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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

UNSUPERVISED MACHINE LEARNING TO IDENTIFY DISTINCT CDAI-BASED 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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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

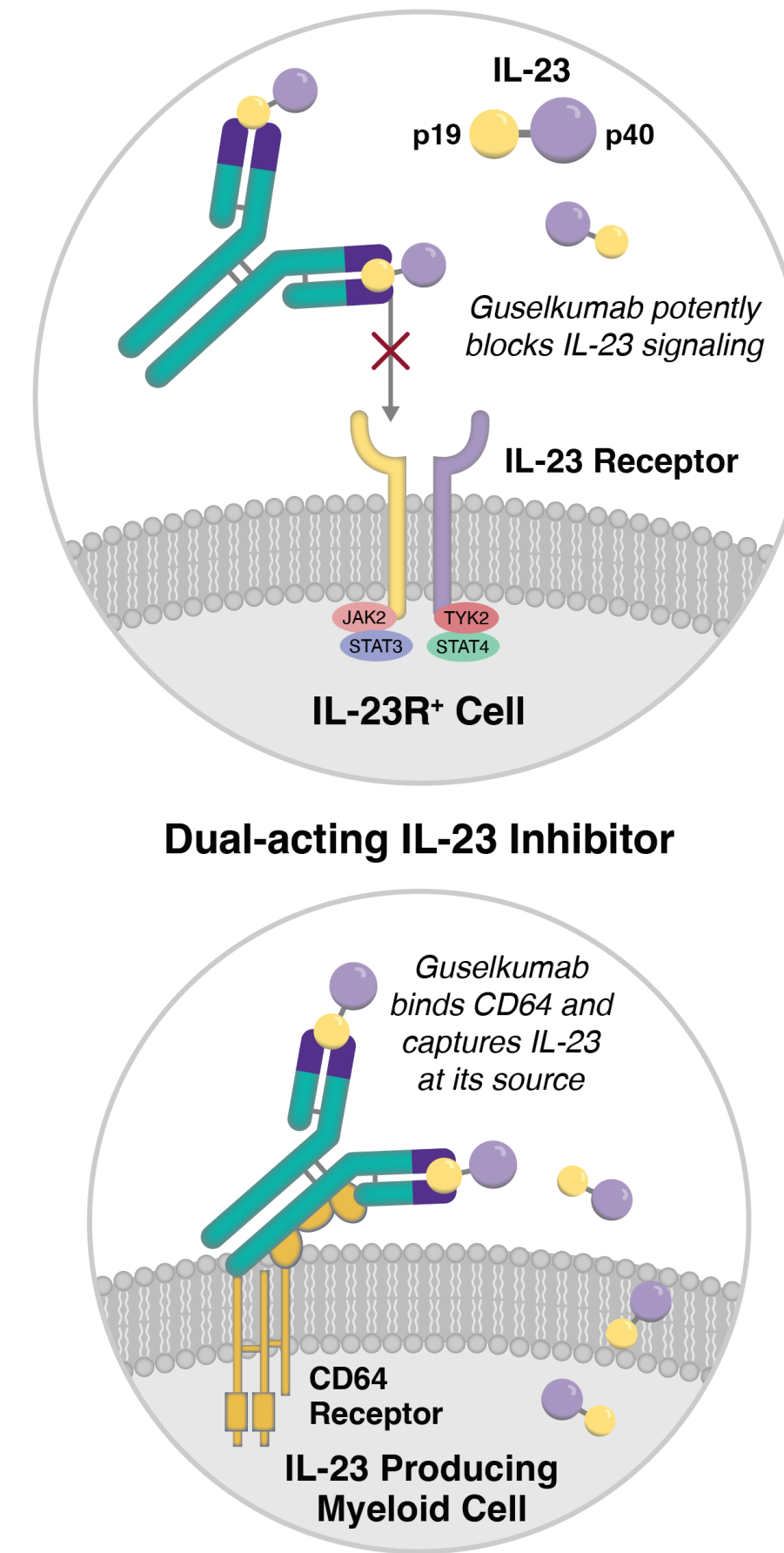
Analysis of individual longitudinal trends of efficacy based on participant-level clinical data provides a better understanding of response to treatment, and may help optimize personalized treatment in IBD

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-23¹

Objective

To use unsupervised learning to identify clusters of guselkumab-treated participants from the Phase 3 GRAVITI² and GALAXI 2 & 3^{3,4} studies characterized by individual Crohn's Disease Activity Index (CAI)-based response trajectories



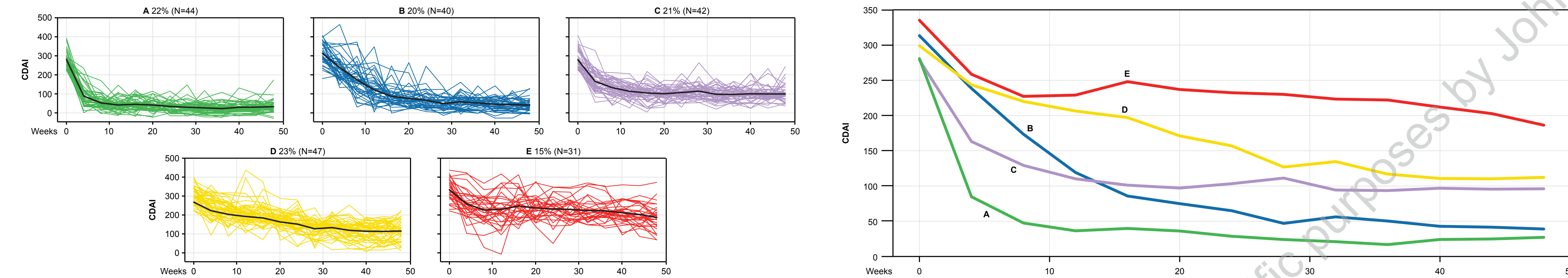
Methods

- 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).

- 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 (CAI ≥300) to green (CAI <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

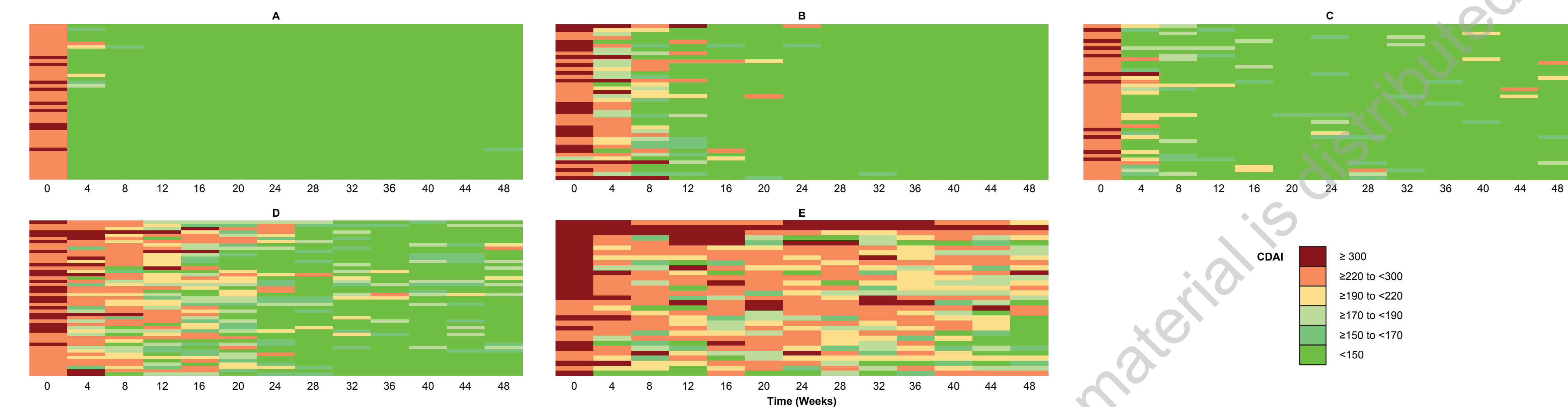
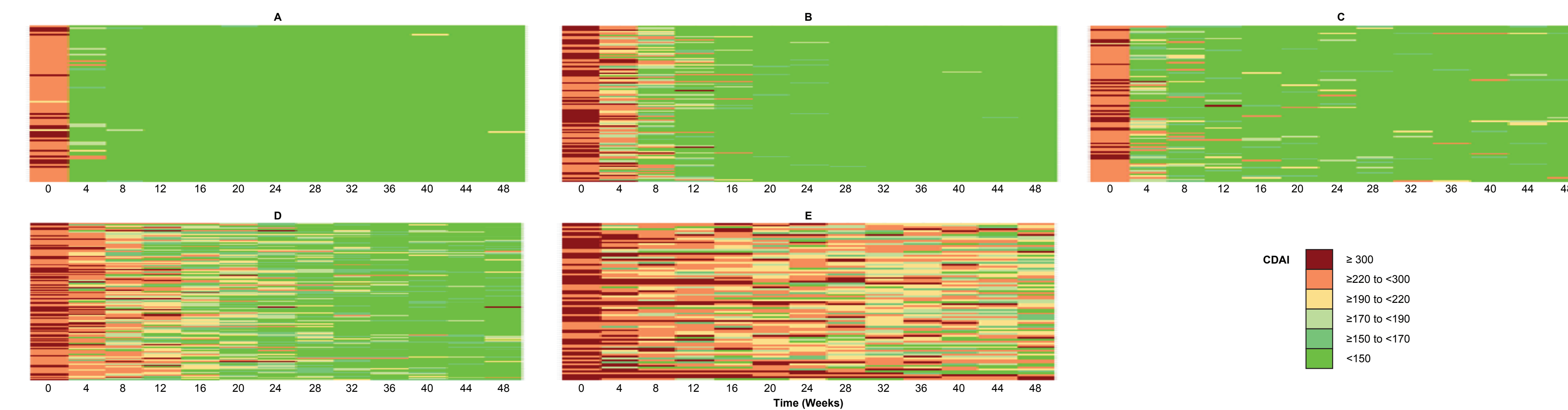
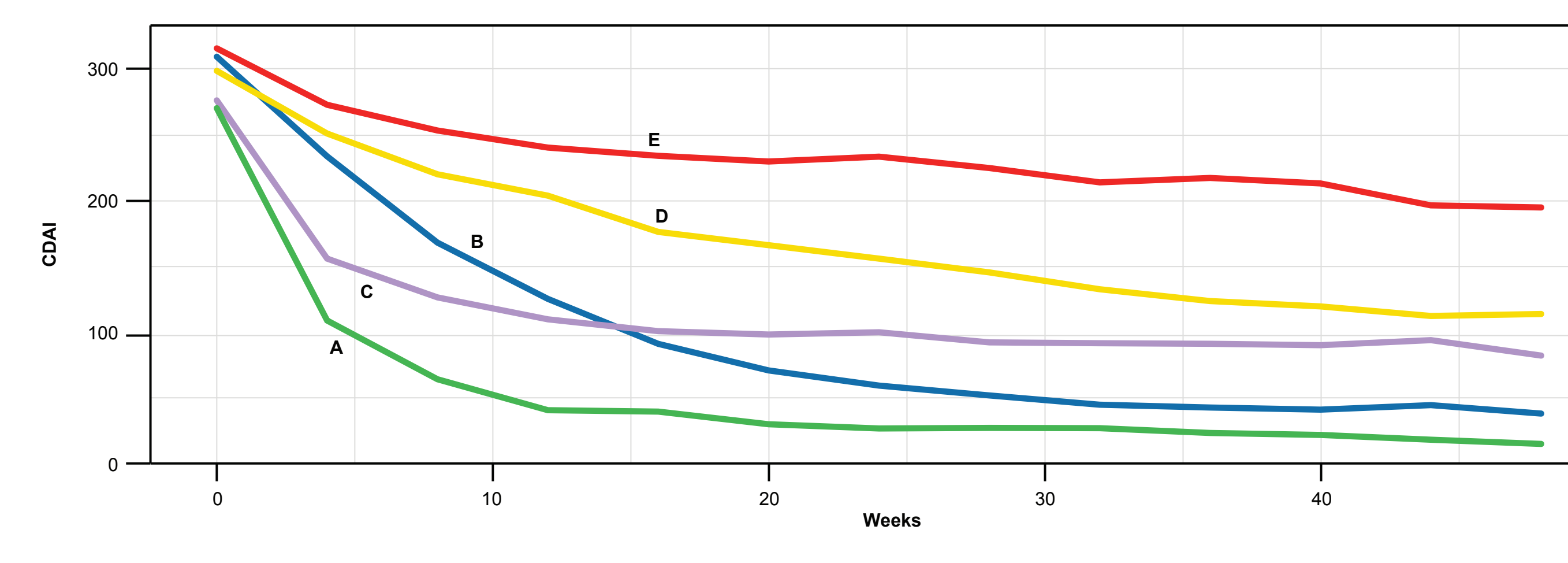


Figure 4. GALAXI 2/3: Participant-Level Clusters Identified Using CDAI Scores From Baseline to Week 48 by Heatmap Analyses



- 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%), and 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 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 (28.0-44.0)
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)
CAI 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)						
Week 0	N=77 6.6 (2.8-16.7)	N=116 6.1 (2.3-24.6)	N=91 6.3 (2.6-14.8)	N=130 6.9 (2.8-21.7)	N=84 6.8 (2.0-23.9)	N=498 6.6 (2.5-21.8)
Week 4	N=74 3.6 (1.5-8.2)	N=114 3.7 (1.2-8.4)	N=89 2.7 (1.1-7.2)	N=129 3.9 (1.2-9.8)	N=81 5.5 (1.6-12.0)	N=487 3.7 (1.2-9.1)
Week 12	N=74 2.0 (0.8-5.8)	N=112 2.1 (0.8-5.4)	N=90 2.4 (1.0-5.5)	N=128 2.7 (0.8-6.3)	N=80 4.5 (1.4-9.1)	N=484 2.5 (0.9-6.7)
Fecal calprotectin in µg/g, median (IQR)						
Week 0	N=77 1040.0 (320.0-2396.0)	N=115 1074.0 (395.0-2126.0)	N=90 1002.0 (376.5-1639.8)	N=130 916.0 (393.8-1793.8)	N=83 967.0 (292.0-1790.0)	N=495 963.0 (361.0-1935.5)
Week 4	N=73 552.0 (171.0-1499.0)	N=111 633.0 (160.0-1585.0)	N=86 503.0 (218.8-1036.2)	N=126 585.5 (154.5-1008.5)	N=82 707.0 (164.5-1326.0)	N=480 586.5 (165.5-1471.8)
Week 12	N=71 250.0 (106.0-581.5)	N=109 260.0 (98.0-702.0)	N=86 248.5 (100.0-673.2)	N=121 368.0 (129.0-902.0)	N=79 382.5 (128.0-875.0)	N=465 287.0 (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%)