ODYSSEY THERAPEUTICS

OD-001 Phase 2a Monotherapy Trial Update

Investor and Analyst Webcast

October 20, 2026



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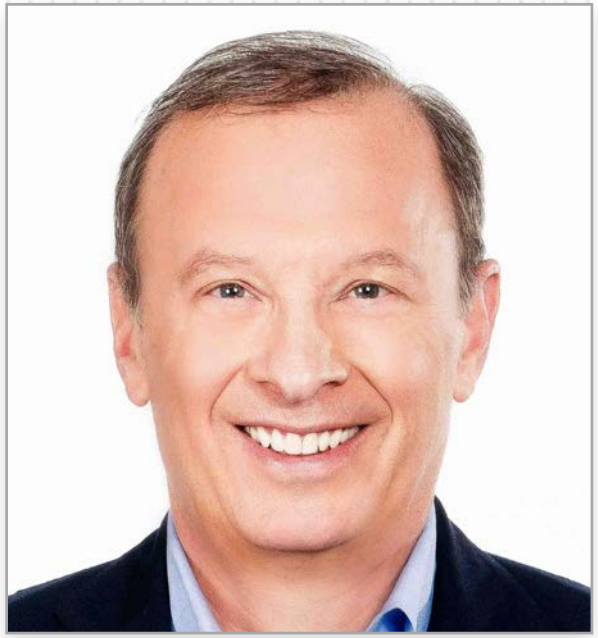
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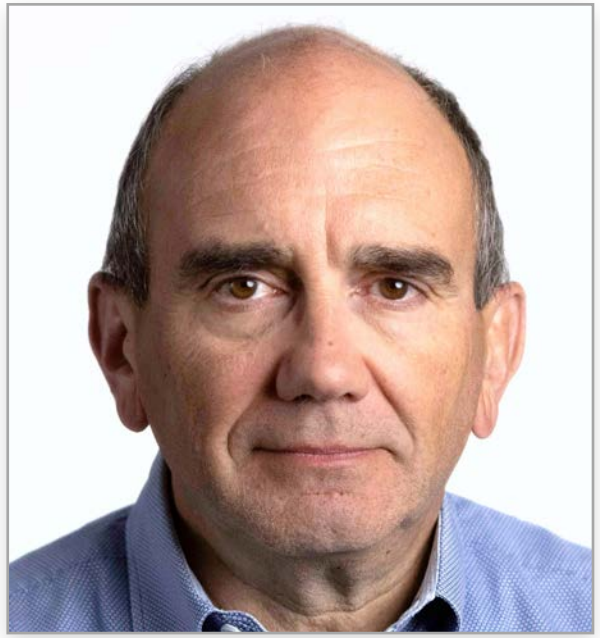
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Overview of Presenters



Gary D. Glick, Ph.D.

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Anthony Opipari, M.D., Ph.D.

Chief Medical Officer



Collin Todd

Senior Vice President, Strategy and Business Development

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Today's Presentation – OD-001 Phase 2a Monotherapy Trial in UC

New information today

Full 10 mg BID dataset

- Shows evidence of a dose response
- Confirms that 20 mg BID is the lowest maximally efficacious dose

Additional analyses

- Systemic and colonic biomarker analyses
- Efficacy by patient segments and across time points
- Transcriptomic assessments
- Comparison by dose

Totality of phase 2a data

Converging lines of evidence support clinical efficacy of OD-001, a first-in-class RIPK2 scaffolding inhibitor

- Robust separation vs. historic placebo rates across numerous efficacy endpoints
- Strong correlation between clinical outcomes with OD-001 and inflammatory biomarkers, mucosal transcriptomics, and histologic improvement

Corroborates that 20 mg BID is the lowest maximally efficacious dose

- Dose was expected to maximally inhibit RIPK2 signaling based on phase 1 ex vivo stimulation assays; dose phenocopies the effect of RIPK2 knockout cells

Supports a potentially competitive profile of OD-001 vis-à-vis approved and investigational ulcerative colitis therapies

- Well tolerated with no SAEs and no discontinuations due to TEAEs
- Efficacy across patient subsets: moderate and severe, AT-experienced, and AT-naïve
- Competitive monotherapy efficacy and tolerability profile

Notes: UC = ulcerative colitis; BID = twice daily; RIPK2 = receptor-interacting protein kinase 2; SAE = serious adverse event; TEAE = treatment-emergent adverse event; AT = advanced therapy.

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Inflammatory Bowel Disease and RIPK2

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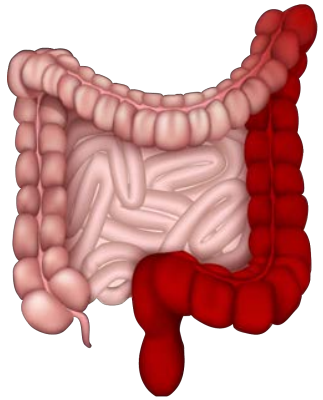
Despite Multiple Approved Drugs, Significant Unmet Need Remains in IBD

IBD encompasses two serious and prevalent diseases, ulcerative colitis (UC) and Crohn's disease (CD)

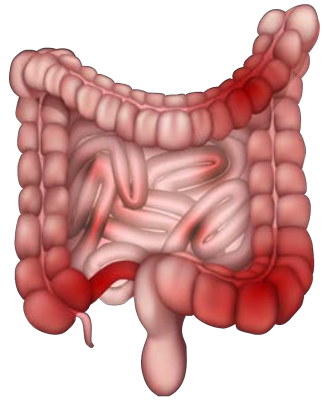
- Despite multiple approved therapies, placebo-adjusted induction remission in UC remains < 30%
- New therapies and combination approaches are needed to address the substantial proportion of patients who fail to respond to current agents and the progressive loss of response over time

UC and CD differ in anatomical distribution and natural history but share pathogenic mechanisms:

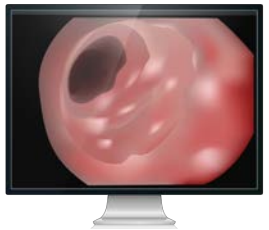
- Intestinal barrier disruption
- Microbial translocation
- Dysregulated innate and adaptive immunity



Ulcerative colitis*



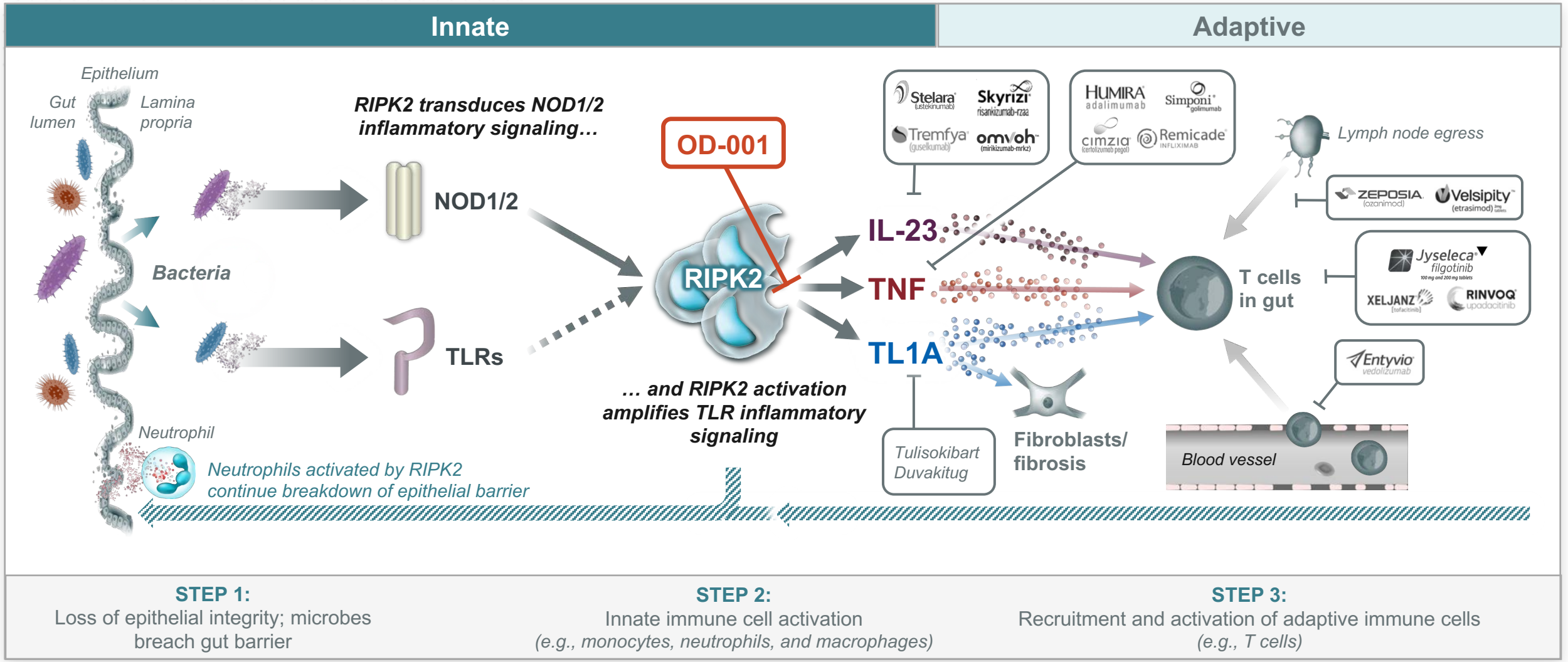
Crohn's disease



* *Drug development typically begins in UC because it is confined to the colon and mucosal pathology can be effectively scored by endoscopy, allowing more efficient trials than in CD, which is characterized by patchy, transmural disease*

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RIPK2 Plays a Central Role in the Pathogenesis of IBD



STEP 1:
Loss of epithelial integrity; microbes breach gut barrier

STEP 2:
Innate immune cell activation
(e.g., monocytes, neutrophils, and macrophages)

STEP 3:
Recruitment and activation of adaptive immune cells
(e.g., T cells)

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RIPK2 Is a Validated Target to Treat IBD

Animal data

- Microbes are required for spontaneous colitis in rodent models
- RIPK2 knockout reduces inflammatory cytokines and improves intestinal histology in animal models of IBD
- Blocking RIPK2 signaling reduces inflammatory cytokines and intestinal disease in mouse models
- RIPK2 knockout mice are developmentally normal

Human data

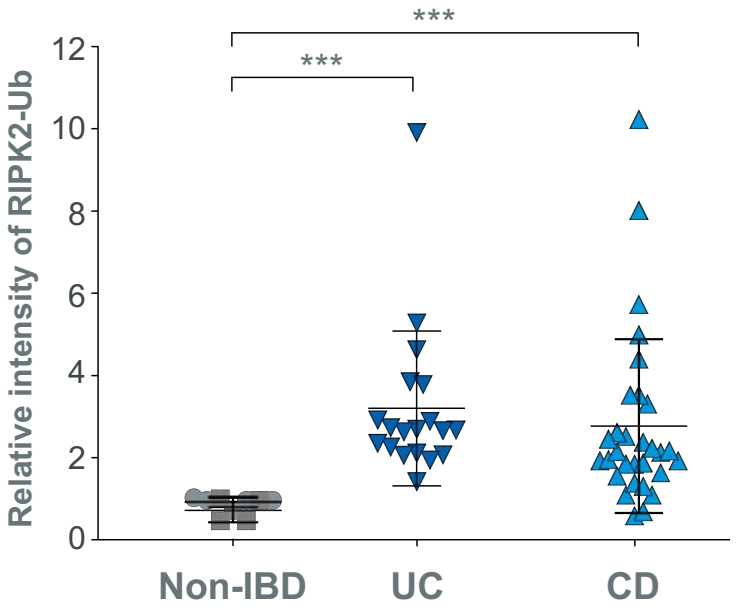
- RIPK2 pathway activation is increased in intestinal tissue from patients with both UC and CD
- RIPK2 ubiquitination is observed across all UC patients, including those with NOD2 LoF variants
- **Genetic validation** of RIPK2*: ATG16L1* and *CARD9* variants are linked to increased IBD risk; protective *CARD9* variants to reduced risk
- **Pharmacologic validation** of RIPK2: Clinical efficacy with OD-001 provides target validation in UC

Sources: Inflamm Bowel Dis 2015;21(4):862; J Med Chem 2022;65(13):9312; J Med Chem 2019;62(14):6482; Proc Natl Acad Sci U S A 2014;111(25):E2559; Am J Physiol Gastrointest Liver Physiol 2021;321(5):G500; Mucosal Immunol 2017;10(4):971; J Biol Chem 2014;289(43):29651; Commun Biol 2020;3(1):140; J Med Chem 2016;59(10):4867; Int Immunol 2019;31(10):669; Sci Signal 2024;17(819):eabn1101; Immunity 2013;39(5):858; Gut 2011;60(9):1229; Nat Immunol 2007;8(2):198; Nature 2012;491(7422):119; United Eur Gastroenterol J 2023;12(1):103; Front Immunol 2019;10:419.

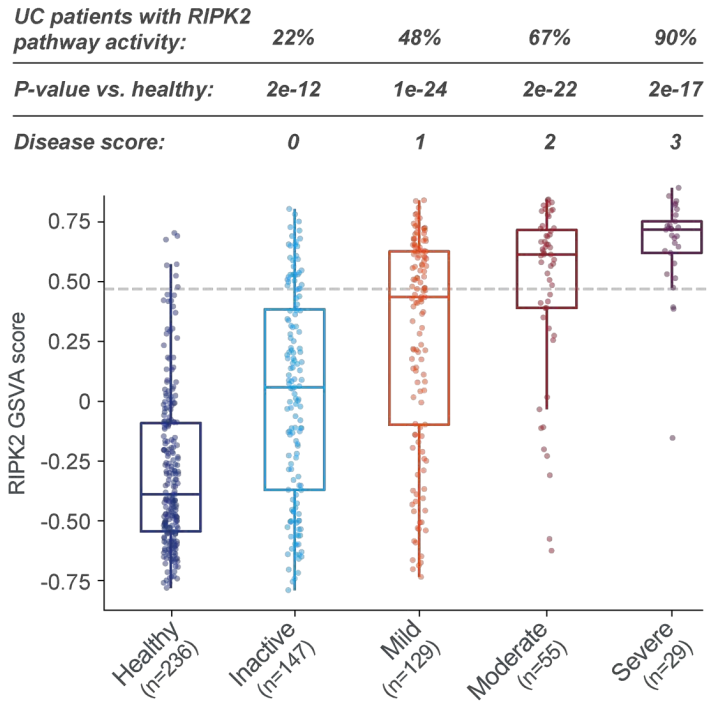
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RIPK2 Is Activated in UC and CD and Correlates With Severity

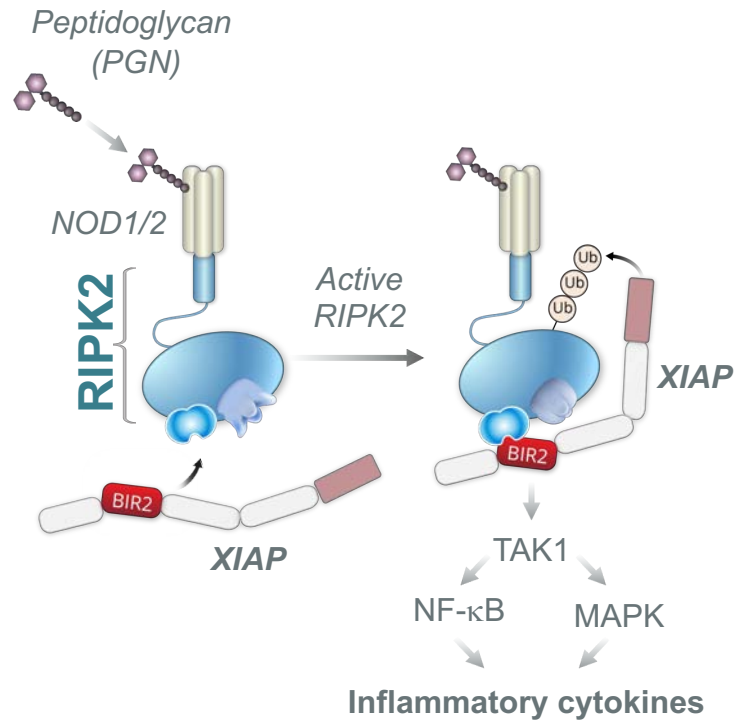
Increased levels of activated (ubiquitinated) RIPK2 in patients with UC and CD



Increased expression of RIPK2-responsive gene signature in IBD patient biopsies



RIPK2 scaffolding with XIAP is necessary for activation and inflammatory signaling



Notes: *** $p < 0.001$; GSVA = gene set variation analysis; GSVA cutoff for % of UC patients with RIPK2 pathway activity is 0.46.
Sources: EMBO J 2018;37(17):e99372; Sci Signal 2024;17(819):eabn1101; gene expression dataset: GSE193677.

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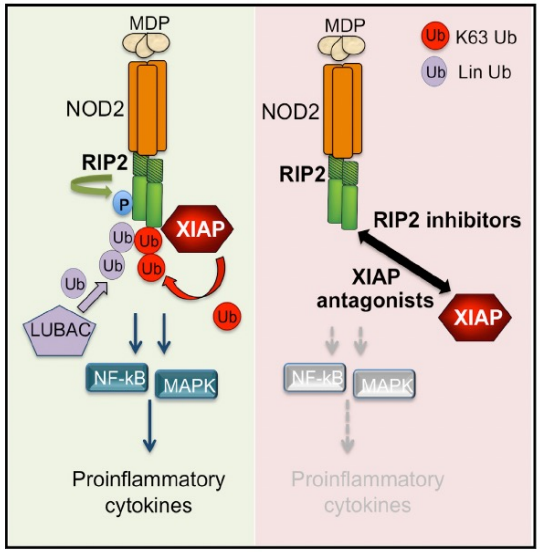
RIPK2 Drugs Must Block Scaffolding to Fully Inhibit NOD2 Signaling

Article

Molecular Cell

Disruption of XIAP-RIP2 Association Blocks NOD2-Mediated Inflammatory Signaling

Graphical Abstract



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In Brief

Goncharov et al. demonstrate that the kinase activity of RIP2 is dispensable for NOD2 signaling. Instead, effective RIP2 kinase inhibitors block NOD2 signaling by disrupting RIP2-XIAP interaction in a similar fashion as XIAP antagonists. These findings provide a novel therapeutic strategy for targeting the NOD2 pathway.

Mol Cell 2018;69(4):551–565

Article

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

THE EMBO JOURNAL

Small molecule inhibitors reveal an indispensable scaffolding role of RIPK2 in NOD2 signaling

Matous Hrdinka[1,†,‡], Lisa Schlicher[1,†], Bing Dai[2], Daniel M Pinkas[3], Joshua C Bufton[3,§], Sarah Picaud[3], Jennifer A Ward[3,4], Catherine Rogers[3,4], Chalada Suebsuwong[5,¶], Sameer Nikhar[6], Gregory D Cuny[6], Kilian VM Huber[3,4], Panagis Filippakopoulos[3], Alex N Bullock[3], Alexei Degterev[2,*] & Mads Gyrd-Hansen[1,**]

Abstract

RIPK2 mediates inflammatory signaling by the bacteria-sensing receptors NOD 1 and NOD2. Kinase inhibitors targeting RIPK 2 are a proposed strategy to ameliorate NOD-mediated pathologies. Here, we reveal that RIPK 2 kinase activity is dispensable for NOD 2 inflammatory signaling and show that RIPK 2 inhibitors function instead by antagonizing XIAP-binding and XIAP-mediated ubiquitination of RIPK 2. We map the XIAP binding site on RIPK 2 to the loop between b2 and b3 of the N-lobe of the kinase, which is in close proximity to the ATP-binding pocket. Through characterization of a new series of ATP pocket-binding RIPK 2 inhibitors, we identify the molecular features that determine their inhibition of both the RIPK2-XIAP interaction, and of cellular and in vivo NOD2 signaling. Our study exemplifies how targeting of the ATP-binding pocket in RIPK2 can be exploited to interfere with the RIPK 2-XIAP interaction for modulation of NOD signaling.

Introduction

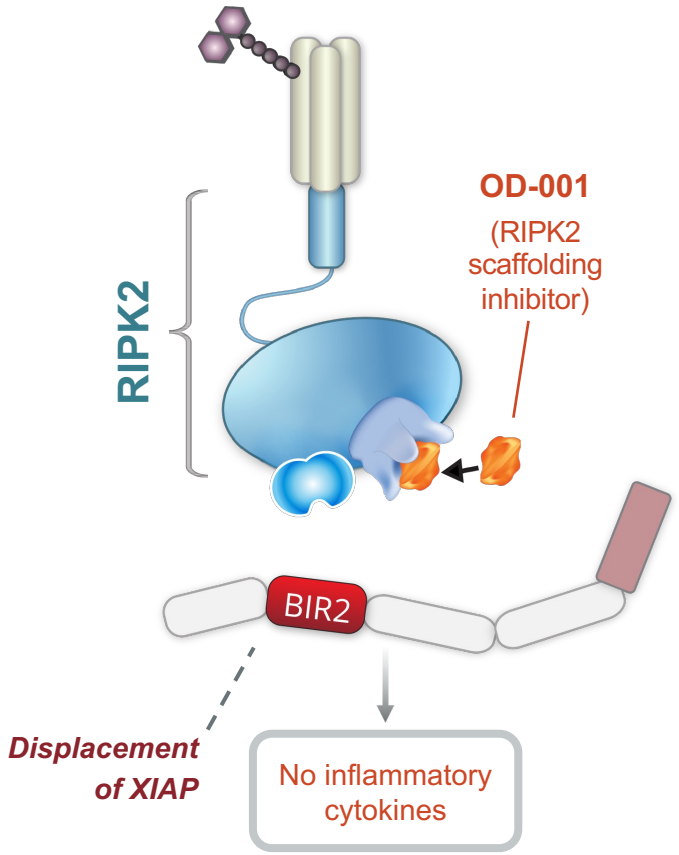
Receptor-interacting kinases (RIPKs) are components ofinnate immune receptor signaling complexes where they become ubiquitinated and contribute to NF- j B-mediated inflammatory signaling and cell death (Hrdinka & Gyrd-Hansen, 2017; Annibaldi & Meier, 2018). The intracellular bacteria-sensing receptors NOD1 and NOD2 (nucleotide-oligomerization domain-containing proteins 1 and 2) stimulate inflammatory signaling by promoting RIPK2 ubiquitination in response to binding ofiE-DAP (D-glutamyl-meso-diaminopimelic acid) and MDP (muramyl dipeptide) constituents of bacterial peptidoglycan, respectively (Girardin et al, 2003). NOD1/2 signaling contributes to gastro-intestinal immunity (Philpott et al, 2014), and genetic variants in NOD2 are the strongest susceptibility factors to Crohn's disease —one of the two major inflammatory bowel diseases afflicting millions in Europe and North America alone (Hugot et al, 2001; Ogura et al, 2001; Ananthakrishnan, 2015). Mutations of

EMBO J 2018;37(17):e99372

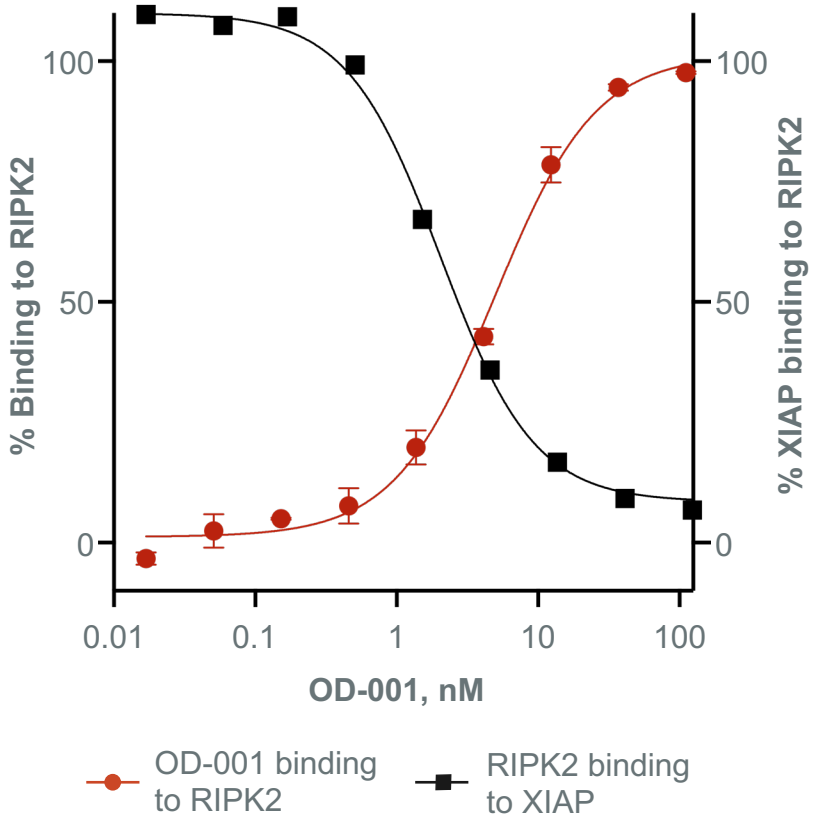
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Blocking RIPK2 Scaffolding With OD-001 Achieves Maximal Inhibition

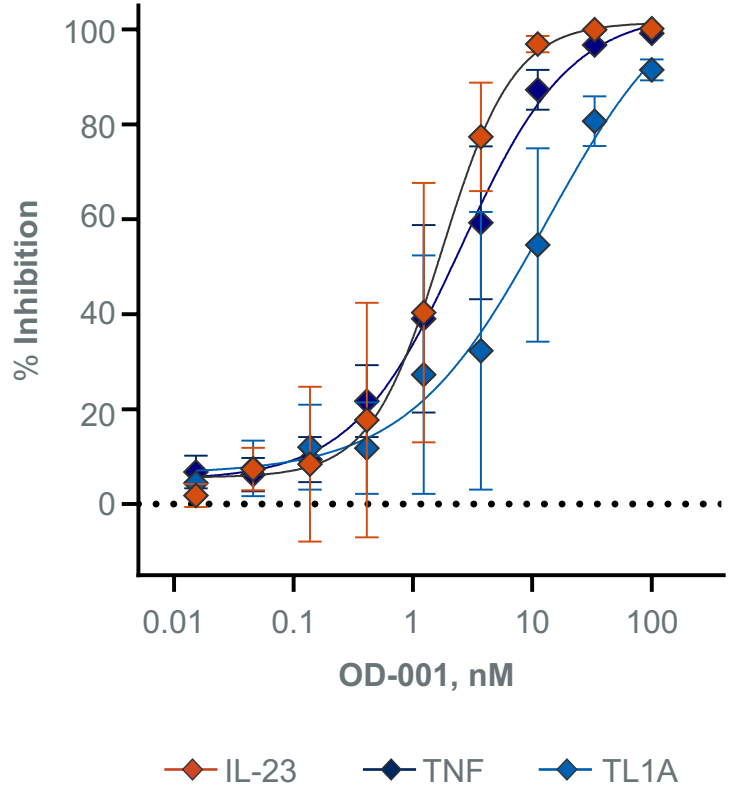
OD-001 is an allosteric scaffolding inhibitor that reduces the affinity for XIAP



Relationship between OD-001 and XIAP binding to RIPK2



OD-001 blocks cytokine production from macrophages stimulated with PGN

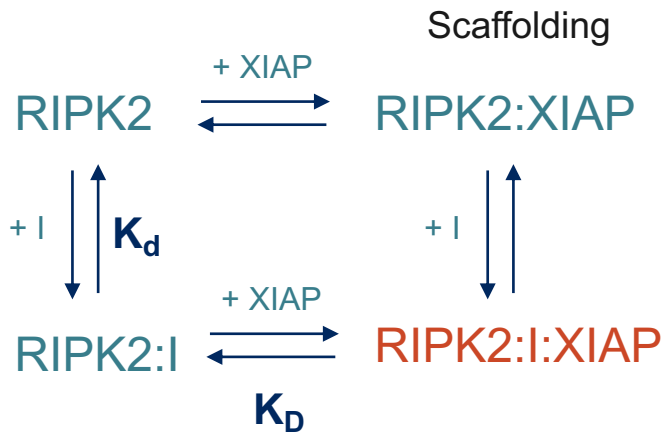


Notes: Binding to RIPK2 was measured by competition with a fluorescent ATP-site tracer in cells. XIAP binding to RIPK2 using recombinant protein was measured by HTRF. Cytokine production was assessed after 24 hours by MSD/ELISA in macrophages treated with compound for 1 hour and then stimulated with PGN.
Sources: EMBO J 2018;37(17):e99372; Mol Cell 2018;69(4):551–565.

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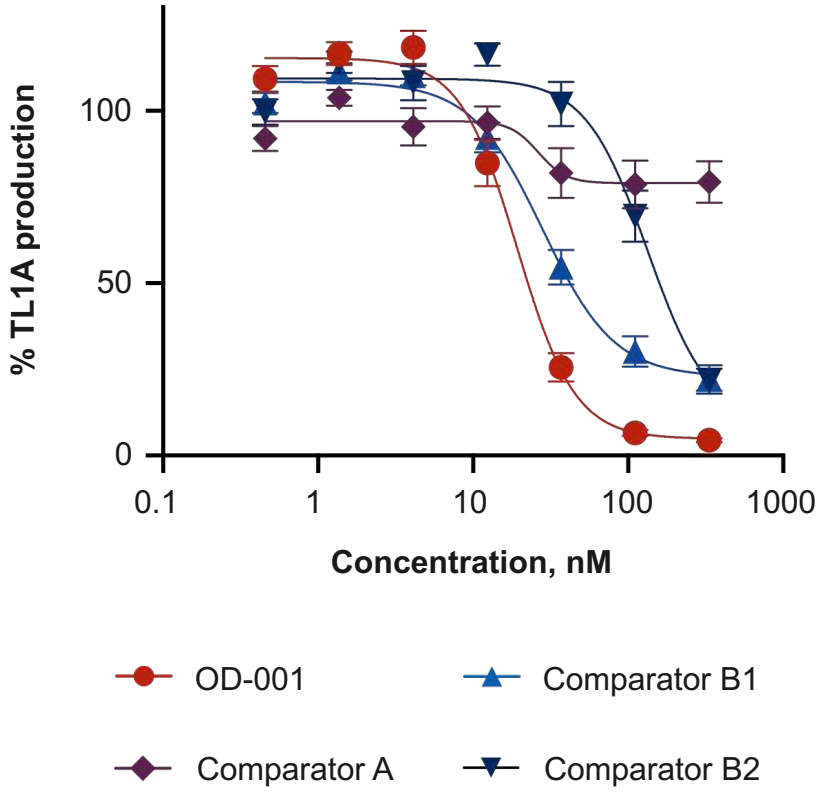
Not All RIPK2 Scaffolding Inhibitors Are the Same

Pharmacology of noncompetitive allosteric inhibitors



- Inhibitor and XIAP can bind simultaneously to RIPK2 to form a ternary complex
- Inhibitor binding to RIPK2 potentially alters the affinity for XIAP
- Extent of scaffolding inhibition depends on **K_D**, *which can vary depending on XIAP concentration*

OD-001 blocks TL1A production in response to microbial stimulation (PGN) in human macrophages



Notes: Human macrophages were treated with compounds for 1 hour and then stimulated with PGN. Cytokine production was assessed after 24 hours by ELISA.
Sources: Comparator A WO2022192760 Example A6; Comparator B1 WO2024254539 Example 253; Comparator B2 WO2024254539 Example 52.

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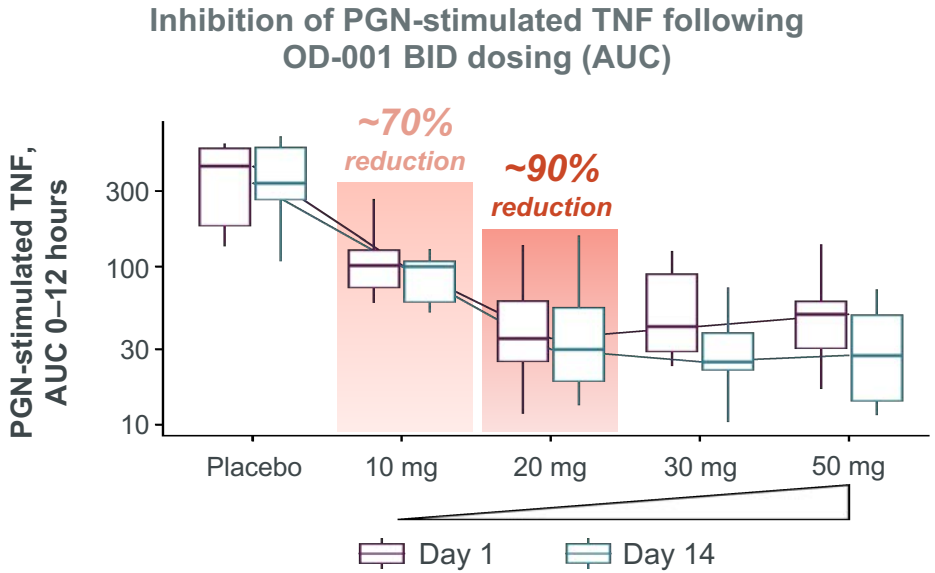
Phase 2a Monotherapy Trial

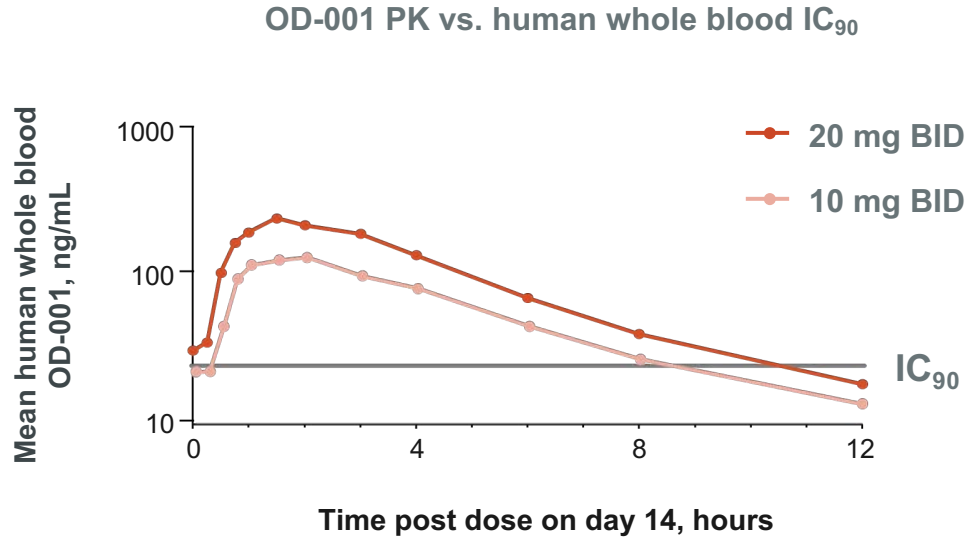
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Rationale and Dose Selection for Proof-of-Concept Phase 2a Trial

- OD-001 is the first *innate immune-targeted therapy* and the first *RIPK2 scaffolding inhibitor* to enter UC clinical development
- Trial was designed to assess safety and efficacy of OD-001 and determine whether to advance the program
  - Partnered with Alimentiv, a leading IBD-specialized CRO with deep investigator experience
  - Primary endpoint: Change from baseline in 3-component mMS at week 12 (90% power at a two-sided 5% significance to detect a 2-point change)
  - Secondary endpoint: Remission rate (≥ 15% placebo-adjusted compared with a historic placebo rate of 10%; 82% power at a two-sided 10% significance)
- Doses selected based on an ex vivo blood assay in the phase 1; 20 mg BID is the lowest dose projected to be maximally effective
  - Level of inhibition with 20 mg BID approximates that observed with RIPK2 knockout cells



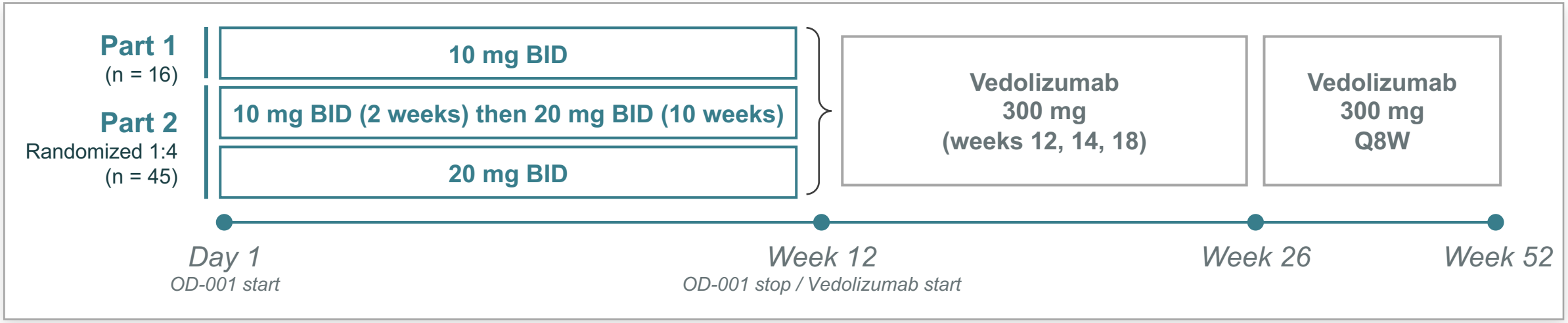


Notes: 3-component modified Mayo Clinical score (mMS) includes endoscopic severity (0–3), stool frequency (0–3), and rectal bleeding (0–3).

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Phase 2a Monotherapy Trial Overview

- Patients with moderately to severely active UC and an mMS of 5–9 were enrolled from 18 sites across seven countries; up to three prior advanced therapies were permitted
- Dosing strategy:
  - Part 1: Initial evaluation at 10 mg BID to ensure safety in UC patients with submaximal RIPK2 inhibition before testing a higher dose with maximal inhibition
  - Part 2: Evaluated 20 mg BID to assess safety and efficacy of maximal RIPK2 inhibition; included a subgroup with step-up dosing from 10 to 20 mg BID
- Design features to minimize placebo effect:
  - Required Mayo endoscopic subscore (MES) ≥ 2 and rectal bleeding subscore ≥ 1
  - Centralized and blinded endoscopy reads
  - Limited concomitant steroid dose to maximum of 20 mg prednisone



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Participant Characteristics Are Similar to Other Contemporary UC Trials

	OD-001 *RIPK2*	Obefazimod *miR-124*		SPY001 *α4β7*	Icotrokinra *IL-23*	Tulisokibart *TL1A*	Duvakitug *TL1A*	Afimkibart *TL1A*
Phase	Phase 2a	Phase 2b	Phase 3	Phase 2, Part A	Phase 2b	Phase 2	Phase 2b	Phase 2b
Age, mean	40	41	42	44	42	41	41	39
Sex, male	49%	59%	-	72%	58%	53%	63%	60%
Advanced therapy-experienced (1)	30%	49%	47%	19%	43%	47%	39%	39%
Modified Mayo score, mean	6.5	7.1	6.9	6.8	6.6	7.0	6.8	7.0 (median)
MES = 3	51%	71%	60%	56%	59%	73%	56%	52%
Median fecal calprotectin, µg/g	1,752	1,647	1,666	-	1,523	1,307	-	1,511
Duration of disease, mean, years	7	8	8	5	8	7	8	7
Concomitant corticosteroid use	23%	52%	40%	42%	37%	55%	42%	42%

Notes: (1) Includes both approved advanced therapies and investigational agents; includes golimumab, etrasimod, ustekinumab, rosnilimab, MORF-057, PN-943, infliximab, icotrokinra, TYK2 inhibitor, adalimumab, and etrolizumab.
Sources: Lancet Gastroenterol Hepatol 2022;7(11):1024–1035; Abivax corporate presentation, March 2023; Abivax phase 3 topline readout, July 2025; obefazimod UEG Week presentation, October 2025; Clin Gastroenterol Hepatol 2026;24(2):525–534; Spyre SKYLINE Part A induction results, April 2026; icotrokinra UEG Week presentation, October 2025; Prometheus Biosciences corporate presentation, March 2023; duvakitug phase 2 investor call, February 2025; Lancet Gastroenterol Hepatol 2025;10(10):882–895.

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Biomarker, Efficacy, and Safety Assessments

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Induction Portion of the OD-001 Phase 2a Trial Is Complete

New clinical data presented today

Total of 56 evaluable patients

- Previously, Odyssey reported results from 49 evaluable patients: 8 treated with 10 mg BID and 41 with 20 mg BID
- After the 8 patients treated with 10 mg BID (~70% target coverage) showed strong efficacy, more patients were enrolled at 10 mg BID to evaluate the signal

First release today:

- Clinical efficacy by patient segments and time points: endoscopic severity and symptomatic remission
- Blood- and stool-based biomarkers of colonic and systemic inflammation

Key implications

Greatest efficacy observed at the dose that maximally inhibits RIPK2

- 20 mg BID phenocopies cytokine inhibition from RIPK2 knockout cells
- Consistent benefit across week 12 endpoints and subgroups by endoscopic severity and AT-experience status, with rapid onset of symptomatic remission

Dose response in colonic and systemic inflammatory markers consistent with clinical efficacy being driven by OD-001

- Blood- and stool-based biomarkers provide an unbiased measure of clinical effect

Favorable tolerability profile with no discontinuations due to OD-001

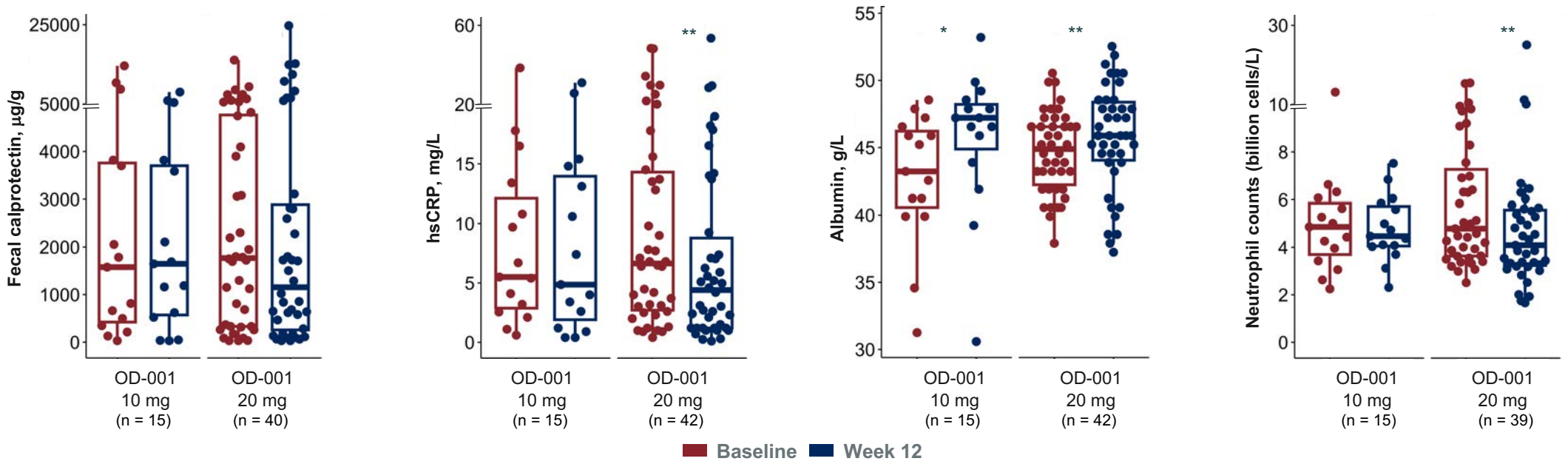
- In total, 5 patients were not evaluable, all for reasons unrelated to OD-001 (3 discontinued early, 1 relocated, and 1 failed to report study data)
- Competitive monotherapy safety profile could enable backbone use in combinations

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Markers of Systemic and Local Inflammation Are Reduced After OD-001 Treatment

- 20 mg BID dosing results in **reduced fecal calprotectin** across treated patients
- 20 mg BID results in **reduced serum C-reactive protein**
- 10 mg and 20 mg BID result in **increased serum albumin**
  - Serum albumin may increase due to increased hepatic synthesis as systemic inflammation declines *and* reduced rectal bleeding as the colonic mucosa heals
- 20 mg BID **reduces neutrophils**, a cell type that expresses RIPK2 and is involved in epithelial barrier breakdown in IBD

Markers of systemic and local inflammation suggest 20 mg BID inhibits colonic and systemic inflammation

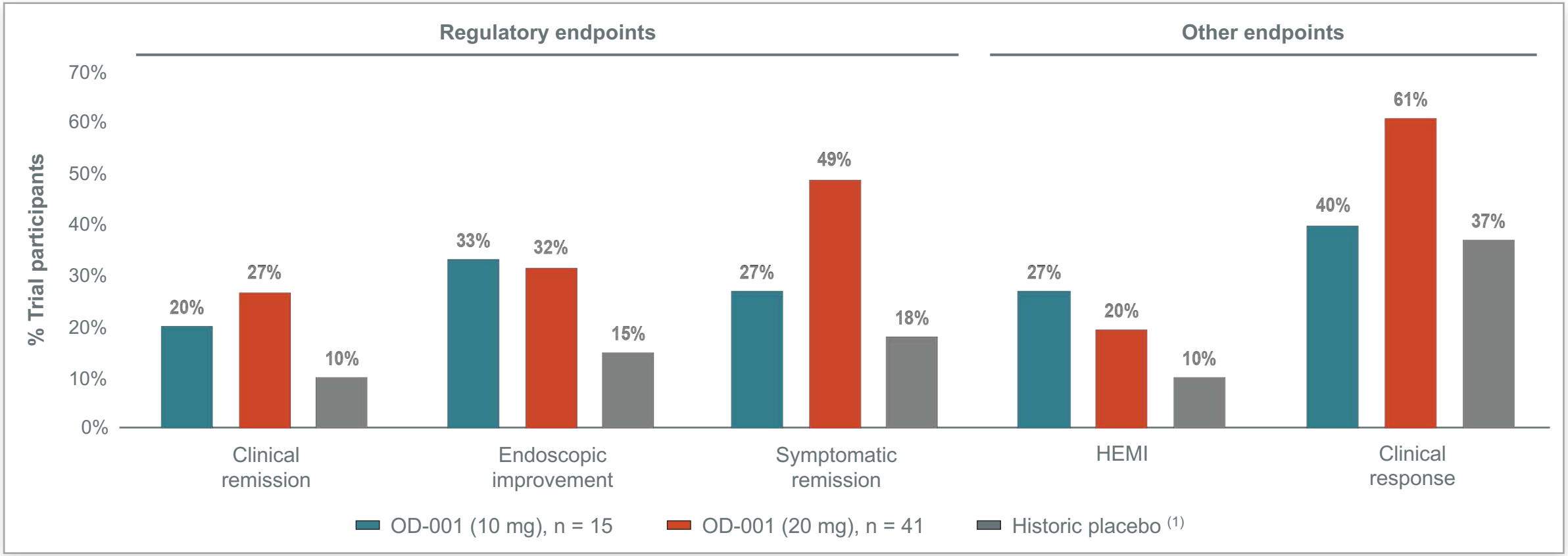


Notes: * $p < 0.05$; ** $p < 0.01$; nominal, unadjusted p values from paired Wilcoxon signed-rank tests comparing baseline and week 12 within each dose group; patients with hsCRP > 5 mg/L: 10 mg, baseline n = 9 and week 12 n = 7; 20 mg, baseline n = 24 and week 12 n = 18. 20 mg n varies by sample availability. Analyses across fecal calprotectin, hsCRP, albumin, and neutrophils include one patient who was not efficacy-evaluable at week 12.

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Efficacy Across Prespecified Week 12 Endpoints vs. Historic Placebo

- Trial met the primary endpoint of change in mMS from baseline in both parts and on a consolidated basis (-2.4, $p < 0.001$)
- Stronger efficacy observed with 20 mg BID



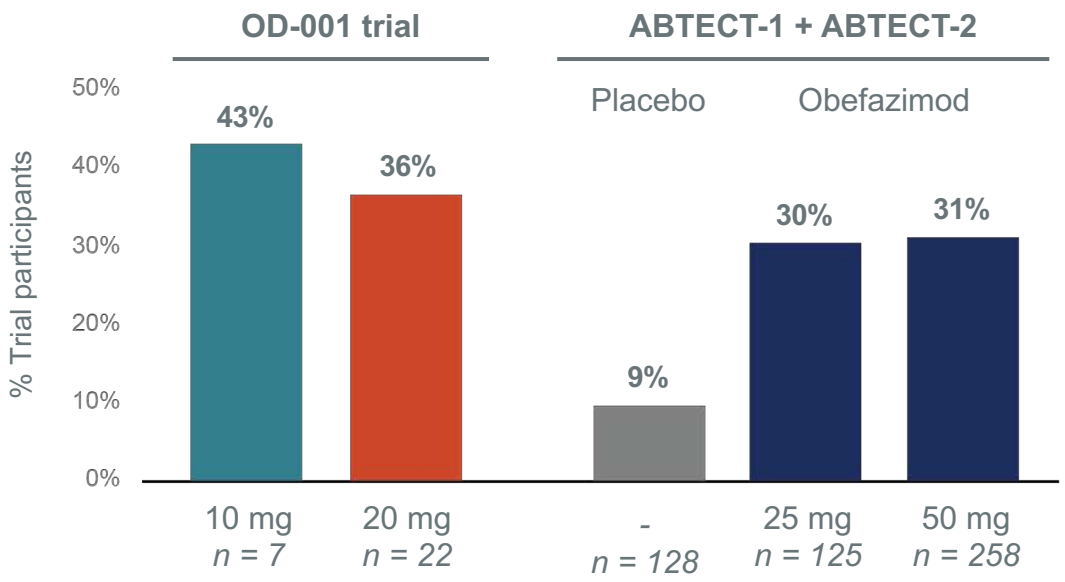
Disclaimer: Data presented are from ongoing studies, which will not be finalized until database lock. Thus, these data are subject to change prior to release of the CSR. Future results may differ from those shown here.
Notes: OD-001 results represent all patients who completed 12 weeks of treatment per protocol (n = 56); histologic-endoscopic mucosal improvement (HEMI) is defined as MES of 0 or 1 and Geboes index score ≤ 3.1. (1) Historic placebo benchmarks are derived from contemporary post-PoC UC studies (2020–2025); benchmark rates and supporting datasets are as follows: clinical remission 10% (average from 11 trials; n = 3,012 total; 820 placebo-treated patients); endoscopic improvement 15% (average from 10 trials; n = 2,920 total; 789 placebo-treated patients); symptomatic remission 18% (average from 5 trials; n = 1,872 total; 517 placebo-treated patients); HEMI 10% (average from 8 trials; n = 2,565 total; 676 placebo-treated patients); clinical response 37% (average from 9 trials; n = 2,633 total; 726 placebo-treated patients). Internal assessment of historic placebo rate is supported by third-party publications assessing placebo rates using individual patient data (J Crohns Colitis 2025;19(10):jjaf191).

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Higher Remission Rate With 20 mg BID Dose in Severe Patients (MES = 3)

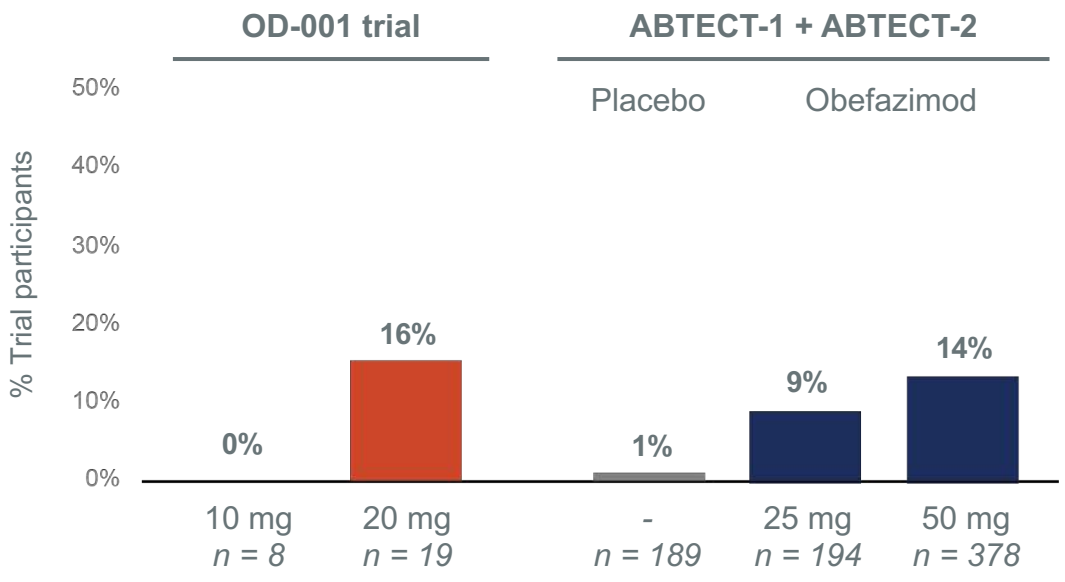
Similar activity between OD-001 doses in patients with moderate disease (MES = 2)

- Clinical remission rates in patients with moderate endoscopic disease are comparable at both doses



Dose-dependent activity in patients with severe disease (MES = 3)

- Greater barrier disruption may increase microbial exposure, requiring greater RIPK2 inhibition for efficacy

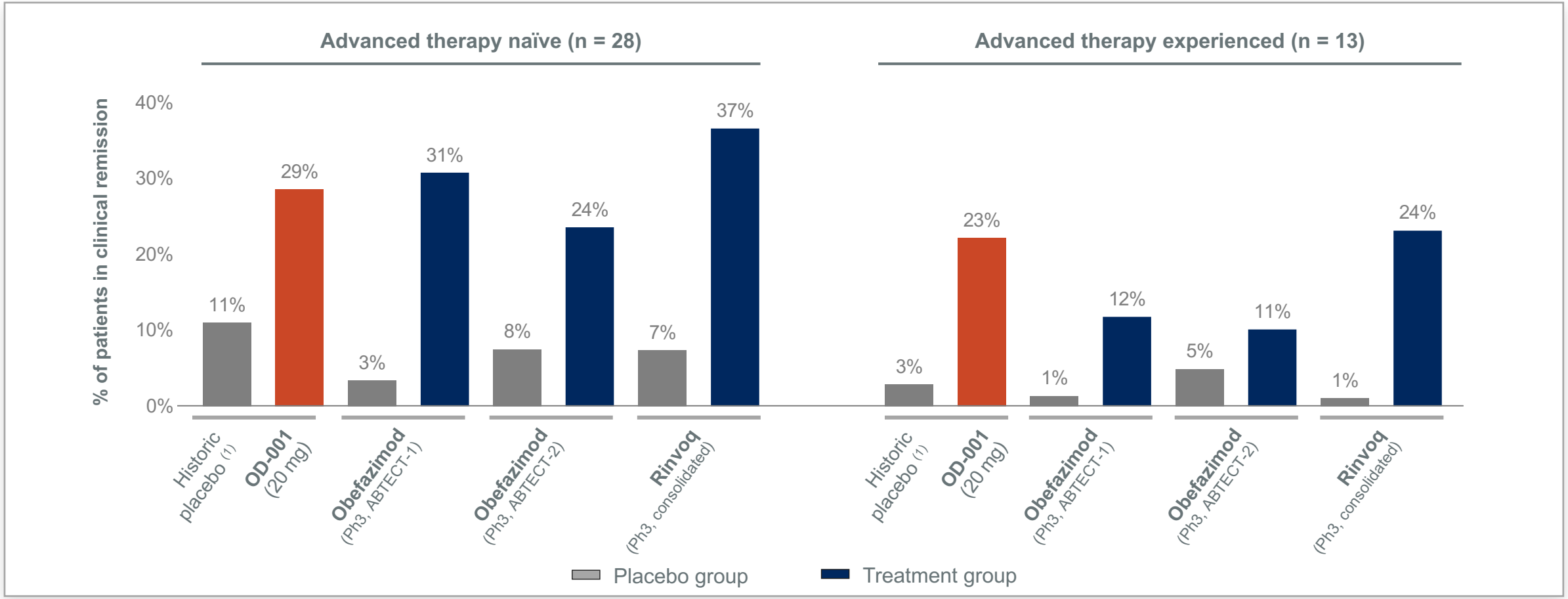


Disclaimer: Cross-trial comparisons are for context only, and no head-to-head study was conducted; differences in study design, patient populations, and other factors should be considered when interpreting results. OD-001 and a comparator have not been approved and may never be approved by any regulatory authority.
Source: Obefazimod ECCO 2026 presentation (P0952).

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Clinical Remission Rate at 20 mg BID Is Similar in AT-Naïve and AT-Experienced Patients

- Existing therapies often show reduced activity in AT-experienced patients, whereas OD-001 shows similar activity in both populations

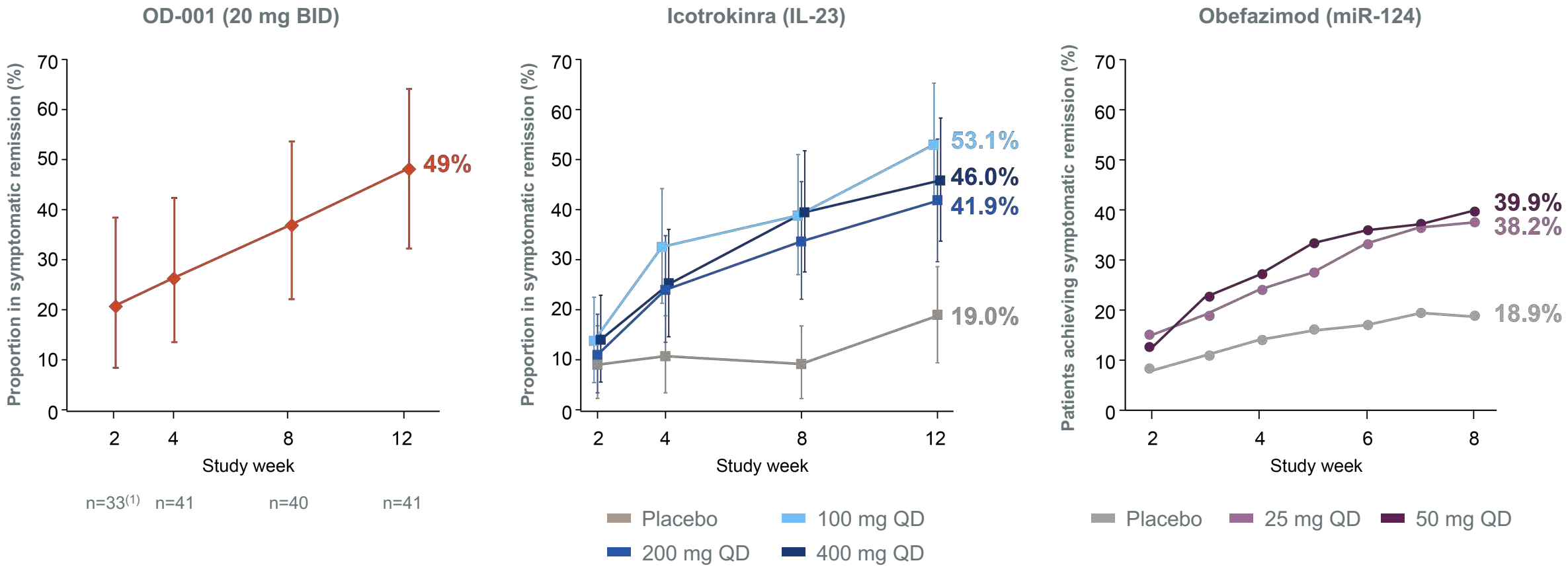


Disclaimer: Cross-trial comparisons are for context only, and no head-to-head study was conducted; differences in study design, patient populations, and other factors should be considered when interpreting results. OD-001 and a comparator have not been approved and may never be approved by any regulatory authority.

Notes: (1) Historic placebo benchmarks are derived from contemporary post-PoC UC studies (2020–2025) and Rinvoq phase 3 studies; dataset represents 1,819 AT-naïve and 1,475 AT-experienced patients treated with active agent or placebo.

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OD-001 Is Competitive With Other Oral Agents on Early Symptomatic Remission, With Increases Through Week 12



Notes: (1) Part 2 patients were randomized 1:4 to either 10 mg BID for the first two weeks followed by escalation to 20 mg BID for weeks 3–12, or 20 mg BID from week 1 through week 12. This staggered dosing design accounts for the difference in n at the week 2 time point.

Sources: Obefazimod ECCO 2026 presentation (P0923); Icotrokinra UEG Week 2025 presentation (OP206).

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OD-001 Is Safe and Well Tolerated Across Doses

	Part 1	Part 2		
	10 mg BID, n = 16	Group 1 10 then 20 mg BID, n = 9	Group 2 20 mg BID, n = 36	Total n = 45
Total number of TEAEs	**11**	**20**	**20**	**40**
Severe (grade ≥ 3) TEAE	1 (anemia) (1)	0	0	0
Drug-related TEAE	0	0	3	3
Liver function abnormality identified as a TEAE	0	0	0	0
Drug-related TEAEs leading to trial drug discontinuation	0	0	0	0
SAE	0	0	0	0
TEAEs of special interest:				
Elevated body temperature that meets specific criteria	0	0	0	0
Elevated hsCRP that meets specific criteria	0	0	0	0
Serious infection	0	0	0	0
Drug-related TEAEs:				
Fever	0	0	2	2
Headache	0	0	1	1

Disclaimer: Data presented are from ongoing studies, which will not be finalized until database lock. Thus, these data are subject to change prior to release of the CSR. Future results may differ from those shown here.
Notes: One participant in Part 1 and three participants in Part 2 discontinued treatment for reasons unrelated to the trial drug. One participant in Part 2 was not evaluable for efficacy. Total of 56 patients between Part 1 and Part 2 completed 12 weeks of induction treatment per protocol. (1) Patient had medical history of anemia with mild anemia at time of enrollment; OD-001 treatment was not discontinued and grade 3 anemia resolved with iron supplementation; TEAE was deemed not related to OD-001 treatment. hsCRP = high-sensitivity C-reactive protein.

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Summary and Conclusions

OD-001 20 mg BID has a competitive efficacy profile vs. approved or leading investigational therapies

- 27% absolute clinical remission rate with rapid onset of symptomatic benefit
- Efficacy across patient subgroups (e.g., AT experience and endoscopic severity) supports potential for broad use

Strong correlation between clinical efficacy and biomarkers supports OD-001 therapeutic conclusions

- Greater reductions in colonic and systemic inflammatory markers observed at 20 mg BID, the dose projected to maximally inhibit RIPK2
- Objective endpoints (endoscopy and biomarkers) are concordant and align with symptomatic benefit

Oral profile with favorable monotherapy safety and tolerability

- No SAEs and no discontinuations due to OD-001 at either dose
- Well-tolerated oral profile meets patient and prescriber preferences and can potentially enable a broad number of combinations

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Transcriptomic Analyses

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Transcriptomic Analysis of Mucosal Biopsies From Baseline and Week 12

- Initial analyses conducted to support target engagement/mechanism of action and to support clinical efficacy endpoints
  - Biopsy timing is not uniform, so analyses reflect sustained treatment-associated biology vs. immediate drug concentration-dependent effects
  - Patient-level analyses ongoing to inform potential patient selection/stratification strategy

OVERVIEW OF MUCOSAL BIOPSY ASSESSMENTS



Unbiased assessment of ~20,000 genes across the whole transcriptome to probe mechanism of action

- **Transcriptional response identified decreases in RIPK2-responsive genes, genes encoding inflammatory cytokines, and gene signatures of specific T cell subsets and fibrosis**
- **Increased expression of genes associated with epithelial homeostasis and mucosal healing**



Correlation between clinical outcome, histology, and biomarkers with transcriptional response

- **Patients with clinical remission or response show concordant improvement across biomarkers and reductions in inflammatory and fibrotic transcriptional profiles**



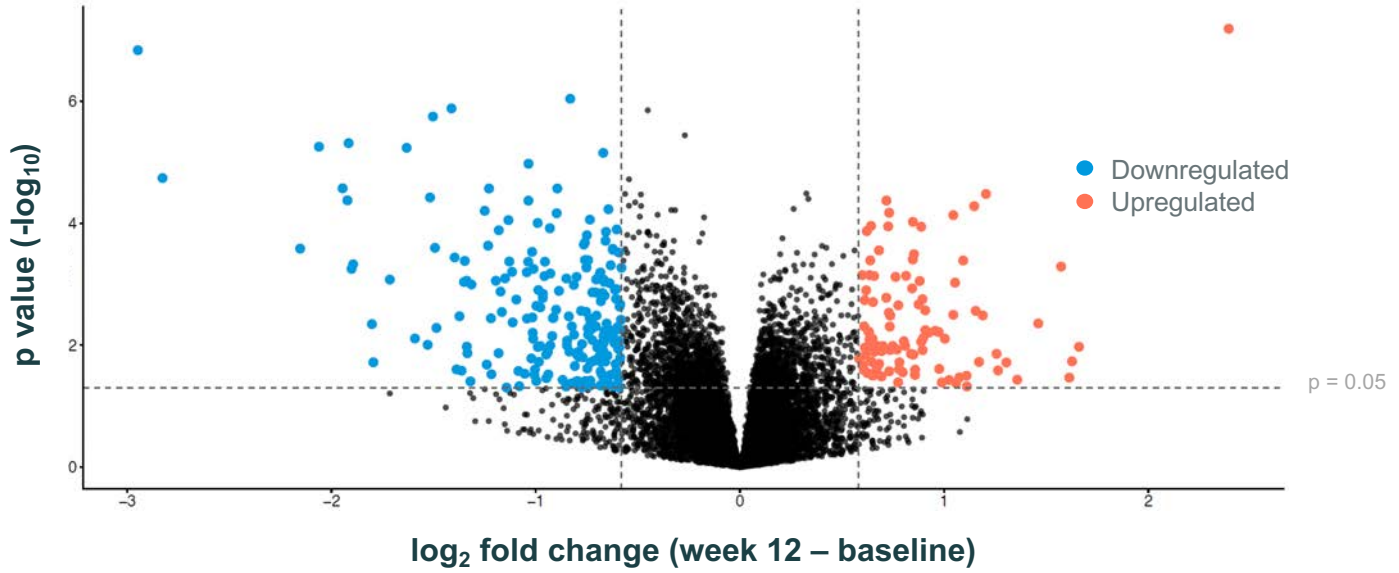
Identification of OD-001-specific effects and comparison to public datasets

- **Transcriptional response to OD-001 overlaps with response to anti-IL-23 antibodies (consistent with RIPK2 inhibition significantly controlling IL-23-based inflammatory signaling)**
- **OD-001 treatment reduces inflammatory AP-1 gene transcription that is implicated in IBD, an effect not observed in response to approved therapies**

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OD-001 Reduces Inflammatory and Fibrotic Gene Expression in IBD

- Transcriptomic analysis on mucosal biopsies from patients treated with 20 mg BID (n = 40) at baseline and week 12 were compared to detect differentially expressed genes
  - Colored dots represent differentially regulated genes with ≥ 1.5-fold change and nominal p < 0.05
- Gene set enrichment analysis was performed on the set of differentially regulated genes to identify biological processes changed following OD-001 treatment
- *RIPK2-regulated genes, cytokines, T cell signaling, and fibrosis gene pathways were **downregulated** after treatment*
- *Gene signatures of mucosal healing were **upregulated** after treatment*



OD-001 reduces RIPK2 and microbial signatures

Gene set	Effect	p_{adj}
RIPK2 signaling	↓	9E-12
Innate host defense response	↓	9E-5
AP-1	↓	6E-4

OD-001 reduces cytokine expression and signaling

Gene set	Effect	p_{adj}
IL-23 signaling	↓	1E-7
TNF/NF-κB signaling	↓	1E-8
TL1A signaling	↓	7E-4

OD-001 reduces T cell activity

Gene set	Effect	p_{adj}
Th17 signaling	↓	6E-26
Th1 signaling (1)	↓	7E-9

OD-001 reduces fibrotic signaling and increases epithelial homeostasis signaling

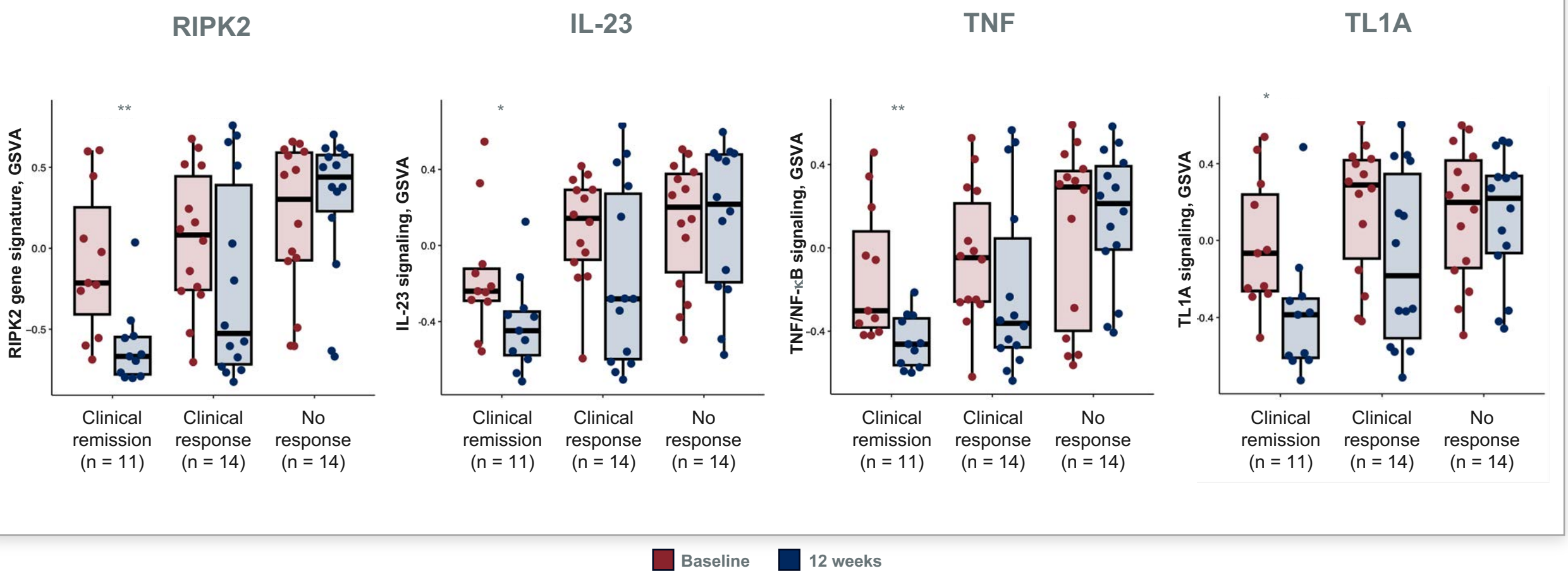
Gene set	Effect	p_{adj}
Inflammatory fibroblasts	↓	2E-4
Penetrating fibrosis (1)	↓	7E-3
Epithelial homeostasis	↑	2E-10

Notes: DESeq2 volcano plot of week 12–baseline change in the 20 mg cohort (n = 40 paired mucosal samples); two additional samples failed RNA-seq QC. Pathway enrichment used hypergeometric testing with FDR adjustment; (1) p values reflect week 12 vs. baseline for only responder/remitter patients (n = 25); all other comparisons are week 12 vs. baseline for the full cohort, including one patient not evaluable for efficacy (n = 40); gene sets from MSigDB: Reactome Antimicrobial Peptides, PID AP-1 pathway, PID IL-23 pathway, Hallmark TNF/NF-κB; Internal: RIPK2 Pathway, cited studies: TL1A, Th17, Th1, Inflammatory Fibroblasts, Penetrating Fibrosis, Epithelial Homeostasis.

Sources: Cell Syst 2015;1(6):417–425; Am J Gastroenterol 2011;106(7):1272–1280; J Leukoc Biol 2017;101(3):727–737; Nat Genet 2025;57(7):1742–1753; Gut 2022;71(7):1289–1301; Sci Rep 2021;11(1):9010.

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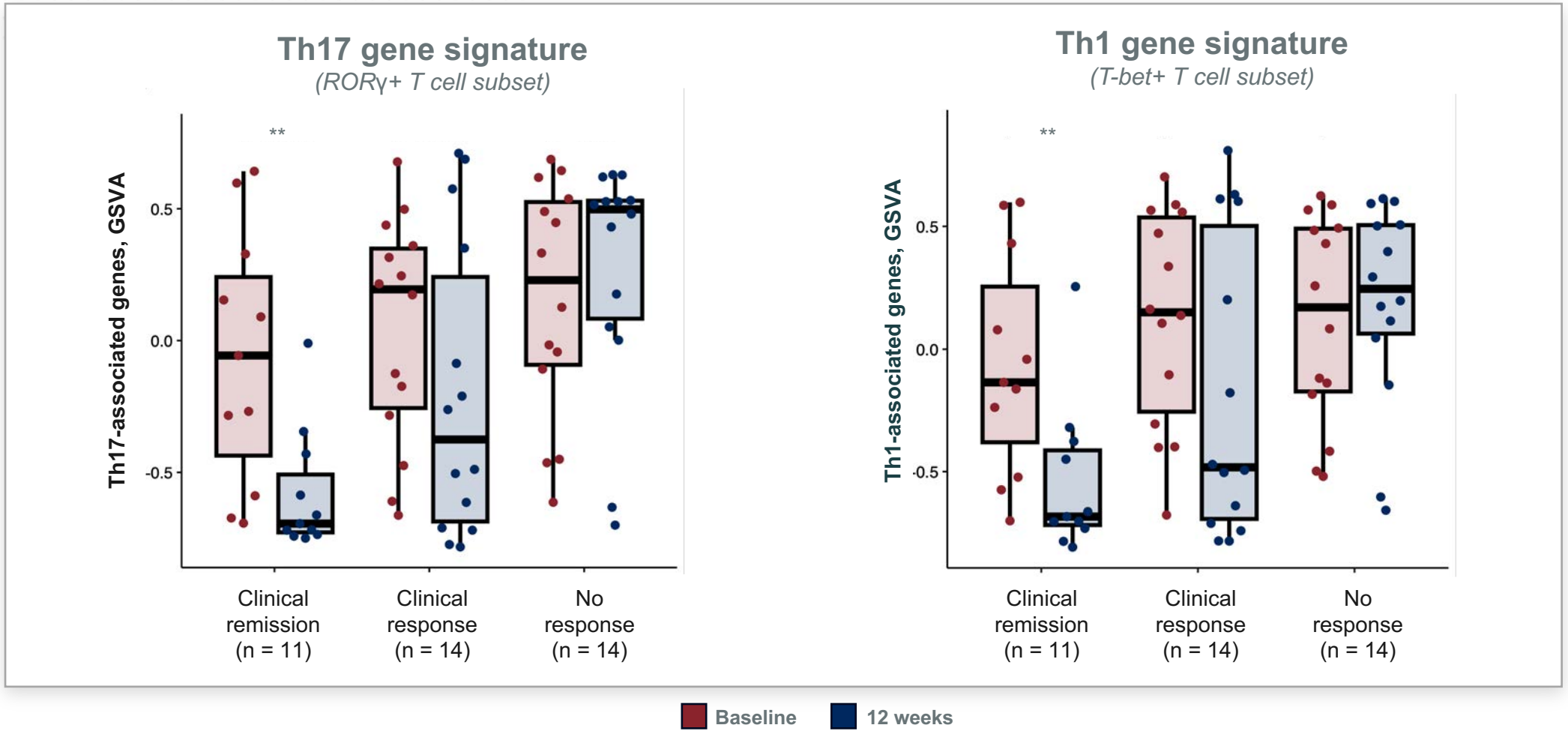
Reductions in RIPK2 Gene Signature and Cytokine Gene Responses Following OD-001 Treatment Track With Clinical Outcomes



Notes: GSVA scores were calculated for prespecified RIPK2 gene signature (internal), TL1A-Th17 gene signature (J Leukoc Biol 2017;101(3):727-737), PID IL-23, and Hallmark TNFα/NF-κB gene sets from MSigDB. Nominal, unadjusted p values are from paired Wilcoxon signed-rank tests. Analysis includes n = 39 paired baseline/week 12 samples from the 20 mg cohort; one patient was not efficacy-evaluable and two non-responder samples failed RNA-seq QC. Clinical remission: mMS ≤ 2, SFS ≤ 1, RBS = 0, and MES ≤ 1 at week 12. Clinical response: ≥ 2-point and > 30% decrease in mMS, with either ≥ 1-point decrease in RBS or absolute RBS 0 or 1 at week 12. * $p < 0.05$; ** $p < 0.01$.
Source: Cell Syst 2015;1(6):417–425.

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Reduction in T Effector Activation Signatures Following OD-001 Treatment

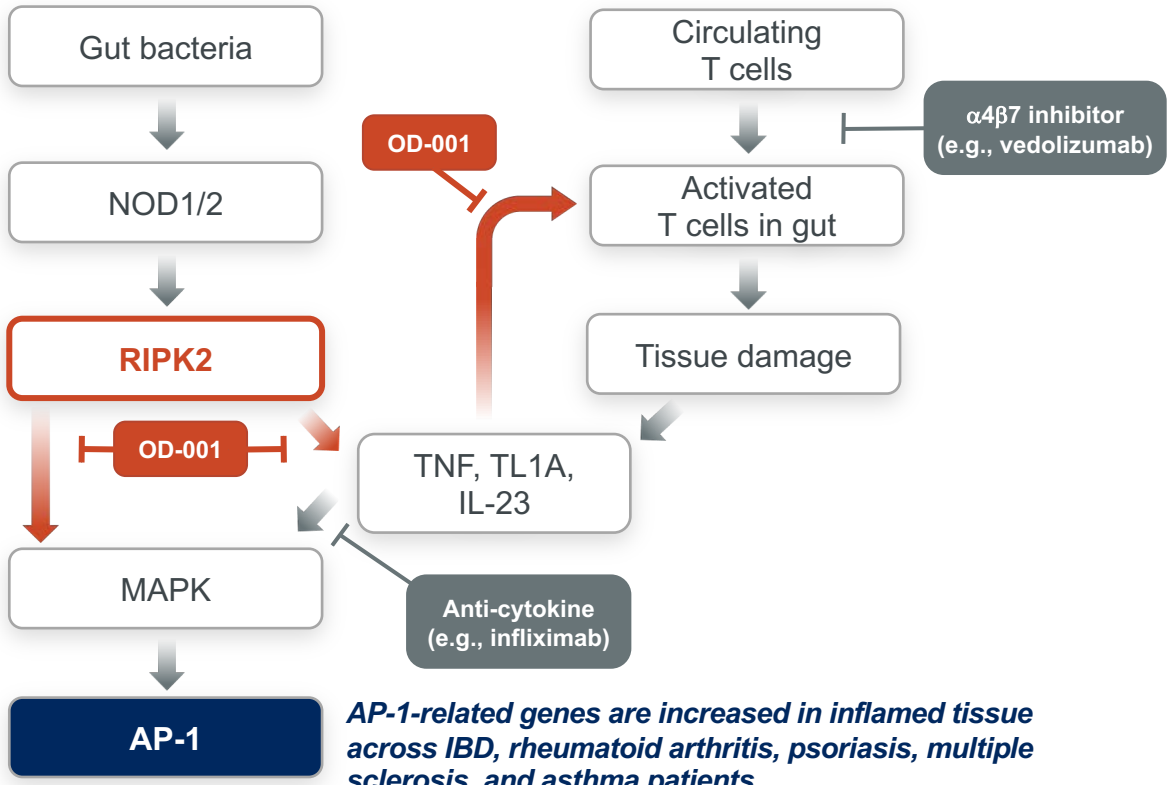


Notes: GSVA scores were calculated for prespecified Th17- and Th1-associated gene sets derived from the ACT1 infliximab mucosal transcriptomic analysis. Nominal, unadjusted p values are from paired Wilcoxon signed-rank tests. Analysis includes n = 39 paired baseline/week 12 samples from the 20 mg cohort; one patient was not efficacy-evaluable and two non-responder samples failed RNA-seq QC. Clinical remission: mMS ≤ 2, SFS ≤ 1, RBS = 0, and MES ≤ 1 at week 12. Clinical response: ≥ 2-point and > 30% decrease in mMS, with either ≥ 1-point decrease in RBS or absolute RBS 0 or 1 at week 12; ** p < 0.01. Source: Am J Gastroenterol 2011;106(7):1272–1280.

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OD-001 Modulates a Distinct Set of Inflammatory Genes Not Addressed With Existing Therapies

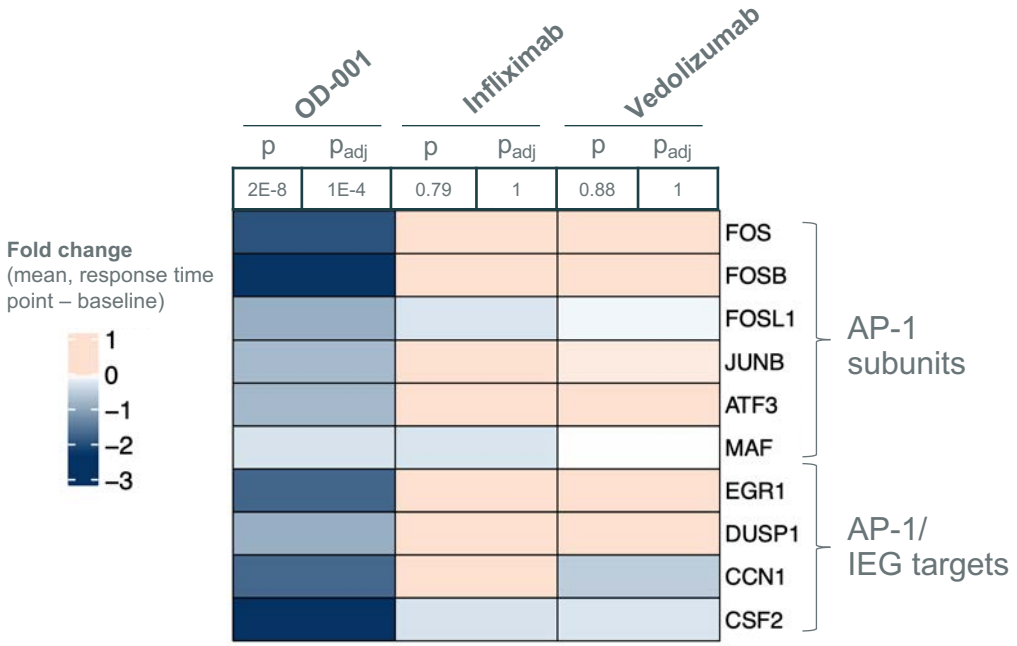
OD-001 blocks direct activation of the MAPK pathway from gut bacteria, addressing redundancy missed by existing anti-cytokine therapies



AP-1-related genes are increased in inflamed tissue across IBD, rheumatoid arthritis, psoriasis, multiple sclerosis, and asthma patients

AP-1 signature downregulation similar to OD-001 is not observed in published anti-TNF and anti-integrin datasets

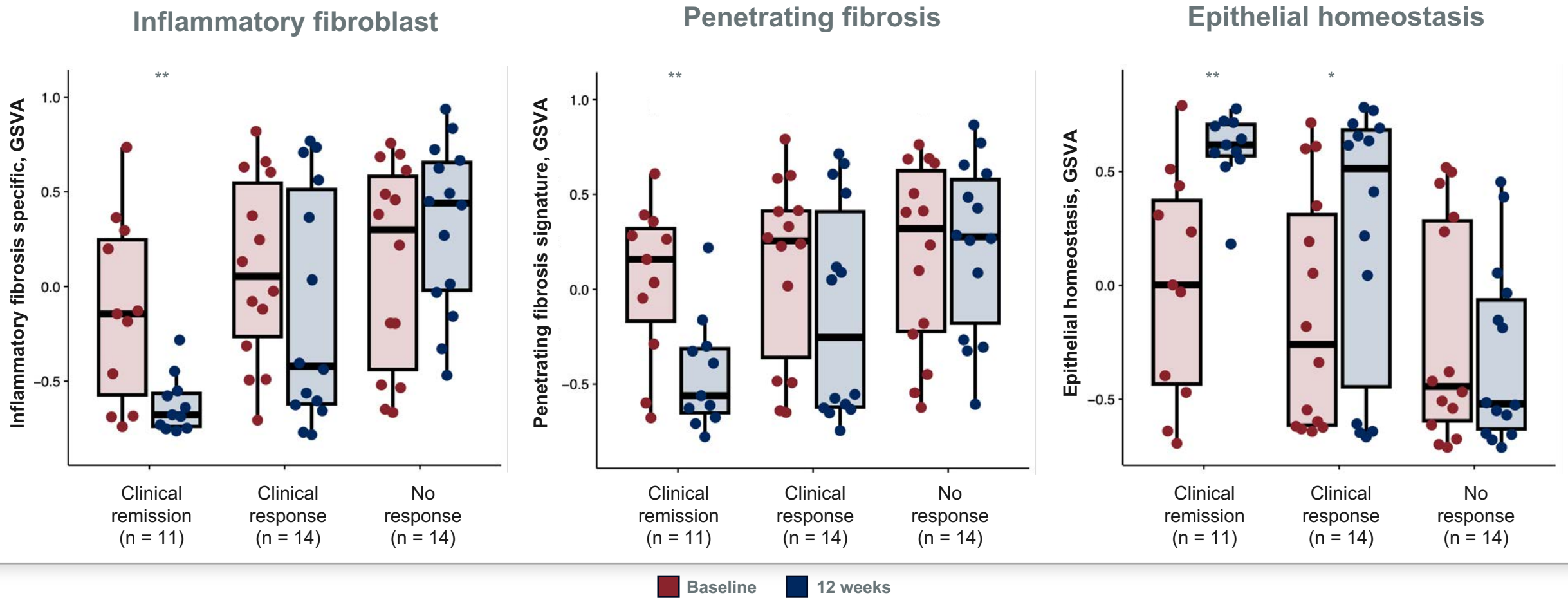
- Comparison of OD-001 responders with responder cohorts from competitor datasets suggests OD-001 effects are not attributable to general mucosal improvement



Notes: Endoscopic responders only. Downregulation: fold-change < 0, FDR q < 0.05. OD-001, n = 13 (20 mg); infliximab, n = 8; vedolizumab, n = 12. Response was MES 0 or 1 at week 12, weeks 4-6, and week 52, respectively. PID AP-1 genes were from MSigDB; enrichment used hypergeometric testing with FDR adjustment. IEG = immediate early genes.
Sources: Gut 2018;67(1):43–52; J Biol Chem 1999;274:33684–33690.

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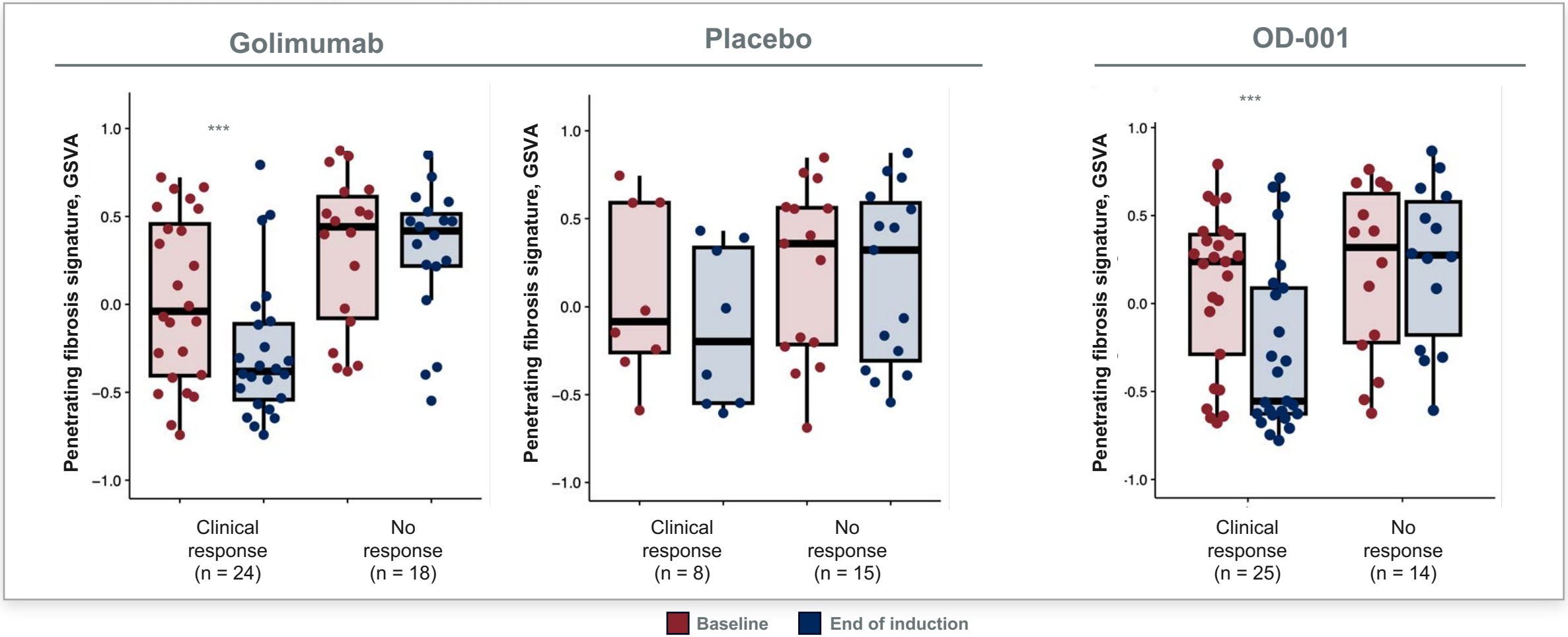
Reduction in Fibrosis-Related Genes and Upregulation of Genes Associated With Healing Align With Clinical Outcomes



Notes: GSVA scores were calculated for prespecified Inflammatory Fibroblast, Penetrating Fibrosis, and Epithelial Homeostasis gene sets. Inflammatory Fibroblast was an internal set informed by Nat Genet 2025;57(7):1742–1753; Penetrating Fibrosis was derived from Gut 2022;71(7):1289–1301; Epithelial Homeostasis used the UC100 gene set downregulated in UC from Sci Rep 2021;11(1):9010. Nominal, unadjusted p values are from paired Wilcoxon signed-rank tests. Analysis includes n = 39 paired baseline/week 12 samples from the 20 mg cohort; one patient was not efficacy-evaluable and two non-responder samples failed RNA-seq QC. Clinical remission: mMS ≤ 2, SFS ≤ 1, RBS = 0, and MES ≤ 1 at week 12. Clinical response: ≥ 2-point and > 30% decrease in mMS, with either ≥ 1-point decrease in RBS or absolute RBS 0 or 1 at week 12. * $p < 0.05$; ** $p < 0.01$.
Sources: Nat Genet 2025;57(7):1742–1753; Gut 2022;71(7):1289–1301; Sci Rep 2021;11(1):9010.

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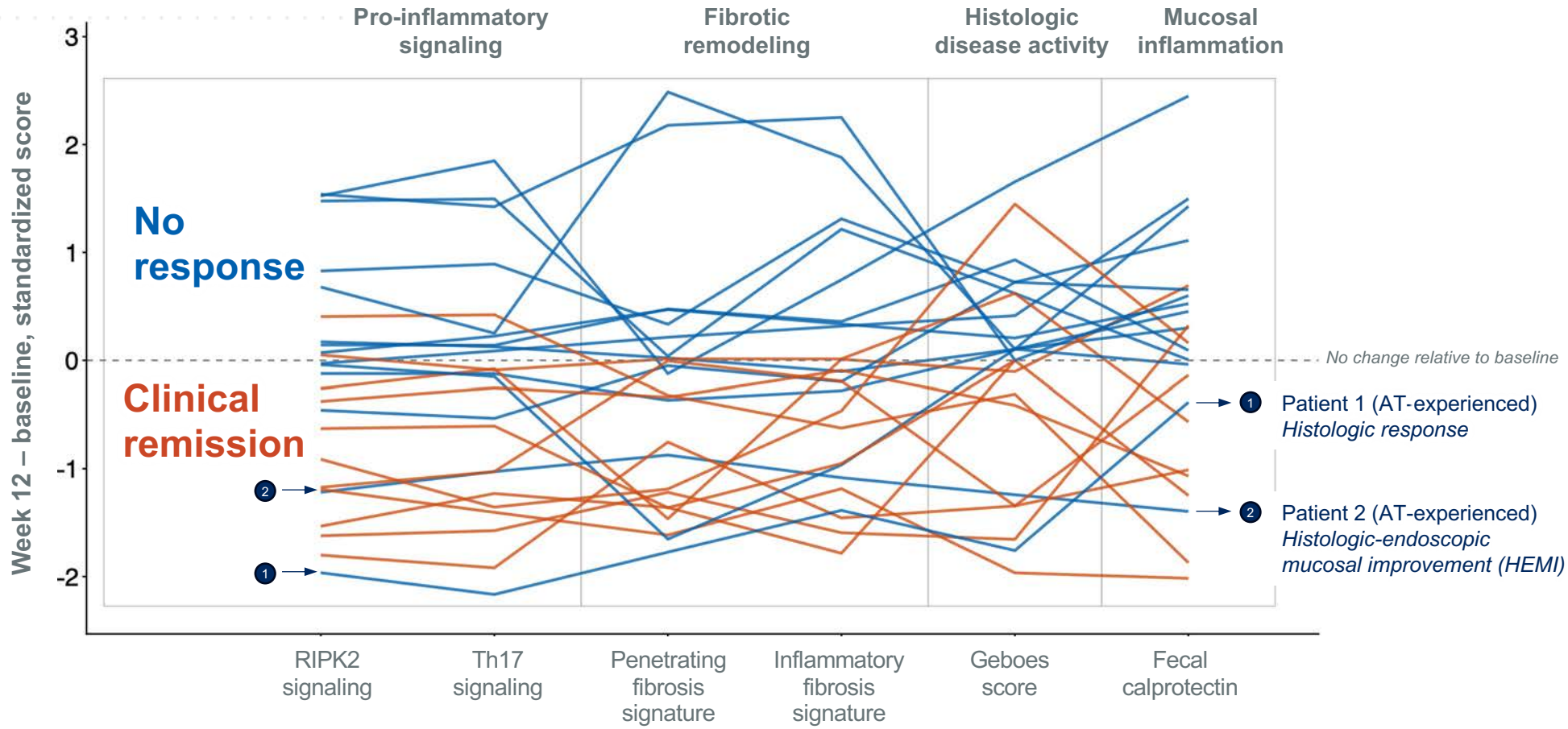
Depth of Reduction in the Penetrating Fibrosis Signature May Differentiate Responders From Effective Treatments Versus Placebo



Notes: GSVA scores were calculated using the prespecified Penetrating Fibrosis Signature from Gut 2022;71(7):1289–1301. Nominal, unadjusted p values are from paired Wilcoxon signed-rank tests. OD-001 analysis includes n = 39 paired baseline/week 12 samples from the 20 mg cohort; one patient was not efficacy-evaluable and two non-responder samples failed RNA-seq QC. Golimumab (n = 42) and placebo (n = 23) mucosal samples were profiled by microarray at screening and week 6; end of induction therefore represents week 12 for OD-001 and week 6 for golimumab/placebo. OD-001 clinical response includes n = 25 responders/remitters. OD-001 clinical remission: mMS ≤ 2, SFS ≤ 1, RBS = 0, and MES ≤ 1 at week 12. OD-001 clinical response: ≥ 2-point and > 30% decrease in mMS, with either ≥ 1-point decrease in RBS or absolute RBS 0 or 1 at week 12. Cross-study comparisons are exploratory and subject to differences in population, response definitions, timing, platform, and sample size. *** $p < 0.001$. Sources: Gut 2022;71(7):1289–1301; Gastroenterology 2014;146(1):85–95.

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Transcriptomic Changes, Histology, and Fecal Calprotectin Show Concordant Effects in Clinical Remitters



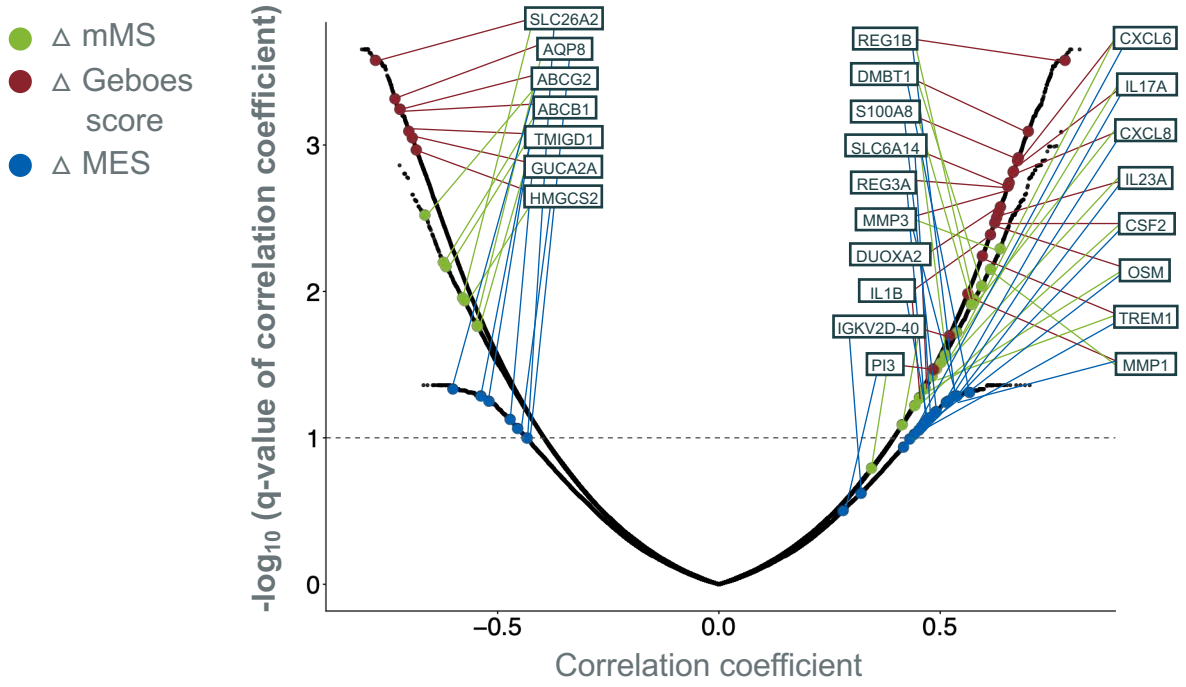
Notes: Values were standardized by dividing by the standard deviation; clinical remission, n = 11; no response, n = 14; clinical remission: mMS ≤ 2 (SFS ≤ 1, RBS = 0, MES ≤ 1) at week 12; one patient treated with 20 mg OD-001 was not evaluable for efficacy and two non-responder patient samples failed QC on RNA-seq and are not included in the analysis.

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Differential Expression of Genes Following OD-001 Treatment Correlates With Efficacy Measures and Overlaps With the Response to Anti-IL-23

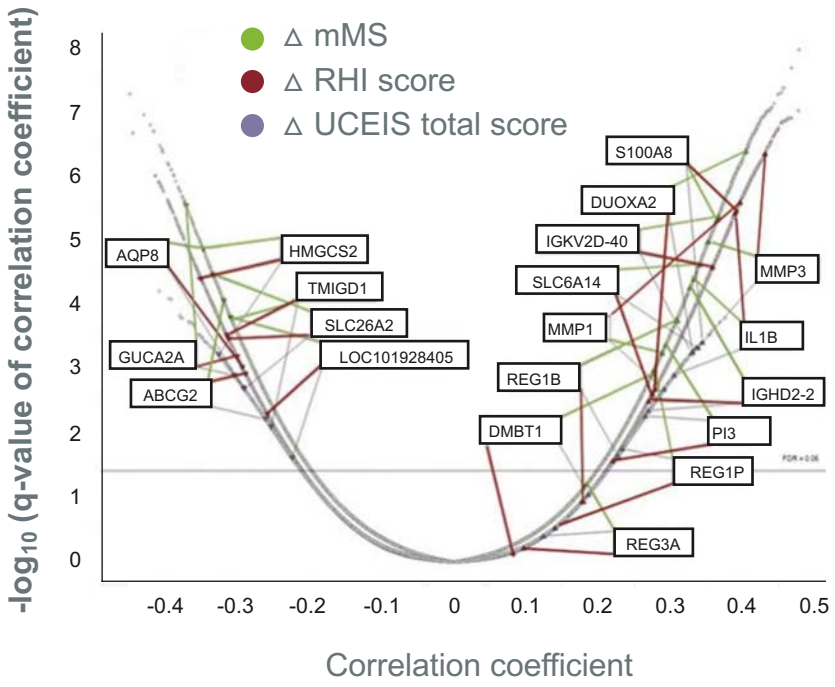
Genes most highly correlated with efficacy measures include IL-1β, IL-23, and IL-17, all of which are associated with inflammation

OD-001



Pearson correlation of baseline-to-week 12 transcript changes with disease activity scores; selected high-ranking IBD inflammatory/myeloid and epithelial genes are labeled

Mirikizumab



Pearson correlation of published correlations of mirikizumab-regulated genes with disease activity scores

Notes: OD-001 analysis includes n = 40 paired baseline/week 12 mucosal samples from the full 20 mg cohort. Partial Pearson correlations assessed gene-expression changes versus Geboes, mMS, and MES, adjusting for baseline value, age, sex, and study site. Positive correlations indicate genes that decrease as disease improves; negative correlations indicate genes that increase. Dashed line denotes FDR q = 0.10. Two samples failed RNA-seq QC. Mirikizumab data are published summary-level associations with mMS, RHI, and UCEIS. RHI = Robarts Histopathology Index; UCEIS = UC Endoscopic Index of Severity. Source: Clin Transl Gastroenterol 2023;14(7):e00578.

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Patient-Level Analyses of Transcriptional Changes With OD-001 Compared With Publicly Available Datasets

- Three public UC transcriptomic datasets were identified that included patient-level data suitable for direct responder-based comparisons with OD-001
- OD-001 downregulates a majority of a published 34-gene mucosal signature that is associated with poor response to anti-TNF therapy, providing mechanistic support for the clinical activity observed in AT-experienced patients
- Patient-level data for a TNF inhibitor (infliximab) and an $\alpha 4\beta 7$ inhibitor (vedolizumab) enable evaluation of similarities and differences in mucosal effects between OD-001 and two distinct approved mechanisms
- Effects of mirikizumab, an approved IL-23 inhibitor, have been presented in summary form, with effects comparable to OD-001, but patient-level data similar to the vedolizumab and infliximab datasets are not publicly available

Sources: Cell 2019;178(3):714–730; Gut 2018;67(1):43–52; Clin Transl Gastroenterol 2023;14(7):e00578.

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Biological Processes Modulated in Responders to OD-001 Are Similar to Other Effective Treatments

COMPARISON	KEY BIOLOGY	IMPLICATION
Shared among all therapies OD-001, infliximab, vedolizumab	↓ Inflammatory monocytes ↓ TNF / NF-κB, Th17, and IL-6 signaling ↑ Epithelial homeostasis	**Common features associated with effective UC therapies**
Shared with infliximab OD-001 + infliximab	↓ Inflammatory cytokine programs ↓ IL-23 / Th17 pathway activity	**Downregulation of inflammatory cytokines is due to OD-001 rather than reduced disease process**
Shared with vedolizumab OD-001 + vedolizumab	↓ Fibrosis / collagen remodeling pathways	**Downregulation of fibrosis genes reflects OD-001 effects independent of TNF inhibition**

Mechanism-specific overlap with infliximab or vedolizumab responders that is absent in responders to the other agent suggests a drug effect of OD-001 beyond general mucosal improvements expected with a placebo response

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Concluding Remarks

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Summary of Key Findings

- Phase 2a trial provides clinical proof of concept for a first-in-class oral therapy targeting RIPK2 with a compelling efficacy and safety profile
  - Biomarkers and transcriptomics link RIPK2 scaffolding inhibition with clinical efficacy
- Efficacy, biomarker, and transcriptomic data support 20 mg BID as projected therapeutic dose
  - Differences observed in inflammatory biomarkers by dose support therapeutic effect
- Similar clinical remission rates irrespective of AT experience at the 20 mg BID dose
- Symptomatic remission as early as week 2 with increased remission rate through week 12 of induction therapy
- No serious infections and no discontinuations due to TEAEs
  - Profile could position OD-001 as a backbone for combinations and long-term oral maintenance therapy
- Transcriptomic analyses show decreases across multiple independent and objective measures of inflammation and fibrosis
  - Differences between the transcriptional response following OD-001 vs. vedolizumab are consistent with complementary therapeutic mechanisms and the potential for additive or synergistic effects of both drugs in combination

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Next Steps for OD-001

- Advance OD-001 in parallel as a monotherapy and in combination for ulcerative colitis
- Establish OD-001 in ulcerative colitis before expanding into Crohn's disease or other inflammatory indications (e.g., spondyloarthritis, a common comorbidity in IBD)
- Placebo-controlled monotherapy and active-controlled combination induction readouts remain on track for H2 2027

Phase 2a combination trial with vedolizumab

- Orthogonal combination designed to address upstream activation and downstream immune cell trafficking to the gut
- Randomized, double-blind trial will assess the efficacy and safety of combination induction vs. vedolizumab plus placebo
- After induction, all patients enter OD-001 monotherapy maintenance (results expected in 2028)
- Trial design was presented at ACG 2026 (October)

Phase 2b monotherapy trial

- Designed to support advancement into phase 3 trials
- Phase 2b will be a randomized, double-blind trial testing multiple OD-001 doses versus placebo
- Further trial design details to be disclosed in the future

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Upcoming Milestones for Lead Programs Through 2028

- In addition to advancing RIPK2, Odyssey expects to file a CTA for OD-002, an SLC15A4 inhibitor, in H2 2026, with phase 1/2a trial initiation expected in H1 2027
  - Phase 1 healthy-volunteer trial will use a validated ex vivo stimulation assay that has translated to efficacy with TLR7/8 antagonists
  - Phase 2 trial will enroll patients with multiple inflammatory diseases, including one cohort of cutaneous lupus patients
- OD-003, a TNFR2 agonist, is currently in IND-enabling studies with projected completion in Q1 2027

2026	2027		2028	
H2	H1	H2	H1	H2
OD-001 Ph2b monotherapy trial initiation	**OD-002** Initiate healthy participant dosing in Ph1/2 trial	**OD-001** Ph2b monotherapy induction readout		**OD-001** First maintenance readout
OD-001 Ph2a vedolizumab combo trial initiation	**OD-003** IND-enabling study completion	**OD-001** Ph2a vedolizumab combo induction readout		**OD-002** Ph2a readouts in multiple indications
OD-002 File CTA		**OD-002** Ph1 results, including ex vivo stimulation assay		

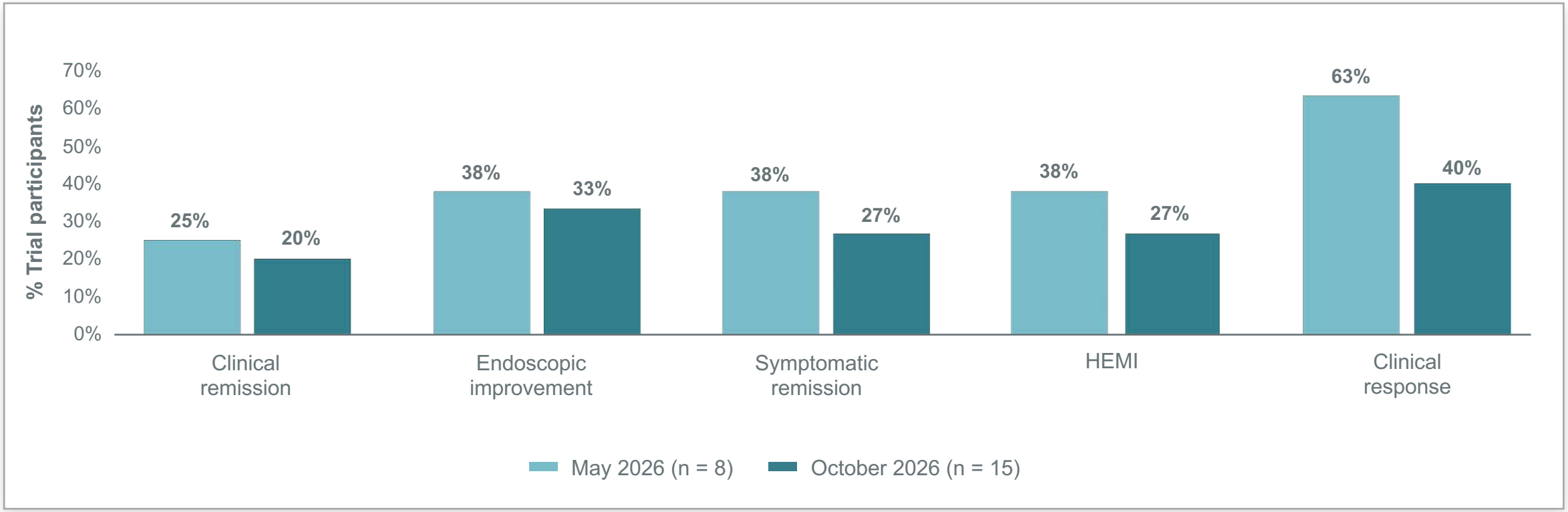
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Appendix

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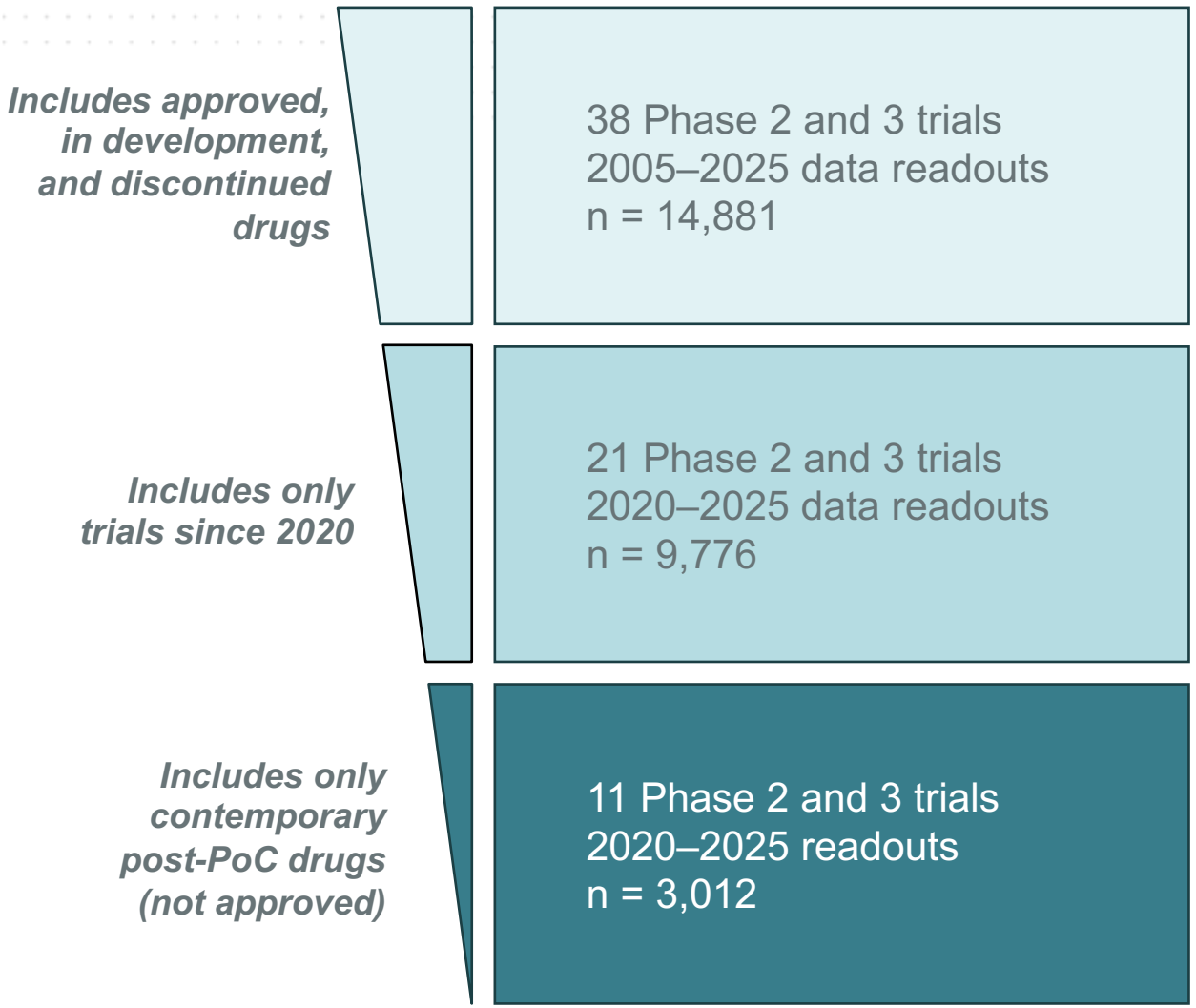
Efficacy Analysis of Complete 10 mg BID Cohort

- Among the seven additional evaluable patients, one reached clinical remission, one had endoscopic improvement, and five had no response
  - All additional patients were enrolled at existing phase 2a clinical trial sites and were naïve to advanced therapy



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Historic Placebo Rates Derived From UC Trial Meta-Analysis



AVERAGE HISTORIC PLACEBO

FDA endpoint

Clinical remission = 10%

11 Phase 2/3 trials
Total = 3,012, placebo group = 820

EMA co-primary endpoints

Endoscopic improvement = 15%

10 Phase 2/3 trials
Total = 2,920, placebo group = 789

Symptomatic remission = 18%

5 Phase 2/3 trials
Total = 1,872, placebo group = 517

HEMI = 10%

8 Phase 2/3 trials
Total = 2,565, placebo group = 676

Clinical response = 37%

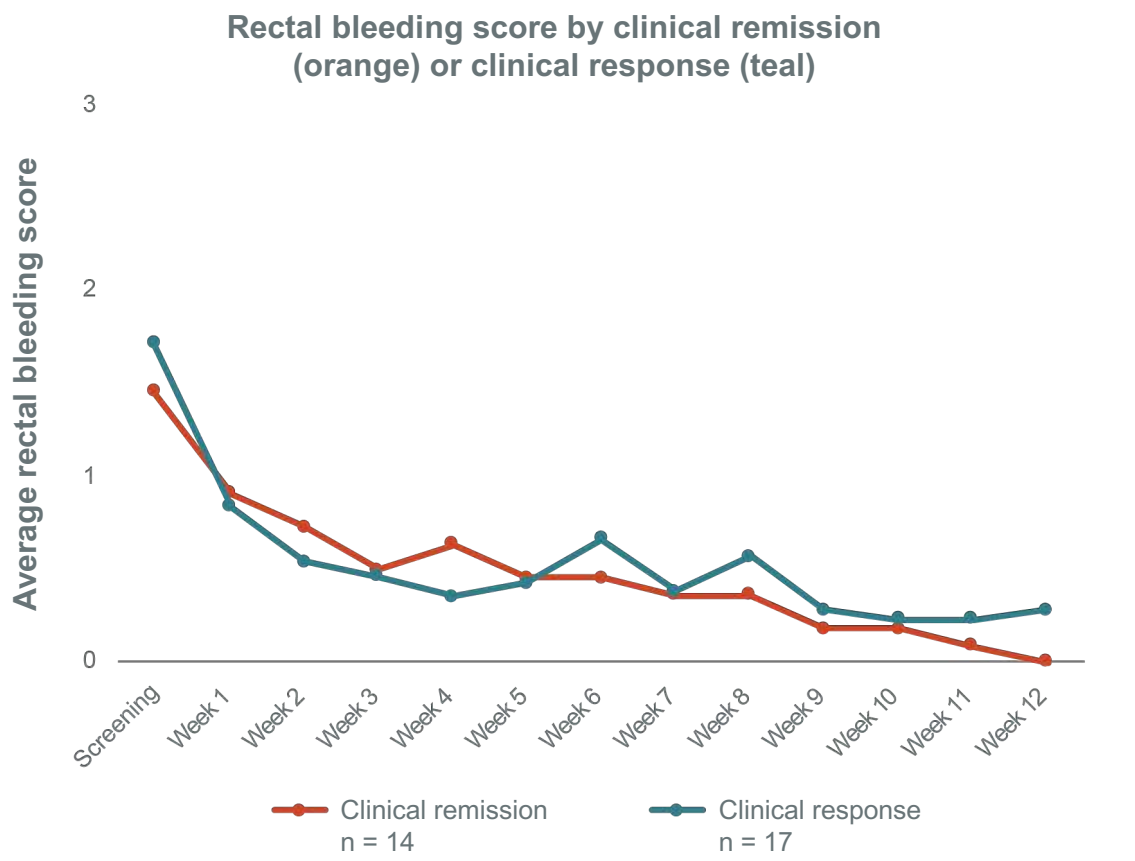
9 Phase 2/3 trials
Total = 2,633, placebo group = 726

Notes: Meta-analysis included 12 approved, 2 discontinued, and 9 in-development UC therapies across 38 trials; placebo benchmarks were derived from contemporary post-PoC UC studies (2020–2025) to account for time-dependent placebo effects; endpoint availability among post-PoC trials (11 trials; n = 3,012): clinical remission reported in 11/11 trials; endoscopic improvement reported in 10/11 trials; symptomatic remission reported in 5/11 trials; HEMI reported in 8/11 trials; clinical response reported in 9/11 trials; for comparability, placebo rates were *also* calculated using the full contemporary dataset (21 trials; n = 9,776), yielding a clinical remission rate of 10%, endoscopic improvement rate of 14%, and clinical response rate of 35%; internal assessment of historic placebo rate is supported by third-party publications assessing placebo rates using individual patient data (J Crohns Colitis 2025;19(10):jjaf191).

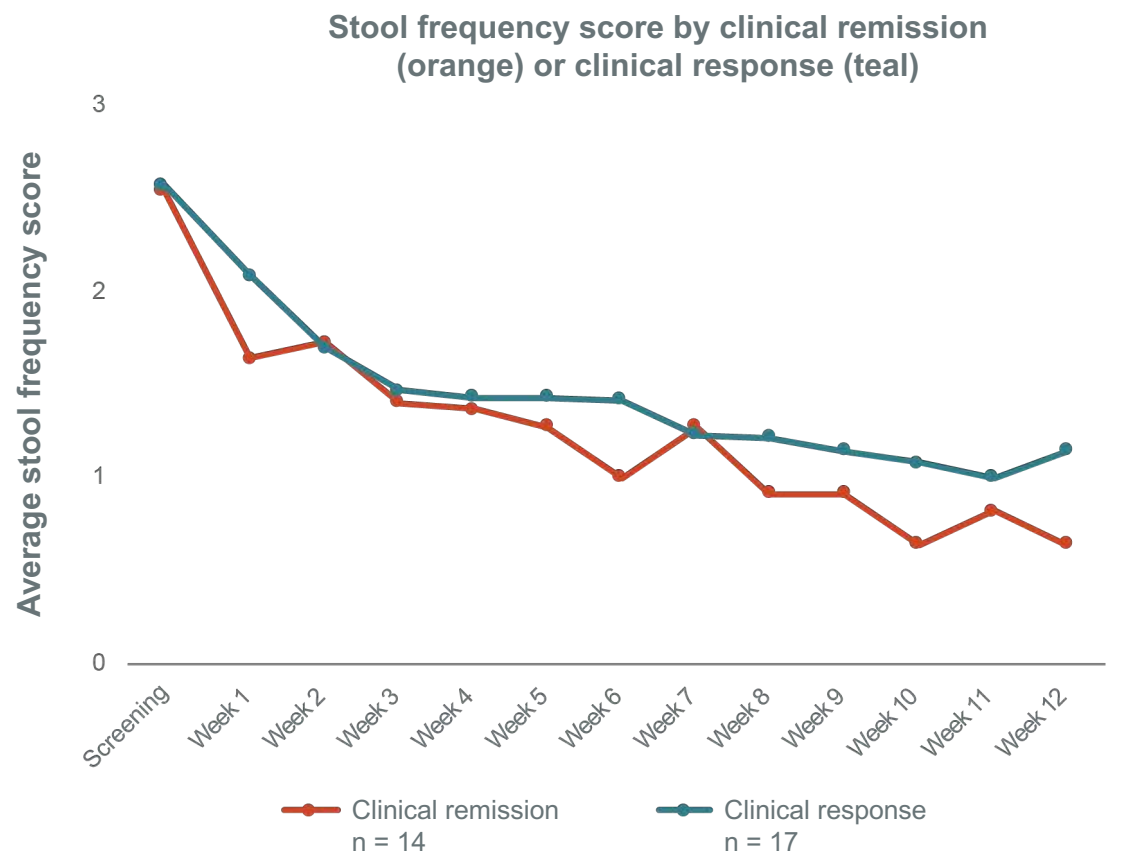
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Clinical Responders at 12 Weeks May Benefit From Continued Treatment

Patients with clinical response showed rapid reductions in rectal bleeding, similar to patients with clinical remission…



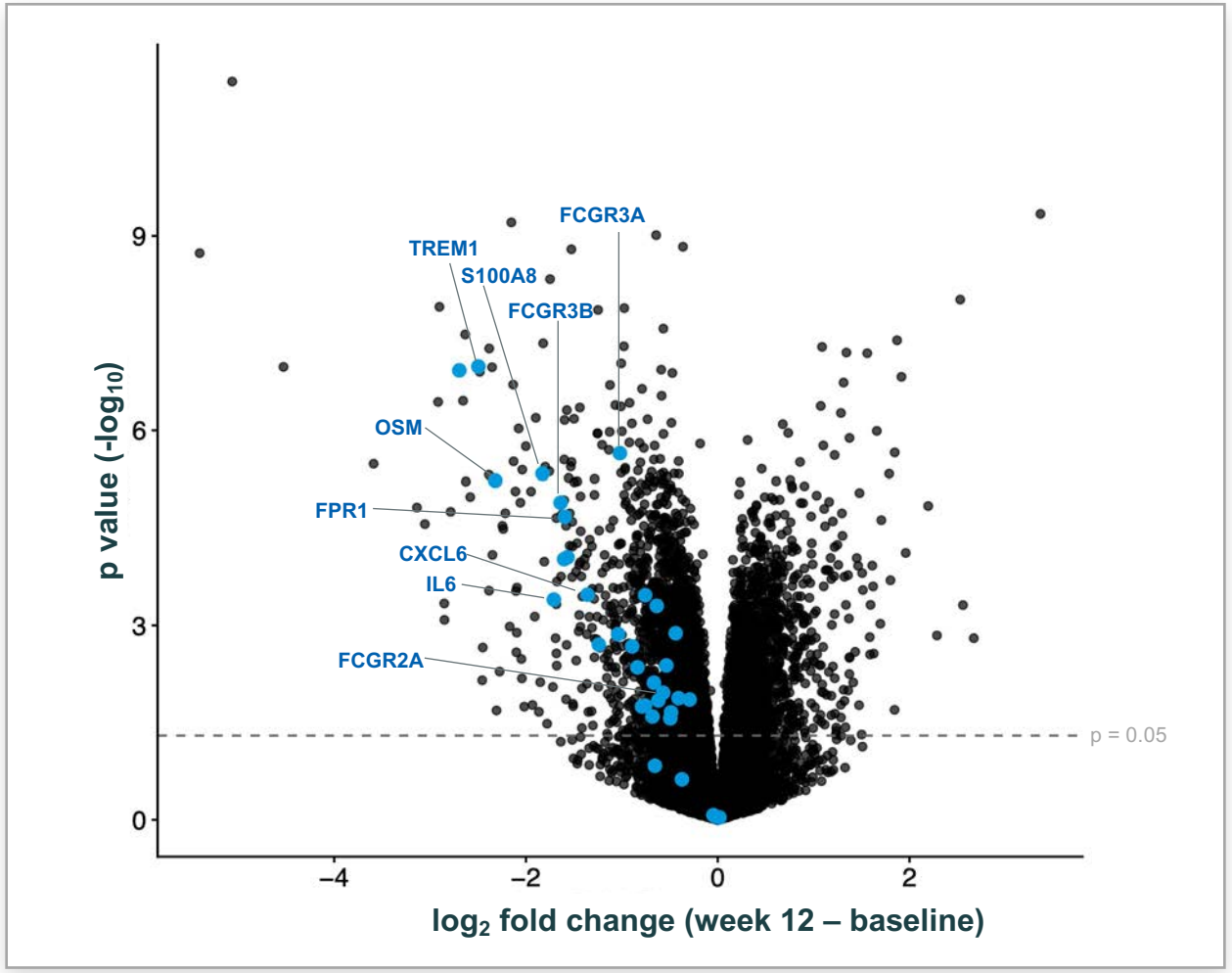
… stool frequency also showed rapid reduction, but rate of improvement appears slower



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OD-001 Treatment Downregulates Genes Associated With Poor Response to Anti-TNF Therapy

- A published 34-gene mucosal signature that is predictive at baseline for patients with non-response to anti-TNF therapy
- OD-001 treatment significantly downregulated 29 of these 34 genes in clinical responders and remitters (n = 25)
- The mucosal signature includes multiple genes linked to myeloid and neutrophil biology, providing mechanistic link to NOD1/2–RIPK2 biology and RIPK2 inhibition

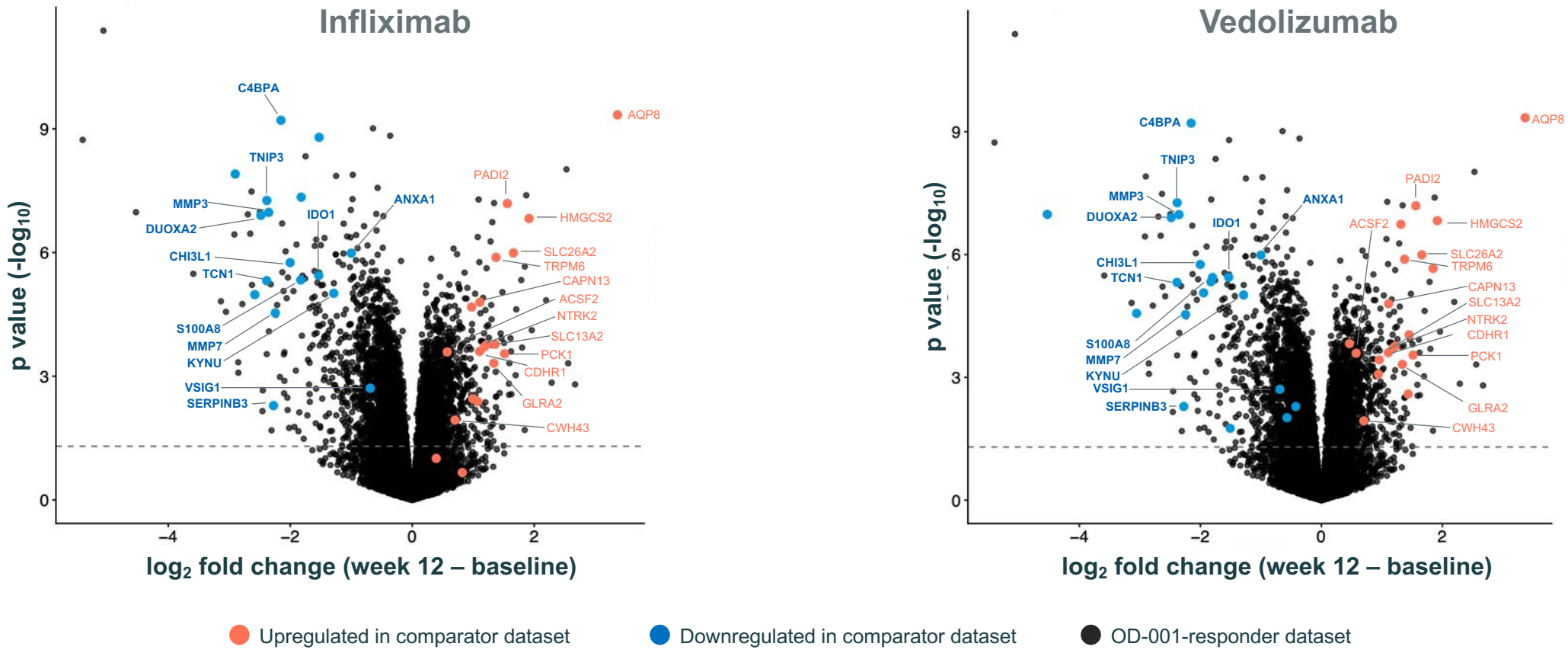


Notes: Volcano plot shows week 12–baseline log2 fold change and nominal significance, calculated with DESeq2 for n = 25 responder/remitter patients. Anti-TNF resistance-associated baseline gene signature: 34 selected genes previously associated with higher pretreatment mucosal expression in anti-TNF non-responders in UC (Cell 2019;178(3):714–730). One patient treated with 20 mg OD-001 is not evaluable for efficacy and two non-responder patient samples failed QC on RNA-seq and are not included in the analysis. Clinical remission: mMS ≤ 2, SFS ≤ 1, RBS = 0, and MES ≤ 1 at week 12. Clinical response: ≥ 2-point and > 30% decrease in mMS, with either ≥ 1-point decrease in RBS or absolute RBS 0 or 1 at week 12.

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Transcriptional Response to OD-001 Overlaps With Gene Changes From Approved Anti-TNF or Anti-α4β7 Therapies

OD-001 responders show concordant mucosal gene changes with infliximab or vedolizumab responders



Notes: Volcano plot shows week 12–baseline log2 fold change and nominal significance, calculated with DESeq2 for n = 25 responder/remitter patients. Blue and red points identify top 20 genes decreasing and increasing in responders to infliximab and vedolizumab. Shared genes are labeled. One patient treated with 20 mg OD-001 is not evaluable for efficacy and two non-responder patient samples failed QC on RNA-seq and are not included in the analysis. Non-responders to all three agents show no-to-minimal changes. Clinical remission: mMS ≤ 2 (SFS ≤ 1, RBS = 0, MES ≤ 1) at week 12. Clinical response: decrease in mMS ≥ 2 and > 30% reduction and either a decrease in RBS ≥ 1 point or an absolute RBS = 0 or 1. Sources: Gut 2018;67(1):43–52.

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