

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

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October 20, 2026, Barcelona, Spain



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Disclosure of Conflicts of Interest

I herewith declare the following paid or unpaid consultancies, business interests, or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

Research grants from AbbVie GK, Boston Scientific Corporation, EA Pharma Co. Ltd., JIMRO Co. Ltd., Kissei Pharmaceutical Co. Ltd., Kyorin Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Mochida Pharmaceutical Co. Ltd., Nippon Kayaku Co. Ltd., Pfizer Inc., Takeda Pharmaceutical Co. Ltd., and Zeria Pharmaceutical Co. Ltd.; consulting fees from AbbVie GK, Abivax, Bristol Myers Squibb, EA Pharma Co. Ltd., Gilead Sciences, Johnson & Johnson, Lilly, Mitsubishi Tanabe Pharma Corporation, and Pfizer Inc.; and lecture fees from AbbVie GK, EA Pharma Co. Ltd., Johnson & Johnson, JIMRO Co., Kissei Pharmaceutical Co. Ltd., Kyorin Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Mochida Pharmaceutical Co., Ltd., Pfizer Inc., and Takeda Pharmaceutical Co. Ltd.

Background



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



Average serum guselkumab 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 moderate to severely active UC



Two guselkumab 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

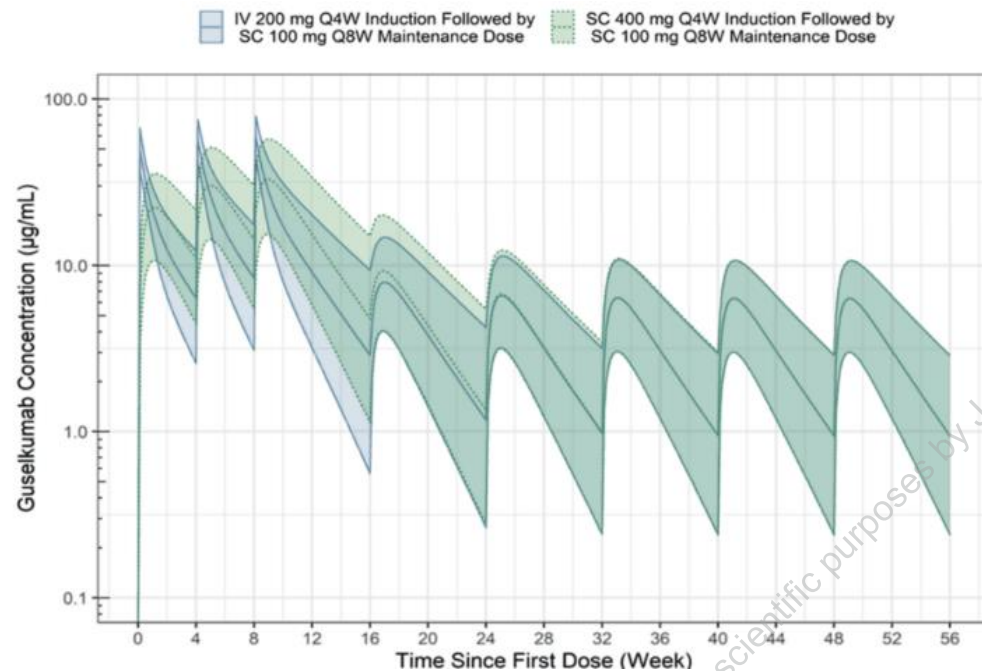


Here, we evaluated covariate impacts on PK and exposure-response (E-R) of guselkumab SC maintenance regimens (100 mg q8w or 200 mg q4w) using pooled data from the QUASAR and ASTRO studies

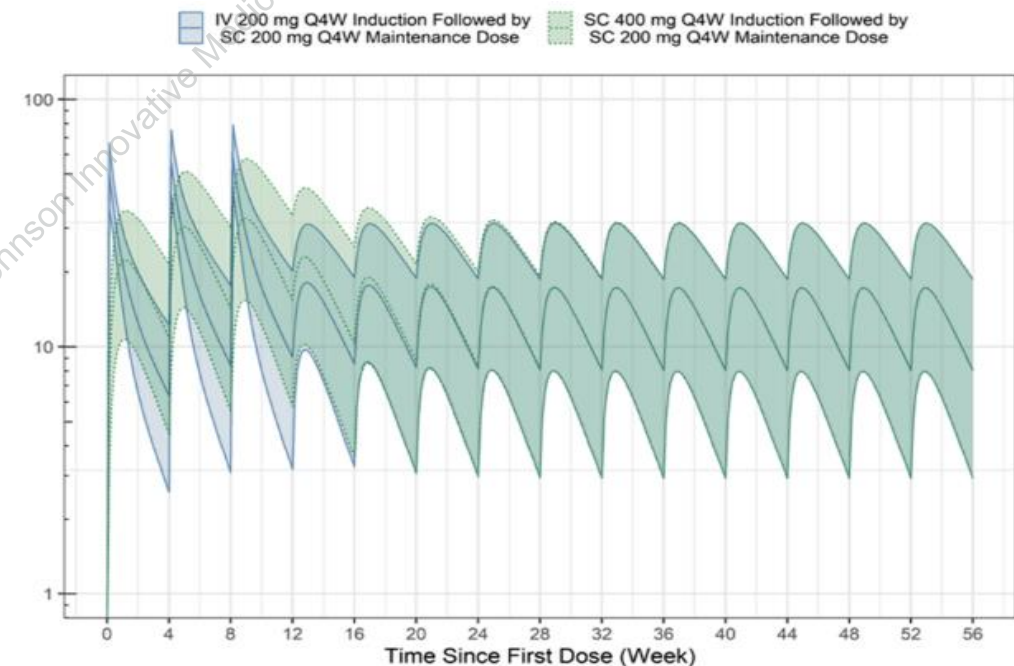
Simulated Pharmacokinetic Profiles

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

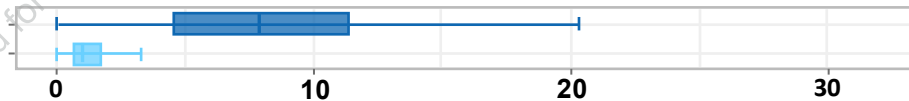
IV or SC Induction followed by
100 mg SC q8w maintenance



IV or SC Induction followed by
200 mg SC q4w maintenance



200 mg SC q4w
100 mg SC q8w



C_{trough, week 44} (µg/mL)

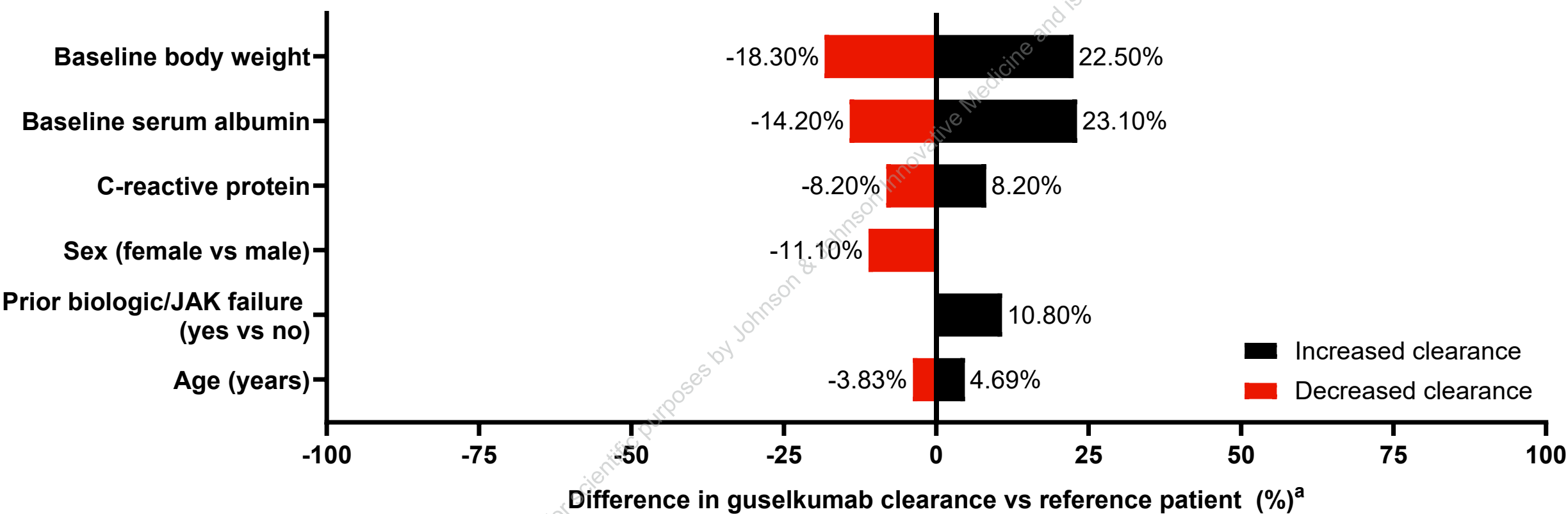
The 2 maintenance regimens provide a 4-fold dose range,
which results in an ~8-fold range in steady-state trough concentrations

The solid line represents the median and the shaded area represents the 90% prediction interval.

C_{trough}=serum trough concentration, IV=intravenous, PK=pharmacokinetic, q4w=every 4 weeks, q8w=every 8 weeks, SC=subcutaneous.

Parameter Estimates in the Population PK Model

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



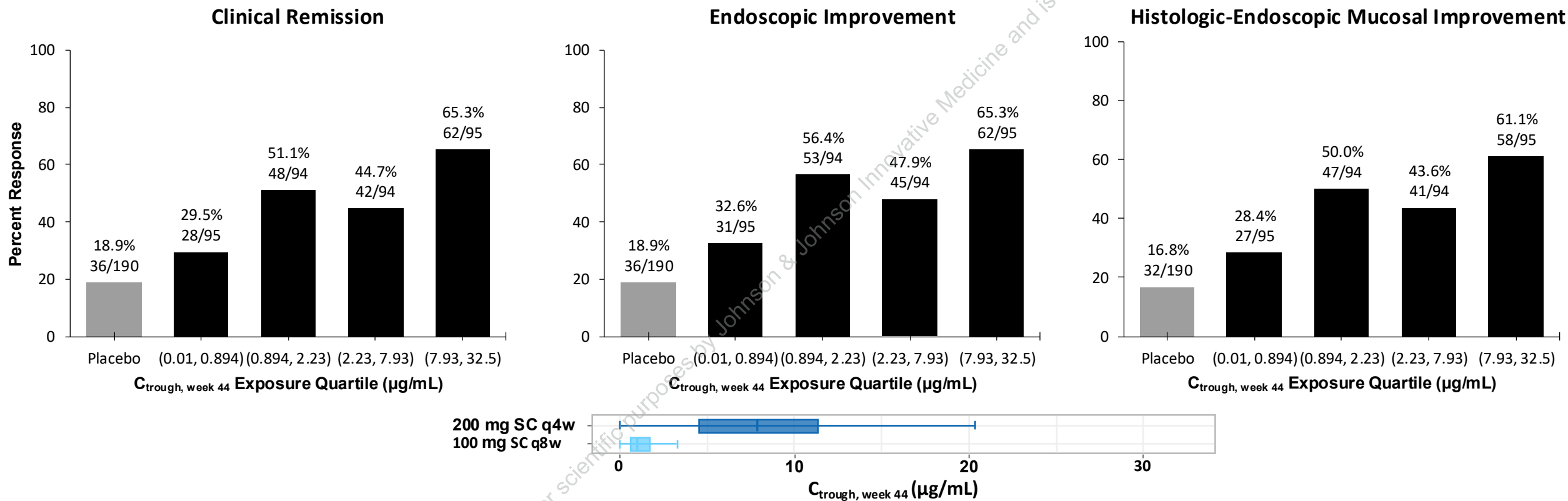
Patients who require higher exposure may benefit from the 200 mg q4w dose

^aThe 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 (red) to the 95th percentile (black) of the population.

$$CL \left(\frac{L}{day} \right) = 0.312 \times \left(\frac{BWT}{70} \right)^{0.538} \times \left(\frac{ALB}{43} \right)^{-1.17} \times \left(\frac{CRP}{4.28} \right)^{0.0365} \times \left(\frac{AGE}{39} \right)^{-0.0741} \times (1.108)^{FBIO} \times (0.889)^{SEX}.$$

ALB=albumin, BWT=body weight, CL=clearance of the central compartment, CRP=C-reactive protein, FBIO=biologic failure status (0=not failure, 1=failure), JAK=Janus kinase, PK=pharmacokinetics, q4w=every 4 weeks.

Guselkumab Exposure-Response at Week M-44

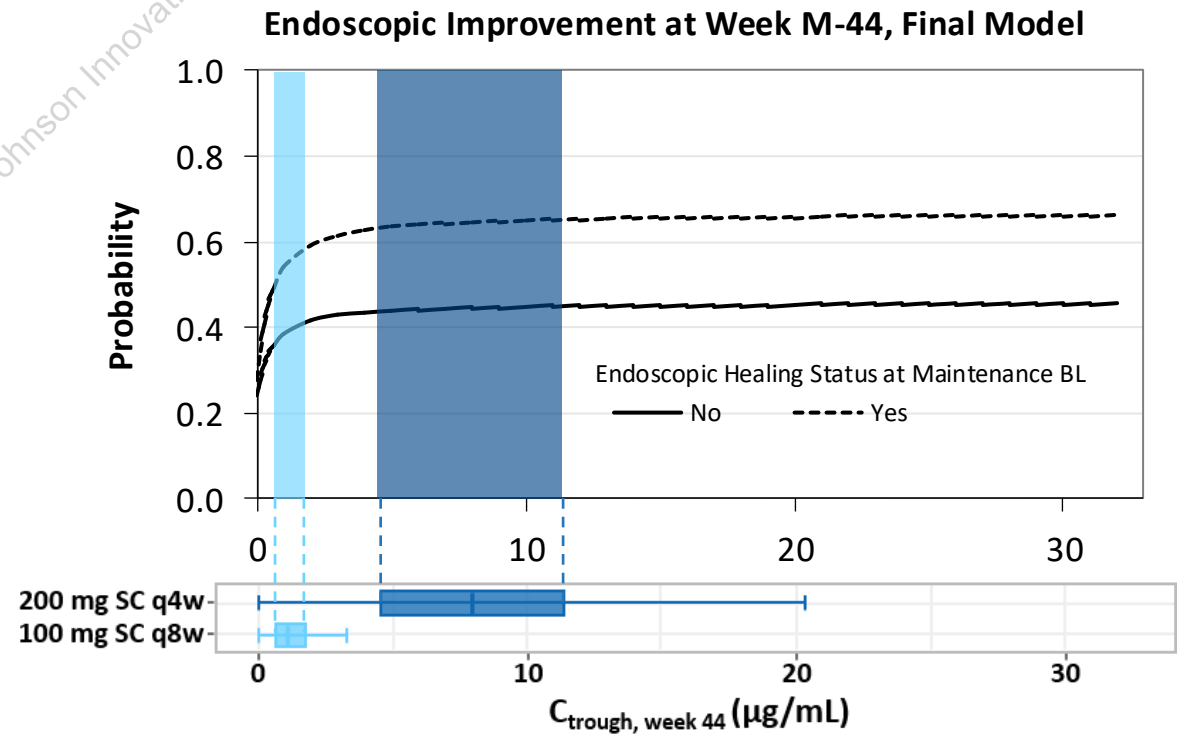
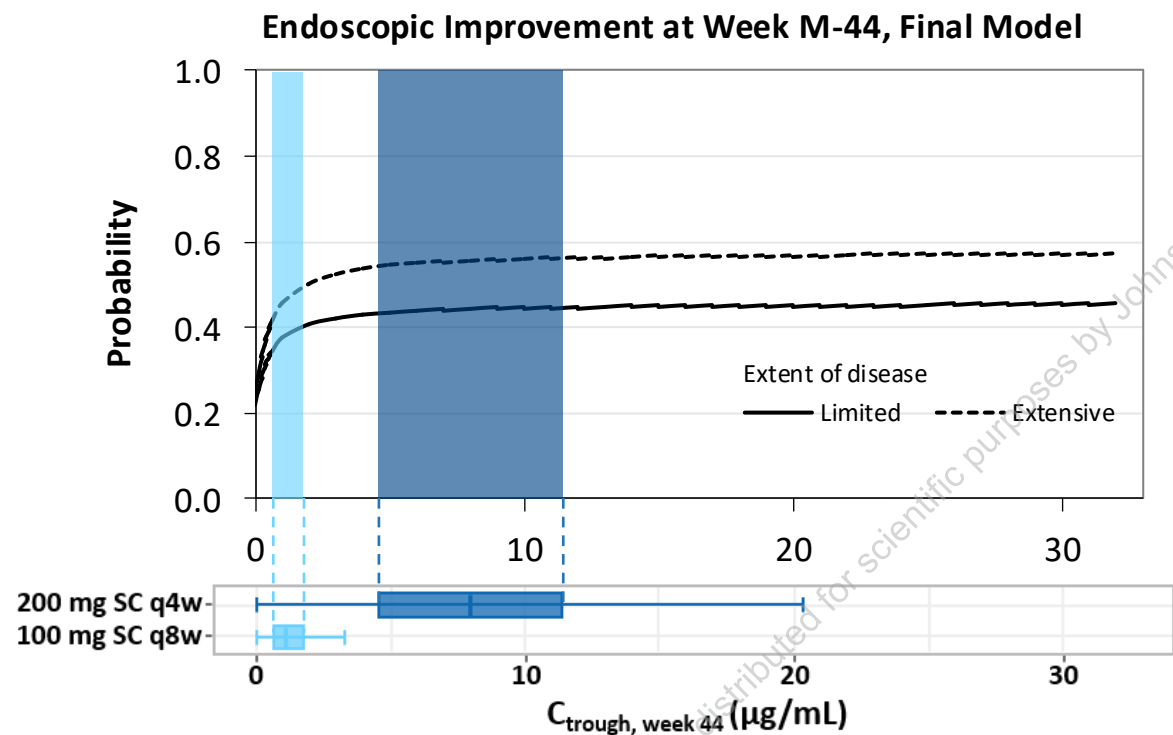


E-R analyses showed that higher serum GUS concentrations during maintenance were associated with greater efficacy at Week M-44 regardless of clearance or half-life, suggesting that some participants may benefit from higher exposure

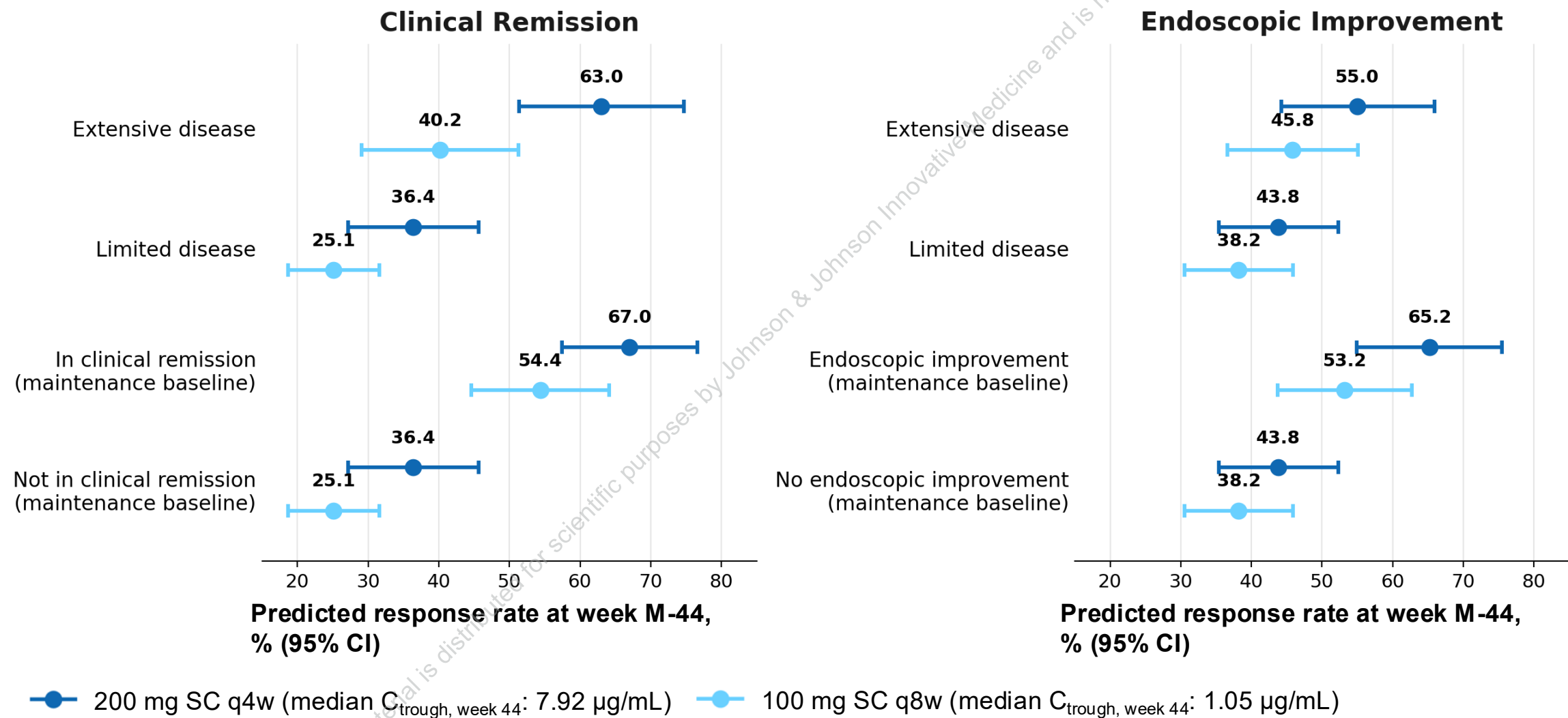
Clinical remission was defined as a stool frequency subscore of 0 or 1 (with no increase from induction baseline), a rectal bleedingsubscore of 0, and an endoscopic subscore of 0 or 1 with no friability present on the endoscopy. Endoscopic improvement was defined as an endoscopic subscore of 0 or 1 with no friability present on the endoscopy. HEMI was defined as 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. C_{trough}=serum trough concentration, E-R=exposure-response, GUS=guselkumab, HEMI=histologic endoscopic mucosal improvement, q4w=every 4 weeks, q8w=every 8 weeks, SC=subcutaneous, week M-44=maintenance week 44.

Exposures for Both 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 with this regimen and higher doses would not be expected to provide greater efficacy

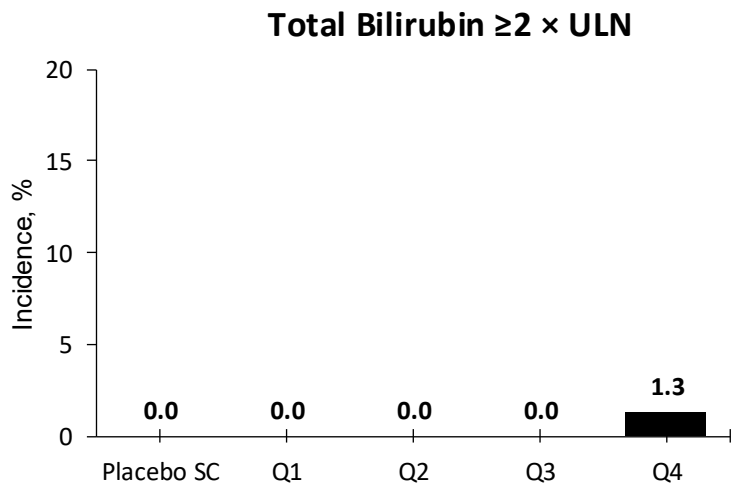
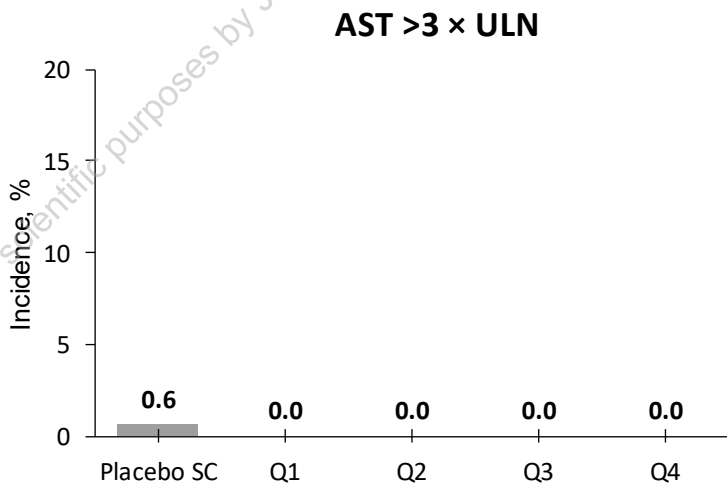
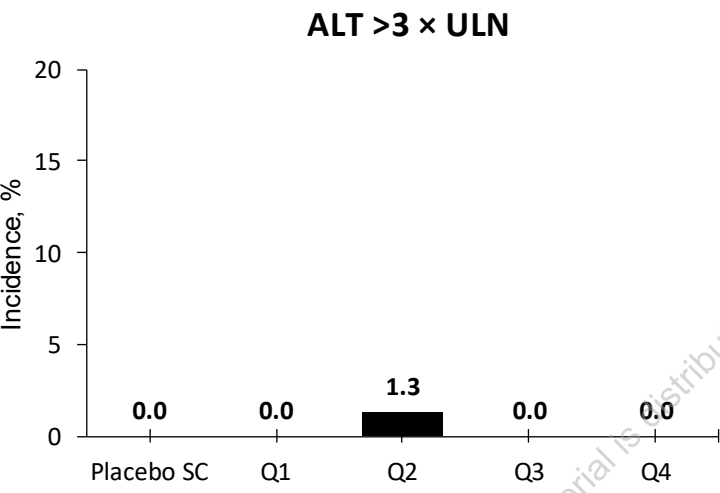
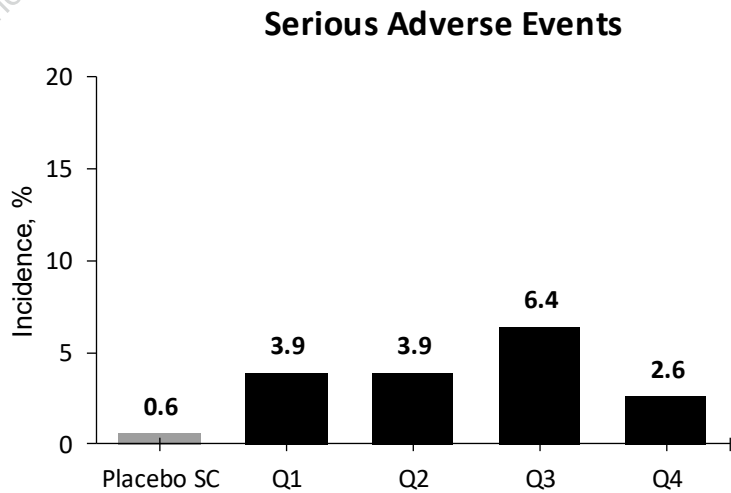
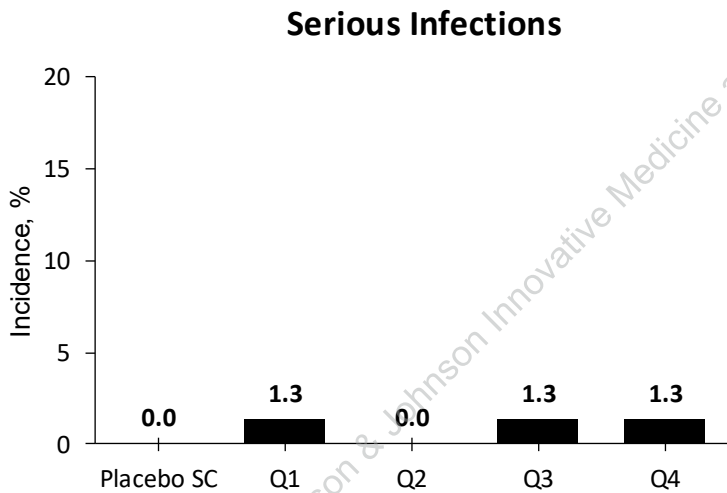
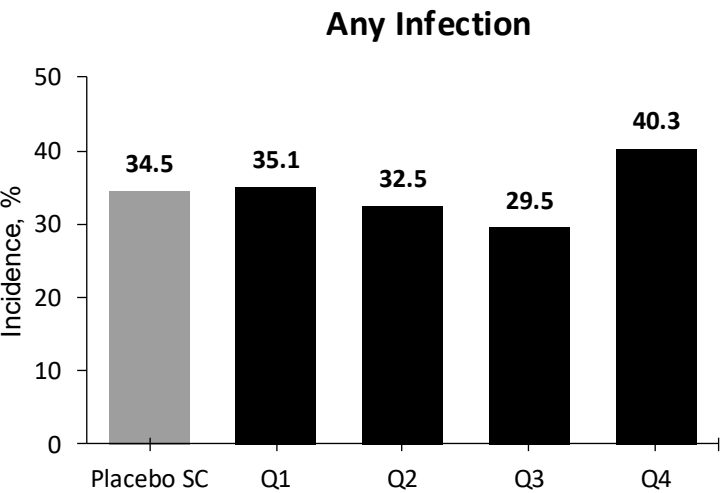


Participants With Extensive Ulcerative Colitis at Induction Baseline Showed a Greater Treatment Effect With 200 mg q4w vs 100 mg SC q8w Maintenance



CI=confidence interval, C_{trough} =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, **PK**=pharmacokinetics, **Q**=quartile, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous, **ULN**=upper limit of normal.

Conclusions



Maintenance PK and efficacy were consistent regardless of IV or SC induction, supporting a common maintenance dosing strategy in UC irrespective of route of induction regimen



E-R efficacy trends suggest that some participants with extensive UC may further benefit from the higher guselkumab exposure with the 200 mg q4w maintenance dose



E-R modeling showed efficacy with both maintenance regimens, but exposures with the 200 mg q4w dose were on the plateau of the E-R curve, suggesting this regimen is more likely to achieve maximal efficacy

Acknowledgments

- The authors thank the participants, investigators, and study personnel who made the QUASAR and ASTRO clinical studies possible
- Medical writing support was provided by Jen Ciarochi, PhD, under the direction of the authors in accordance with Good Publication Practice guidelines (Ann Intern Med. 2022;175:1298-1304)
- This presentation was sponsored by Johnson & Johnson



Thank you

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