Guselkumab maintenance therapy mediates further improvements in intestinal immune homeostasis and mucosal healing in patients with moderately to severely ulcerative colitis

Amy Hart,[1] Sunandini Sridhar,[1] Swati Venkat,[1] Kuan-Hsiang Gary Huang,[1] Shadi Yarandi,[1] Matthew Germinaro,[1] Marion L. Vetter,[1] David T. Rubin,[2] Axel Dignass,[3] Daniel Cua,[1] Tom Freeman,[1] Dawn Waterworth,[1] Bradford McRae,[1] Bram Verstockt,[4] and Patrick Branigan[1]

1Janssen Research & Development LLC, Spring House, PA, USA; 2University of Chicago Medicine Inflammatory Bowel Disease Center, Chicago, IL, USA; 3Department of Medicine I, Agaplesion Markus Hospital, Goethe University, Frankfurt, Germany; 4Department of Gastroenterology and Hepatology, University Hospitals Leuven; and Translational Research in Gastrointestinal Disorders, Department of Chronic Disease, Metabolism, Leuven, Belgium

Su1980

Key Takeaways

- Guselkumab maintenance therapy mediated further downregulation of tissue-based molecular inflammation and upregulation of mucosal healing signals observed post-induction
- These data highlight the role for guselkumab in modulating mesenchymal biology to achieve tissue repair during maintenance treatment
- These data provide insight into the impact of guselkumab on restoring tissue immune homeostasis, supporting clinical efficacy findings

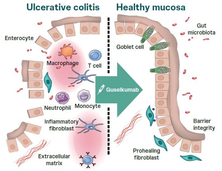
Background

- Guselkumab (GUS) is a dual-acting IL-23p19 subunit inhibitor that potently neutralises interleukin 23 (IL-23) and binds to CD64, a receptor on cells that produce IL-23[1]
- The QUASAR Phase 2b/3 studies have demonstrated efficacy and safety in induction and maintenance phases[2,3]
- The cellular and molecular mechanism of action of GUS induction was also previously reported[4]

Objectives

Here, we report the characterization of the molecular changes that occur during maintenance treatment

Molecular characterization of guselkumab in QUASAR Ph2b induction



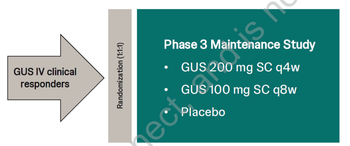
Down
- Inflammatory monocytes
- Inflammatory fibroblasts
- Inflammatory epithelium
- Neutrophils

Up
- Epithelial cells (e.g., goblet cells)
- Pro-healing fibroblasts

Methods

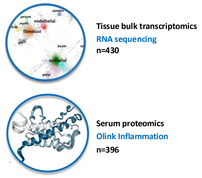
- Molecular analysis of the randomized population was performed comparing maintenance baseline (M0) to Week 44 (M44).
- Transcriptional profiling of colonic biopsies from 396 patients was performed using RNA sequencing and gene modules were evaluated for differential expression.
- Serum proteins measured by the Olink Inflammation panel were evaluated from 430 patients and differential protein abundance was assessed.

Maintenance study design



- Clinical responders to GUS induction treatment (n=568) were randomized 1:1:1 to GUS SC 200mg q4w, GUS SC 100mg q8w, or placebo (PBO; GUS withdrawal)

Molecular analysis



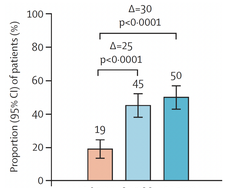
Primary endpoint
Clinical Remission at Week M-44

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.
Clinical remission: Mayo SFS of 0 or 1 and not increased from induction baseline, aMayo RBS of 0, and an MES of 0 or 1 with no friability

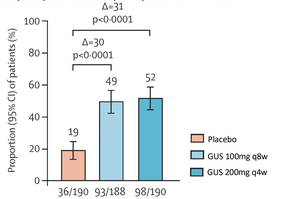
Results

Clinically, both GUS SC maintenance dose regimens were efficacious in achieving primary endpoint and secondary clinical endpoints compared to PBO

Primary endpoint: Clinical Remission at Week M-44



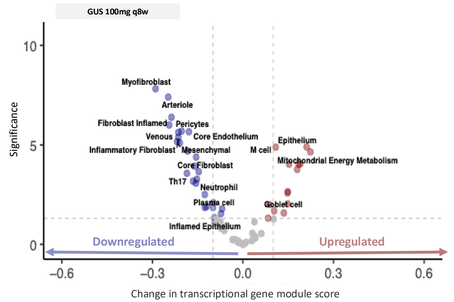
Secondary endpoint: Endoscopic improvement at Week M-44



The Lancet, Volume 405, Issue 10472, 33 - 49

GUS maintenance therapy resulted in further downregulation of inflammatory gene modules and upregulation of healthy epithelium gene modules

Differential expression of transcriptional gene modules representing cell type specific biology

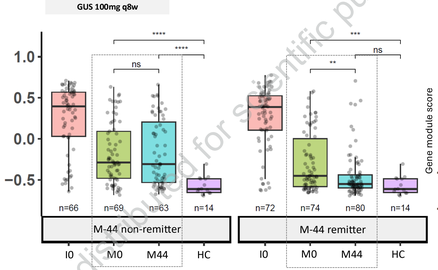


Differential expression of transcriptional gene modules representing cell type specific biology in guselkumab (GUS) treated patients. Y-axis: significance (−log10(Adj.P-value)); X-axis: change in transcriptional gene module score (gene set variation analysis (GSVA) score) (M-44-M-0).

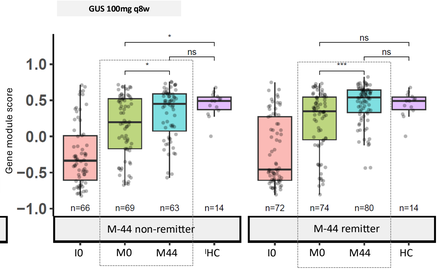
- Both maintenance dose regimens demonstrated comparable changes (GUS 200mg q4w dose regimen not shown)

Patients who achieved clinical remission at maintenance WK44 showed more robust changes in gene modules compared to non-remitters

Inflamed epithelium gene module



Healthy epithelium gene module

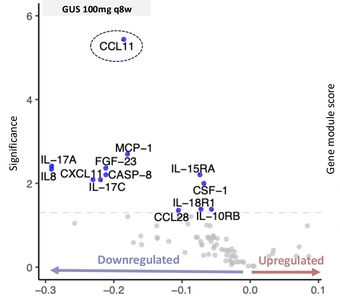


Transcriptional gene module scores in patients from the GUS 100mg q8w group stratified by their M-44 clinical remission status. Y-axis : GSVA score ; X-axis : Timepoints stratified by M-44 clinical remission status. ****p<0.0001, ***p<0.001 , **p<0.01 , *p<0.05. Timepoints: I0 – Induction baseline, M0 – Maintenance baseline, M44 – Maintenance WK44, HC – Healthy control

- Similar changes are observed for other inflammatory modules (e.g., plasma cell, inflammatory fibroblast, neutrophil)
- Healthy epithelium as well as other modules (e.g. crypt) show upregulation to near non-IBD control levels

Serum analysis demonstrated a reduction in chemokine CCL11/Eotaxin-1 in response to GUS maintenance therapy

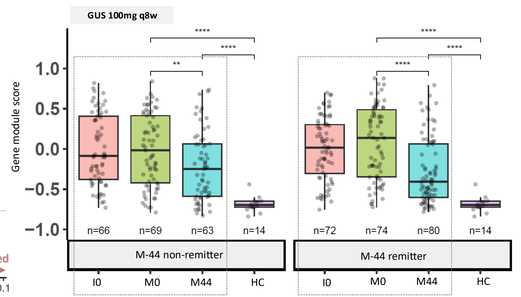
Serum proteomics (Olink Inflammation panel)



- Reduction in chemokine CCL11/Eotaxin-1 in response to GUS maintenance therapy

Unique to GUS maintenance therapy, a significant reduction in modules related to intestinal mesenchymal biology was observed, minimally evident in induction

Myofibroblast gene module



Myofibroblast gene module scores in patients from the GUS 100mg q8w group stratified by their M-44 clinical remission status. Y-axis : GSVA score ; X-axis : Timepoints stratified by M-44 clinical remission status. ****p<0.0001, ***p<0.001 , **p<0.01 , *p<0.05. Timepoints: I0 – Induction baseline, M0 – Maintenance baseline, M44 – Maintenance WK44, HC – Healthy control

- Unique to GUS maintenance therapy, a significant reduction in modules related to intestinal mesenchymal biology was observed, minimally evident in induction

PRESENTED AT: DDW 2025, Abstract number 4243186, Poster number Su1980. May 4th, 2025. **REFERENCES: 1.** Atreya R, Abreu MT, Krueger JG, et al. P165 Guselkumab binding to CD64+ IL-23–producing myeloid cells enhances potency for neutralizing IL-23 signaling. Journal of Crohn's and Colitis. 2024;18(Supplement_1):i470-i470. doi:10.1093/ecco-jcc/jjad212.0295 **2.** The Efficacy and Safety of Guselkumab as Maintenance Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Results From the Phase 3 QUASAR Maintenance Study. Gastroenterol Hepatol. Jul 2024;20(7 Suppl 6):8-9. **3.** Peyrin-Biroulet L, Allegretti JR, Rubin DT, et al. Guselkumab in Patients With Moderately to Severely Active Ulcerative Colitis: QUASAR Phase 2b Induction Study. Gastroenterology. Sep 1 2023;doi:10.1053/j.gastro.2023.08.038 **4.** Sridhar S, Hart A, Venkat S, et al. OP23 Guselkumab induction restores intestinal immune homeostasis and promotes epithelial repair in moderately to severely active Ulcerative Colitis. Journal of Crohn's and Colitis. 2024;18(Supplement_1):i41-i41. doi:10.1093/ecco-jcc/jjad212.0023 **ACKNOWLEDGMENTS:** Authors would like to thank the QUASAR study team for supporting the collection of the biomarker dataset presented in this poster. **DISCLOSURES:** Amy Hart, Sunan Sridhar, Swati Venkat, Kuan-Hsiang Gary Huang, Shadi Yarandi, Matthew Germinaro, Marion Vetter, Daniel Cua, Tom Freeman, Dawn Waterworth, Bradford McRae, and Patrick Branigan are employees of Janssen and may hold stock in Johnson & Johnson. David Rubin reports potential conflicts of interest with Abbvie, Atrudoo, Apex, Avalo Therapeutics, Bristol-Myers Squibb, Buhlmann Diagnostics Corp, Celgene, Connect BioPharma, Intouch Group, Iterative Health, Janssen Pharmaceuticals, Lilly, Pfizer, Samsung Neurologica, and Takeda. Axel Dignass reports fees for participation in clinical trials, review activities such as data monitoring boards, statistical analysis and end point committees from Abivax, AbbVie, Bristol Myers Squibb, Dr Falk Foundation, Galapagos, Gilead, Janssen, and Pfizer; consultancy fees from AbbVie, Amgen, Arena Pharmaceuticals, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Dr Falk Foundation, Ferring Pharmaceuticals, Fresenius Kabi, Galapagos, Janssen, Lilly, MSD, Pfizer, Pharmacosmos, Roche, Sandoz, Stada, Takeda, Tillotts, and Vifor Pharma; payment for lectures including service on speakers bureaus from AbbVie, Biogen, CED Service GmbH, Celltrion, Falk Foundation, Ferring, Galapagos, Gilead, High2MD, Janssen, Materia Prima, MedTriday, MSD, Pfizer, Sandoz, Takeda, Tillotts, and Vifor Pharma; payment for manuscript preparation from AbbVie, Falk Foundation, Janssen, Takeda, Thieme, and UniMed Verlag. Bram Verstockt has received research support from AbbVie, Biora Therapeutics, Landos, Pfizer, Sossei Heptares and Takeda; speaker's fees from AbbVie, Biogen, Bristol Myers Squibb, Celltrion, Chiesi, Eli Lilly, Falk, Ferring, Galapagos, Johnson and Johnson, MSD, Pfizer, Roche, Sandoz, Takeda, Tillotts Pharma, Truvion and Viatris; consultancy fees from AbbVie, Alfasigma, Alimentiv, Applied Strategic, Astrazeneca, Atheneum, BeneventeM, Biora Therapeutics, Bower Capital, Bristol Myers Squibb, Eli Lily, Galapagos, Guidepoint, Landos, Merck, Mylan, Nxera, Inotrem, Ipsos, Johnson and Johnson, Pfizer, Progenity, Sandoz, Sanofi, Santa Ana Bio, Sapphire Therapeutics, Sosei Heptares, Takeda, Tillotts Pharma and Viatris; and holds stock options in Vagustim.