Guselkumab Pharmacokinetics and Exposure-response Relationships Are Consistent Following Intravenous Versus Subcutaneous Induction in Participants with Crohn's Disease

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EM-193863

Key Takeaways

- Average serum guselkumab concentrations and exposure-response efficacy relationships were similar after IV versus SC induction.
- Higher serum guselkumab concentrations after 200 mg IV or 400 mg SC induction did not increase the incidence of safety events.
- These results support the use of either administration route and induction dose regimen at the approved doses (200 mg IV or 400 mg SC) in patients with Crohn's disease.

Background

Guselkumab, a dual-acting IL-23p19 subunit inhibitor, is approved for the treatment of Crohn's disease, with an intravenous (IV) or subcutaneous (SC) induction regimen followed by a SC maintenance regimen.

Guselkumab efficacy and safety in participants with moderately to severely active Crohn's disease were evaluated in the following studies:

- The phase 2 GALAXI 1 study (guselkumab 200, 600, or 1200 mg IV at weeks 0, 4, and 8)
- The phase 3 GALAXI 2 and GALAXI 3 studies (guselkumab 200 mg IV at weeks 0, 4, and 8)
- The phase 3 GRAVITI study (guselkumab 400 mg SC at weeks 0, 4, and 8)

All four studies used treat-through designs and the same SC maintenance dose regimens (guselkumab 100 mg every 8 weeks [q8w] or guselkumab 200 mg every 4 weeks [q4w]).

With an estimated ~50% bioavailability of SC guselkumab, the 2-fold higher SC induction dose was predicted to provide similar overall exposure, lower peak serum concentrations, and noninferior trough concentrations compared with the IV dose.

Objectives

To characterize the pharmacokinetics (PK) and exposure-response for efficacy and safety of IV and SC guselkumab administration routes and confirm assumptions for the development of IV and SC induction formulations.

Methods

Analyses to characterize guselkumab PK

- A population PK model was used to simulate exposure metrics for IV and SC induction using individual post-hoc PK parameters and actual participant dosages.
- Relationships between guselkumab exposure and select efficacy endpoints (clinical response, clinical remission, and endoscopic response) at week 12 were assessed.
- Exposure-response relationships with safety events, including infections, serious infections, serious adverse events, and abnormal liver function measures, were summarized descriptively based on guselkumab concentration quartiles.

Clinical and endoscopic outcome definitions

Clinical response	• ≥100-point reduction from baseline in CDAI score or CDAI score <150
Clinical remission	• CDAI score <150
Endoscopic response	• GALAXI: ≥50% improvement from baseline in SES-CD or SES-CD ≤2 • GRAVITI: ≥50% improvement from baseline in SES-CD

CDAI=Crohn's Disease Activity Index; SES-CD=Simple Endoscopic Score for Crohn's Disease.

Results

SC induction resulted in higher trough serum concentrations (at week 12), lower peak serum concentrations, similar average concentrations (week 0–week 12), and similar area under the concentration-time curves (week 0–week 12) versus IV induction

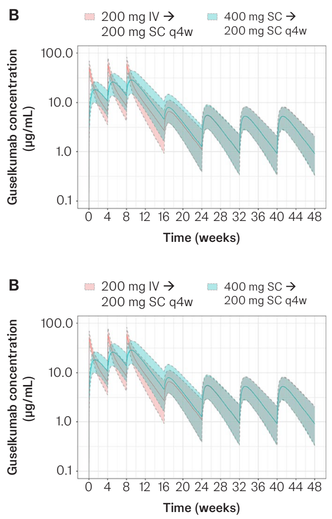
Simulated exposure metrics at week 12 after IV (200 mg q4w) or SC (400 mg q4w) induction regimens

	GUS 200 mg IV q4w (N=622)	GUS 400 mg SC q4w (N=229)
C_{max} (µg/mL)		
Mean (SD)	70.1 (25.1)	27.7 (9.06)
Median (range)	65.8 (34.0–415)	26.6 (6.20–59.2)
$C_{ave,\ week\ 0–12}$ (µg/mL)		
Mean (SD)	21.4 (7.06)	18.9 (6.47)
Median (range)	20.3 (8.26–71.6)	18.2 (3.75–42.1)
$C_{trough,\ week\ 12}$ (µg/mL)		
Mean (SD)	9.76 (5.38)	14.7 (6.65)
Median (range)	8.73 (0.492–32.3)	13.8 (1.14–38.7)
$AUC_{week\ 0–12}$ (day*µg/mL)		
Mean (SD)	1,800 (593)	1,590 (543)
Median (range)	1,700 (694–6,020)	1,530 (315–3,540)

***AUC_{week}** 0–12=area under the concentration-time curve from week 0 to week 12 (induction), **$C_{max,\ week\ 0–12}$**=maximum concentration, **$C_{trough,\ week\ 12}$**=trough concentration at week 12 (induction), **IV**=intravenous, **n**=number, **q4w**=every 4 weeks, **SC**=subcutaneous, **SD**=standard deviation.*

Regardless of Induction route (IV or SC) or maintenance regimen, guselkumab serum concentrations reached steady state by week 24

Simulated guselkumab PK profiles over 48 weeks, comparing 200 mg IV q4w x 3 and 400 mg SC q4w x 3 in the Induction period followed by (A) 200 mg SC q4w or (B) 100 mg SC q8w maintenance treatment

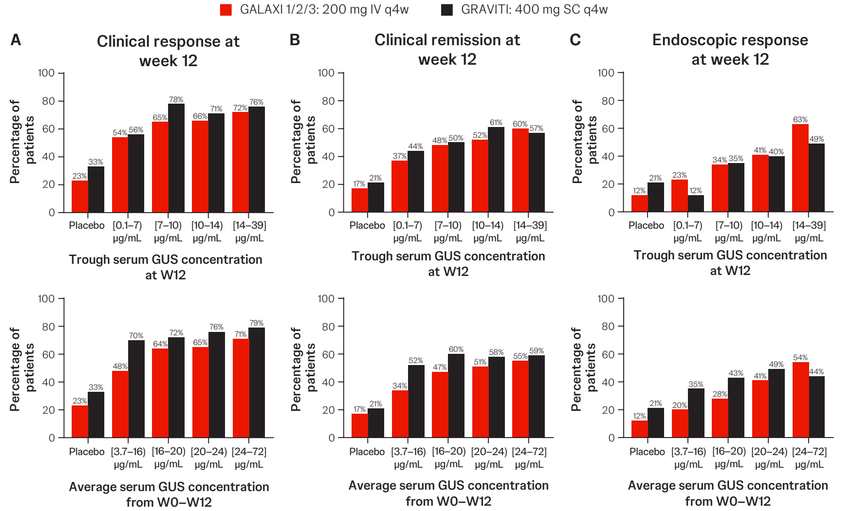


***IV**=intravenous, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **PK**=pharmacokinetic, **SC**=subcutaneous.*

Week 12 efficacy outcomes were comparable within guselkumab concentration quartiles after SC versus IV induction

- Although participants with higher average or trough serum guselkumab concentrations tended to achieve greater rates of week 12 efficacy outcomes, this trend was no longer evident after accounting for a participant's drug clearance or the half-life of the drug (data on file).
- No positive exposure-response trends were seen between peak concentration and week 12 efficacy endpoints (data on file), indicating that efficacy was associated with average concentration rather than peak concentration.

Clinical and endocrinic outcomes at week 12 for guselkumab trough serum concentration quartiles at week 12 and guselkumab average serum concentration quartiles from baseline to week 12 following IV induction in GALAXI or SC induction in GRAVITI



***GUS**=guselkumab, **IV**=intravenous, **q4w**=every 4 weeks, **SC**=subcutaneous, **W**=week.*

Across concentration quartiles, the incidence of safety events was comparable between participants who received guselkumab IV or SC induction regimens

Number of participants with safety events by average serum guselkumab trough concentration quartiles (week 0 through week 12) and average serum guselkumab steady-state trough concentration quartiles (week 12 through week 48)

- No positive associations between serum concentrations and safety events (infections, serious infections, and serious adverse events) or abnormal liver function tests (data on file) were observed through week 48.

Average serum trough GUS concentration through week 12

Through week 12	Placebo	<1st Quartile	≥1st and <2nd Quartile	≥2nd and <3rd Quartile	≥3rd Quartile
PK analysis set					
GALAXI[b,c]	208	152	153	154	152
GRAVITI[b,c]	117	57	57	57	56
Pts with ≥1 treatment-emergent infections, n (%)					
GALAXI	38 (18.3%)	23 (15.1%)	23 (15.0%)	25 (16.2%)	30 (19.7%)
GRAVITI	24 (20.5%)	12 (21.1%)	12 (21.1%)	9 (15.8%)	10 (17.9%)
Pts with ≥1 treatment-emergent serious infections, n (%)					
GALAXI	0	1 (0.7%)	0	0	0
GRAVITI	0	0	0	0	1 (1.8%)
Pts with ≥1 treatment-emergent SAEs, n (%)					
GALAXI	12 (5.8%)	9 (5.9%)	4 (2.6%)	3 (1.9%)	2 (1.3%)
GRAVITI	9 (7.7%)	2 (3.5%)	2 (3.5%)	0	3 (5.4%)

GUS 100 mg SC q8w and 200 mg SC q4w combined average steady-state trough serum GUS concentration through week 48[d,e,f]

Week 12 through week 48	Placebo[f]	<1st Quartile	≥1st and <2nd Quartile	≥2nd and <3rd Quartile	≥3rd Quartile
PK analysis set					
GALAXI	53	143	141	142	143
GRAVITI	110	56	55	57	55
Pts with ≥1 treatment-emergent infections, n (%)					
GALAXI	21 (39.6%)	47 (32.9%)	50 (35.5%)	48 (33.8%)	59 (41.3%)
GRAVITI	21 (19.1%)	22 (39.3%)	22 (40.0%)	13 (22.8%)	18 (32.7%)
Pts with ≥1 treatment-emergent serious infections, n (%)					
GALAXI	3 (5.7%)	1 (0.7%)	0	2 (1.4%)	1 (0.7%)
GRAVITI	0	0	0	0	1 (1.8%)
Pts with ≥1 treatment-emergent SAEs, n (%)					
GALAXI	10 (18.9%)	14 (9.8%)	12 (8.5%)	5 (3.5%)	6 (4.2%)
GRAVITI	8 (7.3%)	6 (10.7%)	5 (9.1%)	4 (7.0%)	5 (9.1%)

*The PK analysis set includes pts randomized to GUS 200 mg IV q4w or GUS 400 mg SC q4w in induction who had evaluable GUS trough concentrations during the induction period (W0 through W12) or at steady state during the maintenance period (W12 through W48). Data for placebo pts are also included as a reference. Includes only pts with a baseline SES-CD ≥6 (≥4 for those with isolated ileal disease). Concentrations below the lowest quantifiable concentration were treated as zero in calculating the summary statistics. The average duration of the follow-up was similar across quartile subgroups. [b]Serum GUS concentration quartiles include data through W12 and are based on pts randomized to GUS 200 mg IV q4w in induction as follows: 1st quartile=5.34 µg/mL, 2nd quartile=17.2 µg/mL, 3rd quartile=31.44 µg/mL. [b]Trough concentration visits: W4 pre-administration, W8 pre-administration, and W12 (included to calculate average trough concentration regardless of GUS treatment at this visit). [c]Serum GUS concentration quartiles include data through W12 and are based on pts randomized to GUS 400 mg SC q4w in induction as follows: 1st quartile=8.85 µg/mL, 2nd quartile=12.07 µg/mL, 3rd quartile=16.08 µg/mL. [d]For GALAXI, includes pts who were in clinical response (as assessed by IWRS) to placebo after induction treatment. For GRAVITI, includes all placebo pts excluding data after a pt is rescued with GUS. [e]GALAXI serum GUS concentration quartiles include data from W12 to W48 and are based on pts randomized to GUS 200 mg IV q4w in induction as follows: 1st quartile=10.96 µg/mL, 2nd quartile=2.68 µg/mL, 3rd quartile=8.34 µg/mL. [f]GRAVITI serum GUS concentration quartiles include data from W12 to W48 and are based on pts randomized to GUS 400 mg SC q4w in induction as follows: 1st quartile=9.29 µg/mL, 2nd quartile=2.87 µg/mL, 3rd quartile=761 µg/mL. [g]Average steady-state trough concentrations were calculated based on the following visits: 1) weeks 24, 32, 40, and 48 for pts randomized to receive GUS 100 mg SC q8w; 2) weeks 20, 24, 28, 32, 36, 40, 44, and 48 for pts randomized to receive GUS 200 mg SC q4w. **AE**=adverse event, **GUS**=guselkumab, **IV**=intravenous, **IWRS**=Interactive Web Response System, **n**=number, **PK**=pharmacokinetic, **pts**=participants, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SAE**=serious adverse event, **SC**=subcutaneous, **SES-CD**=Simple Endoscopic Score for Crohn's Disease, **W**=week.*

PRESENTED AT: United European Gastroenterology (UEG) Week; October 4–7, 2025; Berlin, Germany. **REFERENCES: 1.** Sandborn WJ, et al. *Gastroenterology*. 2022;162(6):1650-64.e8. **2.** Panaccione R, et al. Efficacy and safety of guselkumab therapy in patients with moderately to severely active Crohn's disease: results of the GALAXI 2 & 3 phase 3 studies. *Gastroenterology*. 2024; 166 (5 Supplement):1057b. **3.** Hart A, et al. *Gastroenterology*. 2025;S0016-5085(25)00522-0. **ACKNOWLEDGMENTS:** Medical writing support was provided by Jen Ciarocchi, PhD, under the direction of the authors, in accordance with Good Publication Practice guidelines (*Ann Intern Med*. 2022;175:1298-1304). 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