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# 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

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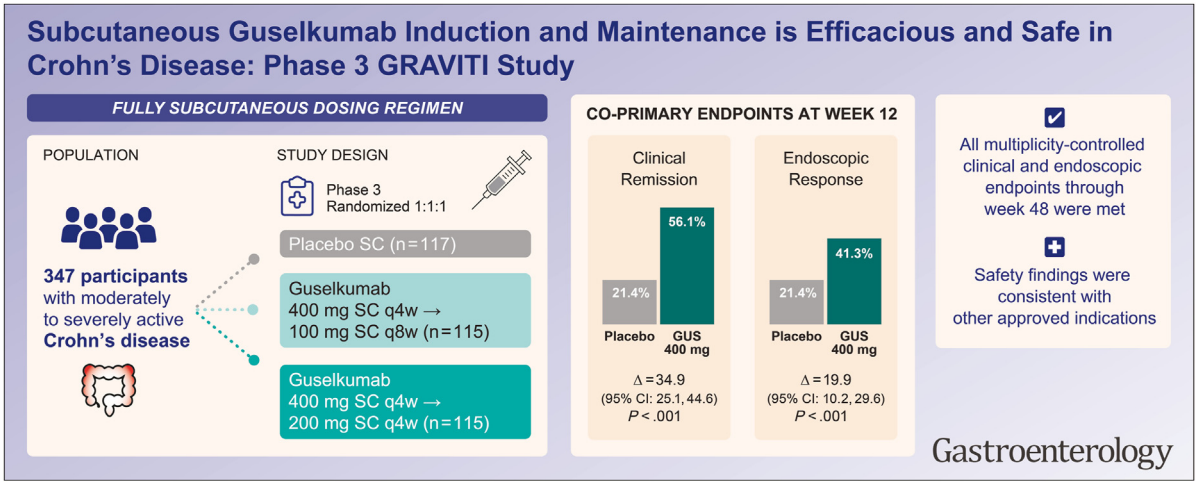


**BACKGROUND & AIMS:** Subcutaneous (SC) induction and maintenance with guselkumab was evaluated in adult participants with moderately to severely active Crohn's disease. **METHODS:** The Phase 3 double-blind, placebo-controlled, treat-through GRAVITI study randomized 347 participants 1:1:1 to guselkumab 400 mg SC every 4 weeks→100 mg SC every 8 weeks (n = 115), guselkumab 400 mg SC every 4 weeks→200 mg SC every 4 weeks (n = 115), or placebo (n = 117). Placebo participants meeting rescue criteria received guselkumab from week 16 onward. Co-primary endpoints were clinical remission at week 12 and endoscopic response at week 12. Additional multiplicity-controlled endpoints were Patient-Reported Outcome-2 remission (week 12), clinical response (week 12), clinical remission (week 24), clinical remission (week 48), and endoscopic response (week 48). Safety was assessed through week 48. **RESULTS:** All multiplicity-controlled endpoints were met. At week 12, significantly greater proportions of participants receiving guselkumab 400 mg achieved clinical remission vs placebo (56.1% vs 21.4%; $\Delta = 34.9$; $P < .001$), and endoscopic response vs placebo (41.3% vs 21.4%; $\Delta = 19.9$; $P < .001$). At week 48, significantly greater proportions of participants in both guselkumab groups (100 mg SC every 8 weeks: 60.0%, $\Delta = 42.8$; 200 mg SC every 4 weeks: 66.1%, $\Delta = 48.9$) achieved clinical remission vs placebo (17.1%; $P < .001$ each) and endoscopic response (44.3%, $\Delta = 37.5$; 51.3%, $\Delta = 44.6$; vs placebo 6.8%; $P < .001$ each). Efficacy was observed in both bionaive participants and those with inadequate response or intolerance to biologics. Adverse event rates were not greater in guselkumab groups vs placebo. **CONCLUSION:** Subcutaneous guselkumab for both induction and maintenance was efficacious in treating participants with moderately to severely active Crohn's disease. Safety findings were consistent with those of guselkumab in approved indications, including ulcerative colitis. (ClinicalTrials.gov, Number: NCT05197049.)

*Keywords:* Crohn's Disease; Efficacy; Endoscopy; Guselkumab; Safety.

Crohn's disease is a chronic, relapsing, inflammatory bowel disease (IBD) that usually requires long-term treatment. Although several classes of advanced therapies for Crohn's disease are currently available, an unmet need still remains for therapies with increased efficacy, favorable benefit/risk profile, and convenient dosing options for induction and maintenance. Interleukin (IL)-23 inhibitors have been shown to be effective in reducing the signs and symptoms of Crohn's disease and ulcerative colitis.[1–5]

Guselkumab is a selective dual-acting IL-23p19 subunit inhibitor that potently neutralizes IL-23 by binding to the p19 subunit and to CD64, a receptor on cells that produce IL-23.[6] Guselkumab (TREMFYA; Janssen Biotech, Inc., Horsham, PA) is approved for the treatment of Crohn's disease,[7] ulcerative colitis,[8] moderate to severe plaque psoriasis,[9–12] and psoriatic arthritis.[13,14] In the double-blind Phase 2 GALAXI 1 study[15] and the 2 identically designed double-blind Phase 3 GALAXI 2 and GALAXI 3 studies,[16–18] guselkumab intravenous (IV) induction (200 mg at weeks 0, 4, and 8) followed by subcutaneous (SC) maintenance (200 mg every 4 weeks or 100 mg every 8 weeks) demonstrated efficacy compared with placebo and a safety profile similar to known indications. In addition, guselkumab demonstrated superiority to ustekinumab for multiple endoscopic-based endpoints at week 48 in pooled data from GALAXI 2 and GALAXI 3.

SC delivery of biologic agents has become increasingly available as an alternative to IV administration across many disease areas, and a patient's individual preference with respect to route of administration is an important factor in treatment selection.[19–23] A fully SC induction and maintenance regimen provides flexible and patient-friendly administration options in their preferred setting, while limiting demands for infusion services/centers.[20,24,25] Currently approved IL-23p19 subunit inhibitors for IBD require IV induction.

Here we present the results through week 48 from the GRAVITI study, which evaluated the efficacy and safety of guselkumab SC induction followed by SC maintenance in participants with moderately to severely active Crohn's disease in a treat-through design.

**WHAT YOU NEED TO KNOW**

BACKGROUND AND CONTEXT

Interleukin-23p19 subunit inhibitors are effective treatment for patients with inflammatory bowel disease, including Crohn's disease. However, currently available interleukin-23p19 treatments require intravenous induction dosing, which may be burdensome for patients and health care providers.

NEW FINDINGS

In the Phase 3 GRAVITI study, subcutaneous induction with guselkumab resulted in significantly greater improvements in clinical and endoscopic outcomes vs placebo.

CLINICAL RESEARCH RELEVANCE

Subcutaneous administration of biologics (vs intravenous administration) may be preferred by patients and health care providers because it provides the option for self-administration, has minimally invasive administration, and requires reduced time and resource utilization. In GRAVITI, subcutaneous guselkumab induction induced clinical remission and endoscopic response in a significantly greater proportion of participants with moderately to severely active Crohn's disease vs placebo.

BASIC RESEARCH RELEVANCE

This treat-through study demonstrated that a fully subcutaneous guselkumab induction and maintenance regimen is effective and well-tolerated in participants with moderately to severely active Crohn's disease. Our findings distinguish guselkumab from the other approved interleukin-23p19 subunit inhibitors for inflammatory bowel disease (ie, risankizumab, mirikizumab) that require intravenous induction.

## Methods

### *Participants*

Adults (age ≥18 years) with moderately to severely active Crohn's disease (≥3 months duration with colitis, ileitis, or ileocolitis previously confirmed by radiography, histology, and/or endoscopy) were included in the study. To be eligible, participants must have had active Crohn's disease, defined as a baseline Crohn's Disease Activity Index (CDAI) score ≥220 but ≤450 and either a mean daily number of liquid or very soft stools ≥4 (based on the unweighted CDAI stool frequency component) or a mean daily abdominal pain score ≥2 (based on the unweighted CDAI component of abdominal pain). Participants also must have had endoscopic evidence of active ileocolonic Crohn's disease defined as a baseline Simple Endoscopic Score for Crohn's Disease (SES-CD) ≥6 (or ≥4 for participants with isolated ileal disease), and the presence of ulceration in at least 1 of the 5 ileocolonic segments at endoscopy as assessed by a blinded central reader.

Participants must have demonstrated an inadequate response or intolerance to oral corticosteroids, azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX), or biologic therapy (infliximab, adalimumab, certolizumab pegol, vedolizumab, or approved biosimilars for these agents). Inadequate response was defined as primary nonresponse (ie, no initial response) or secondary nonresponse (ie, response initially but subsequently lost response). There was no limit to the number of biologic therapies that a participant could have

***Abbreviations used in this paper:*** **6-MP, 6-mercaptopurine; AE, adverse event; AZA, azathioprine; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; IBD, inflammatory bowel disease; IBDQ, Inflammatory Bowel Disease Questionnaire; IL, interleukin; IV, intravenous; MTX, methotrexate; PRO-2, Patient-Reported Outcome-2; PY, participant year; SAE, serious adverse event; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease.**

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previously failed. The study was initiated before Janus kinase inhibitors were approved for Crohn's disease, and therefore Janus kinase inhibitors were not included in the inclusion/exclusion criteria.

Participants receiving oral 5-aminosalicylic acid compounds, AZA, 6-MP, MTX, rectal corticosteroids (including budesonide and beclomethasone dipropionate), antibiotics, and/or enteral nutrition for the treatment of Crohn's disease at baseline were required to maintain a stable dose for a specified period before baseline and through week 48. Participants were permitted to receive oral corticosteroids (up to 40 mg/d prednisone or equivalent) at study entry and were required to maintain a stable dose until week 12, at which point mandatory dose tapering was initiated, unless not medically feasible. Enrolled participants were not to initiate oral or rectal 5-aminosalicylic acid compounds, AZA, 6-MP, MTX, or parenteral or oral corticosteroids as treatment for Crohn's disease from week 0 (baseline) through week 48, unless medically necessary.

Participants were excluded from the study if they received anti–tumor necrosis factor therapy (eg, infliximab, etanercept, certolizumab pegol, adalimumab, golimumab) within 8 weeks before baseline, vedolizumab within 12 weeks of baseline, or other immunomodulatory biologic agents, including approved and investigational biologic agents, within 12 weeks of baseline or within 5 half-lives of baseline, whichever was longer. Participants with prior exposure to IL-12/23 or IL-23 agents were ineligible for this study.

Additional key exclusion criteria were the presence of complications of Crohn's disease that could require surgery, presence or suspicion of an abscess, draining stoma or ostomy, recent surgery, and evidence of enteric infection (in the past 4 months). A complete list of inclusion and exclusion criteria are presented in the Supplementary Material.

## Study Design

GRAVITI was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study with a treat-through design that evaluated the efficacy and safety of 12 weeks of guselkumab SC induction therapy followed by SC maintenance therapy. Participants were enrolled at 143 global sites from 23 countries/territories (beginning February 22, 2022).

The study consisted of a screening phase (up to 5 weeks), a main treatment phase of 24 weeks, and an extension treatment phase. This report includes data for the blinded portion of the study through week 48 (Figure 1).

The guselkumab SC induction dose regimen (400 mg SC at weeks 0, 4, and 8) was selected for this study based on pharmacokinetic modeling using data from the Phase 2 dose-ranging study of guselkumab IV in Crohn's disease (GALAXI 1).[15] In the GALAXI 1 study, similar efficacy was achieved with guselkumab IV induction doses of 200, 600, and 1200 mg administered at weeks 0, 4, and 8, and the 200 mg IV dose was selected for confirmatory evaluation of efficacy and safety in Phase 3 studies (GALAXI 2 and GALAXI 3).[16–18] With an estimated bioavailability of approximately 50%,[7] a SC dosage of 400 mg was expected to result in overall guselkumab exposure that is comparable to the IV dosage of 200 mg.

At baseline, participants were randomized in a 1:1:1 ratio to guselkumab 400 mg SC at weeks 0, 4, and 8 followed by guselkumab 100 mg SC every 8 weeks starting at week 16; guselkumab 400 mg SC at weeks 0, 4, and 8 followed by guselkumab 200 mg SC every 4 weeks starting at week 12; or placebo SC. An interactive web response system was used for permuted-block randomization, stratified by baseline CDAI score ($\leq$300 or >300), baseline SES-CD score ($\leq$12 or >12), and inadequate response or intolerance to biologic therapy status (yes or no) at baseline.

Guselkumab was provided in 2 doses: 100 mg/1 mL in a single-dose prefilled syringe and guselkumab 200 mg/2 mL in a single-dose autoinjector pen. Matching placebo was provided for each dose and device.

To maintain blinding, all treatment groups received 2 SC injections at weeks 0, 4, and 8 (either 2 active or 2 placebo). In addition, all treatment groups received 1 SC injection (either active or placebo) at week 12 and up to 2 or 3 SC injections (either active or placebo) at each visit from week 16 onward, depending on if rescue criteria were met.

Participants in the placebo group were eligible for rescue therapy if they met at least 1 of the following rescue criteria: (1) CDAI score >220 and <70-point reduction from baseline CDAI at both weeks 12 and 16, or (2) SES-CD score increase by $\geq$50% from baseline at week 12. Participants in the placebo group who met the criteria for rescue therapy received guselkumab 400 mg SC at weeks 16, 20, and 24 followed by guselkumab 100 mg SC every 8 weeks. To maintain the blind, participants randomized to guselkumab who met the rescue criteria continued their assigned treatment regimen and received blinded sham rescue with a matching placebo SC injection.

Investigators, study-site personnel, and participants were blinded to study intervention through the week-48 database lock. On study unblinding, placebo participants who were not rescued were discontinued from study intervention.

The study protocol (see Supplementary Material) was approved by investigational review boards or ethics committees at each site, and written informed consent was provided by all participants. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All authors had access to the study data and reviewed and approved the final manuscript.

## Assessments

CDAI score was determined every 4 weeks through week 48. Patient-Reported Outcome (PRO)-2, including symptoms of stool frequency (number of liquid or very soft stools) and abdominal pain, were recorded by participants in a daily diary.

Endoscopic assessments were performed in all participants at screening and at weeks 12 and 48. Video recordings of the ileocolonoscopies were assessed by a central reader blinded to treatment allocation and study visit.

Inflammatory biomarkers (C-reactive protein [CRP] and fecal calprotectin) were assessed. CRP was assessed at baseline and weeks 4, 8, 12, 16, 20, 24, 32, 40, and 48. Fecal calprotectin was assessed at baseline and weeks 4, 8, 12, 24, and 48.

Disease-specific health-related quality of life was assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ)[26] at baseline and weeks 8, 12, 24, and 48.

Safety assessments, including adverse events (AEs) and serious adverse events (SAEs), were evaluated at every study visit in all participants.

Serum guselkumab concentrations were assessed at weeks 0, 4, 8, 12, 16, 20, 24, 32, 40, and 48.

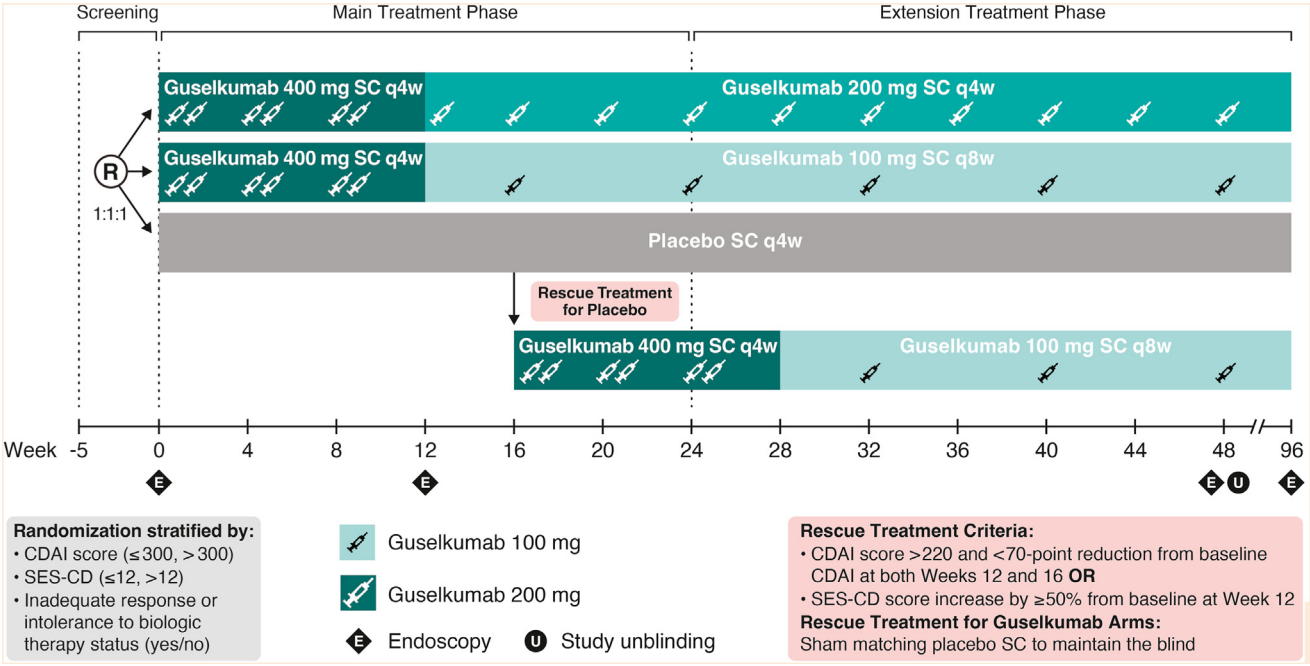


**Figure 1.** Study design. Participants received matching placebo at each time point to maintain the blind. Only active treatment administrations are depicted in the figure.

Serum antibodies to guselkumab were evaluated using a validated, drug-tolerant electrochemiluminescent immunoassay (data on file).

## Outcomes

**Efficacy endpoints.** The co-primary endpoints were clinical remission (CDAI score <150) at week 12 and endoscopic response (≥50% improvement from baseline in the SES-CD score) at week 12. Additional multiplicity-controlled endpoints were PRO-2 remission (an abdominal pain mean daily score ≤1 and stool frequency mean daily score ≤3 and no worsening of abdominal pain or stool frequency from baseline) at week 12, clinical response (CDAI ≥100-point reduction from baseline or clinical remission [CDAI score <150]) at week 12, clinical remission at week 24, clinical remission at week 48, and endoscopic response at week 48. Endoscopic response using an alternative definition (>50% improvement from baseline in SES-CD score or SES-CD score ≤2) was also assessed at weeks 12 and 48.

Additional efficacy endpoints, endoscopic remission (SES-CD score ≤4 and at least a 2-point reduction from baseline and no subscore greater than 1 in any individual component) and deep remission (achieving both clinical remission and endoscopic remission) were assessed at week 48. An alternative definition of endoscopic remission (SES-CD score ≤2) was also evaluated at week 48.

Median change in CRP and fecal calprotectin concentrations from baseline were evaluated over time through week 48. Elevated CRP (>5 mg/L) and elevated fecal calprotectin (>250 mg/kg) were assessed using a central laboratory. IBDQ remission was defined as IBDQ score ≥170.

Incidence of anti-drug antibodies to guselkumab was evaluated.

**Safety.** Proportions of participants with AEs, SAEs, AEs of interest, serious infections, and AEs leading to discontinuation of study agent were evaluated through week 48. Given that placebo-treated participants who met the prespecified criteria could be rescued with guselkumab treatment at week 16, the average duration of follow-up was shorter in the placebo group than in the guselkumab treatment groups. Therefore, follow-up time-adjusted analyses (ie, number of events per 100 participant years; 100 PYs) through week 48 are also provided for AEs, SAEs, AEs leading to discontinuation of study intervention, and serious infections.

## Statistical Analysis

Efficacy analyses included randomized participants who received ≥1 dose of study agent. The 2 randomized guselkumab groups received an identical SC induction regimen through week 12 (guselkumab 400 mg at weeks 0, 4, and 8) and were therefore combined for all week-12 analyses, including the co-primary endpoints; this approach was prespecified. A multiplicity-controlled testing procedure was used to control the Type I error rate at the .05 (2-sided) significance level across the co-primary and additional multiplicity-controlled endpoints. Co-primary and additional multiplicity-controlled endpoints were also evaluated by biologic therapy history (bionaive or an inadequate response or intolerance to biologic therapies).

Participants who had a Crohn's disease–related surgery, a prohibited change in concomitant Crohn's disease medications, discontinued study agent due to lack of efficacy, an AE of worsening Crohn's disease, or discontinued study agent for any other reason other than COVID-19–related reasons or regional crisis before the designated analysis timepoint were considered not to have achieved the binary endpoint from that timepoint onward (ie, treatment failure). Participants who had discontinued study agent due to COVID-19–related reasons (excluding COVID-19 infection) or regional crisis had their observed data used, if available, to determine responder status from that timepoint onward.

To appropriately compare the guselkumab treatment arms to placebo for endpoints after week 16, participants in all

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treatment groups who met rescue criteria were considered not to have met binary endpoints after week 16. Participants with missing endpoint values at the designated analysis timepoint, including missing endoscopies, after accounting for the treatment failure and rescue criteria rules above, were also considered not to have met the endpoint at that timepoint.

Guselkumab treatment group(s) vs placebo in terms of the adjusted treatment difference(s), confidence interval(s) (CI), and *P* value(s) for the binary endpoints were based on the Common Risk Difference using Mantel-Haenszel stratum weights and the Sato variance estimator and tested at a significance level of .05, 2-sided.

Safety analyses included all randomized participants who received at least 1 dose of study agent.

## Results

### *Patient Disposition and Baseline Demographic Characteristics*

At baseline, 347 participants were randomized 1:1:1 to guselkumab 400 mg SC every 4 weeks→100 mg SC every 8 weeks (n = 115); guselkumab 400 mg SC every 4 weeks→200 mg SC every 4 weeks (n = 115); or placebo SC (n = 117). At week 16, 44 participants (37.6%) in the placebo group met the rescue criteria and switched to guselkumab; 14 participants (12.2%) in the guselkumab 400 mg SC every 4 weeks→100 mg SC every 8 weeks group and 14 participants (12.2%) in the guselkumab 400 mg SC every 4 weeks→200 mg SC every 4 weeks also met rescue criteria and received sham rescue with placebo.

A total of 15 participants (4.3%) discontinued study agent before week 12 (placebo SC: 12 of 117 participants [10.3%]; guselkumab 400 mg SC every 4 weeks: 3 of 230 participants [1.3%]) (Supplementary Figure 1). The most common reason for discontinuation of study agent before week 12 across all groups was withdrawal by participant (2.0%). Overall, including the through week-12 data above, 53 participants (15.3%) discontinued study agent before week 48 (placebo SC: 31 of 117 participants [26.5%]; placebo→guselkumab: 5 of 44 participants [11.4%]; guselkumab 400 mg SC every 4 weeks→100 mg SC every 8 weeks: 12 of 115 participants [10.4%]; guselkumab 400 mg SC every 4 weeks→200 mg SC every 4 weeks: 5 of 115 participants [4.3%]) (Supplementary Figure 1). The placebo SC group excluded data after a placebo participant was rescued with guselkumab. The most common reasons for discontinuation through week 48 included withdrawal by participant (14 participants [4.0%]), lack of efficacy (10 participants [2.9%]), and AE of worsening of Crohn's disease (9 participants [2.6%]).

Baseline demographics and disease characteristics were generally comparable, and there were no clinically relevant differences among groups (Table 1). Overall, 58.5% of participants were men, the mean (standard deviation) age was 37.5 (12.89) years, and the mean duration of Crohn's disease was 8.00 (8.053) years. Overall, the mean CDAI score at baseline was 296.9 (52.68) and the mean SES-CD score was 12.0 (6.94). At baseline, participants were receiving the following concomitant therapies: 6-MP/AZA (27.7%), methotrexate (0.9%), oral aminosalicylates (40.6%), and oral corticosteroids (29.7%). Overall, 46.4% (n = 161) of participants at baseline had an inadequate response or intolerance to prior biologic therapy. Of these, most (71.4%; 115 of 161) had prior inadequate response or intolerance to 1 biologic only, whereas 28.6% (46 of 161) had ≥2 biologics. Nearly all had prior inadequate response or intolerance to ≥1 anti–tumor necrosis factor (94.4%; 152 of 161). At baseline, 46.4% (n = 161) of all participants were bionaive. In addition, 7.2% (n = 25) of all participants were exposed to biologics but had no documented history of inadequate response or intolerance.

At baseline, elevated CRP (>5 mg/L) was reported in 54.8% (n = 190) of participants and elevated fecal calprotectin (>250 μg/g) was reported in 71.7% (n = 248) of participants.

### *Efficacy*

**Week 12 endpoints.** The co-primary endpoints were met with guselkumab SC induction treatment. Significantly greater proportions of participants in the combined guselkumab 400 mg SC every 4 weeks group achieved clinical remission at week 12 (56.1% vs 21.4%; Δ = 34.9; 95% CI, 25.1–44.6; $P < .001$) vs placebo (Figure 2*A*).

Significantly greater proportions of the combined guselkumab 400 mg SC every 4 weeks group achieved endoscopic response at week 12 (41.3% vs 21.4%; Δ = 19.9; 95% CI, 10.2–29.6; $P < .001$) vs placebo (Figure 2*A*). Using an alternative definition of endoscopic response (>50% improvement from baseline in SES-CD score or SES-CD score ≤2), greater proportions of participants in the combined guselkumab group achieved endoscopic response at week 12 vs placebo (34.3% vs 14.5%; Δ = 19.7; 95% CI, 10.9–28.4; nominal $P < .001$) (Figure 2*C*).

Significantly greater proportions of participants in the combined guselkumab 400 mg SC every 4 weeks group achieved PRO-2 remission at week 12 vs placebo (49.1% vs 17.1%; Δ = 32.1; 95% CI, 22.9–41.2; $P < .001$) (Figure 2*B*).

Similarly, significantly greater proportions of participants in the combined guselkumab 400 mg SC every 4 weeks group achieved clinical response at week 12 vs placebo (73.5% vs 33.3%; Δ = 40.3; 95% CI, 29.9–50.7; $P < .001$) (Figure 2*B*).

**Week 24 and week 48 endpoints.** Significantly greater proportions of participants in the guselkumab 400 mg SC every 4 weeks→100 mg SC every 8 weeks group (60.9%, Δ = 39.3; 95% CI, 28.0–50.7) and the guselkumab 400 mg SC every 4 weeks→200 mg SC every 4 weeks group (58.3%, Δ = 37.0; 95% CI, 25.6–48.4) achieved clinical remission at week 24 compared with placebo (21.4%; $P < .001$ for both) (Figure 3*A*).

Likewise, significantly greater proportions of participants in the guselkumab 400 mg SC every 4 weeks→100 mg SC every 8 weeks group (60.0%, Δ = 42.8; 95% CI, 31.6–54.0) and the guselkumab 400 mg SC every 4 weeks→200 mg SC every 4 weeks group (66.1%, Δ = 48.9; 95% CI, 37.9–59.9) achieved clinical remission at week 48 vs placebo (17.1%; $P < .001$ for each) (Figure 3*B*). The proportion of participants achieving clinical remission over time through week 48 is shown in Figure 3*C*.

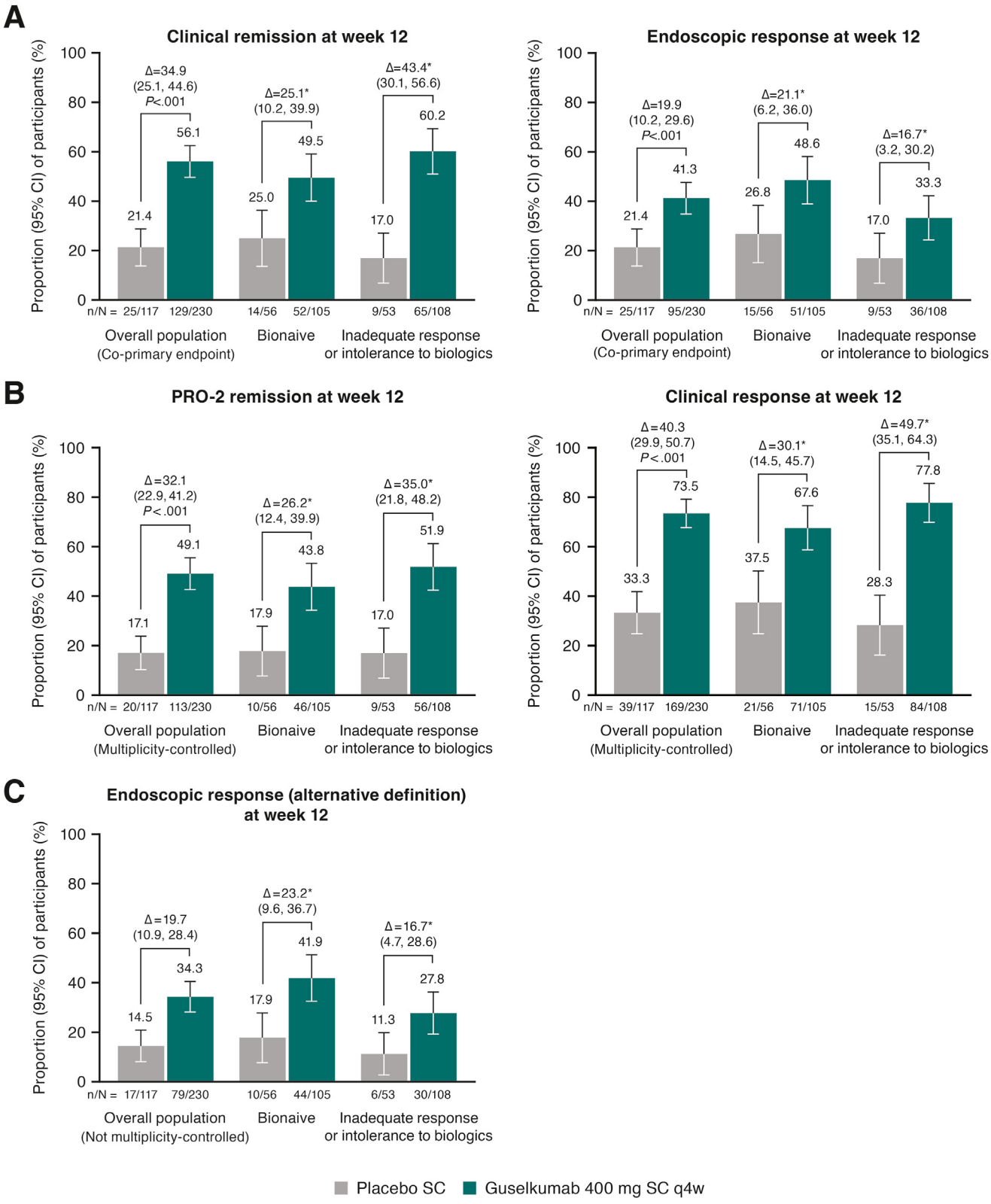
**Table 1.** Baseline Demographics and Disease Characteristics

| | | Guselkumab | | | |
|---|---|---|---|---|---|
| | Placebo SC | 400 mg SC q4w→ 100 mg SC q8w | 400 mg SC q4w→ 200 mg SC q4w | Combined | Total |
| Participants included in efficacy analysis, N | 117 | 115 | 115 | 230 | 347 |
| Age, *y*, mean (SD) | 36.0 (12.71) | 37.4 (13.32) | 39.1 (12.56) | 38.2 (12.95) | 37.5 (12.89) |
| Median (IQR) | 36.0 (24.0; 42.0) | 35.0 (27.0; 47.0) | 39.0 (29.0; 47.0) | 36.0 (28.0; 47.0) | 36.0 (27.0; 45.0) |
| Men, n (%) | 67 (57.3) | 66 (57.4) | 70 (60.9) | 136 (59.1) | 203 (58.5) |
| Race, n (%) | | | | | |
| White | 71 (60.7) | 79 (68.7) | 79 (68.7) | 158 (68.7) | 229 (66.0) |
| Asian | 28 (23.9) | 26 (22.6) | 22 (19.1) | 48 (20.9) | 76 (21.9) |
| Black or African American | 5 (4.3) | 0 | 4 (3.5) | 4 (1.7) | 9 (2.6) |
| Not reported | 13 (11.1) | 10 (8.7) | 10 (8.7) | 20 (8.7) | 33 (9.5) |
| Ethnicity, n (%) | | | | | |
| Not Hispanic or Latino | 93 (79.5) | 94 (81.7) | 98 (85.2) | 192 (83.5) | 285 (82.1) |
| Hispanic or Latino | 9 (7.7) | 10 (8.7) | 8 (7.0) | 18 (7.8) | 27 (7.8) |
| Not reported | 15 (12.8) | 11 (9.6) | 9 (7.8) | 20 (8.7) | 35 (10.1) |
| Weight, *kg*, mean (SD) | 68.13 (16.197) | 70.88 (19.002) | 72.88 (19.283) | 71.88 (19.127) | 70.61 (18.255) |
| Crohn's disease duration, *y*, mean (SD) | 6.96 (7.752) | 9.17 (9.079) | 7.89 (7.126) | 8.53 (8.168) | 8.00 (8.053) |
| CDAI score, mean (SD) | 293.0 (49.09) | 300.4 (54.32) | 297.3 (54.69) | 298.8 (54.41) | 296.9 (52.68) |
| Abdominal pain and stool frequency, n (%) | | | | | |
| Number of liquid or very soft stools ≥4 | 79 (67.5) | 89 (77.4) | 80 (69.6) | 169 (73.5) | 248 (71.5) |
| Abdominal pain score ≥2 | 96 (82.1) | 93 (80.9) | 85 (73.9) | 178 (77.4) | 274 (79.0) |
| Number of liquid or very soft stools ≥4 and abdominal pain score ≥2 | 60 (51.3) | 67 (58.3) | 53 (46.1) | 120 (52.2) | 180 (51.9) |
| SES-CD score, mean (SD) | 12.0 (6.89) | 12.2 (6.85) | 11.8 (7.12) | 12.0 (6.97) | 12.0 (6.94) |
| Involved GI areas,[a] n (%) | | | | | |
| Ileum only | 22 (18.8) | 25 (21.7) | 27 (23.5) | 52 (22.6) | 74 (21.3) |
| Colon only | 40 (34.2) | 41 (35.7) | 40 (34.8) | 81 (35.2) | 121 (34.9) |
| Ileum and colon | 55 (47.0) | 49 (42.6) | 48 (41.7) | 97 (42.2) | 152 (43.8) |
| CRP (mg/L) | | | | | |
| Median (IQR) | 7.9 (2.1; 14.7) | 5.2 (1.7; 13.3) | 5.7 (1.7; 16.1) | 5.5 (1.7; 14.9) | 5.8 (1.8; 14.9) |
| CRP >5 mg/L, n (%) | 70 (59.8) | 59 (51.3) | 61 (53.0) | 120 (52.2) | 190 (54.8) |
| Fecal calprotectin (μg/g), N | 117 | 115 | 114 | 229 | 346 |
| Median (IQR) | 712.0 (243.0; 1724.0) | 610.0 (226.0; 1554.0) | 600.5 (235.0; 1650.0) | 610.0 (228.0; 1608.0) | 643.0 (235.0; 1650.0) |
| Fecal calprotectin >250 μg/g, n (%) | 86 (73.5) | 83 (72.2) | 79 (69.3) | 162 (70.7) | 248 (71.7) |
| IBDQ, N | 111 | 108 | 110 | 218 | 329 |
| Mean (SD) | 125.0 (35.60) | 123.9 (31.95) | 118.6 (30.04) | 121.2 (31.05) | 122.5 (32.65) |

**Table 1.** Continued

| | | Guselkumab | | | |
|---|---|---|---|---|---|
| | Placebo SC | 400 mg SC q4w→ 100 mg SC q8w | 400 mg SC q4w→ 200 mg SC q4w | Combined | Total |
| Crohn's disease medication taken at baseline, n (%) | 79 (67.5) | 74 (64.3) | 84 (73.0) | 158 (68.7) | 237 (68.3) |
| 6-mercaptopurine /azathioprine | 32 (27.4) | 28 (24.3) | 36 (31.3) | 64 (27.8) | 96 (27.7) |
| Methotrexate | 1 (0.9) | 1 (0.9) | 1 (0.9) | 2 (0.9) | 3 (0.9) |
| Oral aminosalicylates | 50 (42.7) | 47 (40.9) | 44 (38.3) | 91 (39.6) | 141 (40.6) |
| Oral corticosteroid use | 33 (28.2) | 32 (27.8) | 38 (33.0) | 70 (30.4) | 103 (29.7) |
| Corticosteroid use (excluding budesonide) | 18 (15.4) | 15 (13.0) | 28 (24.3) | 43 (18.7) | 61 (17.6) |
| Median (IQR) daily prednisone-equivalent dose, mg | 20 (10.0; 20.0) | 20 (10.0; 25.0) | 15.0 (10.0; 25.0) | 20.0 (10.0; 25.0) | - |
| Budesonide | 15 (12.8) | 17 (14.8) | 10 (8.7) | 27 (11.7) | 42 (12.1) |
| Rectal corticosteroid use | 0 | 0 | 0 | 0 | 0 |
| Antibiotics | 3 (2.6) | 3 (2.6) | 8 (7.0) | 11 (4.8%) | 14 (4.0) |
| Biologic naive, n (%) | 56 (47.9) | 53 (46.1) | 52 (45.2) | 105 (45.7) | 161 (46.4) |
| Previous biologic use, n (%) | 64 (54.7) | 60 (52.2) | 62 (53.9) | 122 (53.0) | 186 (53.6) |
| Biologic-experienced, but no documented inadequate response or intolerance to biologics, n (%) | 8 (6.8) | 7 (6.1) | 10 (8.7) | 17 (7.4) | 25 (7.2) |
| Inadequate response or intolerance to prior biologic therapy,[b] n (%) | 53 (45.3) | 55 (47.8) | 53 (46.1) | 108 (47.0) | 161 (46.4) |
| 1 biologic | 40 (75.5) | 37 (67.3) | 38 (71.7) | 75 (69.4) | 115 (71.4) |
| ≥2 biologics | 13 (24.5) | 18 (32.7) | 15 (28.3) | 33 (30.6) | 46 (28.6) |
| 1 anti-TNF | 39 (73.6) | 39 (70.9) | 39 (73.6) | 78 (72.2) | 117 (72.7) |
| ≥1 anti-TNF | 50 (94.3) | 51 (92.7) | 52 (98.1) | 103 (95.4) | 153 (95.0) |
| Anti-TNF only | 45 (84.9) | 42 (76.4) | 47 (88.7) | 89 (82.4) | 134 (83.2) |
| Vedolizumab | 8 (15.1) | 13 (23.6) | 6 (11.3) | 19 (17.6) | 27 (16.8) |
| Vedolizumab only | 3 (5.7) | 4 (7.3) | 1 (1.9) | 5 (4.6) | 8 (5.0) |
| Vedolizumab and ≥1 anti-TNF | 5 (9.4) | 8 (14.5) | 5 (9.4) | 13 (12.0) | 18 (11.2) |

CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; GI, gastrointestinal; IBDQ, Inflammatory Bowel Disease Questionnaire; IQR, interquartile range; q4w/q8w, every 4 or 8 weeks; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; SD, standard deviation; TNF, tumor necrosis factor.
[a]Assessed by a central reader.
[b]Includes adalimumab, certolizumab pegol, infliximab, and vedolizumab (including biosimilars).




*Nominal p-values <.05

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In addition, significantly greater proportions of participants in the guselkumab 400 mg SC every 4 weeks→100 mg SC every 8 weeks group (44.3%; Δ = 37.5; 95% CI, 27.3–47.7) and in the guselkumab 400 mg SC every 4 weeks→200 mg SC every 4 weeks group (51.3%; Δ = 44.6; 95% CI, 34.1–55.0) achieved endoscopic response at week 48 compared with placebo (6.8%; $P < .001$ for each) (Figure 3*D*). Using an alternative definition of endoscopic response, greater proportions of guselkumab-treated participants achieved the endpoint at week 48 compared with placebo, with a similar treatment effect to that observed with the primary definition (Figure 3*D*).

Greater proportions of participants in the guselkumab 400 mg SC every 4 weeks→100 mg SC every 8 weeks group (30.4%; Δ = 24.5; 95% CI, 15.2–33.9) and in the guselkumab 400 mg SC every 4 weeks→200 mg SC every 4 weeks group (38.3%; Δ = 32.4; 95% CI, 22.6–42.3) achieved endoscopic remission at week 48 compared with placebo (6.0%; nominal $P < .001$ for both) (Figure 3*E*). Greater proportions of guselkumab participants in the 400 mg SC every 4 weeks→100 mg SC every 8 weeks group (26.1%; Δ = 21.8; 95% CI, 13.1–30.6) and in the guselkumab 400 mg SC every 4 weeks→200 mg SC every 4 weeks group (33.9%; Δ = 29.8; 95% CI, 20.5–39.2) achieved deep remission (both clinical remission *and* endoscopic remission) at week 48 compared with placebo (4.3%, nominal $P < .001$ for both) (Figure 3*E*).

In addition, greater proportions of bionaive participants and participants with an inadequate response or intolerance to biologics in the guselkumab groups achieved clinical remission at week 12 (Figure 2*A*), endoscopic response at week 12 (Figure 2*A*), PRO-2 remission at week 12 (Figure 2*B*), clinical response at week 12 (Figure 2*B*), clinical remission at week 24 (Figure 3*A*), clinical remission at week 48 (Figure 3*B*), and endoscopic response at week 48 (Figure 3*D*) vs placebo. Efficacy endpoints at weeks 12, 24, and 48 in participants with a prior inadequate response or intolerance to biologic therapy by number of prior biologics are shown in Supplementary Figure 2.

**Additional clinical and endoscopic endpoints.** Of the additional prespecified endpoints evaluated, improvements with guselkumab treatment were observed as early as week 4 (the timepoint at which the first assessment was performed after initial administration of study intervention) and were maintained through 48 weeks. Greater proportions of participants in the guselkumab groups achieved clinical response through week 12 vs placebo, with higher responses observed as early as week 4 with guselkumab (Figure 4*A*). Greater proportions of participants in each guselkumab treatment group achieved PRO-2 remission or clinical response through week 48 compared with placebo (Supplementary Figures 3 and 4, respectively). In addition, greater improvements in CDAI scores from baseline were observed in guselkumab-treated participants vs placebo through week 48 (Supplementary Figure 8). Similarly, greater proportions of guselkumab-treated participants achieved improvements in symptomatic outcomes such as abdominal pain (daily average abdominal score ≤1 among participants with score >1 at baseline; week 48: 59.1% and 67.6% vs 15.9%; Supplementary Figure 9*A*) and stool frequency (daily average number of liquid or very soft stools ≤3 among participants with >3 at baseline; week 48: 59.4% and 72.0% vs 21.6%; Supplementary Figure 9*C*) through week 48 vs placebo.

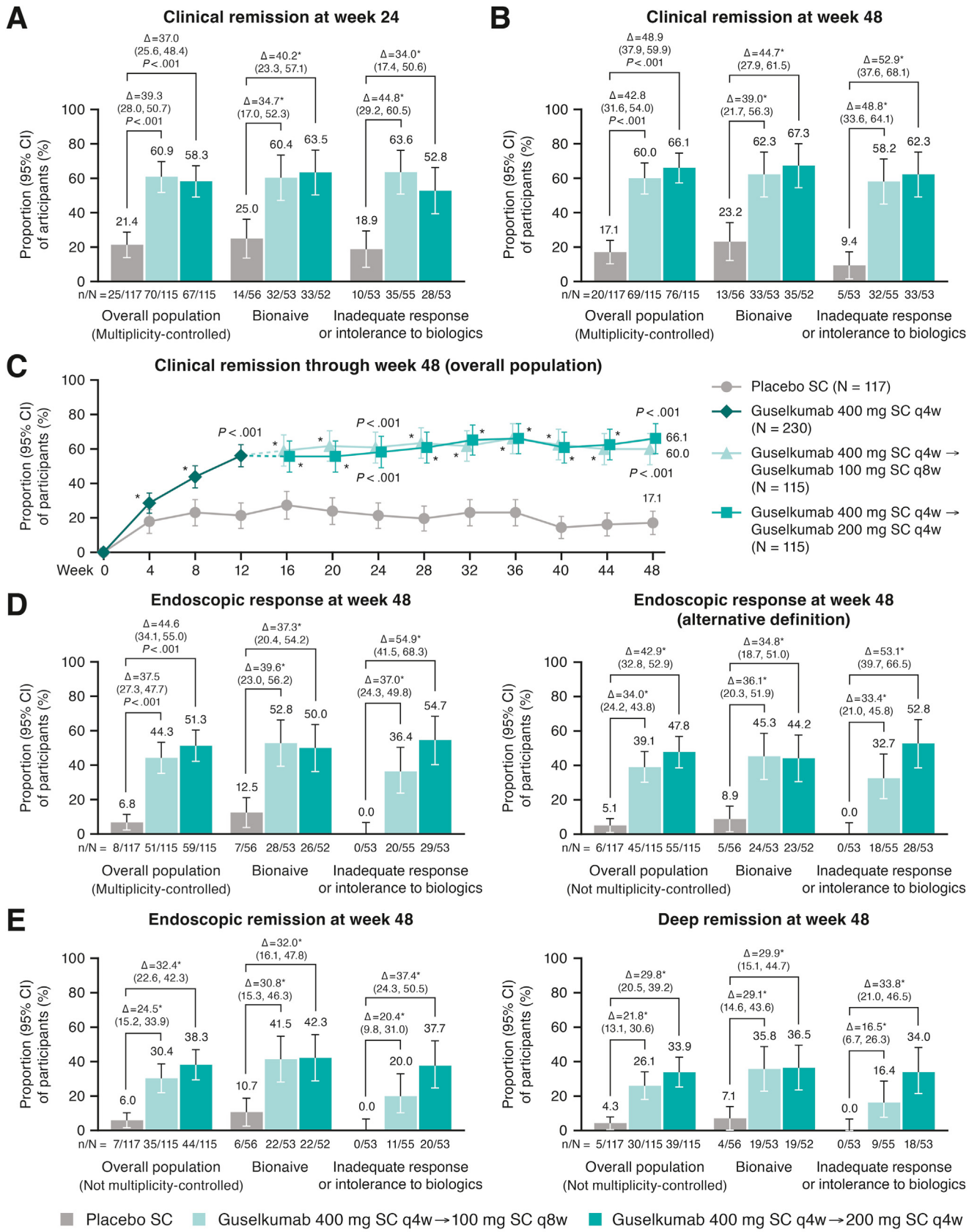
Guselkumab treatment resulted in reductions in corticosteroid use through week 48 (Supplementary Figure 5). Among participants receiving corticosteroids at baseline, greater proportions of guselkumab-treated participants (400 mg SC every 4 weeks→100 mg SC every 8 weeks: 62.5%; 400 mg SC every 4 weeks→200 mg SC every 4 weeks: 81.6%) were not receiving corticosteroids at week 48 vs placebo (18.2%) (Supplementary Figure 6). In addition, greater proportions of guselkumab-treated participants achieved 90-day corticosteroid-free clinical remission at week 48 vs placebo (Supplementary Figure 7). Of the 145 participants in the combined guselkumab group who were in clinical remission at week 48, 142 (97.9%) were not receiving corticosteroids for the 90 days before week 48.

Greater proportions of guselkumab-treated patients achieved endoscopic remission, a stringent endpoint that represents substantial improvement in the intestinal mucosa, at week 12 compared with placebo, as well as at week 48. At week 48, greater proportions of guselkumab participants achieved the composite endpoints of clinical remission and endoscopic response, and endoscopic remission (alternate definition) compared with placebo (Supplementary Table 1).

Greater proportions of guselkumab-treated participants showed improvements in health-related quality of life outcomes assessed by achieving IBDQ remission through week 48 vs placebo (Supplementary Figure 10).

In the efficacy analyses of clinical and endoscopic endpoints, participants who met rescue criteria in any treatment group were considered to have not met dichotomous endpoints after week 16. We also analyzed the data in the guselkumab groups in a "treat-through" manner to replicate real-world clinical practice, in which a patient may remain

**Figure 2.** (*A*) Co-primary endpoints: clinical remission (CDAI <150) at week 12, and endoscopic response (≥50% improvement from baseline in the SES-CD score) at week 12. (*B*) PRO-2 remission (abdominal pain average daily score ≤1 and stool frequency average daily score ≤3, and no worsening of abdominal pain or stool frequency from baseline) at week 12, and clinical response (≥100-point reduction from baseline in CDAI score or CDAI score <150) at week 12. (*C*) Endoscopic response alternative definition (>50% improvement from baseline in the SES-CD score or SES-CD score ≤2) at week 12. Participants who had a Crohn's disease-related surgery, a prohibited change in concomitant Crohn's disease medications, discontinued study agent due to lack of efficacy or an adverse event of worsening Crohn's disease, or discontinued study agent due to COVID-19 infection or for reasons other than lack of efficacy or an adverse event of worsening Crohn's disease, COVID-19 related reasons or regional crisis, before the designated analysis timepoint were considered not to have achieved the binary endpoint from that timepoint onward. Participants who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis had their observed data used, if available, to determine responder status from that timepoint onward.




*Nominal p-value < .05.

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on a therapy beyond the induction period to determine if response can be achieved with a longer duration of treatment. In this scenario, the rescue criteria treatment failure rule was suspended (ie, participants were not considered to be treatment failures if they met rescue criteria). At week 48, in the guselkumab treatment groups, clinical remission, endoscopic response, and endoscopic remission results in the analyses were 3 to 5 percentage points greater at week 48 (Figure 4*B* and *C*) than those in the main analysis in which participants who met rescue criteria were considered to have not met the endpoints. Without rescue criteria treatment failure rules applied, approximately 50% of guselkumab participants achieved endoscopic response at week 48, and approximately 40% achieved endoscopic remission at week 48 (Figure 4*C*).

### Biomarkers

Median CRP concentrations decreased through week 48 with guselkumab treatment compared with placebo. Among participants with an elevated CRP (>5 mg/L) at baseline, a greater proportion of participants receiving guselkumab (41.7%) achieved CRP levels that were within the normal range (≤5 mg/L) at week 12 vs placebo (15.7%) (Figure 5*A*). Median fecal calprotectin concentrations decreased with guselkumab treatment through week 48 compared with placebo. Among participants with elevated fecal calprotectin levels (>250 μg/g) at baseline, a greater proportion of guselkumab-treated participants (37.0%) achieved levels that were ≤250 μg/g at week 12 vs placebo (8.1%) (Figure 5*B*). Overall, CRP and fecal calprotectin levels between weeks 12 and 48 were consistent.

### Safety

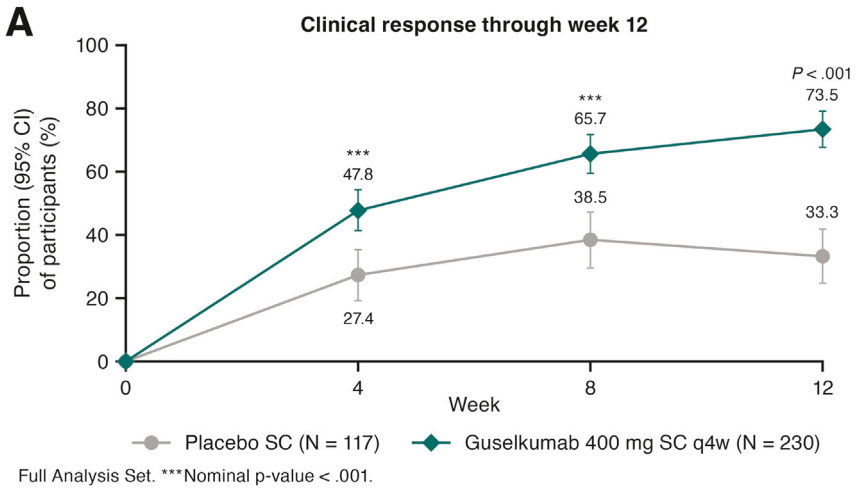
Key safety findings in the safety analysis population through week 48 are reported in Table 2. The average duration of follow-up was 30.0 weeks for the placebo group, 47.0 weeks for the guselkumab 400 mg SC every 4 weeks→100 mg SC every 8 weeks group, and 48.0 weeks for the guselkumab 400 mg SC every 4 weeks→200 mg SC every 4 weeks group. The shorter duration of follow-up for the placebo group was due to the number of participants who met rescue criteria and crossed over to guselkumab.

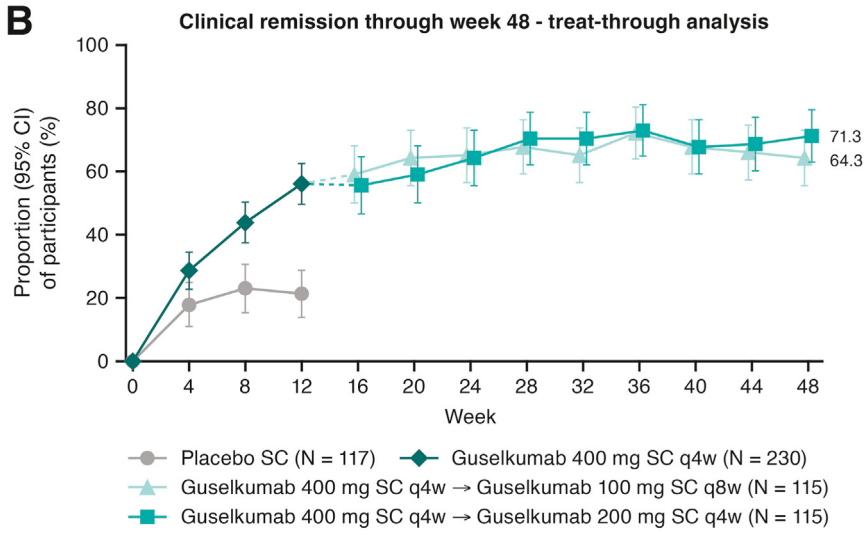
Overall, AEs were reported in 77 of 117 (413.0 events per 100 PYs of follow-up) participants in the placebo group, 95 of 115 (307.2 per 100 PYs) in the guselkumab 400 mg SC every 4 weeks→100 mg SC every 8 weeks group, and 92 of 115 (327.2 per 100 PYs) in the guselkumab 400 mg SC every 4 weeks→200 mg SC every 4 weeks group through week 48. The most commonly reported AEs in the guselkumab groups through week 48 were upper respiratory tract infection, abdominal pain, and COVID-19 (Table 2).

Through week 48, the proportion of guselkumab-treated participants reporting ≥1 SAE or AE leading to discontinuation of study agent were not greater than placebo. SAEs were reported in 16 of 117 (37.1 per 100 PYs) of placebo participants, 15 of 115 (15.5 per 100 PYs) of guselkumab 400 mg SC every 4 weeks→100 mg SC every 8 weeks participants, and 9 of 115 (13.2 per 100 PYs) of guselkumab 400 mg SC every 4 weeks→200 mg SC every 4 weeks participants. The most frequently reported SAEs were complications associated with Crohn's disease. The proportion of participants with AEs leading to discontinuation of study agent through week 48 was 10 of 117 (14.9 per 100 PYs) for the placebo group, 4 of 115 (6.8 per 100 PYs) for the guselkumab 400 mg SC every 4 weeks→100 mg SC every 8 weeks group, and 3 of 115 (2.8 per 100 PYs) in the 400 mg SC every 4 weeks→200 mg SC every 4 weeks group. Crohn's disease was the most frequently reported AE leading to discontinuation of study agent.

The proportions of guselkumab-treated participants with serious infections (1.3%) or AEs of interest were low (Table 2). In the guselkumab treatment groups, no active tuberculosis or anaphylactic or serum sickness reactions were reported through week 48. Through week 48, 1 opportunistic infection was reported in the placebo group (esophageal candidiasis), and 1 in the guselkumab 400 mg SC every 4 weeks→200 mg SC every 4 weeks group (fungal esophagitis). One malignancy (basal cell carcinoma) was reported in a participant in the guselkumab 400 mg SC every 4 weeks→100 mg SC every 8 weeks treatment group through week 48. No major adverse cardiovascular events were reported through week 48. One venous thromboembolism AE was identified in the placebo group and 1 case of portal vein thrombosis was reported in the guselkumab 400 mg SC every 4 weeks→200 mg SC every 4 weeks treatment group in a participant with a medical history and recurrent treatment-emergent AEs of pancreatitis, through week 48.

**Figure 3.** Clinical and endoscopic endpoints during maintenance. (*A*) Clinical remission (CDAI <150) at week 24. (*B*) Clinical remission at week 48. (*C*) Clinical remission over time through week 48. (*D*) Endoscopic response (≥50% improvement from baseline in the SES-CD score) at week 48, and endoscopic response alternative definition (>50% improvement from baseline in the SES-CD score or SES-CD score ≤2) at week 48. (*E*) Endoscopic remission (SES-CD score ≤4 and ≥2-point reduction from baseline and no subscore >1 in any individual component) at week 48, and deep remission (achieving both clinical remission and endoscopic remission) at week 48. In panels *A*, *B*, *D*, and *E*, data are presented for the overall population and subpopulations of bionaive patients and those with inadequate response or intolerance to biologics. In panel *C*, data are presented for the overall population. All participants in all treatment groups who met the rescue criteria were considered not to have met efficacy endpoints after week 16. Participants who had a Crohn's disease-related surgery, a prohibited change in concomitant Crohn's disease medications, discontinued study agent due to lack of efficacy or an adverse event of worsening Crohn's disease, or discontinued study agent due to COVID-19 infection or for reasons other than lack of efficacy or an adverse event of worsening Crohn's disease, COVID-19 related reasons or regional crisis, before the designated analysis timepoint were considered not to have achieved the binary endpoint from that timepoint onward. Participants who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis had their observed data used, if available, to determine responder status from that timepoint onward.



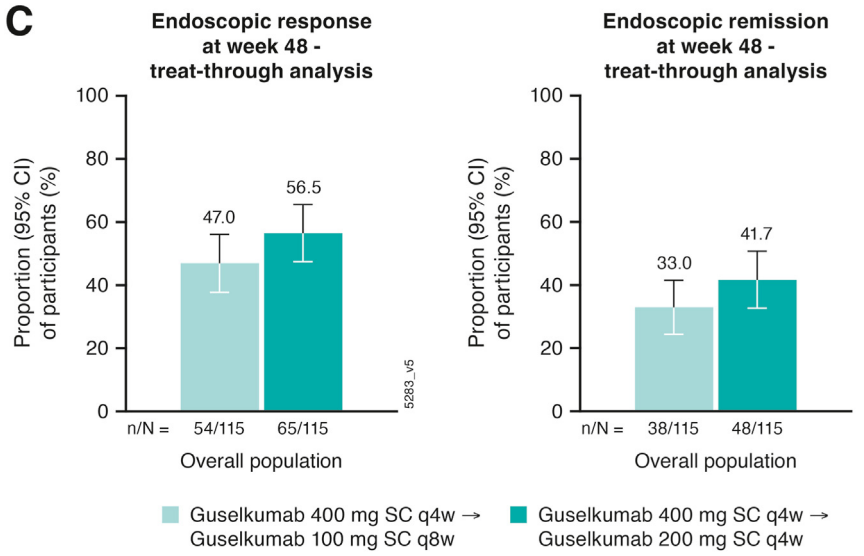




**Figure 4.** Additional clinical and endoscopic endpoints. (*A*) Clinical response (≥100-point reduction from baseline in CDAI score or CDAI score <150) through week 12. (*B*) Clinical remission (CDAI <150) through week 48 – treat-through analysis. (*C*) Endoscopic response (≥50% improvement from baseline in the SES-CD score) at week 48 – treat-through analysis, and endoscopic remission (SES-CD score ≤4 and ≥2-point reduction from baseline and no subscore >1 in any individual component) at week 48 – treat-through analysis. For clinical response (*A*), participants who were missing CDAI score at that visit were considered not having achieved the endpoint at that visit. For clinical remission (*B*), endoscopic response, and endoscopic remission (*C*) (all treat-through), participants who were missing CDAI score or SES-CD score at week 48 were considered not having achieved the endpoint at week 48. Participants who had a Crohn's disease-related surgery, a prohibited change in concomitant Crohn's disease medications, discontinued study agent due to lack of efficacy or an adverse event of worsening Crohn's disease, or discontinued study agent due to COVID-19 infection or for reasons other than lack of efficacy or an adverse event of worsening Crohn's disease, COVID-19 related reasons or regional crisis, before the designated analysis timepoint were considered not to have achieved the binary endpoint from that timepoint onward. Participants who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection), regional crisis, or met rescue criteria had their observed data used, if available, to determine responder status from that timepoint onward.

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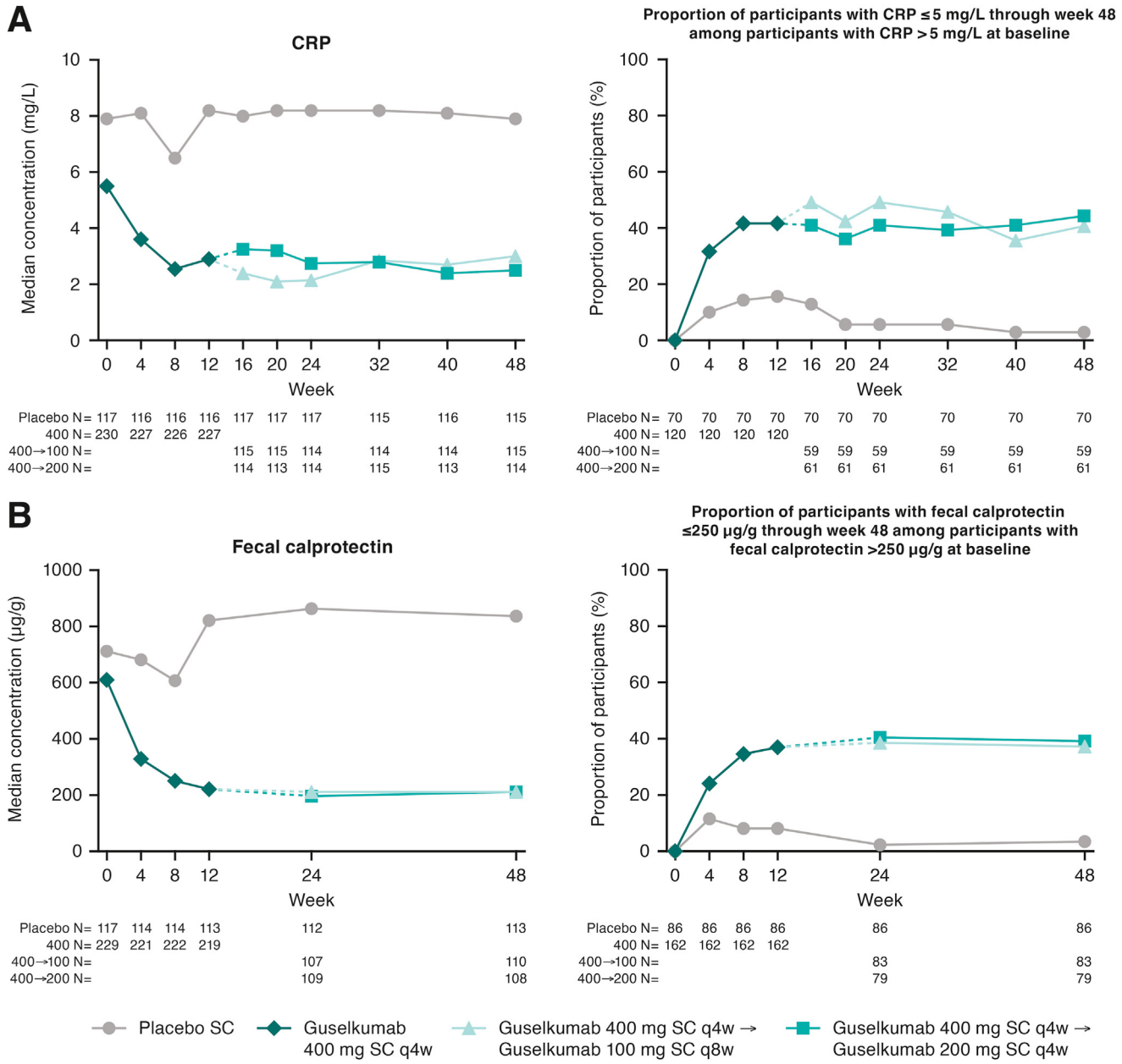


**Figure 5.** Biomarker levels through week 48. (*A*) Median C-reactive protein (CRP) concentration (mg/L) through week 48; proportion of participants with CRP ≤5 mg/L through week 48 among participants with CRP >5 mg/L at baseline. (*B*) Median fecal calprotectin concentration (µg/g) through week 48; proportion of participants with fecal calprotectin ≤250 µg/g through week 48 among participants with fecal calprotectin >250 µg/g at baseline. Participants who met the rescue criteria prior to the analysis timepoint had zero change from baseline for continuous variables or were considered not to have met efficacy endpoints after week 16 for binary endpoints. Participants who had a Crohn's disease-related surgery, a prohibited change in concomitant Crohn's disease medications, discontinued study agent due to lack of efficacy or an adverse event of worsening Crohn's disease, or discontinued study agent due to COVID-19 infection or for reasons other than lack of efficacy or an adverse event of worsening Crohn's disease, COVID-19 related reasons or regional crisis, before the designated analysis timepoint had zero change from baseline for continuous variables or were considered not to have achieved the endpoint from that timepoint onward for binary endpoints. Participants who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis had their observed data used, if available, for continuous variables or to determine responder status from that timepoint onward.

**Table 2.** Key Safety Events Through Week 48: Full Safety Analyses Set

| | | | Guselkumab | | | |
|---|---|---|---|---|---|---|
| | Placebo SC[a] | Placebo → Guselkumab[b] | 400 mg SC q4w → 100 mg SC q8w | 400 mg SC q4w → 200 mg SC q4w | Combined | All Guselkumab |
| Participants included in safety analysis, N | 117 | 44 | 115 | 115 | 230 | 274 |
| Average duration of follow-up, *wk* | 30.0 | 30.6 | 47.0 | 48.0 | 47.5 | 44.8 |
| Average exposure (number of study agent administrations) | 7.1 | 4.7 | 6.8 | 11.8 | 9.3 | 8.5 |
| Total PYs of follow-up, *y* | 67.3 | 25.8 | 103.5 | 105.7 | 209.2 | 235.0 |
| Participants with ≥1 AE, n (%) | 77 (65.8) | 33 (75.0) | 95 (82.6) | 92 (80.0) | 187 (81.3) | 220 (80.3) |
| AEs per 100 PYs of follow-up | 413.0 | 275.6 | 307.2 | 327.2 | 317.3 | 312.8 |
| Most common AEs | | | | | | |
| Upper respiratory tract infection | 12 (10.3) | 8 (18.2) | 15 (13.0) | 15 (13.0) | 30 (13.0) | 38 (13.9) |
| Abdominal pain | 7 (6.0) | 3 (6.8) | 10 (8.7) | 14 (12.2) | 24 (10.4) | 27 (9.9) |
| COVID-19 | 8 (6.8) | 1 (2.3) | 11 (9.6) | 11 (9.6) | 22 (9.6) | 23 (8.4) |
| Participants with ≥1 SAE, n (%) | 16 (13.7) | 1 (2.3) | 15 (13.0) | 9 (7.8) | 24 (10.4) | 25 (9.1) |
| SAEs per 100 PYs of follow-up | 37.1 | 3.9 | 15.5 | 13.2 | 14.3 | 13.2 |
| Serious infections, n (%) | 0 | 1 (2.3) | 2 (1.7) | 1 (0.9) | 3 (1.3) | 4 (1.5) |
| Deaths,[c] n (%) | 0 | 0 | 1 (0.9) | 0 | 1 (0.4) | 1 (0.4) |
| AE leading to discontinuation of study agent, n (%) | 10 (8.5) | 1 (2.3) | 4 (3.5) | 3 (2.6) | 7 (3.0) | 8 (2.9) |
| AEs leading to discontinuation per 100 PYs of follow-up | 14.9 | 3.9 | 6.8 | 2.8 | 4.8 | 4.7 |
| AEs of interest, n (%) | | | | | | |
| Opportunistic infections | 1 (0.9) | 0 | 0 | 1 (0.9)[d] | 1 (0.4) | 1 (0.4) |
| Active tuberculosis | 0 | 0 | 0 | 0 | 0 | 0 |
| Anaphylactic or serum sickness | 0 | 0 | 0 | 0 | 0 | 0 |
| Malignancies | 0 | 0 | 1 (0.9) | 0 | 1 (0.4) | 1 (0.4) |
| Major adverse cardiovascular events | 0 | 0 | 0 | 0 | 0 | 0 |

NOTE. Participants are counted only once for any given event under specific column, regardless of the number of times they actually experienced the event. AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0.
q4w/q8w, every 4 or 8 weeks.
[a]Includes all placebo participants excluding data after a participant is rescued with guselkumab.
[b]Includes placebo participants who were rescued with guselkumab. Data in this group occurred after a participant crossed over to guselkumab.
[c]Fatal gunshot wound (non-suicidal).
[d]Recorded after the database lock.

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Through week 48, the proportions of participants with AEs of hepatic disorder were low (≤5%) and were similar across treatment groups. No serious hepatic disorder AEs were reported. Most of the hepatic disorder AEs were liver test abnormalities that resolved while the participants were still receiving study agent. No participants met the biochemical criteria of Hy's law. The proportion of participants with alanine aminotransferase or aspartate aminotransferase values of at least 5 times upper limit of normal was low (placebo: 1 [0.9%], guselkumab: 3 [1.3%]).

One death, due to a gunshot wound that was not self-inflicted (ie, not a suicide) occurred through week 48 in a participant in the guselkumab 400 mg SC every 4 weeks→100 mg SC every 8 weeks group and was considered unrelated to study agent.

Through week 48, injection-site reactions in participants who received at least 1 dose of guselkumab were reported in association with 1.0% of the 3153 guselkumab injections and 0.3% of the 1782 placebo injections. No serious or severe injection-site reactions were reported, and none led to discontinuation of study intervention.

### *Immunogenicity*

Antibodies to guselkumab were detected in 24 (8.8%) of the 274 guselkumab-treated participants through week 48. Only 3 of 274 participants (1.1% of the total population) were positive for neutralizing antibodies. Through week 48, no impact of antibodies to guselkumab on serum guselkumab concentrations, efficacy, or injection-site reactions was observed.

## Discussion

The Phase 3 double-blind treat-through study, GRAVITI, demonstrated that a fully SC guselkumab induction and maintenance regimen is effective, safe, and well-tolerated in participants with moderately to severely active Crohn's disease. The co-primary endpoints of clinical remission at week 12 and endoscopic response at week 12 were met with guselkumab treatment, indicating that SC induction with guselkumab 400 mg was effective. These results distinguish guselkumab from other approved IL-23p19 subunit inhibitors for IBD (ie, risankizumab, mirikizumab) that require IV induction. Furthermore, the SC induction regimen provides significantly more convenience and flexibility for patients compared with IV induction.

SC administration of biologic agents has been increasingly used across many disease areas[19,20,24] and has proven effective, safe, and well-tolerated. Subcutaneous delivery may be preferred by some patients and health care providers because it offers greater flexibility, requires less time to administer, and minimizes discomfort associated with an IV infusion.[25] In addition, SC administration has resulted in reduced drug delivery–related health care costs and resource utilization.[27] However, some patients may still prefer an IV administration for the reassurance provided by the opportunity to interact with a health care professional, or because they are averse to self-injection.[28] Assessment of patient preferences, including route of administration, is a key component in engaging patients in shared decision making to improve treatment compliance.[29] The availability of both an SC and IV administration of guselkumab will enable patients and health care professionals to choose their preferred route of administration for induction treatment.

In GRAVITI, participants receiving guselkumab SC induction showed rapid improvement in clinical symptoms as early as the first assessment at week 4, which was after only 1 dose of SC guselkumab 400 mg. In addition, a reduction in inflammatory biomarkers was also observed as early as week 4 with guselkumab. Clinical and endoscopic endpoints through week 48 showed that both the 100 mg every 8 weeks and 200 mg every 4 weeks SC guselkumab maintenance doses were effective following SC induction with 400 mg every 4 weeks.

The results presented here from GRAVITI were consistent with those reported in the double-blind, treat-through GALAXI trials in which guselkumab induction was administered IV in participants with moderately to severely active Crohn's disease.[16–18] For example, 41.3% of participants in the GRAVITI study achieved endoscopic response 12 weeks after guselkumab 400 mg every 4 weeks SC induction (placebo: 21.4%), whereas 36.9% of participants in the pooled GALAXI studies achieved endoscopic response 12 weeks after guselkumab 200 mg every 4 weeks IV induction (placebo: 12.2%). Results following maintenance treatment were also similar. For the participants who received 100 mg every 8 weeks maintenance following induction, 47.0% of participants in GRAVITI (treat-through analysis) and 47.9% in GALAXI achieved endoscopic response at week 48. For those who received 200 mg every 4 weeks, 56.5% in GRAVITI and 52.7% in GALAXI achieved endoscopic response at week 48. Although cross-trial comparisons should be made with caution, the GRAVITI and GALAXI studies both had treat-through designs, were double-blinded, had similar study populations, and were enrolled during the same time using some of the same study sites and countries. Both studies also used the same SC maintenance doses. Although there was no active comparator arm in GRAVITI, in the GALAXI trials, both guselkumab dose regimens demonstrated superiority in endoscopic and composite outcomes vs ustekinumab (active comparator) at 1 year when the data from 2 identically designed studies were pooled.

The advantage of a treat-through design is the ability to mimic real-world treatment paradigms and follow the full randomized population on an active treatment. Rescue treatment with guselkumab was provided at week 16 for participants randomized to placebo who met the rescue treatment criteria in the protocol (44 of 117, 37.6%). This feature was included in the study design to provide placebo participants with persistent symptoms or worsening of endoscopic disease an opportunity to receive active treatment. To enable comparisons between the guselkumab and placebo treatment groups at time points after rescue treatment, participants in all treatment groups who met rescue criteria were considered not to have achieved endpoints after week 16. Clinical and endoscopic

outcomes in the guselkumab groups in an analysis in which the rescue criteria treatment failure rule was suspended were approximately 3 to 5 percentage points greater than those in the main analysis, suggesting that some individuals require an extended duration of treatment to eventually achieve treatment targets.

The safety profile of guselkumab is well established in other indications,[8,9,30] and the safety results in the GRAVITI study were consistent with this profile. Key safety event rates per 100 PYs through week 48 were similar between guselkumab and placebo groups. Guselkumab injections were administered using a prefilled syringe and an auto-injector device, and the rate of injection-site reactions with SC induction and maintenance was low. Safety results from GRAVITI through week 48 were similar to those previously presented in the Phase 2 GALAXI 1 guselkumab Crohn's disease study,[31] and the Phase 3 GALAXI 2 and GALAXI 3 studies[16] (NCT03466411).

Immunogenicity rates were low among guselkumab-treated participants through week 48, with SC induction and SC maintenance. Among participants with antibodies, no impact on efficacy or safety was observed.

Several limitations of the study should be considered when interpreting the results. The subcutaneous induction dose of 400 mg was selected based on pharmacokinetic modeling using data from the Phase 2 dose-ranging study of guselkumab IV in Crohn's disease (GALAXI 1).[15] However, dose-ranging studies of SC induction were not conducted. The pharmacokinetic modeling showed that the overall guselkumab exposure of the 400-mg SC dose would be comparable to that of the 200-mg IV induction dose that was selected for use in the Phase 3 studies with IV induction. In addition, dose adjustment of guselkumab SC maintenance therapy from 100 mg to 200 mg was not evaluated.

In conclusion, SC induction followed by SC maintenance treatment with guselkumab resulted in superior clinical and endoscopic improvements in participants with moderately to severely active Crohn's disease through 48 weeks compared with placebo. Safety results were consistent with the established safety profile of guselkumab in previously reported studies in Crohn's disease, ulcerative colitis, and psoriatic diseases. These results build on the GALAXI data[15–18,31] and demonstrate that guselkumab induction efficacy can be achieved rapidly with both SC and IV dosing, providing options for administration that matches patient and health care provider preferences.

## 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.2025.02.033.

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**Conflicts of interest**

The authors disclose the following: Ailsa Hart reports serving as a lecturer and/or on an advisory board for Bristol Myers Squibb, Celltrion, Falk, AbbVie, Johnson & Johnson, Takeda, Pfizer, Galapagos, MSD, and GSK. 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**Data Availability**

The data sharing policy of Johnson & Johnson is available at https://innovativemedicine.jnj.com/our-innovation/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.