PP0548

Impact of subcutaneous guselkumab therapy on molecular inflammation in patients with ulcerative colitis: results from the phase 3 ASTRO study

Swati Venkat,[1] Sunandini Sridhar,[1] Barbara Shaikh,[1] Klebea Sohn,[1] Jared Liu,[1] Christopher Sisk,[1] Bradford McRae,[1] Yelina Alvarez,[1] Tom Baker,[1] Matthew Germinaro,[1] Jessica R. Allegretti,[2] Millie Long,[3] David T. Rubin,[4] Laurent Peyrin-Biroulet,[5] Amy Hart,[1] and Patrick Branigan[1]

[1]Janssen Research & Development, LLC, Spring House, PA, USA [2]Division of Gastroenterology, Hepatology, and Endoscopy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA [3]Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA [4]University of Chicago Medicine Inflammatory Bowel Disease Centre, Chicago, IL, USA [5]University of Lorraine, Inserm, NGERE, F-54000 Nancy, France and Groupe Hospitalier privé Ambroise Paré-Hartmann, Paris IBD Centre, 92200 Neuilly sur Seine, France

Scan the QR code.
The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

This material is distributed for scientific purposes on J&J Medical Connect, and is not for promotional use

Key Takeaways

- Molecular changes in GUS SC and GUS IV induction treatment show significant correlation, supporting the efficacy of both routes of administration in UC.
- Molecular analysis of the ASTRO study corroborate efficacy results observed for GUS SC induction in UC.
- GUS SC induction reduced inflammatory biology towards a normal state while upregulating genes associated with healthy epithelium in patients who achieved clinical remission or HEMI at WK12.

Background

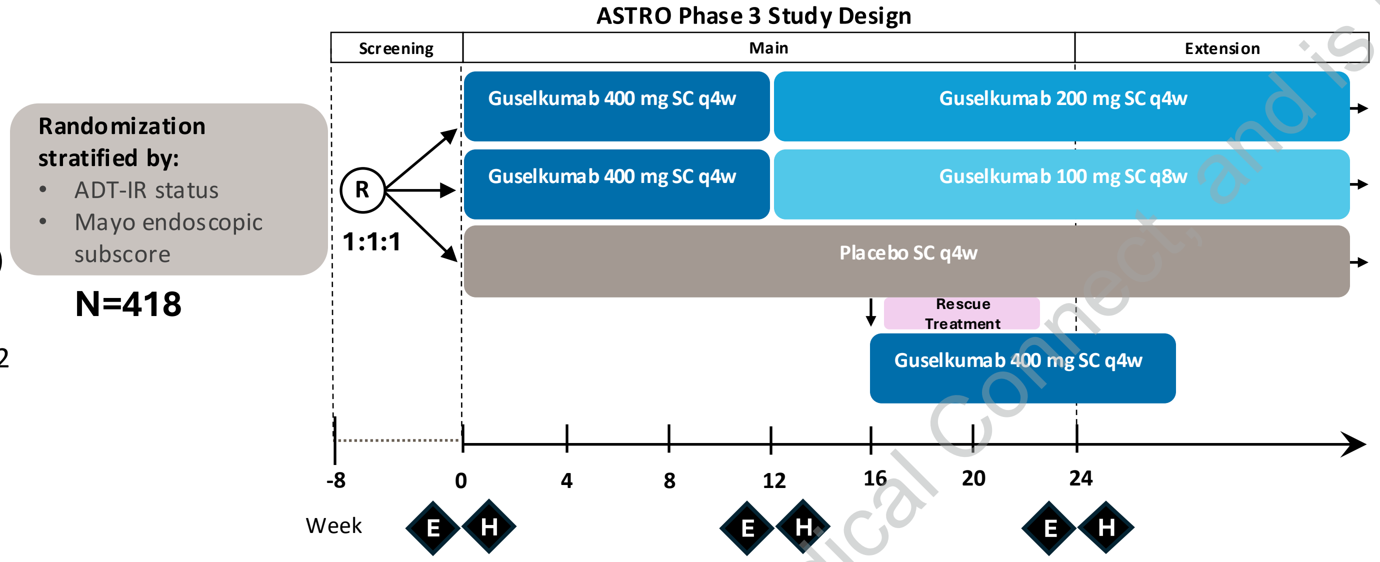
- Guselkumab (GUS) is a dual-acting IL-23p19 subunit inhibitor that potently neutralizes interleukin 23 (IL-23) and binds to CD64, a receptor on cells that produce IL-23[1].
- GUS was effective and safe as intravenous (IV) induction and subcutaneous (SC) maintenance therapy in patients with moderately to severely active ulcerative colitis (UC) (QUASAR)[2].
- Week 12 (WK12) results from the ASTRO phase 3 study demonstrated the efficacy of SC induction therapy with guselkumab in UC[3].

Objectives

- **Delineate molecular changes occurring from induction baseline WK0 to WK12 post GUS SC treatment**
- **Interpret in context of clinical outcomes and correlate to changes in QUASAR Ph3 (GUS IV) induction**

Methods

- Transcriptional profiling with bulk RNA seq (n=339) and histology (n=414) of colonic biopsies from patients was performed.
- Genes and gene co-expression modules (derived from UC single cell RNA sequencing data) were evaluated for differential expression.
- Molecular changes were assessed in the context of clinical remission and combined histologic and endoscopic mucosal improvement (HEMI) at WK12.
- Serum IL-22 levels (n=355) were measured using a high-sensitivity IL-22 assay and change in protein abundance was assessed.



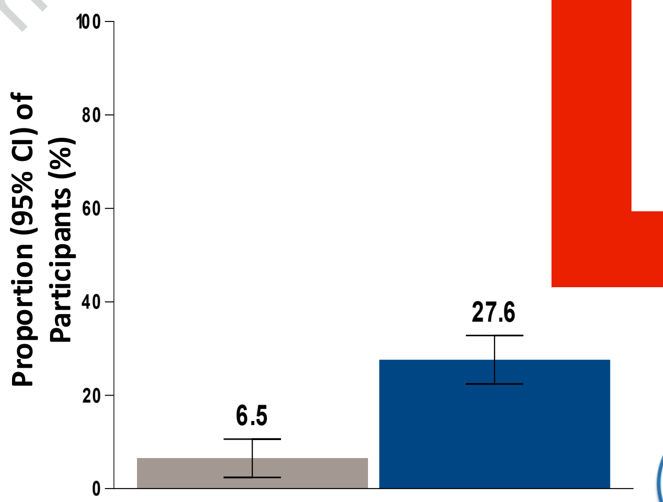


Figure 1. Target Patient Population: Adults with moderately to severely active UC (defined as induction baseline modified Mayo score of 5 to 9 with a Mayo rectal bleeding subscore ≥ 1 and a Mayo endoscopic subscore ≥ 2 based on central review) who had inadequate response/intolerance to conventional therapy and/or biologic and/or JAK inhibitor therapy.

Molecular analyses

Results

GUS 400mg SC induction downregulated inflammatory genes and upregulated healthy epithelium genes in colon tissue at WK12

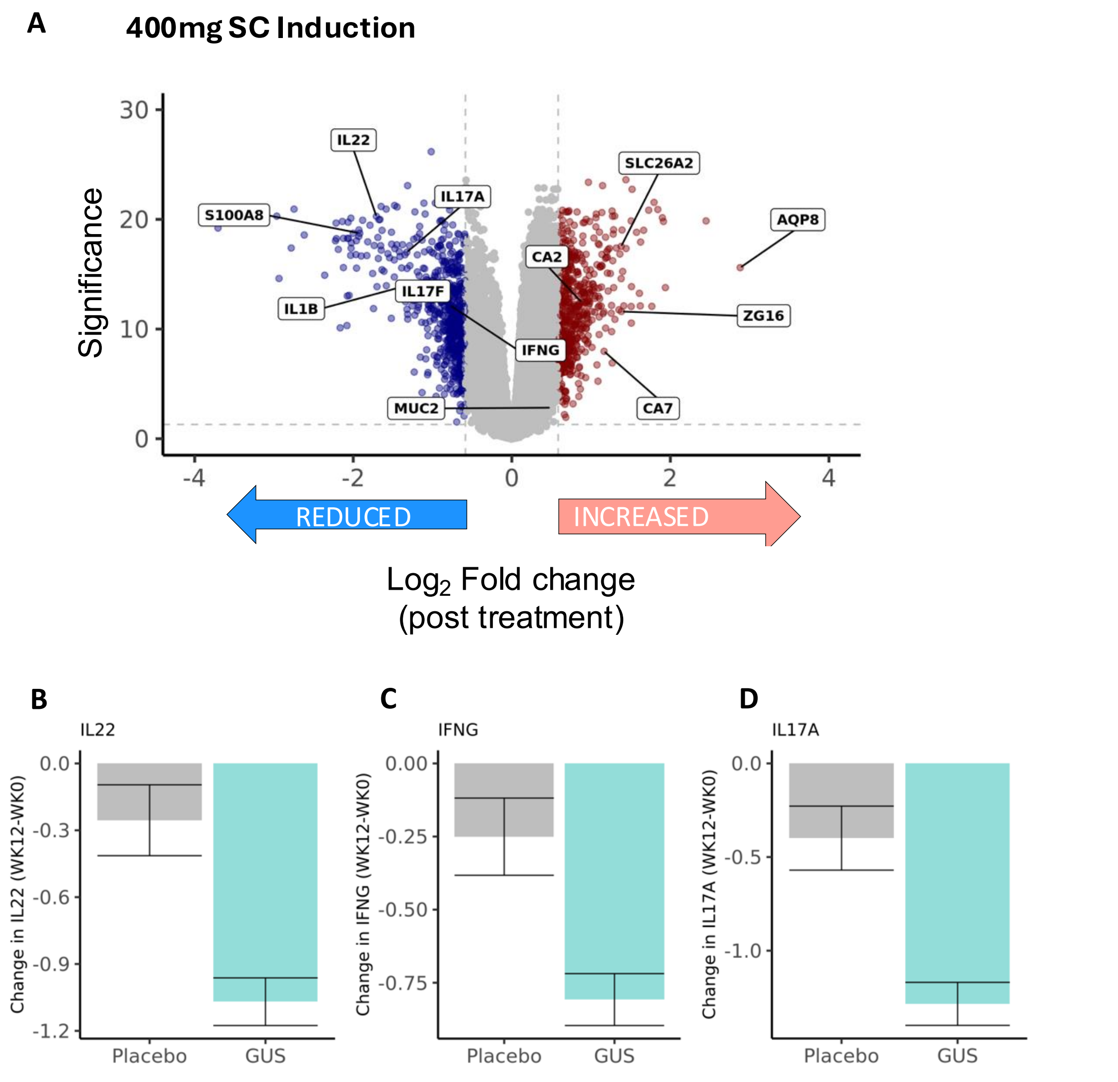


Figure 2. Volcano plot representing differential expression of genes at induction WK12 compared with baseline derived from colon tissue following GUS 400mg SC induction (A). Changes in IL22, IFNG and IL17A (B-D) mRNA expression in colon tissue following GUS 400mg SC induction.

GUS 400mg SC induction demonstrated significant downregulation of inflammatory transcriptional modules in colon tissue at WK12 similar to GUS 200mg IV induction observed in the QUASAR trial

- Representing Th17, IFNG signaling, inflamed epithelium, plasma cell, neutrophil and inflammatory fibroblast biology, and upregulation of healthy epithelium-related gene modules including goblet cells and healthy epithelium (all false discovery rate [FDR]<0.05).
- Response to GUS 400mg SC induction demonstrated significant correlation with transcriptional gene module changes observed in QUASAR with GUS 200mg IV induction (r=0.98, p<0.0001).

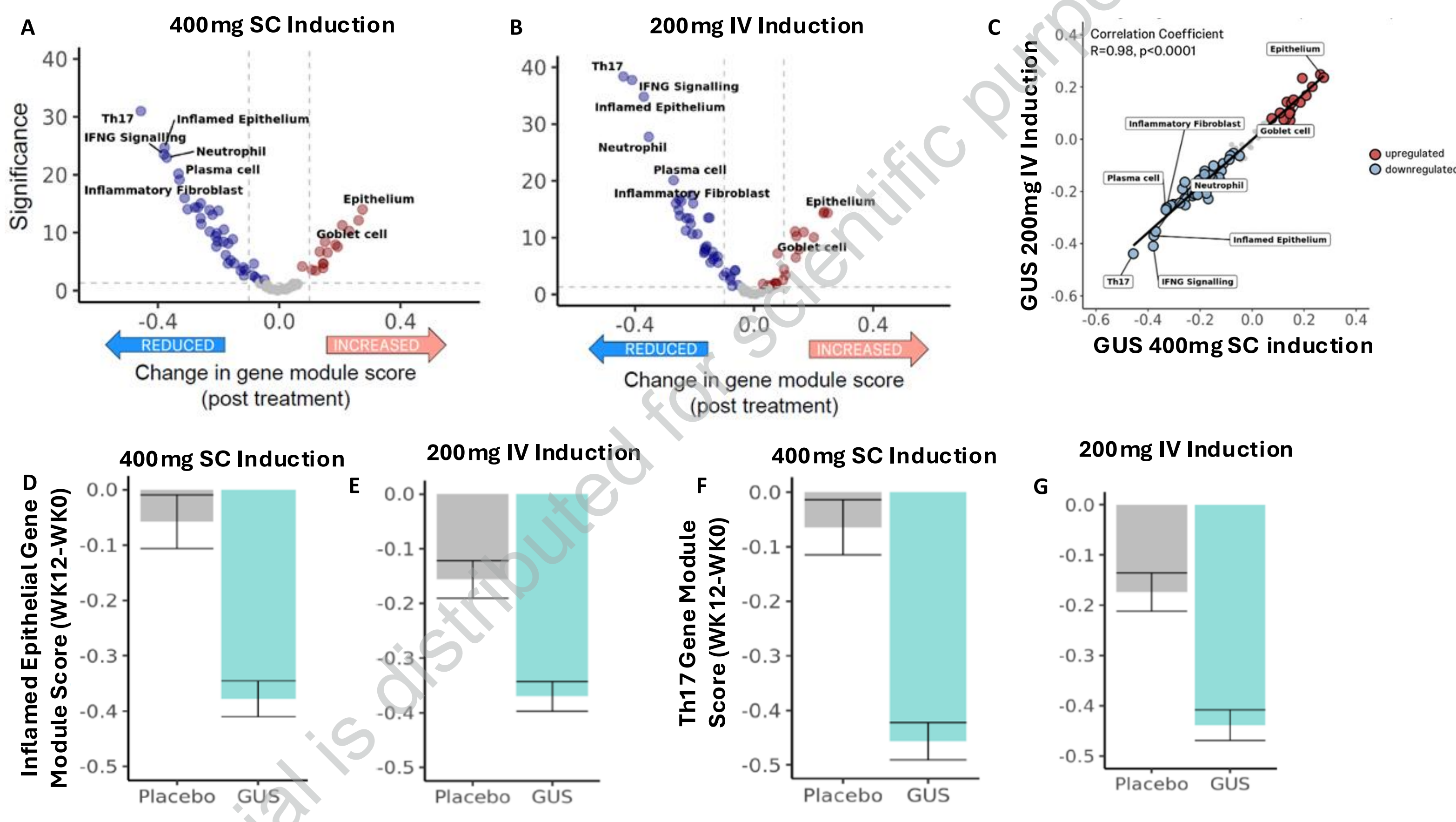


Figure 2. Volcano plots representing differential expression of transcriptional modules at induction WK12 compared with baseline derived from colon tissue following GUS 400mg SC induction (A) or GUS 200mg IV induction (B). Correlation of changes in transcriptional modules at WK12 following GUS 400mg SC induction or GUS 200mg IV induction (C). Changes in the inflamed epithelial (D-E) and Th17 (F-G) transcriptional modules following GUS 400mg SC induction or GUS 200mg IV induction.

Patients who achieved clinical remission at WK12 following 400mg SC demonstrated significant reductions in an inflamed epithelium transcriptional module, nearing non-IBD control levels

- Similar results were obtained for GUS treated patients who achieved HEMI at WK12.
- Subgroup analyses defined by prior treatment history demonstrated similar magnitude of changes in both treatment-naïve and -resistant groups (R=0.93, p<0.0001).

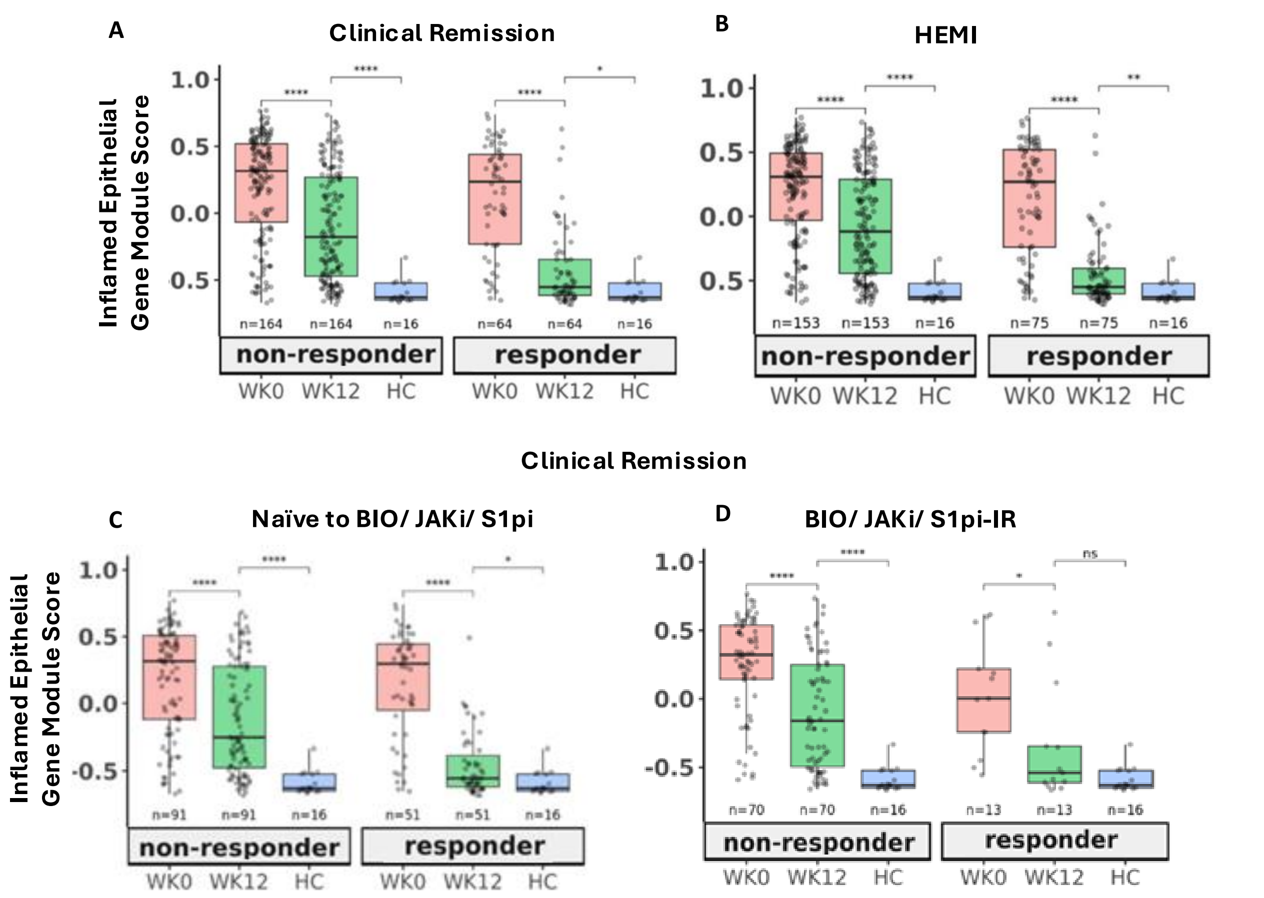


Figure 3. Gene Variation Set Analysis (GSVA) score of the inflamed epithelial transcriptional module in all GUS treated participants stratified by A) Clinical remission and B) Histo-endoscopic mucosal improvement (HEMI). Changes in the inflamed epithelial transcriptional module in all GUS treated participants stratified by previous inadequate response or failure to tolerate conventional therapy (C) or advanced UC therapy (D). Clinical remission: Mayo SFS of 0 or 1 and not increased from induction baseline, a Mayo RBS of 0, and an MES of 0 or 1 with no friability present on endoscopy. HEMI: combination of histologic improvement (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system (Geboes score ≤3·1)) and endoscopic improvement (MES of 0 or 1 with no friability present on endoscopy) endpoints.

Serum IL-22 was significantly decreased at WK12 (p <0.05) following GUS SC 400mg induction

- Similar changes were also observed for tissue IL-22 gene expression (p<0.05) nearing non-IBD control levels at WK12.

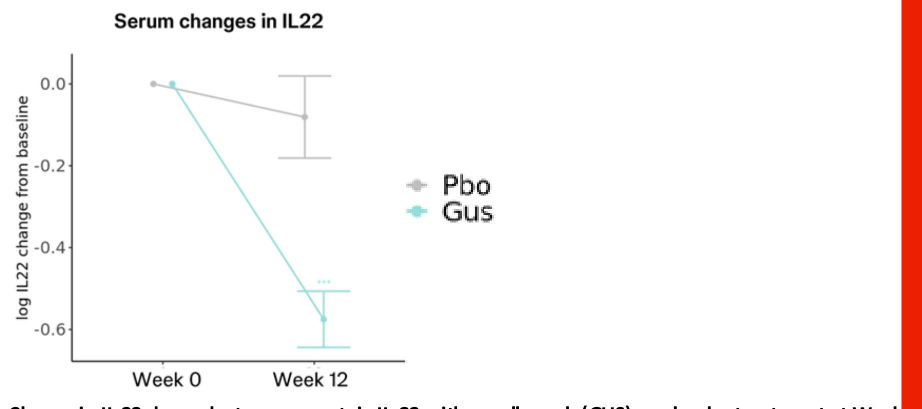


Figure 4: Change in IL-23 dependent serum protein IL-22 with guselkumab (GUS) or placebo treatment at Week 12. Model estimated mean difference from mixed-effect model is shown.

Patients who achieved clinical remission at WK12 demonstrated a greater decrease in Geboes total scores (p<0.05) compared to non-responders

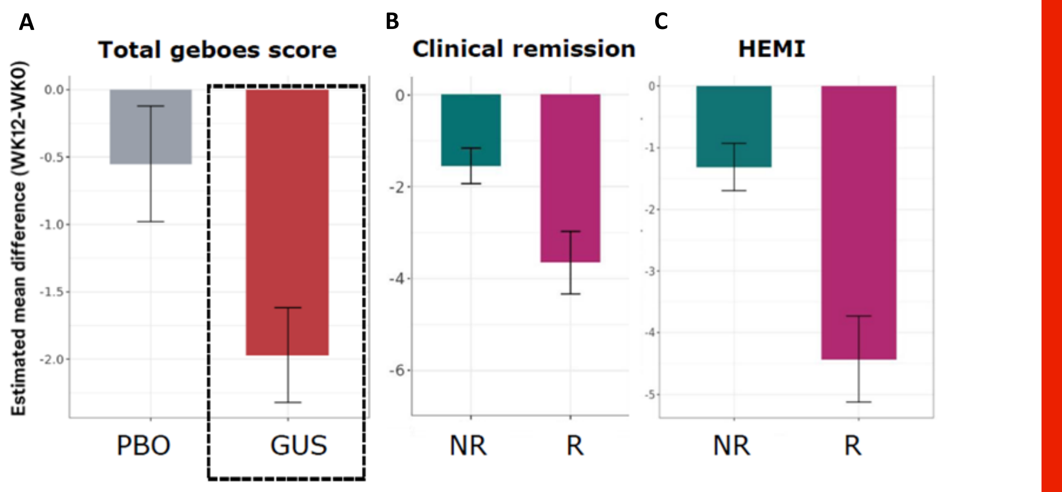


Figure 5. Change in total Geboes score in patients treated with guselkumab (GUS) and placebo (PBO) (A). Changes in GUS treated patients stratified by Clinical remission (B) and Histo-endoscopic mucosal improvement (HEMI) (C)

PRESENTED AT: The 33rd United European Gastroenterology Week Congress, October 4-7, 2025, Berlin, Germany. Conflicts of interest: SV, SS, BS, , KS, JL, CS, BMR, YA, TB, MG, AH and PB are employees of Janssen and may hold stock in Johnson & Johnson. LPB reports grants or contracts from Celltrion, Fresenius Kabi, Medac, MSD, and Takeda; consulting and/or payment or honoraria and/or data safety monitoring board or advisory board participation for AbbVie, Abivax, Adacyte, Alfasigma, Alimentiv, Amgen, Applied Molecular Transport, Arena, Banook, Biogen, Bristol Myers Squibb, Celltrion, Connect Biopharm, Cytoki Pharma, Enthera, Ferring, Fresenius Kabi, Galapagos, Genentech, Gilead, Gossamer Bio, GlaxoSmithKline, IAG Image Analysis, Index Pharmaceuticals, Inotrem, Janssen, Kern Pharma, Lilly, Medac, Mopac, Morphic, MSD, Nordic Pharma, Novartis, Oncodesign Precision Medicine, ONO Pharma, OSE Immunotherapeutics, Pandion Therapeutics, Par' Immune, Pfizer, Prometheus, Protagonist, Roche, Samsung, Sandoz, Sanofi, Satisfay, Takeda, Telavant, Theravance, Thermo Fischer, Tigenix, Tillots, Viatris, Vectivbio, Ventyx, and Ysopia; and meeting attendance/travel support from AbbVie, Alfasigma, Amgen, Celltrion, Connect Biopharm, Ferring, Galapagos, Genentech, Gilead, Gossamer Bio, Janssen, Lilly, Medac, Morphic, MSD, Pfizer, Sandoz, Takeda, Thermo Fischer, and Tillots. JRA reports grant support from Janssen, Merck, and Pfizer; consultancy fees from AbbVie, Adiso, Bristol Myers Squibb, Ferring, Genentech, GlaxoSmithKline, Janssen, Merck, Pfizer, Roivant, and Seres Therapeutics; payments for speaking from AbbVie, Bristol Myers Squibb, and Janssen; and is a steering committee member and investigator for Janssen. DTR reports grant support from Takeda; and has served as a consultant for Abbvie, Abivax SA, Altrubio, Avalo Therapeutics, Bausch Health, Bristol-Myers Squibb, Buhlmann Diagnostics Corp, Celltrion, ClostraBio, Connect BioPharma, Douglas Pharmaceuticals, Eli Lilly & Co., Foresee, Genentech (Roche) Inc., Image Analysis Group, InDex Pharmaceuticals, Iterative Health, Janssen Pharmaceuticals, Odyssey Therapeutics, Pfizer, Sanofi, Takeda Pharmaceuticals, Throne, and Vedanta. ML reports research support from Lilly, Pfizer, and Takeda; consulting for AbbVie, Bristol Myers Squibb, Intercept, Janssen (Johnson & Johnson), Lilly, Pfizer, Prometheus, Roivant, Takeda, and Target RWE.
References: 1. Sachen KL, Hammaker D, Sarabia I, et al. Guselkumab binding to CD64(+) IL-23-producing myeloid cells enhances potency for neutralizing IL-23 signaling. Front Immunol. 2025;16:1532852. doi:10.3389/fimmu.2025.1532852. **2. Rubin DT,** Allegretti JR, Panés J, et al. Guselkumab in patients with moderately to severely active ulcerative colitis (QUASAR): phase 3 double-blind, randomised, placebo-controlled induction and maintenance studies. The Lancet. 2025 Jan 4;405(10472):33-49. **3. Peyrin-Biroulet L,** Allegretti JR, Danese S, et al. OP10 Efficacy and safety of subcutaneous guselkumab induction therapy in patients with Ulcerative Colitis: Results through week 12 from the phase 3 ASTRO study. Journal of Crohn's and Colitis. 2025;19(Supplement_1):i19-i20. doi:10.1093/ecco-jcc/jjae190.0010