Association of Endoscopic, Histologic, and Composite Outcomes With Long-Term Guselkumab Efficacy in Ulcerative Colitis: 2-Year Results From the QUASAR Long-Term Extension

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Poster #0980

Key Takeaways

- **In QUASAR, achievement of endoscopic, histologic, and composite outcomes following induction and 1 year of maintenance therapy was associated with achievement of CS-free clinical remission at LTE week 92**
- **Composite outcomes did not appear to be more strongly associated with CS-free clinical remission than endoscopic or histologic outcomes alone**
- **These findings support endoscopic and histologic outcomes as sensible shorter-term targets associated with longer-term clinical outcomes in moderately to severely active UC**

Background

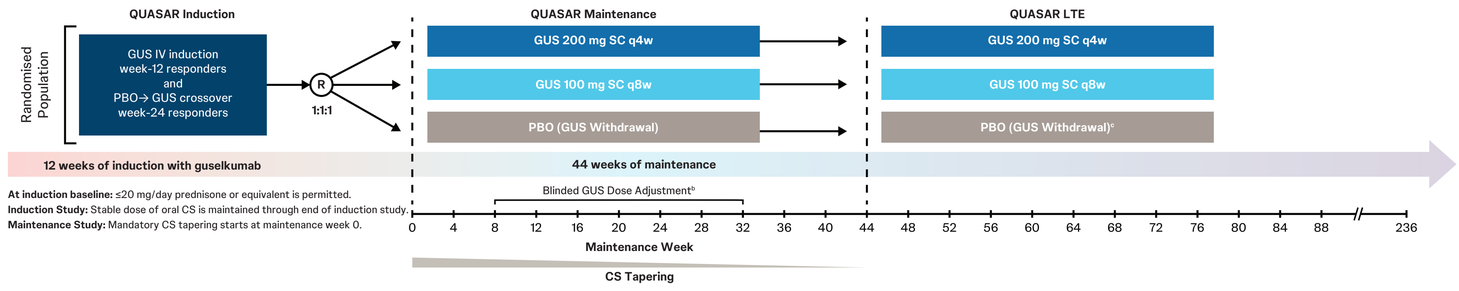
- The QUASAR (NCT04033445) phase 2b/3 program demonstrated that guselkumab (GUS) is efficacious in participants (pts) with moderately to severely active ulcerative colitis (UC)[1,2]
- GUS is a selective, dual-acting interleukin (IL)-23p19 subunit inhibitor that potently neutralises IL-23 and binds to CD64, a receptor on cells that produce IL-23[3]
- Reliable, clinically meaningful efficacy outcomes are needed to guide treat-to-target decisions in UC

Objective

We explored whether achievement of select efficacy outcomes at QUASAR maintenance baseline (week M-0) or at maintenance week 44 (week M-44) was associated with achievement of corticosteroid (CS)-free clinical remission at week 92 in the QUASAR long-term extension (LTE)

Phase 3 QUASAR Maintenance Study Design

Target Population: Adults with moderately to severely active UC[a] who were in clinical response 12 weeks following GUS IV induction



At induction baseline: ≤20 mg/day prednisone or equivalent is permitted.
Induction Study: Stable dose of oral CS is maintained through end of induction study.
Maintenance Study: Mandatory CS tapering starts at maintenance week 0.

[a]Defined as induction baseline modified Mayo score of 5 to 9 with a Mayo rectal bleeding subscore ≥ 1 and a Mayo endoscopic subscore ≥ 2 based on central review. [b]Between weeks M-8 and M-32, randomised pts 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). [c]The study blind was maintained during the LTE until the last pt in the Maintenance Study completed the week M-44 visit. After the Maintenance Study was unblinded to the investigative sites, pts receiving PBO were terminated from study participation. LTE week 236 is the final efficacy visit. The final safety visit was 12 weeks from the last GUS dose (approximately LTE week 244). ***IV****=Intravenous,* ***PBO****=Placebo,* ***q4w****=Every 4 weeks,* ***q8w****=Every 8 weeks,* ***R****=Randomisation,* ***SC****=Subcutaneous.*

Demographic and disease characteristics at week M-0

		GUS 100 mg SC q8w (N=188)	GUS 200 mg SC q4w (N=190)	Combined (N=378)
Demographics				
	Age, yrs, median (IQR)[a]	39.0 (32.0, 47.0)	39.0 (28.0, 53.0)	39.0 (30.0, 50.0)
	Male	54%	53%	53%
Disease Characteristics				
	Modified Mayo score (0-9)	2.6 (1.5)	2.5 (1.5)	2.5 (1.5)
	Clinical remission	35%	36%	36%
	Endoscopic improvement	40%	42%	41%
	Endoscopic remission	22%	25%	23%
	Histologic improvement	61%	60%	60%
	Histo-endoscopic mucosal improvement	35%	35%	35%
	Faecal calprotectin >250 mg/kg	55%[b]	52%[c]	53%[d]
	IBDQ remission	71%	68%[e]	69%[f]

Data are mean (SD) unless noted otherwise. Includes only pts with modified Mayo score 5-9 at induction baseline in clinical response to GUS IV induction and randomised to receive GUS maintenance treatment. IBDQ remission is defined as a total IBDQ score ≥170. [a]At induction baseline. [b]N=185. [c]N=187. [d]N=372. [e]N=189. [f]N=377. ***IBDQ****=Inflammatory Bowel Disease Questionnaire,* ***IQR****=Interquartile range,* ***SD****=Standard deviation.*

Methods

- We evaluated achievement of CS-free clinical remission at LTE week 92 by achievement of endoscopic, histologic, and composite outcomes at week M-0 or at week M-44
- The week M-0 population included pts who were randomised to GUS regardless of whether they entered the LTE
- The week M-44 population included randomised pts who were treated with GUS and entered the LTE, including pts who were randomised to PBO at maintenance baseline but lost response and received a dose adjustment to GUS 200 mg q4w in the maintenance study

Statistical Considerations

- Data are based on nonresponder imputation (NRI) or as observed analyses as noted
- For NRI, pts with ostomy/colectomy or study agent discontinuation due to a lack of therapeutic effect/AE of worsening UC were considered nonresponders; observed values were used if study agent discontinuation was due to COVID-19-related reasons (excluding infection)/regional crises/reasons other than those mentioned
  - After accounting for these rules, pts missing ≥1 outcome component were considered nonresponders

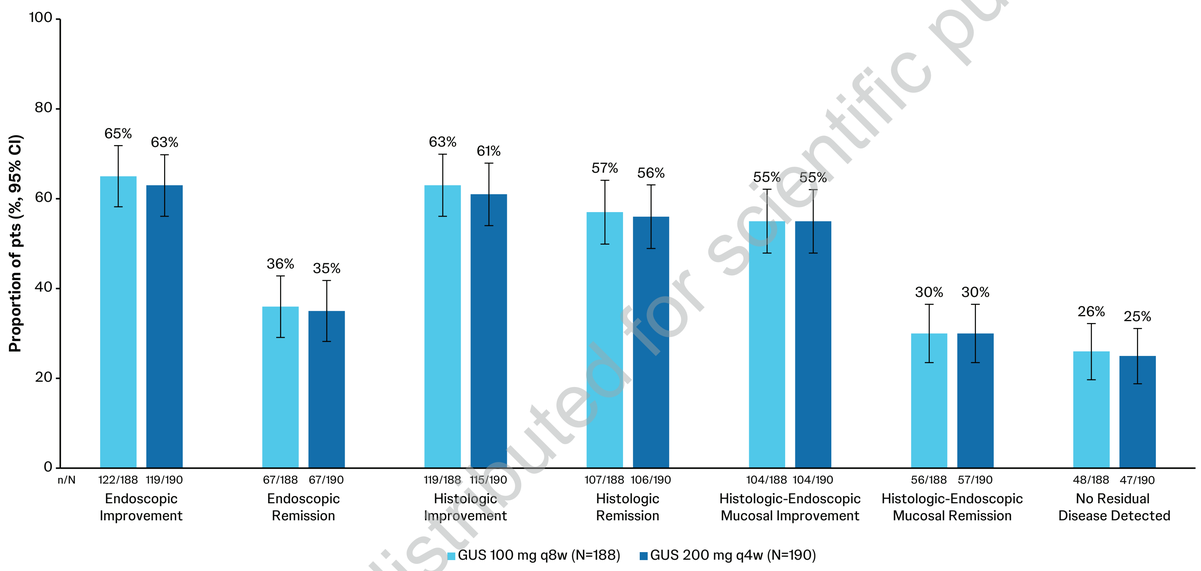
Outcomes Evaluated

- **CS-free Clinical Remission:** Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline, Mayo rectal bleeding subscore of 0, and Mayo endoscopic subscore of 0 or 1 without the use of corticosteroids for ≥8 weeks prior to week 92 of the LTE
- **Endoscopic Improvement:** Mayo endoscopic subscore of 0 or 1
- **Endoscopic Remission:** Mayo endoscopic subscore of 0
- **Histologic Improvement:** Neutrophil infiltration in <5% of crypts, no crypt destruction and no erosions, ulcerations, or granulation tissue according to the Geboes grading system
- **Histologic Remission:** Absence of neutrophils from the mucosa (both lamina propria and epithelium), no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system
- **Histologic-Endoscopic Mucosal Improvement:** Combination of histologic improvement and endoscopic improvement
- **Histologic-Endoscopic Mucosal Remission:** Combination of histologic remission and endoscopic remission
- **No Residual Disease Detected:** Combination of symptomatic remission (stool frequency subscore of 0 or 1 and not increased from induction baseline and a rectal bleeding score of 0), histologic remission, endoscopic remission, and faecal calprotectin ≤250 mg/kg

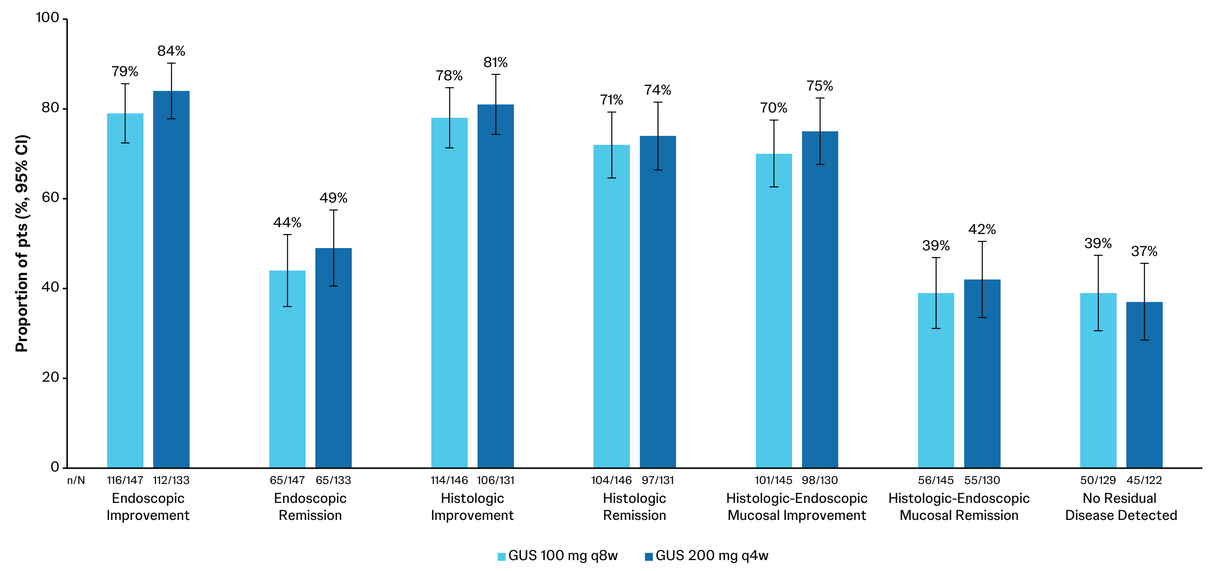
Results

Achievement of endoscopic, histologic, and composite outcomes at LTE week 92 among pts randomised to GUS

NRI



As Observed

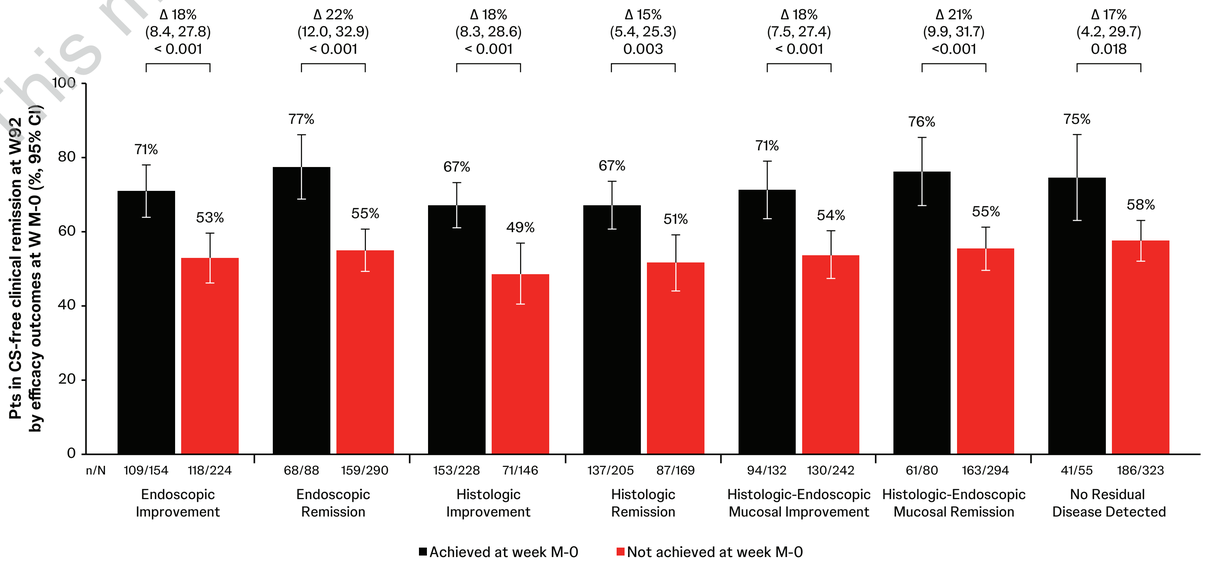


Includes pts with modified Mayo score 5-9 at induction baseline who were in clinical response to GUS IV induction and randomised to receive GUS 100 mg SC q8w or GUS 200 mg SC q4w at maintenance study entry. ***CI****=Confidence interval.*

For NRI analyses, pts who had an ostomy or colectomy or discontinued study agent before LTE week 92 due to lack of therapeutic effect or due to an adverse event (AE) of worsening UC were considered not to have achieved the outcome. For pts who discontinued study agent due to COVID-19-related reasons (excluding COVID-19 infection), regional crises, or reasons other than those mentioned, observed values were used, if available. After accounting for the above rules, pts missing ≥1 component pertaining to an outcome were considered nonresponders. Pts with a nonevaluable biopsy were considered not to have achieved histology outcomes. As observed analyses were based on data available at LTE week 92.

Among GUS-randomised pts regardless of whether they entered the LTE, achievement of efficacy outcomes at week M-0 was associated with greater achievement of CS-free clinical remission at LTE week 92

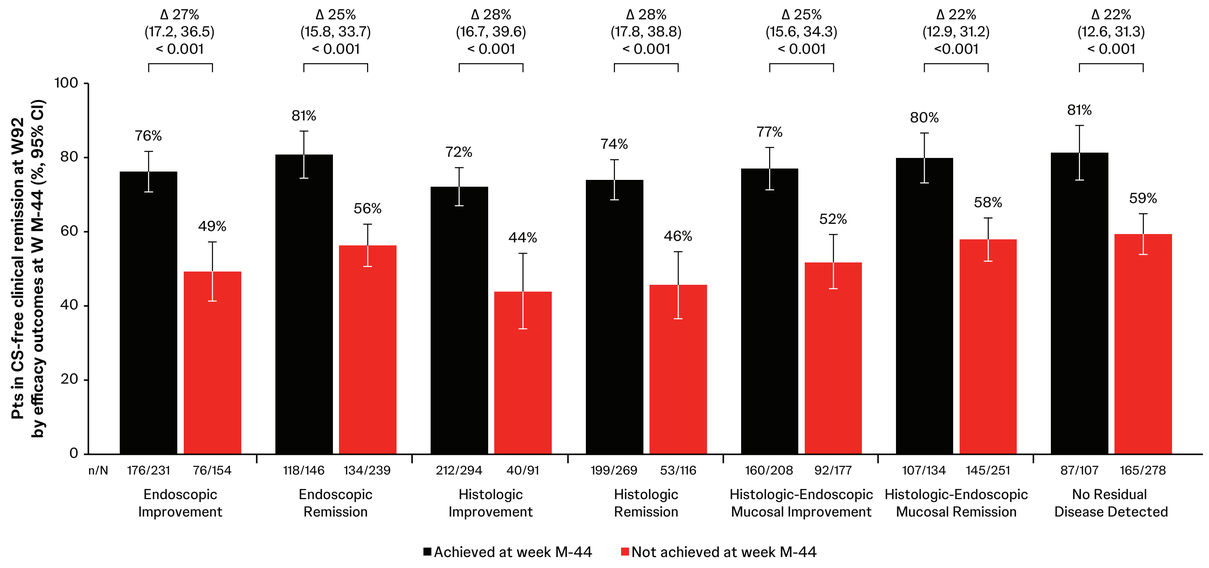
- Across outcomes, 67–77% of pts who achieved an outcome at week M-0 achieved CS-free clinical remission at LTE week 92 versus 49–58% of pts who did not (15–22% difference; all nominal $p<0.05$)



Based on NRI analyses. All p-values are nominal. Includes pts with modified Mayo score 5-9 at induction baseline who were in clinical response to GUS IV induction and randomised to receive GUS 100 mg SC q8w or GUS 200 mg SC q4w at maintenance study entry regardless of whether they entered the LTE. Pts who did not enter the LTE were considered CS-free clinical remission nonresponders at LTE week 92.

Among GUS-treated pts who entered the LTE, achievement of efficacy outcomes at week M-44 was associated with greater achievement of CS-free clinical remission at LTE week 92

- Across outcomes, 72–81% of pts who achieved an outcome at week M-44 achieved CS-free clinical remission at LTE week 92 versus 44–59% of pts who did not (22–28% difference; all nominal $p<0.001$)



Based on NRI analyses. All p-values are nominal. Includes pts with modified Mayo score 5-9 at induction baseline who 1) were in clinical response to GUS IV induction and randomised to receive GUS 100 mg SC q8w or GUS 200 mg SC q4w at maintenance study entry who entered the LTE; and 2) pts in clinical response to GUS IV induction randomised to PBO at maintenance study entry who experienced a dose adjustment to GUS 200 mg SC q4w during the maintenance study and who entered the LTE.

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