Efficacy of Guselkumab in Moderately to Severely Active Ulcerative Colitis by Extent of Disease and Inflammatory Burden: Subgroup Analysis of the Phase 3 QUASAR Maintenance Study

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Background

Guselkumab (GUS) is a dual-acting IL-23p19 subunit inhibitor that potently neutralizes IL-23 and binds to CD64, a receptor on cells that produce IL-23[1]

The QUASAR clinical development program evaluated GUS intravenous (IV) induction and subcutaneous (SC) maintenance dose regimens in participants with moderately to severely active ulcerative colitis (UC) (NCT04033445)[2,3]

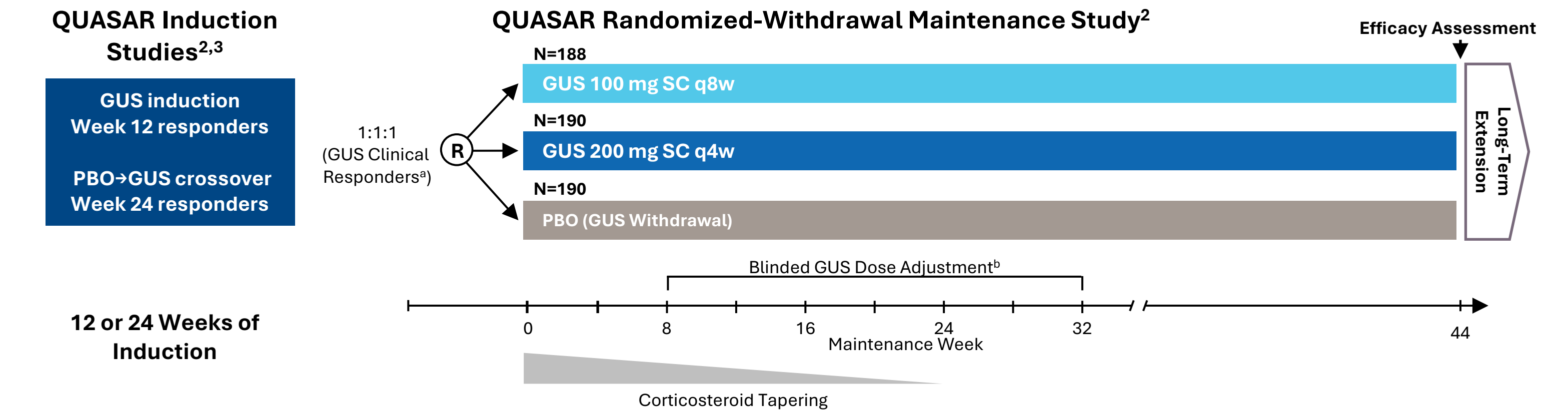
In the Phase 3 QUASAR maintenance study, both GUS SC maintenance dose regimens, i.e., GUS 100 mg SC every 8 weeks (q8w) and GUS 200 mg SC every 4 weeks (q4w), were efficacious compared with placebo (PBO)[2]

Objective

To evaluate the efficacy of the GUS 100 mg SC q8w and GUS 200 mg SC q4w maintenance dose regimens in clinically relevant subgroups of QUASAR participants:

- Extensive UC disease vs disease limited to left side of the colon at induction baseline
- High inflammatory burden, based on c-reactive protein (CRP) concentration >3 mg/L vs ≤3 mg/L at maintenance baseline

QUASAR– Study Design



Population

QUASAR induction studies:
- Moderately to severely active UC for ≥3 months
  - mMayo score 5–9
- History of inadequate response/intolerance to corticosteroids, immunosuppressants, biologics, or JAK inhibitors

QUASAR maintenance study:
- Clinical responders to 12 weeks of GUS IV induction therapy[a]

*[a]PBO Week 12 induction responders and GUS Week 24 induction responders could also enter the maintenance period but were not randomized at start of the maintenance study. [b]Between Week 8 and Week 32, randomized patients meeting loss of clinical response criteria (based on the modified Mayo score and required an endoscopic assessment) were eligible for a blinded dose adjustment as follows: PBO SC → GUS 200 mg SC q4w; GUS 100 mg SC q8w → GUS 200 mg SC q4w; GUS 200 mg SC q4w → GUS 200 mg SC q4w (sham adjustment). **GUS**=guselkumab, **IV**=intravenous, **JAK**=Janus kinase, **mMayo**=modified Mayo, **PBO**=placebo, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **R**=randomized, **SC**=subcutaneous, **UC**=ulcerative colitis.*

Subgroup Analyses

Subgroups

- Extent of UC disease at induction study baseline, per investigator based on screening endoscopy and patient history:
  - Extensive
  - Limited to the left side of the colon
- Inflammatory burden based on CRP concentration at maintenance baseline:
  - Elevated CRP: >3 mg/L
  - Normal CRP: ≤3 mg/L

Endpoints

- Clinical remission: Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline, rectal bleeding subscore of 0, and endoscopic subscore of 0 or 1 with no friability present on the endoscopy
- Maintenance of clinical remission: clinical remission at Week 44 among participants in clinical remission at maintenance baseline
- Endoscopic improvement: endoscopic subscore of 0 or 1 with no friability present on the endoscopy
- Histo-endoscopic mucosal improvement (HEMI): achieving both histologic improvement (defined as neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system [i.e., Geboes score ≤3.1]) and endoscopic improvement
- Endoscopic remission: endoscopic subscore of 0

Handling of Intercurrent Events and Missing Data

Intercurrent events:
- Participants who had an ostomy or colectomy, dose adjustment, or prohibited change in UC medication, or who discontinued study agent due to lack of efficacy or an adverse event of worsening of UC prior to Week 44 were considered not to have achieved the endpoint
- For participants who discontinued study agent due to COVID-19–related reasons (excluding COVID-19 infection) or regional crisis in Russia and Ukraine prior to Week 44, observed values were used if available
- Participants who discontinued study agent for other reasons prior to Week 44 were considered not to have achieved the endpoint

Nonresponder imputation for missing data:
- After accounting for intercurrent events, participants who were missing one or more of the components pertaining to an endpoint at Week 44 were considered not to have achieved the endpoint
- Participants who had an unevaluable biopsy were considered not to have achieved histologic endpoints

Key Takeaways

- **For participants with moderately to severely active UC with extensive disease or high inflammatory burden, greater efficacy at Week 44 was observed with GUS 200 mg SC q4w compared with GUS 100 mg SC q8w**
- **For those with disease limited to the left side of the colon or with normal CRP levels (≤3 mg/L) at maintenance baseline, response rates were similar with both GUS maintenance dose regimens**
- **Across subgroups, proportions of participants achieving clinical and histologic-endoscopic efficacy endpoints were greater with both GUS dose regimens vs PBO**

Results

Baseline characteristics were balanced across treatment groups

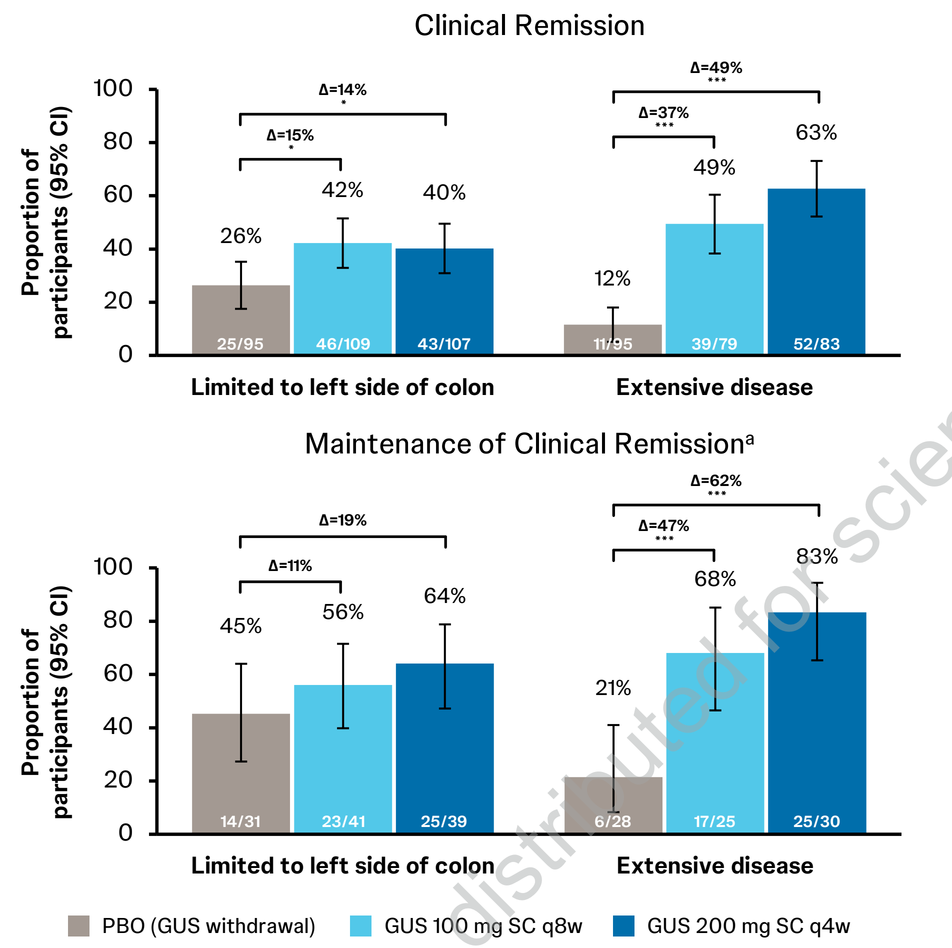
	GUS 100 mg SC q8w (N=188)	GUS 200 mg SC q4w (N=190)	Placebo (GUS withdrawal) (N=190)
Demographics and UC Treatment History			
Age, yrs	40.3 (13.0)	40.6 (14.7)	41.2 (13.6)
Male	54%	53%	57%
Race, Asian/Black/White/Other[a]	20/1/74/5%	23/1/71/5%	18/1/75/6%
BIO/JAKi-naïve	56%	51%	57%
BIO/JAKi-IR	41%	46%	39%
Induction Baseline Disease Characteristics			
UC disease duration, yrs	7.8 (8.5)	8.4 (8.4)	7.3 (6.3)
mMayo score	6.8 (1.2)	6.9 (1.1)	7.0 (1.1)
Extent of disease			
Limited to left side of colon	58%	56%	50%
Extensive	42%	44%	50%
CRP, median (IQR) mg/L	3.9 (1.4, 10.4)[b]	3.6 (1.4, 9.1)[c]	4.2 (1.6, 8.4)
Elevated CRP (>3 mg/L)	56%[b]	56%[c]	62%
Maintenance Baseline Disease Characteristics			
mMayo score	2.6 (1.5)	2.5 (1.5)	2.5 (1.6)
CRP, median (IQR) mg/L	1.4 (0.4, 4.0)	1.4 (0.6, 3.4)	1.5 (0.6, 4.0)
Elevated CRP (>3 mg/L)	34%	29%	33%

At baseline of the induction study,
- **257 (45%)** participants had **extensive UC disease** at induction baseline

GUS IV induction reduced median CRP levels from induction baseline
At maintenance study baseline,
- **182 (32%)** participants had persistently **elevated CRP** (>3mg/L)

Data shown are mean (SD) unless otherwise noted. [a]Includes American Indian or Alaska Native, Native Hawaiian, or other Pacific Islander; multiple races; and not reported; [b]N=185; [c]N=187.
***BIO/JAKi-IR**=history of inadequate response or intolerance to a biologic (TNFα antagonists and vedolizumab) or Janus kinase inhibitor (tofacitinib), **BIO/JAKi-naïve**=biologic and Janus kinase inhibitor naïve, **CRP**=C-reactive protein, **GUS**=guselkumab, **IQR**=interquartile range, **IV**=intravenous, **mMayo**=modified Mayo, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous, **SD**=standard deviation, **TNF**=tumor necrosis factor, **UC**=ulcerative colitis.*

Clinical remission at Week 44 in subgroups defined by extent of UC disease

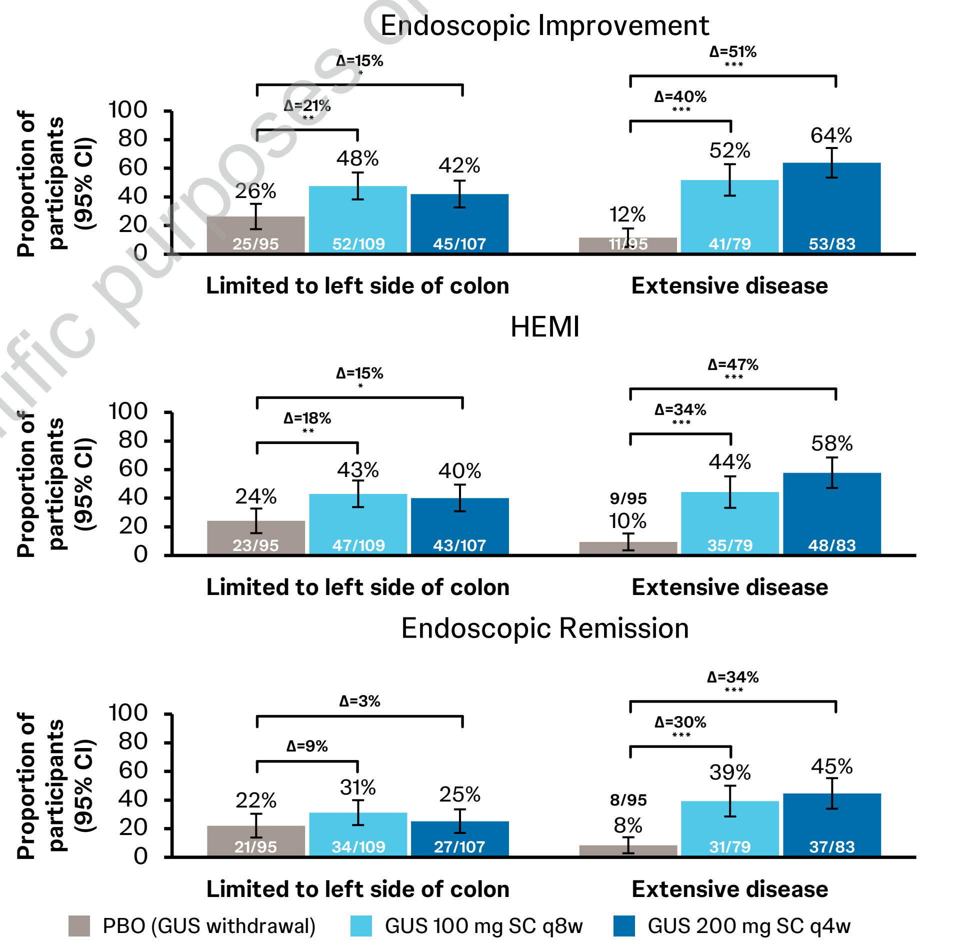


Nominal *p<0.05, **p<0.01, ***p<0.001 vs PBO

- For participants with **extensive UC disease**, the proportion achieving clinical remission at Week 44 was numerically greater with GUS 200 mg SC q4w relative to GUS 100 mg SC q8w

*Includes participants with modified Mayo score of 5-9 at induction baseline who achieved clinical response to GUS induction and were re-randomized at maintenance study entry. [a]Denominator includes only participants with clinical remission at maintenance baseline. **CI**=confidence interval, **GUS**=guselkumab, **PBO**=placebo, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous, **UC**=ulcerative colitis.*

Endoscopic and histologic endpoints at Week 44 in subgroups defined by extent of UC disease



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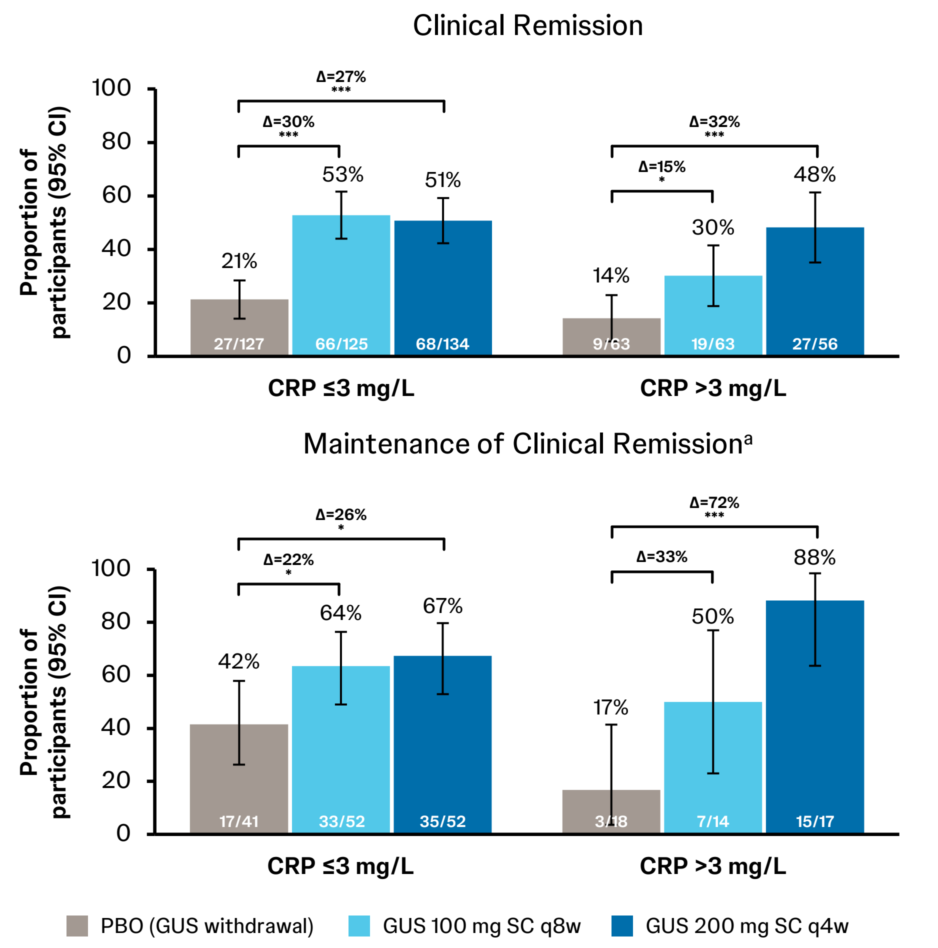
Clinical remission at Week 44 in subgroups defined by inflammatory burden at maintenance baseline



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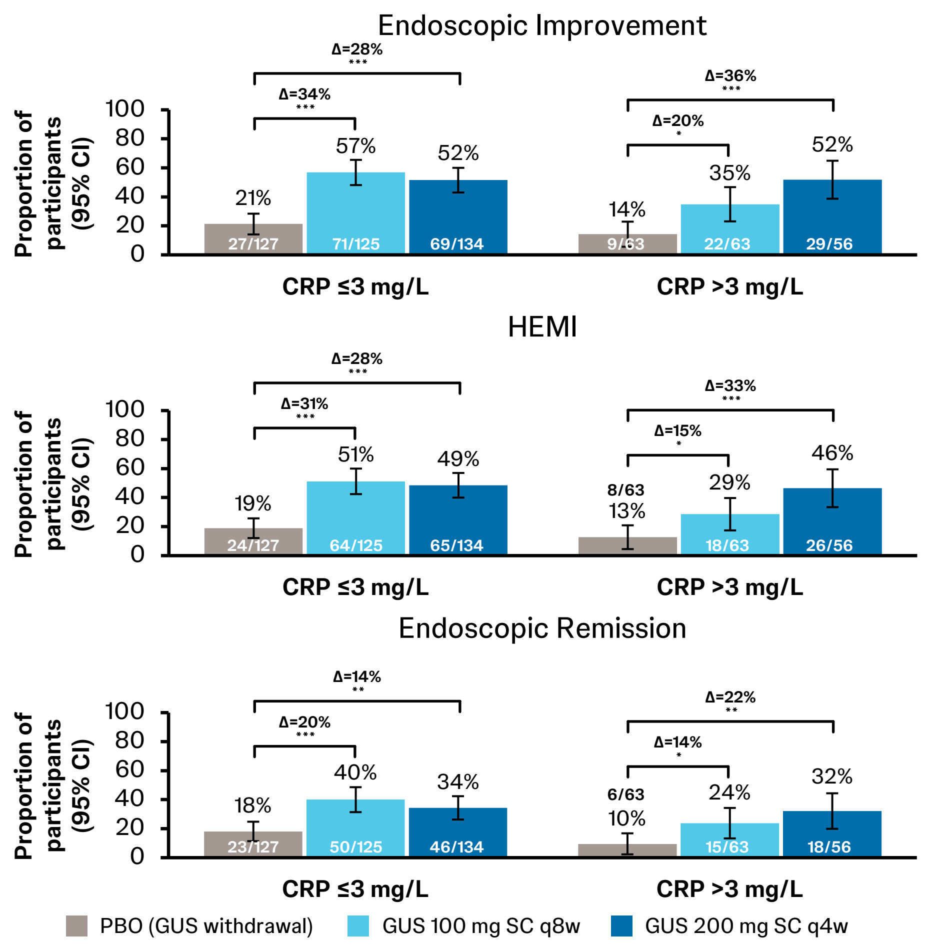
- For participants with **high inflammatory burden** (CRP >3 mg/L) at maintenance baseline, the proportion achieving clinical remission at Week 44 was numerically greater with GUS 200 mg SC q4w relative to GUS 100 mg SC q8w

*Includes participants with modified Mayo score of 5-9 at induction baseline who achieved clinical response to GUS induction and were re-randomized at maintenance study entry. [a]Denominator includes only participants with clinical remission at maintenance baseline. **CI**=confidence interval, **CRP**=C-reactive protein, **GUS**=guselkumab, **PBO**=placebo, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous, **UC**=ulcerative colitis.*

Endoscopic and histologic endpoints at Week 44 in subgroups defined by inflammatory burden at maintenance baseline



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