Efficacy and Safety of Guselkumab Maintenance Therapy Among Guselkumab Induction Week 24 Clinical Responders: Results From the Phase 3 QUASAR Maintenance Study

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Background

- Guselkumab (GUS) is a dual-acting interleukin (IL)-23p19 subunit inhibitor that blocks IL-23 and binds to CD64, a receptor on cells that produce IL-23[1]
- Positive results for the QUASAR Phase 2b/3 induction studies of intravenous (IV) GUS in patients with moderately to severely active ulcerative colitis (UC) have been previously presented[2-4]
  - More than half of clinical nonresponders to GUS IV at induction Week 12 (I-12) responded to GUS subcutaneous (SC) treatment at Week I-24

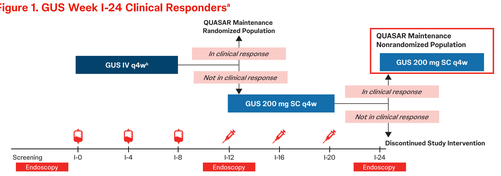
Objective

To present the efficacy and safety results of GUS SC treatment through maintenance Week 44 among GUS Week I-24 clinical responders in the Phase 3 QUASAR maintenance study

Methods

- Patients who were in clinical response after 12 weeks of IV GUS in the QUASAR induction studies were randomized in the QUASAR maintenance study (**Figure 1**)
- Nonresponders to IV GUS at Week I-12 received SC GUS 200 mg at Weeks I-12, I-16, and I-20 (**Figure 1**)
- Those who were in clinical response at Week I-24 (GUS Week I-24 Responders) received SC GUS 200 mg every 4 weeks during the maintenance study in a blinded fashion and were evaluated as part of the nonrandomized study population (**Figure 1**)
- Overall, 60.6% (123 of 203) of Week I-12 nonresponders to IV GUS achieved clinical response at Week I-24 and entered the maintenance study phase

Figure 1. GUS Week I-24 Clinical Responders[a]



[a]Clinical response was defined as a decrease from induction baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1-point decrease from induction baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1; *GUS IV induction doses were 200 and 400 mg q4w in Phase 2b and 200 mg q4w in Phase 3. **q4w**=every 4 weeks.

Table 1. Definitions of Clinical, Endoscopic, and Quality of Life Outcomes

Outcome	Definition
Clinical outcomes at maintenance Week 44	
Clinical response	A decrease from induction baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1-point decrease from induction baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1
Symptomatic remission	A stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0
Corticosteroid-free clinical remission	Clinical remission at maintenance Week 44 without any use of corticosteroids for ≥8 weeks prior to maintenance Week 44
Clinical remission	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 endoscopic subscore of 0 or 1 with no friability
Endoscopic outcomes at maintenance Week 44	
Endoscopic improvement	A Mayo endoscopic subscore of 0 or 1 with no friability
Histo-endoscopic mucosal improvement	Achieving a combination of 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 (normalization)	A Mayo endoscopic subscore of 0
Quality of life outcomes at maintenance Week 44	
IBDQ remission	A total IBDQ score ≥170
Fatigue response	A ≥7-point improvement from induction baseline in the PROMIS Fatigue Short Form 7

IBDQ=Inflammatory Bowel Disease Questionnaire; **PROMIS**=Patient-Reported Outcomes Measurement Information System.

Analysis Methods

- Efficacy outcomes at maintenance Week 44 (**Table 1**) and safety throughout the maintenance study are reported for GUS Week I-24 Responders
- Analyses included patients with modified Mayo score 5-9 at induction baseline who received ≥1 GUS maintenance dose
- Patients who had an ostomy or colectomy, a prohibited change in UC medication, or discontinued study agent due to lack of efficacy or an adverse event (AE) of worsening of UC, or due to other reasons except for COVID-19-related reasons (excluding COVID-19 infection) or regional crisis in Russia and Ukraine before maintenance Week 44 were considered not to have achieved the endpoint; for patients who discontinued study agent due to COVID-19-related reasons (excluding COVID-19 infection) or regional crisis in Russia and Ukraine before maintenance Week 44, their observed values (if available) were used
- Patients who were missing one or more of the components pertaining to an endpoint or had unevaluable biopsies at maintenance Week 44 were considered not to have achieved the endpoint

Key Takeaways

- **In this refractory population of GUS Week I-24 Responders who had higher UC disease burden at induction baseline, continued treatment with GUS 200 mg SC q4w maintained or improved endoscopic, histologic, symptomatic, and quality of life outcomes**
- **Safety results were consistent with the overall population and safety profile of GUS in its approved indications**
- **Overall, these results support continuing GUS treatment in this more refractory patient population**

Results

- GUS Week I-24 Responders had high UC severity at induction baseline: 74.8% had severe disease (modified Mayo score 7-9), 77.2% had a Mayo endoscopy subscore of 3, 48% had extensive UC, and median C-reactive protein was 5.0 mg/L (upper limit of normal, 3 mg/L) (**Table 2**)
- Over half (59.3%) of the GUS Week I-24 Responders had a history of documented inadequate response or intolerance to biologic or JAK inhibitor therapy for UC (**Table 2**)

Table 2. Patient Characteristics and Medication History at Induction Baseline for Patients who Entered the Maintenance Study

	GUS Week I-24 Responders (N=123)	GUS IV Week I-12 Responders (N=568)
Demographics		
Age in years, mean (SD)	41.5 (14.3)	40.7 (13.8)
Male, n (%)	73 (59.3)	311 (54.8)
Disease characteristics		
UC disease duration in years, mean (SD)	7.2 (5.4)	7.81 (7.8)
Modified Mayo score[a] (0-9), mean (SD)	7.0 (1.0)	6.9 (1.1)
Modified Mayo score of 7-9 (severe), n (%)	92 (74.8)	363 (63.9)
Mayo endoscopy subscore of 3 (severe), n (%)	95 (77.2)	377 (66.4)
Extensive UC, n (%)	59 (48.0)	257 (45.2)
C-reactive protein in mg/L, median (IQR)	5.0 (1.6; 14.3)	3.9 (1.5; 9.2)[b]
Fecal calprotectin in mg/kg, median (IQR)	1720.5 (811.0; 3275.0)[c]	1605.0 (669.0; 3337.0)[d]
Medication history at induction baseline, n (%)		
Oral corticosteroid use	53 (43.1)	227 (40.0)
Azathioprine or 6-mercaptopurine use	26 (21.1)	122 (21.5)
Biologic therapy history, n (%)		
Biologic/JAK inhibitor-naïve[e,f]	46 (37.4)	309 (54.4)
History of inadequate response or intolerance to biologic and/or JAK inhibitor therapy	73 (59.3)	240 (42.3)
One biologic or JAK inhibitor	39 (53.4)	138 (57.5)
Two or more biologics and/or JAK inhibitors	34 (46.6)	102 (42.5)

[a]Modified Mayo score: 3-component (stool frequency, rectal bleeding, and endoscopic subscores) Mayo score without the physician's global assessment; [b]N=562; [c]N=114; [d]N=506; [e]Biologic therapy included tumor necrosis factor-α antagonists and vedolizumab; [f]JAK inhibitor therapy included tofacitinib. **IQR**=interquartile range; **JAK**=Janus kinase; **SD**=standard deviation.

- In general, clinical disease characteristics at maintenance baseline in the GUS Week I-24 Responders reflected a higher level of disease activity (as measured by lower proportions of patients in clinical remission and endoscopic improvement) than patients in the primary analysis population (**Table 3**)

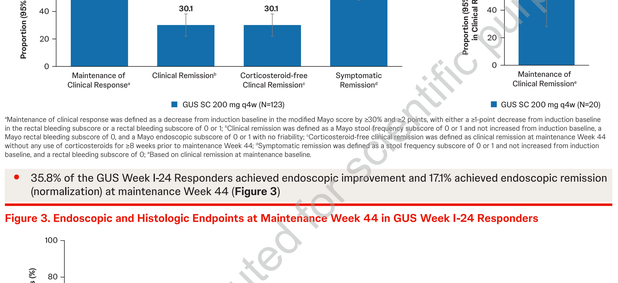
Table 3. Disease Characteristics at Maintenance Baseline

	GUS Week I-24 Responders (N=123)	GUS IV Week I-12 Responders (N=568)
Clinical remission,[a] n (%)	20 (16.3)	194 (34.2)
Endoscopic improvement,[b] n (%)	29 (23.6)	222 (39.1)
Endoscopic remission,[c] n (%)	12 (9.8)	127 (22.4)
IBDQ remission,[d] n (%)	67 (54.5)	404 (71.5)[e]
Modified Mayo score (0-9), mean (SD)	3.4 (1.4)	2.5 (1.5)
C-reactive protein, median in mg/L (IQR)	2.0 (0.9; 6.2)	1.5 (0.6; 3.8)
Fecal calprotectin (mg/kg), median in mg/kg (IQR)	530.5 (186.0; 1335.0)[f]	303.5 (79.5; 1194.0)[g]

[a]Clinical remission was defined as a Mayo stool frequency subscore of 0 or 1 and not increased from baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopic subscore of 0 or 1 with no friability; [b]Endoscopic improvement was defined as a Mayo endoscopic subscore of 0 or 1 with no friability; [c]Endoscopic remission (normalization) was defined as a Mayo endoscopic subscore of 0; [d]IBDQ remission was defined as a total IBDQ score ≥170; [e]N=565; [f]N=122; [g]N=560.

- 67.5% of the GUS Week I-24 Responders achieved clinical response and 30.1% achieved clinical remission at maintenance Week 44 (**Figure 2A**)
- Half of those in clinical remission at maintenance baseline maintained clinical remission at maintenance Week 44 (**Figure 2B**)

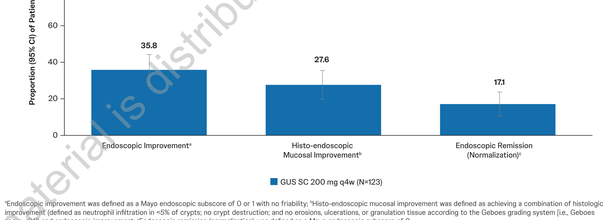
Figure 2. Clinical Endpoints at Maintenance Week 44 in GUS Week I-24 Responders



[a]Maintenance of clinical response was defined as a decrease from induction baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1-point decrease from induction baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1; [b]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 endoscopic subscore of 0 or 1 with no friability; [c]Corticosteroid-free clinical remission was defined as clinical remission at maintenance Week 44 without any use of corticosteroids for ≥8 weeks prior to maintenance Week 44; [d]Symptomatic remission was defined as a stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0; [e]Based on clinical remission at maintenance baseline.

- 35.8% of the GUS Week I-24 Responders achieved endoscopic improvement and 17.1% achieved endoscopic remission (normalization) at maintenance Week 44 (**Figure 3**)

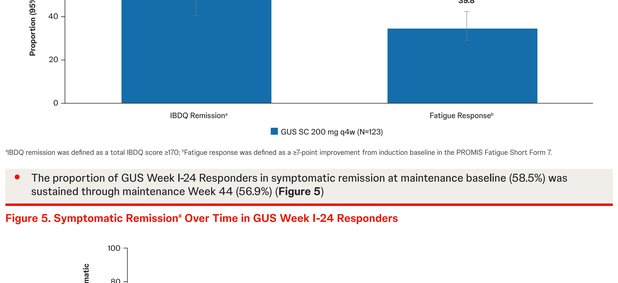
Figure 3. Endoscopic and Histologic Endpoints at Maintenance Week 44 in GUS Week I-24 Responders



[a]Endoscopic improvement was defined as a Mayo endoscopic subscore of 0 or 1 with no friability; [b]Histo-endoscopic mucosal improvement was defined as achieving a combination of 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; [c]Endoscopic remission (normalization) was defined as a Mayo endoscopic subscore of 0.

- 54.5% of the GUS Week I-24 Responders achieved IBDQ remission and 39.8% achieved fatigue response at maintenance Week 44, suggesting improvements in health-related quality of life (**Figure 4**)

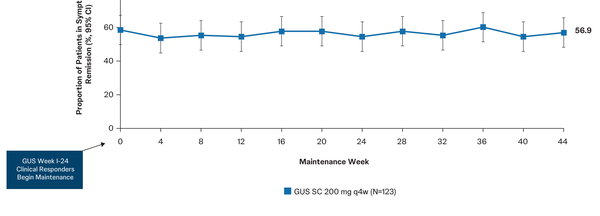
Figure 4. Quality of Life Endpoints at Maintenance Week 44 in GUS Week I-24 Responders



[a]IBDQ remission was defined as a total IBDQ score ≥170; [b]Fatigue response was defined as a ≥7-point improvement from induction baseline in the PROMIS Fatigue Short Form 7.

- The proportion of GUS Week I-24 Responders in symptomatic remission at maintenance baseline (58.5%) was sustained through maintenance Week 44 (56.9%) (**Figure 5**)

Figure 5. Symptomatic Remission[a] Over Time in GUS Week I-24 Responders



[a]Symptomatic remission was defined as a stool frequency subscore of 0 or 1 and not increased from induction baseline and a rectal bleeding subscore of 0.

- GUS maintenance therapy was well tolerated among the GUS Week I-24 Responders (**Table 4**)
  - AEs were reported for 78.0% of GUS Week I-24 Responders, serious AEs for 5.7%, and serious infections for 1.6%; no deaths were reported
  - No active tuberculosis, anaphylaxis, serum sickness, opportunistic infections, major adverse cardiovascular events, or clinically important hepatic disorders were reported among the GUS Week I-24 Responders
  - One patient reported malignancy (renal cell carcinoma; unrelated)

Table 4. Summary of AEs Through Maintenance Week 44

	GUS 200 mg SC q4w	
	GUS Week I-24 Responders (N=123)	Randomized GUS 200 mg SC q4w (N=190)[a]
Average duration of follow-up in weeks	42.8	39.2
Average exposure (# of administrations)	10.3	9.6
Deaths, n (%)	0	0
Patients with 1 or more, n (%):		
AEs	96 (78.0)	133 (70.0)
Serious AEs	7 (5.7)	12 (6.3)
AEs leading to discontinuation	5 (4.1)	5 (2.6)
Infections	53 (43.1)[b]	59 (31.1)
Serious infections	2 (1.6)[c]	2 (1.1)
Patients with 1 or more targeted AE, n (%):		
Active tuberculosis	0	0
Malignancies	1 (0.8)	1 (0.5)
Anaphylactic reactions	0	0
Serum sickness reactions	0	0
Opportunistic infections	0	0
Major adverse cardiovascular event (MACE)	0	1 (0.5)
Clinically important hepatic disorders[d]	0	0

Patients were counted only once for any given event.
[a]Includes patients who were GUS IV Week I-12 Responders and were randomized to GUS 200 mg SC q4w maintenance; [b]COVID-19 was the most commonly reported AE of infection (n=22); [c]One event each of appendicitis and complicated appendicitis; [d]Defined as hepatic disorder AEs reported as serious AEs or AEs leading to discontinuation of study agent.

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