

UNITED EUROPEAN  
GASTROENTEROLOGY

**ueg week**

# Molecular differentiation of guselkumab and ustekinumab in moderately to severely active Crohn's disease

Post hoc analysis of the GALAXI 2 and 3 phase 3 studies

**Dylan Richards,<sup>1</sup> Klebea Sohn,<sup>1</sup> Martha Zeeman,<sup>1</sup> Ruchi Patel,<sup>1</sup> Bradford McRae,<sup>1</sup> Nat Terry,<sup>1</sup> Marion Vetter,<sup>1</sup> Walter Reinisch,<sup>2</sup> Daniel Cua,<sup>1</sup> and Patrick Branigan<sup>1</sup>**

<sup>1</sup>Janssen Research & Development, LLC, Spring House, PA, USA; <sup>2</sup>Division of Gastroenterology & Hepatology, Medical University of Vienna, Vienna, Austria.

October 5, 2025, Berlin

UNITED EUROPEAN  
GASTROENTEROLOGY

**ueg week**

## Disclosure of Conflicts of Interest

**Dylan Richards, Klebea Sohn, Martha Zeeman, Ruchi Patel, Bradford McRae, Nat Terry, Marion Vetter, Daniel Cua, and Patrick Branigan** are current or former employees of Janssen and may hold stock in Johnson & Johnson.

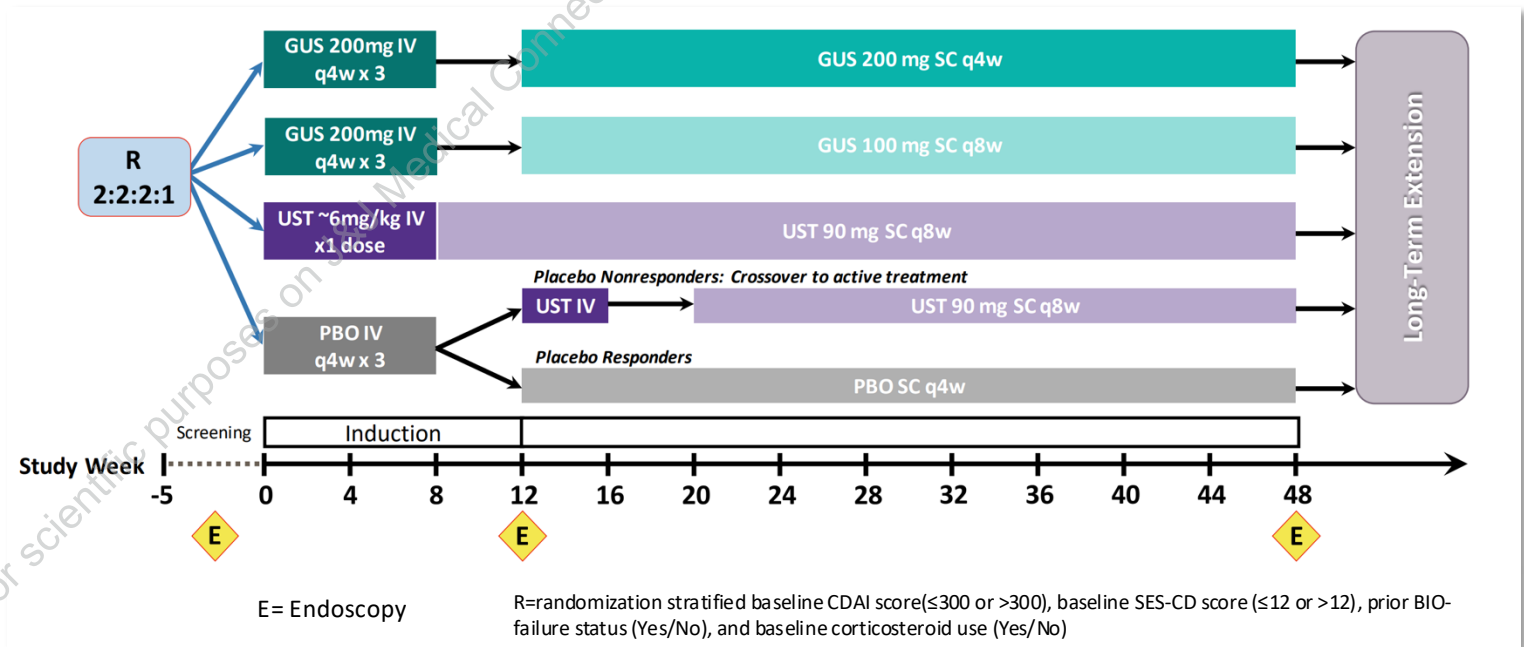
**Walter Reinisch** has served as a speaker for AbbVie, Celltrion, Ferring, Janssen, Galapagos Medice, MSD, Roche, Pfizer, Sobi, Takeda, as a consultant for AbbVie, Amgen, AOP Orphan, Boehringer Ingelheim, Bristol Myers Squibb, Calyx, Celltrion, Eli Lilly, Galapagos, Gilead, Index Pharma, Janssen, Medahead, Microbiotica, Pfizer, Takeda; as an advisory board member for AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Galapagos, Janssen, Pfizer, and has received research funding from AbbVie, Janssen, Sandoz, Sanofi, Takeda.

This material is distributed for scientific purposes only. It is not for promotional use.

# Background - Guselkumab superior to ustekinumab across multiple endoscopic endpoints in pooled phase 3 GALAXI Crohn's disease studies

- Guselkumab (GUS) is a selective, dual-acting interleukin (IL)-23p19 subunit inhibitor that potently blocks IL-23 and binds to CD64, a receptor on immune cells that produces IL-23<sup>1</sup>
- Ustekinumab (UST) is an IL-12/23p40 subunit inhibitor

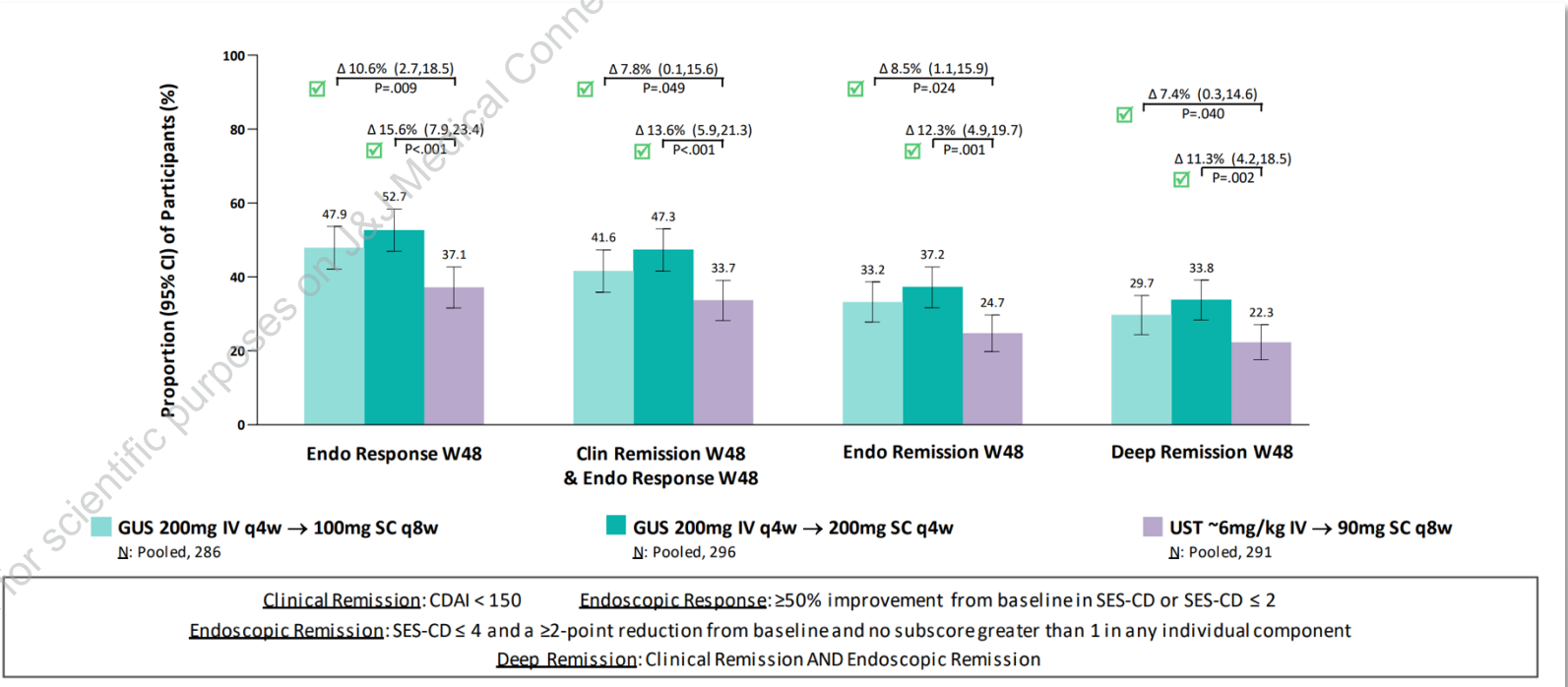
GALAXI Phase 3 program: GALAXI 2 & GALAXI 3 identical trials with randomized, double-blind, placebo-controlled, treat-through design



# Background - Guselkumab superior to ustekinumab across multiple endoscopic endpoints in pooled phase 3 GALAXI Crohn's disease studies

- Guselkumab (GUS) is a selective, dual-acting interleukin (IL)-23p19 subunit inhibitor that potently blocks IL-23 and binds to CD64, a receptor on immune cells that produces IL-23<sup>1</sup>
- Ustekinumab (UST) is an IL-12/23p40 subunit inhibitor
- GUS achieved statistical superior efficacy over UST at WK48 in endoscopic endpoints<sup>2</sup>**

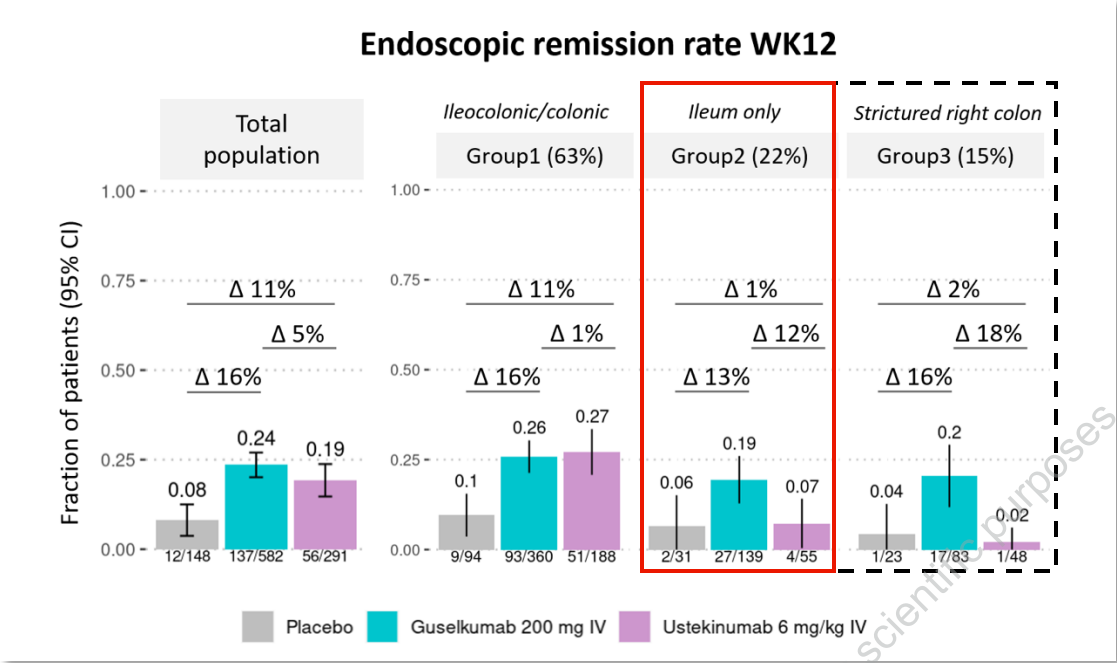
GALAXI Phase 3 program: GALAXI 2 & GALAXI 3 identical trials with randomized, double-blind, placebo-controlled, treat-through design



1. Sachen KL, et al. *Front Immunol.* 2025;16:1532852. doi: 10.3389/fimmu.2025.1532852  
 2. Panaccione R, et al. *Gastroenterology.* 2024; 5 (Supplement): p1057b

# Background - In GALAXI, exploratory analyses revealed endoscopic differentiation with GUS vs UST at WK12

Greater endoscopic remission with GUS vs UST in isolated ileal and strictured right colon patients at WK12



Richards D, et al. DDW 2025, Su1861  
 "Endoscopic Patient Clustering" moderated poster UEGW 2025, MP532

Differences in endoscopic response and biological features across ileal and colonic Crohn's disease (CD) suggest distinct mechanisms for healing

2021 NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY

Location is important: differentiation between ileal and colonic Crohn's disease

Raja Atreya<sup>1</sup> and Britta Siegmund<sup>2</sup>

Objective: Here, we investigated the mechanistic differences between GUS and UST in CD from the GALAXI Ph3 program.

# Differential effects of pathway engagement between GUS and UST in patients with isolated ileal disease

Analysis of serum pharmacodynamic (PD) markers focused on subset of patients

- Serum **IFN $\gamma$**  downstream of IL-23 and IL-12 pathway
- Serum **IL-17A, IL-22** downstream of IL-23 pathway

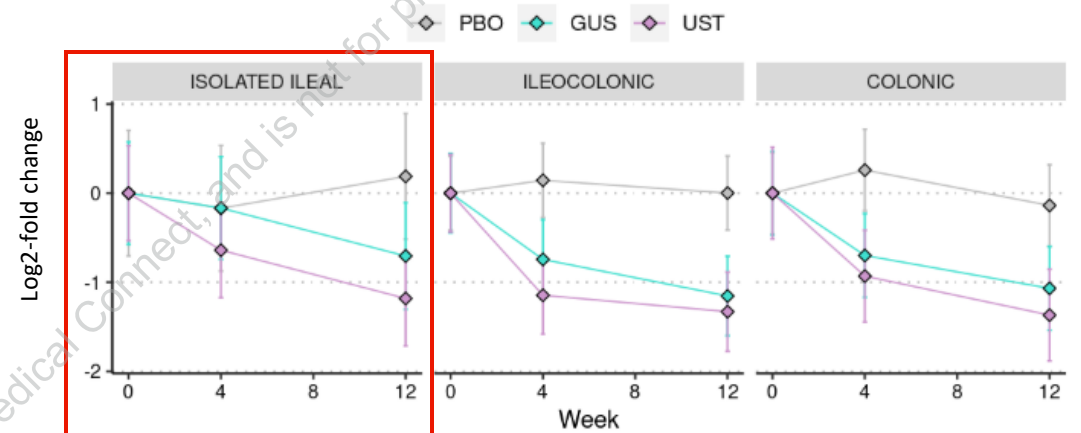
# of sampled patients

	Isolated Ileal	Ileo-colonic	Colonic
PBO	8	23	19
GUS	12	20	18
UST	14	20	15

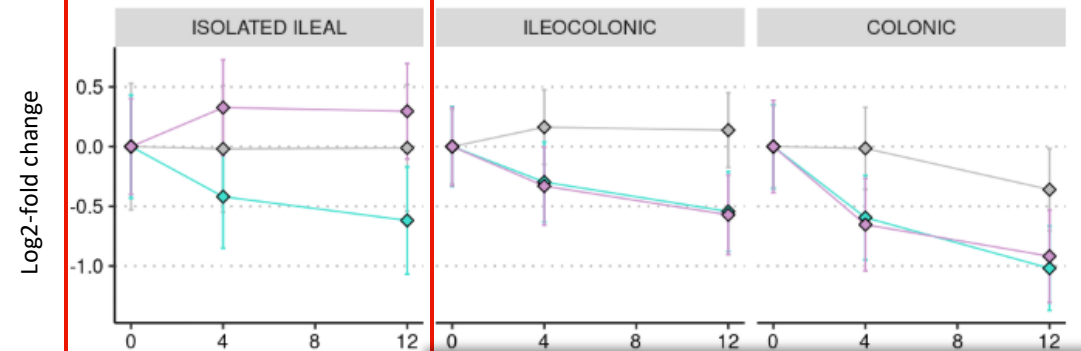
- Changes in IFN $\gamma$  gives evidence of PD effect of both GUS and UST across all patient groups
- By WK12 in isolated ileal patients, UST showed no changes in IL-23 pathway markers (IL-22, IL-17A), consistent with limited WK12 endoscopic efficacy

**This suggests a greater impact of IL-23p19 inhibition with GUS over IL-12/23p40, independent of disease area**

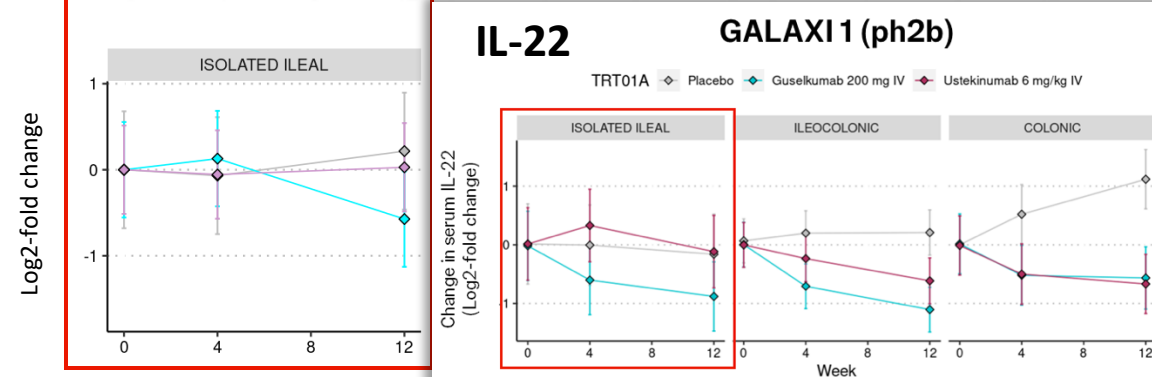
IFN $\gamma$



IL-17A



IL-22



# Tissue transcriptomic analysis supports mechanistic differentiation at the site of disease

## Transcriptomic profiling using RNA-sequencing

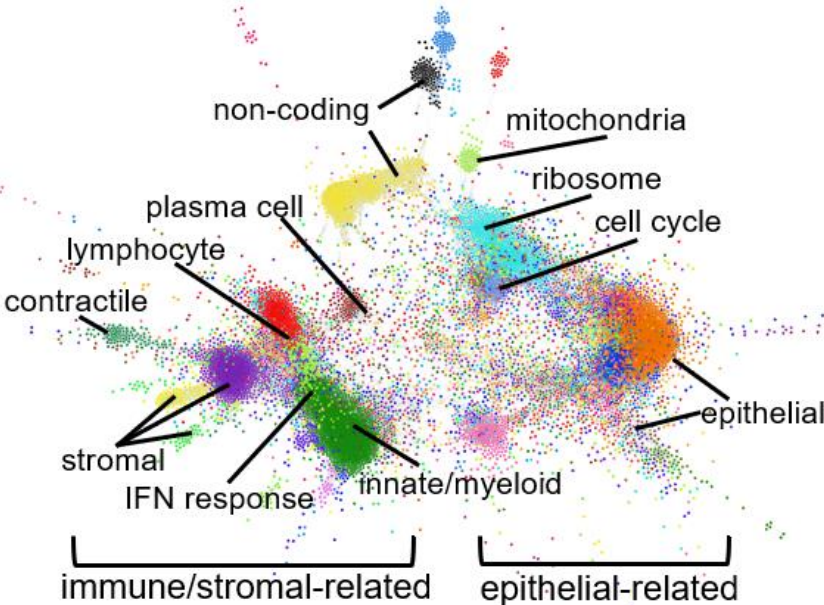
- Segment: **Ileum**, rectum
- Treatments: PBO, GUS, UST
- Timepoints: WK0, WK12, WK48

## Analysis approach

- For each segment, differential analysis over time per treatment arm was performed using linear mixed effects models in representative subject samples<sup>1</sup> (i.e., molecularly inflamed samples ( $bMIS^2 > 0$ ) from segments with  $SES-CD > 0$  at baseline)
- Interpretation/visualization using gene correlation networks (GCN) and gene set variation analysis (GSVA) with previously established single cell-derived modules<sup>3</sup>

# of sampled patients

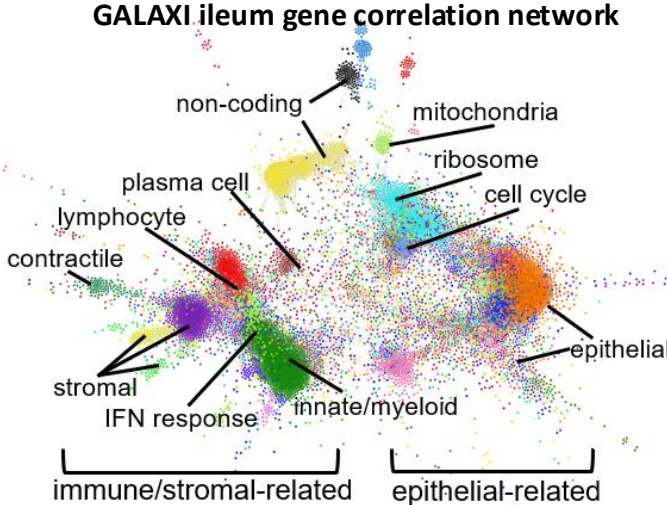
	Ileum	Rectum
PBO	23	23
GUS	114	67
UST	42	28



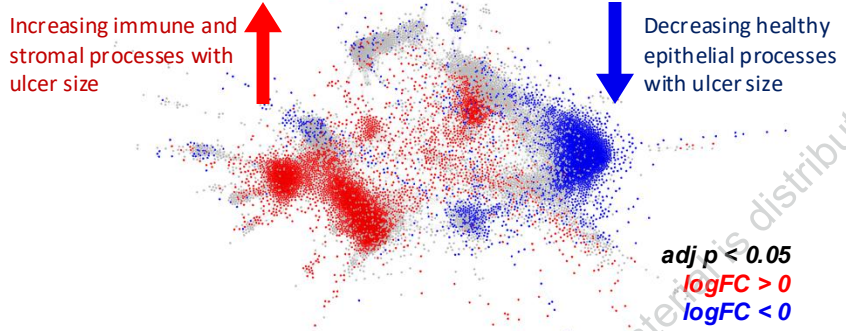
**GALAXI ileum gene correlation network:** Each cluster of genes (dots with similar color) represent co-expressed genes due to their association with a cell type or pathway.

1. Richards et al. ECCO 2024; P006  
2. Argmann et al. 2023. Gut;0:1-17  
3. Desai et al. UEGW 2022; OP186

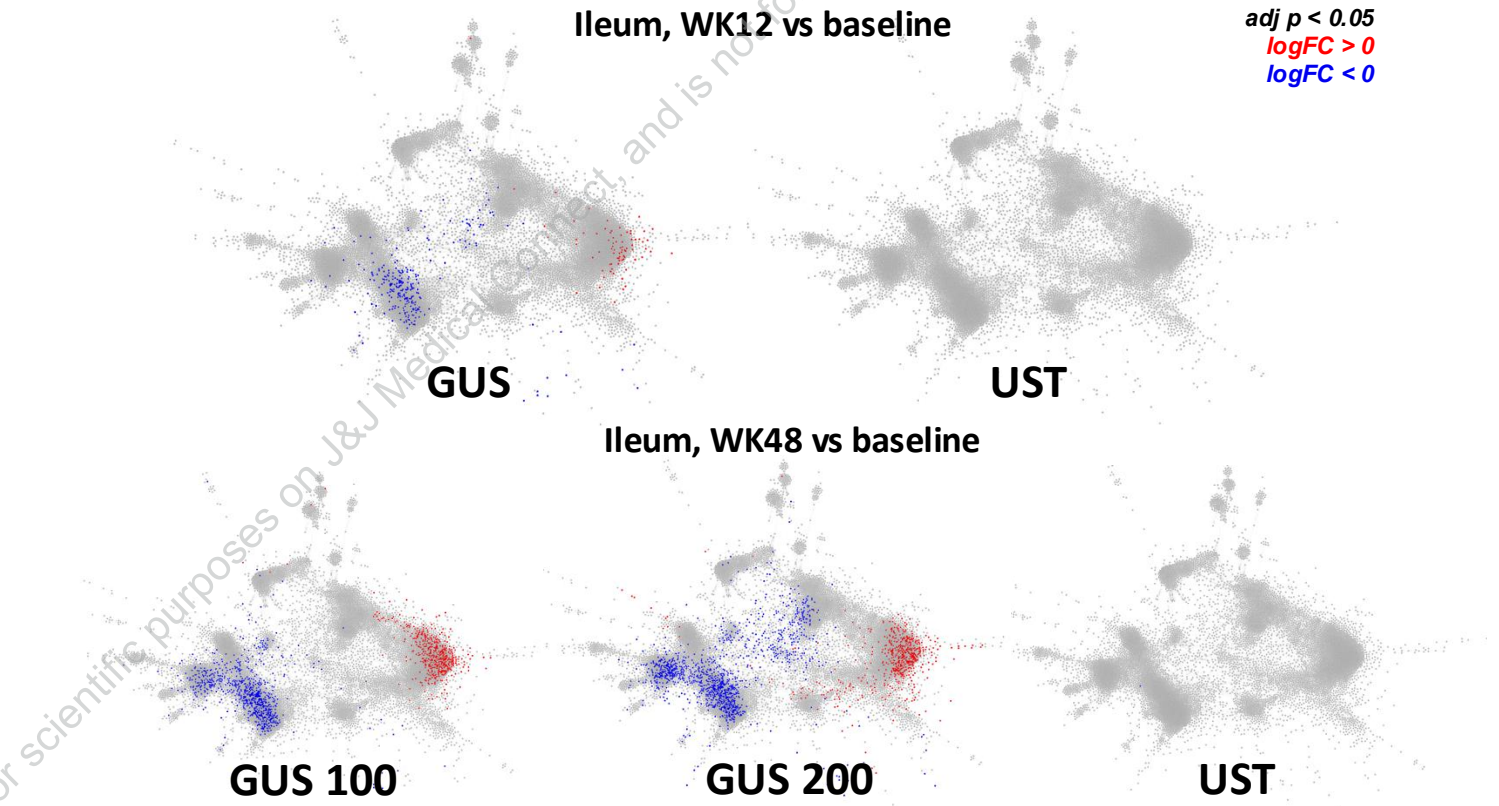
# Greater reversal of CD molecular disease profile with GUS in tissue than UST at WK12 and WK48



**Transcriptional changes in disease**  
(genes associated with ulcer size)



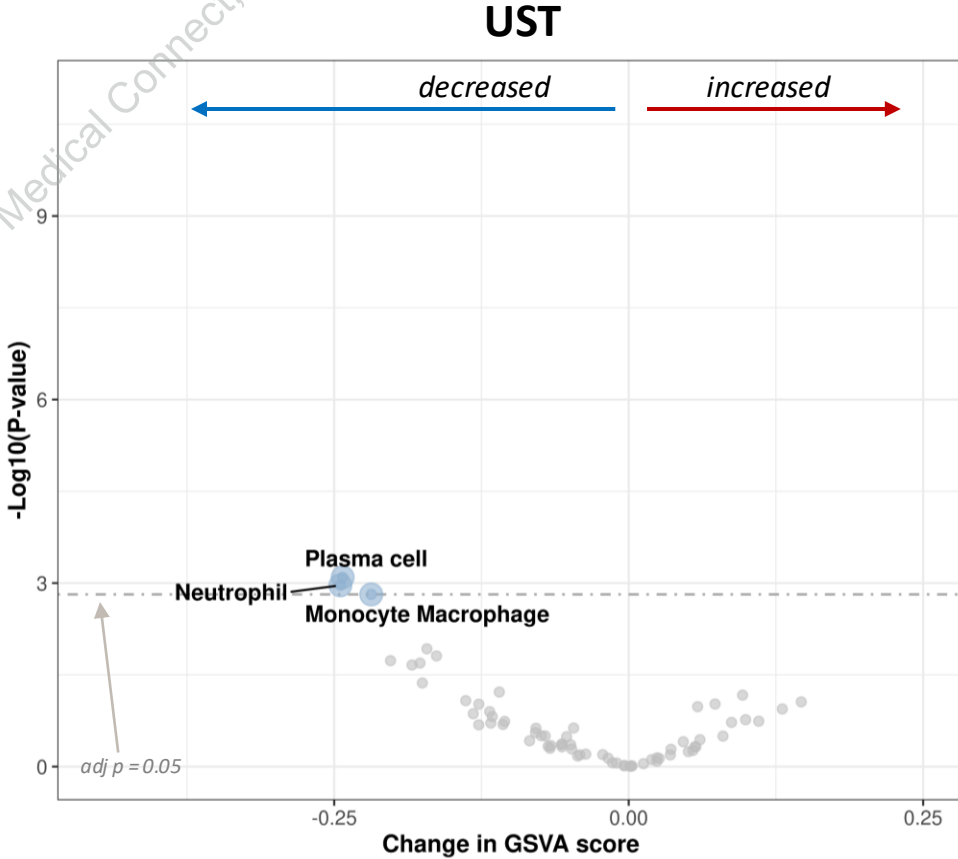
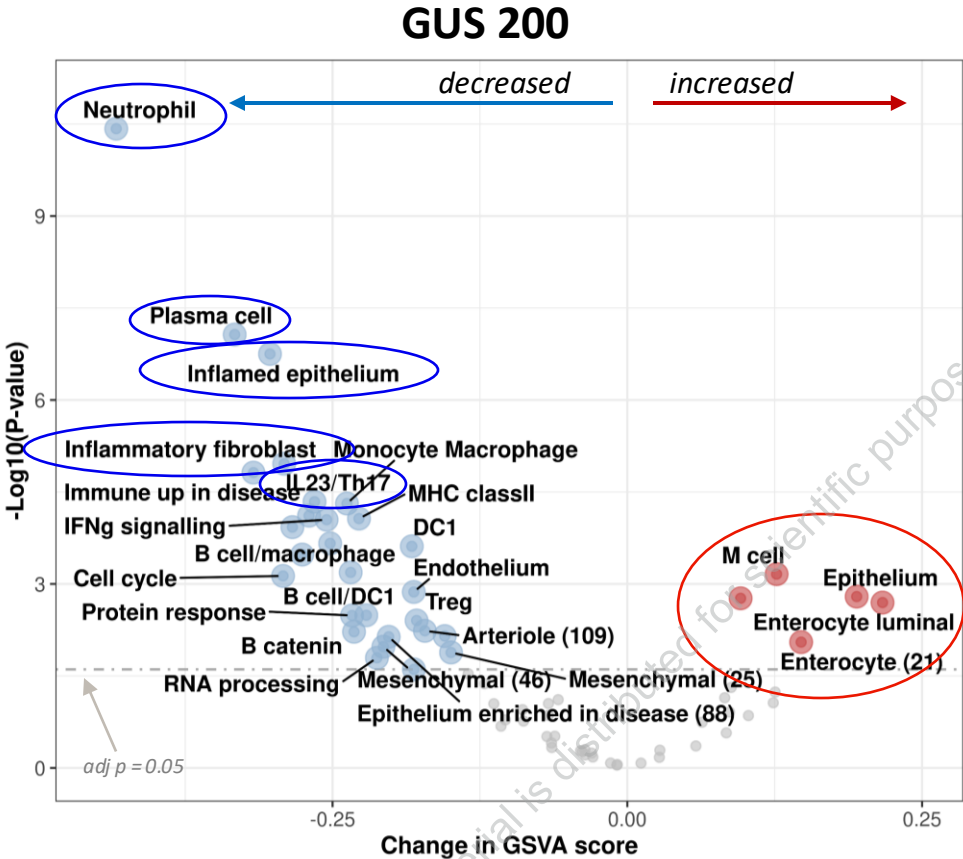
J&J Innovative Medicine



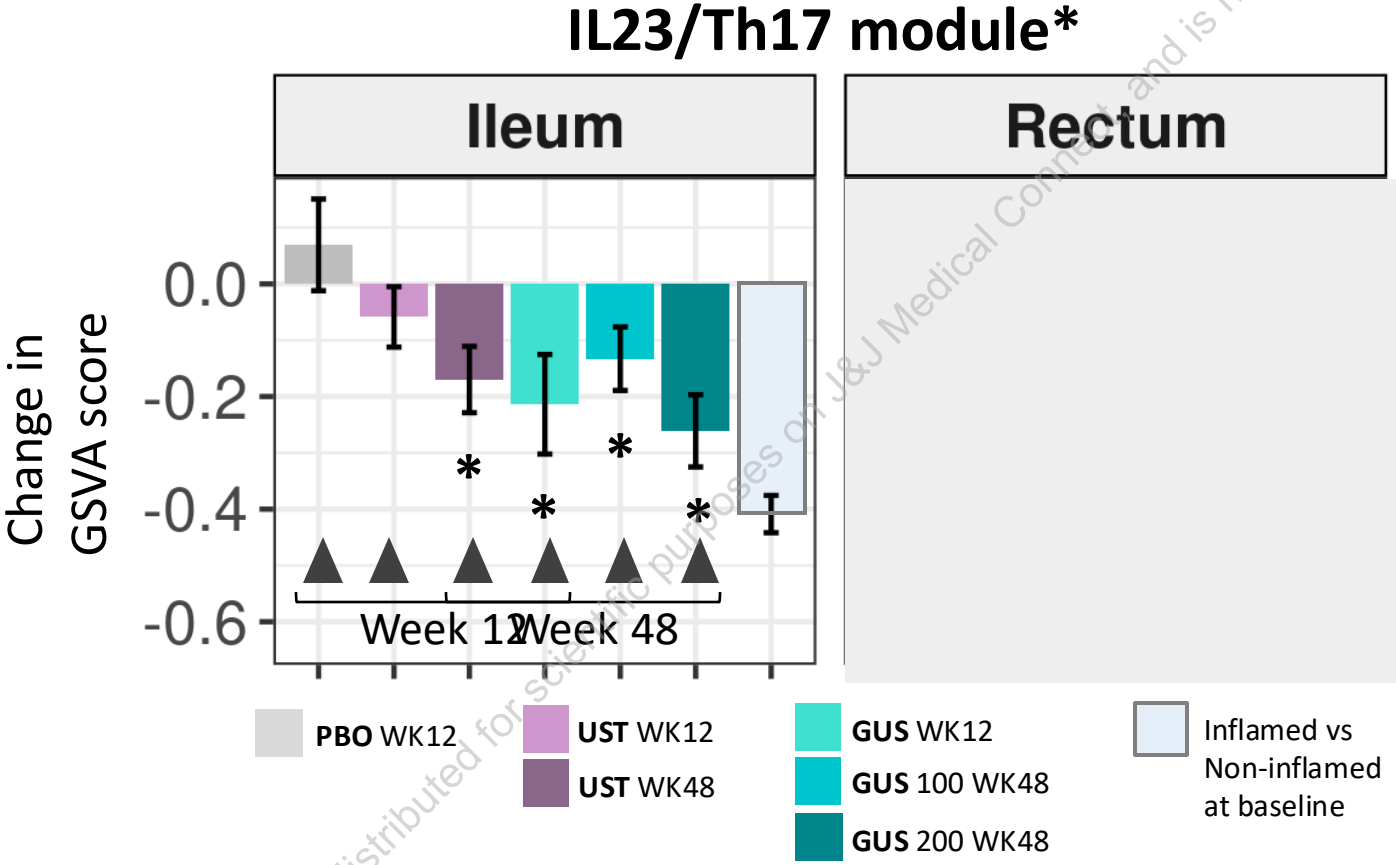
- In ileum, GUS showed significant reduction in inflammatory processes with increased epithelial features at WK12 and WK48; UST showed minimal transcriptomic changes in the ileum with  $adj\ p < 0.05$
- In rectum (not shown), both GUS and UST showed significant gene changes at WK12 and WK48, with GUS showing a greater degree of changes by WK48

# GUS decreases key inflammatory modules more than UST, including IL-23-related biology, and increases healthy epithelial processes

Differential analysis of single cell-derived modules  
Ileum, WK48 vs BL



# GUS shows greater decrease in T cell IL-23 biology compared to UST in ileum and rectum



\* IL23/Th17 module, derived from T cell single cell GCN, contains 8 genes related to T17 transcriptional state (e.g., IL22, IL17A)

\* Adjusted by T cell core module

# Conclusions

In GALAXI Ph3, despite inhibition of serum IFN $\gamma$  with UST, GUS showed greater changes in IL-23-related serum markers (IL-22, IL-17A) and greater reversal of tissue disease molecular features consistent with reported superior endoscopic efficacy.

..... GUS decreased IL-23/Th17 tissue module more than UST in ileum and rectum at WK12 and WK48

Notably in isolated ileal CD, UST showed no change in IL-23 related PD markers (serum IL-22 and IL-17A) by WK12, consistent with limited endoscopic remission previously observed in this sub-group.

..... Tissue molecular analysis indicates limited degree of changes with UST in ileum tissue

These data demonstrate differential effects of targeting IL-23p19 and IL-12/23p40 across tissue segments and CD patient populations with differing disease locations

UNITED EUROPEAN  
GASTROENTEROLOGY

**ueg** week

## Acknowledgments

- The authors thank the participants, investigators, and study personnel who made the GALAXI program possible
- This work was supported by Johnson & Johnson

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