Pharmacokinetics and Exposure-response Relationships of Guselkumab Intravenous or Subcutaneous Induction in Participants with Ulcerative Colitis

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Key Takeaways

- **Average serum guselkumab concentrations and exposure-response patterns were consistent after IV or SC induction**
- **These PK and exposure-response results underscore the observed clinical efficacy and support the use of either induction administration route in patients with moderately to severely active ulcerative colitis**

Background

Guselkumab, a dual-acting interleukin-23p19 subunit inhibitor, is approved for the treatment of ulcerative colitis (UC), with an intravenous (IV) or subcutaneous (SC) induction regimen followed by a SC maintenance regimen

The guselkumab clinical development program in participants with moderately to severely active UC consisted of the phase 2b/3 QUASAR studies (IV induction: 200 mg every 4 weeks [q4w] at weeks 0, 4, and 8; SC maintenance: 100 mg every 8 weeks [q8w] or 200 mg q4w) and the phase 3 ASTRO study (SC induction: 400 mg q4w at weeks 0, 4, and 8; SC maintenance: same regimens as QUASAR)

- All studies had randomized, double-blind, placebo-controlled, parallel group designs

Based on an estimated 50% bioavailability of SC administered guselkumab, the 400 mg SC q4w induction dose was expected to provide similar exposure and non-inferior trough concentrations compared with the 200 mg IV q4w induction dose

Objective

To evaluate the pharmacokinetics (PK) and exposure-response of IV and SC guselkumab induction in participants with moderately to severely active UC

Methods

Analyses to compare guselkumab PK exposure after 200 mg IV versus 400 mg SC induction through week 12

- Individual post-hoc PK parameter values and participant dosing information from QUASAR and ASTRO were used to simulate concentration-time profiles and calculate individual induction exposure metrics
  - Post-hoc PK parameter values were estimated with the established QUASAR 2-compartment linear population PK model with first-order absorption and first-order elimination
  - Individual induction exposure metrics include $C_{max,\ week\ 8}$, $C_{ave,\ week\ 0–12}$, $C_{trough,\ week\ 12}$, and $AUC_{week\ 0–12}$
- Comparative graphical exposure-response analysis (QUASAR versus ASTRO) was conducted for key week 12 efficacy outcomes according to the overall exposure ($C_{ave,\ week\ 0–12}$) quartiles from the combined study populations

Week 12 Efficacy Endpoints in the Exposure-response Analysis

Clinical remission (primary endpoint)	• A stool frequency subscore of 0 or 1 (with no increase from baseline), a rectal bleeding subscore of 0, and an endoscopic subscore of 0 or 1 with no friability
Clinical response	• A ≥30% reduction and a ≥2-point decrease from baseline in the modified Mayo score, with either a ≥1-point decrease in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1
Endoscopic improvement	• An endoscopic subscore of 0 or 1 with no friability
Histologic-endoscopic mucosal improvement	• A combination of histologic healing and endoscopic improvement, where histologic healing is defined as neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system

Clinical remission, clinical response, and endoscopic improvement are based on the modified Mayo score, which consists of three components—the stool frequency, rectal bleeding, and endoscopic subscores.

***$AUC_{week\ 0–12}$**=area under the concentration-time curve from week 0 to week 12 (induction), **$C_{ave,\ week\ 0–12}$**=average concentration from week 0 to week 12 (induction), **$C_{max,\ week\ 8}$**=maximum concentration at week 8, **$C_{trough,\ week\ 12}$**=trough concentration at week 12, **IV**=intravenous, **PK**=pharmacokinetics, **SC**=subcutaneous.*

Results

Consistent with model predictions, SC induction resulted in similar average concentrations (week 0–week 12), similar area under the concentration-time curves (week 0–week 12), lower peak concentrations (at week 8), and higher trough concentrations (at week 12) compared with the PK parameters of IV induction

Comparison of Model-predicted Guselkumab PK Exposures Following 200 mg IV q4w and 400 mg SC q4w Induction Dose Regimens

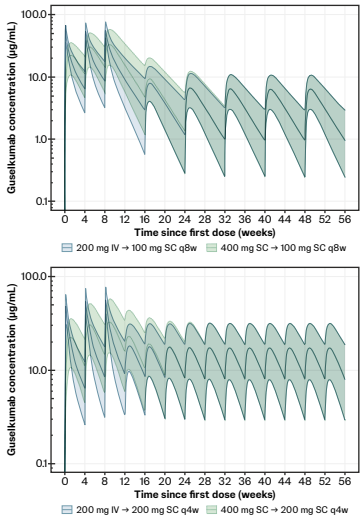
		GUS 200 mg IV q4w (N=644)	GUS 400 mg SC q4w (N=331)
	$C_{max,\ week\ 8}$ (µg/mL)		
	Mean (SD)	68.9 (14.1)	28.8 (8.8)
	Geometric mean (95% CI)	67.5 (66.5–68.6)	27.3 (26.3–28.3)
	Median (range)	67.6 (39.9–134)	28.3 (7.6–59.7)
	$C_{ave,\ week\ 0–12}$ (µg/mL)		
	Mean (SD)	21.1 (5.8)	19.0 (6.1)
	Geometric mean (95% CI)	20.3 (19.9–20.8)	17.9 (17.2–18.6)
	Median (range)	20.5 (7.6–46.4)	18.6 (3.9–40.5)
	$C_{trough,\ week\ 12}$ (µg/mL)		
	Mean (SD)	9.9 (5.0)	14.1 (6.3)
	Geometric mean (95% CI)	8.6 (8.3–9.0)	12.6 (11.9–13.3)
	Median (range)	9.1 (0.8–32.8)	13.5 (0.9–38.4)
	$AUC_{week\ 0–12}$ (day µg/mL)		
	Mean (SD)	1770 (487)	1590 (515)
	Geometric mean (95% CI)	1710 (1670–1740)	1500 (1450–1560)
	Median (range)	1720 (638–3900)	1560 (324–3400)

***$AUC_{week\ 0–12}$**=area under the concentration-time curve from week 0 to week 12 (induction), **$C_{ave,\ week\ 0–12}$**=average concentration from week 0 to week 12 (induction), **CI**=confidence interval, **$C_{max,\ week\ 8}$**=maximum concentration at week 8, **$C_{trough,\ week\ 12}$**=trough concentration at week 12, **GUS**=guselkumab, **IV**=intravenous, **PK**=pharmacokinetics, **q4w**=every 4 weeks, **SC**=subcutaneous, **SD**=standard deviation.*

Guselkumab steady-state concentration was reached by week 24 regardless of induction route (IV or SC)

- Population PK model-based simulations showed that serum guselkumab concentrations were comparable by week 24 after the same maintenance dose regimen, regardless of induction route

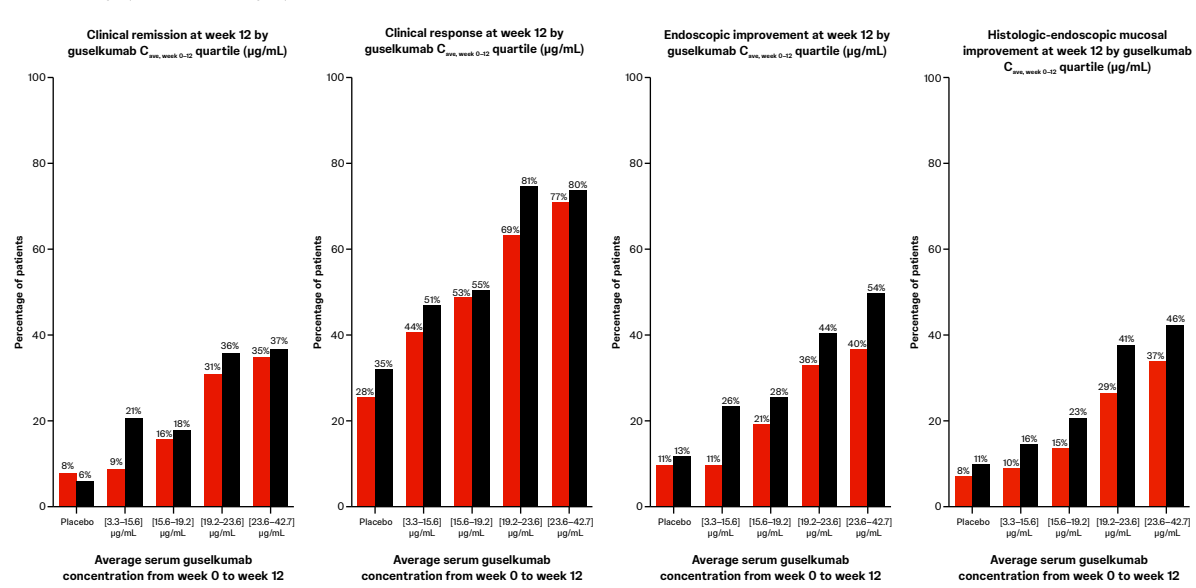
Simulated Guselkumab PK Profiles Comparing 200 mg IV q4w x 3 and 400 mg SC q4w x 3 Induction Followed by 100 mg SC q8w or 200 mg SC q4w Maintenance Therapy



The solid line represents the median and the shaded area represents the 90% prediction interval.
***IV**=intravenous, **PK**=pharmacokinetics, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous.*

Key efficacy outcomes at week 12 were comparable or numerically higher within the same guselkumab concentration quartiles following SC versus IV induction

Week 12 Efficacy Endpoints by Average Serum Guselkumab Concentration Quartiles in QUASAR (200 mg IV q4w) and ASTRO (400 mg SC q4w)



*$C_{ave,\ week\ 0–12}$=average concentration from week 0 to week 12 (induction), **IV**=intravenous, **q4w**=every 4 weeks, **SC**=subcutaneous.*

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