Guselkumab induction therapy results in molecular resolution of inflammation in moderately to severely active ulcerative colitis: Results from the Phase 3 QUASAR induction study

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Key Takeaways

- **Guselkumab treatment resulted in a global reduction in tissue inflammation and establishment of a pro-healing environment confirming the mechanistic findings of the Phase 2b induction study**
- **Guselkumab's early clinical efficacy is reflected by serum proteomic changes that is consistent between the Phase 3 and Phase 2b induction studies**
- **These molecular changes were closely correlated with the clinically relevant endpoints such as histo-endoscopic mucosal improvement illustrating mechanisms underlying clinical efficacy outcomes**

Background

Guselkumab (GUS) is a selective dual-acting IL-23p19 subunit inhibitor that potently neutralizes interleukin 23 (IL-23) and binds to CD64, a receptor on cells that produce IL-23[1] that is now approved in the United States for treatment of moderately to severely active ulcerative colitis (UC).

GUS has demonstrated efficacy in UC based on the results of the QUASAR Phase 2b/3 studies[2,3].

Mechanistic data from the Phase 2b induction study demonstrated a restoration of intestinal homeostasis and initiation of epithelial repair associated with clinical response to guselkumab4. These findings were examined in the larger Phase 3 QUASAR induction study presented here.

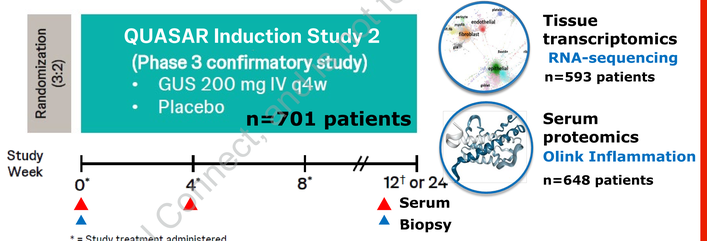
Objectives

To validate mechanistic observations from QUASAR Ph2b induction and to further characterize molecular changes induced by guselkumab treatment with the larger Ph3 QUASAR induction study.

Methods

Molecular changes from baseline to induction WK12 were evaluated in the QUASAR Phase 3 induction study

- At induction baseline, 701 patients with moderately to severely active UC were randomized 3:2 to receive GUS 200mg IV induction or placebo (PBO) and clinical efficacy was assessed at Week 12 (WK12)
- Molecular analysis of the randomized population was performed comparing induction WK12 to baseline (WK0) for tissue transcriptomics. WK4 and WK12 were compared to WK0 for serum proteomics
- Transcriptional profiling of colonic biopsies from 593 patients was performed with bulk RNA-sequencing and transcriptional gene modules were evaluated for differential expression
- Serum proteomic profiling of 648 patients was conducted using a targeted Olink Inflammation panel and differential protein abundance was assessed



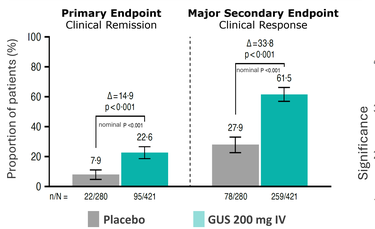
Tissue transcriptomics
RNA-sequencing
n=593 patients

Serum proteomics
Olink Inflammation
n=648 patients

Results

QUASAR Phase 3 induction study: Guselkumab induction therapy was effective versus placebo in patients with UC

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



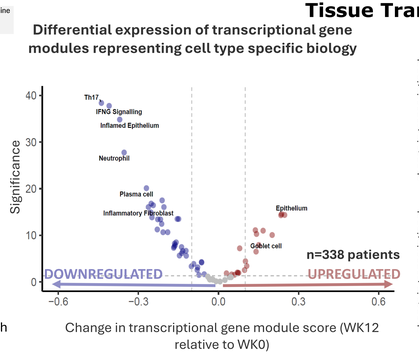
Significantly higher proportions of patients treated with GUS 200mg IV achieved primary and major secondary clinical endpoints at WK12 compared with PBO[3]

Clinical remission: A Mayo stool frequency subscore of 0 or 1 and not increased from baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopic subscore of 0, or 1 with no friability

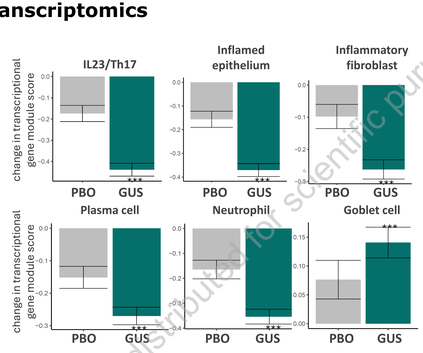
Clinical response: A decrease from induction baseline in the modified Mayo score by ≥ 30% and ≥ 2 points, with either a ≥ 1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1

n/N= number of patients

Guselkumab induction therapy resulted in transcriptional downregulation of inflammatory signals and upregulation of healthy epithelium signals at WK12

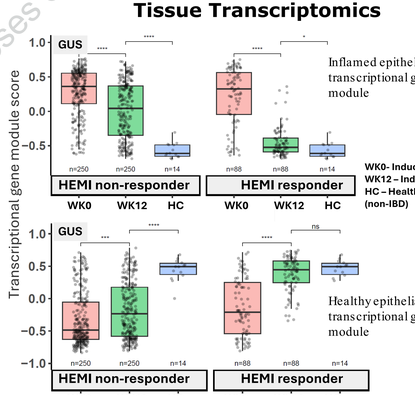


Differential expression of transcriptional gene modules representing cell type specific biology in guselkumab (GUS) treated patients. Y-axis: significance (–log10(Adj.P-value)); X-axis: change in transcriptional gene module score (gene set variation analysis (GSVA) score) (WK12-WK0)



Change in transcriptional gene module scores from induction baseline to induction WK12 in Placebo (PBO) and Guselkumab (GUS) groups. Y-axis: change in GSVA score (WK12 –WK0). PBO (n=214); GUS (n=338) P<0.0001

Patients who achieved HEMI at WK12 demonstrated the most robust changes in transcriptional gene module expression nearing non-IBD control levels

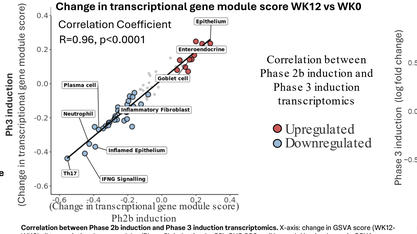


WK0- Induction baseline
WK12 – Induction WK12
HC – Healthy Control (non-IBD)

Transcriptional gene module scores in patients from the GUS group stratified by their HEMI (Histological Endoscopic Mucosal Improvement) response status. Y-axis: transcriptional gene module score. HEMI: Histo-Endoscopic Mucosal Improvement (stratification of patients by HEMI response status. ***p<0.001, ****p<0.0001, ns= number of patients

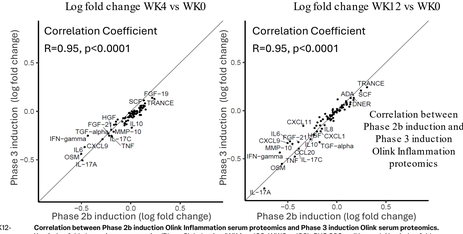
Histo-endoscopic mucosal improvement: Achieving a combination of histologic improvement (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue per Geboes grading system) and endoscopic improvement

Transcriptional gene modules changes at WK12 correlated with changes observed in the Phase 2b induction study



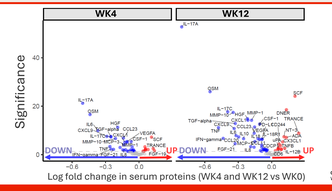
Correlation between Phase 2b induction and Phase 3 induction transcriptomics. X-axis: change in GSVA score (WK12-WK0) all transcriptional gene modules (Phase 2b Induction (n=82), GUS 200mg IV group); Y-axis: change in GSVA score (WK12-WK0) all transcriptional gene modules (Phase 3 Induction (n=338)); Correlation plot (R=0.96, p<0.0001), n= number of patients

Inflammatory serum protein changes correlated with changes observed in the Phase 2b induction study



Correlation between Phase 2b induction Olink Inflammation serum proteomics and Phase 3 induction Olink serum proteomics. X-axis: log fold change in serum proteins (Phase 2b Induction (WK4: n=385; WK12 n=377) ; Correlation plot (WK4: R=0.95, p<0.0001, WK12: R=0.96, p<0.0001), n= number of patients

Inflammatory serum proteins were reduced as early as WK4 and continued to decline through WK12



Olink Inflammation proteomics

Inflammatory serum proteins were reduced as early as WK4, and continued to decline through WK12
IFNγ, IL-17A, OSM, and IL-6 (FDR<0.05)

Changes serum proteins in Phase 3 Induction study at WK4 and WK12 relative to baseline analyzed using Olink Inflammation panel. Y-axis: significance (–log10(Adj.P-value)); X-axis: log fold change in serum proteins from WK4 (n=385) and WK12 (n=377) relative to WK0. n= number of patients

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