

Pharmacokinetics and Exposure-Response Relationships of Subcutaneous Guselkumab Maintenance in Participants with Moderately to Severely Active Ulcerative Colitis

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Background

Guselkumab (GUS), a dual-acting IL-23p19 subunit inhibitor, is approved for ulcerative colitis (UC) with either intravenous (IV) or subcutaneous (SC) induction and SC maintenance

Average serum GUS concentrations and efficacy at week 12 were comparable following IV or SC induction in the Phase 2/3 QUASAR and Phase 3 ASTRO studies in participants with moderately to severely active UC

Two GUS maintenance doses are approved for UC: 100 mg every 8 weeks (q8w) and 200 mg every 4 weeks (q4w); however, the pharmacokinetic (PK) parameters related to maintenance dose efficacy have not been reported

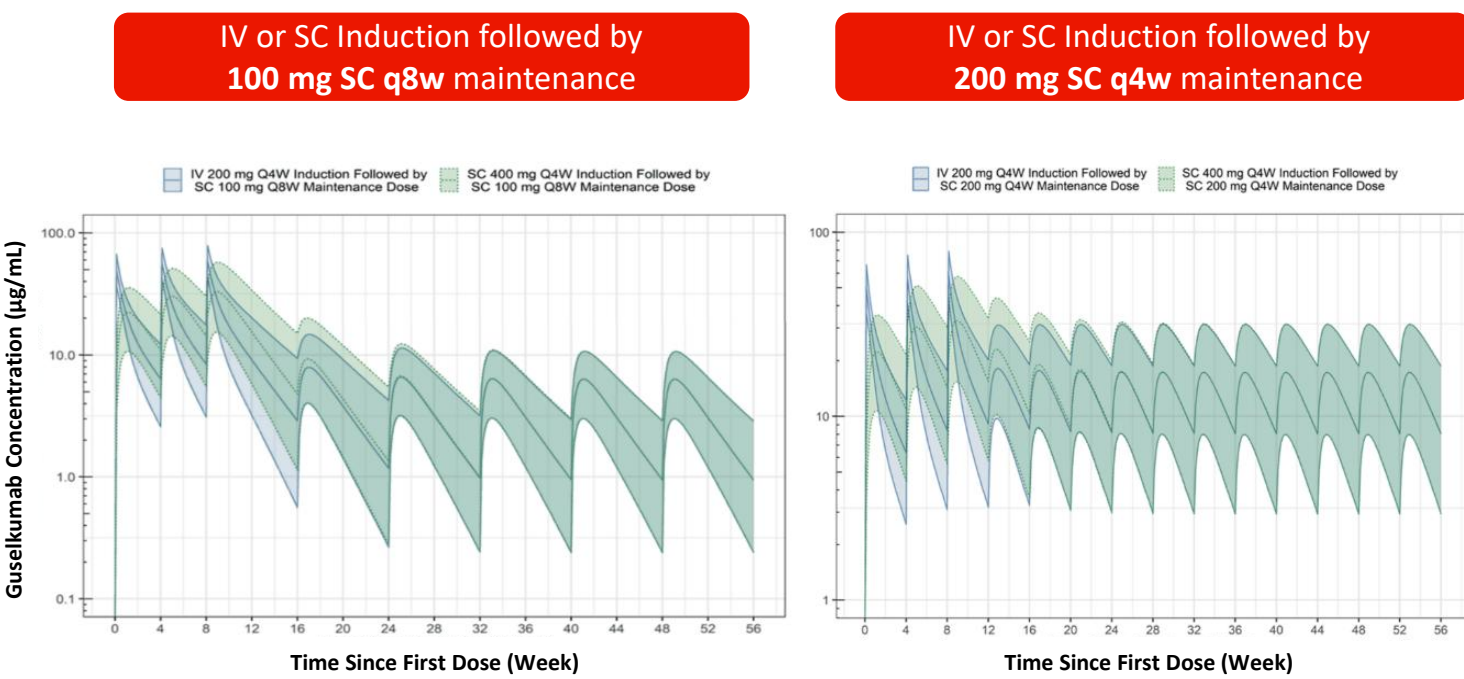
Objective

Here, we evaluated covariate impacts on PK and exposure-response (E-R) of GUS SC maintenance regimens (100 mg every q8w or 200 mg q4w) using pooled data from the QUASAR and ASTRO studies

Results

Maintenance concentrations within each dose were similar regardless of induction route, with steady state achieved by week 24

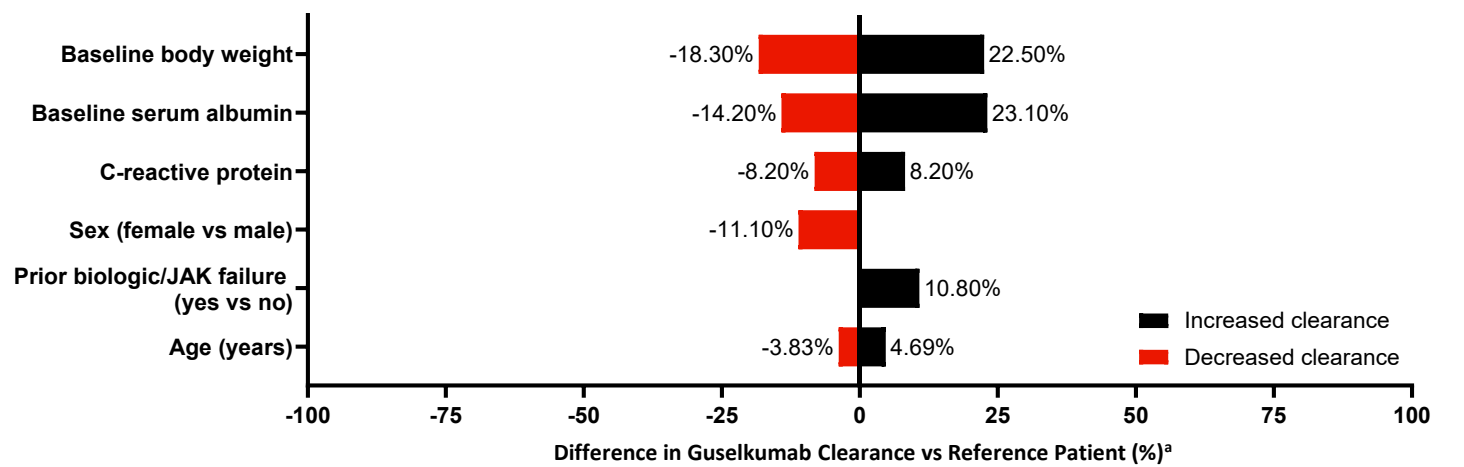
- Overall, the 2 maintenance dose regimens (100 mg SC q8w and 200 mg SC q4w) provide a 4-fold dose range and an approximately 8-fold range of steady-state trough concentrations



Simulated guselkumab PK profiles comparing 200 mg IV q4w and 400 mg IV q4w induction followed by 100 mg SC q8w (left) or 200 mg SC q4w (right) maintenance therapy. The solid line represents the median and the shaded area represents the 90% prediction interval.
IV=intravenous, PK=pharmacokinetic, q4w=every 4 weeks, q8w=every 8 weeks, SC=subcutaneous.

Covariate effects were modest relative to exposure differences between maintenance regimens, and were insufficient to justify covariate-adjusted dosing, supporting the use of fixed doses

- Patients who require higher exposure may further benefit from the 200 mg q4w dose



*The magnitude of change in the parameter estimate caused by a continuous covariate was expressed as a range, i.e., % change from the median value when the covariate factor varied from the 5th percentile to the 95th percentile of the population.
 $CL_{(50)} = 0.312 \times \left(\frac{BW}{70} \right)^{0.738} \times \left(\frac{ALB}{4.1} \right)^{-1.17} \times \left(\frac{CRP}{0.28} \right)^{0.0365} \times \left(\frac{AGE}{35} \right)^{-0.0741} \times (1.108)^{JAK} \times (0.889)^{PFX}$
ALB=albumin, BW=body weight, CL=clearance of the central compartment, CRP=C-reactive protein, JAK=Janus kinase, PK=pharmacokinetics, q4w=every 4 weeks.

Methods

- QUASAR and ASTRO had similar eligibility criteria and baseline patient characteristics, and evaluated the same maintenance regimens (100 mg SC q8w or 200 mg SC q4w); induction was administered as 200 mg IV in QUASAR and 400 mg SC in ASTRO

- Participants had a modified Mayo score of 5–9 at induction baseline (BL), a Mayo endoscopic subscore ≥ 2 per central review, had received ≥ 1 GUS dose, and had ≥ 1 PK measurement

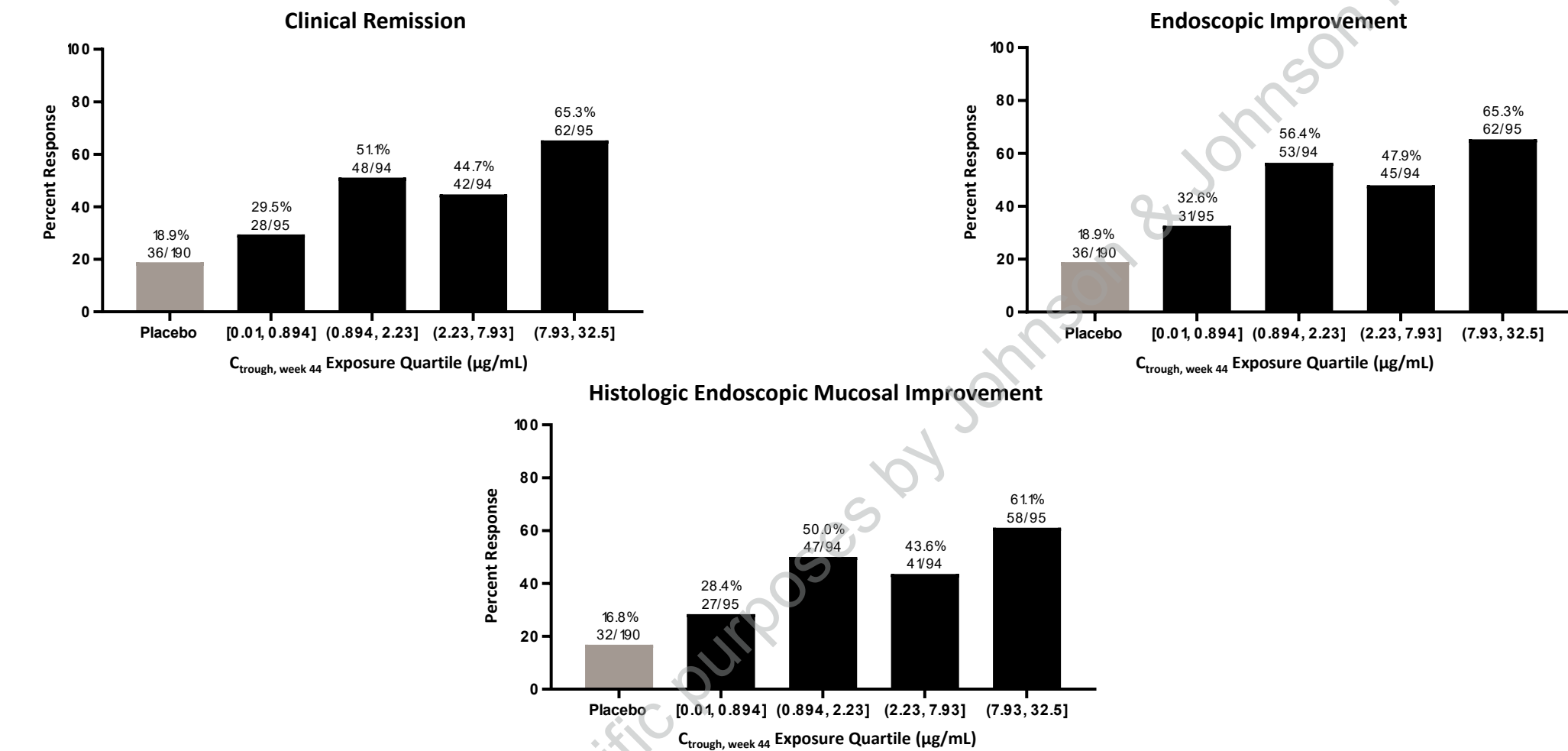
- Model-predicted steady-state trough concentrations ($C_{trough, week 24}$) in QUASAR and ASTRO were compared between treatment groups; medians and 95% prediction intervals of the simulated GUS concentration-time profiles were graphically compared

- Population PK modeling for parameter estimates, using a 2-compartment linear PK model with first-order absorption and elimination, was performed using pooled QUASAR PK data through maintenance week 44 (M-44)

- E-R efficacy relationships (clinical remission, endoscopic improvement, histologic-endoscopic mucosal improvement [HEMI]) at week M-44 were explored descriptively and via modeling

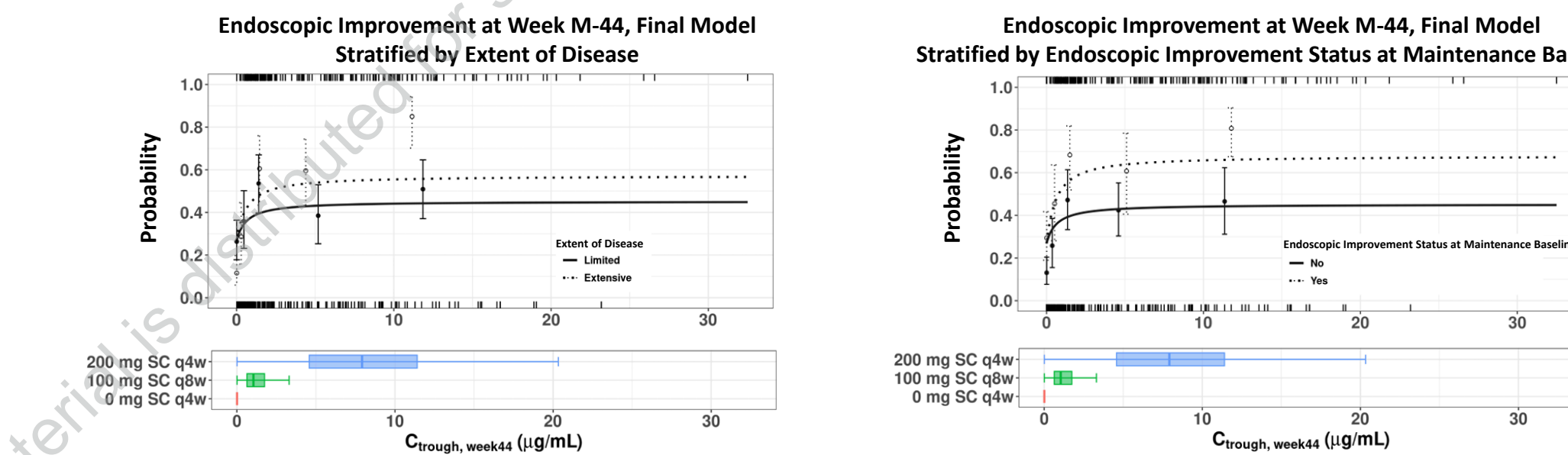
- Associations between exposure and safety (infections, serious infections, serious adverse events, and abnormal liver function tests), covariate impacts on E-R, and immunogenicity impacts on efficacy and safety were also analyzed

E-R analyses showed that higher serum GUS concentrations during maintenance were associated with greater efficacy at week M-44 regardless of clearance or half-life, suggesting that some participants may benefit from higher exposure



Proportion of participants with clinical remission, endoscopic improvement, and histologic-endoscopic mucosal improvement at week M-44 by serum guselkumab $C_{trough, week 44}$ quartiles.
 $C_{trough, week 44}$ =serum trough concentration, week M-44=maintenance week 44.

Exposures for both GUS maintenance dose regimens were associated with substantial efficacy for most participants; 200 mg SC q4w exposures were at the plateau of the E-R curves, suggesting that maximal response is more likely to be achieved with this regimen



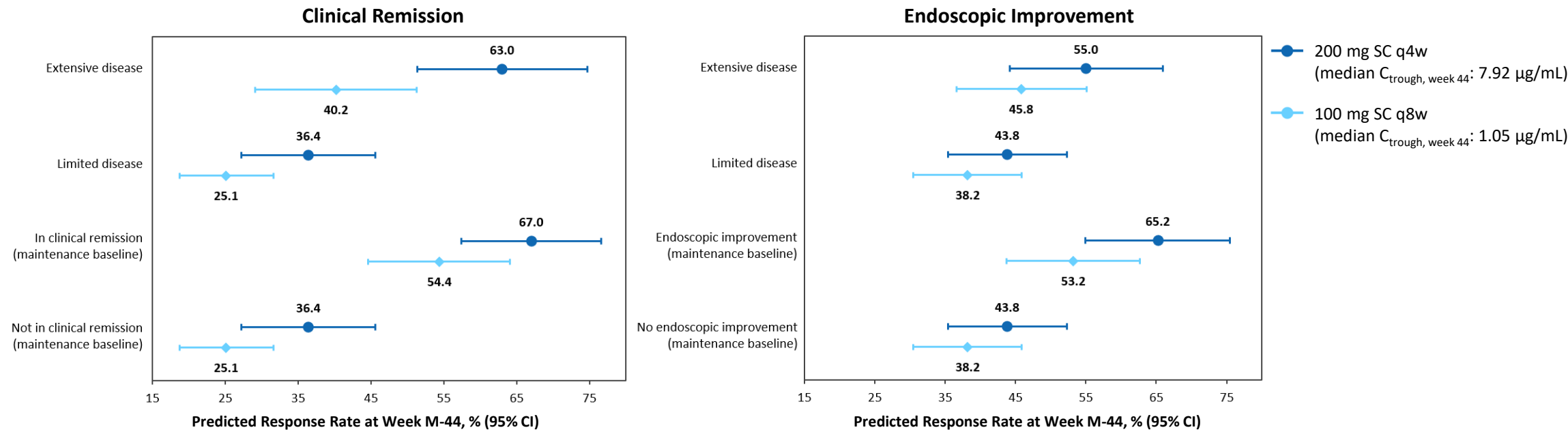
Model-predicted E-R relationships for endoscopic improvement at week 48 using $C_{trough, week 44}$ as the PK exposure metric in participants with ulcerative colitis, stratified by extent of disease and endoscopic improvement status at maintenance baseline.
 $C_{trough, week 44}$ =trough concentration at week 44, E-R=exposure-response, GUS=guselkumab, q4w=every 4 weeks, q8w=every 8 weeks, SC=subcutaneous.

Clinical and endoscopic outcome definitions

- Clinical remission**
 - A stool frequency subscore of 0 or 1 (with no increase from induction baseline), a rectal bleeding subscore of 0, and an endoscopic subscore of 0 or 1 with no friability present on the endoscopy
- Endoscopic improvement**
 - An endoscopic subscore of 0 or 1 with no friability present on the endoscopy
- HEMI**
 - A combination of histologic improvement and endoscopic improvement, where histologic improvement was defined as neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system

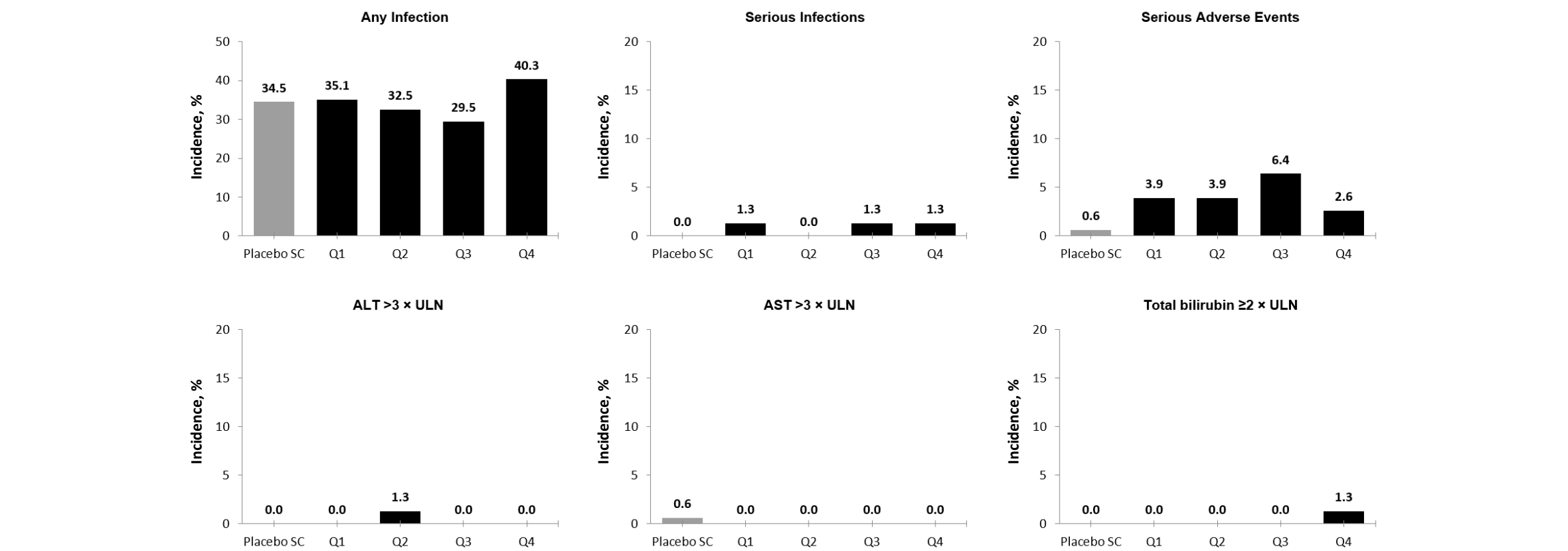
HEMI=histologic-endoscopic mucosal improvement.

Participants with extensive UC at induction BL showed a greater treatment effect with 200 mg q4w vs 100 mg SC q8w maintenance



Model predicted clinical remission and endoscopic improvement rates at week M-44 by median $C_{trough, week 44}$ in each of the subcutaneous maintenance treatment groups, stratified by extent of disease at induction baseline and clinical remission or endoscopic improvement status at maintenance baseline.
CI=confidence interval, $C_{trough, week 44}$ =serum trough concentration, SC=subcutaneous, q4w=every 4 weeks, q8w=every 8 weeks, week M-44=maintenance week 44.

No associations were found between GUS concentrations and infections, serious infections, serious adverse events, or abnormal liver function tests



Includes only participants with a modified Mayo score of 5–9 at induction baseline. Quartiles are based on participants in GUS 100 mg SC q8w and 200 mg SC q4w treatment groups as follows: Q1<1.22 µg/mL, Q2=1.22–3.82 µg/mL, Q3=3.82–9.49 µg/mL, Q4=9.49 µg/mL.
ALT=alanine transaminase, AST=aspartate aminotransferase, GUS=guselkumab, Q=quartile, q4w=every 4 weeks, q8w=every 8 weeks, ULN=upper limit of normal, SC=subcutaneous.

- Immunosuppressant (AZA, 6-MP, MTX) use did not impact GUS concentrations (data not shown)

- Among participants receiving GUS, the incidence of anti-drug antibodies (11.6%) and neutralizing antibodies (1.8%) to GUS was low and not associated with GUS PK, efficacy, or safety

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