

Effects of Subcutaneous Guselkumab Induction and Maintenance on Histologic Outcomes in Patients with Moderately to Severely Active Crohn's Disease in GRAVITI, a Phase 3 Double-blind, Placebo-controlled, Treat-through Study

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Key Takeaways

- Compared to placebo, participants with moderately to severely active Crohn's disease receiving SC induction and maintenance treatment with guselkumab achieved greater rates of histologic response, histologic remission, histo-endoscopic response, and histo-endoscopic remission through Week 48
- These results support the use of histologic and composite histologic and endoscopic endpoints as measures of Crohn's disease activity and the overall efficacy of SC guselkumab in Crohn's disease

Background

Assessment of histologic disease activity is becoming increasingly important as a measure of treatment efficacy in Crohn's disease

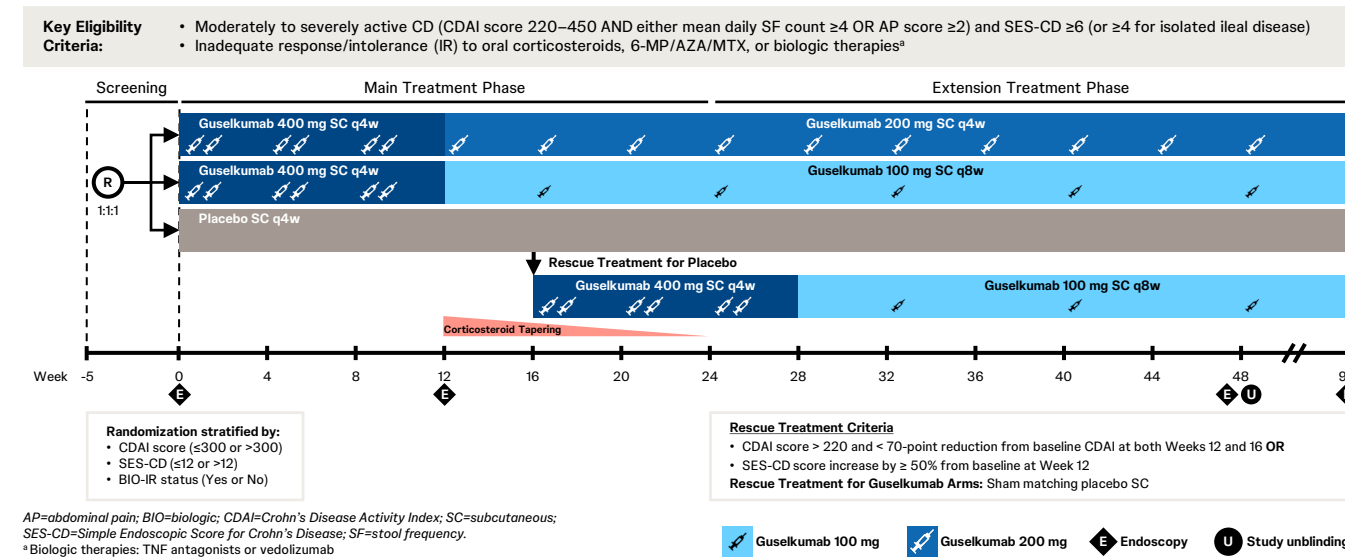
Guselkumab is a dual-acting IL-23p19 subunit inhibitor

Guselkumab was efficacious in double-blind, placebo-controlled, treat-through trials in participants with moderately to severely active Crohn's disease using IV induction and SC maintenance (GALAXI 2 & 3) or SC induction and maintenance (GRAVITI)

Objective

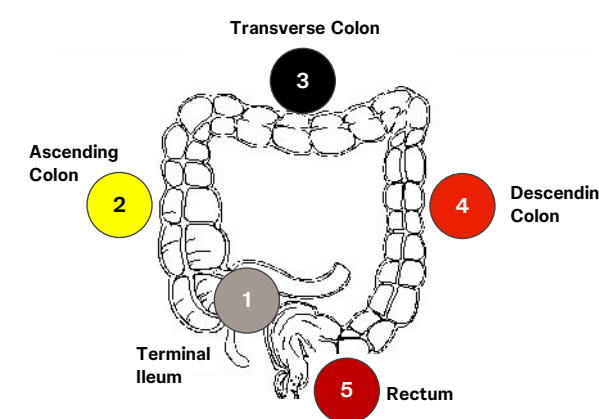
Here we report histologic outcomes following guselkumab SC induction and maintenance from GRAVITI (NCT05197049)

Methods



Assessments

- Two biopsies were obtained from the most affected area (or if no disease activity present, from normal-appearing mucosa) in 5 segments: terminal ileum, ascending colon, transverse colon, descending colon, and rectum
- In a segment with ulcers, biopsies were taken from the edge of the ulcer



Endpoints

- Histologic response: $\geq 50\%$ reduction in RHI score from baseline or a score ≤ 3 with sub-scores of lamina propria neutrophils and neutrophils in epithelium must be equal to 0, with no ulcers or erosions
- Histologic remission: RHI score ≤ 3 with sub-scores of lamina propria neutrophils, neutrophils in the epithelium and erosions or ulcerations equal to 0
- Histo-endoscopic response: $\geq 50\%$ reduction in RHI score from baseline or a score ≤ 3 with sub-scores of lamina propria neutrophils and neutrophils in epithelium must be equal to 0, with no ulcers or erosions AND $\geq 50\%$ improvement from baseline in SES-CD or SES-CD ≤ 2
- Histo-endoscopic remission: RHI score ≤ 3 with sub-scores of lamina propria neutrophils, neutrophils in the epithelium and erosions or ulcerations equal to 0 AND SES-CD ≤ 4 and at least a 2-point reduction from baseline and no subscore greater than 1 in any individual component

Statistical Considerations

- Histologic endpoints in GRAVITI were exploratory and not controlled for multiple comparisons; p-values are nominal
- Histologic response was assessed in participants in the full analysis set with baseline histologic disease, defined as RHI score > 0 for any of Items 2-4 of RHI (lamina propria neutrophils, neutrophils in epithelium, or erosions or ulcerations)
- Histologic remission, histo-endoscopic response, and histo-endoscopic remission were assessed in the full analysis set
- Adjusted treatment differences, 95% CIs, and p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator, using stratification factors of baseline CDAI score (≤ 300 or >300), baseline SES-CD (≤ 12 or >12), and prior history of inadequate response or intolerance to biologics (Yes or No)

- Participants who had a CD-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.), had a prohibited change in CD medication, discontinued study intervention for any reason (other than COVID-19 related reasons [excluding COVID-19 infection] or regional crisis), or who met rescue criteria at Week 16 were considered non-responders at Week 48. Participants who discontinued study intervention due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis had their observed data used, if available. After accounting for the aforementioned data handling rules, participants who were missing data pertaining to an endpoint at a designated timepoint were considered not to have achieved the endpoint.

Results

Baseline disease characteristics and Crohn's disease medication history

Full analysis set	Guselkumab			
	Placebo SC (N=117)	400 mg SC q4w \rightarrow 100 mg SC q8w (N=115)	400 mg SC q4w \rightarrow 200 mg SC q4w (N=115)	400 mg SC q4w induction combined (N=230)
Characteristics				
CD duration in years, mean (SD)	7.0 (7.75)	9.2 (9.08)	7.9 (7.13)	8.5 (8.17)
CDAI score, mean (SD)	293.0 (49.09)	300.4 (54.32)	297.3 (54.69)	298.8 (54.41)
SES-CD score, mean (SD)	12.0 (6.89)	12.2 (6.85)	11.8 (7.12)	12.0 (6.97)
CRP (mg/L), median (IQR)	7.9 (2.1; 14.7)	5.2 (1.7; 13.3)	5.7 (1.7; 16.1)	5.5 (1.7; 14.9)
Fecal calprotectin ^a (μ g/g), median (IQR)	712.0 (243.0; 1724.0)	610.0 (226.0; 1554.0)	600.5 (235.0; 1650.0)	610.0 (228.0; 1608.0)
Baseline histologic disease ^b	94 (80.3%)	91 (79.1%)	88 (76.5%)	179 (77.8%)
Involved GI areas by central reader, n (%)				
Colon only	40 (34.2%)	41 (35.7%)	40 (34.8%)	81 (35.2%)
Ileum only	22 (18.8%)	25 (21.7%)	27 (23.5%)	52 (22.6%)
Ileum and Colon	55 (47.0%)	49 (42.6%)	48 (41.7%)	97 (42.2%)
Medication details				
Biologic naïve	56 (47.9%)	53 (46.1%)	52 (45.2%)	105 (45.7%)
History of inadequate response/intolerance ^c to biologics, n (%)	53 (45.3%)	55 (47.8%)	53 (46.1%)	108 (47.0%)
Baseline use of 6-MP/AZA/MTX	33 (28.2%)	29 (25.2%)	37 (32.2%)	66 (28.7%)
Baseline oral corticosteroid use	33 (28.2%)	32 (27.8%)	38 (33.0%)	70 (30.4%)

CDAI=Crohn's Disease Activity Index; SC=subcutaneous; SD=standard deviation; SES-CD=Simple Endoscopic Score for Crohn's Disease. ^aBased on N=117 for placebo, N=115 for guselkumab 400 mg q4w \rightarrow 100 mg SC q8w, N=114 for guselkumab 400 mg \rightarrow 200 mg SC q4w, and N=229 for guselkumab combined; ^bRobarts Histopathology Index (RHI) score > 0 for any of Items 2-4 of RHI (lamina propria neutrophils, neutrophils in epithelium, or erosions or ulcerations); ^cPrimary nonresponse, secondary nonresponse, or intolerance.

- Of the 347 participants randomized into GRAVITI, 273 (78.7%) had histologic disease at baseline per RHI score
- SC induction therapy with guselkumab (400 mg SC at Weeks 0/4/8) resulted in greater rates of histologic response, histologic remission, histo-endoscopic response, and histo-endoscopic remission compared to placebo at Week 12 based on RHI
- At Week 12, similar outcomes were observed using GHAS or Geboes scoring criteria

- At Week 48, greater proportions of participants receiving guselkumab 100 mg SC q8w or 200 mg SC q4w maintenance achieved RHI-based histologic response, histologic remission, histo-endoscopic response, and histo-endoscopic remission compared to placebo
- At Week 48, similar outcomes were observed using GHAS or Geboes scoring criteria

