Unsupervised Machine Learning to Identify Distinct Response Patterns to Guselkumab in Participants With Crohn's Disease: Post Hoc Analysis of the GRAVITI and GALAXI 2/3 Studies

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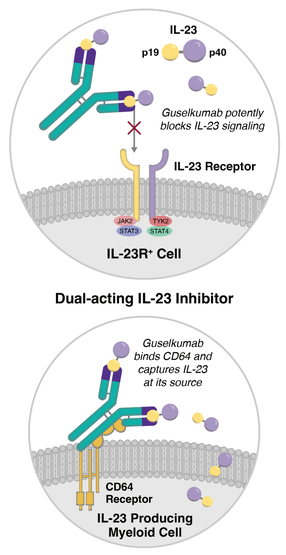
Key Takeaways

- Unsupervised machine learning using CDAI responses of guselkumab-treated participants detected 5 distinct response clusters in both the GRAVITI and GALAXI 2/3 studies
- Through Week 48, distinct patient populations could be separated by degrees and dynamics of clinical response which were similar with either SC or IV induction
- A correlation was observed for the clinical response trajectories and rates of endoscopic remission at Week 12 and Week 48
- Further investigation of participant characteristics related to these response patterns may direct long-term therapies and contribute to an individualized precision medicine approach to IBD

Background

- Typically, Crohn's disease (CD) trials report efficacy using binary endpoints including clinical remission or endoscopic response, aggregating the outcomes of all participants at specified timepoints
- Analysis of individual longitudinal trends of efficacy based on participant-level clinical data provides a better understanding of response to treatment, and may help optimize personalized treatment in IBD
- Artificial intelligence, including machine learning, may be useful in a clinical setting to possibly identify patterns and predictors of individual treatment response in patients with CD
- Guselkumab is a selective, dual-acting interleukin (IL)-23p19 subunit inhibitor that potently blocks IL-23 and binds to CD64, a receptor on immune cells that produce IL-23[1]



Objective

- **To use unsupervised learning to identify clusters of guselkumab-treated participants from the Phase 3 GRAVITI[2] and GALAXI 2 & 3[3,4] studies characterized by individual Crohn's Disease Activity Index (CDAI)-based response trajectories**

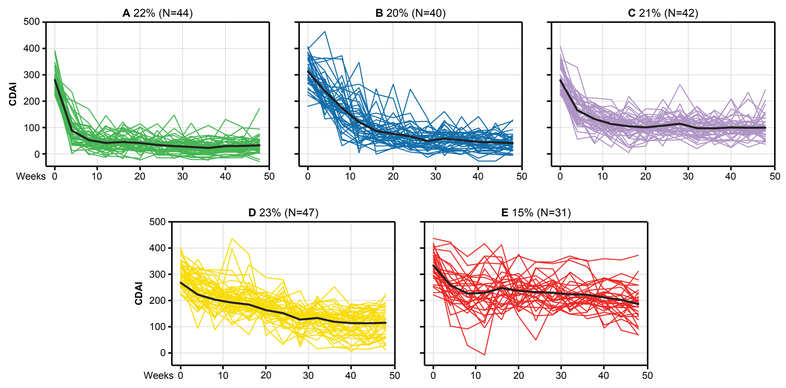
Methods

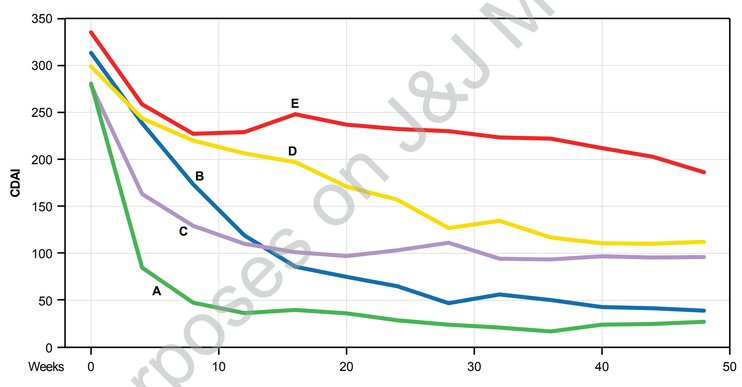
- Participants with moderately to severely active CD from three Phase 3, randomized, double-blind, treat-through studies:
  - GRAVITI: guselkumab subcutaneous [SC] induction and SC maintenance
  - GALAXI 2 and GALAXI 3: guselkumab intravenous [IV] induction and SC maintenance
- Unsupervised machine learning approach with latent class trajectory modeling was applied using CDAI scores from Weeks 0-48 of individual guselkumab-treated participants
- CDAI data was collected every 4 weeks from Week 0 (baseline) to Week 48
- Only guselkumab-treated participants with CDAI data available at all 13 collection timepoints were analyzed
- Participants could be separated into distinct clusters using dynamics of longitudinal CDAI score responses
- The optimal number of clusters was determined by evaluating multiple clustering metrics
- A clustering model was first developed using GRAVITI participants' CDAI trajectories and was subsequently applied to the pooled GALAXI 2/3 data
- Demographic and disease characteristics at Baseline, Week 4, and Week 12 were assessed for association with response patterns
- CDAI scores were also visualized by cluster as a heatmap using participant-level data corresponding to CDAI scores from Baseline to Week 48
  - <150, ≥150 to <170, ≥170 to <190, ≥190 to <220, ≥220 to <300, and ≥300
- Participants in endoscopic remission (SES-CD score ≤4 and at least a 2-point reduction from baseline and no subscore greater than 1 in any individual component) at Week 12 and Week 48 were assessed
- All post hoc analyses are descriptive

Results

- Five distinct patient subpopulations were detected representing clusters with different CDAI response dynamics from the GRAVITI data (N=204) arranged by response dynamics from greatest response (A) to partial/nonresponders (E): A (N=44; 22% of participants), B (N=40; 20%), C (N=42; 21%), D (N=47; 23%), and E (N=31; 15%)
- Improvements in CDAI scores were observed in all clusters **(Figure 1)**

Figure 1. GRAVITI: 5 Distinct Clusters Identified by Machine Learning Using CDAI Scores From Baseline to Week 48

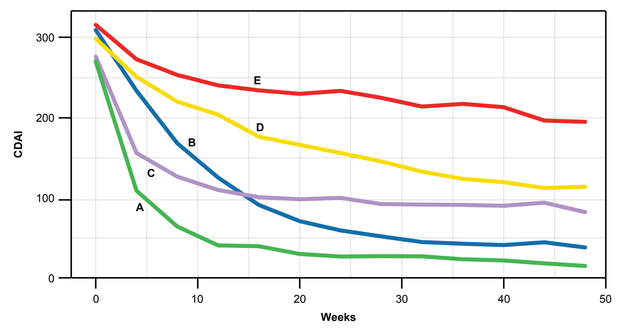




Only guselkumab-treated participants with CDAI scores available at each of the 13 visits were included in the analysis (N=204).

- Applying the clustering method to the pooled GALAXI 2/3 data (N=498) resulted in identification of 5 similar response trajectory clusters A (N=77; 15%), B (N=116; 23%), C (N=91, 18%); D (N=130, 26%); E (N=84, 17%) **(Figure 2)**

Figure 2. Pooled GALAXI 2/3: 5 Distinct Clusters Identified by Machine Learning Using CDAI Scores From Baseline to Week 48



Only guselkumab-treated participants with CDAI scores available at each of the 13 visits were included in the analysis (N=498). GALAXI 2 and GALAXI 3 were also analyzed separately (data not shown), and the pooled GALAXI 2/3 outcomes were similar to each study individually.

- Heatmap analysis of the participant-level CDAI scores through Week 48 enabled visualization of the treatment response profiles of the 5 unique clusters for the GRAVITI **(Figure 3)** and for the pooled GALAXI 2/3 **(Figure 4)** data
- Participant-level data are represented in a gradual color scheme, ranging from red (CDAI ≥300) to green (CDAI <150)
- Response patterns by cluster were similar between GRAVITI and GALAXI 2/3

Figure 3. GRAVITI: Participant-Level Clusters Identified Using CDAI Scores From Baseline to Week 48 by Heatmap Analyses

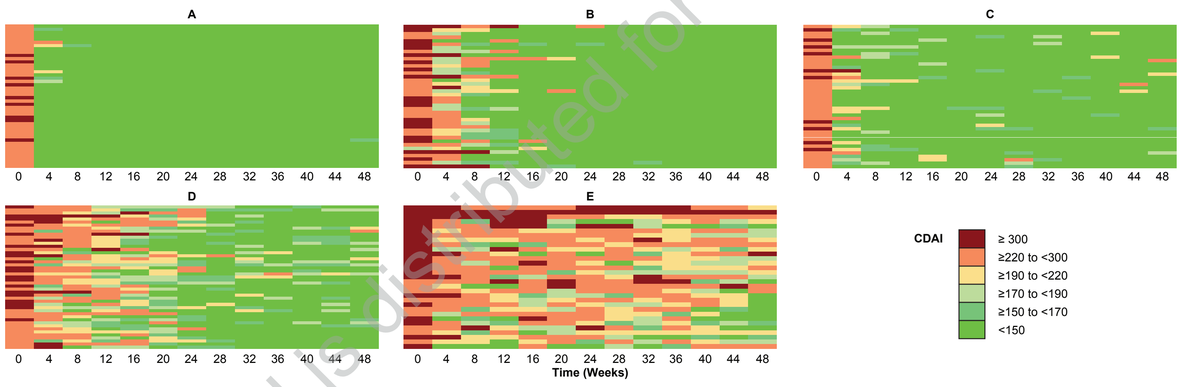
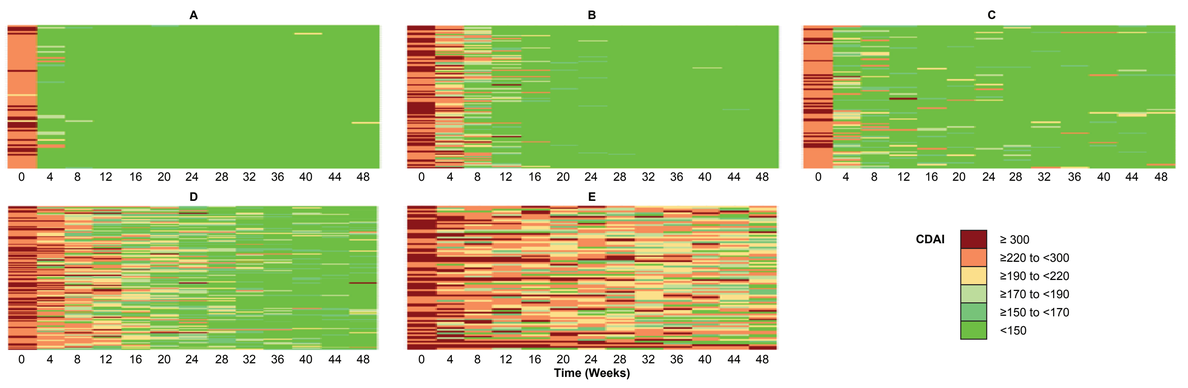


Figure 4. GALAXI 2/3: Participant-Level Clusters Identified Using CDAI Scores From Baseline to Week 48 by Heatmap Analyses



- In GALAXI 2/3, baseline median [IQR] CD duration and baseline median CDAI scores showed trends indicative of response trajectories from clusters A to E **(Table 1)**
- GRAVITI data confirmed these trends (data not shown)

Table 1. GALAXI 2/3 Baseline Characteristics by Predicted Clusters

	A (N=77)	B (N=116)	C (N=91)	D (N=130)	E (N=84)	Overall (N=498)
Demographics						
Men, n (%)	56 (72.7%)	68 (58.6%)	54 (59.3%)	62 (47.7%)	52 (61.9%)	292 (58.6%)
Age, years median (IQR)	32.0 (26.0-42.0)	32.0 (24.8-40.0)	34.0 (28.0-46.5)	36.0 (28.2-46.0)	38.0 (28.8-49.2)	34.0 (26.0-44.0)
Characteristics						
CD duration in years, median (IQR)	4.3 (2.1-8.4)	4.6 (1.6-10.1)	5.2 (1.6-10.5)	4.3 (1.5-9.3)	5.6 (2.5-14.6)	4.6 (1.8-10.7)
CDAI score, median (IQR)	254.0 (238.0-297.0)	300.5 (259.8-352.2)	267.0 (243.5-303.0)	289.5 (256.2-335.0)	314.0 (274.2-345.2)	286.0 (252.0-334.0)
SES-CD score, median (IQR)	10.0 (7.0-16.0)	13.0 (7.0-17.2)	10.0 (7.0-17.0)	11.0 (7.0-17.0)	11.0 (7.0-18.0)	11.0 (7.0-17.0)
BIO-IR, n (%)	34 (44.2%)	58 (50.0%)	52 (57.1%)	54 (41.5%)	48 (57.1%)	246 (49.4%)

BIO-IR= inadequate response or intolerance to biologics; CD= Crohn's disease; IQR= interquartile range; SES-CD= Simple Endoscopic Score for Crohn's Disease.

- Median [IQR] CRP and median fecal calprotectin levels at Week 4 and Week 12 were associated with trajectory groups **(Table 2)**
- GRAVITI data confirmed these trends (data not shown)

Table 2. GALAXI 2/3 Biomarkers by Predicted Clusters

	A	B	C	D	E	Overall
Biomarkers						
CRP in mg/L, median (IQR)						
	N=77	N=116	N=91	N=130	N=84	N=498
Week 0	6.6 (2.8-16.7)	6.1 (2.3-24.6)	6.3 (2.6-14.8)	6.9 (2.8-21.7)	6.8 (2.0-23.9)	6.6 (2.5-21.8)
	N=74	N=114	N=89	N=129	N=81	N=487
Week 4	3.6 (1.5-8.2)	3.7 (1.2-8.4)	2.7 (1.1-7.2)	3.9 (1.2-9.8)	5.5 (1.6-12.0)	3.7 (1.2-9.1)
	N=74	N=112	N=90	N=128	N=80	N=484
Week 12	2.0 (0.8-5.8)	2.1 (0.8-5.4)	2.4 (1.0-5.5)	2.7 (0.8-6.3)	4.5 (1.4-9.1)	2.5 (0.9-6.7)
Fecal calprotectin in µg/g, median (IQR)						
	N=77	N=115	N=90	N=130	N=83	N=495
Week 0	1040.0 (352.0-2396.0)	1074.0 (395.0-2126.0)	1002.0 (376.5-1639.8)	916.0 (393.8-1793.8)	967.0 (292.0-1790.0)	963.0 (361.0-1835.5)
	N=73	N=111	N=88	N=126	N=82	N=480
Week 4	552.0 (171.0-1499.0)	633.0 (160.0-1585.0)	503.0 (218.8-1036.2)	585.5 (154.5-1608.5)	707.0 (164.5-1326.0)	586.5 (168.5-1471.8)
	N=71	N=109	N=86	N=121	N=78	N=465
Week 12	250.0 (106.0-581.5)	260.0 (98.0-702.0)	248.5 (100.0-673.2)	368.0 (129.0-902.0)	382.5 (129.2-875.0)	287.0 (115.0-802.0)

CRP= C-reactive protein; IQR= interquartile range.

- In GALAXI 2/3, the proportions of participants achieving endoscopic remission at Week 12 and Week 48 were associated with trajectory groups (**Table 3**)

Table 3. GALAXI 2/3 Endoscopic Remission by Predicted Clusters

	A (N=77)	B (N=116)	C (N=91)	D (N=130)	E (N=84)	Overall (N=498)
Proportion of Participants in Endoscopic Remission, n (%)						
Week 12	26 (33.8%)	33 (28.4%)	29 (31.9%)	28 (21.5%)	12 (14.3%)	128 (25.7%)
Week 48	36 (46.8%)	58 (50.0%)	40 (44.0%)	48 (36.9%)	18 (21.4%)	200 (40.2%)

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