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INFLAMMATORY BOWEL DISEASE

Guselkumab in Patients With Moderately to Severely Active Ulcerative Colitis: QUASAR Phase 2b Induction Study

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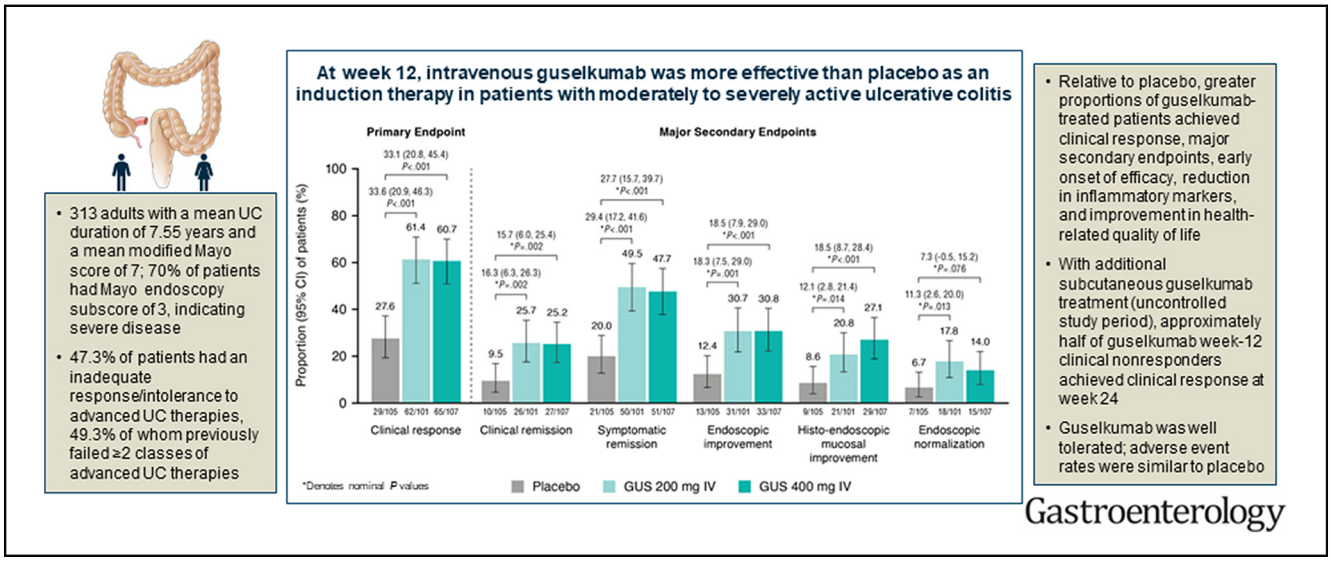

BACKGROUND & AIMS: The QUASAR Phase 2b Induction Study evaluated the efficacy and safety of guselkumab, an interleukin-23p19 subunit antagonist, in patients with moderately to severely active ulcerative colitis (UC) with prior inadequate response and/or intolerance to corticosteroids, immunosuppressants, and/or advanced therapy. **METHODS:** In this double-blind, placebo-controlled, dose-ranging, induction study, patients were randomized (1:1:1) to receive intravenous guselkumab 200 or 400 mg or placebo at weeks 0/4/8. The primary endpoint was clinical response (compared with baseline, modified Mayo score decrease ≥30% and ≥2 points, rectal bleeding subscore ≥1-point decrease or subscore of 0/1) at week 12. Guselkumab and placebo week-12 clinical nonresponders received subcutaneous or intravenous guselkumab 200 mg, respectively, at weeks 12/16/20 (uncontrolled study period). **RESULTS:** The primary analysis population included patients with baseline modified Mayo scores ≥5 and ≤9 (intravenous guselkumab 200 mg, n = 101; 400 mg, n = 107; placebo, n = 105). Week-12 clinical response percentage was greater with guselkumab 200 mg (61.4%) and 400 mg (60.7%) vs placebo (27.6%; both $P < .001$). Greater proportions of guselkumab-treated vs placebo-treated patients achieved all major secondary endpoints (clinical remission, symptomatic remission, endoscopic improvement, histo-endoscopic mucosal improvement, and endoscopic normalization) at week 12. Among guselkumab week-12 clinical nonresponders, 54.3% and 50.0% of patients in the 200- and 400-mg groups, respectively, achieved clinical response at week 24. Safety was similar among guselkumab and

placebo groups. **CONCLUSIONS:** Guselkumab intravenous induction was effective vs placebo in patients with moderately to severely active UC. Guselkumab was safe, and efficacy and safety were similar between guselkumab dose groups. ClinicalTrials.gov number: NCT04033445.

Keywords: Advanced Therapy; Interleukin-23p19 Subunit Antagonist; QUASAR; Ulcerative Colitis.

Ulcerative colitis (UC) is a chronic and disabling inflammatory bowel disease (IBD).[1–3] Advanced therapies approved for the treatment of UC include tumor necrosis factor (TNF)-α antagonists, the interleukin (IL)-12/23 antagonist ustekinumab, the $\alpha4\beta7$ integrin antagonist vedolizumab, Janus kinase (JAK) inhibitors, and the sphingosine 1-phosphate receptor modulator ozanimod.[4–11] Despite the availability of these therapies, many patients fail to respond to treatment or lose their initial response over time.[12–15] Therefore, there is an important unmet need for more effective therapies for UC, especially over the long term.

IL-23 blockade has been shown to be effective in moderately to severely active UC[16–18] and Crohn's disease.[19–21] Guselkumab, a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody, binds with high affinity and specificity to the p19 subunit of human IL-23, blocking the binding of extracellular IL-23 to the cell surface IL-23 receptor and inhibiting IL-23–specific intracellular signaling and subsequent activation of cytokine production.[22] Guselkumab is approved in several countries for the treatment of other inflammatory diseases including moderate-to-severe plaque psoriasis and active psoriatic arthritis.[22,23] In a recent Phase 2, double-blind, placebo-controlled study in patients with moderately to severely active Crohn's disease with prior inadequate response and/or intolerance to corticosteroids, immunosuppressants, or biologic therapy, guselkumab induced greater clinical and endoscopic improvements at week 12 compared with placebo and had a favorable safety profile.[21]

In a Phase 2b/3 clinical development program for guselkumab in UC (NCT04033445), the efficacy and safety of guselkumab compared with placebo is being evaluated in patients with moderately to severely active UC in 3 separate studies under a single protocol called QUASAR. Here, we report the efficacy and safety results of guselkumab as induction therapy in the QUASAR Phase 2b Induction Study.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Interleukin-23 plays a crucial role in the pathogenesis of inflammatory bowel disease. Efficacy and safety of the interleukin-23p19 subunit inhibitor guselkumab were evaluated in patients with moderately to severely active ulcerative colitis.

NEW FINDINGS

At week 12, clinical response was significantly greater with intravenous guselkumab induction vs placebo. Efficacy and safety were similar between dose groups. Additional subcutaneous treatment in the uncontrolled study period provided benefit to clinical nonresponders.

LIMITATIONS

Not all major secondary endpoints were sufficiently powered to detect differences between guselkumab and placebo.

CLINICAL RESEARCH RELEVANCE

These results, in addition to the established efficacy and safety of guselkumab in approved indications and clinical proof-of-concept in Crohn's disease, suggest that guselkumab is a promising therapy for ulcerative colitis.

BASIC RESEARCH RELEVANCE

Guselkumab efficacy in patients with ulcerative colitis confirms that interleukin-23–specific intracellular signaling has an important role in the pathogenesis of inflammatory bowel disease.

Materials and Methods

The QUASAR protocol includes a Phase 2b dose-ranging induction study (QUASAR Phase 2b Induction Study), a Phase 3 induction study (QUASAR Phase 3 Induction Study), and a Phase 3 randomized withdrawal maintenance study (QUASAR Maintenance Study). The QUASAR Phase 2b Induction Study was a randomized, double-blind, placebo-controlled, dose-ranging clinical study conducted between September 2019 and February 2022, with participants randomized in 141 centers across 27 countries/territories. The primary objective of the study was to evaluate the efficacy and safety of guselkumab in patients with moderately to severely active UC. Guselkumab dose response was also evaluated to inform induction dose selection for the QUASAR Phase 3 Induction Study.

Study Population

Eligible patients were aged $\geq$18 years and had confirmed diagnosis of moderately to severely active UC for $\geq$3 months before screening. The primary analysis population for this study consisted of randomized and treated patients with a modified Mayo score of $\geq$5 and $\leq$9 at induction baseline (week 0). Although the protocol allowed enrollment of patients who had a modified Mayo score of 4, which was limited to $\leq$5% of the total enrolled population, patients with a modified Mayo score of 4 were excluded from the primary analysis population. The modified Mayo score (range 0–9) is calculated as the sum of stool frequency, rectal bleeding, and endoscopy subscores.[24]

Abbreviations used in this paper: **AE, adverse event; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; HRQoL, health-related quality of life; IBD, inflammatory bowel disease; IBDQ, Inflammatory Bowel Disease Questionnaire; IL, interleukin; IV, intravenous; JAK, Janus kinase; PROMIS-Fatigue SF-7a, Patient-Reported Outcomes Measurement Information System-Fatigue Short Form 7a; SC, subcutaneous; TNF-α, tumor necrosis factor alpha; UC, ulcerative colitis.**

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At baseline, patients were also required to have a Mayo rectal bleeding subscore ≥1 and a Mayo endoscopy subscore ≥2 obtained during central review of the screening endoscopy video.

Patients were also required to have had an inadequate response and/or intolerance to corticosteroids, immunosuppressants, and/or advanced therapy. This could include a history of inadequate response, loss of response, or intolerance to oral corticosteroids (including budesonide and beclomethasone dipropionate) or immunosuppressants (6-mercaptopurine or azathioprine), and a history of corticosteroid dependence (ie, an inability to successfully taper corticosteroids without a return of UC symptoms). Inadequate response and/or intolerance to advanced therapy could include a primary nonresponse (ie, no initial response), secondary nonresponse (ie, responded initially with subsequent loss of response), or intolerance to ≥1 TNF-α antagonist, integrin-receptor antagonist (vedolizumab), and/or JAK inhibitor (tofacitinib) at a dosage approved for the treatment of UC.

Previous use of IL-12 and/or IL-23 inhibitors was prohibited. Patients were also required to discontinue the following medications before receiving the first dose of study treatment: TNF-α antagonists for ≥8 weeks; integrin-receptor antagonist vedolizumab for ≥12 weeks; and JAK inhibitors for ≥2 weeks or 5 half-lives, whichever was longer. The use of immunosuppressants (except 6-mercaptopurine, azathioprine, or methotrexate), biologics, investigational IBD medications, and thalidomide or related agents was prohibited. Patients could receive concomitant immunosuppressants (6-mercaptopurine, azathioprine, or methotrexate if taking for ≥12 weeks) but must have been at a stable dose for ≥4 weeks before screening and had to maintain a stable dose through the end of induction. Patients could receive oral 5-aminosalicylic acid but must have been at a stable dose for ≥2 weeks before screening and had to maintain a stable dose through the end of induction. Patients could receive oral corticosteroids (≤20 mg/d prednisone or equivalent) but must have been at a stable dose for ≥2 weeks before screening and had to maintain a stable dose through the end of induction. These concomitant medications could only be reduced in dose or discontinued if required because of toxicity or medical necessity per investigator judgment.

Other key exclusion criteria were a diagnosis of Crohn's disease, UC limited to the rectum only or to <20 cm of the colon, imminent colectomy, gastrointestinal surgical interventions within 2 months before screening, history of extensive colonic resection, presence of stoma, and presence or history of fistula.

Study Design

Patients were randomly assigned (1:1:1) to receive intravenous (IV) guselkumab 200 mg or 400 mg or placebo IV at weeks 0, 4, and 8 as induction therapy (Supplementary Figure 1). An Interactive Web Response System was used for permuted block randomization stratified by advanced therapy failure status (ie, inadequate response/intolerance to advanced therapy [Yes/No]), region (Eastern Europe, Asia, or rest of the world), and concomitant use of corticosteroids at baseline (Yes/No). The study investigators, site personnel, central laboratory, central readers, and patients were blinded to patient treatment assignment throughout the study.

At week 12, patients were evaluated for clinical response, defined as a decrease in the modified Mayo score from baseline of ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1 (see Supplement). Clinical response status (using Interactive Web Response System data) determined subsequent study intervention (Supplementary Figure 1). Patients who achieved clinical response to IV guselkumab or placebo at week 12 entered the QUASAR Maintenance Study and were not included in evaluations beyond week 12 for this induction study.

Patients initially randomized to IV guselkumab who did not achieve clinical response at week 12 received guselkumab 200 mg subcutaneously (SC) at weeks 12, 16, and 20. Patients initially randomized to placebo who did not achieve clinical response at week 12 crossed over to receive guselkumab induction (200 mg IV) at weeks 12, 16, and 20. This part of the study was uncontrolled. Matching IV or SC placebo was administered to all week-12 nonresponders to maintain blinding. Patients who achieved clinical response at week 24 entered the QUASAR Maintenance Study. Patients who were not in clinical response at week 24 did not receive further study treatment and had a safety follow-up visit approximately 12 weeks after receiving their last dose of guselkumab.

The protocol was approved by the Sterling institutional review board for US sites (approval number: 7439) and local ethics committees at each participating center for all other sites. All participants provided written informed consent. The study was conducted in compliance with the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines. All authors had access to data summaries and reviewed and approved the final manuscript.

Assessments

The primary efficacy endpoint was clinical response at week 12. The major secondary endpoints were clinical remission (a Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy); symptomatic remission (a Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline and a Mayo rectal bleeding subscore of 0); endoscopic improvement (a Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy); histo-endoscopic mucosal improvement, a combined endpoint of endoscopic improvement and histologic improvement (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system, ie, Geboes score ≤3.1);[25] and endoscopic normalization (a Mayo endoscopy subscore of 0) at week 12. Clinical response at week 12 was selected as the primary endpoint because it provides more statistical power to detect a treatment difference at the planned sample size for interim analysis (ie, first 150 randomized patients) than the primary endpoint for the QUASAR Phase 3 Induction Study (clinical remission at week 12).

Additional prespecified endpoints included change from baseline in partial Mayo score (range 0–9; calculated as the sum of stool frequency, rectal bleeding, and physician's global assessment subscores) through week 12; achievement of a

stool frequency subscore of 0 or 1 or a rectal bleeding subscore of 0 through week 12; median serum concentrations of C-reactive protein (CRP) and fecal calprotectin through week 12; change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) total score and Patient-Reported Outcomes Measurement Information System-Fatigue Short Form 7a (PROMIS-Fatigue SF-7a) score at week 12; and achievement of IBDQ remission (total IBDQ score $\geq$170), clinically meaningful improvement in total IBDQ score ($\geq$16-point improvement from baseline),[26] >20-point improvement in total IBDQ score,[27] or fatigue response ($\geq$7-point reduction from baseline in PROMIS-Fatigue SF-7a score) at week 12. Symptomatic response (decrease from induction baseline in Mayo symptomatic score [sum of the stool frequency and the rectal bleeding subscores] by $\geq$30% and $\geq$1 point, with either a $\geq$1-point decrease from baseline in the rectal bleeding subscore or a subscore of 0/1) through week 12 was evaluated post hoc.

Adverse events (AEs), serious AEs, and signs or symptoms of infections were assessed throughout the study. Safety was also evaluated based on clinical laboratory tests, including hematology, blood chemistry, and serology. In addition, the presence of antibodies to guselkumab in serum was determined using a validated, sensitive, and drug-tolerant electrochemiluminescence method using the Meso Scale Discovery platform (Rockville, MD).[22]

Statistical Analysis

The primary efficacy population was based on a modified intention-to-treat principle and included all randomized and treated patients with a baseline modified Mayo score of $\geq$5 and $\leq$9 who received $\geq$1 dose of study treatment analyzed according to the assigned treatment.

A step-up Hochberg multiple testing procedure was used to control the type-I error at a 2-sided .05 significance level over the 2 comparisons of guselkumab to placebo for the primary endpoint. The major secondary endpoints were tested at the 2-sided .05 significance level regardless of the significance of the primary endpoint and were not adjusted for multiplicity; thus, all *P* values except those for the primary endpoint are nominal.

Dichotomous endpoints were compared between each guselkumab group and placebo with the use of Cochran-Mantel-Haenszel chi-square test (2-sided) stratified by advanced therapy failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No). The adjusted treatment difference and confidence intervals were based on the Wald statistic with Cochran-Mantel-Haenszel weight. Continuous endpoints were analyzed using a mixed-effect model for repeated measures or analysis of covariance with adjustment for baseline value, treatment group, advanced therapy failure status, and concomitant use of corticosteroids at baseline.

To evaluate the consistency of the treatment effect for the primary endpoint, clinical response was analyzed in prespecified subgroups. Clinical response, clinical remission, symptomatic remission, endoscopic improvement, histo-endoscopic mucosal improvement, and endoscopic normalization at week 12 were prespecified to be analyzed based on history of inadequate response/intolerance to advanced therapy status subgroups.

Patients who had a prohibited change in UC medication, had an ostomy or colectomy, or discontinued study treatment because of lack of efficacy or an AE of worsening of UC before an analysis time point were considered not to have achieved the dichotomous endpoints and had their baseline value carried forward from the time of the event onward for the continuous endpoints (ie, consistent with nonresponder imputation for dichotomous endpoints). Data after discontinuation of study treatment due to coronavirus disease 2019 (COVID)-19–related reasons (excluding COVID-19 infection) were considered to be missing. Patients missing 1 or more modified Mayo subscore (stool frequency, rectal bleeding, or endoscopy) or other component pertaining to an endpoint at week 12 were considered not to have achieved the endpoint.

The minimum sample size for this study was 150 patients required for an interim analysis based on statistical power considerations. The assumptions for sample size were based on data from a Phase 3 ustekinumab induction study[28] and a Phase 2 mirikizumab study[29] in patients with moderately to severely active UC. Based on these studies, the clinical response rates in this study were assumed to be 30% for placebo and 60% for each guselkumab dose. With these assumed rates, 150 patients for the interim analysis would be sufficient to provide $\geq$80% statistical power to detect a treatment difference in the primary endpoint of clinical response at week 12 between guselkumab and placebo at a .05 significance level. The study was not powered to detect treatment differences between guselkumab and placebo for the major secondary endpoints. While interim data were being analyzed, enrollment into this study was allowed to continue.

The primary safety population included all randomized and treated patients with a baseline modified Mayo score of $\geq$5 and $\leq$9 (excluding patients with a modified Mayo score of 4) who received $\geq$1 dose of study treatment, analyzed according to the treatment they actually received. The frequency and types of AEs were summarized. Selected safety analyses were also provided for all treated patients, regardless of baseline modified Mayo score.

Immunogenicity analyses included all guselkumab-treated patients with a modified Mayo score of $\geq$5 and $\leq$9 at baseline who had $\geq$1 blood sample obtained after their first guselkumab dose.

Results

Patient Disposition and Baseline Demographics

A total of 313 patients were included in the primary analysis (placebo, N = 105; guselkumab 200 mg IV, N = 101; guselkumab 400 mg IV, N = 107) (Figure 1). Only 1 patient withdrew from the study for COVID-19–related reasons.

Baseline demographic and disease characteristics were similar among treatment groups and indicative of patients with moderately to severely active UC (Table 1). Overall, 40.9% of patients were female and had a mean age of 41.6 years, mean UC duration of 7.6 years, a mean Mayo score of 9.2, and a mean modified Mayo score of 7.0. Seventy percent of patients had a Mayo endoscopy subscore of 3, indicating severe disease. Of the 313 patients assessed, 125 (39.9%) were using oral corticosteroids at baseline and 148 (47.3%) had prior inadequate response/intolerance to advanced therapy for UC.

Efficacy

Primary and major secondary efficacy endpoints at week 12. At week 12, significantly greater proportions

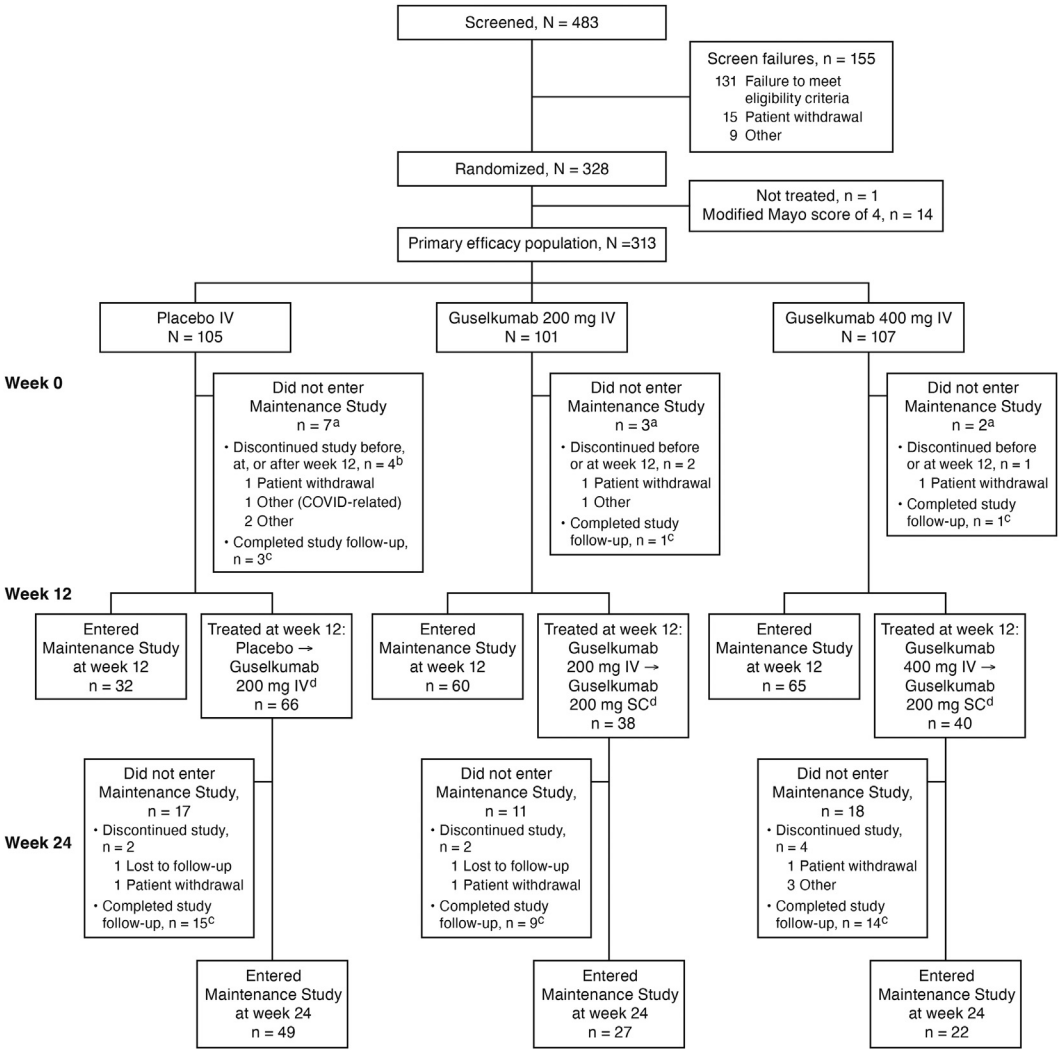

Figure 1. Patient disposition. [a]Among patients treated at week 0 who did not receive additional treatment at week 12. [b]Two patients discontinued after week 12. [c]Patients who discontinued the study treatment but returned for their safety follow-up visit were considered to have completed study participation. [d]Patients who were not in clinical response at week 12 as determined using Interactive Web Response System data and received treatment at week 12. COVID, coronavirus; IV, intravenous; N, total population; n, subset; SC, subcutaneous.

of patients in the guselkumab 200 mg (61.4% [62/101]; adjusted treatment difference 33.6 [20.9, 46.3], $P < .001$) and 400 mg (60.7% [65/107]; adjusted treatment difference 33.1 [20.8, 45.4], $P < .001$) groups achieved the primary endpoint of clinical response compared with the placebo group (27.6% [29/105]) (Figure 2). Similarly, greater proportions of guselkumab-treated patients than placebo-treated patients achieved the major secondary endpoints at week 12 (clinical remission, symptomatic remission, endoscopic improvement, histo-endoscopic mucosal improvement, and endoscopic normalization) (Figure 2). No apparent guselkumab dose response was observed for any of these endpoints.

Among the 148 patients with a history of inadequate response/intolerance to prior advanced therapy, 75 (50.7%) had prior inadequate response/intolerance to only 1 advanced therapy class, 73 (49.3%) to $\geq$2 advanced therapy classes, 133 (89.9%) to $\geq$1 TNF-α antagonist, 78 (52.7%) to vedolizumab, and 31 (20.9%) to tofacitinib (Table 1). Among the 165 patients without a history of inadequate response/intolerance to advanced therapy, 154 (93.3%) were advanced therapy naïve and 11 (6.7%) were advanced therapy experienced. In both subgroups of patients without (Supplementary Figure 2*A*) or with (Supplementary Figure 2*B*) a history of inadequate response/intolerance to advanced UC therapy, greater proportions of guselkumab-treated than placebo-treated patients achieved the clinical endpoints at week 12. Within these subgroups, achievement of the clinical endpoints at week 12 was similar between the guselkumab 200-mg and 400-mg treatment groups.

Efficacy through week 12. Efficacy was observed at the earliest time points assessed. Starting at week 2, greater proportions of guselkumab-treated vs placebo-treated patients achieved symptomatic response (Figure 3*A*). At week 12, 65.3%, 66.4%, and 37.1% of patients in the guselkumab 200-mg and 400-mg and placebo groups, respectively, achieved symptomatic response (both nominal $P < .001$).

Table 1. Patient Demographics and Baseline UC Disease Characteristics (Primary Efficacy Population)

		Guselkumab		
	Placebo (N = 105)	200 mg IV (N = 101)	400 mg IV (N = 107)	Total (N = 313)
Age, *y*, mean (SD)	41.2 (15.05)	43.3 (14.28)	40.4 (13.84)	41.6 (14.40)
Female, n (%)	39 (37.1)	41 (40.6)	48 (44.9)	128 (40.9)
Race, n (%)				
Asian	24 (22.9)	23 (22.8)	27 (25.2)	74 (23.6)
Black or African American	1 (1.0)	1 (1.0)	1 (0.9)	3 (1.0)
White	77 (73.3)	73 (72.3)	74 (69.2)	224 (71.6)
Not reported/multiple	3 (2.9)	4 (4.0)	5 (4.7)	12 (3.8)
Weight, *kg*, mean (SD)	68.8 (16.30)	70.3 (16.50)	71.7 (18.58)	70.3 (17.16)
Disease duration, *y*, mean (SD)	7.7 (7.16)	7.0 (6.00)	7.9 (7.15)	7.6 (6.79)
Extensive UC, n (%)	46 (43.8)	48 (47.5)	59 (55.1)	153 (48.9)
Mayo score, mean (SD)	9.0 (1.31)	9.2 (1.29)	9.3 (1.35)	9.2 (1.32)
Modified Mayo score, mean (SD)	6.9 (1.06)	7.0 (1.06)	7.0 (0.99)	7.0 (1.04)
Modified Mayo score 7–9 (severe), n (%)	69 (65.7)	71 (70.3)	78 (72.9)	218 (69.6)
Partial Mayo score, mean (SD)	6.3 (1.14)	6.6 (1.15)	6.5 (1.23)	6.5 (1.18)
Endoscopy subscore of 3 (severe), n (%)	75 (71.4)	66 (65.3)	78 (72.9)	219 (70.0)
Geboes total score, n	101	99	103	303
Mean (SD)	12.3 (5.35)	12.8 (4.64)	13.1 (4.50)	12.7 (4.84)
Geboes high activity subscore (0–10),[a] n	101	99	103	303
Mean (SD)	5.4 (3.29)	5.6 (2.99)	5.7 (2.96)	5.6 (3.08)
Extraintestinal manifestation present,[b] n (%)	13 (12.4)	15 (14.9)	22 (20.6)	50 (16.0)
CRP, n	105	99	104	308
Median (IQR), *mg/L*	4.9 (1.4; 10.8)	4.3 (1.6; 17.8)	4.4 (1.9; 8.8)	4.6 (1.6; 11.3)
Abnormal (>3 mg/L), n/n (%)	64/105 (61.0)	63/99 (63.6)	66/104 (63.5)	193/308 (62.7)
Fecal calprotectin, n	91	95	101	287
Median (IQR), *mg/kg*	1457.0 (749.0; 3054.0)	1667.0 (771.0; 2859.0)	1578.0 (811.0; 2860.0)	1564.0 (767.0; 2860.0)
Abnormal (>250 mg/kg), n/n (%)	81/91 (89.0)	85/95 (89.5)	91/101 (90.1)	257/287 (89.5)
Albumin, *g/L,* median (IQR)	43.0 (41.0; 46.0)	43.0 (40.0; 45.0)	43.0 (40.0; 46.0)	43.0 (41.0; 46.0)
IBDQ total score (32–224), n	101	99	104	304
Mean (SD)	124.8 (31.91)	125.5 (30.63)	124.2 (34.11)	124.8 (32.18)
PROMIS-Fatigue SF-7a, n	101	99	104	304
Mean (SD)	56.9 (9.7)	56.7 (8.9)	56.8 (8.2)	56.8 (8.9)
Receiving corticosteroids, immunosuppressants, or aminosalicylates for UC treatment at baseline, n (%)	95 (90.5)	92 (91.1)	96 (89.7)	283 (90.4)
Oral corticosteroids	40 (38.1)	41 (40.6)	44 (41.1)	125 (39.9)
Immunosuppressants	17 (16.2)	25 (24.8)	27 (25.2)	69 (22.0)
Oral aminosalicylates	79 (75.2)	74 (73.3)	89 (83.2)	242 (77.3)
No history of inadequate response/intolerance to advanced therapies,[c] n (%)	54 (51.4)	55 (54.5)	56 (52.3)	165 (52.7)
Advanced therapy naïve, n/n (%)	51/54 (94.4)	52/55 (94.5)	51/56 (91.1)	154/165 (93.3)
Advanced therapy experienced, n/n (%)	3/54 (5.6)	3/55 (5.5)	5/56 (8.9)	11/165 (6.7)

Table 1. Continued

	Placebo (N = 105)	Guselkumab 200 mg IV (N = 101)	Guselkumab 400 mg IV (N = 107)	Total (N = 313)
History of inadequate response/intolerance to ≥1 UC advanced therapy,[c] n (%)	51 (48.6)	46 (45.5)	51 (47.7)	148 (47.3)
≥1 TNF-α antagonist, n/n (%)	46/51 (90.2)	41/46 (89.1)	46/51 (90.2)	133/148 (89.9)
Vedolizumab, n/n (%)	29/51 (56.9)	22/46 (47.8)	27/51 (52.9)	78/148 (52.7)
Tofacitinib, n/n (%)	15/51 (29.4)	10/46 (21.7)	6/51 (11.8)	31/148 (20.9)
1 advanced therapy class, n/n (%)	23/51 (45.1)	27/46 (58.7)	25/51 (49.0)	75/148 (50.7)
≥2 advanced therapy classes, n/n (%)	28/51 (54.9)	19/46 (41.3)	26/51 (51.0)	73/148 (49.3)

NOTE. Unless otherwise noted, the denominators used to calculate proportions of patients were those listed in the heading for each treatment group.
IQR, interquartile range; N, total population; n, subset; SD, standard deviation.
[a]The continuous histology score was derived as the sum of Geboes Grades 3, 4, and 5 that defined histologic improvement.
[b]Extraintestinal manifestations assessed were arthritis/arthralgia, aphthous stomatitis, erythema nodosum, iritis/uveitis, primary sclerosing cholangitis, and pyoderma gangrenosum.
[c]Advanced therapy refers to TNF-α antagonists, vedolizumab, and/or tofacitinib.

The mean decrease from baseline in partial Mayo score was greater in the guselkumab groups vs the placebo group at week 4, the earliest time point assessed for this endpoint, and continued through week 12 (Figure 3*B*). At week 12, the mean decrease from baseline in partial Mayo score was 3.51 in the guselkumab 200-mg group and 3.44 in the 400-mg group compared with 1.40 in the placebo group (both nominal $P < .001$). In addition, greater proportions of guselkumab-treated vs placebo-treated patients achieved a stool frequency subscore of 0 or 1 (Figure 3*C*) or a rectal bleeding subscore of 0 (Figure 3*D*) through week 12. At week 12, in the guselkumab 200-mg and 400-mg and placebo groups, respectively, 57.4%, 57.0%, and 27.6% (both nominal $P < .001$) achieved a stool frequency subscore of 0 or 1 and 67.3%, 56.1%, and 34.3% (nominal $P < .001$ and $P = .002$, respectively) achieved a rectal bleeding subscore of 0.

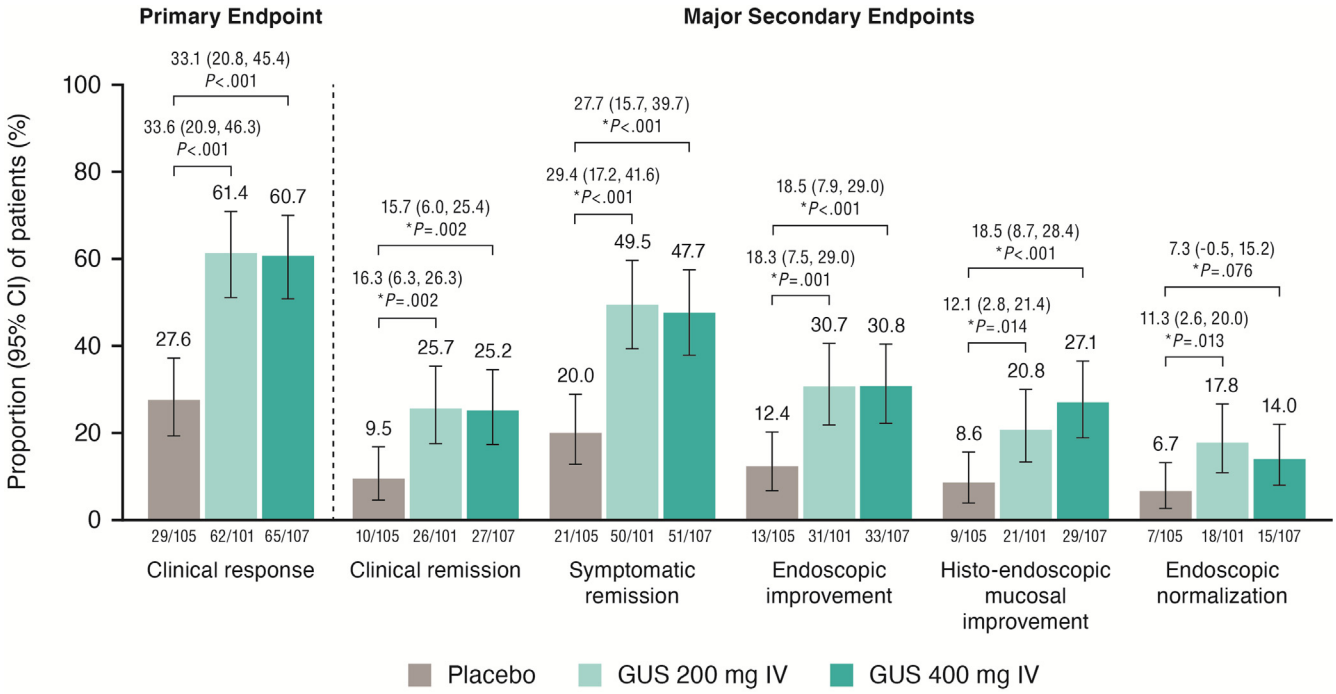

Figure 2. The primary endpoint of clinical response at week 12 and the major secondary endpoints of clinical remission, symptomatic remission, endoscopic improvement, histo-endoscopic mucosal improvement, and endoscopic normalization all at week 12 (*P* values for major secondary endpoints are nominal). *Denotes nominal *P* values. Primary efficacy population. All *P* values are based on the Cochran-Mantel-Haenszel chi-square test. The adjusted treatment difference and confidence intervals were based on the Wald statistic with Cochran-Mantel-Haenszel weight. CI, confidence interval; GUS, guselkumab.

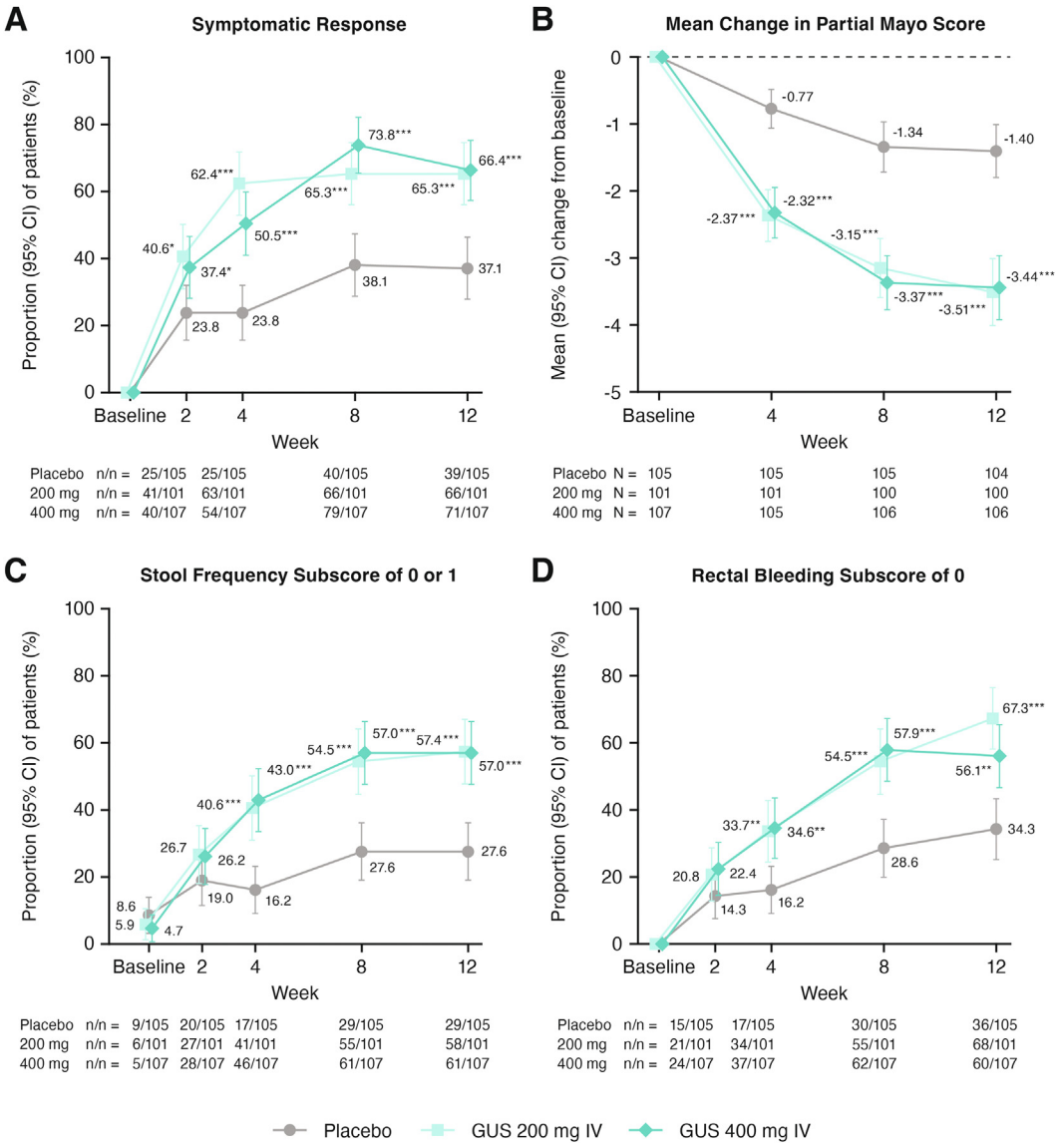

Figure 3. Symptomatic response (post hoc) (*A*), partial Mayo score (*B*), stool frequency subscore of 0 or 1 (*C*), and rectal bleeding subscore of 0 (*D*) through week 12. Primary efficacy population. All *P* values are nominal and were based on MMRM for partial Mayo score and Cochran-Mantel-Haenszel chi-square test for all other endpoints: **P* < .05, ***P*<.01, ****P*<.001. For partial Mayo score, MMRM was used to account for missing data under the assumption of missing at random. The first post-baseline measurement of physician's global assessment was at week 4. For stool frequency and rectal bleeding subscores and symptomatic response, patients with a missing score at the designated time point (stool frequency and/or rectal bleeding for symptomatic response) were considered not to have met the endpoint. CI, confidence interval; GUS, guselkumab; MMRM, mixed-effect model for repeated measures. N, total population; n, subset.

Inflammatory biomarker assessments. At baseline, the median concentrations of serum CRP and fecal calprotectin were comparable across treatment groups (Table 1). At the earliest time point assessed (week 4) and continuing through week 12, greater median reductions from baseline in levels of CRP and fecal calprotectin were observed in the guselkumab groups compared with the placebo group (Supplementary Figure 3*A* and *B*). At week 12, median CRP levels were reduced by 2.31 mg/L in the guselkumab 200-mg group and 1.06 mg/L in the 400-mg group compared with an increase of 0.06 mg/L in the placebo group (both nominal $P < .001$). Median fecal calprotectin concentrations were reduced by 745.00 mg/kg in the guselkumab 200-mg group and 558.50 mg/kg in the 400-mg group compared with 0.00 mg/kg in the placebo group (both nominal $P < .001$).

Among patients with abnormal levels of CRP (>3 mg/L) at baseline (range: 61.0%–63.6%) (Table 1), greater proportions of patients in the guselkumab groups achieved CRP normalization (≤3 mg/L) compared with placebo as early as the first post-baseline measurement at week 4 continuing through week 12. At week 12, among patients with abnormal CRP at baseline, 50.8% of patients in the guselkumab 200-mg group and 37.9% in the guselkumab 400-mg

group achieved CRP normalization (≤3 mg/L) compared with 18.8% in the placebo group (nominal $P < .001$ and $P = .012$, respectively). Among patients with abnormal fecal calprotectin levels (>250 mg/kg) at baseline (range: 89.0%–90.1%) (Table 1), greater proportions of patients in the guselkumab groups than in the placebo group achieved fecal calprotectin normalization (≤250 mg/kg) at week 12 (34.1% and 31.9% in the guselkumab 200-mg and 400-mg groups, respectively; 9.9% in the placebo group; both nominal $P < .001$).

Health-related quality of life at week 12. At week 12, greater proportions of patients in the guselkumab 200- and 400-mg groups compared with the placebo group had improvement in health-related quality of life (HRQoL) as assessed with the IBDQ (Supplementary Figure 4). IBDQ remission was achieved by 52.5% and 55.1% of patients in the guselkumab 200- and 400-mg groups, respectively, compared with 26.7% in the placebo group (both nominal $P < .001$). A clinically meaningful improvement in total IBDQ score was achieved by 71.3% and 73.8% of patients in the guselkumab 200- and 400-mg groups, respectively, compared with 48.6% in the placebo group (both nominal $P < .001$). In addition, 67.3% and 72.0% of patients in the guselkumab 200- and 400-mg groups, respectively, achieved a >20-point improvement in total IBDQ score compared with 40.0% of patients in the placebo group (both nominal $P < .001$). The mean (standard deviation) increase from baseline in total IBDQ score (indicative of improvement) was greater in patients in the guselkumab 200- and 400-mg groups (40.8 [32.9] and 44.6 [37.6], respectively) compared with the placebo group (17.8 [34.7]; both nominal $P < .001$).

Fatigue response as measured by PROMIS-Fatigue SF-7a was also greater at week 12 with guselkumab compared with placebo (44.6% [nominal $P = .026$] and 40.2% [nominal $P = .101$] in the guselkumab 200-mg and 400-mg groups, respectively, vs 29.5% in the placebo group) (Supplementary Figure 4). At week 12, mean (standard deviation) decrease from baseline in PROMIS-Fatigue SF-7a score was 6.3 (9.6; nominal $P = .009$) and 7.1 (9.7; nominal $P < .001$) in the guselkumab 200- and 400-mg groups, respectively, and 3.1 (7.8) in the placebo group.

Clinical response at week 24 by baseline randomization group among week-12 clinical nonresponders. Among guselkumab week-12 clinical nonresponders (based on electronic case report form) who received SC guselkumab treatment, 54.3% (19 of 35) in the guselkumab 200 mg IV→guselkumab 200 mg SC group and 50.0% (19 of 38) in the guselkumab 400 mg IV→guselkumab 200 mg SC group achieved a clinical response at week 24 (Figure 4). Cumulatively, clinical response at induction week 12 or 24 was achieved by 80.2% (81 of 101) of patients initially randomized to guselkumab 200 mg IV and 78.5% (84 of 107) initially randomized to guselkumab 400 mg IV. In both subgroups of patients without (Supplementary Figure 5*A*) and with (Supplementary Figure 5*B*) a history of inadequate response/intolerance to advanced therapy, substantial proportions of guselkumab week-12 clinical nonresponders achieved a clinical response at week 24.

Among patients randomized to placebo who were week-12 clinical nonresponders and received guselkumab 200 mg IV at weeks 12, 16, and 20, 65.2% (43 of 66) achieved clinical response at week 24 (Supplementary Figure 6), which is similar to the proportion of patients randomized to guselkumab 200 mg IV who achieved clinical response at week 12 (61.4%) (Figure 2). Moreover, the results for the other clinical endpoints in the placebo IV→guselkumab 200 mg IV group at week 24 were also generally similar to those reported for the guselkumab 200-mg and 400-mg IV groups at week 12 (Supplementary Figure 6 and Figure 2).

Safety

In the primary safety population, through week 12, the proportions of patients who experienced 1 or more AE were comparable among treatment groups (44.6% in the guselkumab 200-mg group, 49.5% in the 400-mg group, and 56.2% in the placebo group) (Table 2). Serious AEs occurred at a low frequency (1.0% in the guselkumab 200-mg group, 2.8% in the 400-mg group, and 5.7% in the placebo group). The proportions of participants who experienced 1 or more infections were 13.9% in the guselkumab 200-mg group, 9.3% in the 400-mg group, and 12.4% in the placebo group. Two patients in the placebo group reported serious infections (one was receiving corticosteroids); no serious infections were reported in either guselkumab group through week 12. The most frequently reported AEs were anemia, headache, and COVID-19.

AEs leading to discontinuation of therapy were not greater in either guselkumab group compared with the placebo group. No patient discontinued study treatment due to COVID-19 infection; however, 1 patient terminated study participation before week 12 due to COVID-19–related reasons. No cases of active tuberculosis, opportunistic infections, or death were reported. No antibodies to guselkumab were observed at any time through week 12, and no cases of anaphylaxis or serum-sickness–like reactions were reported.

The safety results for all treated patients regardless of baseline modified Mayo score were consistent with the results in the primary safety population (Supplementary Table 1). In this population, 1 case of malignancy was reported with a baseline modified Mayo score of 4. On study day 15, a patient in the IV guselkumab 200-mg group with a medical history of treated basal cell carcinoma had their annual dermatology examination. An excisional biopsy was performed on a skin nodule known to have existed before randomization. The excised nodule was diagnosed as basal cell carcinoma. Safety in week-12 clinical nonresponders who received additional guselkumab administered subcutaneously was consistent with safety through week 12 (Supplementary Table 2).

Discussion

This study in patients with moderately to severely active UC demonstrates that, compared with placebo, guselkumab IV induction treatment resulted in significantly higher clinical response rates at week 12. Guselkumab induction

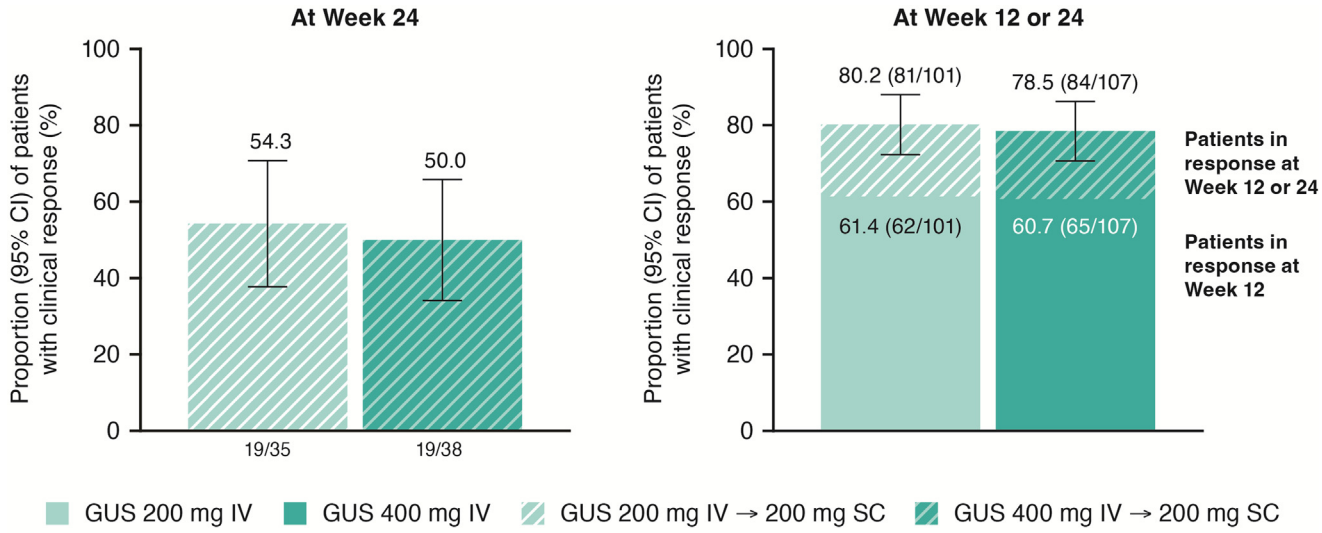

Figure 4. Clinical response at week 24 among week-12 clinical nonresponders to guselkumab and cumulative clinical response at weeks 12 or 24 among patients randomized to guselkumab. Primary efficacy population. Patients missing 1 or more modified Mayo subscore (stool frequency, rectal bleeding, or endoscopy) pertaining to this endpoint at the designated time point were considered not to have achieved clinical response. CI, confidence interval; GUS, guselkumab.

therapy also resulted in higher rates of achievement for all major secondary endpoints at week 12 compared with placebo. The efficacy of guselkumab was observed among patients with and without a prior inadequate response/intolerance to advanced UC therapies. Consistent with results from previous trials in patients with UC,[28,30,31] patients

Table 2. Overall Summary of AEs through Week 12 (Primary Safety Population)

		Guselkumab		
	Placebo IV (N = 105)	200 mg IV (N = 101)	400 mg IV (N = 107)	Combined (N = 208)
Average duration of follow-up, *wk*	12.1	12.1	12.2	12.2
Average exposure (number of administrations)	2.9	3.0	3.0	3.0
Patients with ≥1, n (%)				
AE	59 (56.2)	45 (44.6)	53 (49.5)	98 (47.1)
AE within 1 h of infusion	2 (1.9)	2 (2.0)	0	2 (1.0)
Serious AE	6 (5.7)	1 (1.0)	3 (2.8)	4 (1.9)
Death	0	0	0	0
Discontinuation for AE	3 (2.9)	1 (1.0)	0	1 (0.5)
Malignancy	0	0	0	0
Infection[a]	13 (12.4)	14 (13.9)	10 (9.3)	24 (11.5)
Serious infection	2 (1.9)	0	0	0
Most frequent AEs,[b] n (%)				
Anemia	10 (9.5)	7 (6.9)	8 (7.5)	15 (7.2)
Headache	7 (6.7)	3 (3.0)	6 (5.6)	9 (4.3)
COVID-19 infection	4 (3.8)	6 (5.9)	2 (1.9)	8 (3.8)
Abdominal pain	2 (1.9)	4 (4.0)	3 (2.8)	7 (3.4)
Arthralgia	2 (1.9)	2 (2.0)	4 (3.7)	6 (2.9)
Colitis ulcerative	6 (5.7)	1 (1.0)	4 (3.7)	5 (2.4)
Diarrhea	2 (1.9)	3 (3.0)	1 (0.9)	4 (1.9)
Lymphopenia	5 (4.8)	1 (1.0)	2 (1.9)	3 (1.4)
Pyrexia	4 (3.8)	2 (2.0)	1 (0.9)	3 (1.4)

N, total population; n, subset.
[a]Infections as assessed by the investigator.
[b]Occurred in at least 3% of patients in any treatment group.

without a history of an inadequate response/intolerance to advanced therapy had higher clinical response percentages than those with this history. Clinical efficacy based on symptomatic response was evident as early as week 2 (first timepoint assessed), and reductions in serum levels of inflammatory biomarkers were observed as early as week 4 (first timepoint assessed). In addition, the efficacy of the guselkumab doses tested in this study, 200 mg and 400 mg, was similar across all endpoints at week 12, and no dose-related differences in clinical outcomes were noted.

Improvements in HRQoL, patient-reported symptom outcomes, and fatigue were also greater in the guselkumab groups compared with the placebo group at week 12. Fatigue is a common symptom experienced by patients with IBD.[32] In a qualitative patient interview study conducted on patients with UC (N = 11), fatigue was ranked as the second or third most important symptom by 1 patient each.[33] Chronic fatigue may be associated with psychological comorbidity, sleep disturbances, anemia, micronutrient deficiencies,[32] and pain[34] and could substantially affect the HRQoL in patients with IBD.

In this study, additional treatment with guselkumab 200 mg administered SC in patients who did not respond to guselkumab 200- or 400-mg IV induction therapy at week 12 allowed more than half of the week-12 guselkumab clinical nonresponders to achieve clinical response at week 24. The clinical benefit of additional guselkumab treatment administered SC in patients who did not respond to guselkumab at week 12 was similar regardless of the IV guselkumab induction dose received at weeks 0, 4, and 8, suggesting that there was no incremental benefit with the higher dose. Overall, approximately 80% of patients randomized to receive IV guselkumab (200 mg or 400 mg) achieved clinical response at week 12 or 24. Efficacy with extended treatment was also observed in the subgroups of patients with or without a history of inadequate response/intolerance to advanced therapy. Data from this patient cohort suggest that the efficacy of guselkumab increases over time.

Overall, both guselkumab doses were well tolerated in this study, as reflected in the low discontinuation rate and the generally comparable rates of AEs in guselkumab and placebo groups. Moreover, the safety results in this study were consistent with the known safety profile of guselkumab in the approved indications of plaque psoriasis and psoriatic arthritis.

Although this trial was conducted during the COVID-19 pandemic, COVID-19 did not significantly affect the ability to monitor and conduct the trial according to the protocol or the integrity of the efficacy or safety results. There were no treatment discontinuations because of COVID-19 infection, and rates of infection were comparable among treatment groups.

While this study was being conducted, guselkumab efficacy in UC was demonstrated in a Phase 2a, proof-of-concept, double-blind study of guselkumab monotherapy and combination therapy with the TNF-α antagonist, golimumab, in patients with moderately to severely active UC who were naïve to TNF-α antagonists and had an inadequate response/intolerance to corticosteroids or immunosuppressants (NCT03662542).[18] In this study, guselkumab plus golimumab combination therapy resulted in greater clinical response and remission rates through week 38 than either agent alone, with similar AE rates. Collectively, these results in UC as well as the previously published results demonstrating guselkumab efficacy and safety in Crohn's disease[21] provide clinical proof-of-concept for guselkumab in IBD.

The unique molecular properties of guselkumab may play a role in its efficacy in IBD. Guselkumab neutralizes IL-23 with high affinity and potency and has been shown to bind to CD64 (high-affinity Fc gamma receptor 1 [FcγR1]) on human inflammatory monocytes.[35] Guselkumab bound to CD64 on human inflammatory monocytes can still bind and neutralize IL-23, and this process does not induce myeloid cell activation (ie, cytokine production).[36] CD64^{+} mononuclear phagocytes are enriched in inflamed tissue in IBD and serve as the predominant source of IL-23.[37,38] Therefore, guselkumab may be enriched within the inflamed tissue microenvironment by binding to CD64, neutralizing IL-23 at its cellular source,[39] and suppressing immune activation at the critical "myeloid/T-cell" interface. The relevance of the findings from these in vitro studies to clinical outcomes in patients with IBD are being investigated.

The collection of data in a treat-through, blinded fashion in this study helps in the understanding of the therapeutic benefit of additional guselkumab treatment administered subcutaneously in patients with UC who did not initially achieve clinical response to IV guselkumab at week 12. This study had a broad patient population with high disease burden and treatment refractoriness, including a substantial subpopulation with both disease refractory to $\geq$2 advanced therapies and severe endoscopic disease (ie, baseline Mayo endoscopy subscore of 3). However, patients with isolated proctitis were excluded, which limits the generalizability of the findings. Another limitation of this study is that only the primary endpoint was multiplicity controlled. The major secondary endpoints were not sufficiently powered for interim analysis due to sample size. Although other endpoints were prespecified, they may be subject to type 1 error and should be interpreted with caution. The efficacy and safety of guselkumab induction and maintenance therapy in a larger patient population will be evaluated in Phase 3 (NCT04033445).

In conclusion, guselkumab induction therapy at 200 mg and 400 mg in patients with moderately to severely active UC demonstrated superior efficacy compared with placebo at week 12. Greater proportions of guselkumab-treated compared with placebo-treated patients achieved clinical and HRQoL endpoints with consistent results among patients with or without prior inadequate response/intolerance to advanced therapy. Furthermore, week-12 IV guselkumab clinical nonresponders benefited from additional guselkumab treatment administered subcutaneously during the uncontrolled study period. The safety results were consistent with the known and favorable safety profile of guselkumab in approved indications, and the efficacy and safety of guselkumab were comparable at both doses. Larger

Phase 3 studies of guselkumab in patients with UC are warranted.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2023.08.038.

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Data Availability

The data-sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access Project site at http://yoda.yale.edu.