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

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Poster #75

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**
- **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**

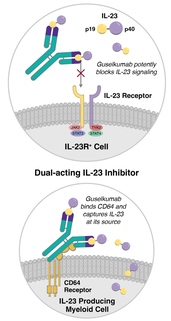
Background

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

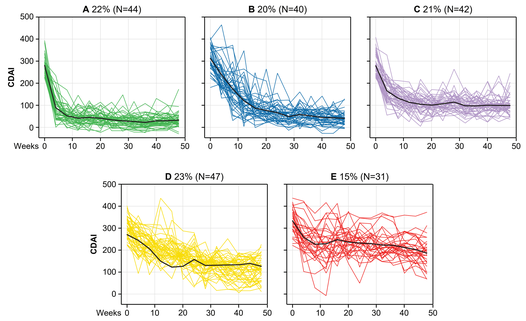
Methods

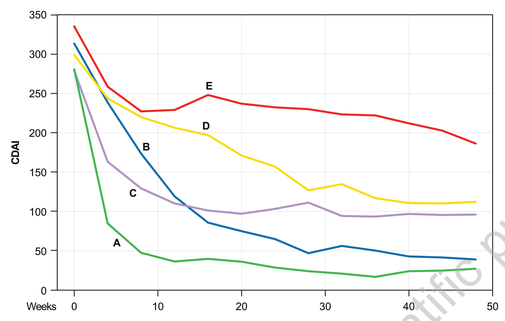
- Participants with moderately to severely active CD from three Phase 3, randomized, double-blind, treat-through studies:
  - GRAVITI: guselkumab subcutaneous [SC] induction and SC maintenance
  - GALAXI 2 and GALAXI 3: guselkumab intravenous [IV] induction and SC maintenance
- Unsupervised machine learning 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
- 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 response (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

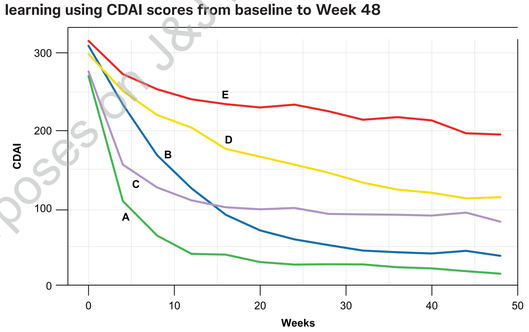




Only guselkumab-treated participants with CDAI scores available at each of the 13 visits were included in the analysis (N=204).

- 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.

- 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 predicted clusters by baseline characteristics

	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 predicted clusters by biomarkers

	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.

- 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

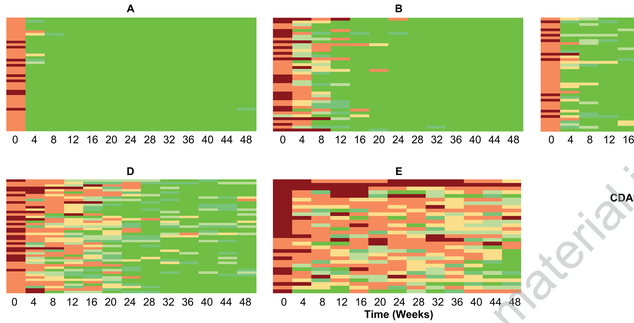
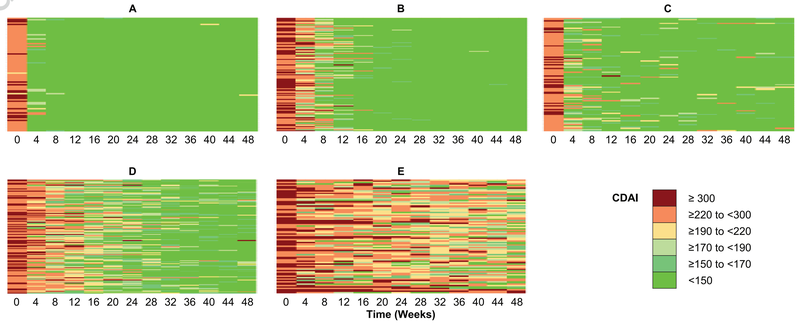


Figure 4. GALAXI 2/3: participant-level clusters identified using CDAI scores from baseline to Week 48 by heatmap analyses



PRESENTED BY: P. Dulai at Advances in Inflammatory Bowel Diseases (AIBD); December 8-10, 2025; Orlando, FL, USA. **REFERENCES:** 1. Sidiqui K, Hammaker D, Sarabia I, et al. *Frontiers in Immunology.* 2025;16:1532852. **2.** Hart A, Panaccione R, Steinwurz F, et al. *Gastroenterology.* 2024;169:308–325. **3.** Panaccione R, Danese S, Feagan BG, et al. *Gastroenterology.* 2024;166:S1057b. **4.** Panaccione R, Feagan BG, Afzali A, et al. *Lancet.* 2025 Jul 26;406:358–375. **ACKNOWLEDGMENTS:** Medical writing support was provided by Kristin Ruley Sharples, PhD of Johnson & Johnson under the direction of the authors in accordance with Good Publication Practice guidelines (*Ann Intern Med.* 2022;175:1298–1304). **DISCLOSURES: P. S. Dulai** reports consulting and/or research support from AbbVie, Abivax, Alimentiv, Bristol Myers Squibb, Celltrion, Eli Lilly, Genentech, Genoscopy, Johnson & Johnson, Merck, Pfizer, Sanofi, and Takeda. **G. D'Haens** reports consultancy activities for AbbVie, Agomab, Alimentiv, AstraZeneca, AMT, Bristol Myers Squibb, Boehringer Ingelheim, Celltrion, Eli Lilly, Exelixis, Galapagos, GlaxoSmithKline, Immunic, Johnson & Johnson, Pfizer, Polpharma, Procise Diagnostics, Prometheus Laboratories, Prometheus Biosciences, Progenity, Takeda, and Ventyx; speaker's bureau for AbbVie, Bristol Myers Squibb, Galapagos, Pfizer, and Takeda; and data monitoring board activities for AbbVie, AstraZeneca, Galapagos, and Seres Health. **W. Reinisch** reports speaker fees from AbbVie, Celltrion, Ferring, Galapagos, Medice, Johnson & Johnson, MSD, Pfizer, Roche, Sobi, Takeda; consultant fees from AbbVie, Amgen, AOP Orphan, Boehringer Ingelheim, Bristol Myers Squibb, Calyx, Celltrion, Eli Lilly, Galapagos, Gilead, Index Pharma, Johnson & Johnson, Medahead, Microbiotica, Pfizer, Takeda; an advisory board member for AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Galapagos, Johnson & Johnson, Pfizer, and research funding from AbbVie, Johnson & Johnson, Sandoz, Sanofi, and Takeda. **A. Hart** reports serving as a lecturer and/or on an advisory board for AbbVie, Bristol Myers Squibb, Celltrion, Falk, Galapagos, GSK, Johnson & Johnson, MSD, Pfizer, and Takeda. **C. Valiathan** was an employee of Johnson & Johnson at the time of these analyses and may own stock/stock options in Johnson & Johnson. **S. Rani, R. Van Rampelbergh, M. Olurinde, L-L. Gao, Z. Yang,** and **T. Hoops** are employees of Johnson & Johnson and may own stock/stock options in Johnson & Johnson. **S. Schreiber** reports personal fees from AbbVie, Amgen, Arena, Biogen, Bristol Myers Squibb, Celgene, Celltrion Healthcare, Dr. Falk Pharma, Fresenius, Galapagos, Gilead, I-Mab, Hikma, Johnson & Johnson, MSD, Mylan, Pfizer, Protagonist, Sandoz, Takeda, and Ventyx.