# Comparison of pharmacodynamic and mechanistic response of guselkumab subcutaneous and intravenous induction in moderately to severely active Crohn's disease: molecular analysis of the GRAVITI and GALAXI Phase 3 studies

Dylan Richards*,[1] Ruchi Patel*,[1] Klebea Sohn,[1] Amy Hart,[1] Tae Lee,[1] Jared Liu,[1] Christopher Sisk,[1] Mobolaji Olurinde,[1] Natalie A. Terry,[1] Bradford McRae,[1] Walter Reinisch,2 Brian Feagan,3 Flavio Steinwurz,[4] Remo Panaccione,[5] Geert D'Haens,[6] and Patrick Branigan[1]

[1]Janssen Research & Development, LLC, Spring House, PA, USA; [2] Division Gastroenterology & Hepatology, Medical University of Vienna, Vienna, Austria; [3]Alimentiv, Inc, Western University, London, Ontario, Canada; [4]Hospital Israelita Albert Einstein, São Paulo, Brazil; [5]Inflammatory Bowel Disease Unit, Division of Gastroenterology and Hepatology, University of Calgary, Calgary, Canada; [6]Department of Gastroenterology, Amsterdam University Medical Centers, Amsterdam, Netherlands. * co-primary authors

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## Key Takeaways

- **Induction treatment with SC and IV guselkumab demonstrate similar pharmacodynamic responses in Crohn's disease**
- **GUS SC induction achieved significant anti-inflammatory effects in serum and tissue**
- **GUS SC induction showed segment-specific changes across all 5 segments consistent with endoscopic improvements across disease locations**

## Background

Guselkumab (GUS) is a selective dual-acting IL-23p19 subunit inhibitor that demonstrated efficacy with intravenous (IV) induction in patients with moderately to severely active Crohn's disease (CD) in the GALAXI trials.[1]

Subcutaneous (SC) induction with GUS evaluated in the Ph3 GRAVITI trial was also efficacious in treating patients with CD[2]

Here we present a comparison of the pharmacodynamic (PD) response of GUS SC and GUS IV induction therapy in inflammatory serum proteins from GRAVITI and GALAXI-2/ GALAXI-3, and an assessment of the mechanistic response in biopsy tissue following GUS SC induction at WK12 from GRAVITI.

## Objectives

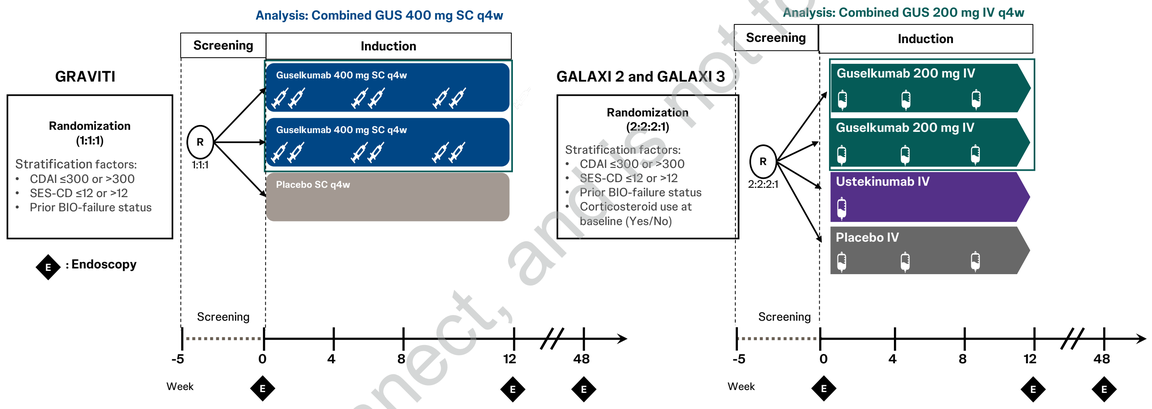
**Compare the PD response of guselkumab SC and IV induction on serum inflammatory proteins in CD**

**Define tissue transcriptional changes following GUS SC induction at WK12**

**Assess molecular inflammation associated with segmental endoscopic response to GUS SC induction**

## Methods

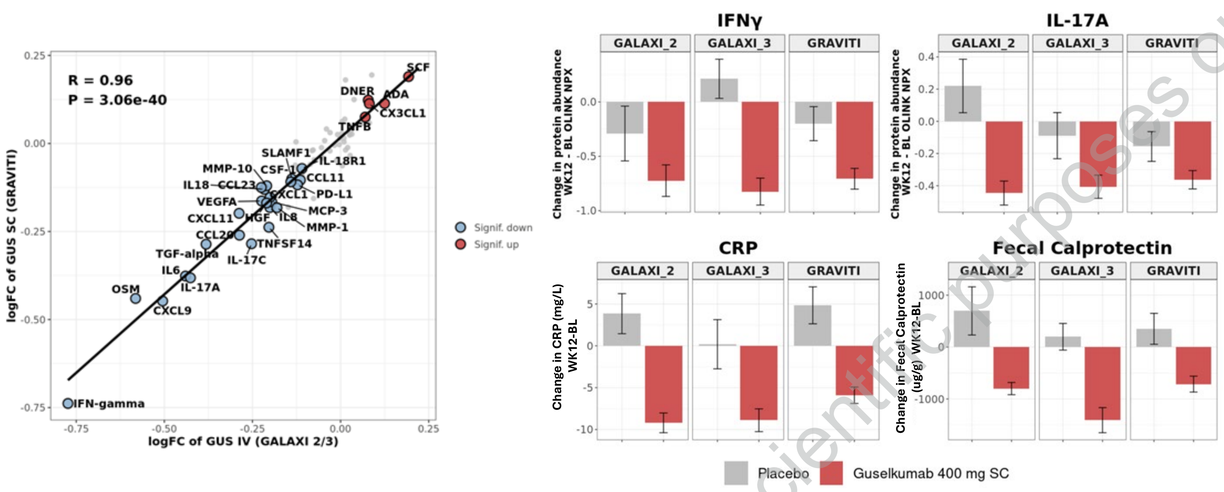
- Serum proteins were evaluated from 290 GRAVITI patients randomized to PBO or GUS 400mg SC q4w, and from 292 GALAXI patients randomized at PBO or GUS 200mg IV q4w at Weeks 0 and 12 using a 92-analyte inflammatory protein panel.
- Transcriptional profiling from each of the five anatomic segments in GRAVITI was conducted with samples from 277 patients at WK0 and WK12 using RNA sequencing.
- Disease location (ileal, colonic, ileocolonic) was based on the central reader's assessment
- Tissue inflammation scores (bMIS[3] and MAS[4]) were used to assess segmental molecular inflammation and correlation with segmental histology scores defined by Global Histologic Activity Score (GHAS), endoscopic scores, and sub-scores defined by Simple Endoscopic Score for CD (SES-CD).
- Analysis of treatment effect was performed using molecularly inflamed samples (defined as bMIS >0) from segments with SES-CD >0 at baseline. Transcriptional gene modules were evaluated for differential expression.




## Results

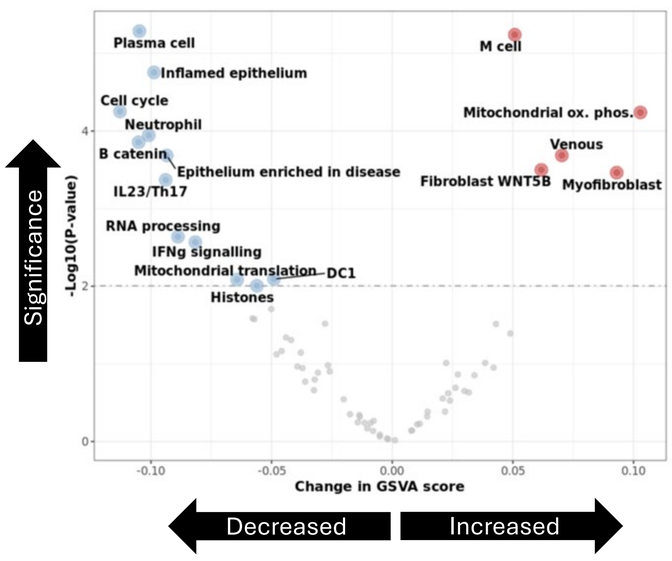
### *In serum, protein changes observed with GUS SC induction (GRAVITI) at WK12 were highly correlated with those observed with GUS IV induction (GALAXI-2 and GALAXI-3).*

- Changes observed with GUS 400mg SC q4w (n=290) and GUS 200mg IV q4w (n=292) at induction WK12 (R=0.96, p<0.05)
- Similar reductions were observed with SC and IV induction for IFN$_\gamma$, IL-17A, CRP and fecal calprotectin relative to PBO at WK12 (p<0.05)




*CRP and fecal calprotectin data generated independently at the Central Lab during the trial*

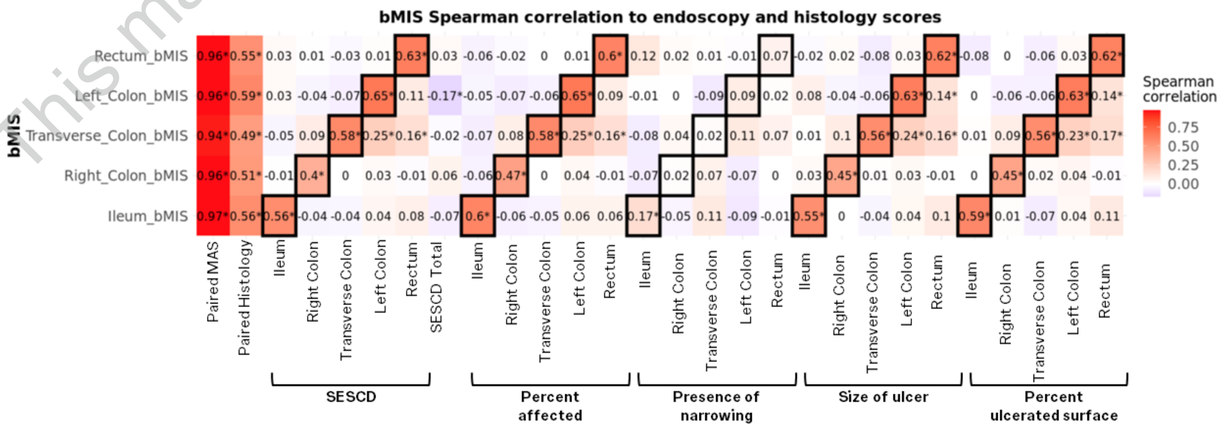
- RNA expression was assessed in molecularly inflamed samples (defined as bMIS >0) from segments with SES-CD >0 at baseline
- Data represent combined biopsies from 5 segments obtained from the combined GUS 400mg SC induction groups at baseline and Week 12 (n = 277 patients)
- Reductions were observed in modules representing inflammatory pathways and increases were observed in modules representing epithelial cells and repair mechanisms.




*Volcano plot representing changes in transcriptional modules observed in the combined GUS 400mg SC induction groups at WK12 relative to baseline*

### *Segmental molecular inflammation assessed by bMIS correlated with segmental histological and endoscopic sub scores at baseline*

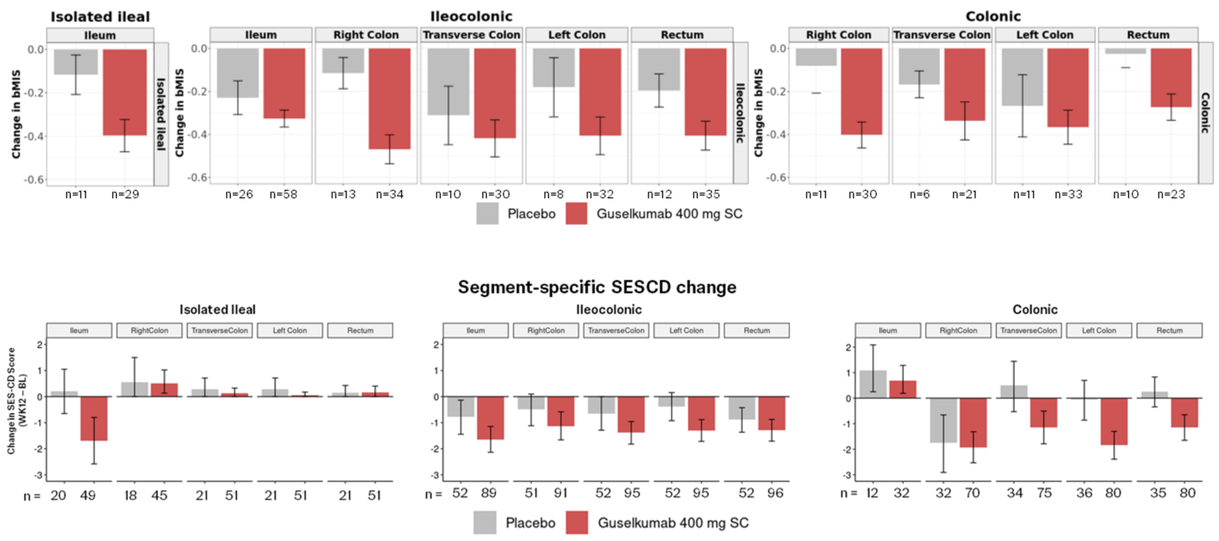
- A Tissue inflammation score (bMIS) was used to assess segmental molecular inflammation and correlation with segmental histology scores defined by GHAS, and endoscopic scores and sub-scores defined by SES-CD
- Higher correlation of inflammation (bMIS/ MAS) was observed with paired histology and endoscopic sub-scores
- Presence of narrowing was not associated with inflammation or histologic assessments




*Footnote order: p-values. Data shown are mean (SD) unless otherwise noted. [a,b]Footnotes. Abbreviations in alphabetical order, format: **BSA**=Body surface area, **W**=Weeks*

### *Compared to PBO, GUS SC induction decreases molecular inflammation in 5 anatomic segments corresponding to segmental endoscopic improvement in patient sub-groups*

- Assessment of segmental molecular inflammation (bMIS) in isolated ileal, colonic and ileocolonic disease in patient sub-groups
- Reductions in segmental molecular inflammation are observed in segments involved at baseline and reflect improvements in SES-CD Scores in isolated ileal, colonic and ileocolonic disease sub-groups



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**DISCLOSURES:** Dylan Richards, Ruchi Patel, Klebea Sohn, Amy Hart, Tae Lee, Jared Liu, Christopher Sisk, Mobolaji Olurinde, Natalie Terry, Bradford McRae, and Patrick Branigan are employees of Janssen and may hold stock in Johnson & Johnson.
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