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Guselkumab for the Treatment of Crohn's Disease: Induction Results From the Phase 2 GALAXI-1 Study

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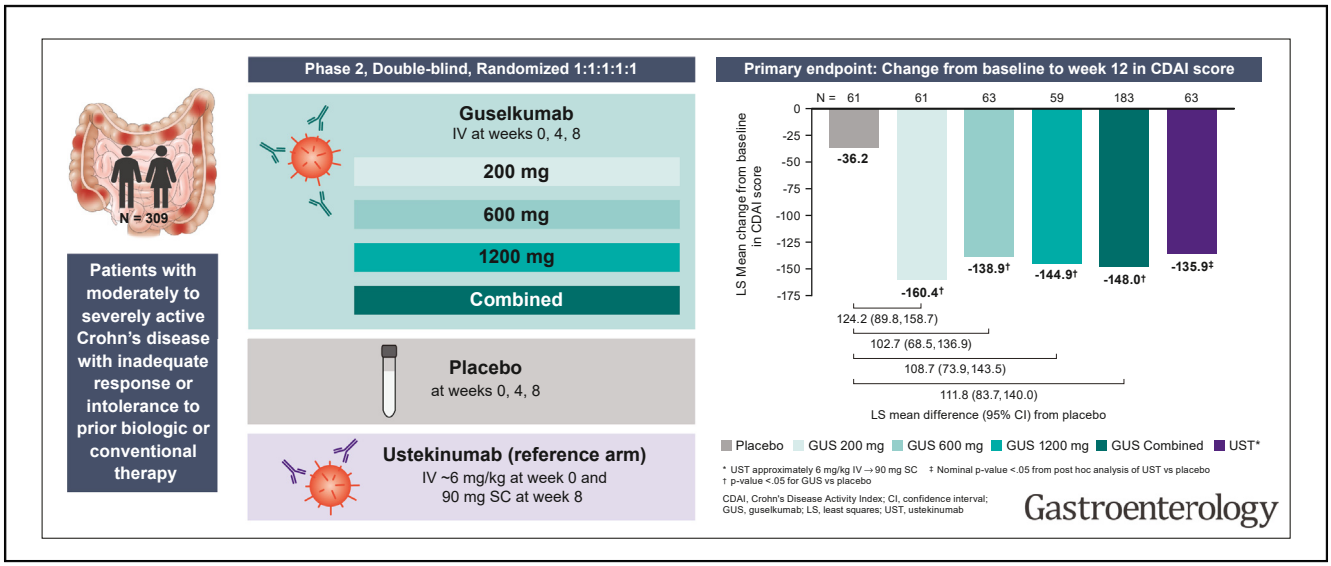

BACKGROUND & AIMS: Guselkumab, a selective p19 interleukin-23 antagonist, is approved for the treatment of plaque psoriasis and psoriatic arthritis. This study evaluated the efficacy and safety of guselkumab in patients with moderately to severely active Crohn's disease with inadequate response or intolerance to conventional or biologic therapy. **METHODS:** GALAXI-1, a phase 2, double-blind, placebo-controlled study, randomized patients 1:1:1:1:1 to intravenous guselkumab 200 mg, 600 mg, or 1200 mg at weeks 0, 4, and 8; intravenous ustekinumab approximately 6 mg/kg at week 0 and 90 mg subcutaneously at week 8; or placebo. Change from baseline in Crohn's Disease Activity Index score (primary end point), clinical remission, clinical response, Patient Reported Outcomes-2 remission, clinical-biomarker response, endoscopic response (major secondary end points), and safety in guselkumab-treated patients vs placebo were evaluated through week 12. Ustekinumab was a reference arm. **RESULTS:** Of 309 patients evaluated, approximately 50% had disease refractory to prior biologic therapy. At week 12, significantly greater reductions in Crohn's Disease Activity Index from baseline (least squares means: 200 mg: −160.4, 600 mg: −138.9, and 1200 mg: −144.9 vs placebo: −36.2; all, $P < .05$) and significantly greater proportions of patients achieved clinical remission in each guselkumab group vs placebo (Crohn's Disease Activity Index <150; 57.4%, 55.6%, and 45.9% vs 16.4%; all, $P < .05$). Greater proportions of patients receiving guselkumab achieved clinical response, Patient Reported Outcomes-2 remission, clinical-biomarker response, and endoscopic response at week 12 vs placebo. Efficacy of ustekinumab vs placebo was also demonstrated. Safety event rates were

generally similar across treatment groups. **CONCLUSIONS:** At week 12, all 3 dose regimens of guselkumab induced greater clinical and endoscopic improvements vs placebo, with a favorable safety profile. ClinicalTrials.gov, Number: NCT03466411.

Keywords: Crohn's Disease Activity Index; GALAXI-1; Guselkumab; Interleukin-23.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Interleukin (IL)-23 plays a central role in gut inflammation. The efficacy and safety of guselkumab (IL-23p19 subunit inhibitor) were evaluated in patients with moderately to severely active Crohn's disease.

NEW FINDINGS

Guselkumab induced greater clinical and endoscopic improvements compared with placebo at week 12. Safety was generally comparable to the established profile in psoriasis and psoriatic arthritis.

LIMITATIONS

Results are based on a limited number of patients who received 12 weeks of induction therapy. Ustekinumab was used as a reference arm and the study was not designed to compare the 2 agents with adequate statistical power.

IMPACT

IL-23p19 inhibition with guselkumab resulted in clinical and endoscopic improvement in patients with Crohn's disease with an inadequate response or intolerance to prior conventional or biologic therapy supporting initiation of pivotal induction and maintenance studies in Crohn's disease.

Crohn's disease is a chronic inflammatory bowel disease (IBD) that usually requires long-term treatment. Conventional therapies including corticosteroids, thiopurines, and methotrexate have been used commonly as first-line therapies to treat Crohn's disease. However, these agents are often ineffective in maintaining clinical remission and have considerable toxicity.[1] In addition, patients with refractory or more severe disease may not benefit sufficiently from conventional therapies and often need treatment with biologics.[1,2] Currently, several biologics are available for the treatment of moderately to severely active Crohn's disease that selectively target inflammatory pathways central to disease pathogenesis. Despite the increased effectiveness of biologics, many patients experience treatment failure, intolerance, and decreased efficacy over time.[3–5] Therefore, a need remains for novel biologic therapies that target new pathways that may offer greater efficacy and durable long-term disease control for patients with Crohn's disease.

Preclinical and clinical studies have reported the importance of the interleukin (IL)-12–T-helper 1 and IL-23–T-helper 17 pathways in Crohn's disease.[3,6–9] IL-12 has been suggested to be involved in the initiation of intestinal inflammation, while IL-23 may be important in maintaining the intestinal inflammatory response.[10] IL-23 is a heterodimer consisting of p40 and p19 protein subunits; the p40 subunit is shared with IL-12, whereas p19 is specific to IL-23.[11] IL-23 is required for terminal differentiation of T-helper 17 cells[12] and activation of the IL-23 receptor activates the downstream pathways, which promotes expression of tumor necrosis factor, IL-17, and interferon-gamma.[13] IL-23 activation also results in T cell, natural killer cell, and lymphoid cell responses, which cause inflammation and changes in the intestinal microbiome.[14] Increased IL-23 and T-helper 17 cell cytokine levels have been identified in the intestinal mucosa, plasma, and serum of patients with IBD.[13] Currently, several IL-23 inhibitors are being investigated in clinical trials for the treatment of IBD.[15–18]

Guselkumab is a fully human IgG1 lambda monoclonal antibody that selectively inhibits the p19 subunit of IL-23. The binding of guselkumab to IL-23 blocks interaction between extracellular IL-23 to the cell surface IL-23R receptor, inhibiting IL-23–specific intracellular signaling and subsequent activation of cytokine production. Guselkumab is currently approved for and has demonstrated efficacy and safety in the short- and long-term treatment of other inflammatory diseases, including moderate-to-severe plaque psoriasis[19–22] and active psoriatic arthritis.[23,24] Studies targeting the IL-23 pathway in psoriasis have shown greater efficacy compared with those targeting IL-12/23,[25,26] suggesting the potential for similar findings in IBD. Here, we present results from the induction portion of the phase 2, dose-ranging, placebo- and active-controlled GALAXI-1 study that evaluated the efficacy and safety of guselkumab in patients with moderately to severely active Crohn's disease.

Materials and Methods

GALAXI-1 is an ongoing phase 2, randomized, double-blind, placebo- and active-controlled, multicenter study with participants randomized at 128 sites in 32 countries. The primary objective of the study was to evaluate the efficacy and safety of guselkumab in participants with moderately to severely active Crohn's disease who had an inadequate response or intolerance to conventional therapy or biologic therapy.

Abbreviations used in this paper: **AE, adverse event; AP, abdominal pain; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; IBD, inflammatory bowel disease; IBDQ, Inflammatory Bowel Disease Questionnaire; IL, interleukin; IV, intravenous; LSM, least squares mean; PRO-2, Patient Reported Outcome-2; SAE, serious adverse event; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency.**

Most current article

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Study Population

Patients enrolled in GALAXI-1 were 18 years or older, with moderately to severely active Crohn's disease of ≥3 months' duration. For this study, active Crohn's disease was defined as having both clinically active Crohn's disease (Crohn's Disease Activity Index [CDAI] score ≥220 but ≤450) and either mean daily stool frequency (SF) >3, based on the unweighted CDAI component of the number of liquid or very soft stools, or mean daily abdominal pain (AP) score >1, based on the unweighted CDAI component of AP, and endoscopic evidence of ileocolonic Crohn's disease (a Simple Endoscopic Score for Crohn's disease [SES-CD][27] score ≥3, as assessed by central endoscopy reading at the screening endoscopy, with a score for ulceration ≥1). Enrollment of patients who had an SES-CD score of 3 (for patients with isolated ileal disease) or SES-CD scores of 3–6 (for patients with colonic or ileocolonic disease) was limited to 10% maximum of the enrolled population.

Patients with an inadequate response or intolerance to prior conventional treatment included those who had demonstrated an inadequate response, loss of response, or intolerance to 1 or more of the following conventional Crohn's disease therapies: oral corticosteroids (including budesonide and beclomethasone dipropionate) or immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate), and patients who demonstrated corticosteroid dependence (ie, an inability to successfully taper corticosteroids without a return of the symptoms of Crohn's disease). Patients could have been naïve to biologic therapy (ie, a tumor necrosis factor antagonist or biosimilar, vedolizumab, or ustekinumab) or may have been exposed but had not demonstrated inadequate response or intolerance.

Patients with an inadequate response or intolerance to prior biologic therapy included those who had demonstrated an inadequate response, loss of response, or intolerance to 1 or more biologic therapies (ie, a tumor necrosis factor antagonist or biosimilar, vedolizumab) approved for Crohn's disease treatment. Inadequate response was defined as primary nonresponse (ie, no initial response) or secondary nonresponse (ie, response initially with subsequent loss of response). Patients who had demonstrated an inadequate response and/or intolerance to ustekinumab were not eligible.

Study Design

Patients were randomized in a 1:1:1:1:1 ratio to receive intravenous (IV) guselkumab 200 mg, 600 mg, or 1200 mg at weeks 0, 4, and 8; ustekinumab approximately 6 mg/kg IV at week 0 and subcutaneous 90 mg at week 8; or placebo (Figure 1). Patients were allocated to a treatment group using permuted block randomization with baseline CDAI score (≤300 or >300) and inadequate response or intolerance to prior biologic therapy (yes/no) as stratification variables.

The study protocol was approved by the Institutional Review Board or Ethics Committee at each participating investigative center. All patients provided written informed consent. Safety data were periodically reviewed by an independent, external data monitoring committee. All authors had access to the study data and reviewed and approved the final manuscript.

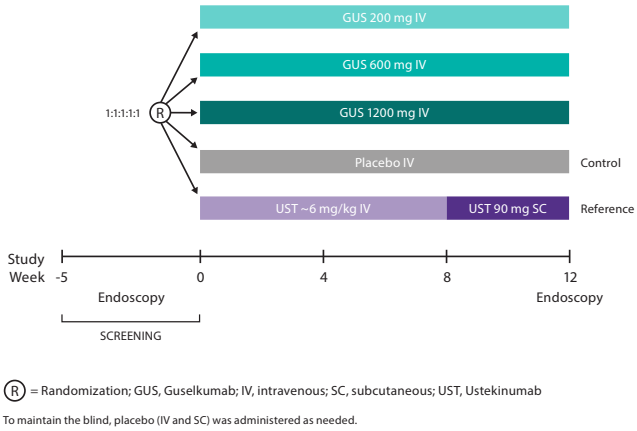


Figure 1. Study design.

Efficacy and Safety Assessments

Efficacy assessments included CDAI; Patient Reported Outcome-2 (PRO-2; based on the unweighted CDAI components of SF and AP scores); centrally read endoscopic assessments of the terminal ileum and colon based on the presence and absence of mucosal ulcerations (endoscopic healing) and the SES-CD (endoscopic response and remission, change from baseline in SES-CD); inflammatory markers, including C-reactive protein (CRP) and fecal calprotectin; fistula assessment (closure of opening and draining fistulas at baseline); and health-related quality of life outcomes measures (ie, Inflammatory Bowel Disease Questionnaire [IBDQ], and Patient-Reported Outcomes Measurement Information System Fatigue Short Form-7a; Supplementary Material) to assess the impact of Crohn's disease and improvements post treatment on patients' well-being.

Serum guselkumab concentrations were measured at weeks 0,4, 8, and 12 using a validated, specific, and sensitive electrochemiluminescence immunoassay method using the Meso Scale Discovery platform (Gaithersburg, MD). The presence of antibodies to guselkumab in serum was determined by a validated, sensitive, and drug-tolerant assay that incorporates an acid dissociation step to improve detection of anti-guselkumab antibodies in the presence of excess guselkumab.

Safety evaluations including adverse events (AEs), serious AEs (SAEs), infections, and serious infections, were conducted at each study visit.

Study End Points

The primary end point was the change from baseline in CDAI score at week 12. The major secondary end points were clinical remission at week 12 (defined as a CDAI score <150); clinical response at week 12 (defined as ≥100-point reduction from baseline in CDAI score or CDAI score <150); PRO-2 remission at week 12 (defined as the unweighted CDAI component of daily AP score ≤1, and the unweighted CDAI

component of daily average SF score ≤3 (ie, AP ≤1 and SF ≤3 and no worsening from baseline); endoscopic response at week 12 (defined as at least 50% improvement from baseline in SES-CD score or SES-CD score ≤2); and clinical-biomarker response at week 12 (defined as clinical response and ≥50% reduction from baseline in CRP or fecal calprotectin). Analyses of these end points were based on comparisons between each guselkumab dose group and the placebo group. Ustekinumab was included as a reference arm; comparisons of ustekinumab to placebo at week 12 were done post-hoc, and no formal comparisons between ustekinumab and placebo at week 12 were planned before study unblinding.

Statistical Analysis

The primary efficacy analysis was based on the primary efficacy analysis set, defined as all randomized patients who received 1 or more doses of study drug (including a partial dose), except for those participants whose induction dosing was discontinued during a temporary study pause. The primary end point of change from baseline in CDAI score at week 12 was analyzed using a mixed-effect model repeated measure approach with treatment group, visit, baseline CDAI score, inadequate response or intolerance to prior biologic therapy (yes/no), an interaction term of visit with treatment group, and an interaction term of visit with baseline CDAI score as explanatory variables. The estimates for the treatment difference between each guselkumab dose group and the placebo group were provided by the difference in the least squares means (LSMs). The 95% confidence interval for the differences in LSMs and *P* values were calculated based on the mixed-effect model repeated measure.

Analysis of all major secondary end points, except for endoscopic response at week 12, were compared between each guselkumab dose group and the placebo group using the Cochran-Mantel-Haenszel χ^2 test (2-sided) stratified by baseline CDAI score (≤300 or >300) and an inadequate response or intolerance to prior biologic therapy (yes/no), at a significance level of .05. Endoscopic response at week 12 was compared between each guselkumab dose group and the placebo group using the Cochran-Mantel-Haenszel χ^2 test (2-sided) stratified by SES-CD score (≤12 or >12) and an inadequate response or intolerance to prior biologic therapy (yes/no), at a significance level of .05.

The primary end point of the change from baseline in the CDAI score at week 12 and the first major secondary end point of clinical remission at week 12 were controlled for multiplicity at the .05 significance level based on a fixed sequence testing procedure, starting with the highest dose of guselkumab 1200 mg (vs placebo). If all 3 guselkumab doses were positive for the primary end point, testing continued on to the first major secondary end point of clinical remission at week 12 using the same fixed sequence testing procedure. For end points that were not multiplicity-controlled, nominal *P* values are presented. All *P* values for ustekinumab vs placebo are nominal and based on post-hoc analyses.

The safety analysis set consists of all randomized patients who received at least 1 dose of study drug (including a partial dose). The safety data were analyzed according to actual treatment received.

Results

Patient Disposition and Baseline Demographic Characteristics

Baseline characteristics are described in Table 1. A total of 309 patients were included in the primary efficacy analysis set. The mean (standard deviation) age was 38.8 (13.36) years with a mean (standard deviation) Crohn's disease duration of 8.8 (8.70) years. In the combined guselkumab group, 54.6% (101 of 185) of patients had an inadequate response or intolerance to prior biologic therapy and 45.4% (84 of 185) to conventional therapy.

Through week 12, six patients in the primary efficacy analysis set discontinued the study, all due to withdrawal by the patient (Supplementary Figure 1). A temporary pause was instituted during the study to evaluate an SAE of "toxic hepatitis" in a patient treated with guselkumab. Patients who had their induction treatment paused due to the evaluation of this event were discontinued from the study (n = 51). Data from these discontinued patients were included in the safety analyses, but were not included in the primary efficacy analysis.

Efficacy

Primary end point. At week 12, the primary end point was achieved, with significantly greater LSM reductions from baseline in CDAI score observed for the guselkumab 200 mg (–160.4), 600 mg (–138.9), and 1200 mg (–144.9) groups compared with placebo (–36.2) ($P < .05$ for all comparisons) (Figure 2). No apparent dose response was observed across the doses investigated.

Major secondary end points. At week twelve, 53.0% (98 of 185) of patients in the combined guselkumab group were in clinical remission compared with 16.4% (10 of 61) in the placebo group ($P < .05$; Figure 3). Similarly, 65.9% (122 of 185) of patients in the combined guselkumab group and 24.6% (15 of 61) of patients in the placebo group achieved clinical response at week 12 (nominal $P < .05$). PRO-2 remission and clinical-biomarker response were achieved in 42.7% (79 of 185) and 47.0% (87 of 185) of patients in the combined guselkumab groups compared with 16.4% (10 of 61) and 6.6% (4 of 61) in the placebo groups, respectively (nominal $P < .05$). Endoscopic response at week 12 was achieved in 35.7% (66 of 185) of patients in the combined guselkumab group compared with 11.5% (7 of 61) in the placebo group (nominal $P < .05$; Figure 3). No apparent dose response was observed across these end points.

In the subgroup of patients with inadequate response or intolerance to prior biologic therapy, 47.5% (48 of 101) in the combined guselkumab group and 10.0% (3 of 30) in the placebo group achieved clinical remission at week 12 (Figure 4*A*). More than one-half of patients receiving guselkumab in this subgroup (62.4% [63 of 101]) achieved clinical response at week 12 compared with 20.0% (6 of 30) of patients in the placebo group. PRO-2 remission at week 12 was achieved in 40.6% (41 of 101) of patients in the combined guselkumab group compared with 13.3% (4 of

Table 1. Baseline Demographics and Disease Characteristics in the Primary Efficacy Analysis Set

Characteristic	Placebo[a]	Guselkumab 200 mg	Guselkumab 600 mg	Guselkumab 1200 mg	Guselkumab Combined	Ustekinumab	Total
Patients included in efficacy analysis, n	61	61	63	61	185	63	309
Age, *y*							
n	61	61	63	61	185	63	309
Mean (SD)	38.9 (12.95)	40.3 (13.67)	39.0 (14.35)	39.6 (13.72)	39.6 (13.86)	36.1 (12.02)	38.8 (13.36)
Men	37 (60.7)	38 (62.3)	36 (57.1)	31 (50.8)	105 (56.8)	41 (65.1)	183 (59.2)
Weight, *kg*							
n	61	61	63	61	185	63	309
Mean (SD)	67.0 (16.21)	71.1 (15.94)	67.5 (14.75)	73.9 (19.74)	70.8 (17.04)	69.4 (16.25)	69.8 (16.73)
Crohn's disease duration, *y*							
n	61	61	63	61	185	63	309
Mean (SD)	8.7 (6.54)	10.7 (12.17)	10.4 (9.74)	6.7 (6.91)	9.3 (9.95)	7.4 (6.17)	8.8 (8.70)
CDAI score							
n	61	61	63	61	185	63	309
Mean (SD)	300.8 (49.91)	304.6 (57.24)	305.8 (58.77)	305.8 (54.46)	305.4 (56.57)	313.3 (61.30)	306.1 (56.30)
Median	296.0	300.0	299.0	293.0	299.0	298.0	297.0
IQR	267.0–333.0	258.0–348.0	254.0–347.0	257.0–340.0	257.0–345.0	264.0–361.0	260.0–345.0
PRO-2							
n	61	61	63	61	185	63	309
Mean (SD)	143.3 (41.97)	147.2 (45.13)	141.9 (42.83)	146.1 (39.47)	145.0 (42.37)	147.2 (42.43)	145.1 (42.18)
Median	140.0	144.0	137.0	146.0	141.0	140.0	141.0
IQR	116.0–167.0	117.0–173.0	117.8–168.0	121.0–169.4	117.8–168.0	119.0–170.0	117.0–169.0
SES-CD							
n	61	61	63	61	185	63	309
Mean (SD)	12.8 (7.98)	12.6 (7.99)	12.4 (7.37)	11.7 (7.14)	12.2 (7.48)	15.1 (8.75)	12.9 (7.91)
Median	10.0	11.0	12.0	10.0	11.0	15.0	11.0
IQR	7.0–18.0	7.0–17.0	6.0–17.0	6.0–17.0	6.0–17.0	7.0–21.0	7.0–18.0
CRP concentration, *mg/L*							
n	61	61	63	61	185	63	309
Median	4.4	6.3	5.8	4.8	5.7	8.8	5.7
IQR	1.9–10.2	1.3–27.8	1.6–28.1	2.2–13.9	1.8–22.3	1.8–21.1	1.8–19.6

Table 1. Continued

Characteristic	Placebo[a]	Guselkumab				Ustekinumab	Total
		200 mg	600 mg	1200 mg	Combined		
Fecal calprotectin, *mg/kg*							
n	60	58	63	60	181	62	303
Median	488.5	561.5	596.0	687.0	605.0	957.0	610.0
IQR	192.5–1692.0	169.0–1669.0	222.0–1641.0	190.0–1689.5	181.0–1654.0	339.0–1852.0	195.0–1730.0
IBDQ							
n	57	60	63	61	184	63	304
Mean (SD)	120.8 (30.12)	126.8 (33.97)	128.2 (32.46)	122.8 (37.95)	126.0 (34.73)	130.6 (32.12)	125.9 (33.42)
Median	123.0	127.0	134.0	121.0	127.0	134.0	126.0
IQR	102.0–136.0	99.0–148.5	101.0–146.0	97.0–150.0	100.0–146.0	106.0–153.0	101.0–146.5
Disease location							
n	61	61	63	61	185	63	309
Ileum only	16 (26.2)	22 (36.1)	23 (36.5)	15 (24.6)	60 (32.4)	12 (19.0)	88 (28.5)
Colon only	26 (42.6)	27 (44.3)	18 (28.6)	31 (50.8)	76 (41.1)	29 (46.0)	131 (42.4)
Ileum and colon	19 (31.1)	12 (19.7)	22 (34.9)	15 (24.6)	49 (26.5)	22 (34.9)	90 (29.1)
History of fistula	18 (29.5)	18 (29.5)	23 (36.5)	17 (27.9)	58 (31.4)	23 (36.5)	99 (32.0)
Patients with 1 or more open or draining fistulas at baseline	3 (4.9)	7 (11.5)	9 (14.3)	8 (13.1)	24 (13.0)	10 (15.9)	37 (12.0)
Crohn's disease medication taken at baseline	60 (98.4)	61 (100.0)	63 (100.0)	61 (100.0)	185 (100.0)	63 (100.0)	308 (99.7)
1 or more medications for Crohn's disease	45 (73.8)	44 (72.1)	47 (74.6)	46 (75.4)	137 (74.1)	53 (84.1)	235 (76.1)
Immunomodulatory therapy[b]	26 (42.6)	15 (24.6)	18 (28.6)	25 (41.0)	58 (31.4)	26 (41.3)	110 (35.6)
Corticosteroids[c]	24 (39.3)	24 (39.3)	19 (30.2)	20 (32.8)	63 (34.1)	26 (41.3)	113 (36.6)
Dose, *mg/d*, median (IQR)	20.0 (10.0–30.0)	20.0 (20.0–25.0)	20.0 (10.0–25.0)	20.0 (15.0–22.5)	20.0 (15.0–25.0)	20.0 (15.0–32.5)	20.0 (15.0–25.0)
History of biologic use[d]	42 (68.9)	36 (59.0)	39 (61.9)	36 (59.0)	111 (60.0)	44 (69.8)	197 (63.8)
Patients with an inadequate response to or intolerance to biologic therapy	30 (49.2)	32 (52.5)	35 (55.6)	34 (55.7)	101 (54.6)	37 (58.7)	168 (54.4)
Anti-TNF only	25 (41.0)	26 (42.6)	27 (42.9)	31 (50.8)	84 (45.4)	32 (50.8)	141 (45.6)
1 or more anti-TNFs	29 (47.5)	30 (49.2)	35 (55.6)	33 (54.1)	98 (53.0)	37 (58.7)	164 (53.1)
Vedolizumab	5 (8.2)	6 (9.8)	8 (12.7)	3 (4.9)	17 (9.2)	5 (7.9)	27 (8.7)

Table 1. Continued

Characteristic	Placebo[a]	Guselkumab				Ustekinumab	Total
		200 mg	600 mg	1200 mg	Combined		
Vedolizumab and 1 or more anti-TNFs	4 (6.6)	4 (6.6)	8 (12.7)	2 (3.3)	14 (7.6)	5 (7.9)	23 (7.4)
Biologic-naïve	19 (31.1)	25 (41.0)	24 (38.1)	25 (41.0)	74 (40.0)	19 (30.2)	112 (36.2)
Patients with an inadequate response to or intolerance to conventional therapies	31 (50.8)	29 (47.5)	28 (44.4)	27 (44.3)	84 (45.4)	26 (41.3)	141 (45.6)

NOTE. Data presented as n (%) unless otherwise noted. The n for each parameter reflects non-missing values.
IQR, interquartile range; SD, standard deviation; TNF, tumor necrosis factor.
[a]Placebo includes all patients randomized to placebo. At week 12, patients who were clinical responders continued placebo treatment and those who were nonresponders crossed-over to ustekinumab.
[b]Immunomodulatory therapy included azathioprine, mercaptopurine, and methotrexate.
[c]Corticosteroids included budesonide and beclomethasone dipropionate.
[d]Biologics included infliximab, adalimumab, certolizumab pegol, or vedolizumab.

Figure 2. Primary efficacy end point. LSM change from baseline in CDAI score at week 12. CI, confidence interval; GUS, guselkumab; LS, least squares; UST, ustekinumab.

30) in the placebo group. Endoscopic response at week 12 was achieved in 30.7% (31 of 101) of patients in the combined guselkumab group compared with 13.3% (4 of 30) in the placebo group. Consistent with the overall population, no apparent dose response was observed across these end points among this subgroup of patients with inadequate response or intolerance to prior biologic therapy.

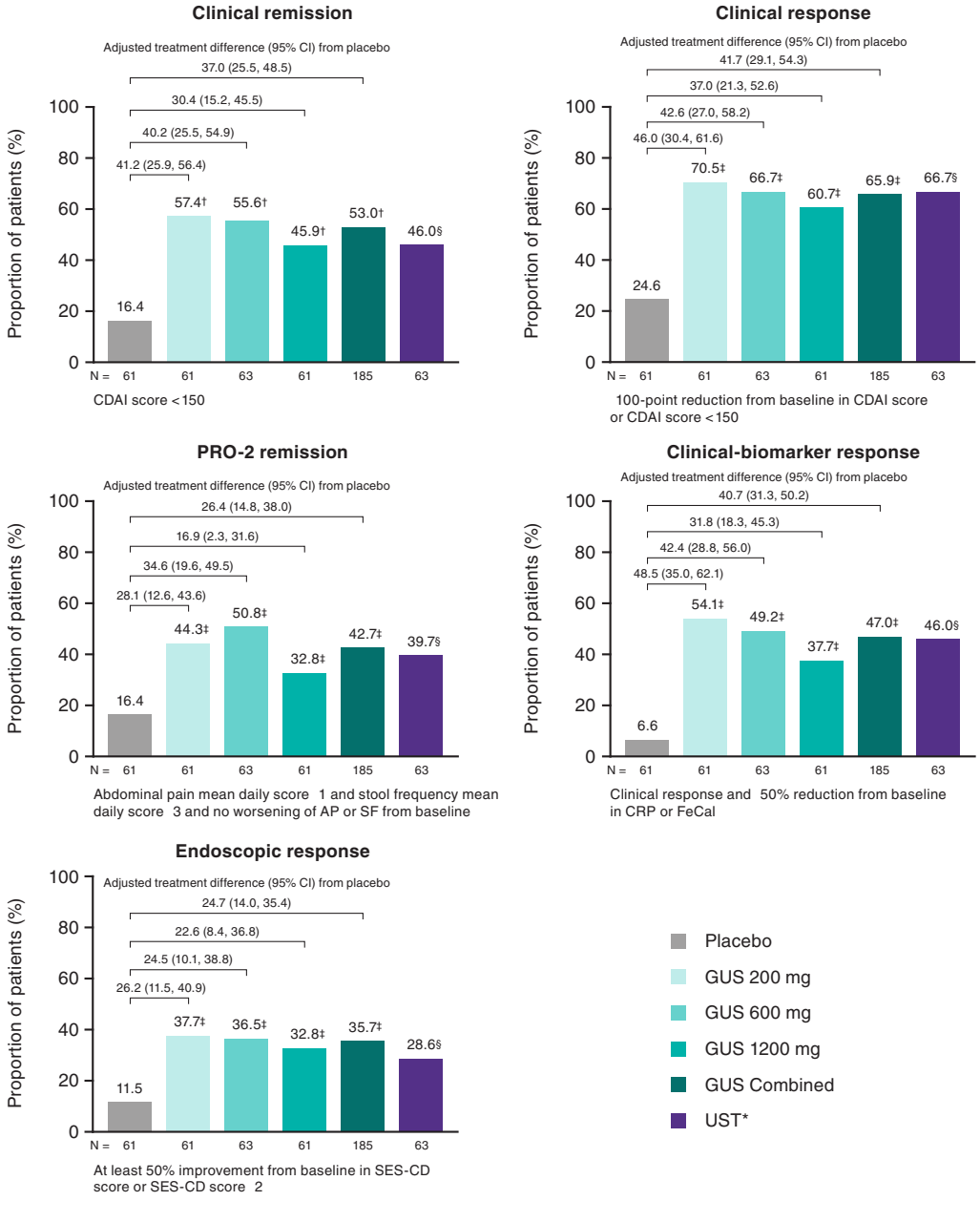
In the subgroup of patients with inadequate response or intolerance to prior conventional therapy, 59.5% (50 of 84) of patients in the combined guselkumab group and 22.6% (7 of 31) in the placebo group achieved clinical remission (Figure 4*B*). In addition, 70.2% (59 of 84) of patients in the combined guselkumab group and 29.0% (9 of 31) in the placebo group achieved clinical response. PRO-2 remission at week 12 was achieved in 45.2% (38 of 84) of patients in the combined guselkumab group and 19.4% (6 of 31) in the placebo group. Endoscopic response at week 12 was achieved in 41.7% (35 of 84) of patients in the combined guselkumab group compared with 9.7% (3 of 31) of patients in the placebo group. Consistent with the overall population, no apparent dose response was observed across these end points among this subgroup of patients with inadequate response or intolerance to prior conventional therapy.

Onset of Response

From week 0 through week 12, the LSM change in CDAI continued to decrease over time for all guselkumab dose groups (Figure 5). The proportion of patients achieving clinical response and clinical remission continued to increase over time, with the greatest increase reported in the guselkumab 200-mg dose group. Separation from placebo was observed as early as week 4.

Other End Points

At week 12, greater LSM reductions from baseline in SES-CD scores were reported among all guselkumab dose



* UST approximately 6 mg/kg IV → 90 mg SC; †p-value <.05 for GUS vs placebo; ‡Nominal p-value <.05 for GUS vs placebo; §Nominal p-value <.05 from post hoc analysis of UST vs placebo

Figure 3. Prespecified major secondary end points. Proportion of patients achieving clinical remission, clinical response, PRO-2 remission, clinical-biomarker response, and endoscopic response at week 12. CI, confidence interval; SC, subcutaneous; UST, ustekinumab.

groups compared with placebo (Supplementary Figure 2). Greater improvement was observed from baseline in fecal calprotectin (Supplementary Table 1) and CRP (Supplementary Table 2) concentrations among guselkumab-treated patients compared with placebo-treated patients.

At week 12, 50.8% and 71.9% of patients in the combined guselkumab group were in IBDQ remission (Supplementary Table 3) and IBDQ response (Supplemental Table 4) compared with 23.0% and 41.0% of patients in the placebo group, respectively. Greater changes from baseline in Patient-Reported Outcomes Measurement Information System Fatigue Short Form-7a total score were observed in all guselkumab dose groups compared with placebo (Supplementary Table 5).

Pharmacokinetics and Efficacy

No apparent exposure response between systemic guselkumab exposure and change in CDAI, clinical remission, or endoscopic response was observed at week 12. Of the 185 patients in the combined guselkumab group with at least 1 post-baseline pharmacokinetic sample, 146 patients

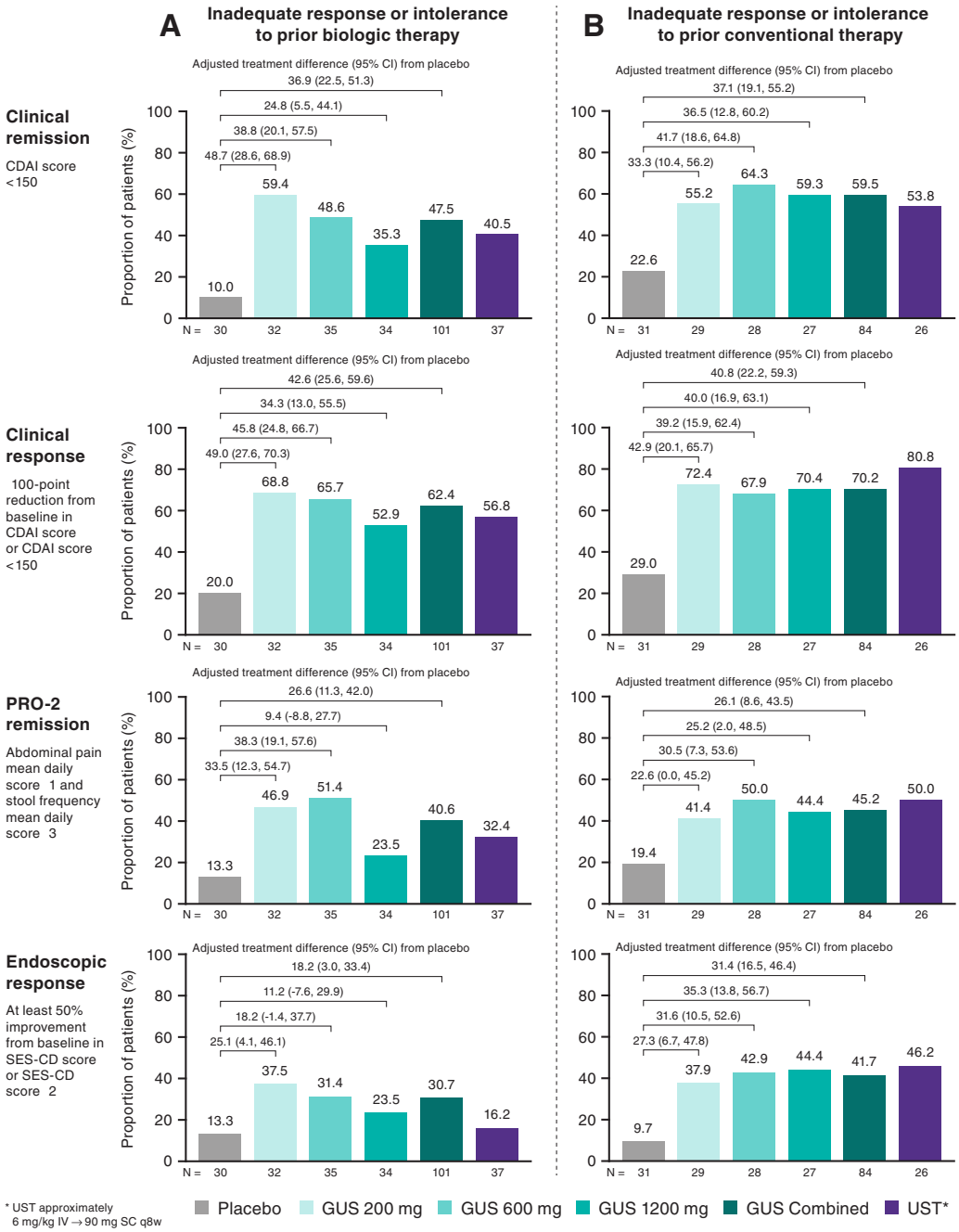


Figure 4. Efficacy in patients with an inadequate response or intolerance to prior biologic or conventional therapy. (*A*) Proportion of patients with an inadequate response or intolerance to prior biologic therapy achieving clinical remission, clinical response, PRO-2 remission, and endoscopic response at week 12; (*B*) proportion of patients with an inadequate response or intolerance to prior conventional therapy achieving clinical remission, clinical response, PRO-2 remission, and endoscopic response at week 12. CI, confidence interval; GUS, guselkumab; SC, subcutaneous; UST, ustekinumab.

had a serum guselkumab concentration at week 12. At week 12, 52.8% (19 of 36) and 59.5% (22 of 37) of patients in the lower 2 guselkumab concentration quartiles were in clinical remission compared with 47.2% (17 of 36) and 56.8% (21 of 37) in the upper 2 concentration quartiles (Supplementary Table 6). Likewise, at week 12, the proportions of patients in endoscopic response were 22.2% (8 of 36) and 40.5% (15 of 37) in the lower 2 quartiles compared with 30.6% (11 of 36) and 32.4% (12 of 37) in the upper 2 quartiles (Supplementary Table 6). Through week 12, 1 patient (0.5%) was positive for antibodies to guselkumab, with a titer of 1:23.

Safety

Of the 360 patients included in the safety analysis set, the proportion of patients with 1 or more AEs through week 12 was similar across treatment groups (placebo: 60.0%;

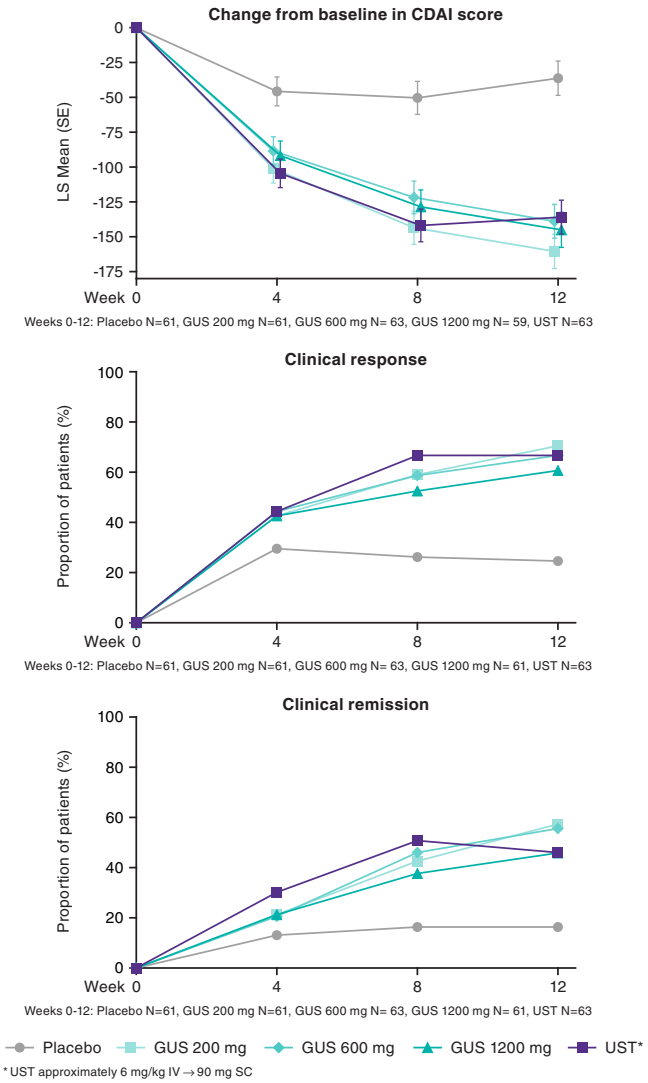


Figure 5. Efficacy responses over time from weeks 0 to 12. LSM (standard error [SE]) change from baseline in CDAI score; proportion of patients achieving clinical response; proportion of patients achieving clinical remission. GUS, guselkumab; LS, least squares; SC, subcutaneous; UST, ustekinumab.

combined guselkumab: 45.7%; and ustekinumab: 50.7%) (Table 2). Among the guselkumab dose groups, no relationship was evident between dose and the proportion of patients with AEs. The rates of infection were 21.4% in the placebo group, 15.1% in the combined guselkumab group, and 12.7% in the ustekinumab group. The proportion of patients with at least 1 AE leading to discontinuation of the study agent was low across all treatment groups through week 12.

Proportions of patients with at least 1 SAE (placebo: 5.7%; combined guselkumab: 3.7%; and ustekinumab: 5.6%) or at least 1 serious infection (0.0%, 1.4%, and 1.4%, respectively) were low and generally comparable among groups. Three serious infections occurred in the combined guselkumab group through week 12:1 event of viral gastroenteritis and 1 event of enterovesical fistula, both occurring in the guselkumab 600 mg group, and 1 event of anal abscess in the guselkumab 200 mg group. One serious infection classified as an abdominal infection occurred in the ustekinumab group after the induction dose. All serious infections were assessed by an investigator and were considered not related to study drug. No serious hypersensitivity reactions (anaphylaxis or serum sickness) occurred. No deaths and no cases of active tuberculosis or opportunistic infections were reported through week 12.

An SAE of "toxic hepatitis" was reported in a 44-year-old female patient with Crohn's disease who received guselkumab 1200 mg IV at weeks 0, 4, and 8, and a single 200 mg subcutaneous maintenance dose at week 12. Liver tests at baseline and through week 8 were normal. After week 8, the patient developed an acute gastrointestinal illness lasting approximately 5 days, with symptoms of fever, mild epigastric pain, and diarrhea. The patient's family members had similar gastrointestinal symptoms. Laboratory tests collected at the week-12 visit before dosing revealed marked aminotransferase elevations (alanine aminotransferase >15 times the upper limit of the normal range and aspartate aminotransferase >10× upper limit of the normal range), slightly elevated alkaline phosphatase, and normal bilirubin. The patient was hospitalized and treated with IV prednisolone, IV fluids, and cholestyramine. An extensive diagnostic evaluation did not identify a clear etiology. The patient recovered without sequelae, and liver enzymes normalized within approximately 3 months. The patient stopped treatment and was discontinued from the study.

Discussion

For patients with Crohn's disease, there remains a need to target new pathways for effective treatment therapies, including inhibition of IL-23.[16–18] Selective blockade of the p19 subunit of IL-23 with guselkumab induced greater clinical and endoscopic improvements vs placebo, providing evidence for further pivotal induction and maintenance studies in Crohn's disease.

In this phase 2, dose-ranging study conducted in patients with moderately to severely active Crohn's disease, guselkumab treatment resulted in greater improvements in clinical and endoscopic end points relative to placebo. All guselkumab doses evaluated (200 mg, 600 mg, and 1200 mg IV) achieved the primary end point and demonstrated clinically meaningful decrements in CDAI scores compared with placebo at week 12. Separation from placebo was observed as early as week 4, indicating rapid onset of action with continued substantial improvement through week 12. Although the lowest dose (200 mg) had the greatest numeric reduction from baseline in CDAI score at week 12, the differences between the individual dose groups were small and not considered clinically meaningful. Furthermore, no dose–response or consistent exposure–response relationship was observed across the clinical and endoscopic outcomes evaluated.

Table 2. Key Safety Events Through Week 12

Variable	Placebo	Guselkumab 200 mg	Guselkumab 600 mg	Guselkumab 1200 mg	Guselkumab Combined	Ustekinumab[a]
Patients included in safety analysis, n	70	73	73	73	219	71
Mean duration of follow-up, *wk*	12.1	12.2	12.0	11.7	12.0	12.2
Mean exposure (no. of study agent administrations)	2.8	2.7	2.7	2.7	2.7	1.9
Patients with 1 or more AEs	42 (60.0)	32 (43.8)	37 (50.7)	31 (42.5)	100 (45.7)	36 (50.7)
Most common AEs[b]						
Anemia	5 (7.1)	1 (1.4)	3 (4.1)	2 (2.7)	6 (2.7)	2 (2.8)
Hemoglobin decreased	5 (7.1)	1 (1.4)	1 (1.4)	2 (2.7)	4 (1.8)	0 (0.0)
Headache	0 (0.0)	2 (2.7)	5 (6.8)	5 (6.8)	12 (5.5)	1 (1.4)
Upper respiratory tract infection	4 (5.7)	1 (1.4)	1 (1.4)	1 (1.4)	3 (1.4)	4 (5.6)
Abdominal pain	3 (4.3)	1 (1.4)	0 (0.0)	1 (1.4)	2 (0.9)	4 (5.6)
Arthralgia	2 (2.9)	2 (2.7)	3 (4.1)	1 (1.4)	6 (2.7)	4 (5.6)
Nasopharyngitis	3 (4.3)	3 (4.1)	4 (5.5)	3 (4.1)	10 (4.6)	3 (4.2)
Patients with 1 or more 1 SAEs	4 (5.7)	3 (4.1)	4 (5.5)	1 (1.4)	8 (3.7)	4 (5.6)
Patients with 1 or more 1 AEs leading to discontinuation of study agent	2 (2.9)	1 (1.4)	0 (0.0)	1 (1.4)	2 (0.9)	0 (0.0)
Patients with 1 or more 1 infections[c]	15 (21.4)	9 (12.3)	13 (17.8)	11 (15.1)	33 (15.1)	9 (12.7)
Patients with 1 or more 1 serious infections[c]	0 (0.0)	1 (1.4)	2 (2.7)	0 (0.0)	3 (1.4)	1 (1.4)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

NOTE. Data presented as n (%) unless otherwise noted. Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
[a]Patients received a single ustekinumab IV induction dose (6 mg/kg) at week 0. At week 8, patients received 1 ustekinumab subcutaneous maintenance dose (90 mg).
[b]Occurred in ≥5% of patients in any treatment group. AEs are coded using MedDRA, version 23.0.
[c]Infection as assessed by the investigator.

In the combined guselkumab group, 54.6% of patients had an inadequate response or intolerance to prior biologic therapy and 45.4% had an inadequate response or intolerance to prior conventional therapy. Consistent with previous biologic studies in similar populations, the absolute response rates were generally high in patients who were naïve to biologic treatment. Notably, the benefit of guselkumab was seen in both of these populations, with similar treatment effects vs placebo observed within the range of guselkumab doses tested in this study. Greater proportions of patients receiving guselkumab in each of the subgroups achieved clinical remission, clinical response, and PRO-2 remission compared with placebo; similar results were observed for endoscopic response, suggesting an overall benefit with guselkumab treatment across the broad target population of patients with moderately to severely active Crohn's disease.

Consistent with improvements observed across clinical and endoscopic end points, reduction in levels of inflammatory markers (ie, fecal calprotectin and CRP) through week 12 with guselkumab treatment were observed, indicating resolution of the underlying inflammatory disease process. Improvements in patient-reported outcomes, including IBDQ and Patient-Reported Outcomes Measurement Information System Fatigue Short Form-7a , were reported in patients treated with guselkumab. These are important outcomes for patients with Crohn's disease whose health-related quality of life is often negatively affected by their disease.[28]

Ustekinumab is an approved, effective, and widely used therapy for the treatment of adult patients with moderately to severely active Crohn's disease. All *P* values presented for the ustekinumab reference arm vs placebo are nominal and from post-hoc analyses. The dose of ustekinumab in this study is the highest approved induction/maintenance dose regimen and was previously evaluated in the phase 3 ustekinumab Crohn's disease clinical development program.[7,29–31] In this phase 2 study, ustekinumab was included as a reference arm to inform phase 3 study considerations, and there were no formal comparisons planned between guselkumab and ustekinumab in this study. Larger studies are needed to appropriately evaluate potential differences in efficacy and safety between guselkumab and ustekinumab. In an era when there are an increasing number of treatment options available, the generation of comparative efficacy data would provide important insights

to inform clinical practice. Moreover, ustekinumab, which targets IL-12/23, has an overlapping mechanism of action with guselkumab, and biomarker data generated from this study and the phase 3 studies of guselkumab in Crohn's disease could provide valuable insights on targeted IL-23 blockade compared with dual targeting of both IL-12/23. Patients with prior inadequate response to ustekinumab were excluded from this study, limiting our ability to ascertain the efficacy of IL-23 blockade in patients who have not adequately responded to IL-12/23 blockade. In the NAVIGATE trial of patients with moderate to severe plaque psoriasis, guselkumab was effective and superior to ustekinumab in patients with suboptimal response to ustekinumab.[26] Assuming that the mechanism by which IL-23 blockade exerts efficacy in psoriasis and inflammatory bowel disease is similar, it is possible that the more specific targeting of IL-23 signaling (vs IL-12/23 signaling) may confer incremental clinical benefit and deserves a more thorough evaluation in future clinical studies.

The safety profile of guselkumab through week 12 was consistent with that established from clinical trials conducted in the approved indications of psoriasis and psoriatic arthritis. Overall, immunogenicity was low among guselkumab-treated patients through week 12.

This study has some limitations. First, the effects of guselkumab were only evaluated through 12 weeks in this induction dose-finding study, and longer-term maintenance data are needed. Furthermore, our ability to draw conclusions regarding the efficacy of guselkumab in clinically relevant subgroups of patients with Crohn's disease, including those with variable disease duration, an inadequate response to 1 or more advanced therapies, fistulizing disease, or extraintestinal manifestations, was limited by the small sample size.

In summary, all 3 doses of guselkumab evaluated induced clinically meaningful improvements in patients with moderately to severely active Crohn's disease, with a favorable safety profile. The results from this 12-week study of guselkumab further substantiate the clinical relevance of targeting IL-23 in the treatment of Crohn's disease. Phase 3 studies evaluating the efficacy and safety of guselkumab for the treatment of Crohn's disease are currently underway.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2022.01.047.

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Equal; Methodology: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).

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 Yale Open Data Access Project site at http://yoda.yale.edu.

Conflicts of interest

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Geert R. D'Haens: serves as an investigator, consultant, and steering committee member for Janssen. 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Supplementary Material

Inflammatory Bowel Disease Questionnaire

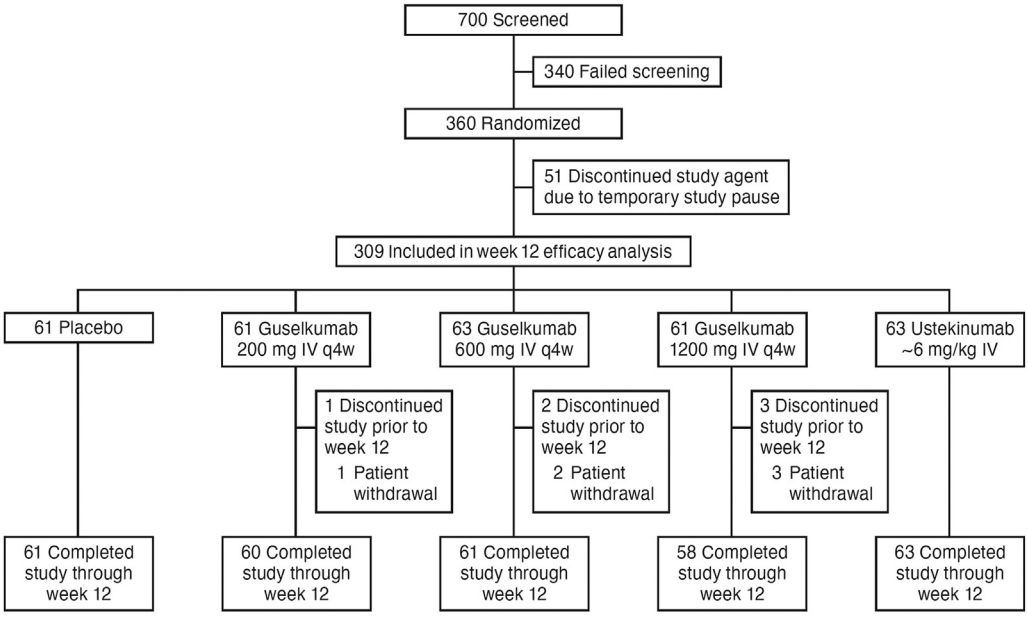
The IBDQ is a validated, 32-item, self-reported questionnaire for participants with IBD to evaluate patient-reported outcomes across the following 4 dimensions: bowel symptoms (eg, loose stools or abdominal pain), systemic symptoms (eg, fatigue and altered sleep pattern), social function (eg, work attendance or need to cancel social events), and emotional function (anger, depression, and irritability). Scores range from 32 to 224, with higher scores indicating better outcomes.

IBDQ remission (based on IBDQ $\geq$170) and IBDQ response ($\geq$16-point improvement from baseline) were evaluated at week 8 and week 12.

Patient-Reported Outcomes Measurement Information System Fatigue Short Form 7a

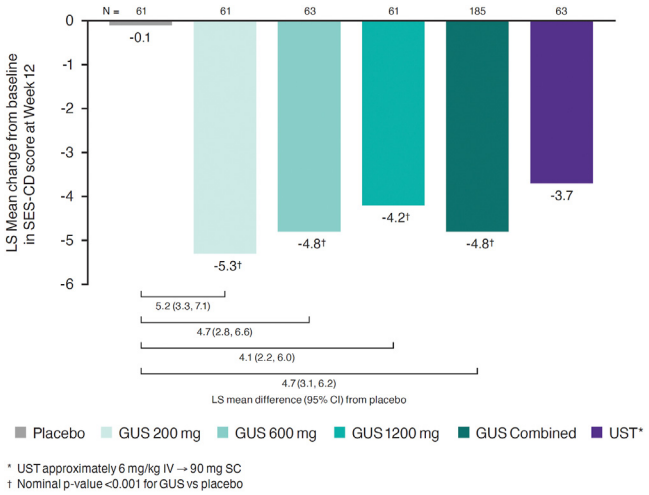
The Patient-Reported Outcomes Measurement Information System Fatigue Short Form 7a contains 7 items evaluating fatigue-related symptoms (ie, tiredness, exhaustion, mental tiredness, and lack of energy) and associated impacts on daily activities (ie, activity limitations related to work, self-care, and exercise) with a recall period of past 7 days.

Change from baseline in the Patient-Reported Outcomes Measurement Information System Fatigue Short Form 7a total score was evaluated at week 8 and week 12.



IV, intravenous; q4w, every 4 weeks

Supplementary Figure 1. CONSORT (Consolidated Standards of Reporting Trials) patient flow.



* UST approximately 6 mg/kg IV → 90 mg SC
† Nominal p-value <0.001 for GUS vs placebo

Supplementary Figure 2. Least squares (LS) mean change from baseline in SES-CD at week 12. CI, confidence interval; GUS, guselkumab; SC, subcutaneous; UST, ustekinumab.

Supplementary Table 1. Summary of Change From Baseline Through Week 12 in Fecal Calprotectin Concentration ($\mu g/g$)

Variable	Placebo	Guselkumab				Ustekinumab[a]
		200 mg	600 mg	1200 mg	Combined	
Patients included in efficacy analysis, n	61	61	63	61	185	63
Change from baseline						
Week 4[b,c]						
n	58	54	61	57	172	61
Mean (SD)	–780.29 (4921.267)	–819.83 (3228.528)	–756.85 (2557.196)	55.19 (2877.458)	–507.52 (2897.438)	–559.38 (1145.657)
Median	–42.50	–55.50	–105.00	–117.00	–99.50	–266.00
IQR	–592.00 to 80.00	–910.00 to 17.00	–627.00 to 49.00	–616.00 to 248.00	–762.50 to 44.00	–1049.00 to 0.00
Range	–34,441.0 to 8338.0	–23,093.0 to 1749.0	–17,830.0 to 786.0	–5474.0 to 15,587.0	–23,093.0 to 15,587.0	–4584.0 to 2178.0
P value[d]	—	.111	.217	.281	.110	—
Week 8[b,c]						
n	57	57	61	56	174	60
Mean (SD)	–460.63 (5255.365)	–785.30 (2889.375)	–815.54 (2805.127)	–407.88 (1655.190)	–674.43 (2517.241)	–267.68 (1375.064)
Median	7.00	–131.00	–122.00	–223.00	–150.00	–175.00
IQR	–370.00 to 527.00	–1001.00 to 0.00	–943.00 to 0.00	–1221.00 to 4.00	–1001.00 to 1.00	–967.50 to 85.00
Range	–35,375.0 to 7469.0	–20,498.0 to 2626.0	–16,894.0 to 5548.0	–5536.0 to 4933.0	–20,498.0 to 5548.0	–5012.0 to 4546.0
P value[d]	—	.001	.014	.006	<.001	—
Week 12[b,c]						
n	54	52	60	52	164	55
Mean (SD)	–954.91 (4973.267)	–599.44 (1125.692)	–526.20 (4668.652)	–501.83 (1268.297)	–541.70 (2964.945)	–466.62 (1197.621)
Median	0.00	–165.00	–163.50	–131.50	–152.50	–118.00
IQR	–637.00 to 146.00	–1060.00 to –12.00	–922.50 to 45.50	–921.50 to 109.50	–958.50 to 36.00	–882.00 to 0.00
Range	–34,867.0 to 4154.0	–5373.0 to 1148.0	–18,497.0 to 27,520.0	–5165.0 to 1754.0	–18,497.0 to 27,520.0	–5505.0 to 2632.0
P value[d]	—	0.001	0.115	0.040	0.006	—

IQR, interquartile range; SD, standard deviation.

[a]Patients received a single ustekinumab IV induction dose (approximately 6 mg/kg) at week 0. At week 8, patients received 1 ustekinumab subcutaneous maintenance dose (90 mg).

[b]Patients who had a prohibited change in concomitant Crohn's disease medication, a Crohn's disease–related surgery, or discontinued study agent due to lack of efficacy or an adverse event of worsening Crohn's disease before the designated analysis time point had their baseline value carried forward from that time point onward. Patients who had discontinued study agent due to any other reasons before the designated analysis time point had their observed data used, if available, from that time point onward.

[c]Patients who had a missing fecal calprotectin value at the designated analysis time point did not have their missing data imputed.

[d]The *P* values for the comparisons of each guselkumab treatment group with the placebo group were based on mixed-effect model repeated measure analysis, including change from baseline in log-transformed fecal calprotectin concentration as the response; and treatment group, visit, log-transformed baseline fecal calprotectin concentration, inadequate response or intolerance to prior biologic therapy (yes/no), baseline CDAI score stratification ($\leq$300, $>$300), an interaction term of visit with treatment group, and an interaction term of visit with baseline log-transformed fecal calprotectin concentrations as explanatory variables.

Supplementary Table 2. Summary of Change From Baseline Through Week 12 in C-Reactive Protein Concentration (*mg/L*)

Variable	Placebo	Guselkumab 200 mg	Guselkumab 600 mg	Guselkumab 1200 mg	Guselkumab Combined	Ustekinumab[a]
Patients included in efficacy analysis, n	61	61	63	61	185	63
Change from baseline						
Week 4[b,c]						
n	60	60	63	58	181	63
Mean (SD)	0.79 (15.939)	–9.51 (31.787)	–10.56 (22.891)	–3.69 (10.147)	–8.01 (23.522)	–11.25 (24.801)
Median	–.09	–1.57	–1.63	–1.20	–1.44	–3.24
IQR	–2.10 to 2.84	–12.20 to 0.03	–10.06 to 0.11	–3.67 to 0.40	–8.45 to 0.08	–11.29 to –0.09
Range	–74.4 to 73.0	–147.3 to 104.3	–126.5 to 22.7	–44.7 to 16.6	–147.3 to 104.3	–94.0 to 49.8
P value[d]	—	.039	.022	.126	.016	—
Week 8[b,c]						
n	60	59	62	57	178	62
Mean (SD)	0.67 (11.618)	–9.06 (45.465)	–10.04 (26.942)	–4.65 (10.450)	–7.99 (31.104)	–11.30 (24.231)
Median	0.22	–2.65	–2.04	–1.59	–2.00	–2.01
IQR	–1.81 to 3.46	–17.05 to –0.01	–10.35 to 0.00	–6.24 to 0.09	–9.26 to 0.00	–11.18 to 0.22
Range	–38.8 to 23.6	–149.1 to 263.3	–137.7 to 55.5	–49.4 to 15.3	–149.1 to 263.3	–96.3 to 31.8
P value[d]	—	<.001	<.001	.001	<.001	—
Week 12[b,c]						
n	60	57	61	56	174	62
Mean (SD)	3.60 (27.961)	–13.16 (26.790)	–12.37 (27.879)	–2.27 (11.422)	–9.38 (23.824)	–9.43 (23.008)
Median	0.07	–4.84	–2.26	–0.74	–1.99	–1.45
IQR	–1.73 to 2.29	–10.50 to –0.17	–13.08 to –0.06	–3.74 to 1.06	–9.31 to 0.06	–8.07 to 0.07
Range	–71.4 to 136.8	–150.0 to 22.0	–130.6 to 58.0	–43.7 to 39.8	–150.0 to 58.0	–95.7 to 9.3
P value[d]	—	<.001	<.001	.049	<.001	—

IQR, interquartile range; SD, standard deviation.

[a]Patients received a single ustekinumab IV induction dose (approximately 6 mg/kg) at week 0. At week 8, patients received 1 ustekinumab subcutaneous maintenance dose (90 mg).

[b]Patients who had a prohibited change in concomitant Crohn's disease medication, a Crohn's disease–related surgery, or discontinued study agent due to lack of efficacy or an adverse event of worsening Crohn's disease before the designated analysis time point had their baseline value carried forward from that time point onward. Patients who had discontinued study agent due to any other reasons before the designated analysis time point had their observed data used, if available, from that time point onward.

[c]Patients who had a missing CRP value at the designated analysis time point did not have their missing data imputed.

[d]The *P* values for the comparisons of each guselkumab treatment group with the placebo group were based on mixed effect repeated measures mode analysis, including change from baseline in log-transformed CRP concentration as the response; and treatment group, visit, log-transformed baseline CRP concentration, inadequate response or intolerance to prior biologic therapy (yes/no), baseline CDAI score stratification ($\leq$300, $>$300), an interaction term of visit with treatment group, and an interaction term of visit with log-transformed baseline CRP concentration as explanatory variables.

Supplementary Table 3. Patients in Inflammatory Bowel Disease Questionnaire Remission at Week 8 and Week 12

Variable	Placebo	Guselkumab				Ustekinumab[a]
		200 mg	600 mg	1200 mg	Combined	
Patients included in efficacy analysis, n	61	61	63	61	185	63
Week 8						
n	61	61	63	61	185	63
Patients in IBDQ remission, n (%)[b,c]	12 (19.7)	31 (50.8)	28 (44.4)	26 (42.6)	85 (45.9)	37 (58.7)
P value[e]	—	<.001	.002	.007	<.001	—
Week 12						
n	61	61	63	61	185	63
Patients in IBDQ remission, n (%)[b,c]	14 (23.0)	34 (55.7)	32 (50.8)	28 (45.9)	94 (50.8)	31 (49.2)
Adjusted treatment difference (95% CI)[d]	—	34.0 (18.2–49.8)	29.5 (14.6–44.5)	24.2 (8.4–40.0)	29.0 (16.6–41.4)	—
P value[e]	—	<.001	<.001	.005	<.001	—

NOTE. IBDQ remission is defined as IBDQ score ≥170.
CI, confidence interval.
[a]Patients received a single ustekinumab IV induction dose (approximately 6 mg/kg) at week 0. At week 8, patients received 1 ustekinumab subcutaneous maintenance dose (90 mg).
[b]Patients who had a prohibited change in concomitant Crohn's disease medication, a Crohn's disease–related surgery, or discontinued study agent due to lack of efficacy or an adverse event of worsening Crohn's disease before the designated analysis time point were considered not to be in IBDQ remission from that analysis time point onward. Patients who had discontinued study agent due to any other reasons before the designated analysis time point had their observed data used to determine responder and nonresponder status from that time point onward.
[c]Patients who had insufficient data to calculate IBDQ score at the designated analysis time point were considered not to be in IBDQ remission at that time point.
[d]The CIs were based on the Wald statistic with Cochran-Mantel-Haenszel weight for pairwise comparisons of each guselkumab treatment group with the placebo treatment group.
[e]The *P* values for pairwise comparisons of each guselkumab treatment group with the placebo treatment group were based on Cochran-Mantel-Haenszel χ^2 test stratified by baseline CDAI score (≤300 or >300) and inadequate response or intolerance to prior biologic therapy (yes/no).

Supplementary Table 4. Patients With Inflammatory Bowel Disease Questionnaire Response at Week 8 and Week 12

Variable	Placebo	Guselkumab				Ustekinumab[a]
		200 mg	600 mg	1200 mg	Combined	
Patients included in efficacy analysis, n	61	61	63	61	185	63
Week 8						
n	61	61	63	61	185	63
Patients in IBDQ response, n (%)[b,c]	25 (41.0)	43 (70.5)	44 (69.8)	38 (62.3)	125 (67.6)	50 (79.4)
P value[e]	—	.001	.001	.015	<.001	—
Week 12						
n	61	61	63	61	185	63
Patients in IBDQ response, n (%)[b,c]	25 (41.0)	42 (68.9)	47 (74.6)	44 (72.1)	133 (71.9)	48 (76.2)
Adjusted treatment difference (95% CI)[d]	—	28.7 (12.3–45.1)	34.9 (19.6–50.1)	33.3 (17.6–48.9)	32.0 (18.5–45.5)	—
P value[e]	—	.001	<.001	<.001	<.001	—

NOTE. IBDQ response is defined as ≥16-point improvement from baseline.
CI, confidence interval.
[a]Patients received a single ustekinumab IV induction dose (approximately 6 mg/kg) at week 0. At week 8, patients received 1 ustekinumab subcutaneous maintenance dose (90 mg).
[b]Patients who had a prohibited change in concomitant Crohn's disease medication, a Crohn's disease–related surgery, or discontinued study agent due to lack of efficacy or an adverse event of worsening Crohn's disease before the designated analysis time point were considered not to be in IBDQ response from that time point onward. Patients who had discontinued study agent due to any other reasons before the designated analysis time point had their observed data used to determine responder and nonresponder status from that time point onward.
[c]Patients who had insufficient data to calculate IBDQ score at the designated time point were considered not to be in IBDQ response at that time point.
[d]The CIs were based on the Wald statistic with Cochran-Mantel-Haenszel weight for pairwise comparisons of each guselkumab treatment group with the placebo treatment group.
[e]The *P* values for pairwise comparisons of each guselkumab treatment group with the placebo treatment group were based on Cochran-Mantel-Haenszel χ^2 test stratified by baseline CDAI score (≤300 or >300), and inadequate response or intolerance to prior biologic therapy (yes/no).

Supplementary Table 5. Summary of Change From Baseline in the PROMIS Fatigue Short-Form 7a Total Score at Week 8 and Week 12

Variable	Placebo	Guselkumab				Ustekinumab[a]
		200 mg	600 mg	1200 mg	Combined	
Patients included in efficacy analysis, n	61	61	63	61	185	63
Change from baseline						
Week 8[b,c]						
n	54	59	62	56	177	63
Mean (SD)	–1.47 (7.970)	–5.69 (8.194)	–6.07 (7.419)	–6.04 (9.096)	–5.94 (8.191)	–6.25 (8.042)
Median	0.00	–5.00	–5.60	–4.15	-5.00	–5.60
IQR	–4.60 to 2.90	–10.70 to 0.00	–11.20 to 0.00	–10.20 to –1.60	–10.70 to 0.0)	–10.20 to –1.80
Range	–24.4 to 15.5	–32.6 to 9.3	–27.1 to 13.9	–36.0 to 13.4	–36.0 to 13.9	–37.9 to 11.6
P value[d]	—	<.001	<.001	<.001	<.001	—
Week 12[b,c]						
n	56	58	61	57	176	63
Mean (SD)	–0.96 (7.443)	–6.73 (8.205)	–6.16 (8.306)	–8.07 (8.989)	–6.96 (8.490)	–7.09 (9.492)
Median	–1.40	–7.00	–5.60	–8.80	–6.95	–6.90
IQR	–5.00 to 3.70	–11.40 to 0.00	–11.20 to 0.00	–14.30 to –3.20	–12.75 to 0.00	–13.00 to 0.00
Range	–20.5 to 15.6	–26.7 to 8.4	–30.9 to 20.9	–27.9 to 12.5	–30.9 to 20.9	–35.2 to 18.7
P value[d]	—	< .001	<.001	<.001	<.001	—

IQR, interquartile range; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation.
[a]Patients received a single ustekinumab IV induction dose (approximately 6 mg/kg) at week 0. At week 8, patients received 1 ustekinumab subcutaneous maintenance dose (90 mg).
[b]Patients who had a prohibited change in concomitant Crohn's disease medication, a Crohn's disease–related surgery, or discontinued study agent due to lack of efficacy or an adverse event of worsening Crohn's disease before the designated analysis time point had their baseline value carried forward from that time point onward. Patients who had discontinued study agent due to any other reasons before the designated analysis time point had their observed data used from that time point onward.
[c]Patients who had insufficient data to calculate PROMIS Fatigue Short-Form 7a (PROMIS F-SF) total score at the designated analysis time point did not have their missing data imputed.
[d]The *P* values for the comparisons of each guselkumab treatment group with the placebo group were based on mixed effect repeated measures model analysis including change from baseline in PROMIS F-SF total score as the response; and treatment group, visit, baseline PROMIS F-SF total score, inadequate response or intolerance to prior biologic therapy (yes/no), baseline CDAI score stratification ($\leq$300, >300), an interaction term of visit with treatment group and an interaction term of visit with baseline PROMIS F-SF total score as explanatory variables.

Supplementary Table 6. Patients in Clinical Remission or Endoscopic Response at Week 12 by Serum Guselkumab Concentration Quartiles at Week 12

Variable	Guselkumab combined
Patients included in the efficacy analysis with at least 1 post-baseline PK sample, n	185
Patients with serum guselkumab concentration at week 12, n	146
Serum guselkumab concentrations (μg/mL) at week 12	
$<1^{st}$ quartile[a]	
n	36
Patients in clinical remission at week 12,[b,c] n (%)	19 (52.8)
Patients in endoscopic response at week 12,[b,d] n (%)	8 (22.2)
$\geq 1^{st}$ and $<2^{nd}$ quartile[a]	
n	37
Patients in clinical remission at week 12,[b,c] n (%)	22 (59.5)
Patients in endoscopic response at week 12,[b,d] n (%)	15 (40.5)
$\geq 2^{nd}$ and $<3^{rd}$ quartile[a]	
n	36
Patients in clinical remission at week 12,[b,c] n (%)	17 (47.2)
Patients in endoscopic response at week 12,[b,d] n (%)	11 (30.6)
$\geq 3^{rd}$ quartile[a]	
n	37
Patients in clinical remission at week 12,[b,c] n (%)	21 (56.8)
Patients in endoscopic response at week 12,[b,d] n (%)	12 (32.4)

NOTE. Clinical remission is defined as CDAI score <150. Endoscopic response is defined as at least 50% improvement from baseline in SES-CD score or SES-CD score $\leq$2.

[a]Quartiles are based on patients in each treatment group as follows: 200 mg IV every 4 weeks (q4w): 1^{st} quartile = 6.02 μg/mL, 2^{nd} quartile = 8.77 μg/mL, 3^{rd} quartile = 14.36 μg/mL; 600 mg IV q4w: 1^{st} quartile = 18.60 μg/mL, 2^{nd} quartile = 27.61 μg/mL, 3^{rd} quartile = 36.77 μg/mL; 1200 mg IV q4w: 1^{st} quartile = 33.54 μg/mL, 2^{nd} quartile = 50.40 μg/mL, 3^{rd} quartile = 64.20 μg/mL; combined: 1^{st} quartile = 10.82 μg/mL, 2^{nd} quartile = 24.94 μg/mL, 3^{rd} quartile = 47.12 μg/mL.

[b]Patients who had a prohibited change in concomitant Crohn's disease medication, a Crohn's disease–related surgery, or discontinued study agent due to lack of efficacy or an AE of worsening Crohn's disease before week 12 were considered not to be in clinical remission at week 12. Patients who had discontinued study agent due to any other reasons before week 12 had their observed week 12 data used, if available, to determine responder and nonresponder status at week 12.

[c]Patients who had insufficient data to calculate the CDAI score at week 12 were considered not to be in clinical remission at week 12.

[d]The total SES-CD score at week 12 was based on all observed segments scored at week 12. Patients who had insufficient data to calculate the SES-CD score at week 12 were considered not to be in endoscopic response at week 12.