

Pharmacokinetics and Exposure-Response Relationships of Subcutaneous Guselkumab Maintenance in Participants With Moderately to Severely Active Crohn’s Disease

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Background

Guselkumab (GUS), a dual-acting IL-23p19 subunit inhibitor, is efficacious in patients with Crohn’s disease (CD) after intravenous (IV) or subcutaneous (SC) induction and SC maintenance

In the phase 2/3 GALAXI and phase 3 GRAVITI studies in participants with moderate to severe CD, average serum GUS concentrations following IV or SC induction were similar through week (W)12 and similar efficacy was observed

Objective

Here, we evaluated the pharmacokinetics (PK) and exposure-response (E-R) of GUS following SC maintenance regimens (100 mg every 8 weeks [q8w] or 200 mg every 4 weeks [q4w]) using data from GALAXI and GRAVITI

Methods

- The GALAXI and GRAVITI studies had treat-through designs, 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 GALAXI and 400 mg SC in GRAVITI
- Population PK modeling (2-compartment linear PK model with first-order absorption and first-order elimination) was performed on pooled GALAXI (through W48) and GRAVITI (through W24) PK data
- E-R efficacy relationships at W48 and covariate impacts were explored descriptively and via modeling
- Associations between exposure and safety outcomes (infections, serious infections, serious adverse events, and abnormal liver function tests) were also investigated
- Analyzed participants had received ≥ 1 GUS dose and had a Simple Endoscopic Score for CD (SES-CD) ≥ 6 (or ≥ 4 for participants with isolated ileal CD) and ≥ 1 post-baseline (BL) PK value

Clinical and endoscopic outcome definitions

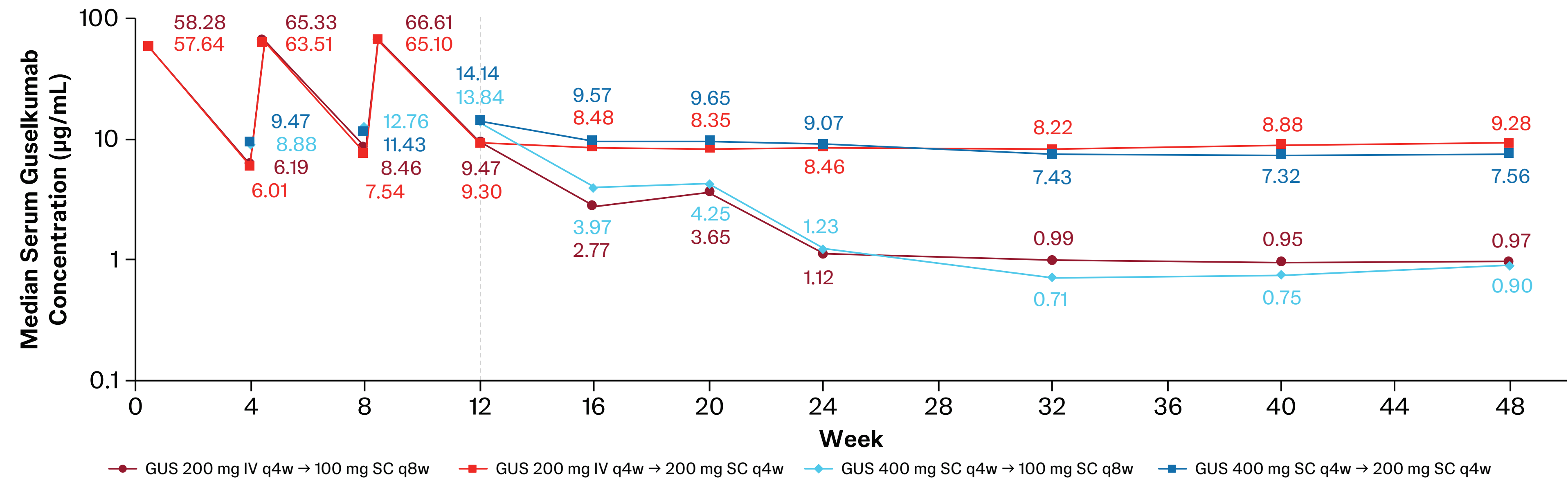
- Clinical remission**
 - CDAI score <150
- Endoscopic response**
 - GALAXI: $\geq 50\%$ improvement from baseline in SES-CD or SES-CD ≤ 2
 - GRAVITI: $\geq 50\%$ improvement from baseline in SES-CD

CDAI=Crohn’s Disease Activity Index, SES-CD=Simple Endoscopic Score for Crohn’s Disease.

Results

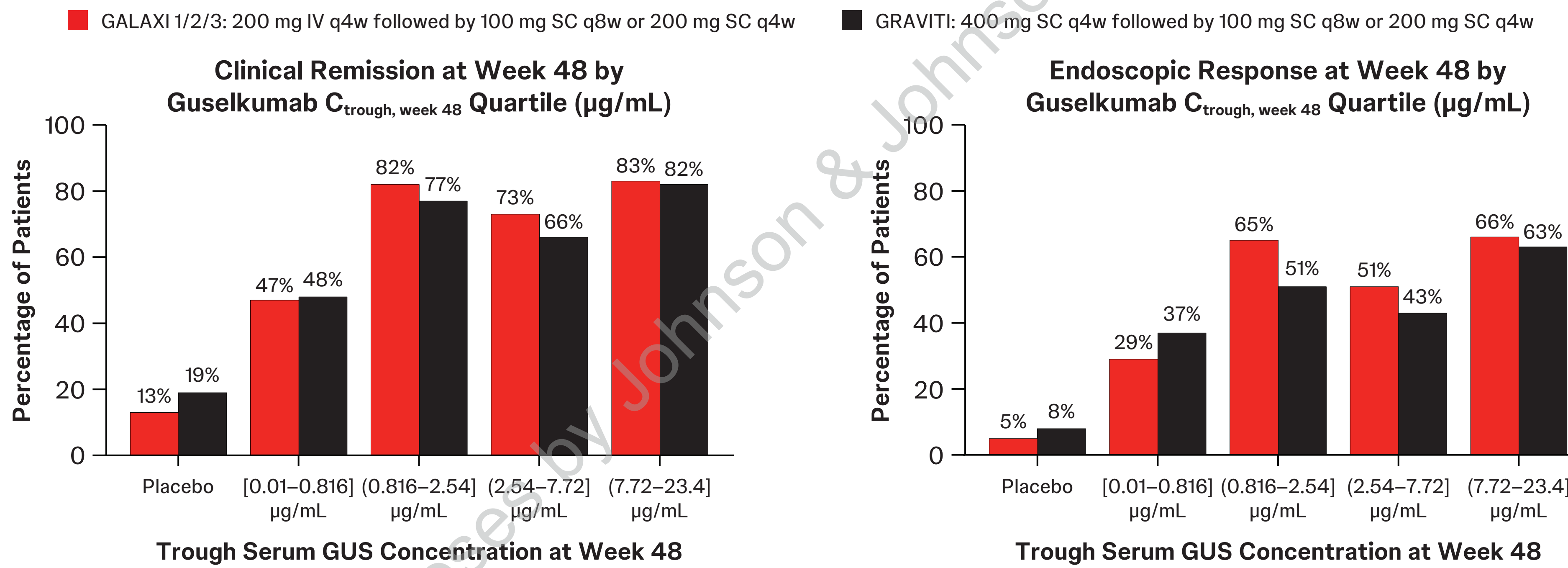
Median GUS concentrations converged following initiation of SC maintenance dosing, with similar concentrations within each maintenance dose group regardless of IV or SC induction; steady state was reached by approximately W24

- 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



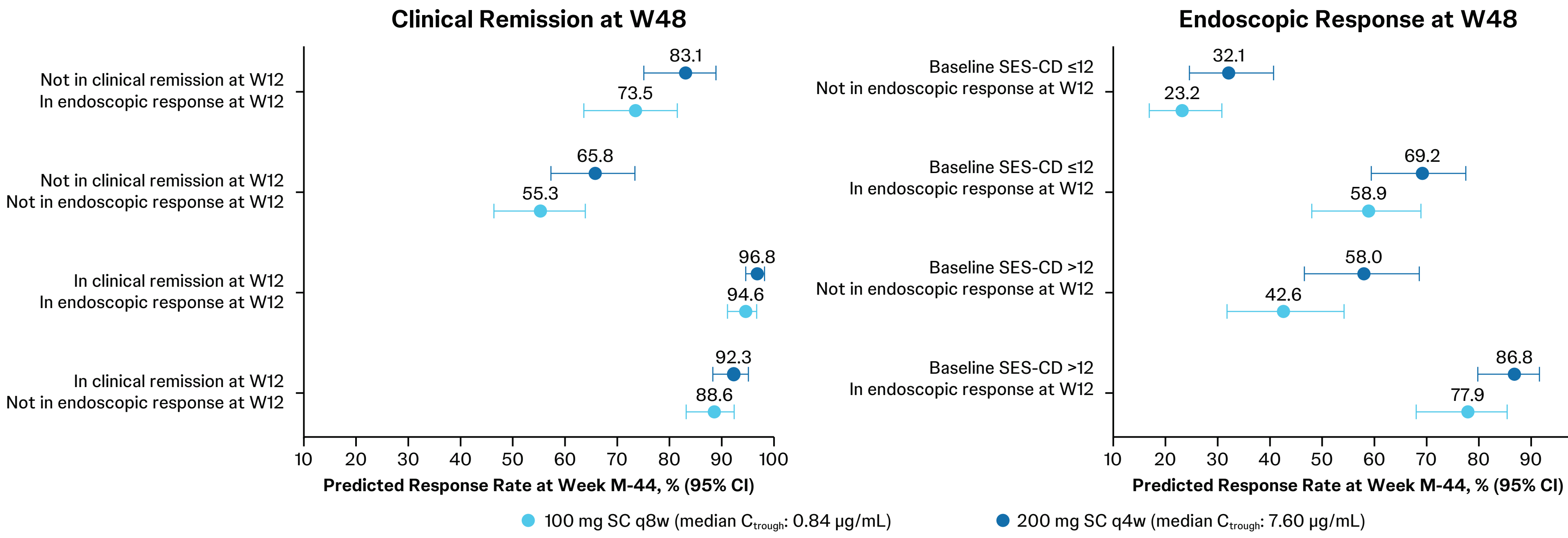
Postinduction concentrations for the IV induction doses are shown at weeks 0, 4, and 8; all other values are predose (trough) concentrations. Maintenance dosing starts at week 12 for 200 mg q4w and at week 16 for 100 mg q8w. Concentrations are plotted on a logarithmic scale. GUS=guselkumab, IV=intravenous, q4w=every 4 weeks, q8w=every 8 weeks, SC=subcutaneous.

Positive E-R trends were observed between steady-state guselkumab concentration and W48 efficacy (clinical remission and endoscopic response) and remained after accounting for clearance or half-life



Exposure-response trends at week 48 during maintenance treatment. Response rate was calculated based on model-predicted median C_{trough, week 48} which is 0.84 µg/mL for the 100 mg SC q8w regimen and 7.60 µg/mL for the 200 mg SC q4w regimen. C_{trough, week 48}=trough concentration at week 48. GUS=guselkumab, IV=intravenous, SC=subcutaneous.

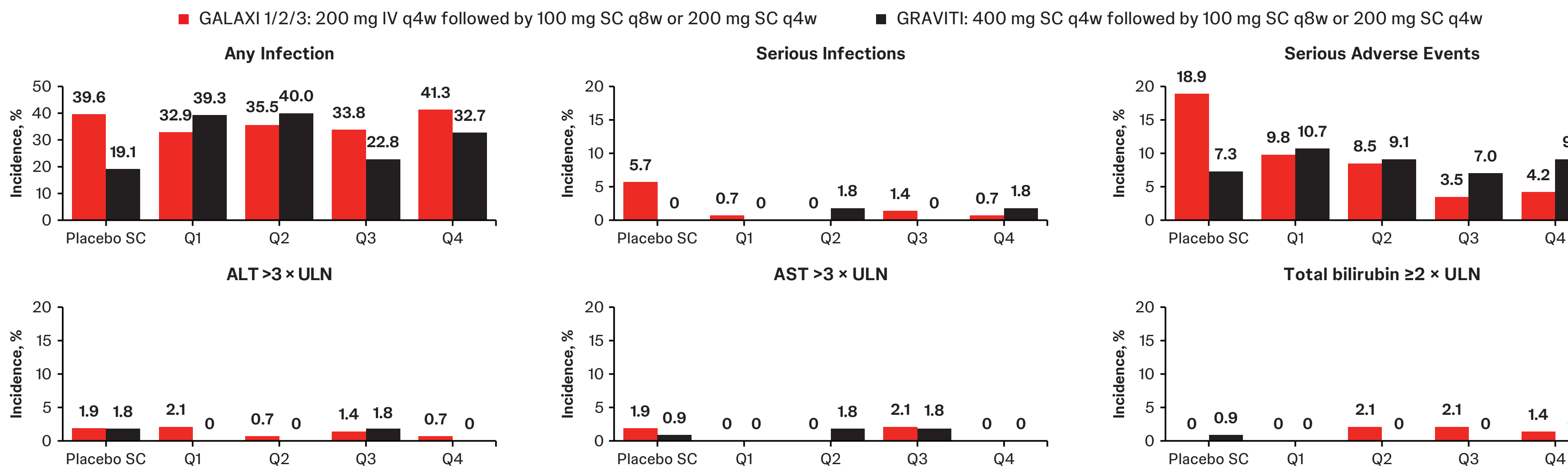
In the E-R model, participants who had not achieved clinical remission by W12, and those with a baseline SES-CD >12 who had not achieved an endoscopic response by W12, were more likely to achieve W48 outcomes when treated with the 200 mg maintenance regimen compared with the 100 mg maintenance regimen



Model-predicted week 48 response rates for SC maintenance treatment groups, stratified by covariates. Response rate was calculated based on model-predicted median C_{trough, week 48} which is 0.84 µg/mL for the 100 mg SC q8w regimen and 7.60 µg/mL for the 200 mg SC q4w regimen. C_{trough, week 48}=trough concentration at week 48. GUS=guselkumab, IV=intravenous, SC=subcutaneous.

No associations between guselkumab concentrations and infections, serious infections, serious adverse events, or liver function tests were observed

- Immunosuppressants did not impact guselkumab concentrations (data not shown)



The PK analysis set includes participants 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 participants are also included as a reference. Incidence only participants with a baseline SES-CD ≤ 4 (or ≤ 2 for those with isolated ileal disease). Concentrations below the lowest quantifiable concentration were treated as zero in calculating the summary statistics. For GALAXI, includes participants who were in clinical response (as assessed by IRRS) to placebo after induction treatment. For GRAVITI, includes all placebo participants excluding data after a participant was rescued with GUS. GALAXI serum GUS concentration quartiles include data from W12 to W48 and are based on participants randomized to GUS 200 mg IV q4w in induction as follows: Q1= <0.816 µg/mL, Q2= ≥ 0.816 – <2.54 µg/mL, Q3= ≥ 2.54 – <7.72 µg/mL, Q4= ≥ 7.72 µg/mL. GRAVITI serum GUS concentration quartiles include data from W12 to W48 and are based on participants randomized to GUS 400 mg SC q4w in induction as follows: Q1= <0.816 µg/mL, Q2= ≥ 0.816 – <2.54 µg/mL, Q3= ≥ 2.54 – <7.72 µg/mL, Q4= ≥ 7.72 µg/mL. Average steady-state trough concentrations were calculated based on the following visits: 1) weeks 24, 32, 40, and 48 for participants randomized to receive GUS 100 mg SC q8w; 2) weeks 20, 24, 28, 32, 36, 40, 44, and 48 for participants randomized to receive GUS 200 mg SC q4w. GUS=guselkumab, ALT=alanine transaminase, AST=aspartate aminotransferase, IV=intravenous, IRRS=Interactive Web Response System, PK=pharmacokinetic, q4w=every 4 weeks, q8w=every 8 weeks, SC=subcutaneous, SES-CD=Simple Endoscopic Score for Crohn’s Disease, W=week.