Efficacy of Subcutaneous Guselkumab in Moderately to Severely Active Ulcerative Colitis by Induction Week 12 Clinical Response Status: Week 48 Results From the Phase 3 ASTRO Study

Silvio Danese,[1] Millie Long,[2] Laurent Peyrin-Biroulet,[3] Tadakazu Hisamatsu,[4] Thomas Baker,[5] Yelina Alvarez,[5] Lingjing Jiang,[6] Hongyan Zhang,[6] David T. Rubin,[7] Jessica R. Allegretti[8]

[1]San Raffaele and University Vita-Salute San Raffaele, Gastroenterology and Endoscopy, Milan, Italy; [2]University of North Carolina at Chapel Hill, Department of Gastroenterology, Chapel Hill, NC, United States; [3]Hopitaux De Brabois, Department of Gastroenterology and Inserm U954, France Vandœuvre-lès-Nancy, France; [4]Kyorin University School of Medicine, Department of Gastroenterology and Hepatology, Tokyo, Japan; [5]Johnson & Johnson, Immunology, Spring House, PA, United States; [6]Johnson & Johnson, Statistics and Decision Sciences, Spring House, PA, United States; [7]University of Chicago Medicine Inflammatory Bowel Disease Center, Gastroenterology-Hepatology & Nutrition, Chicago, IL, United States; [8]Brigham and Women's Hospital, Division of Gastroenterology-Hepatology and Endoscopy, Harvard Medical School, Boston, MA, United States

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Background

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

The phase 3, randomized, double-blind, treat-through ASTRO study (NCT05528510) showed that a subcutaneous (SC) induction and maintenance treatment regimen with GUS was efficacious in patients with moderately to severely active ulcerative colitis (UC)[2,3]

Objective

This exploratory analysis of the ASTRO study evaluated clinical and endoscopic outcomes at Week 48 based on clinical response to GUS SC induction at Week 12

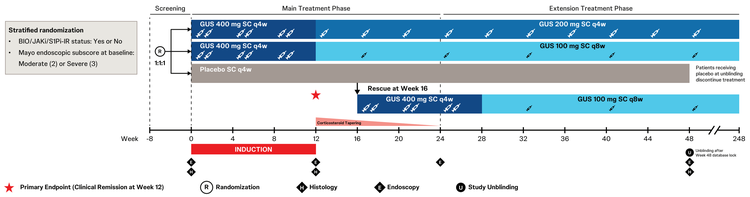
Methods

ASTRO used a treat-through design where GUS patients were assigned to 1 of 2 SC induction→SC maintenance regimens at Week 0 and remained on that regimen through Week 48 regardless of their clinical response status after induction (Week 12)

ASTRO – Study Design

Key Inclusion Criteria

- Baseline (Week 0) mMayo score of 5 to 9
- Baseline Mayo rectal bleeding subscore ≥1, Mayo endoscopic subscore ≥2 (centrally reviewed)
- IR to BIO, JAKi, or S1Pi
  OR naïve to BIO/JAKi/S1Pi (or exposed to BIO/JAKi/S1Pi without IR) and IR to corticosteroids, 6-MP, or AZA



6-MP=mercaptopurine; *AZA*=azathioprine; *BIO*=biologics (includes tumour necrosis factor alpha blockers and vedolizumab; *IR*=inadequate response/intolerance; *JAKi*=Janus kinase inhibitors; *mMayo*=modified Mayo; *q4w*=every 4 weeks; *q8w*=every 8 weeks; *S1Pi*=sphingosine-1-phosphate inhibitors.

Definitions of Clinical and Endoscopic Outcomes

Outcome	Definition
Efficacy outcome at Week 12	
Clinical response	A decrease in mMayo score from baseline by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or achieving a rectal bleeding subscore of 0 or 1
Efficacy outcomes at Week 48	
Clinical response	Same as above
Clinical remission	A Mayo stool frequency subscore of 0 or 1 and no increase from baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability
Endoscopic improvement	A Mayo endoscopy subscore of 0 or 1 with no friability
Endoscopic remission	A Mayo endoscopy subscore of 0

Analysis Methods

- Week 48 efficacy outcomes were evaluated according to Week 12 clinical response status
- Patients who, before Week 48, had an ostomy or colectomy, a prohibited change in UC medications,[a] discontinued study agent due to lack of efficacy or an adverse event of worsening of UC were considered not to have achieved the endpoint at Week 48
- Patients who discontinued study agent due to COVID-19-related reasons (excluding COVID-19 infection) or regional crisis, had their observed values used, if available. Patients who discontinued study agent before Week 48 due to other reasons were considered not to have achieved the endpoint at Week 48
- Patients who were missing one or more of the components pertaining to an endpoint at Week 48 were considered not to have achieved the endpoint
- Nonresponder imputation for patients who met rescue criteria in GUS groups at Week 12 and Week 16 was suspended in these analyses

[a]Initiation of rectal 5-aminosalicylate (5-ASA) compounds, parenteral/rectal corticosteroids, immunomodulatory agents other than 6-MP/AZA/methotrexate (MTX; including biologic agents), experimental inflammatory bowel disease medications, or thalidomide/related agents; initiation or increase above baseline in the dose of oral corticosteroids; oral 5-ASA compounds, or 6-MP/AZA/MTX due to worsening of disease; or any switch among oral corticosteroids (excluding prednisone equivalent changes), among 5-ASA compounds, or between 6-MP/AZA and MTX due to worsening of disease.

Key Takeaways

- **Among patients with moderately to severely active UC in the ASTRO study, those who achieved clinical response after GUS SC induction had better clinical and endoscopic outcomes at Week 48 than those who did not achieve clinical response after induction**
- **A subset of patients who were not in clinical response after induction but continued GUS SC maintenance achieved clinical and endoscopic endpoints at Week 48**
- **Overall, these results suggest a benefit of continued GUS treatment after Week 12 regardless of induction clinical response status**

Results

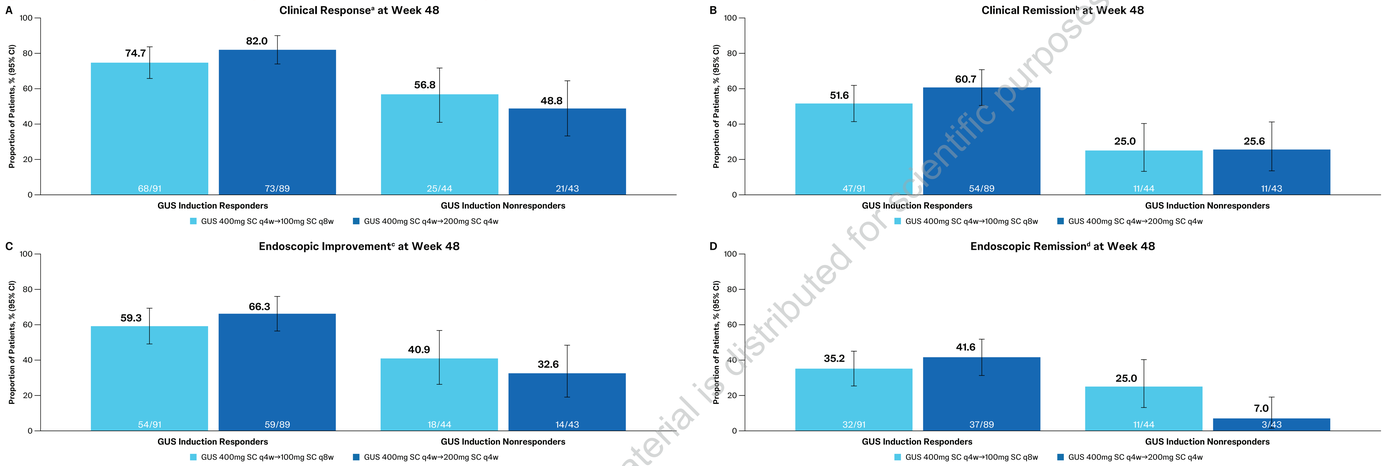
Population

- 267 GUS-treated patients were included in this analysis
- 67.4% (180/267) of patients achieved clinical response to GUS 400 mg SC induction at Week 12

Efficacy Outcomes

- Among GUS induction responders: a majority achieved clinical response (74.7-82.0%; **Figure 1A**), over half achieved clinical remission (51.6-60.7%; **Figure 1B**) or endoscopic improvement (59.3-66.3%; **Figure 1C**), and more than one-third achieved endoscopic remission (35.2-41.6%; **Figure 1D**) at Week 48
- Among GUS induction nonresponders: approximately half achieved clinical response (48.8-56.8%; **Figure 1A**), one-quarter achieved clinical remission (25.0-25.6%; **Figure 1B**), approximately one-third achieved endoscopic improvement (32.6-40.9%; **Figure 1C**), and 7.0-25.0% achieved endoscopic remission (**Figure 1D**) at Week 48

Figure 1. Clinical Outcomes at Week 48 by GUS Induction Week 12 Clinical Response[a] Status



*Clinical response was defined as a decrease in mMayo score from baseline by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or achieving a rectal bleeding subscore of 0 or 1; [b]Clinical remission was defined as a Mayo stool frequency subscore of 0 or 1 and no increase from baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability; [c]Endoscopic improvement was defined as as an endoscopy subscore of 0 or 1 with no friability; [d]Endoscopic remission was defined as an endoscopy subscore of 0. **CI**=confidence interval.

- At baseline, larger proportions of GUS induction nonresponders had mMayo scores and Mayo endoscopy scores indicating severe and extensive UC compared to responders; GUS induction nonresponders also appeared to be slightly more refractory to BIO/JAKi/S1Pi than responders (**Table 1**)

Table 1. Baseline Characteristics and Medication History of GUS Induction Week 12 Responders and Nonresponders

	GUS Induction Week 12 Responders (N=180)	GUS Induction Week 12 Nonresponders (N=87)
Demographics		
Age in yrs, mean (IQR)	41.6 (14.0)	44.9 (15.1)
Male	56.7%	66.7%
Disease characteristics		
UC duration in years, mean (SD)	8.09 (7.02)	8.21 (6.72)
mMayo score (0-9), mean (SD)	6.7 (1.1)	6.7 (1.2)
mMayo score of 7-9 (severe)	57.2%	67.8%
Mayo endoscopy subscore of 3 (severe)	50.0%	65.5%
Extensive UC	48.9%	62.1%
UC-related concomitant medications		
Oral corticosteroid use	30.0%	36.8%
6-MP/AZA use	22.2%	16.1%
Oral 5-ASA compound use	78.9%	75.9%
BIO/JAKi/S1Pi naïve, n (%)	115 (63.9%)	43 (49.4%)
BIO/JAKi/S1Pi-IR, n (%)	63 (35.0%)	43 (49.4%)
One class[a]	47 (74.6%)	29 (67.4%)
≥2 classes[a]	16 (25.4%)	14 (32.6%)

[a]Denominator is patients who were BIO/JAKi/S1Pi-IR; **SD**=standard deviation.

- Although the GUS induction nonresponders who did not achieve clinical remission at Week 48 appeared to be slightly more refractory at baseline than those who achieved clinical remission at Week 48, no clear differentiating factors were observed between the two groups (**Table 2**)

Table 2. Baseline Characteristics and Medication History of GUS Induction Week 12 Nonresponders by Remission Status at Week 48

	GUS Induction Week 12 Nonresponders	
	Achieved Clinical Remission at Week 48 (N=22)	Did Not Achieve Clinical Remission at Week 48 (N=65)
Demographics		
Age in yrs, mean (IQR)	43.1 (16.4)	45.5 (14.8)
Male	68.2%	66.2%
Disease characteristics		
UC duration in years, mean (SD)	6.71 (5.93)	8.72 (6.93)
mMayo score (0-9), mean (SD)	6.9 (1.6)	6.6 (1.1)
mMayo score of 7-9 (severe)	77.3%	64.6%
Mayo endoscopy subscore of 3 (severe)	72.7%	63.1%
Extensive UC	54.5%	64.6%
UC-related concomitant medications		
Oral corticosteroid use	31.8%	38.5%
6-MP/AZA use	36.4%	9.2%
Oral 5-ASA compound use	90.9%	70.8%
BIO/JAKi/S1Pi naïve, n (%)	15 (68.2%)	28 (43.1%)
BIO/JAKi/S1Pi-IR, n (%)	7 (31.8%)	36 (55.4%)
One class[a]	5 (71.4%)	24 (66.7%)
≥2 classes[a]	2 (28.6%)	12 (33.3%)

[a]Denominator is patients who were BIO/JAKi/S1Pi-IR.

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