Efficacy of Guselkumab versus Placebo in Crohn's Disease Based On Prior Response/Exposure to Biologic Therapy: Results of the GALAXI 2 & 3 Phase 3 Studies

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Background

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

GALAXI 2 & 3 independently established[2] the short- and long-term efficacy of IV induction and SC maintenance therapy with guselkumab compared with placebo with favorable benefit/risk profile in moderately to severely active Crohn's disease

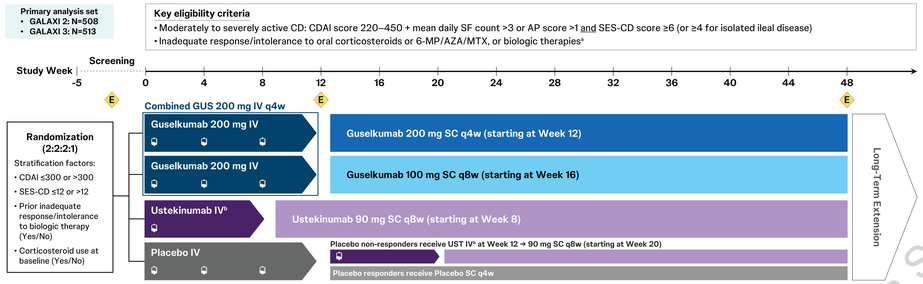
Guselkumab 200 mg IV induction followed by 100 mg q8w or 200 mg q4w SC maintenance demonstrated statistical superiority to ustekinumab at Week 48 in prespecified, multiplicity-controlled analyses of pooled data from GALAXI 2 & 3

Objective

To compare efficacy outcomes with guselkumab versus placebo in the BIO-naïve and BIO-IR (inadequate response/intolerance) subpopulations using the pooled GALAXI 2 & 3 dataset

Methods

Identically Designed, Double-Blind, Treat-Through Phase 3 Studies With Active Comparator



a. Biologic therapies: TNF antagonists or vedolizumab (participants with a history of inadequate response or intolerance to ustekinumab were excluded). b. Ustekinumab IV ~6 mg/kg.
Note: To maintain treatment masking, all participants received active and/or placebo IV q4w through Week 12 and active and/or placebo SC q4w through Week 48.
6-MP=mercaptopurine; AP=abdominal pain; AZA=azathioprine; CDAI=Crohn's Disease Activity Index; E=endoscopy; IV=intravenous; MTX=methotrexate; q4w=every 4 weeks; q8w=every 8 weeks; SC=subcutaneous; SES-CD=Simple Endoscopic Score for Crohn's Disease; SF=stool frequency.

Endpoints and Statistical Considerations

Co-primary endpoints (each guselkumab regimen vs placebo)
- Clinical response at Week 12 AND clinical remission at Week 48 (patient-level)
- Clinical response at Week 12 AND endoscopic response at Week 48 (patient-level)

Major secondary endpoints (combined guselkumab 200 mg IV vs placebo)
- Clinical remission at Week 12
- Endoscopic response at Week 12

Subpopulation Analyses
- BIO-IR: participants with a history of inadequate response or intolerance to biologic therapy
- BIO-naïve: participants without a history of exposure to biologic therapy

Statistical Considerations
- Subpopulation analyses in the individual trials and the pooled Week 12 comparisons were prespecified but not multiplicity controlled
- Analyses of the co-primary endpoints in the pooled GALAXI 2 & 3 dataset were performed post hoc
- Participants with treatment failure or missing data were considered to not have met the endpoint
- All p-values are nominal

Key Takeaways

- **In analyses of data pooled across the double-blind GALAXI 2 & 3 trials, guselkumab was efficacious versus placebo in the overall population and BIO-naïve and BIO-IR subpopulations for the Week 12 endpoints and the long-term Week 12/48 co-primary endpoints**
  - Clinical remission at Week 12
  - Endoscopic response at Week 12
  - Clinical response at Week 12 AND clinical remission at Week 48 (patient-level)
  - Clinical response at Week 12 AND endoscopic response at Week 48 (patient-level)
- **Treatment effects compared to placebo were similar between BIO-naïve and BIO-IR subpopulations, indicating efficacy in BIO-naïve participants and the more refractory BIO-IR group**

Results

Baseline CD Medication History

	Placebo N=148	Guselkumab: 200 mg IV q4w → 100 mg SC q8w N=286	Guselkumab: 200 mg IV q4w → 200 mg SC q4w N=296	Guselkumab: Combined 200 mg IV q4w N=582
Biologic naïve (BIO-naïve), n (%)	61 (41.2%)	116 (40.6%)	128 (43.2%)	244 (41.9%)
History of inadequate response/intolerance to biologic therapy (BIO-IR), n (%)	78 (52.7%)	153 (53.5%)	147 (49.7%)	300 (51.5%)
At least one anti-TNF	76 (97.4%)	149 (97.4%)	143 (97.3%)	292 (97.3%)
Two or more anti-TNFs	23 (29.5%)	31 (20.3%)	31 (21.1%)	62 (20.7%)
Vedolizumab	13 (16.7%)	25 (16.3%)	18 (12.2%)	43 (14.3%)

Note: Participants with a history of inadequate response or intolerance to ustekinumab were excluded.

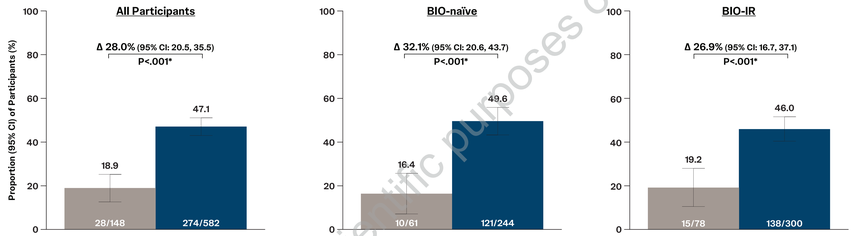
Baseline Characteristics

	BIO-naïve N = 426[a]	BIO-IR N = 534[a]
Age (years), mean (SD)	36.3 (13.16)	36.9 (12.79)
Female sex	44.6%	41.8%
Crohn's disease duration (years), mean (SD)	5.04 (6.058)	8.54 (7.585)
CDAI score, mean (SD)	292.9 (51.73)	294.9 (52.95)
SES-CD score, mean (SD)	11.9 (6.72)	13.7 (7.54)
Endoscopic disease severity (SES-CD score), n (%)		
Moderate (7–16)	231 (54.2%)	284 (53.2%)
Severe (>16)	98 (23.0%)	162 (30.3%)
Involved GI areas by central reader, n (%)		
Ileum only	108 (25.4%)	104 (19.5%)
Colon only	169 (39.7%)	213 (39.9%)
Ileum and Colon	149 (35.0%)	217 (40.6%)
CRP (mg/L), median (IQR)	4.8 (1.7; 13.0)	8.4 (3.1; 24.7)
>3 mg/L, n (%)	272 (63.8%)	402 (75.3%)
Fecal calprotectin (µg/g), median (IQR)	728.0 (244.0; 1612.0)	1225.0 (445.0; 2494.0)
>250 µg/g, n (%)	314 (74.6%)	445 (84.6%)
Concomitant CD medications at baseline, n (%)		
6-MP/AZA	127 (29.8%)	136 (25.5%)
MTX	1 (0.2%)	15 (2.8%)
Oral corticosteroids	192 (45.1%)	158 (29.6%)

a. Includes all participants (including those randomized to ustekinumab) in the BIO-naïve or BIO-IR subpopulation of the primary analysis set (pooled GALAXI 2 & 3).

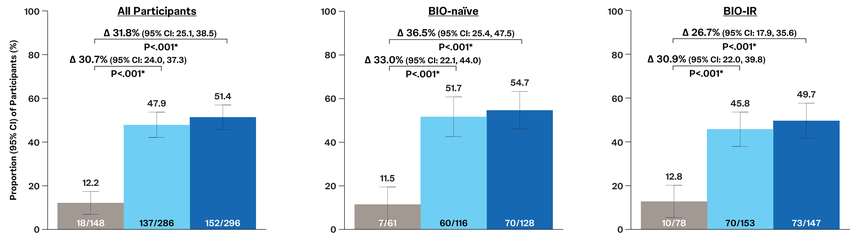
Clinical Remission at Week 12

Clinical remission: CDAI < 150



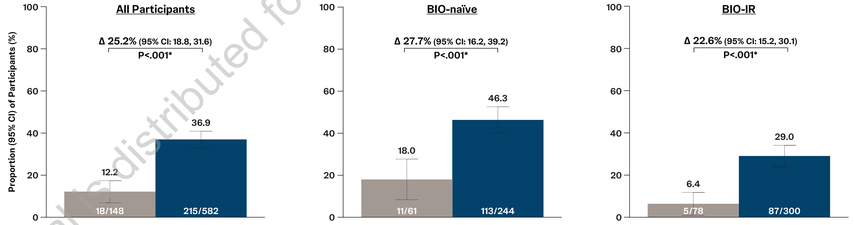
Clinical Response at Week 12 AND Clinical Remission at Week 48

Clinical response: ≥100-point reduction from baseline CDAI score or CDAI < 150; Clinical remission: CDAI score <150



Endoscopic Response at Week 12

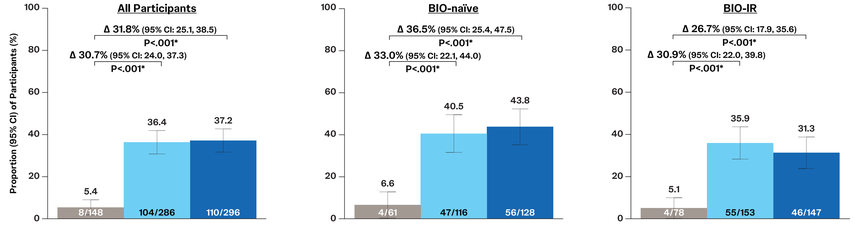
Endoscopic response: ≥50% improvement from baseline in SES-CD or SES-CD ≤ 2



*Nominal p-value.
Results from the pooled GALAXI 2 & 3 dataset presented as n (%); Δ% (adjusted treatment difference) vs placebo; p-value vs placebo. Adjusted treatment differences and p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), BIO-IR status (Yes or No; this variable used only in analyses of the overall population), and baseline corticosteroid use (Yes or No). Participants with CD-related surgery; a prohibited change in concomitant CD medication; or who discontinued study agent due to lack of efficacy, AE of worsening CD or discontinued study agent for any other reason other than COVID-19-related reasons or regional crisis prior to the analysis timepoint were considered not to have met the endpoint criteria. Participants who discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis had their observed data used, if available, to determine responder and non-responder status from that timepoint onwards. After accounting for these scenarios participants with insufficient data to calculate the outcome measure at the designated analysis timepoint were considered not to have achieved the endpoint at that timepoint.

Clinical Response at Week 12 AND Endoscopic Response at Week 48

Clinical response: ≥100-point reduction from baseline in CDAI or CDAI < 150; Endoscopic response: ≥50% improvement from baseline in SES-CD or SES-CD ≤ 2



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