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]

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

This presentation was supported by Janssen Research & Development, LLC, Spring House, PA, USA

Conflicts of Interest

AH, SS, SW, K-HGH, SY, MG, MLV, DC, TF, DW, BM and PB are current or former employees of Janssen and may hold stock in Johnson & Johnson.

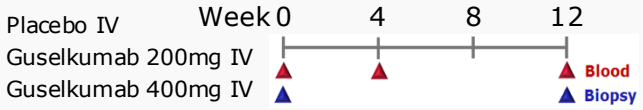
BV reports support from Abbvie, Biora Therapeutics, Landos, Pfizer, Sossei Heptares, Takeda, Celltrion and Sanofi; speaker's fees from Abbvie, Biogen, Bristol Myers Squibb, Celltrion, Chiesi, Eli Lily, Falk, Ferring, Galapagos, Johnson and Johnson, MSD, Pfizer, R-Biopharm, Sandoz, Takeda, Tillots Pharma, Truvion and Viatris; consultancy fees from Abbvie, Alfasigma, Alimentiv, Applied Strategic, Astrazeneca, Atheneum, BenevolentAI, Biora Therapeutics, Boxer Capital, Bristol Myers Squibb, Eli Lily, Galapagos, Guidepont, Landos, Merck, Mylan, Nxera, Inotrem, Ipsos, Johnson and Johnson, Pfizer, Progenity, Sandoz, Sanofi, Santa Ana Bio, Sapphire Therapeutics, Sosei Heptares, Takeda, Tillots Pharma and Viatris; and holds stock options in Vagustim

DTR reports potential conflicts of interest with Abbvie, Altrubio, Apex, Avalo Therapeutics, Bristol-Myers Squibb, Buhlmann Diagnostics Corp, Celgene, Connect BioPharma, Intouch Group, Iterative Health, Janssen Pharmaceuticals, Lilly, Pfizer, Samsung Neurologica, and Takeda

AD 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, High5MD, Janssen, Materia Prima, MedToday, MSD, Pfizer, Sandoz, Takeda, Tillotts, and Vifor Pharma; payment for manuscript preparation from Abbvie, Falk Foundation, Janssen, Takeda, Thieme, and UniMed Verlag

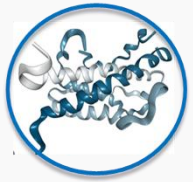
QUASAR Phase 2b: guselkumab induction therapy restored immune homeostasis and promoted epithelial repair at WK12

QUASAR Ph2b induction

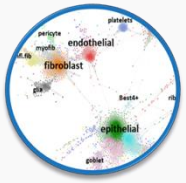


Molecular changes evaluated; WK12 relative to WK0

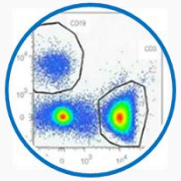
Molecular analysis



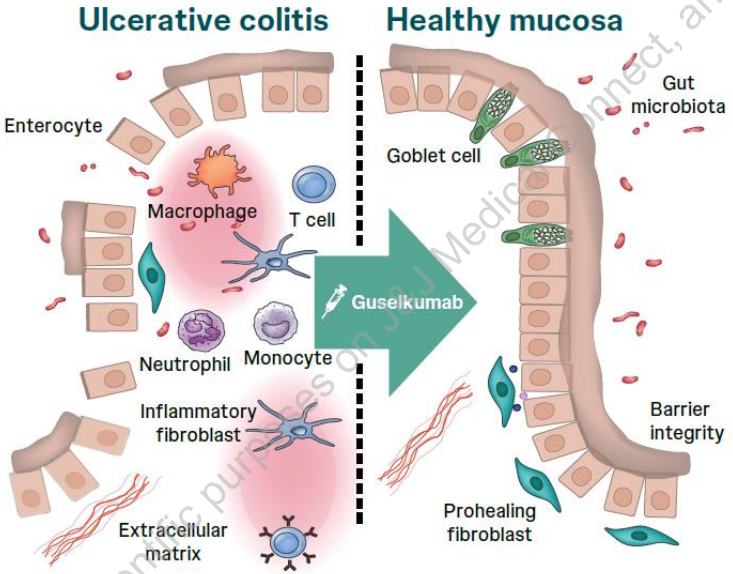
Serum proteomics



Tissue bulk and single cell transcriptomics



Tissue immunophenotyping



Restores immune homeostasis

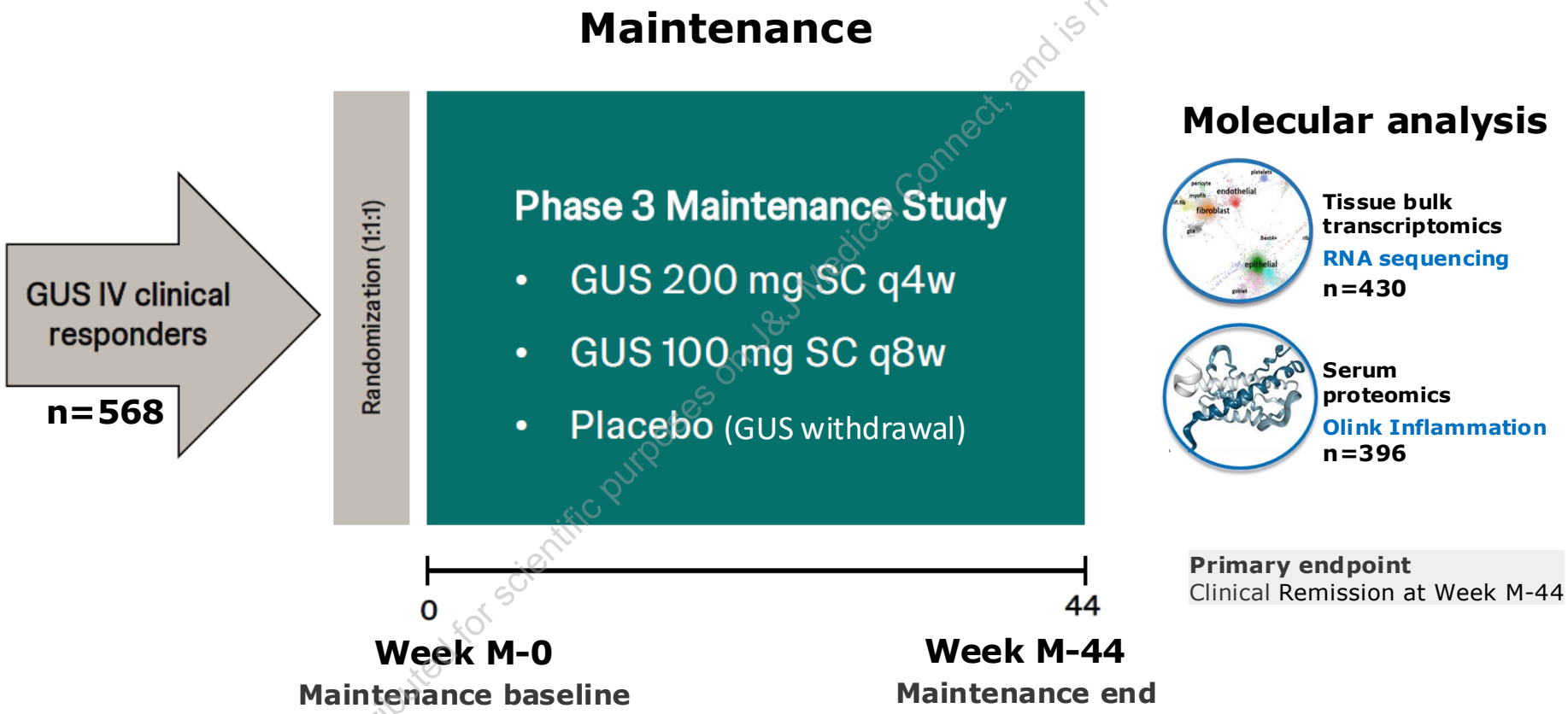
- Inflammatory monocytes
- Inflammatory fibroblasts
- Inflammatory epithelium
- Neutrophils

Promotes epithelial repair

- Epithelial cells (enterocytes, goblet cells)
- Prohealing fibroblasts (ADAMDEC1+ cells)

Sridhar S, Hart A, Venkat S, et al. Journal of Crohn's and Colitis (ECCO 2024 oral). 2024;18(Supplement_1):i41-i41
Sridhar S, Hart A, Venkat S, et al. Gastroenterology (DDW 2024 poster). 05/01 2024;166:S-790
Hart and Sridhar, et al. (manuscript in preparation)

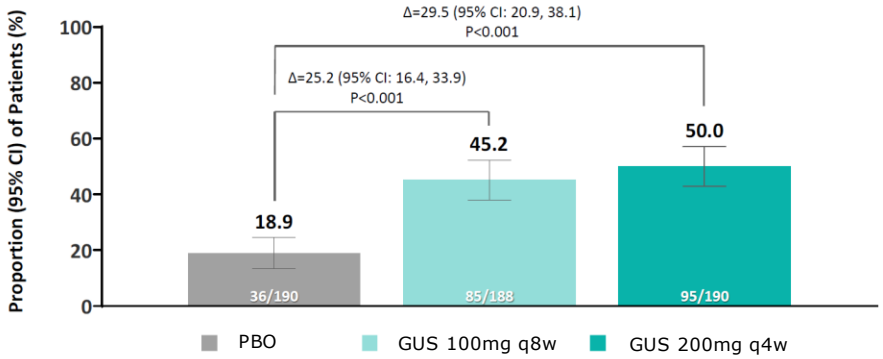
Molecular changes were evaluated from the end of induction to maintenance WK44 in the QUASAR Phase 3 study



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

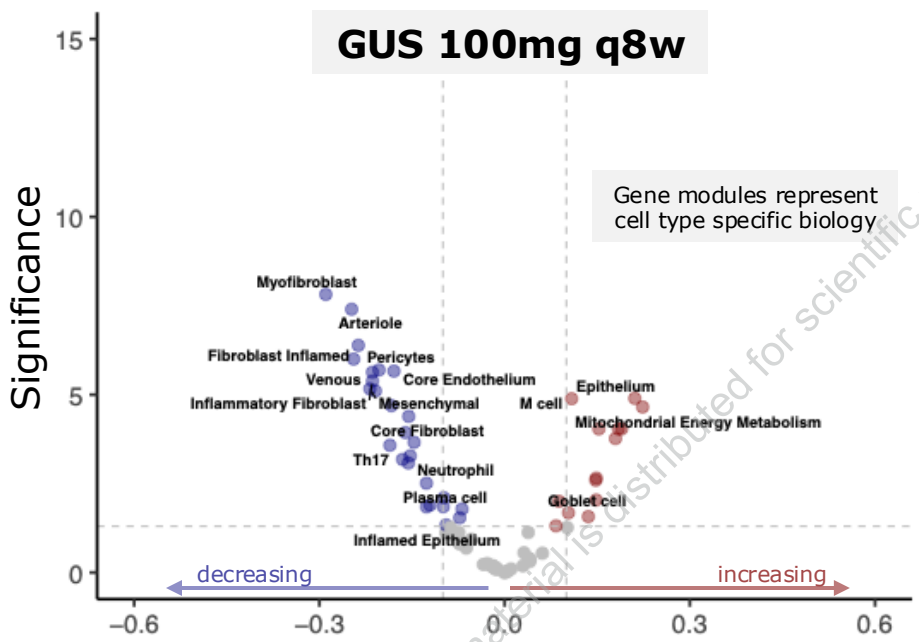
Maintenance WK44 demonstrated further improvements in anti-inflammatory and pro-healing molecular changes that were observed at induction WK12

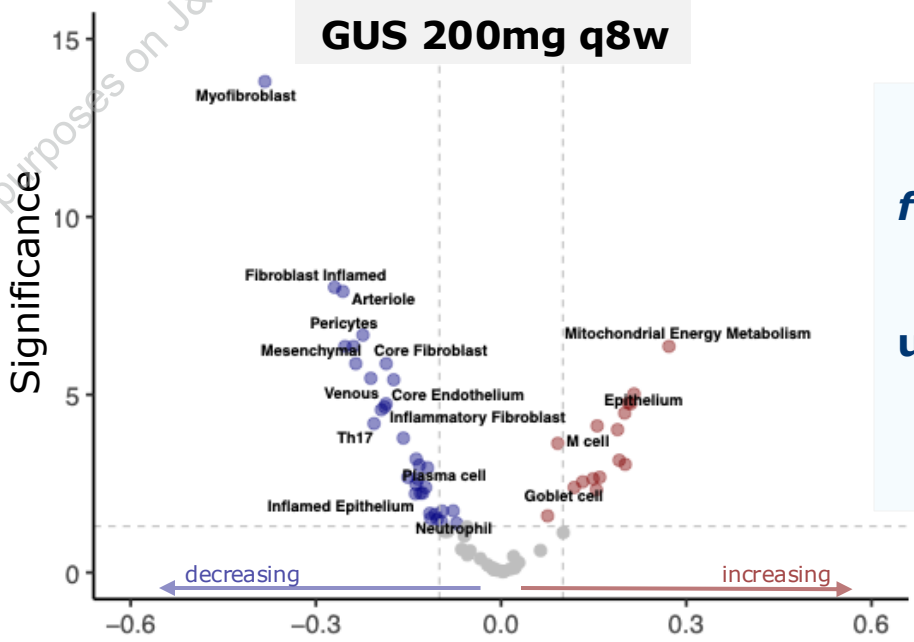
Primary endpoint: Clinical Remission at Week M-44



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

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



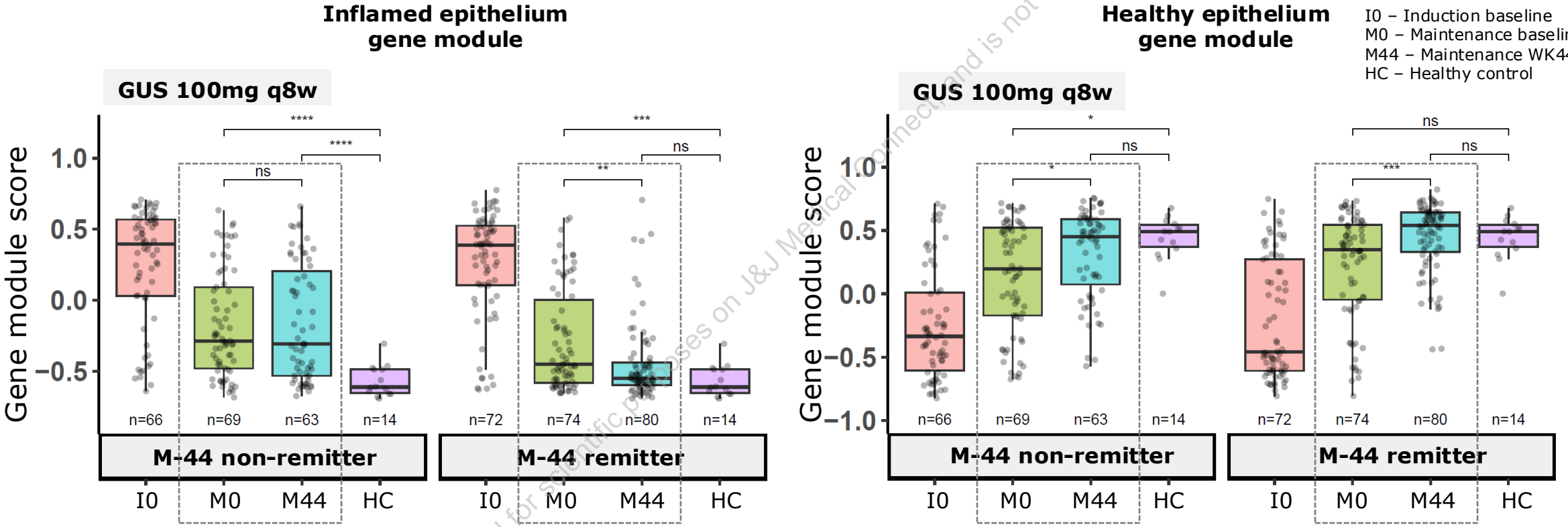


Change in gene module score (M-44 relative to M-0)

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

Tissue Transcriptomics

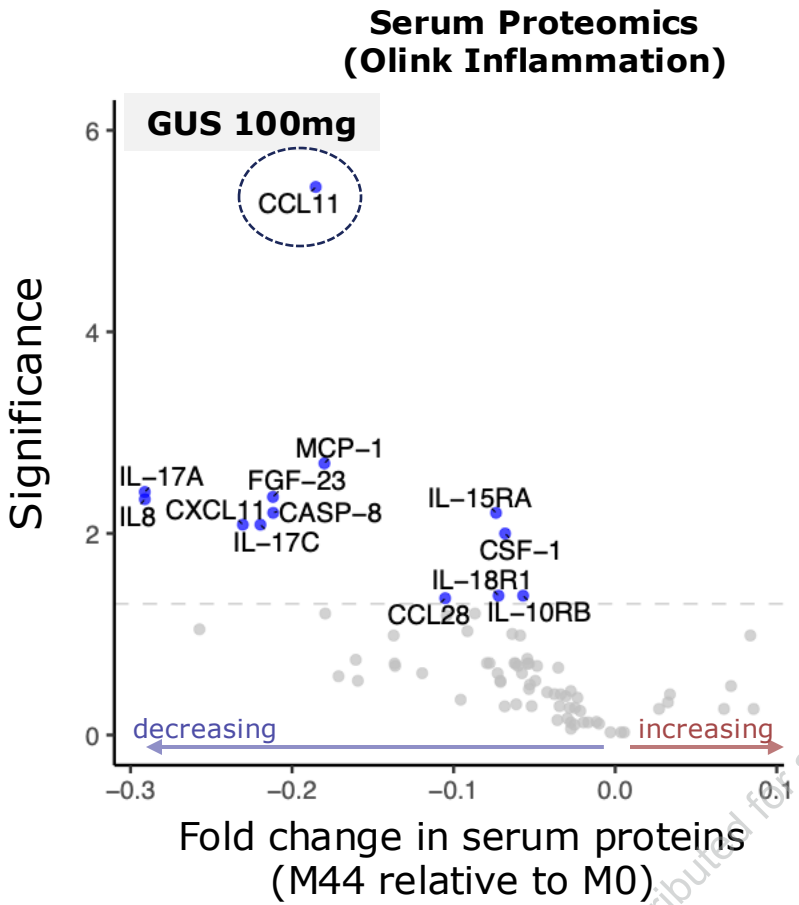
Changes in gene modules at maintenance WK44 were correlated with clinical remission

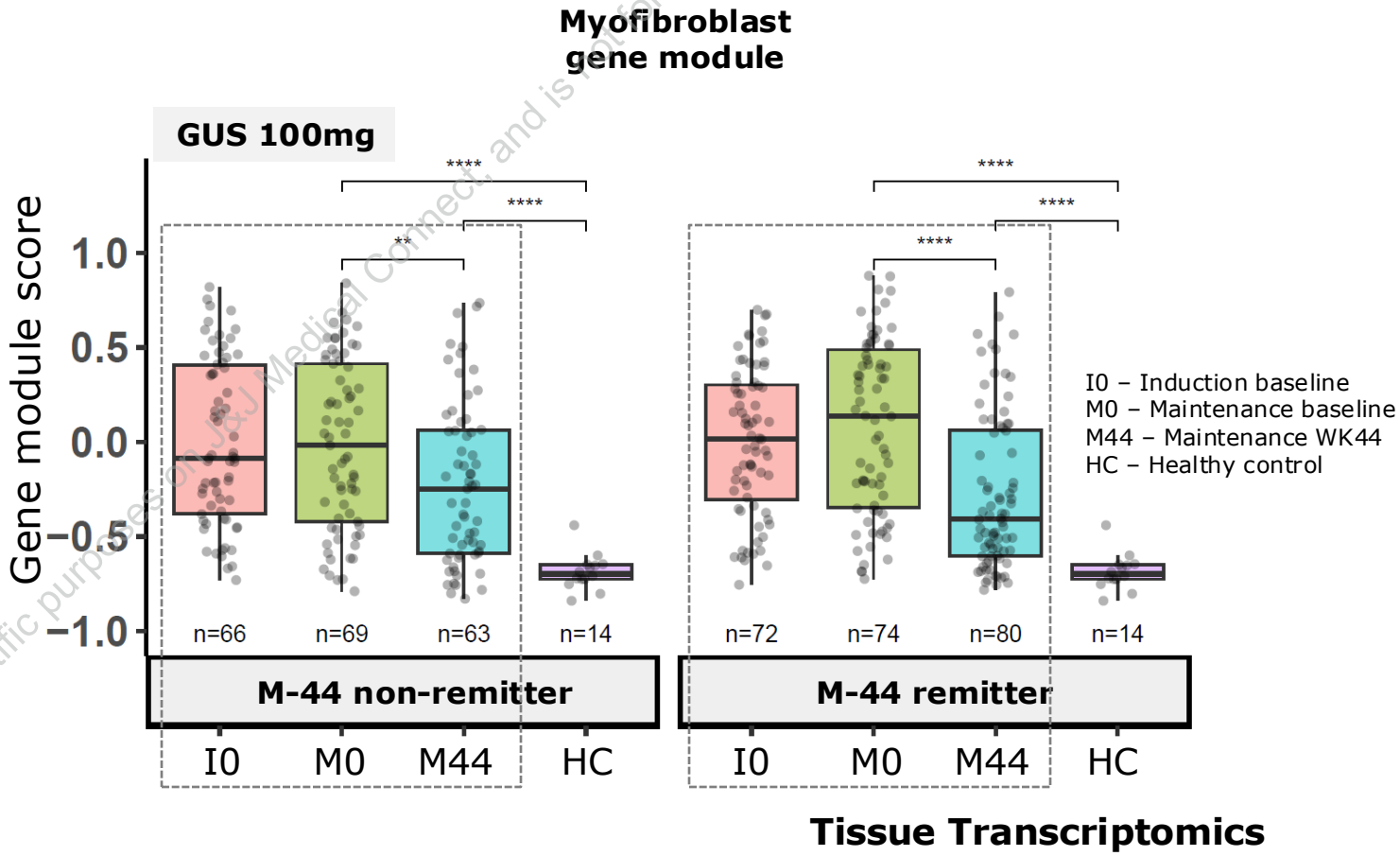


Patients who achieved clinical remission at maintenance WK44 showed more robust changes in gene modules compared to non-remitters

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

Maintenance therapy demonstrated unique changes related to mesenchymal biology





Serum analysis demonstrated a 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

Conclusions

Guselkumab maintenance therapy mediated further downregulation of tissue-based molecular inflammation and upregulation of mucosal healing signals observed post-induction

- Maintenance WK44 clinical remitters demonstrated the most significant molecular changes
- Both guselkumab maintenance dose regimens showed similar molecular effects

- 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**