately dose-proportional Cmax and AUC across studied SC dose range (10–300 mg) [7]. |

| Parameter | Typical value / range (source) |
|---|---|
| Typical steady-state troughs (examples) | 100 mg SC q8w: mean trough 1.0–1.4 μg/mL; 200 mg SC q4w: mean troughs substantially higher. Exact troughs vary by PopPK simulations and indication [12]. |
| Immunogenicity (ADA) | Low to moderate incidence (varies by study/assay; most ADAs non-neutralizing; reported UC trial cumulative ADA rates vary by follow-up) [7]. |

Notes: SC, subcutaneous; Vd, apparent volume of distribution; CL, clearance; ADA, anti-drug antibody. Data derived from population pharmacokinetic models, product label, and QUASAR program trials .

## Efficacy, Safety, and Comparative Positioning of Guselkumab in Ulcerative Colitis

### Efficacy

Guselkumab has shown robust efficacy in patients with moderately to severely active UC. In the phase 2b QUASAR induction study, intravenous guselkumab at weeks 0, 4, and 8 achieved significantly higher rates of clinical response at week 12 compared with placebo (61.4% and 60.7% vs 27.6%, P<0.001), along with improvements in clinical remission, endoscopic outcomes, and histo-endoscopic mucosal healing [9,10]. Delayed responders who crossed over to open treatment achieved additional benefits by week 24, underscoring the potential for durable disease control. Among week-12 nonresponders, clinical response was achieved by 54.3% (200 mg) and 50.0% (400 mg) at week 24. Safety was comparable between the guselkumab and placebo groups. [9]. The phase 3 QUASAR program confirmed these findings, demonstrating both induction and maintenance efficacy with intravenous induction followed by subcutaneous maintenance dosing, with sustained clinical and endoscopic remission through one year [13]. Biomarker analyses revealed early reductions in fecal calprotectin and C-reactive protein, correlating with endoscopic and histologic healing, further supporting the biological rationale of IL-23 blockade [9,10,13].

### Safety

Guselkumab's safety profile in UC is consistent with its previously established use in psoriasis and psoriatic arthritis. Nasopharyngitis, headache, arthralgia, and injection-site reactions are the most commonly reported adverse events, with overall rates similar to placebo in induction trials [9,10,13]. Serious adverse events and infections occurred infrequently and did not outperform placebo during the induction period [9,10,13]. As with other biologics, tuberculosis screening and avoidance of live vaccines are advised prior to initiation [7]. Rare events such as hypersensitivity reactions, hepatic enzyme elevations, and opportunistic infections have been reported across indications, but no new signals have emerged in UC trials [7]. Immunogenicity remains low; anti-guselkumab antibodies are detected in a small proportion of patients, and the majority are non-neutralizing, with little effect on efficacy. No malignancy signal has emerged to date, but ongoing pharmacovigilance is required.

Comparative positioning of guselkumab in Ulcerative Colitis

Golimumab, an anti–TNF-α monoclonal antibody, has shown efficacy for both induction and maintenance. In the PURSUIT-J maintenance study, 56.3% of induction responders maintained clinical response for 54 weeks, 50.0% achieved clinical remission between weeks 30 and 54, and 59.4% had mucosal healing compared to 16.1% for placebo [14]. Real-world evidence supports similar findings, with short-term clinical remission rates of 35–48% and 39–40% maintained at 52 weeks, respectively, though persistence decreases over longer durations [14,15]. Table 2 compares Guselkumab with Golimumab in UC.

While cross-trial comparisons are limited by differences in patient populations and study designs, guselkumab appears to provide durable efficacy in both biologic-naïve and biologic-experienced patients, while golimumab efficacy is generally attenuated in those with prior biologic exposure. The safety profiles for both agents are favorable, with no new safety signals detected in long-term guselkumab extension data or golimumab post-marketing surveillance. Head-to-head trials are required to determine the relative positioning of IL-23 inhibitors versus TNF antagonists in UC treatment algorithms.

When compared to other biologic agents for UC, guselkumab has comparable efficacy and a better safety profile. Anti-TNF therapies, such as infliximab and adalimumab, offer rapid induction benefits but are limited by immunogenicity and long-term response loss [16]. Vedolizumab, a gut-selective anti-α4β7 integrin, has an excellent safety profile but frequently has delayed onset of action[16]. Ustekinumab, which targets the IL-12/23 p40 subunit, is effective and well-tolerated for both biologic-naïve and biologic-experienced patients [16]. Emerging IL-23p19 inhibitors, such as risankizumab, mirikizumab, and guselkumab, show strong efficacy with potential for longer-lasting remission while preserving IL-12 signaling and avoiding potential safety trade-offs associated with broader IL-12/23 blockade [17–19].

According to network meta-analyses, IL-23p19 inhibitors outperform other advanced therapies in terms of induction and maintenance remission, particularly in patients with prior biologic exposure [18,19]. Overall, guselkumab is now a validated therapeutic option for moderate-to-severe UC, with efficacy and safety results that place it alongside established agents and within the expanding IL-23 class as shown in Table 2.

Table 2: Comparative Summary of Guselkumab and Other Biologics in Ulcerative Colitis

| Agent (class) | Key trials / evidence | Induction efficacy | Maintenance / remission | Key safety / clinical notes | Key References |
|---|---|---|---|---|---|
| Guselkumab (IL-23p19) | QUASAR Phase-2b & Phase-3 | Week-12 clinical response: 61.4–60.7% vs 27.6% placebo | Sustained remission through 44–92 weeks | Favorable safety; low immunogenicity | Peyrin-Biroulet 2023; Rubin 2025; Dignass |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | 2022 [9,10,13] |
| Golimumab (anti-TNF) | PURSUIT & PURSUIT-J | Effective induction in biologic-naïve patients | Week-54: 56.3% maintained response; 50% remission; 59.4% mucosal healing | Rapid onset; immunogenicity; infection risk | Hibi 2017; Ersbøll 2025 [14,15] |
| Infliximab / Adalimumab (anti-TNF) | ACT / ULTRA trials | Rapid induction benefit; high early response rates | Effective maintenance but loss of response common | Infection risk; immunogenicity | Ungaro 2017; AGA 2020; Ananthakrishnan 2024 [1,16] |
| Vedolizumab (anti-α4β7 integrin) | GEMINI program | Slower onset of induction | Durable maintenance, esp. biologic-naïve | Gut-selective; excellent systemic safety | Neurath 2019; AGA 2020 [2,3] |
| Ustekinumab (IL-12/23 p40) | UNIFI trial | Effective induction and maintenance | Durable remission across subgroups | Favorable safety; broader IL-12/23 blockade | Ananthakrishnan 2024; AGA 2020 [2,16] |
| Other IL-23p19 (risankizumab, mirikizumab) | JAMA 2024; LUCENT-3 OLE | Strong induction efficacy | Promising long-term durability | Favorable safety; strong NMA rankings | Louis 2024; Shehab 2025; Barberio 2025 [17,18,20] |
| Notes: LOR, loss of response; NMA, network meta-analysis; OLE, open-label extension | | | | | |

## Discussion

Guselkumab is a fully human IgG1λ monoclonal antibody that selectively targets the p19 subunit of IL-23, inhibiting IL-23–driven Th17 responses implicated in UC pathogenesis. Clinical biomarker data from induction trials (notably the QUASAR program) demonstrate rapid reductions in fecal calprotectin, and C-reactive protein as early as Week 4 with sustained decreases by Week 12, paralleling higher rates of clinical, endoscopic, and histologic response vs placebo. Guselkumab has a typical IgG antibody pharmacokinetic profile, with slow subcutaneous absorption and a long terminal half-life due to low systemic clearance. The drug's exposure is

dose-proportional, and its disposition is largely restricted to the extracellular space, with body weight as the main covariate. Taken together, these pharmacodynamics and pharmacokinetics properties explain the rationale for intravenous or high-exposure induction followed by subcutaneous maintenance regimens and support the PopPK-based exposure-response relationships observed in IBD programs.

**Interpretation of Efficacy**

The QUASAR study shows that that guselkumab provides significant rates of disease remission for moderate-to-severe UC, both during induction and maintenance, including in biologic-experienced populations. The high cumulative response (77% by Week 24), significant endoscopic remission (a third of treated patients by Week 44), and durability through Week 92 are all strong indicators of long-term disease control [9,10,13]. These findings suggest that guselkumab not only alleviates symptoms but also promotes mucosal healing, which is increasingly recognized as a critical therapeutic goal in UC to reduce long-term complications.

The East Asian subgroup analysis confirms that efficacy is broadly consistent across diverse ethnic populations, though absolute rates are slightly lower in some subgroups, as seen with other biologics. This is most likely due to baseline disease characteristics, prior treatment exposure, or pharmacogenomic differences.

**Safety and Toxicity Considerations**

Guselkumab's safety profile in UC is favorable, with no major unexpected adverse events and rates of serious infection in QUASAR comparable to placebo and other biologics. Long-term (92-week) data showing very high steroid-free remission among those in clinical remission suggest a benefit in reducing steroid exposure, which is a major contributor to morbidity in UC [9,10,13].

However, limitations remain: while the follow-up is relatively long in clinical trial terms, it may not be sufficient to detect very rare safety events (malignancy, opportunistic infection) or events in special populations (severe comorbidity, elderly). Post-marketing real-world safety data will be critical.

**Comparative Positioning vs Other Biologics/Small Molecules**

In network meta-analyses, guselkumab performs exceptionally well, particularly for corticosteroid-free remission and some endoscopic/maintenance outcomes. These rankings indicate that it is competitive with, or superior to, many established biologic options in specific clinical settings [20].

Anti-TNFs (infliximab, adalimumab) continue to induce a rapid response, but long-term durability is frequently compromised by immunogenicity. Guselkumab appears to maintain response with less frequent dosing and reduced immunogenicity [16].

Vedolizumab's gut-selectivity provides safety benefits, but its onset is slower and some patients do not achieve deep healing quickly. IL-12/23 inhibitors, such as ustekinumab, are also effective; however, IL-23p19 inhibitors, such as guselkumab, may have slightly stronger effects on the Th17 axis and achieve higher proportions of endoscopic or

Table 2 provides an in-depth comparison of guselkumab and other biologics in ulcerative colitis.

### Strengths, Limitations, and Implications

The current evidence has several strengths, including large randomized controlled trials, well-powered maintenance and induction arms, the inclusion of biologic-experienced patients, and long-term follow-up for a significant proportion of participants up to 92 weeks. Furthermore, consistency across geographic subgroups improves external validity.

## Limitations

Indirect comparisons across biologic therapies for ulcerative colitis warrant cautious interpretation due to significant methodological heterogeneity across trials. Discrepancies in study endpoints, assessment schedules, and the treatment histories of patient populations can introduce substantial bias into network meta-analyses [20]. Safety evaluations face similar constraints, as the typical duration and sample size of clinical trials are often insufficient to detect low-frequency but clinically significant adverse events like opportunistic infections or malignancies [16]. While the QUASAR program provides strong, randomized evidence for guselkumab's efficacy and short-term safety, its full therapeutic profile requires further investigation [9]. Therefore, forthcoming data from ongoing phase 3 studies and post-marketing surveillance are critical to ascertain its comparative effectiveness and definitively establish its long-term safety profile in a real-world setting.

### Clinical implications

Based on available evidence, guselkumab should be considered a viable first- or second-line biologic option in moderate-to-severe UC, particularly when deep remission, steroid-free remission, and endoscopic healing are desired. The intravenous induction to achieve early high exposure followed by subcutaneous maintenance provides flexibility. Patient factors influencing selection include prior biologic/JAK exposure, comorbidity (ie., infection risk, hepatic disease, etc.), dosing interval preference, and cost/access.

## Conclusion

Guselkumab, a selective IL-23p19 monoclonal antibody, is highly effective for inducing and maintaining remission in patients with moderate-to-severe ulcerative colitis, including those who have failed prior biologics. The extensive QUASAR program provides strong evidence for long-term clinical, endoscopic, and histologic remission, resulting in high rates of corticosteroid-free maintenance. Furthermore, its favorable safety profile—characterized by low immunogenicity and adverse events comparable to placebo and other approved biologics—has yielded no new safety

signals in the UC population. Guselkumab, which ranks favorably among other advanced personalized UC therapies such as anti-TNFs and vedolizumab, is a compelling option within the expanding IL-23 inhibitor category. Long-term studies and direct comparative trials are required to fully establish its role in relation to other advanced therapies.

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