Efficacy and Safety of Guselkumab in Patients With Moderately to Severely Active Crohn's Disease: Results of the GALAXI 2 & 3 Phase 3 Studies

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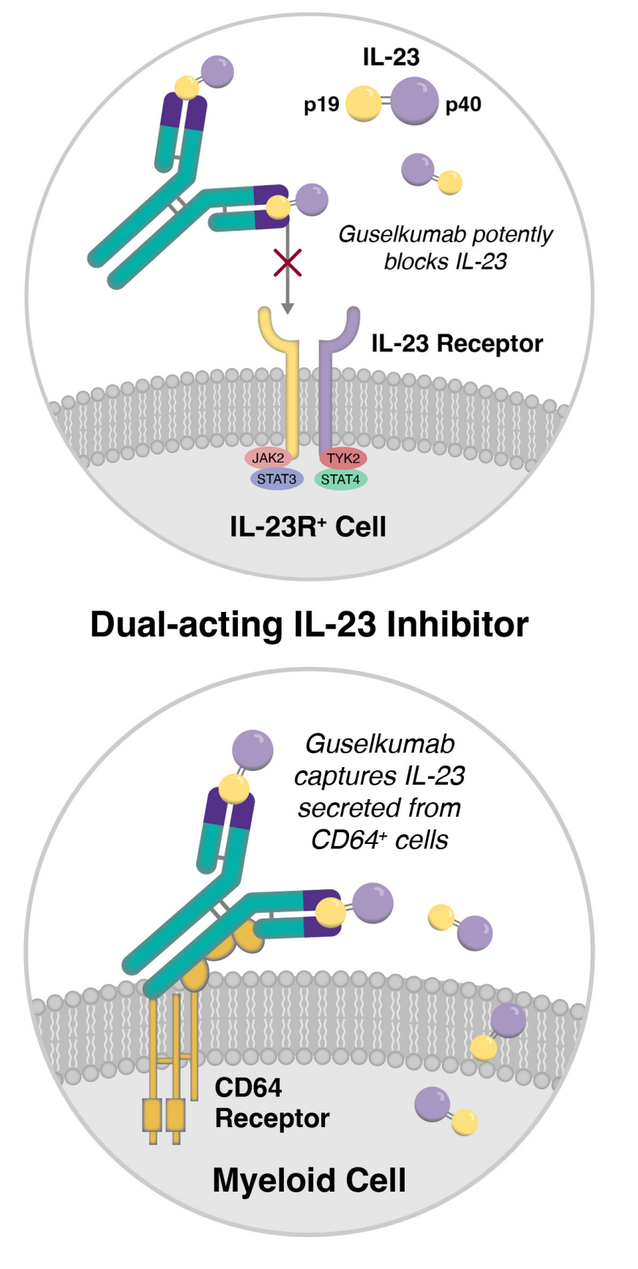
Key Takeaways

- The two double-blinded GALAXI Phase 3 studies independently established the short- and long-term efficacy of the dual-acting IL-23 inhibitor GUS compared to PBO in participants with moderately to severely active CD
- GUS demonstrated statistical superiority to UST in prespecified and multiplicity-controlled analyses of pooled data at W48 for:
  - Endoscopic response
  - Endoscopic remission
  - Clinical remission and endoscopic response
  - Deep remission (clinical remission and endoscopic remission)
- Both GUS SC maintenance doses were efficacious
- Safety data for both GUS dosing regimens through W48 were consistent with the known and favorable safety profile of GUS in approved indications

Background

- Guselkumab (GUS) is a dual-acting interleukin (IL)-23p19 subunit inhibitor that potently neutralizes IL-23 and binds to CD64, a receptor on cells that produce IL-23[1]
- In the Phase 2 GALAXI 1 trial, GUS intravenous (IV) induction[2] followed by subcutaneous (SC) maintenance[3] was safe and showed efficacy in participants with Crohn's disease (CD)
- Endoscopic healing is associated with improved long-term outcomes, therefore, modern trials in CD include both clinical and endoscopic endpoints[4]
- GALAXI 2 & 3 are identically designed randomized, double-blind, double-dummy, registrational, placebo (PBO)- and active-comparator (ustekinumab; UST) treat-through Phase 3 trials of GUS IV induction and SC maintenance therapy in participants with moderately-to-severely active CD



Objective

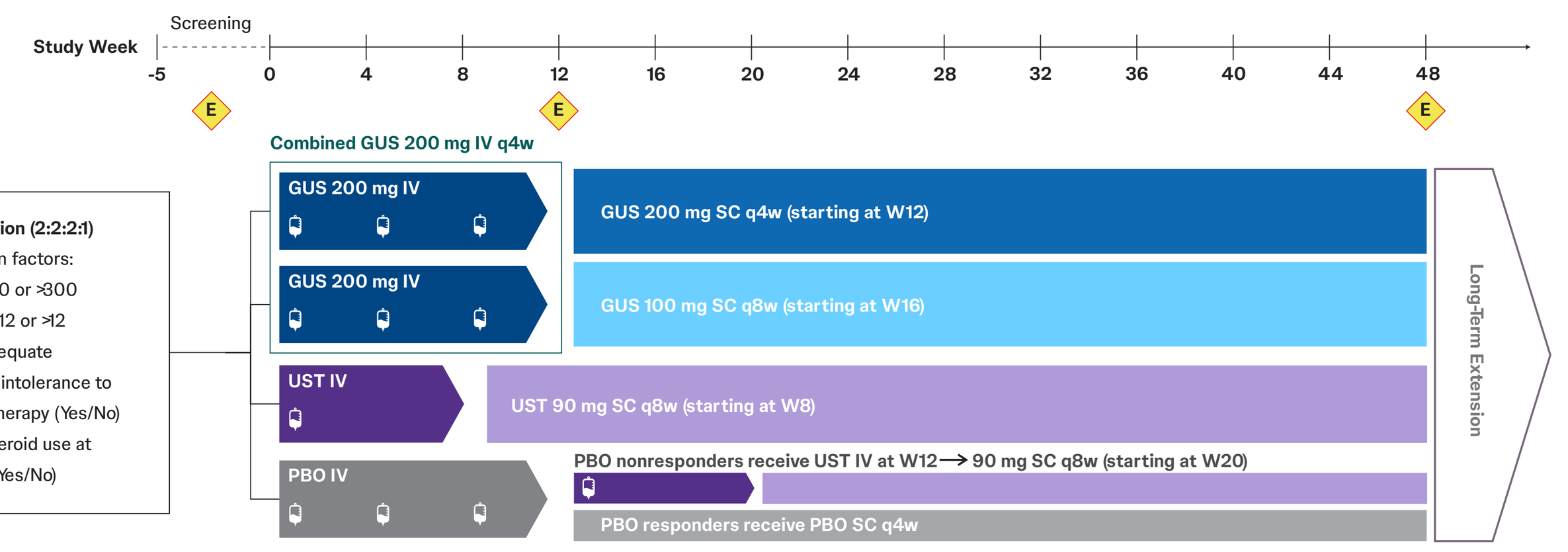
- To report Week (W) 48 results from the Phase 3 GALAXI 2 & 3 studies in participants with moderately to severely active CD

Methods

Double-Blind, Treat-Through Design: GALAXI 2 & 3

Primary Analysis Set
- GALAXI 2: 508 participants
- GALAXI 3: 513 participants

Eligibility Criteria
- Moderately to severely active CD (Clinical Disease Activity Index score 220–450 + mean daily Stool Frequency count >3 OR Abdominal Pain score >1) and Simple Endoscopic Score for CD score[a] ≥6 (or ≥4 for isolated ileal disease)
- Inadequate response/intolerance to oral corticosteroids or 6-mercaptopurine/azathioprine/methotrexate, or biologic therapies[b]



[a]Scored at screening by central reader with minimum scores of 1 for "size of ulcer" and "ulcerated surface"; [b]Biologic therapies: TNF antagonists or vedolizumab. Note: To maintain treatment masking, all participants received active and/or PBO IV q4w through W12 and active and/or PBO SC q4w through W48. CDAI=Clinical Disease Activity Index; E=Endoscopy; IV=Intravenous; GUS=Guselkumab; PBO=Placebo; q4w=Every 4 weeks; q8w=Every 8 weeks; SC=Subcutaneous; SES-CD=Simple Endoscopic Score for Crohn's Disease; TNF=Tumor necrosis factor; UST=Ustekinumab; W=Week.

Endpoints and Statistical Considerations

Composite Co-Primary Endpoints: GUS vs PBO
- Clinical response at W12 **and** clinical remission at W48
- Clinical response at W12 **and** endoscopic response at W48

Major Secondary Endpoints

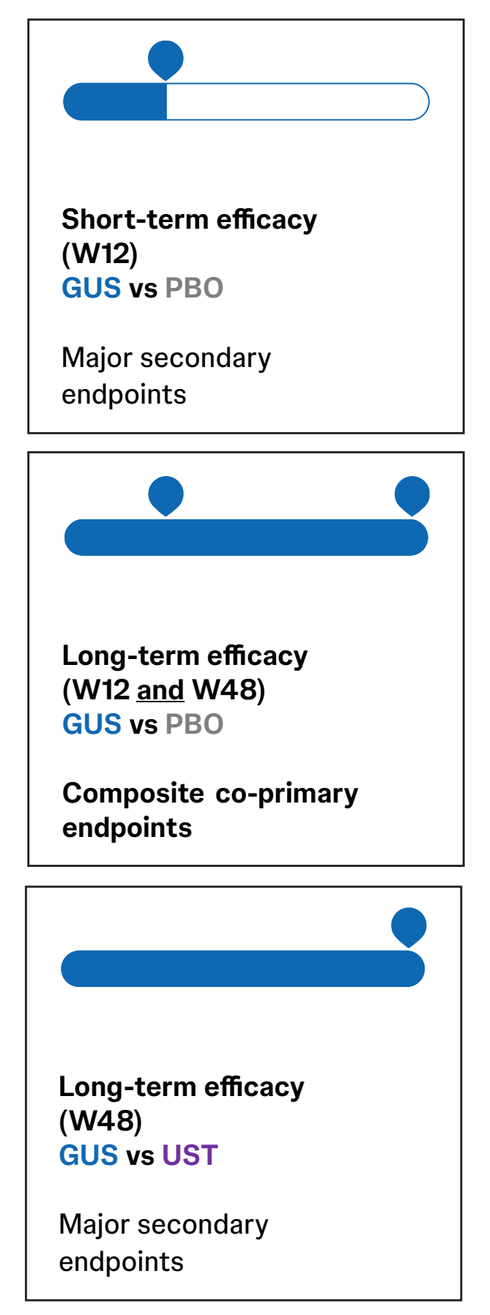
GUS vs PBO
- Clinical remission at W12
- Endoscopic response at W12

GUS vs UST
- Endoscopic response at W48
- Endoscopic remission at W48
- Clinical remission and endoscopic response at W48
- Deep remission at W48
- Clinical remission at W48

Statistical Considerations
- Participants with treatment failure or missing data were considered to not have met the endpoint
- **In each trial,** co-primary and major secondary endpoints[a] were multiplicity controlled at the 0.05 level
- GUS vs UST endpoints were multiplicity-controlled using **pooled W48 data** from GALAXI 2 & 3
- Data pooling was prespecified

[a]Adjusted treatment differences and p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator.

Endpoint Time Frames



GUS=Guselkumab; PBO=Placebo; UST=Ustekinumab; W=Week.

Results

Baseline Demographics & Disease Characteristics

Pooled GALAXI 2 & 3

	PBO	GUS 200 mg IV q4w → 100 mg SC q8w	GUS 200 mg IV q4w → 200 mg SC q4w	UST	Total
Primary analysis set, N	148	286	296	291	1021
Participant age (years), mean (SD)	34.8 (12.15)	36.0 (12.24)	36.9 (13.27)	37.4 (13.20)	36.5 (12.82)
Male sex, %	59.5	53.8	60.1	57.7	57.6
CD duration (years), mean (SD)	7.1 (7.5)	7.1 (6.7)	7.1 (7.2)	7.3 (7.5)	7.2 (7.2)
CDAI score, mean (SD)	293.4 (52.7)	296.3 (54.3)	295.9 (52.7)	293.1 (52.0)	294.8 (52.9)
SES-CD score, mean (SD)	13.3 (7.5)	13.2 (7.4)	12.5 (7.2)	12.9 (7.0)	12.9 (7.3)
Endoscopic disease severity (SES-CD score), n (%)					
Moderate (7–16)	77 (52.0)	164 (57.3)	147 (49.7)	159 (54.6)	547 (53.6)
Severe (>16)	43 (29.1)	81 (28.3)	79 (26.7)	75 (25.8)	278 (27.2)
Involved GI areas by central reader, n (%)					
Ileum only	31 (20.9)	59 (20.6)	80 (27.0)	55 (18.9)	225 (22.0)
Colon only	62 (41.9)	113 (39.5)	112 (37.8)	116 (39.9)	403 (39.5)
Ileum and Colon	55 (37.2)	114 (39.9)	104 (35.1)	120 (41.2)	393 (38.5)
CRP (mg/L), median (IQR)	5.1 (1.5; 15.8)	7.7 (2.6; 21.8)	6.2 (2.7; 21.3)	7.2 (2.4; 19.4)	6.5 (2.3; 19.5)
Fecal calprotectin (μg/g), median (IQR)	962.0 (255.0; 2595.0)	969.0 (404.0; 2085.0)	1045.5 (323.0; 2006.0)	882.5 (338.5; 1853.5)	969.5 (348.5; 2052.5)

CD=Crohn's disease; CDAI=Clinical Disease Activity Index; CRP=C-reactive protein; GI=Gastrointestinal; GUS=Guselkumab; IQR=Interquartile range; IV=Intravenous; PBO=Placebo; q4w=Every 4 weeks; q8w=Every 8 weeks; SC=Subcutaneous; SD=Standard deviation; SES-CD=Simple Endoscopic Score for Crohn's Disease; UST=Ustekinumab.

Baseline CD Medication History

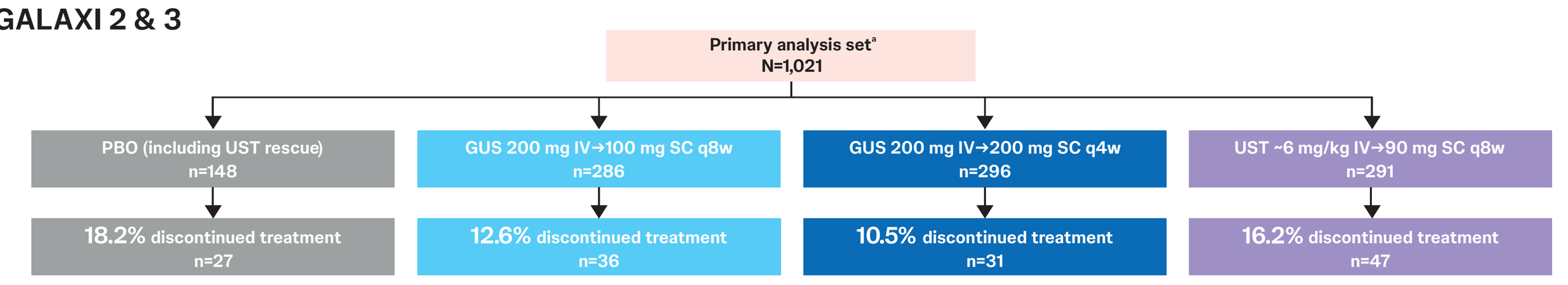
Pooled GALAXI 2 & 3

	PBO	GUS 200 mg IV q4w → 100 mg SC q8w	GUS 200 mg IV q4w → 200 mg SC q4w	UST	Total
Primary analysis set, N	148	286	296	291	1021
No history of inadequate response/intolerance[a] to biologic therapy, n (%)	70 (47.3)	133 (46.5)	149 (50.3)	135 (46.4)	487 (47.7)
Biologic naïve	61 (41.2)	116 (40.6)	128 (43.2)	121 (41.6)	426 (41.7)
Biologic experienced, but no documented nonresponse/intolerance	9 (6.1)	17 (5.9)	21 (7.1)	14 (4.8)	61 (6.0)
History of inadequate response/intolerance[a] to biologic therapy, n (%)	78 (52.7)	153 (53.5)	147 (49.7)	156 (53.6)	534 (52.3)
At least one anti-TNF	76 (97.4)	149 (97.4)	143 (97.3)	147 (94.2)	515 (96.4)
Two or more anti-TNFs	23 (29.5)	31 (20.3)	31 (21.1)	46 (29.5)	131 (24.5)
Vedolizumab	13 (16.7)	25 (16.3)	18 (12.2)	31 (19.9)	87 (16.3)
Participants with ≥1 CD medication at baseline, n (%)	96 (64.9)	207 (72.4)	217 (73.3)	210 (72.2)	730 (71.5)
6-MP/AZA/MTX	40 (27.0)	87 (30.4)	97 (32.8)	83 (28.5)	307 (30.1)
Oral corticosteroids	51 (34.5)	109 (38.1)	106 (35.8)	109 (37.5)	375 (36.7)

[a]Primary nonresponse, secondary nonresponse, or intolerance. 6-MP=6-mercaptopurine; AZA=Azathioprine; CD=Crohn's disease; GUS=Guselkumab; IV=Intravenous; MTX=Methotrexate; PBO=Placebo; q4w=Every 4 weeks; q8w=Every 8 weeks; SC=Subcutaneous; TNF=Tumor necrosis factor; UST=Ustekinumab.

Treatment Disposition Through W48

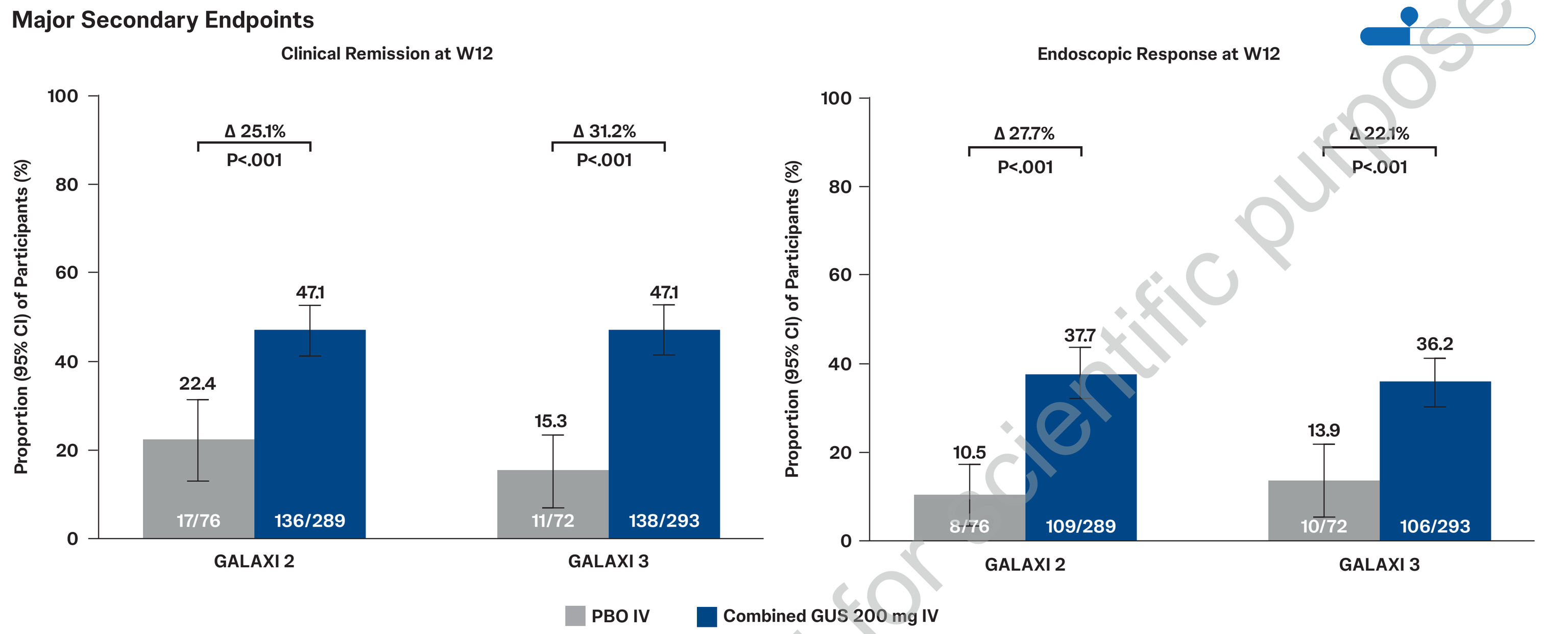
Pooled GALAXI 2 & 3



[a]Primary analysis set: all randomized participants with a screening SES-CD ≥6 (or ≥4 for participants with isolated ileal disease) who received at least 1 (partial or complete) dose of study intervention. GUS=Guselkumab; IV=Intravenous; PBO=Placebo; q4w=Every 4 weeks; q8w=Every 8 weeks; SC=Subcutaneous; SES-CD=Simple Endoscopic Score for Crohn's Disease; UST=Ustekinumab; W=Week.

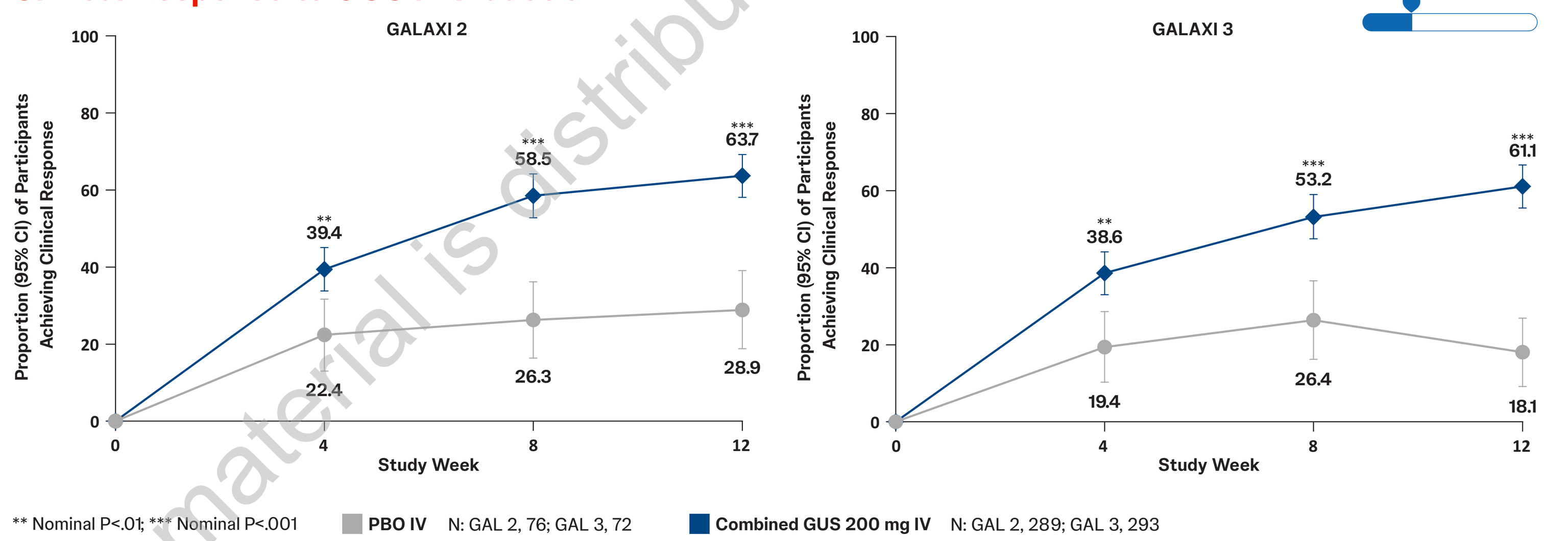
Efficacy of GUS IV Induction

Major Secondary Endpoints



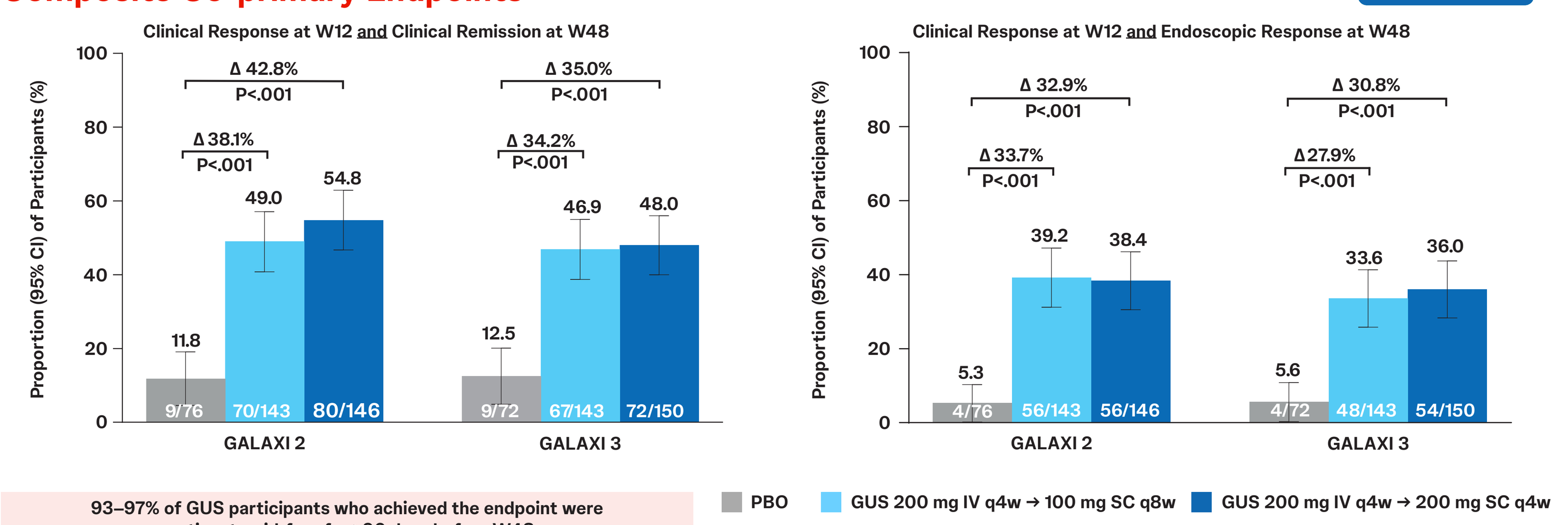
Clinical Remission: CDAI <150; Endoscopic Response: ≥50% improvement from baseline in SES-CD or SES-CD ≤2. CDAI=Clinical Disease Activity Index; CI=Confidence interval; GUS=Guselkumab; IV=Intravenous; PBO=Placebo; SES-CD=Simple Endoscopic Score for Crohn's Disease; W=Week.

Clinical Response to GUS IV Induction



Clinical Response: ≥100-point reduction from baseline in CDAI or CDAI <150. CDAI=Clinical Disease Activity Index; CI=Confidence interval; GAL=GALAXI; GUS=Guselkumab; IV=Intravenous; PBO=Placebo.

Composite Co-primary Endpoints

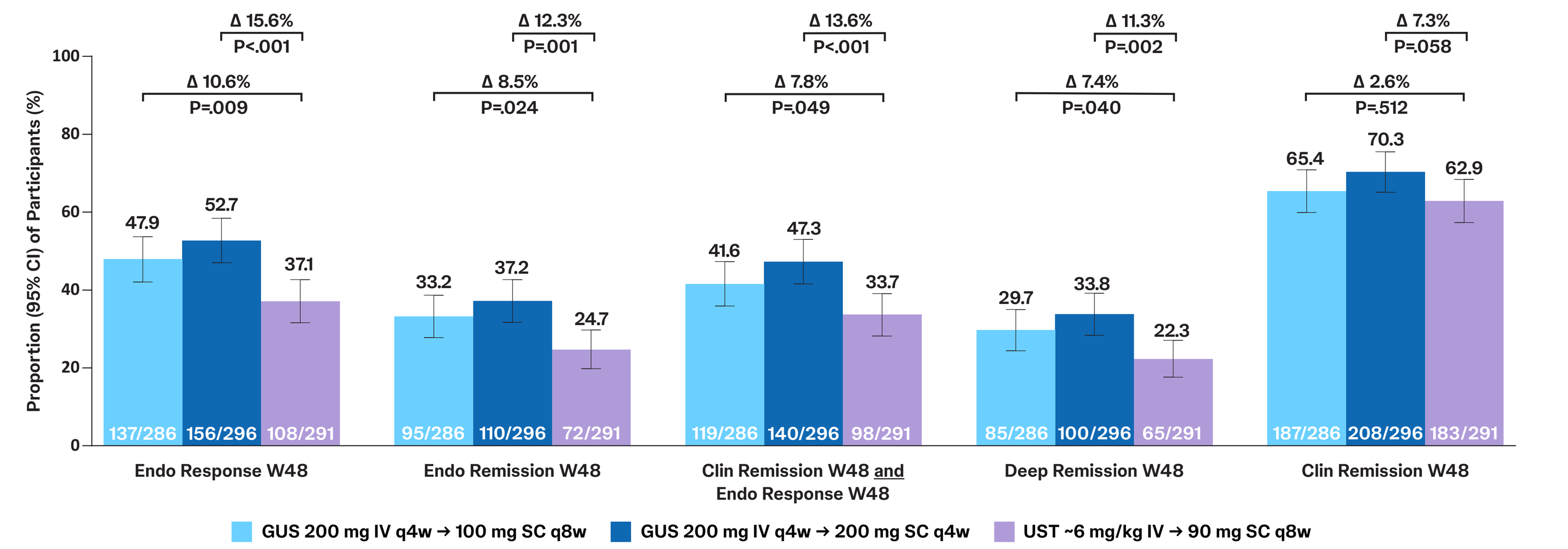


93–97% of GUS participants who achieved the endpoint were corticosteroid-free for ≥90 days before W48

Clinical Response: ≥100-point reduction from baseline in CDAI or CDAI <150. Clinical Remission: CDAI <150. Endoscopic Response: ≥50% improvement from baseline in SES-CD or SES-CD ≤2. CDAI=Clinical Disease Activity Index; CI=Confidence interval; GUS=Guselkumab; IV=Intravenous; PBO=Placebo; q4w=Every 4 weeks; q8w=Every 8 weeks; SC=Subcutaneous; SES-CD=Simple Endoscopic Score for Crohn's Disease; W=Week.

GUS vs UST: Efficacy at W48

Pooled GALAXI 2 & 3: Major Secondary Endpoints



Endoscopic Response: ≥50% improvement from baseline in SES-CD or SES-CD ≤2. Endoscopic Remission: SES-CD ≤4 and a ≥2-point reduction from baseline and no subscore greater than 1 in any individual component. Clinical Remission: CDAI <150. Deep Remission: Clinical Remission and Endoscopic Remission. CDAI=Clinical Disease Activity Index; CI=Confidence interval; GUS=Guselkumab; IV=Intravenous; q4w=Every 4 weeks; q8w=Every 8 weeks; SC=Subcutaneous; SES-CD=Simple Endoscopic Score for Crohn's Disease; UST=Ustekinumab; W=Week.

Summary of AEs Through W48

Pooled GALAXI 2 & 3

	PBO IV → SC[a]	GUS 200 mg IV q4w → 100 mg SC q8w	GUS 200 mg IV q4w → 200 mg SC q4w	UST ~6 mg/kg IV → 90 mg SC q8w
All-treated safety analysis set, N	153	296	299	300
Avg. duration of follow-up, weeks	21.8	46.2	46.7	45.5
Total participant–years of follow-up	64.0	261.8	267.3	261.4
Deaths	0	0	0	0
Participants with ≥1 AE, n (%)	82 (53.6)	225 (76.0)	233 (77.9)	236 (78.7)
AEs/100 participant–years of follow-up	499.7	327.3	353.5	340.5
Participants with ≥1 serious AE	16 (10.5)	32 (10.8)	21 (7.0)	35 (11.7)
Participants with ≥1 AEs leading to discontinuation of study agent	13 (8.5)	21 (7.1)	19 (6.4)	22 (7.3)
Participants with ≥1 serious infection[b]	2 (1.3)	1 (0.3)	3 (1.0)	12 (4.0)

Five most frequent AEs in participants receiving GUS were:	COVID-19	Upper respiratory tract infection	Worsening of CD	Arthralgia	Headache

[a]Events attributed to participants randomized to PBO, except where a participant is randomized to PBO and crosses over to UST (only events that occur while participants are on PBO are included); [b]Infections defined as any adverse event coded to MedDRA organ class "Infections and infestations". AE=Adverse event; CD=Crohn's disease; COVID=Coronavirus disease; GUS=Guselkumab; IV=Intravenous; MedDRA=Medical Dictionary for Regulatory Activities; PBO=Placebo; q4w=Every 4 weeks; q8w=Every 8 weeks; SC=Subcutaneous; UST=Ustekinumab; W=Week.

AEs of Interest Through W48

Pooled GALAXI 2 & 3

	PBO IV → SC[a]	GUS 200 mg IV q4w → 100 mg SC q8w	GUS 200 mg IV q4w → 200 mg SC q4w	UST ~6 mg/kg IV → 90 mg SC q8w
All-treated safety analysis set, N	153	296	299	300
Avg. duration of follow-up, weeks	21.8	46.2	46.7	45.5
Participants with ≥1 AE[b], n (%)				
Active tuberculosis	0	1 (0.3)	0	0
Malignancies	0	0	1 (0.3)	0
Anaphylactic or serum sickness-like reactions	0	0	0	2 (0.7)
Opportunistic infections	1 (0.7)	1 (0.3)	2 (0.7)	0
MACE	0	1 (0.3)	0	0
VTE	0	0	0	1 (0.3)
Clinically important hepatic disorders[c]	0	3 (1.0)	1 (0.3)	0

[a]Events attributed to participants randomized to PBO, except where a participant is randomized to PBO and crosses over to UST (events occurring after receiving UST are not counted); [b]Participants are counted only once for any given event, regardless of the number of times they actually experienced the event. AEs are coded using MedDRA Version 26.0. MACE were identified by clinical review. VTE terms are based on customized MedDRA query. Hepatic disorder AEs are defined as the narrow terms in the MedDRA SMQ of "Drug Related Hepatic Disorders - Comprehensive Search"; [c]Clinically important hepatic disorders are defined as hepatic disorder AEs reported as SAEs or AEs leading to discontinuation of study intervention. AE=Adverse event; Avg=Average; GUS=Guselkumab; IV=Intravenous; MACE=Major adverse cardiovascular event; MedDRA=Medical Dictionary for Regulatory Activities; PBO=Placebo; q4w=Every 4 weeks; q8w=Every 8 weeks; SAE=Serious adverse event; SC=Subcutaneous; SMQ=Standardized MedDRA Queries; UST=Ustekinumab; VTE=Venous thromboembolism; W=Week.

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