Characterization of Serum Inflammatory Proteins in Response to guselkumab or ustekinumab Induction and Maintenance Dosing in Moderately to Severely Active Crohn's Disease: Analysis of GALAXI Ph3

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Key Takeaways

- GUS treatment attenuated key inflammatory serum cytokines associated with the IL-23 pathway in CD
- Responses at WK48 to GUS 200mg SC q4w and 100mg SC q8w dosing were similar
- Differential response at WK48 provides rationale for further exploration of mechanistic differences between IL23p19 and IL-12/ 23p40

Background

Guselkumab (GUS) is a selective dual-acting IL-23p19 subunit inhibitor that potently blocks interleukin 23 (IL-23) and binds to CD64, a receptor on cells that produce IL-23.[1]

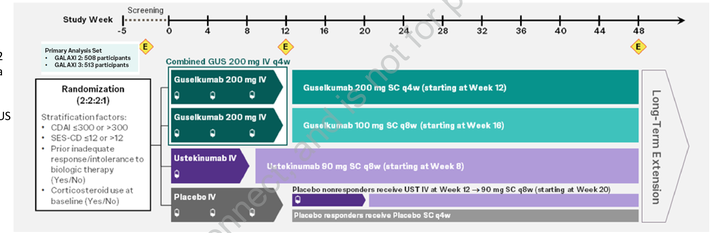
Guselkumab demonstrated efficacy with intravenous (IV) induction and subcutaneous (SC) maintenance in patients with moderately to severely active Crohn's disease (CD) in the Phase 2/3 GALAXI program.[2]

Objectives

Here we report characterization of serum inflammatory proteins associated with response to guselkumab (GUS) or ustekinumab (UST) induction and maintenance dosing using pooled samples from the Phase 3 GALAXI 2 and 3 studies.

Methods

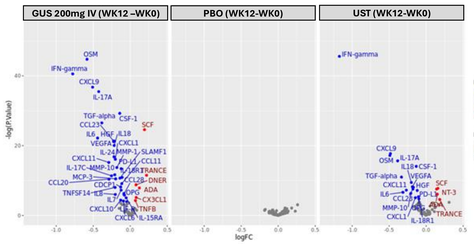
- Serum samples were evaluated in a subset of 409 patients from GALAXI 2 and GALAXI 3 at WK0, WK12 and WK48 for inflammatory proteins using a targeted 92-analyte inflammation panel.
- GUS induction groups (200 mg IV) were combined for analysis and the GUS maintenance doses were evaluated separately.
- Differential protein abundance was assessed by treatment group comparisons relative to WK0 in the context of endoscopic response and previous inadequate response to or intolerance to TNF therapy.



Results

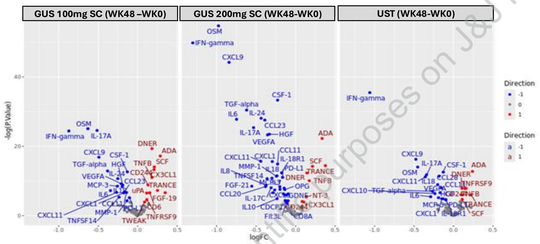
At WK12, GUS and UST induction treatment significantly reduced serum inflammatory proteins compared with PBO.

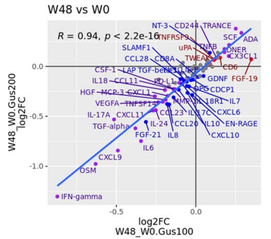
- Including OSM, IFNγ, CXCL9, IL-17A, TGFα and CSF-1 (P≤0.001).



At WK48, continued reduction in serum inflammatory proteins was observed with greater changes observed in the 200mg SC q4w group compared with the 100mg SC q8w group.

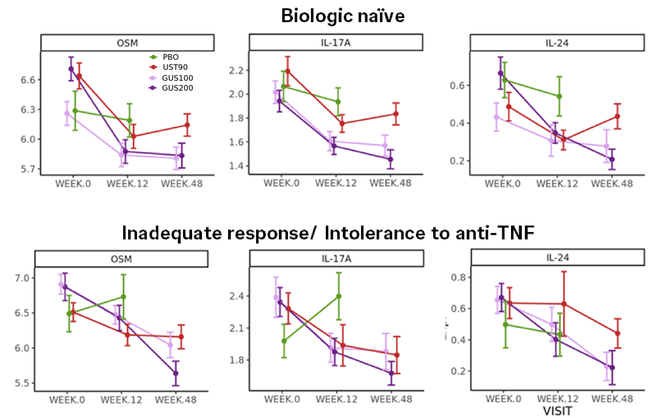
- GUS 200mg SC q4w and GUS 100mg SC q8w maintained similar responses at Wk48 with greater magnitude of change observed in the 200mg SC q4w maintenance group.





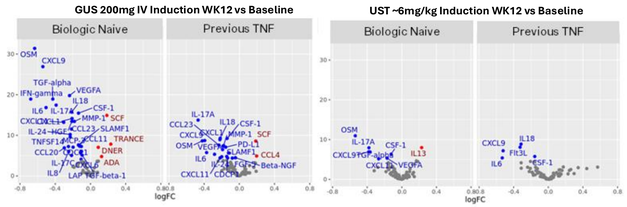
Mechanistic differences between the selective blockade of IL-23p19 and IL-12/23p40 were also apparent at WK48 in patients with previous TNF exposure

- GUS compared to UST maintained greater suppression of IL-17A (part of IL-23 pathway), OSM (characteristic of TNF non-response biology), and IL-24 (associated with inflammatory fibroblasts).



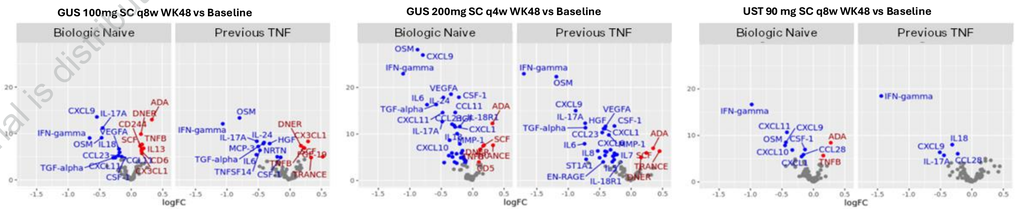
At WK12, in patients with inadequate response or intolerance to previous TNF therapy, only GUS reduced IL-17A and OSM.

- In contrast, there were no changes in these cytokines with UST or PBO in this population.
- IL-17A and OSM have been associated with nonresponse to TNF therapy.



At WK48, in both biologic naïve patients and in patients with inadequate response to or intolerance to previous TNF therapy, GUS maintained reduction of inflammatory proteins and increased proteins associated with epithelial repair in serum compared with UST.

- GUS 200mg SC q4w and GUS 100mg SC q8w maintenance dosing maintained similar responses at Wk48 in all comers.
- In comparison, UST 90mg SC q8w WK48 maintenance dosing reduced serum IFNγ but had minimal impact on other inflammatory proteins in TNF experienced patients.



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