SUPPLEMENTARY MATERIAL

Central Reader Process

The endoscopic findings were assessed by the investigator (ie, local endoscopist) during the endoscopy procedure (either sigmoidoscopy or colonoscopy) and by the central reader who reviewed a video of the endoscopy. Participant eligibility at baseline was based on the final reported endoscopy subscore as determined by the following process:

- If the local endoscopist and the central reader agreed on the endoscopy subscore, the agreed score was the final reported endoscopy subscore.
- If there was a discrepancy between the local endoscopist and the central reader subscores, the video endoscopy was submitted to a second central reader (designated for adjudication). The median score of the 3 completed reads (ie, local read, central read 1, and central read 2 designated for adjudication) was the final reported endoscopy subscore.

Biopsy Methodology

During each endoscopy, a total of up to 6 colonic biopsy samples were collected from a single predefined anatomic location (rectum [within 15-20 cm from anal verge]). Four adjacent biopsies were collected from all study participants (2 biopsies for histology and 2 biopsies for RNA transcriptomics). Two additional adjacent biopsies and a paired blood sample for peripheral blood mononuclear cell isolation were collected for single cell RNA-sequence analysis from patients at predefined investigative sites. Biopsies were to be collected from representative areas that are consistent with the inflammation status visually observed during endoscopy. The biopsies designated for histology were collected in 10% neutral-buffered formalin and were processed and embedded into 2 independent paraffin blocks by the Central Laboratory. One

biopsy was prepared as multiple ribbon sections and stained with hematoxylin and eosin (H&E), while the second biopsy was retained and used as a backup. H&E-stained slides were provided to the Central Reader (gastrointestinal pathologist) for histologic assessment based on the Geboes grading scale, Robarts Histologic Index, and the Nancy Index. The Central Reader reported an overall score based on assessment of the worst features observed from serial sections of a single biopsy.

Supplementary Table S1. Overall summary of adverse events through week 12 in all treated patients regardless of modified Mayo score at baseline

		Guselkumab		
	Placebo IV (N=108)	200 mg IV (N=108)	400 mg IV (N=111)	Combined (N=219)
Average duration of follow-up, weeks	12.2	12.1	12.2	12.2
Average exposure (number of administrations)	2.9	3.0	3.0	3.0
Patients with ≥1, n (%)				
AE	62 (57.4)	48 (44.4)	54 (48.6)	102 (46.6)
AE within 1 hour of infusion	2 (1.9)	2 (1.9)	0	2 (0.9)
Serious AE	6 (5.6)	1 (0.9)	3 (2.7)	4 (1.8)
Death	0	0	0	0
Discontinuation for AE	3 (2.8)	1 (0.9)	0	1 (0.5)
Malignancy	0	1 (0.9)	0	1 (0.5)
Infection[a]	14 (13.0)	14 (13.0)	10 (9.0)	24 (11.0)
Serious infection	2 (1.9)	0	0	0
Most frequent AEs,[b] n (%)				
Anaemia	10 (9.3)	8 (7.4)	8 (7.2)	16 (7.3)
Headache	8 (7.4)	3 (2.8)	6 (5.4)	9 (4.1)
COVID-19 infection	5 (4.6)	6 (5.6)	2 (1.8)	8 (3.7)
Abdominal pain	3 (2.8)	4 (3.7)	3 (2.7)	7 (3.2)
Arthralgia	3 (2.8)	2 (1.9)	4 (3.6)	6 (2.7)
Colitis ulcerative	6 (5.6)	1 (0.9)	4 (3.6)	5 (2.3)
Diarrhoea	2 (1.9)	4 (3.7)	1 (0.9)	5 (2.3)
Lymphopenia	5 (4.6)	1 (0.9)	2 (1.8)	3 (1.4)

Pyrexia	5 (4.6)	2 (1.9)	1 (0.9)	3 (1.4)

[a]Infections as assessed by the investigator.

[b]Occurred in at least 3% of patients in any treatment group. AE, adverse event; COVID-19, Coronavirus disease 2019; IV, intravenous; N, total population; n, subset.

Supplementary Table S2. Overall summary of adverse events from week 12 through the final safety visit in week-12 clinical nonresponders who received subcutaneous guselkumab at weeks 12, 16, and 20

	Placebo IV → Guselkumab 200 mg IV (N=66)	Guselkumab IV → Guselkumab 200 mg SC (N=78)
Average duration of follow-up, weeks	13.9	14.6
Average exposure (number of administrations)	2.9	2.9
Patients with ≥1, n (%)		
AE	34 (51.5)	33 (42.3)
AE within 1 hour of infusion	0	1 (1.3)
Serious AE	2 (3.0)	3 (3.8)
Death	0	0
Discontinuation for AE	2 (3.0)	2 (2.6)
Discontinuation for COVID-19 infection	0	0
Malignancy	0	0
Infection[a]	10 (15.2)	6 (7.7)
COVID-19 infection	1 (1.5)	1 (1.3)
Serious infection	1 (1.5)	0
Most frequent AEs,[b] n (%)		
Upper respiratory tract infection	2 (3.0)	0

Includes only patients with modified Mayo score 5-9 at induction baseline.

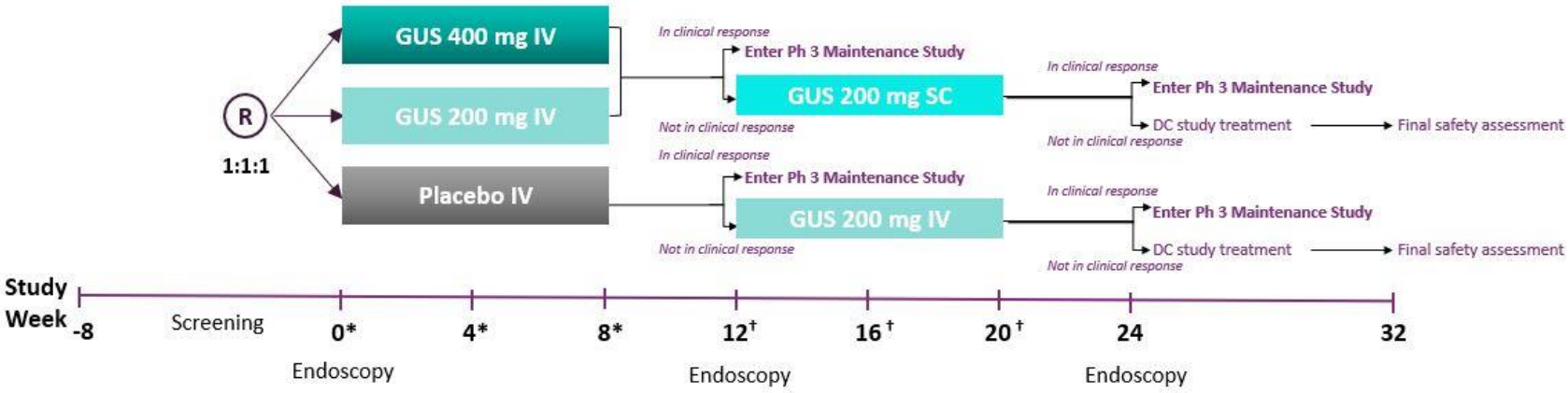
[a]Infections as assessed by the investigator.

[b]Occurred in at least 3% of patients in either treatment group.

AE, adverse event; COVID-19, Coronavirus disease 2019; IV, intravenous; N, total population; n, subset; SC, subcutaneous.

Supplementary Figures

Supplementary Figure S1. Overview of QUASAR Phase 2b Induction study design

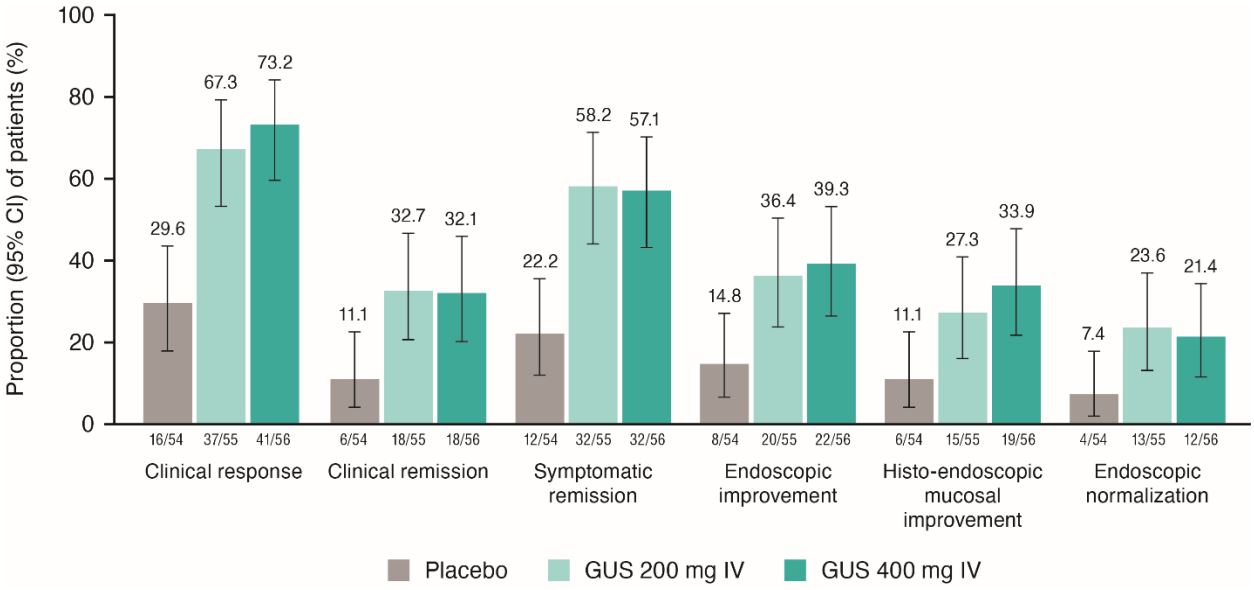


R = Randomization * = Study treatment administered † = Study treatment administered to week 12 clinical nonresponders DC = Discontinue

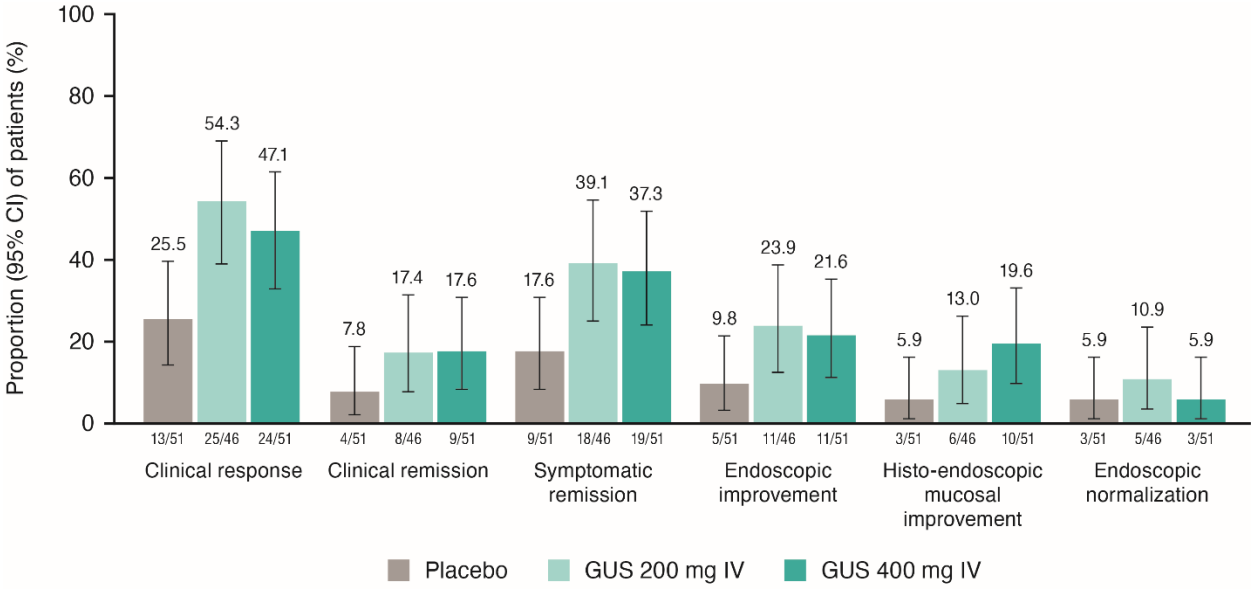
GUS = guselkumab IV = intravenous Ph = Phase SC = subcutaneous

Supplementary Figure S2. Clinical, endoscopic, and histo-endoscopic endpoints at week 12 in patients without (A) and with (B) a history of inadequate response/intolerance to advanced therapy for UC

A



B



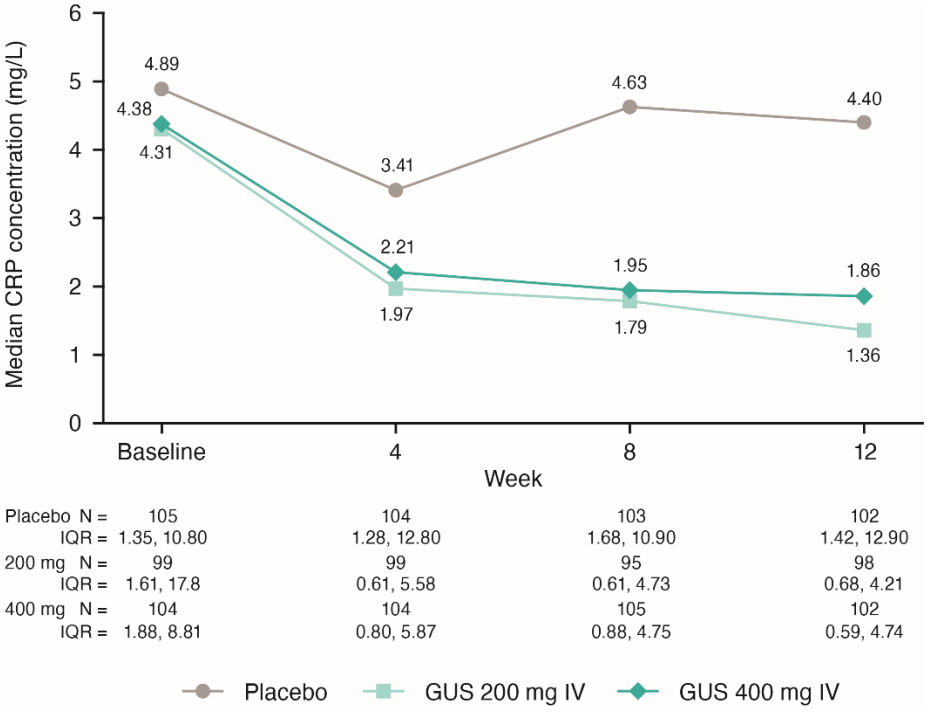
Primary efficacy population. Patients missing 1 or more modified Mayo subscore (stool frequency, rectal bleeding, or endoscopy) or other component pertaining to an endpoint at week 12 were considered not to have achieved the endpoint.

Advanced therapy refers to TNFα antagonists, vedolizumab, and/or tofacitinib. Clinical response was defined as a decrease in modified Mayo score from baseline by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1. Clinical remission was defined as a Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy. Symptomatic remission was defined as a Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline and a Mayo rectal bleeding subscore of 0. Endoscopic improvement was defined as a Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy. Histo-endoscopic mucosal improvement was a combined endpoint of endoscopic improvement and histologic improvement (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system, ie, Geboes score ≤3.1). Endoscopic normalization was defined as a Mayo endoscopy subscore of 0.

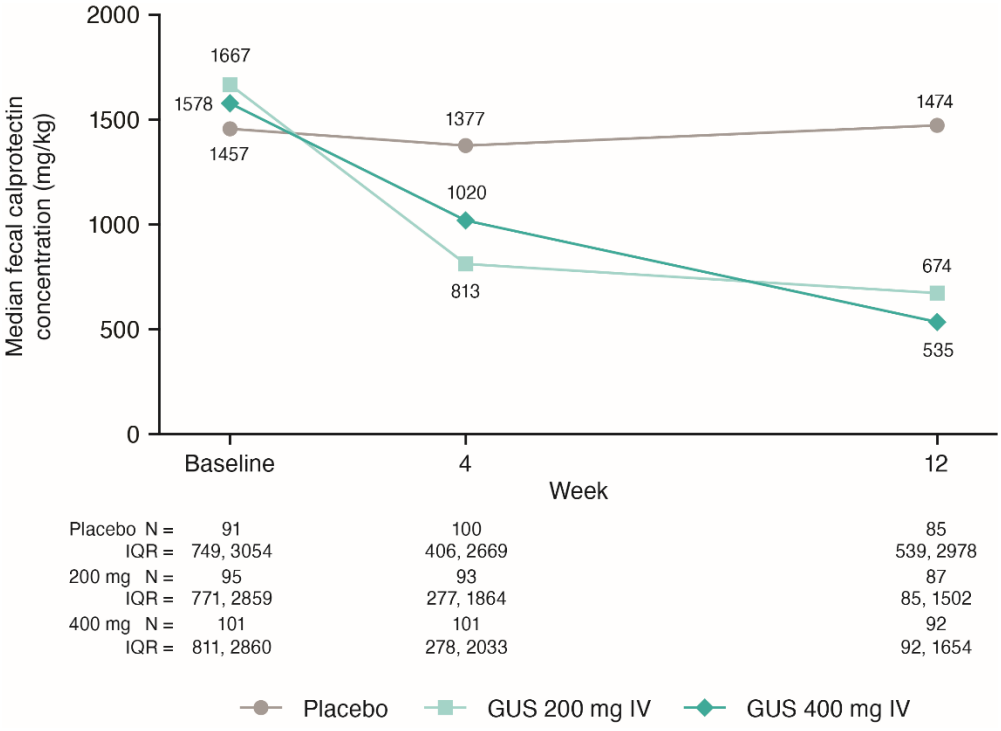
CI, confidence interval; GUS, guselkumab; IV, intravenous; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.

Supplementary Figure S3. Median serum CRP (A) and fecal calprotectin (B) concentrations through week 12

A



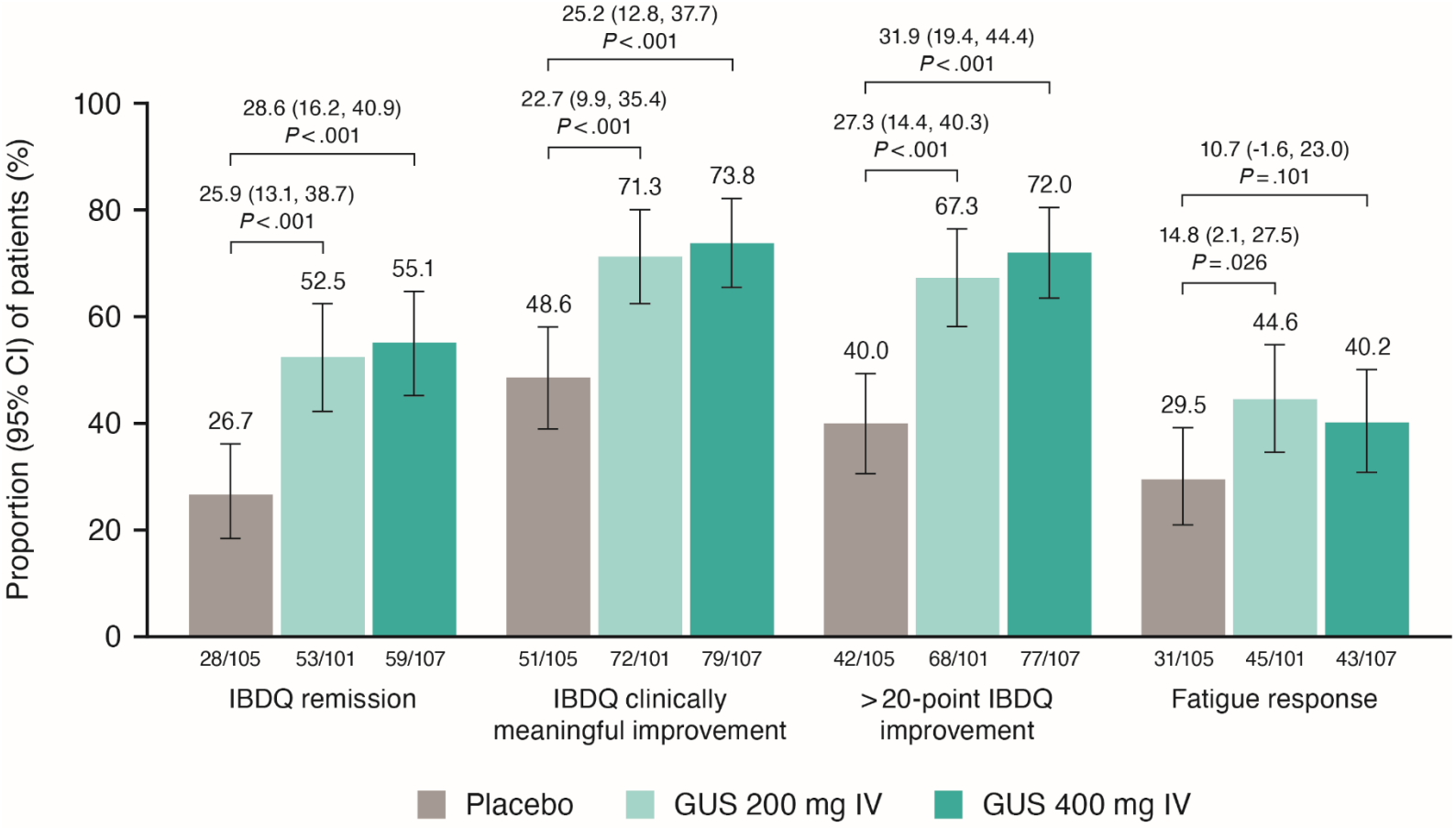
B



Primary efficacy population. A mixed-effect model for repeated measures was used to account for missing data under the assumption of missing at random.

CRP, C-reactive protein; GUS, guselkumab; IQR, interquartile range; IV, intravenous.

Supplementary Figure S4. Achievement of IBDQ remission, IBDQ improvement, and fatigue response at week 12 (*P* values are nominal)



Primary efficacy population. All *P* values are nominal and based on the Cochran-Mantel-Haenszel chi-square test. Patients missing a score at either induction baseline or week 12 (IBDQ clinically meaningful improvement and fatigue response) or week 12 only (IBDQ

remission) were considered not to have achieved the endpoint. The adjusted treatment difference and confidence intervals were based on the Wald statistic with Cochran-Mantel-Haenszel weight. IBDQ remission was defined as total IBDQ score ≥170. Clinically meaningful improvement in total IBDQ score was defined as ≥16-point improvement from baseline. Fatigue response was defined as ≥7-point reduction from baseline in PROMIS-Fatigue SF-7a score.

CI, confidence interval; GUS, guselkumab; IBDQ, Inflammatory Bowel Disease Questionnaire; IV, intravenous; PROMIS-Fatigue SF-7a, Patient-Reported Outcomes Measurement Information System-Fatigue Short Form 7a.

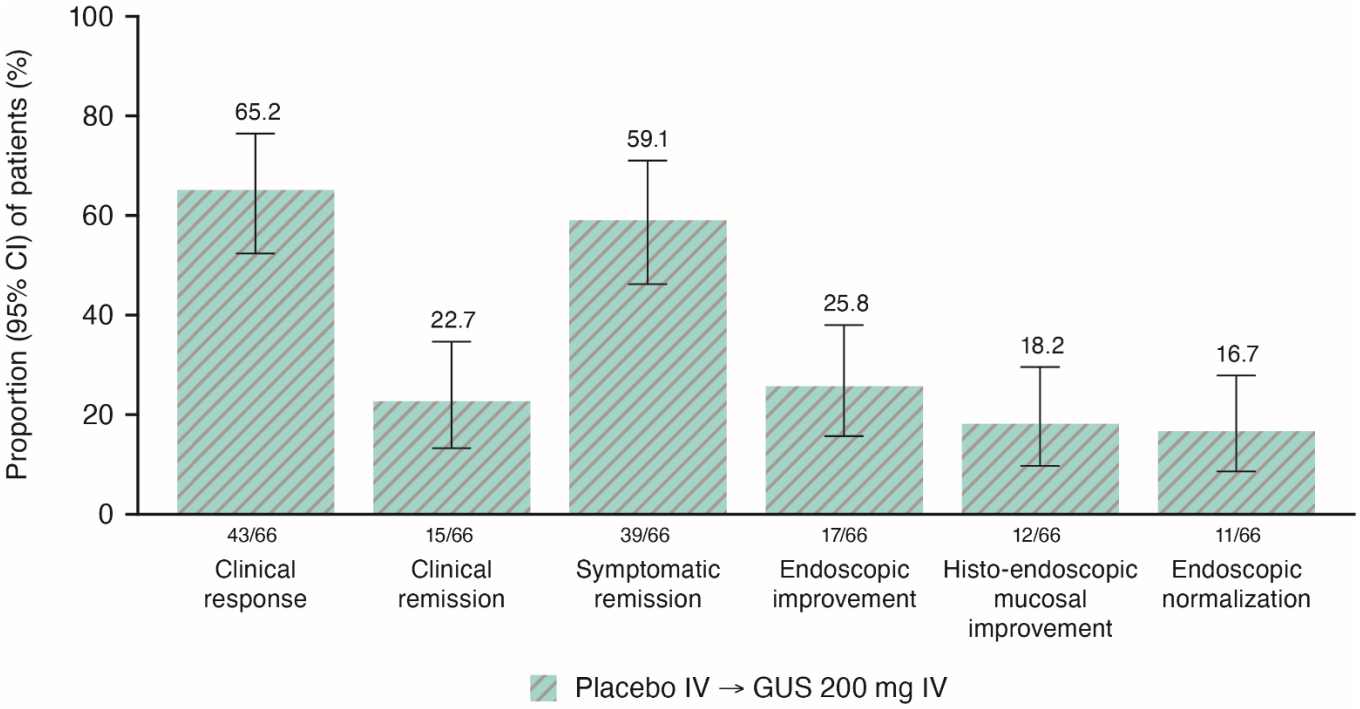
Supplementary Figure S5. Clinical response at week 24 among week-12 clinical nonresponders to guselkumab and cumulative clinical response at weeks 12 or 24 among patients randomized to guselkumab without (A) or with (B) inadequate response/intolerance to advanced therapies

Primary efficacy population. ADT refers to TNFα antagonists, vedolizumab, and/or tofacitinib. Week-12 clinical nonresponders were patients who were not in clinical response to IV guselkumab (based on electronic case report form data) who received SC guselkumab treatment. Patients missing one or more modified Mayo subscore (stool frequency, rectal bleeding, or

endoscopy) pertaining to this endpoint at the designated time point were considered not to have achieved clinical response.

ADT, advanced therapy; CI, confidence interval; GUS, guselkumab; IV, intravenous; SC, subcutaneous; TNFα, tumor necrosis factor alpha.

Supplementary Figure S6. Clinical and endoscopic efficacy endpoints at week 24 among week-12 clinical nonresponders to placebo



Patients missing 1 or more modified Mayo subscore (stool frequency, rectal bleeding, or endoscopy) or other component pertaining to an endpoint at week 24 were considered not to have achieved the endpoint. Clinical response was defined as a decrease in modified Mayo score from baseline by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1. Clinical remission was defined as a Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability present on the

endoscopy. Symptomatic remission was defined as a Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline and a Mayo rectal bleeding subscore of 0. Endoscopic improvement was defined as a Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy. Histo-endoscopic mucosal improvement was a combined endpoint of endoscopic improvement and histologic improvement (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system, ie, Geboes score ≤3.1). Endoscopic normalization was defined as a Mayo endoscopy subscore of 0.

CI, confidence interval; GUS, guselkumab; IV, intravenous.