Efficacy and Safety of Subcutaneous Guselkumab Induction Therapy in Patients With Ulcerative Colitis: Results Through Week 12 From the Phase 3 ASTRO Study

Laurent Peyrin-Biroulet,[1] Jessica R. Allegretti,[2] Silvio Danese,[3] Matthew Germinaro,[4] Thomas Baker,[4] Yelina Alvarez,[4] Silke Jörgens,[4] Lingjing Jiang,[4] Hongyan Zhang,[4] Stacey Fitch,[4] Tadakazu Hisamatsu,[5] David T. Rubin,[6] Millie Long[7] on behalf of the ASTRO Investigators

[1]University of Lorraine, Inserm, NGERE, F-54000 Nancy, France and Groupe Hospitalier privé Ambroise Paré-Hartmann, Paris IBD Centre, 92200 Neuilly sur Seine, France; [2]Division of Gastroenterology, Hepatology, and Endoscopy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [3]Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele, Milan, Italy; [4]Johnson & Johnson, Spring House, PA, USA; [5]Kyorin University School of Medicine, Tokyo, Japan; [6]University of Chicago Medicine Inflammatory Bowel Disease Centre, Chicago, IL, USA; [7]Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Background

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

Intravenous (IV) induction followed by subcutaneous (SC) maintenance was efficacious and safe in participants with moderately to severely active ulcerative colitis (UC) in the QUASAR Phase 3 studies[2]

- GUS is approved in some countries for UC, including the United States

SC induction provides patients and healthcare providers with greater flexibility and requires less time compared to IV

Objectives

The ASTRO study (NCT05528510) evaluated the efficacy and safety of GUS SC induction in participants with moderately to severely active UC

Methods

- ASTRO study: Phase 3, randomized, double-blind, placebo-controlled, treat-through design

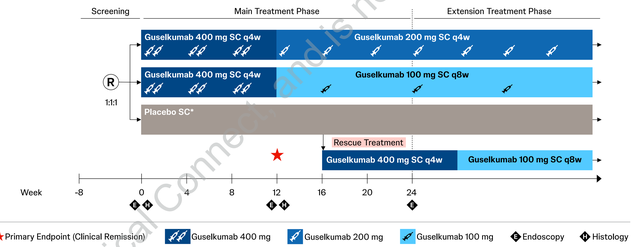
Key eligibility criteria

- Baseline (Week 0) modified Mayo score of 5 to 9, inclusive
- Baseline Mayo rectal bleeding subscore ≥ 1, Mayo endoscopic subscore ≥ 2 (centrally reviewed)
- Inadequate response/intolerance (IR) to TNFα blockers, vedolizumab, Janus kinase inhibitors, or S1P inhibitors (BIO/JAKi/S1Pi-IR) **OR** naïve to BIO/JAKi/S1Pi (or exposed to BIO/JAKi/S1Pi without IR) and IR to corticosteroids, 6-mercaptopurine (6-MP), or azathioprine (AZA)

Stratified randomization

- BIO/JAKi/S1Pi-IR status: Yes or No
- Mayo endoscopic subscore at baseline: Moderate (2) or Severe (3)

FIGURE 1: ASTRO study design



*All Week 12 endpoints compared GUS 400 mg SC to placebo; data from the two randomized GUS groups were combined as pts in both groups received the same GUS 400 mg SC induction regimen prior to Week 12. q4w=Every 4 weeks; q8w=Every 8 weeks; R=Randomization; SC=Subcutaneous.

Key Takeaways

- **Week 12 results from ASTRO establish the efficacy of SC induction therapy with GUS in UC**
- **Clinically meaningful benefit was also observed in patients naïve to BIO/JAKi/S1Pi and in those with BIO/JAKi/S1Pi-IR**
- **The safety of SC induction therapy was consistent with the well-characterized and favourable safety profile of GUS in approved indications**
- **These results complement the QUASAR[2] data, demonstrating that both IV and SC induction with GUS are efficacious therapeutic options, thus providing patients and healthcare providers the flexibility to choose the induction route of administration that aligns with their preferences**

Results

Demographics and baseline clinical characteristics

TABLE 1: Demographics and baseline disease characteristics

	Placebo SC	Combined GUS 400 mg SC q4w
Full analysis set, N	139	279
Age in years, mean (SD)	39.5 (13.58)	42.9 (14.43)
Male, n (%)	90 (64.7%)	166 (59.5%)
UC disease duration in years, mean (SD)	6.61 (6.228)	8.04 (6.847)
Modified Mayo score[a] (0-9), mean (SD)	6.8 (1.09)	6.7 (1.18)
Modified Mayo score of 7-9 (severe), n (%)	87 (63.0%)	172 (61.6%)
Mayo endoscopic subscore of 3 (severe), n (%)	78 (56.1%)	156 (55.9%)
Extensive UC, n (%)	73 (52.5%)	151 (54.1%)
C-reactive protein,[b] median in mg/L (IQR)	3.8 (1.2; 10.9)	4.1 (1.5; 8.2)
C-reactive protein[b] >3 mg/L, n (%)	77 (55.8%)	161 (58.3%)
Fecal calprotectin,[c] median in mg/kg (IQR)	1749.0 (617.0; 3202.0)	1494.5 (678.0; 2963.0)
Fecal calprotectin[c] >250 mg/kg, n (%)	119 (90.8%)	226 (89.0%)

[a]Modified Mayo score: 3-component (stool frequency, rectal bleeding, and endoscopy subscores) Mayo score without the physician's global assessment. [b]Based on N=138 for Placebo SC, N=276 for Combined GUS 400 mg SC q4w. [c]Based on N=131 for Placebo SC, N=254 for Combined GUS 400 mg SC q4w. GUS=Guselkumab; IQR=Interquartile range; q4w=Every 4 weeks; SC=Subcutaneous; SD=Standard deviation; UC=Ulcerative colitis.

TABLE 2: UC-related medication history and baseline UC medications

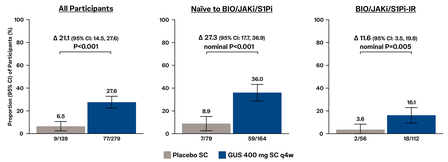
	Placebo SC	Combined GUS 400 mg SC q4w
Full analysis set, N	139	279
Naïve to BIO/JAKi/S1Pi, n (%)	79 (56.8%)	164 (58.8%)
BIO/JAKi/S1Pi-IR, n (%)	112 (40.1%)	112 (40.1%)
One class[a]	39 (69.6%)	78 (69.6%)
Two classes[a]	13 (23.2%)	21 (18.8%)
Three or more classes[a]	4 (7.1%)	13 (11.6%)
At least one anti-TNF[b] (regardless of other BIO/JAKi/S1Pi)	39 (69.6%)	88 (78.6%)
Vedolizumab[a] (regardless of other BIO/JAKi/S1Pi)	25 (44.6%)	49 (43.8%)
JAK inhibitors[c] (regardless of other BIO/S1Pi)	11 (19.6%)	19 (17.0%)
Ozanimod[a] (regardless of other BIO/JAKi)	2 (3.6%)	3 (2.7%)
History of IR or dependence to corticosteroids, n (%)	104 (74.8%)	208 (74.6%)
History of IR to 6-MP or AZA, n (%)	56 (40.3%)	108 (38.7%)
Baseline oral corticosteroid use, n (%)	46 (33.1%)	91 (32.6%)
Baseline use of 6-MP, AZA, or MTX, n (%)	28 (20.1%)	56 (20.1%)

[a]Denominator is patients who were BIO/JAKi/S1Pi-IR. AZA=Azathioprine; GUS=Guselkumab; IR=Inadequate response; JAKi=Janus kinase inhibitor; q4w=Every 4 weeks; MTX=Methotrexate; SC=Subcutaneous; TNF=Tumor necrosis factor; UC=Ulcerative colitis.

Primary endpoint: clinical remission at Week 12

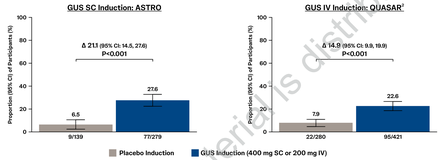
- **Clinical remission:** A Mayo stool frequency subscore of 0 or 1 and not increased from baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopic subscore of 0, or 1 with no friability

FIGURE 2: Clinical remission at Week 12



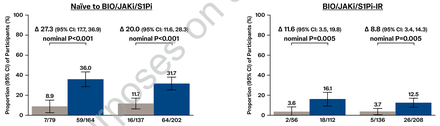
Data presented as n (%) & (adjusted treatment difference) vs placebo. Subpopulation analyses were not multiplicity controlled. Patients who, prior to Week 12, had an ostomy or colectomy, a prohibited change in concomitant UC medications, discontinued study agent due to lack of efficacy or an AE of worsening UC were considered not to meet the endpoint criteria at Week 12. Patients who discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis had their observed data used, if available. Patients who discontinued study agent for other reasons prior to Week 12 were considered not to meet the endpoint criteria at Week 12. After accounting for these scenarios, patients who were missing data necessary for calculation of the outcome measure at Week 12 were considered not to have achieved that endpoint at Week 12. AE=Adverse event; CI=Confidence interval; GUS=Guselkumab; IR=Inadequate response; JAKi=Janus kinase inhibitor; q4w=Every 4 weeks; SC=Subcutaneous.

FIGURE 3: Clinical remission at Week 12: SC or IV GUS induction in both ASTRO and QUASAR studies



CI=Confidence interval; GUS=Guselkumab; IV=Intravenous; SC=Subcutaneous.

FIGURE 4: Clinical remission at Week 12: SC or IV GUS induction in naïve to BIO/JAKi/S1Pi vs BIO/JAKi/S1Pi-IR

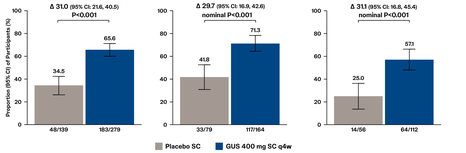


CI=Confidence interval; GUS=Guselkumab; IV=Intravenous; IR=Inadequate response; JAKi=Janus kinase inhibitor; SC=Subcutaneous.

Clinical response at Week 12

- **Clinical response:** A decrease from baseline in the modified Mayo score 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

FIGURE 5: Clinical response at Week 12



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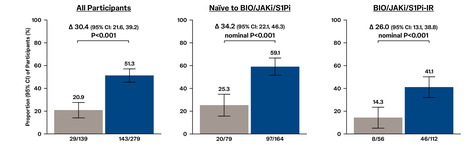
Symptomatic remission at Week 12

- **Symptomatic remission:** A stool frequency subscore of 0 or 1 and not increased from baseline, and a rectal bleeding subscore of 0

FIGURE 6: Symptomatic remission at Week 12



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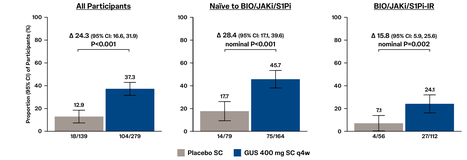
Endoscopic improvement at Week 12

- **Endoscopic improvement:** An endoscopic subscore of 0, or 1 with no friability

FIGURE 7: Endoscopic improvement at Week 12

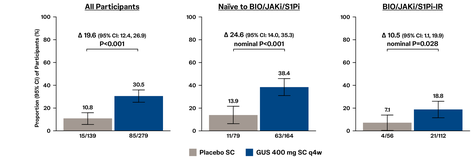


Data presented as n (%) & (adjusted treatment difference) vs placebo. Subpopulation analyses were not multiplicity controlled. Patients who, prior to Week 12, had an ostomy or colectomy, a prohibited change in concomitant UC medications, discontinued study agent due to lack of efficacy or an AE of worsening UC were considered not to meet the endpoint criteria at Week 12. Patients who discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis had their observed data used, if available. Patients who discontinued study agent for other reasons prior to Week 12 were considered not to meet the endpoint criteria at Week 12. After accounting for these scenarios, patients who were missing data necessary for calculation of the outcome measure at Week 12 were considered not to have achieved that endpoint at Week 12. AE=Adverse event; CI=Confidence interval; GUS=Guselkumab; IR=Inadequate response; JAKi=Janus kinase inhibitor; q4w=Every 4 weeks; SC=Subcutaneous; UC=Ulcerative colitis.

Histo-endoscopic mucosal Improvement at Week 12

- **Histo-endoscopic mucosal improvement:** Achieving a combination of histologic improvement (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue per Geboes grading system) and endoscopic improvement

FIGURE 8: Histo-endoscopic mucosal improvement at Week 12



Data presented as n (%) & (adjusted treatment difference) vs placebo. Subpopulation analyses were not multiplicity controlled. Patients who, prior to Week 12, had an ostomy or colectomy, a prohibited change in concomitant UC medications, discontinued study agent due to lack of efficacy or an AE of worsening UC were considered not to meet the endpoint criteria at Week 12. Patients who discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis had their observed data used, if available. Patients who discontinued study agent for other reasons prior to Week 12 were considered not to meet the endpoint criteria at Week 12. After accounting for these scenarios, patients who were missing data necessary for calculation of the outcome measure at Week 12, including an unevaluable biopsy, were considered not to have achieved those endpoints at Week 12. AE=Adverse event; CI=Confidence interval; GUS=Guselkumab; IR=Inadequate response; JAKi=Janus kinase inhibitor; q4w=Every 4 weeks; SC=Subcutaneous; UC=Ulcerative colitis.

TABLE 3: Summary of adverse events through Week 12

	Placebo SC	Combined GUS 400 mg SC q4w
Safety analysis set, N	139	279
Average duration of follow-up, weeks	12.2	12.3
Average exposure, number of administrations	3.0	3.0
Deaths, n (%)	1 (0.7%)	0
Patients with 1 or more:		
AEs, n (%)	73 (52.5%)	110 (39.4%)
AEs by severity, n (%)		
Mild	42 (30.2%)	62 (22.2%)
Moderate	24 (17.3%)	43 (15.4%)
Severe	7 (5.0%)	5 (1.8%)
Serious AEs, n (%)	11 (7.9%)	7 (2.5%)
AEs leading to discontinuation of study agent, n (%)	8 (5.8%)	3 (1.1%)
Infections,[a] n (%)	28 (20.1%)	42 (15.1%)
Serious infections[a]	0	2 (0.7%)

- These 2 serious infections were **pilonidal disease** and **gastroenteritis**
  - Both were moderate in intensity, did not interrupt study drug administration, and resolved

Most common AEs among combined GUS 400 mg SC group:	Worsening of Ulcerative Colitis	Arthralgia	Headache
	4.7% Combined GUS	3.9% Combined GUS	3.6% Combined GUS
	12.2% Placebo	0.7% Placebo	1.4% Placebo

[a]Infections were defined as any adverse event coded to the MedDRA system organ class 'Infections and infestations'. AE=Adverse event; GUS=Guselkumab; q4w=Every 4 weeks; SC=Subcutaneous.

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