OP72

Efficacy and Safety of Subcutaneous Guselkumab Induction Therapy in Patients With Moderately to Severely Active Crohn's Disease: Results Through Week 48 From the Phase 3 GRAVITI Study

Remo Panaccione,[1] Ailsa Hart,[2] Flavio Steinwurz,[3] Silvio Danese,[4] Tadakazu Hisamatsu,[5] Qian Cao,[6] Mobolaji Olurinde,[7] Marion L. Vetter,[7] Zijiang Yang,[7] Yuhua Wang,[7] Jewel Johanns,[7] Natalie A. Terry,[7] Bruce E. Sands,[8] Geert D'Haens[9] on behalf of the GRAVITI Investigators

[1]University of Calgary, Calgary, AB, Canada; [2]London North-West University Healthcare NHS Trust, London, UK; [3]Hospital Israelita Albert Einstein, São Paulo, Brazil; [4]IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele, Milano, Italy; [5]Kyorin University, Tokyo, Japan; [6]Sir Run Run Shaw Hospital Affiliated with School of Medicine, Zhejiang University, Hangzhou, China; [7]Janssen Research & Development, LLC, Spring House, PA, USA; [8]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [9]Department of Gastroenterology, Amsterdam University Medical Centers, Amsterdam, The Netherlands

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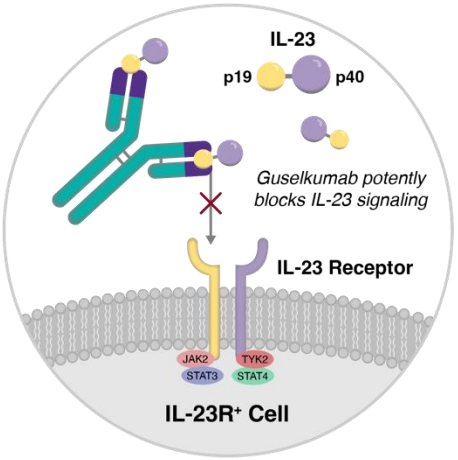
Background and Objective

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

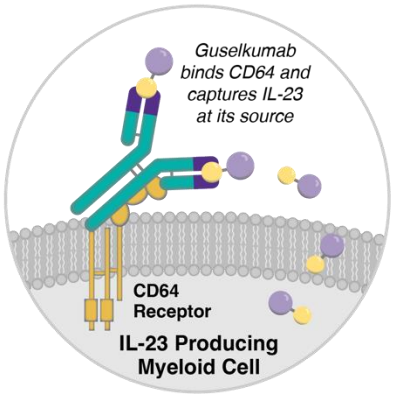
IV induction with guselkumab was effective and safe in participants with moderately to severely active Crohn's disease[2]

Flexibility in the route of administration of induction therapy (IV or SC) may be preferred by patients and healthcare providers

Study Objective: The GRAVITI study (NCT05197049) evaluated the efficacy and safety of guselkumab SC induction and maintenance in participants with moderately to severely active Crohn's disease



Dual-acting IL-23 Inhibitor

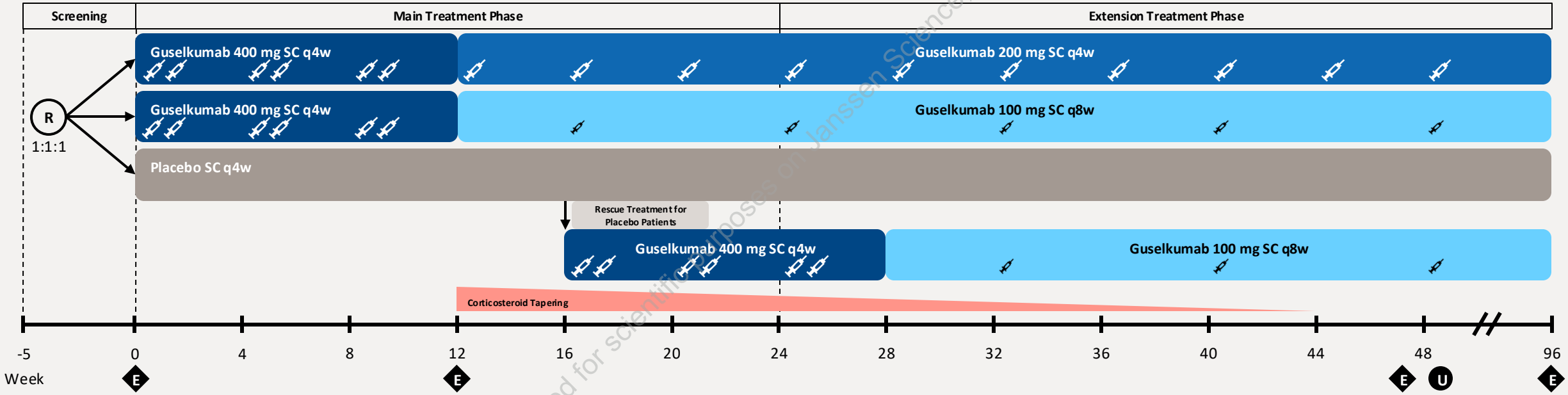


1. Atreya R, Abreu MT, Krueger JG, et al. *J Crohns Colitis*. 2024;18(suppl):S470.
2. Panaccione R, Danese S, Feagan BG, et al. *Gastroenterology*. 2024; 166(5): S1057b.

Phase 3, Double-blind, Treat-through Design: GRAVITI

Key eligibility criteria

- Moderately to severely active CD (CDAI score 220–450 AND either mean daily SF count ≥4 OR AP score ≥2) and SES-CD score ≥6 (or ≥4 for isolated ileal disease)
- Inadequate response/intolerance to oral corticosteroids, 6-MP/AZA/MTX, or biologic therapies[a]



Randomization stratified by:

- CDAI score (≤300 or >300)
- SES-CD (≤12 or >12)
- Prior BIO-failure status

: Guselkumab 100 mg

: Guselkumab 200 mg

E : Endoscopy

U : Study unblinding

Rescue Treatment Criteria

- CDAI score > 220 and < 70-point reduction from baseline CDAI at both Weeks 12 and 16 **OR**
- SES-CD score increase by ≥ 50% from baseline at Week 12

Rescue Treatment for Guselkumab Arms: Sham matching placebo SC to maintain the blind

AP=abdominal pain. BIO=biologic. CDAI=Crohn's disease activity index. SC=subcutaneous. SES-CD=simple endoscopic score for Crohn's disease. SF=stool frequency.

[a] Biologic therapies: TNF antagonists or vedolizumab

Endpoints and Statistical Considerations

Endpoints

Co-primary endpoints
- Clinical remission at Week 12
- Endoscopic response at Week 12

Additional multiplicity-controlled endpoints
- PRO-2 remission at Week 12
- Clinical response at Week 12
- Clinical remission at Week 24
- Clinical remission at Week 48
- Endoscopic response at Week 48

Other endpoints
- Endoscopic remission at Week 48
- Deep remission at Week 48

Statistical considerations

- Participants meeting prespecified treatment failure rules or had missing data were considered not to have met the endpoint
- Participants in all treatment groups (placebo or guselkumab) who met rescue criteria were considered not to have met endpoints after Week 16
- Endpoints assessed through Week 12 compared the combined guselkumab 400 mg SC treatment arm to placebo; assessments after Week 12 compared each guselkumab SC maintenance regimen to placebo[a]

[a] The confidence intervals for the proportion of participants meeting the endpoint in each treatment group were based on the normal approximation confidence limits. The adjusted treatment difference(s), confidence interval(s), and p-value(s) were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification factors are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), and BIO-failure status at baseline (yes or no).

Baseline Demographics and Disease Characteristics

Primary analysis set	Placebo (N=117)	Guselkumab 400 mg SC q4w → 100 mg SC q8w (N=115)	Guselkumab 400 mg SC q4w → 200 mg SC q4w (N=115)	Total (N=347)
Demographics				
Age in years, mean (SD)	36.0 (12.71)	37.4 (13.32)	39.1 (12.56)	37.5 (12.89)
Male, n (%)	67 (57.3%)	66 (57.4%)	70 (60.9%)	203 (58.5%)
Characteristics				
CD duration in years, mean (SD)	7.0 (7.75)	9.2 (9.08)	7.9 (7.13)	8.0 (8.05)
CDAI score, mean (SD)	293.0 (49.09)	300.4 (54.32)	297.3 (54.69)	296.9 (52.68)
SES-CD score, mean (SD)	12.0 (6.89)	12.2 (6.85)	11.8 (7.12)	12.0 (6.94)
Endoscopic disease severity (SES-CD score), n (%)				
Moderate (7–16)	61 (52.1%)	64 (55.7%)	49 (42.6%)	174 (50.1%)
Severe (>16)	25 (21.4%)	26 (22.6%)	27 (23.5%)	78 (22.5%)
Involved GI areas by central reader, n (%)				
Colon only	40 (34.2%)	41 (35.7%)	40 (34.8%)	121 (34.9%)
Ileum only	22 (18.8%)	25 (21.7%)	27 (23.5%)	74 (21.3%)
Ileum and Colon	55 (47.0%)	49 (42.6%)	48 (41.7%)	152 (43.8%)
CRP in mg/L, median (IQR)	7.9 (2.1; 14.7)	5.2 (1.7; 13.3)	5.7 (1.7; 16.1)	5.8 (1.8; 14.9)
Fecal calprotectin in µg/g,[a] median (IQR)	712.0 (243.0; 1724.0)	610.0 (226.0; 1554.0)	600.5 (235.0; 1650.0)	643.0 (235.0; 1650.0)

CDAI= Crohn's disease activity index. CRP= C-reactive protein. IQR= interquartile range. SC= subcutaneous. SD= standard deviation. SES-CD= simple endoscopic score for Crohn's disease.

[a] Based on N=117 for placebo, N=115 for guselkumab 400 mg q4w → 100 mg SC q8w, N=114 for guselkumab 400 mg → 200 mg SC q4w, and N=346 for total.

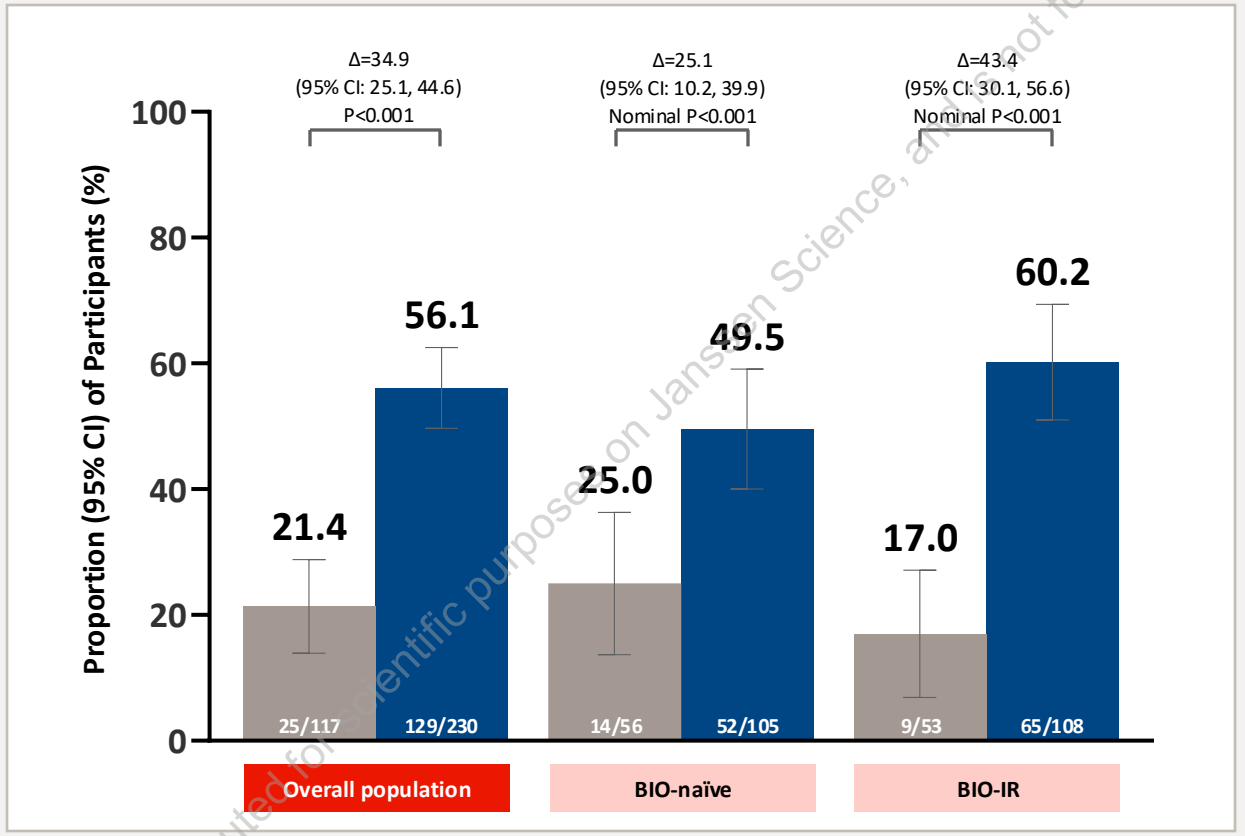
Baseline CD Medication History and Concomitant Medications

Primary analysis set	Placebo (N=117)	Guselkumab 400 mg SC q4w → 100 mg SC q8w (N=115)	Guselkumab 400 mg SC q4w → 200 mg SC q4w (N=115)	Total (N=347)
Medication history				
No history of inadequate response/intolerance[a] to biologic therapy, n (%)	64 (54.7%)	60 (52.2%)	62 (53.9%)	186 (53.6%)
Biologic naïve	56 (87.5%)	53 (88.3%)	52 (83.9%)	161 (86.6%)
Biologic experienced, but no documented nonresponse/intolerance	8 (12.5%)	7 (11.7%)	10 (16.1%)	25 (13.4%)
History of inadequate response/intolerance[a] to biologic therapy, n (%)	53 (45.3%)	55 (47.8%)	53 (46.1%)	161 (46.4%)
At least one anti-TNF	50 (94.3%)	51 (92.7%)	52 (98.1%)	153 (95.0%)
Two or more anti-TNFs	11 (20.8%)	12 (21.8%)	13 (24.5%)	36 (22.4%)
Vedolizumab	8 (15.1%)	13 (23.6%)	6 (11.3%)	27 (16.8%)
Concomitant Medications				
Participants with ≥1 CD medication at baseline, n (%)	79 (67.5%)	74 (64.3%)	84 (73.0%)	237 (68.3%)
6-mercaptopurine/Azathioprine/Methotrexate	33 (28.2%)	29 (25.2%)	37 (32.2%)	99 (28.5%)
Oral corticosteroids	33 (28.2%)	32 (27.8%)	38 (33.0%)	103 (29.7%)

CD= Crohn's disease. SC= subcutaneous. TNF= tumor necrosis factor.

[a] Primary nonresponse, secondary nonresponse, or intolerance.

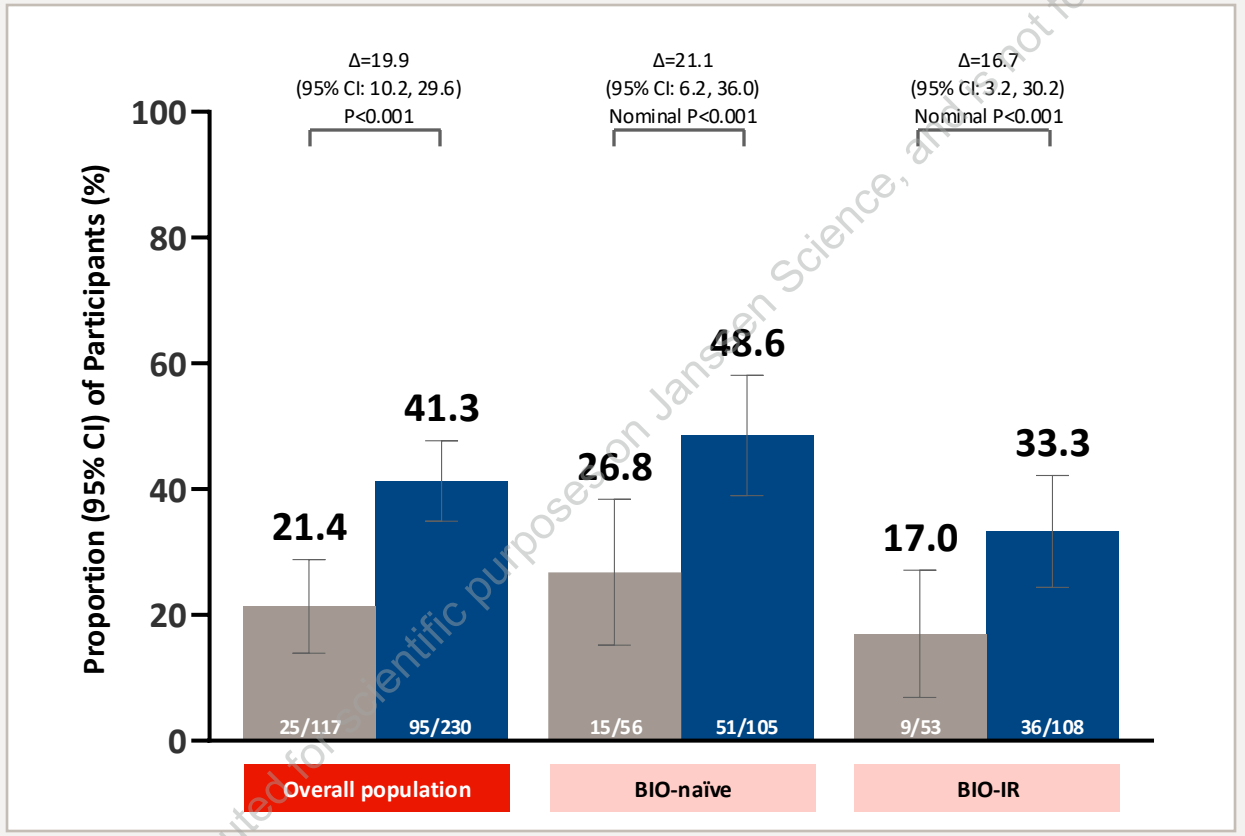
Clinical Remission at Week 12



Clinical remission: CDAI score <150

BIO-IR= history of inadequate response or intolerance to previous biologic therapy.
Note: Clinical remission at Week 12 was **multiplicity-controlled** for the overall population, not the BIO-naïve and BIO-IR subpopulations.

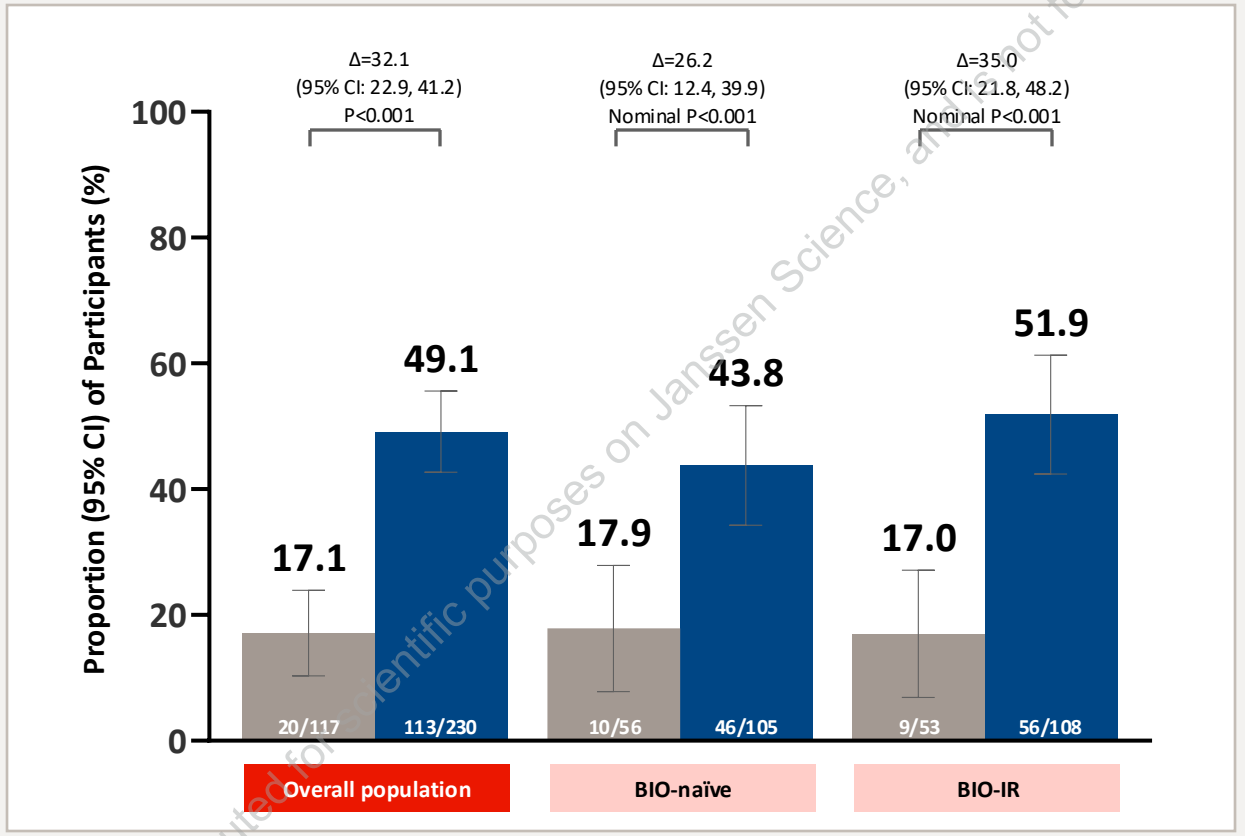
Endoscopic Response at Week 12



Endoscopic response: ≥50% improvement from baseline in SES-CD score

BIO-IR= history of inadequate response or intolerance to previous biologic therapy.
Note: Endoscopic response at Week 12 was **multiplicity-controlled** for the overall population, not the BIO-naïve and BIO-IR subpopulations.

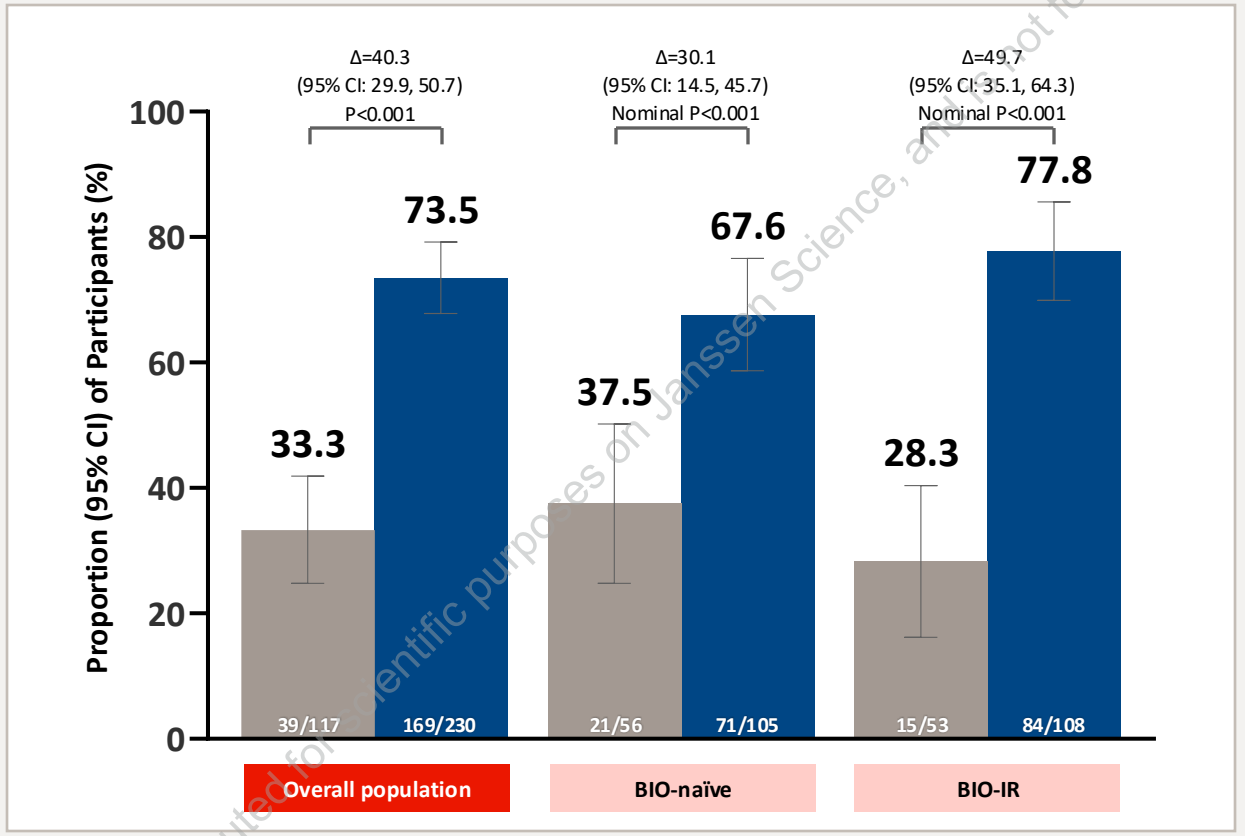
PRO-2 Remission at Week 12



PRO-2 remission: Abdominal pain average daily score ≤1 and stool frequency average daily score ≤3, and no worsening of abdominal pain or stool frequency from baseline

BIO-IR= history of inadequate response or intolerance to previous biologic therapy.
Note: PRO-2 remission at Week 12 was **multiplicity-controlled** for the overall population, not the BIO-naïve and BIO-IR subpopulations.

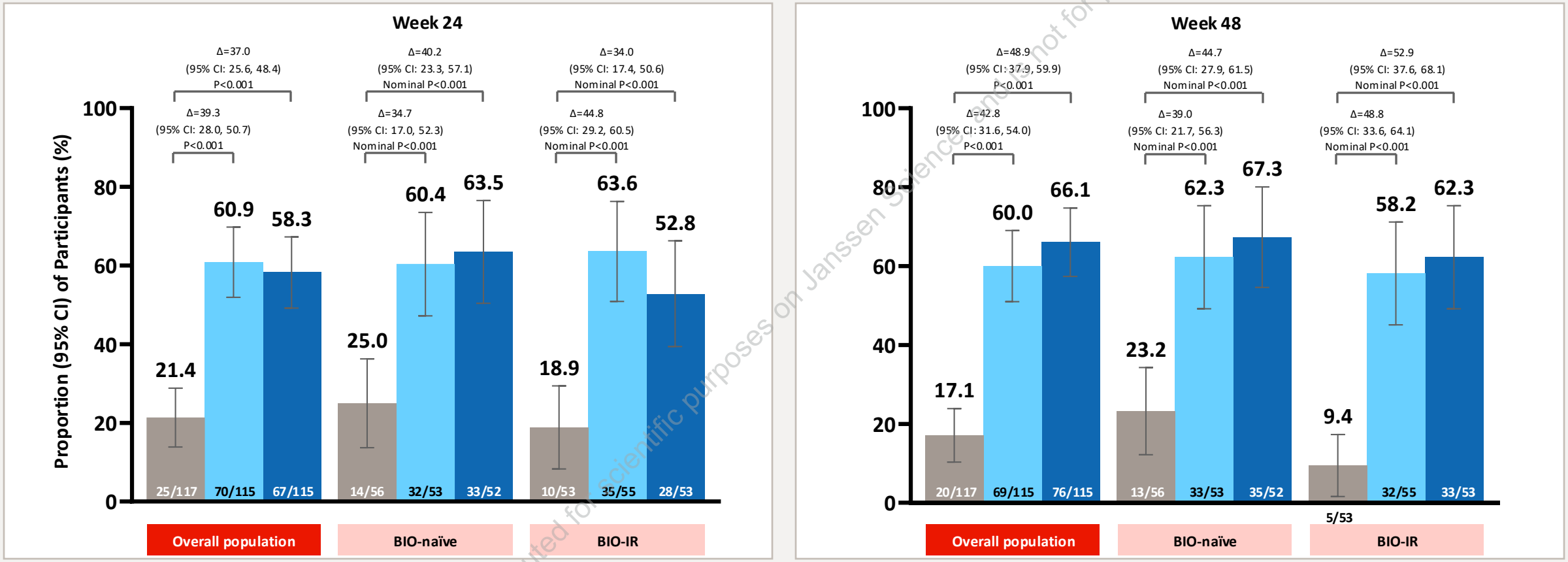
Clinical Response at Week 12



Clinical response: ≥100-point reduction from baseline in CDAI score or CDAI score <150

BIO-IR= history of inadequate response or intolerance to previous biologic therapy.
Note: Clinical response at Week 12 was **multiplicity-controlled** for the overall population, not the BIO-naïve and BIO-IR subpopulations.

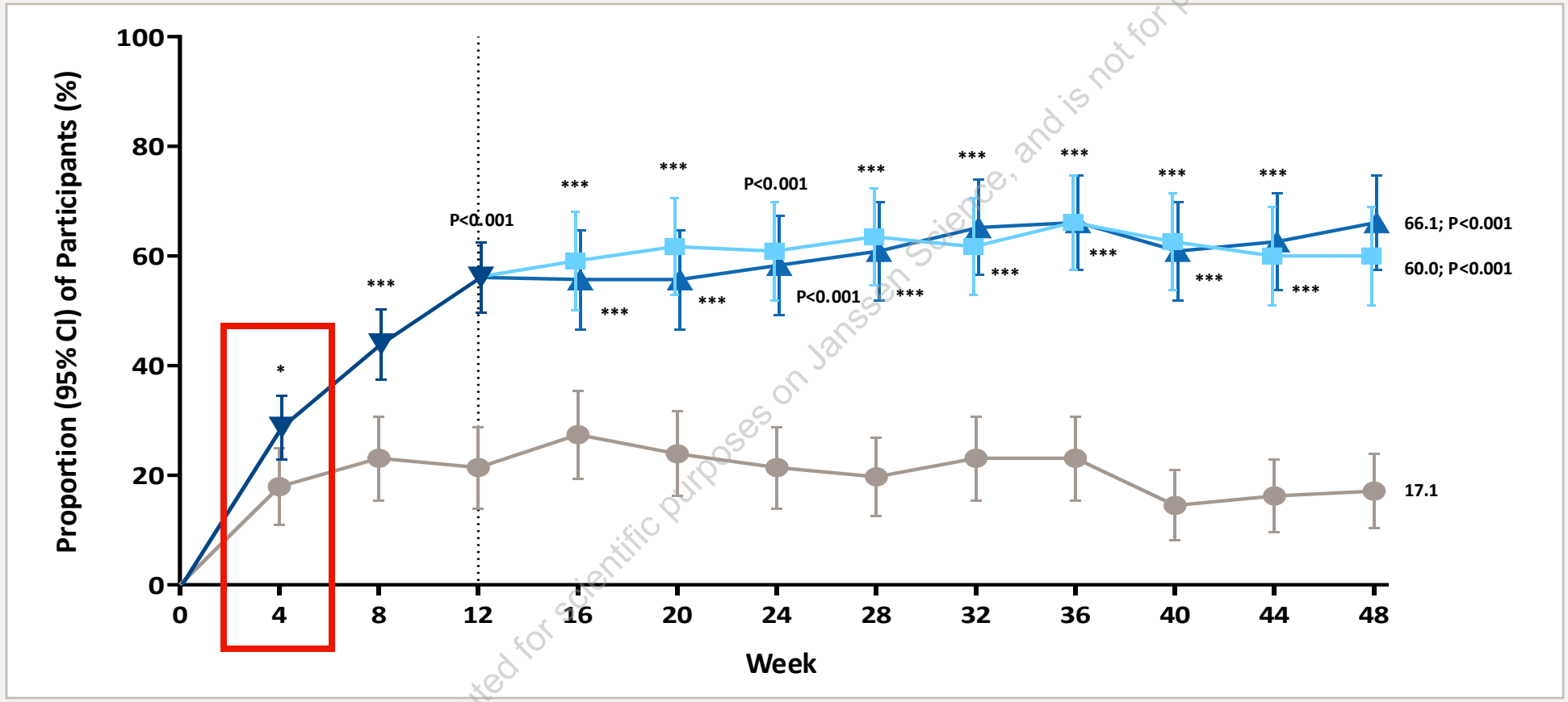
Clinical Remission at Weeks 24 and 48



Clinical remission: CDAI score <150

BIO-IR= history of inadequate response or intolerance to previous biologic therapy.
Note: Clinical remission at Weeks 24 and 48 were **multiplicity-controlled** for the overall population, not the BIO-naïve and BIO-IR subpopulations.

Clinical Remission Through Week 48

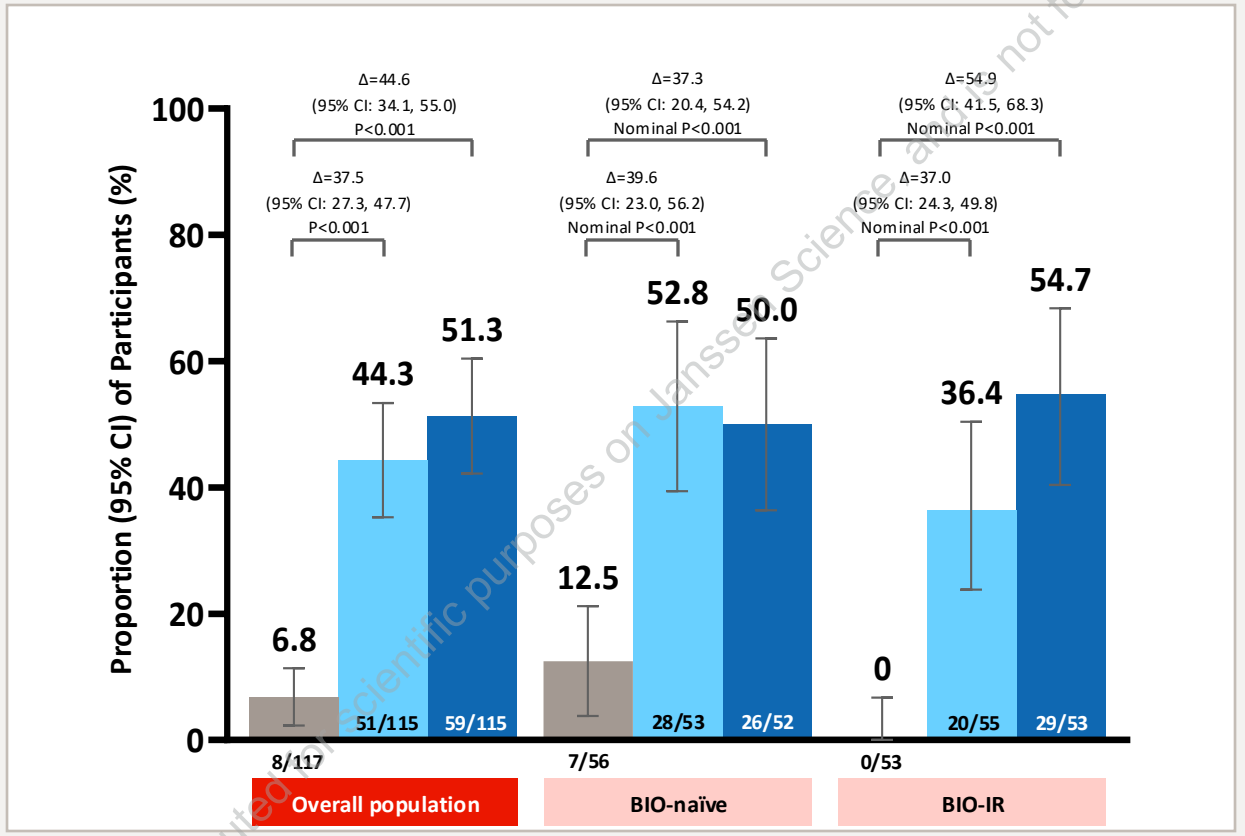


● Placebo SC (N=117) ■ GUS 400 mg SC q4w → GUS 100 mg SC q8w (N=115) ▲ GUS 400 mg SC q4w → GUS 200 mg SC q4w (N=115) ▼ GUS Combined (N=230)

Clinical remission: CDAI score <150

** Nominal P<0.05. *** Nominal P<0.001.*
Note: Clinical remission at Weeks 12, 24 and 48 were **multiplicity-controlled** for the overall population.

Endoscopic Response at Week 48

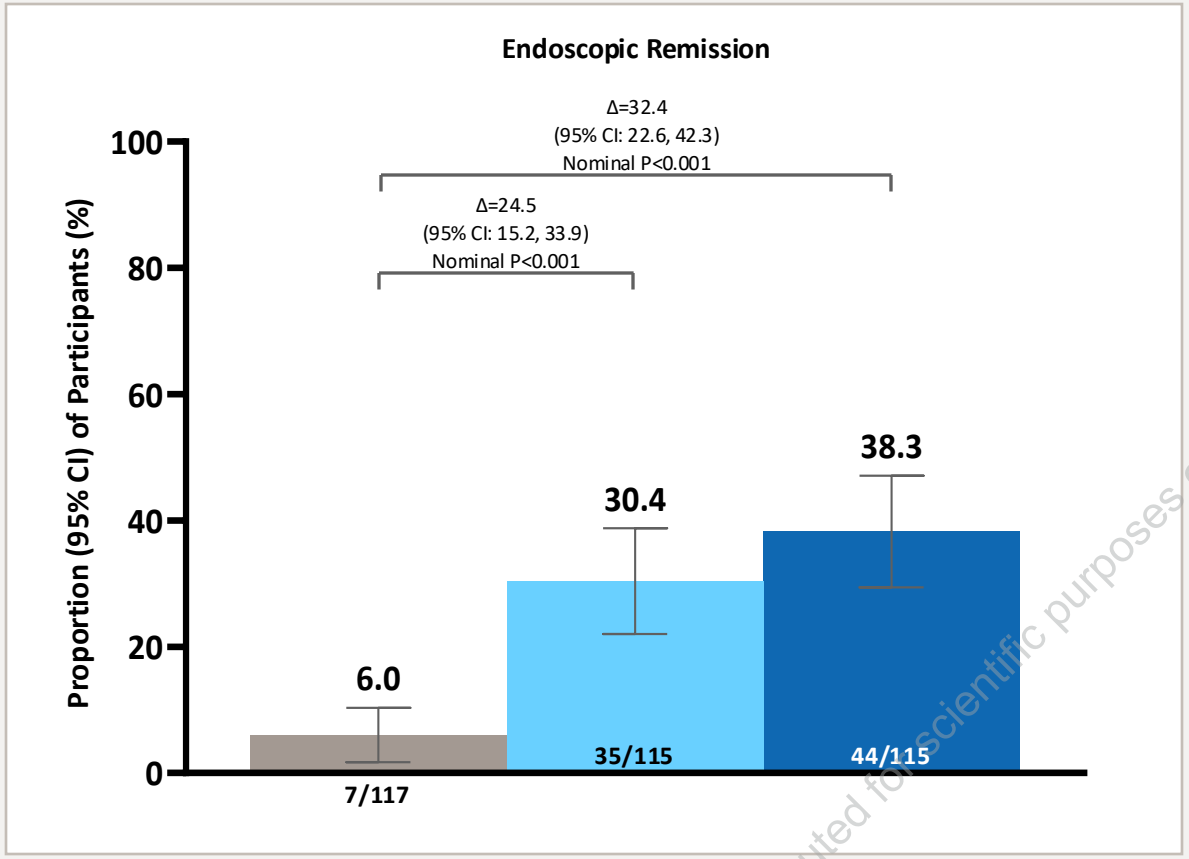


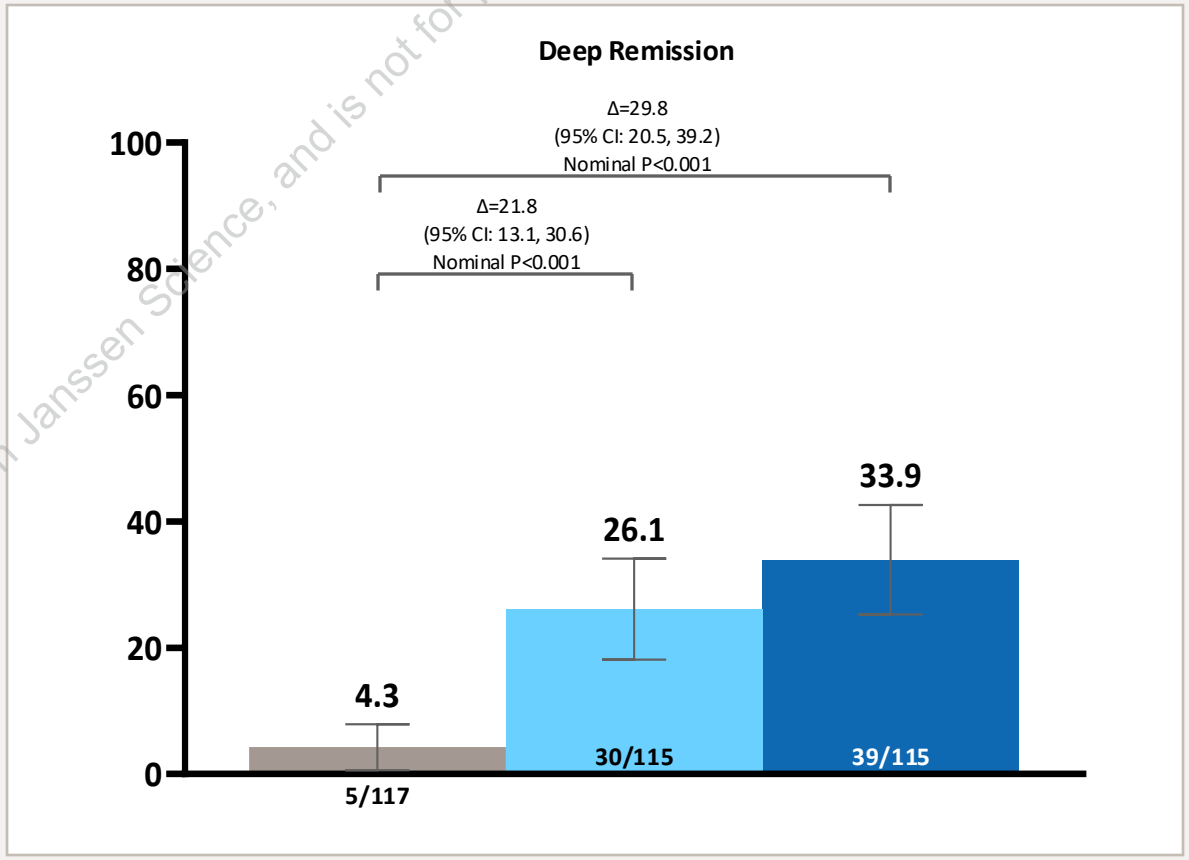
Placebo SC **GUS 400 mg SC q4w → GUS 100 mg SC q8w** **GUS 400 mg SC q4w → GUS 200 mg SC q4w**

Endoscopic response: ≥50% improvement from baseline in SES-CD score

BIO-IR= history of inadequate response or intolerance to previous biologic therapy.
Note: Endoscopic response at Week 48 was **multiplicity-controlled** for the overall population, not the BIO-naïve and BIO-IR subpopulations.

Endoscopic Remission and Deep Remission at Week 48





Placebo SC | GUS 400 mg SC q4w → GUS 100 mg SC q8w | GUS 400 mg SC q4w → GUS 200 mg SC q4w

Endoscopic remission: SES-CD score ≤4 and at least a 2-point reduction from baseline and no subscore greater than 1 in any individual component
Deep remission: Clinical remission (CDAI score <150) and endoscopic remission

Note: Endoscopic remission and deep remission at Week 48 were **not** multiplicity-controlled endpoints; the reported p-values are nominal.

Summary of Adverse Events Through Week 48

Safety analysis set	Placebo[a] (N=117)	Guselkumab 400 mg SC q4w → 100 mg SC q8w (N=115)	Guselkumab 400 mg SC q4w → 200 mg SC q4w (N=115)
Average duration of follow-up, weeks	30.0	47.0	48.0
Average exposure, number of administrations	7.1	6.8	11.8
Total PYs of follow-up, years	67.3	103.5	105.7
Deaths,[b] n (%)	0	1 (0.9%)	0
Participants with 1 or more:			
AEs, n (%)	77 (65.8%)	95 (82.6%)	92 (80.0%)
Events per 100 PYs follow-up	413.0	307.2	327.2
SAEs, n (%)	16 (13.7%)	15 (13.0%)	9 (7.8%)
Events per 100 PYs follow-up	37.1	15.5	13.2
AEs leading to discontinuation of study agent, n (%)	10 (8.5%)	4 (3.5%)	3 (2.6%)
Events per 100 PYs follow-up	14.9	6.8	2.8
Serious infections, n (%)	0	2 (1.7%)	1 (0.9%)

Five most frequent AEs in participants receiving GUS were:

- Upper respiratory tract infection (GUS 14% vs PBO 10%)
- Abdominal pain (GUS 10% vs PBO 6%)
- COVID-19 (GUS 8% vs PBO 7%)
- Crohn's disease (GUS 6% vs PBO 20%)
- Headache (GUS 6% vs PBO 4%)

AE= adverse event. DC= discontinuation. PY= participant-years. SAE= serious adverse event. SC= subcutaneous.

[a] Includes all placebo participants excluding data after a participant is rescued with guselkumab. [b] Fatal gunshot wound (non-suicidal).

Note: Participants are counted only once for any given event under specific column, regardless of the number of times they actually experienced the event.

Adverse events are coded using MedDRA Version 26.0.

Adverse Events of Interest Through Week 48

Safety analysis set	Placebo[a] (N=117)	Guselkumab 400 mg SC q4w → 100 mg SC q8w (N=115)	Guselkumab 400 mg SC q4w → 200 mg SC q4w (N=115)
Average duration of follow-up, weeks	30.0	47.0	48.0
Average exposure, number of administrations	7.1	6.8	11.8
AEs of special interest, n (%)			
Active tuberculosis	0	0	0
Malignancies[b]	0	1 (0.9%)	0
Anaphylactic or serum sickness like reactions	0	0	0
Opportunistic infections[c]	1 (0.9%)	0	1 (0.9%)
Major adverse cardiovascular events (MACE)	0	0	0

Overall, 31 of 3153 guselkumab injections (1.0%) through Week 48 had injection-site reactions

AE= adverse event. SC= subcutaneous.

[a] Includes all placebo participants excluding data after a participant is rescued with guselkumab. [b] Basal cell carcinoma of skin; participant continued in the study. [c] Esophageal candidiasis for the placebo participant and fungal esophagitis for the guselkumab participant.

Note: Participants are counted only once for any given event under specific column, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 26.0.

Key Takeaways

The GRAVITI study demonstrated that guselkumab SC induction followed by SC maintenance was superior to placebo across all multiplicity-controlled clinical and endoscopic endpoints through Week 48

Efficacy was observed in biologic-naïve participants and those with prior inadequate response or intolerance to biologics

Safety findings were consistent with the known favorable safety profile of guselkumab in approved indications and other studies in IBD

These results complement the GALAXI data[1] and demonstrate that both IV and SC induction with guselkumab are efficacious therapeutic options, enabling patients and healthcare professionals to choose the route of administration that aligns with their preferences

1. Panaccione R, Danese S, Feagan BG, et al. *Gastroenterology*. 2024; 166(5): S1057b.

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