New Therapies with a Focus on TL1A

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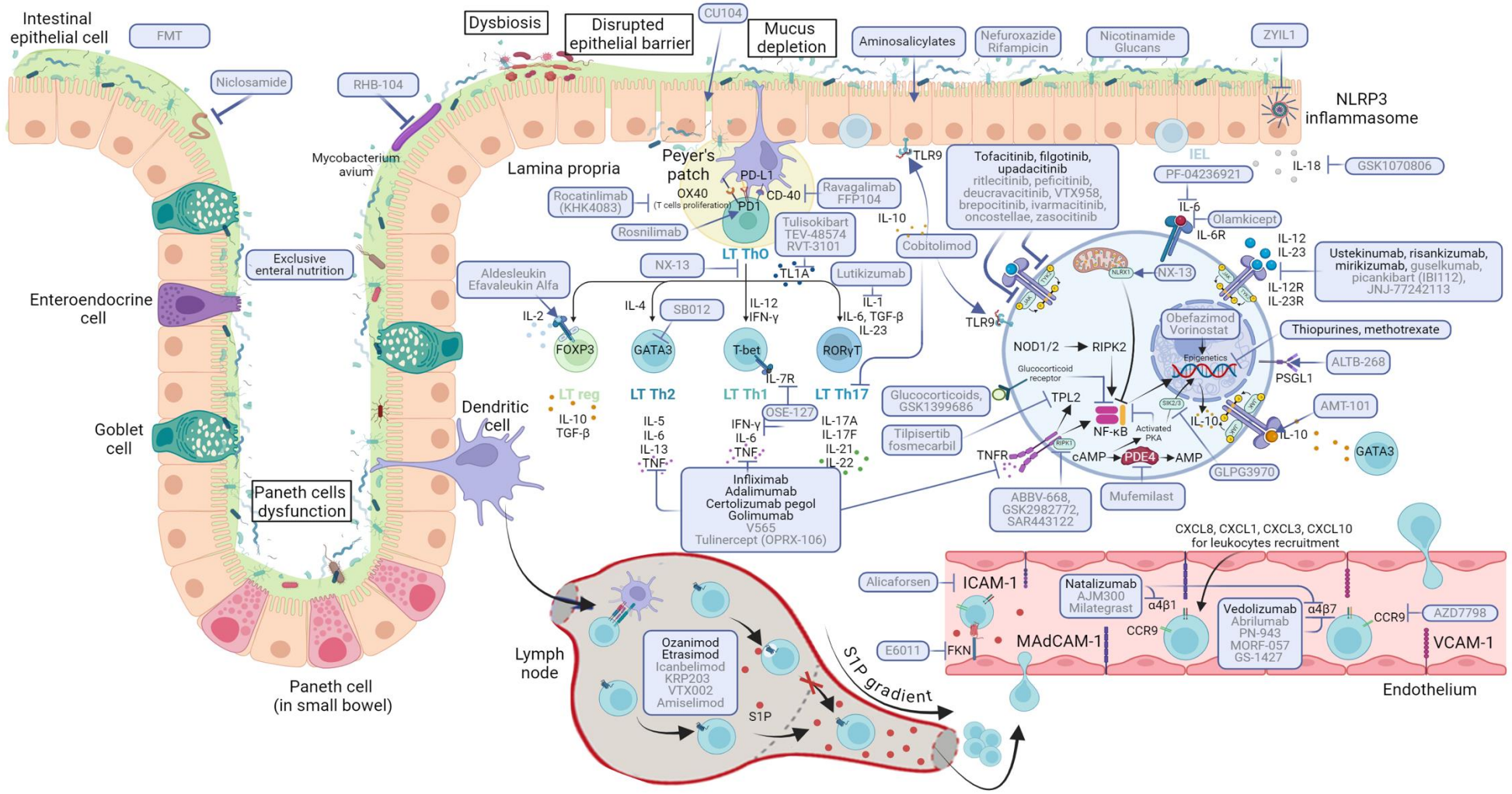
Conflict of Interest

Commercial or Non-Profit Interest	Relationship
AbbVie, Alimentiv, Amgen, Anaptys Bio, Asahi Kasei Pharma, Asieris, Astra Zeneca, Biomebank, Blackbird Laboratories, Boehringer Ingelheim, Bristol Myers Squibb, Caldera Therapeutics, Calluna, Celltrion, CX4 Discovery, Domain Therapeutics, Eli Lilly, Endpoint Health, Enthera, Ensho, Exeliom Biosciences, Ferring Ventures, Flagship Pioneering, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genentech, Gilead, Granite Bio, Janssen, Merck, Metacrine, Mountainfield, MRM Health, Nxera, Organon, OSE Immunotherapeutics, Pandion, Pendopharm, Pfizer, Prometheus Biosciences, Roche, Salvina, Sanofi, Shattuck Labs, Sorriso, Spyre, Synedgen, Takeda, Teva, Thabor Therapeutics, Union Therapeutics, Ventus, Ventyx, Vividion, Xencor, Zealand Pharma	**Advisory Board, Consultant**
AbbVie, Ferring, Eli Lilly, Fresenius Kabi, Janssen, Pfizer, Takeda, Tillotts	**Speaker**

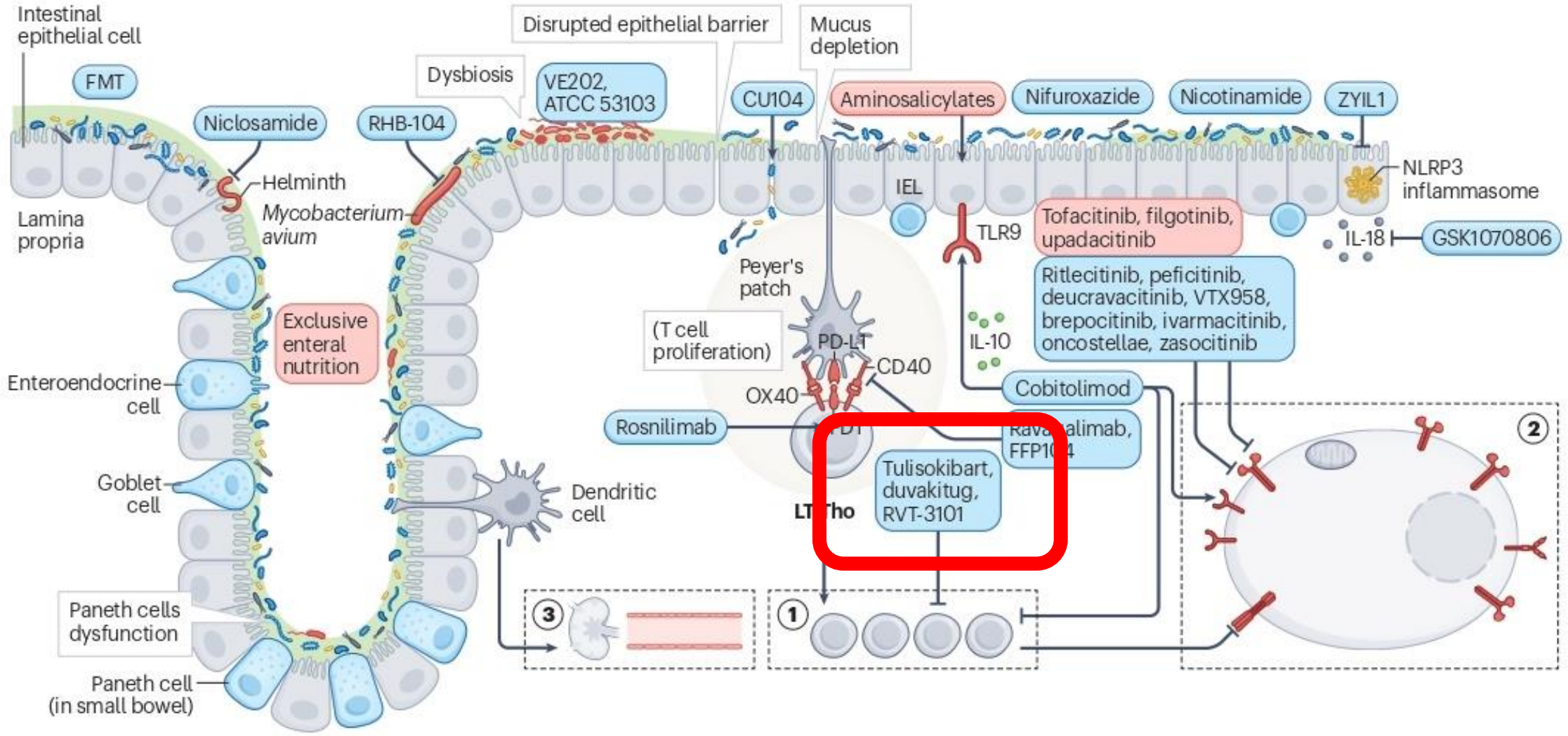
Novel Therapies for IBD

IBD Pathogenesis: from mechanisms to drugs



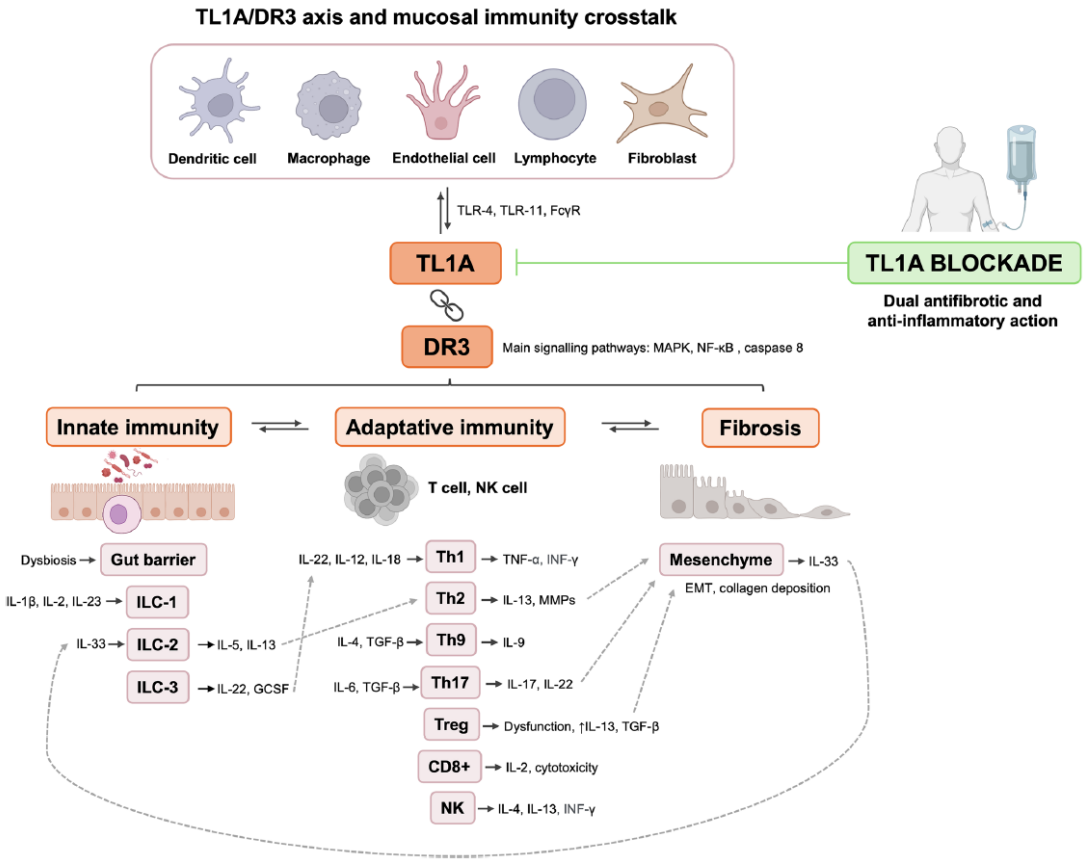
Vieujean S, Jairath V, et al , Nature Review Gastro 2025

Interleukin Inhibitors: TL1A



Vieujean S, Jairath V, et al , Nature Review Gastro 2025

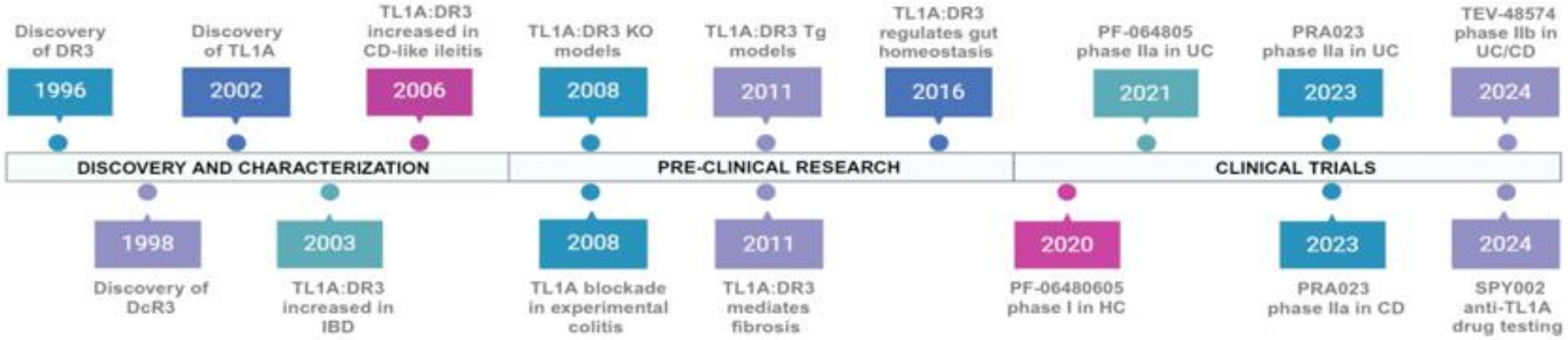
TL1A: Key mediator of inflammation and fibrosis in IBD



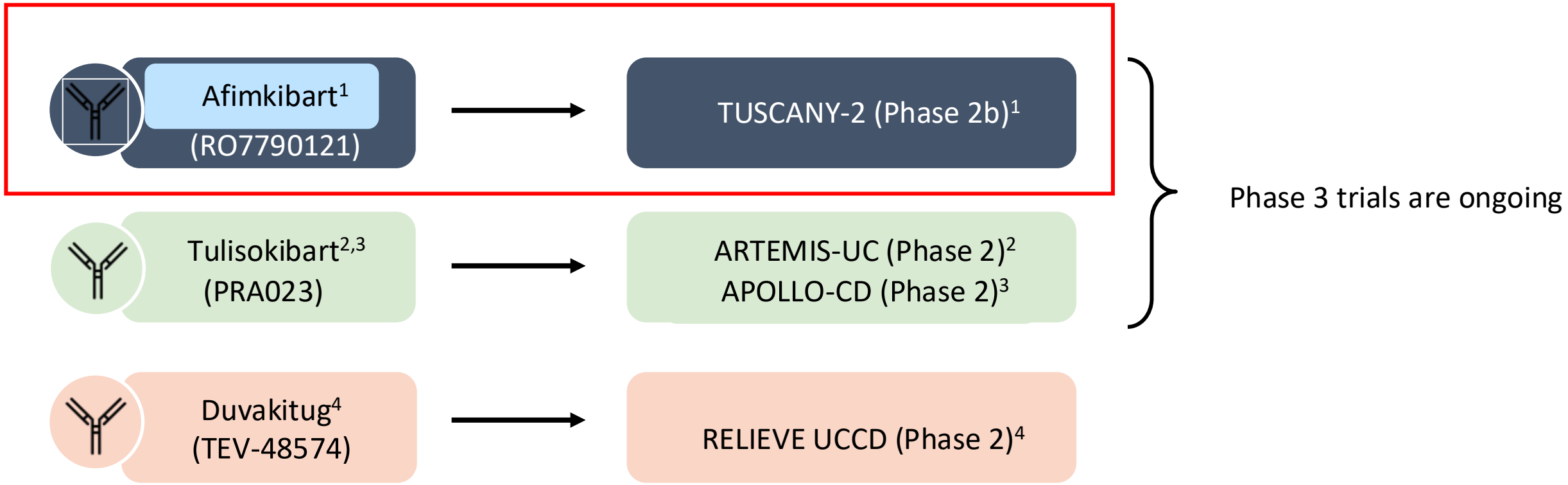
- Member of the tumor necrosis factor (TNF) superfamily
- Implicated in the pathogenesis of inflammatory bowel disease (IBD)
- TL1A and its associated receptor (DR3) are significantly upregulated in inflamed intestinal tissues
- Preclinical have validated TL1A as a target to treat colitis and intestinal fibrosis
- TL1A-encoding gene (*TNFSF15*) polymorphisms are associated with increased IBD risk

Solitano V, Jairath V BioDrugs 2025

Timeline of anti-TL1A/DR3 therapeutics development



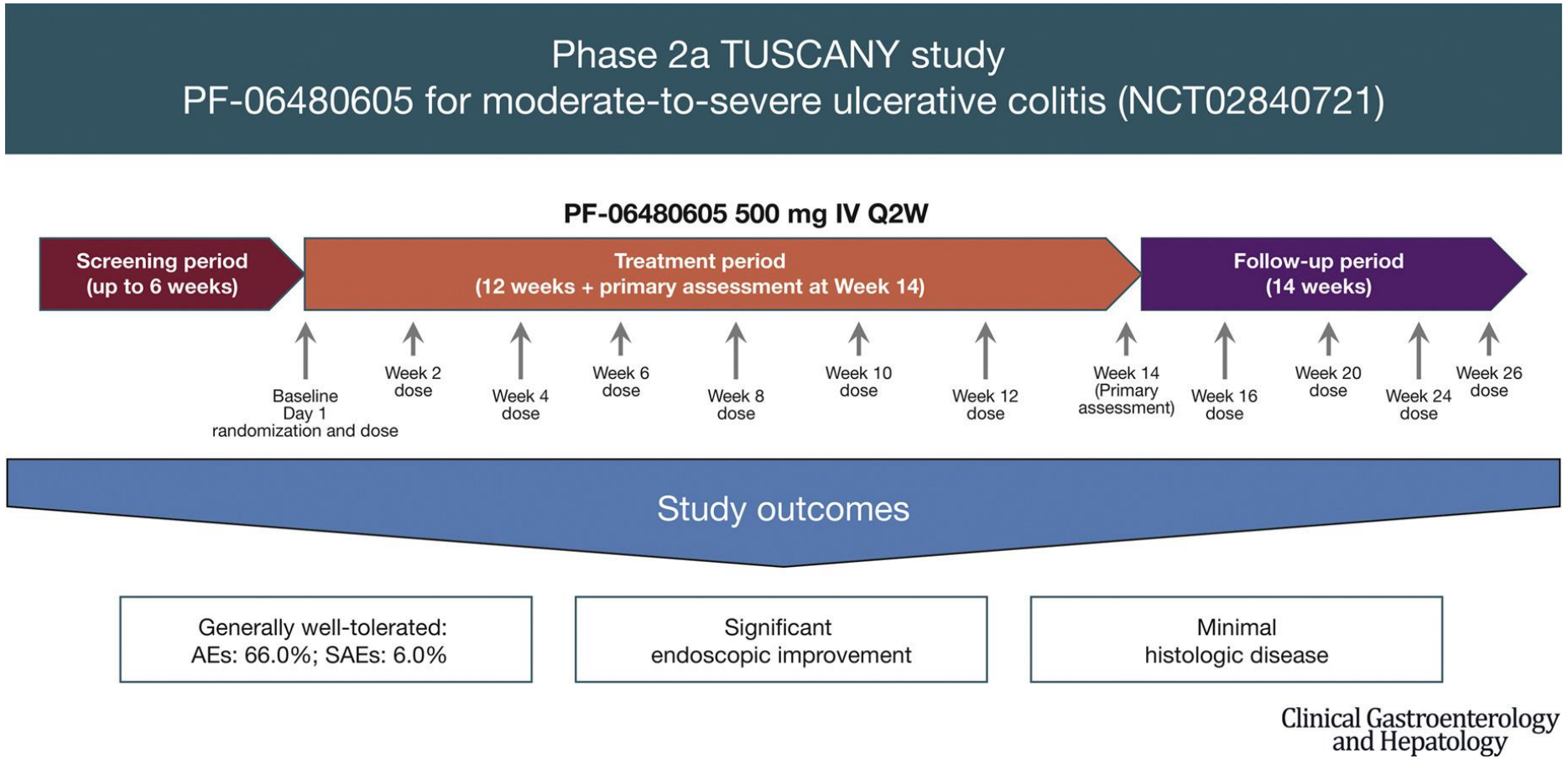
Novel anti-TL1A treatments have reported positive phase 2 studies in IBD and transitioned to phase 3



IBD, inflammatory bowel disease; CD, Crohn's disease; TL1A, tumour necrosis factor-like ligand 1A; UC, ulcerative colitis.

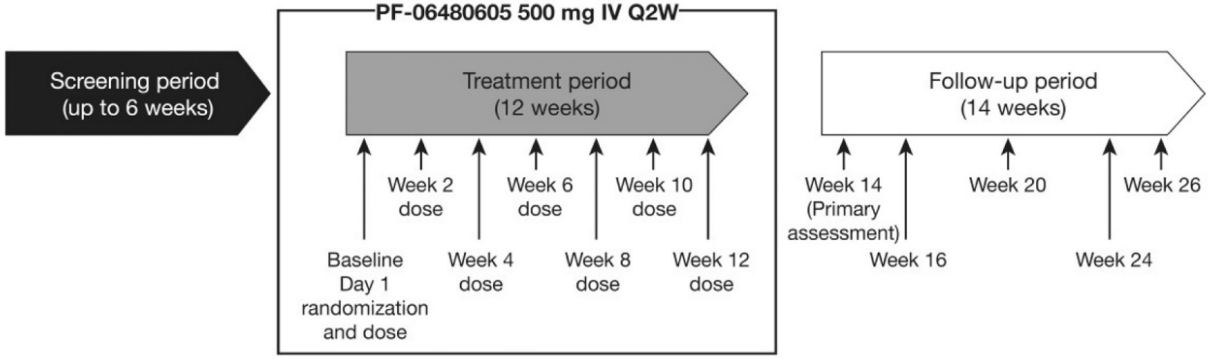
1. ClinicalTrials.gov identifier: NCT04090411. Accessed 4 February, 2025; 2. ClinicalTrials.gov identifier: NCT04996797. Accessed 4 February, 2025; 3. ClinicalTrials.gov identifier: NCT05013905. Accessed 4 February, 2025; 4. ClinicalTrials.gov identifier: NCT05499130. Accessed 4 February, 2025.

TUSCANY Phase 2a Trial: Simon's Two Stage, Adaptive Open Label Trial

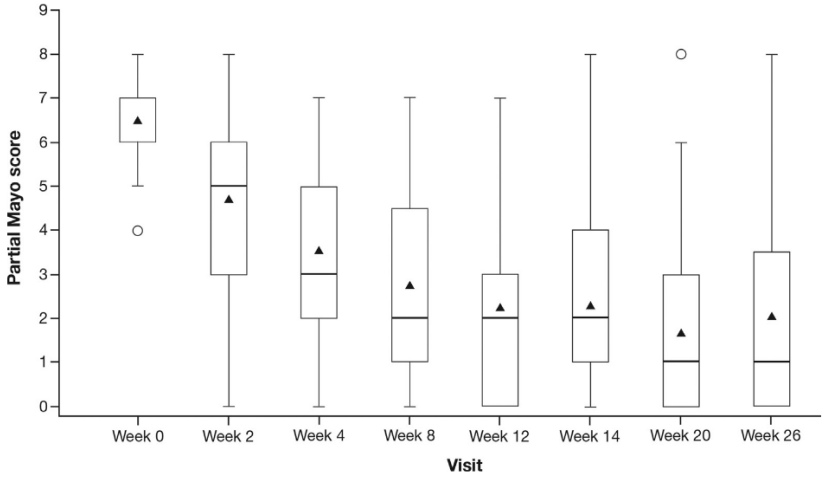


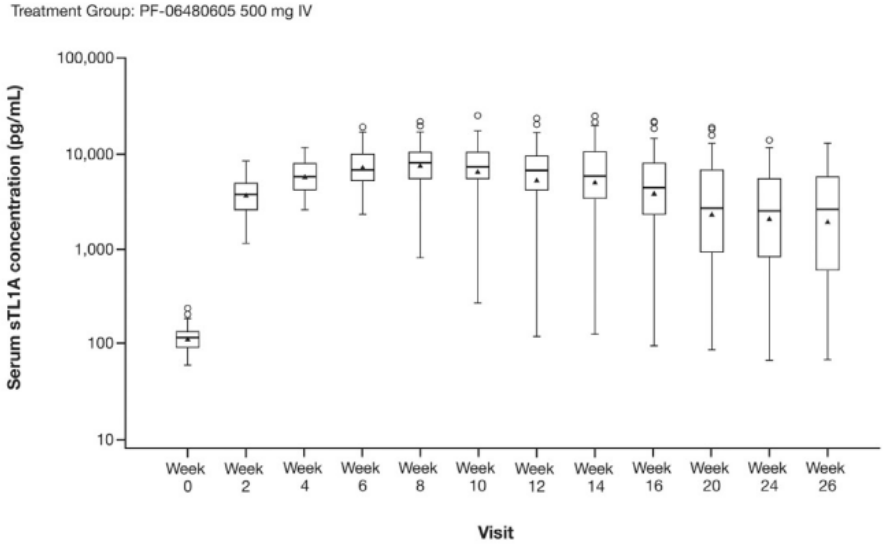
Danese S et. al, CGH, 2021

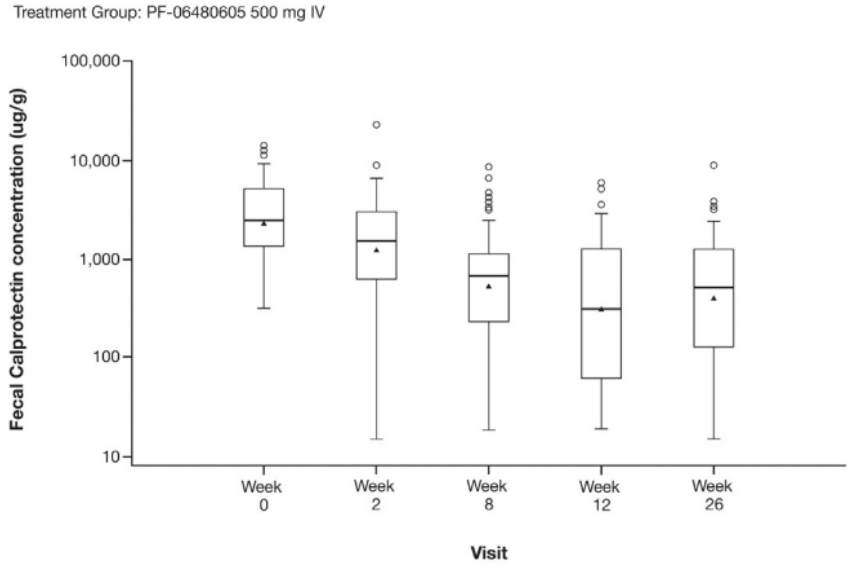
TUSCANY Phase 2a Trial



Supplementary Figure 1. Study design. On the basis of the results of an interim analysis conducted on the 12 participants at the end of the first stage (per Simon's two-stage design), the study did not meet the futility criteria, and therefore enrollment continued into the second stage. IV, intravenous; Q2W, every 2 weeks.





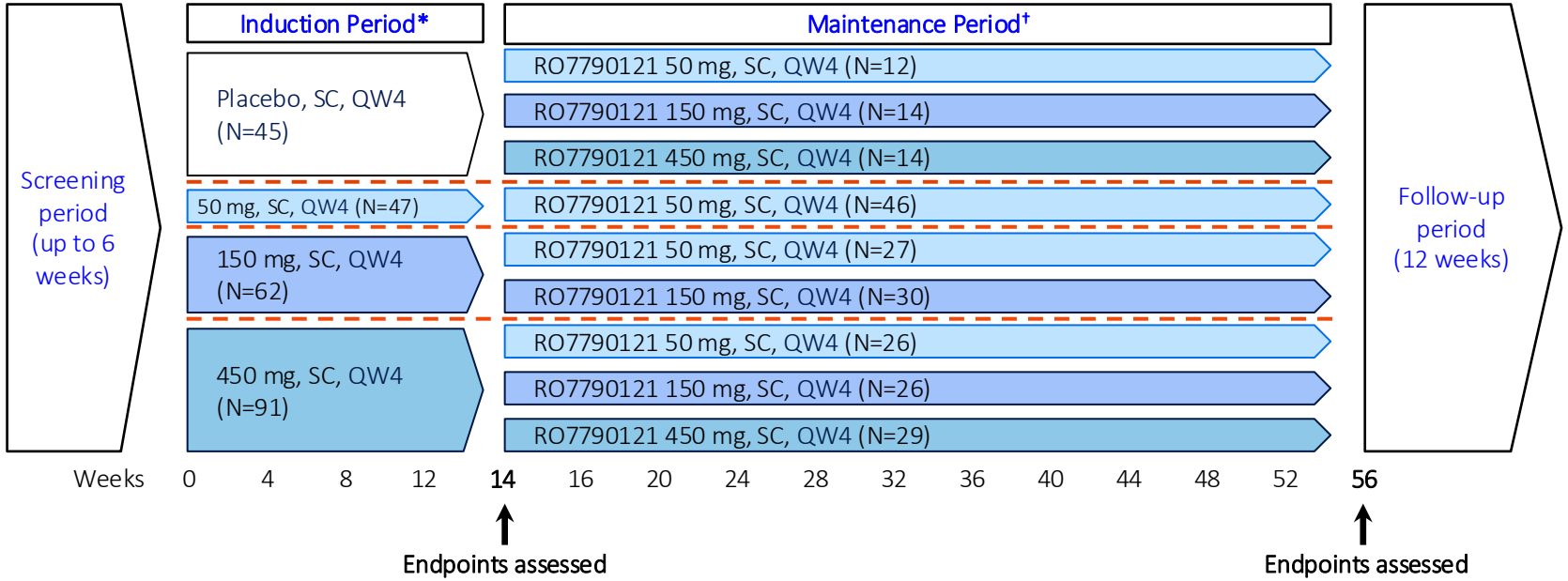


Danese S et. al, CGH, 2021

TUSCANY-2: A randomised, double-blind, placebo-controlled, treat-through, dose-ranging, phase 2b study

Key eligibility criteria

- Patients aged 18–75 years, with moderately-to-severely active UC (total Mayo Score [tMS] ≥6, endoscopic subscore ≥2)
- Previously failed conventional or advanced therapy



Primary endpoint	Secondary endpoints	Exploratory endpoint
• Clinical remission by tMS at week 14 • Safety	• Clinical remission by modified Mayo Score (mMS) at week 14 • Clinical remission by tMS, mMS at week 56 • Endoscopic improvement at weeks 14 and 56	• Efficacy by pre-specified biomarker status

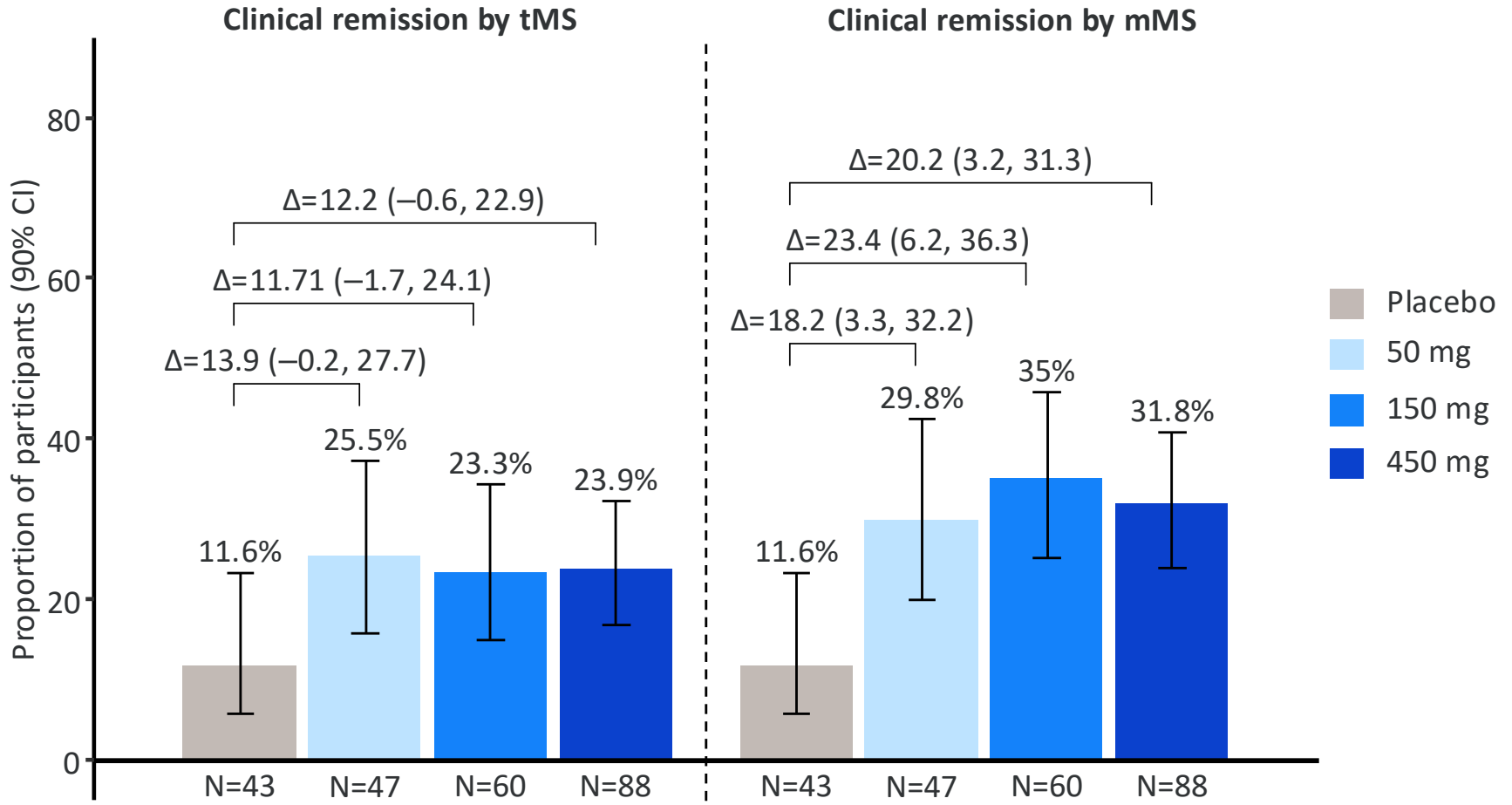
Clinical remission by tMS: tMS ≤2, with no individual subscore >1
Clinical remission by mMS: endoscopic subscore =0 or 1, ≥1-point decrease from baseline to achieve a stool frequency subscore =0 or 1, and rectal bleeding subscore =0)
Endoscopic improvement: endoscopic subscore =0 or 1

Danese S et. al, Lancet Gastro 2024

TUSCANY-2: Baseline Characteristics

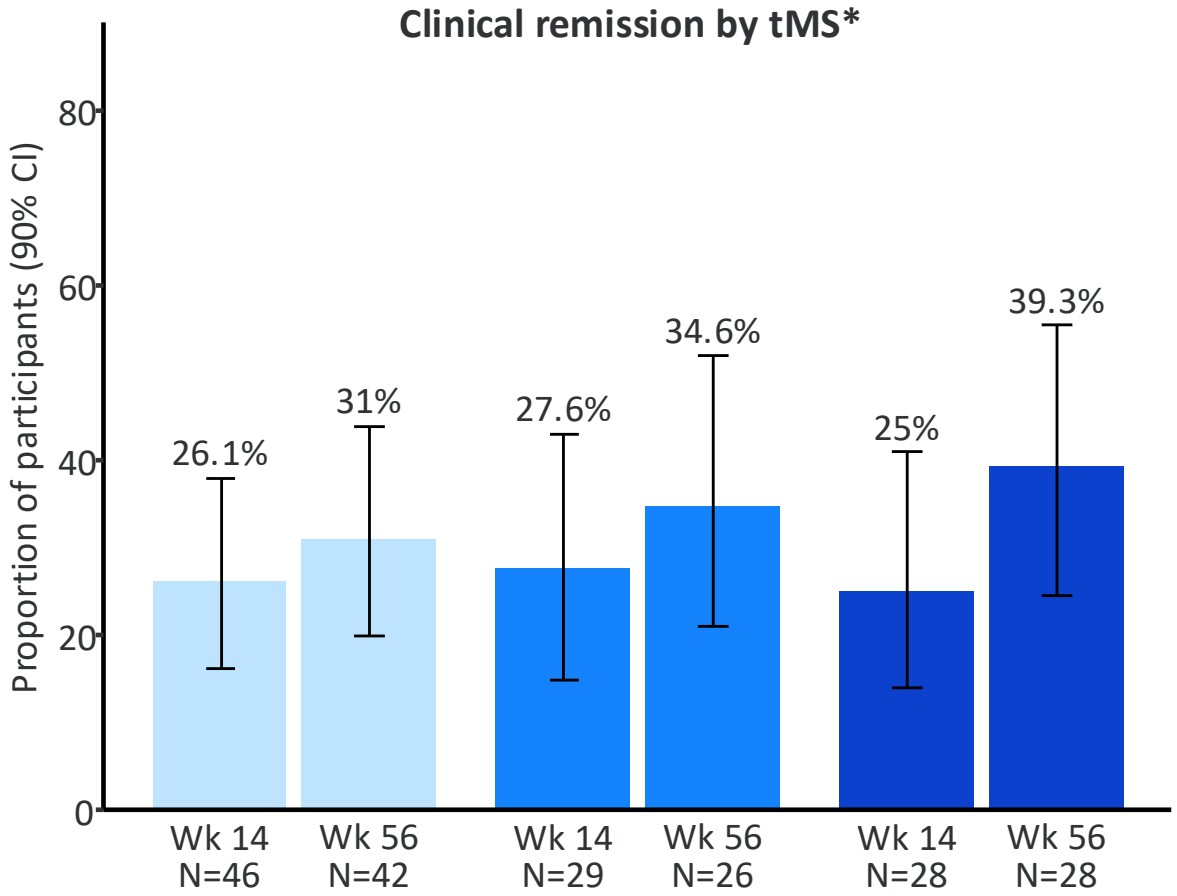
	Placebo (n=45)	50 mg (n=47)	150 mg (n=62)	450 mg (n=91)	Overall (N=245)
Age (yr), mean (SD)	39.9 (12.9)	37.8 (13.9)	42.2 (13)	41.6 (13.8)	40.7 (13.5)
Sex, female, n (%)	21 (46.7)	19 (40.4)	23 (37.1)	36 (39.6)	99 (40.4)
BMI, mean (SD)	24.4 (5.0)	23.6 (5.4)	24.7 (5.2)	24.6 (5.1)	24.4 (5.1)
Disease duration (yr), mean (SD)	7.6 (7.3)	6.8 (7.7)	7.3 (7.4)	7.5 (6.8)	7.3 (7.2)
Pancolitis, n (%)	19 (42.2)	16 (34.0)	23 (37.1)	38 (41.8)	96 (39.2)
mMS, median (IQR)*	7.0 (6.0–8.0)	6.0 (5.0–7.0)	7.0 (6.0–8.0)	7.0 (6.0–8.0)	7.0 (6.0–8.0)
Endoscopy subscore, n (%)					
2	22 (48.9)	28 (59.6)	23 (37.1)	44 (48.4)	117 (47.8)
3	23 (51.1)	19 (40.4)	39 (62.9)	47 (51.6)	128 (52.2)
Faecal calprotectin (ug/g), median (IQR)	1560.0 (927.0–4497.0)	1354.0 (488.0–2299.0)	2112.0 (922.0–3972.0)	1349.5 (702.0–2730.0)	1511.0 (738.0–3152.0)
Steroid use at baseline, n (%)	11 (24.4)	19 (40.4)	32 (51.6)	41 (45.1)	103 (42.0)
Number of prior advanced therapy failures†, n (%)					
0	28 (62.2)	28 (59.6)	41 (66.1)	52 (57.1)	149 (60.8)
1	6 (13.3)	7 (14.9)	10 (16.1)	14 (15.4)	37 (15.1)
2	4 (8.9)	5 (10.6)	4 (6.5)	15 (16.5)	28 (11.4)
≥ 3	7 (15.5)	7 (14.9)	7 (11.3)	10 (11.0)	31 (12.6)

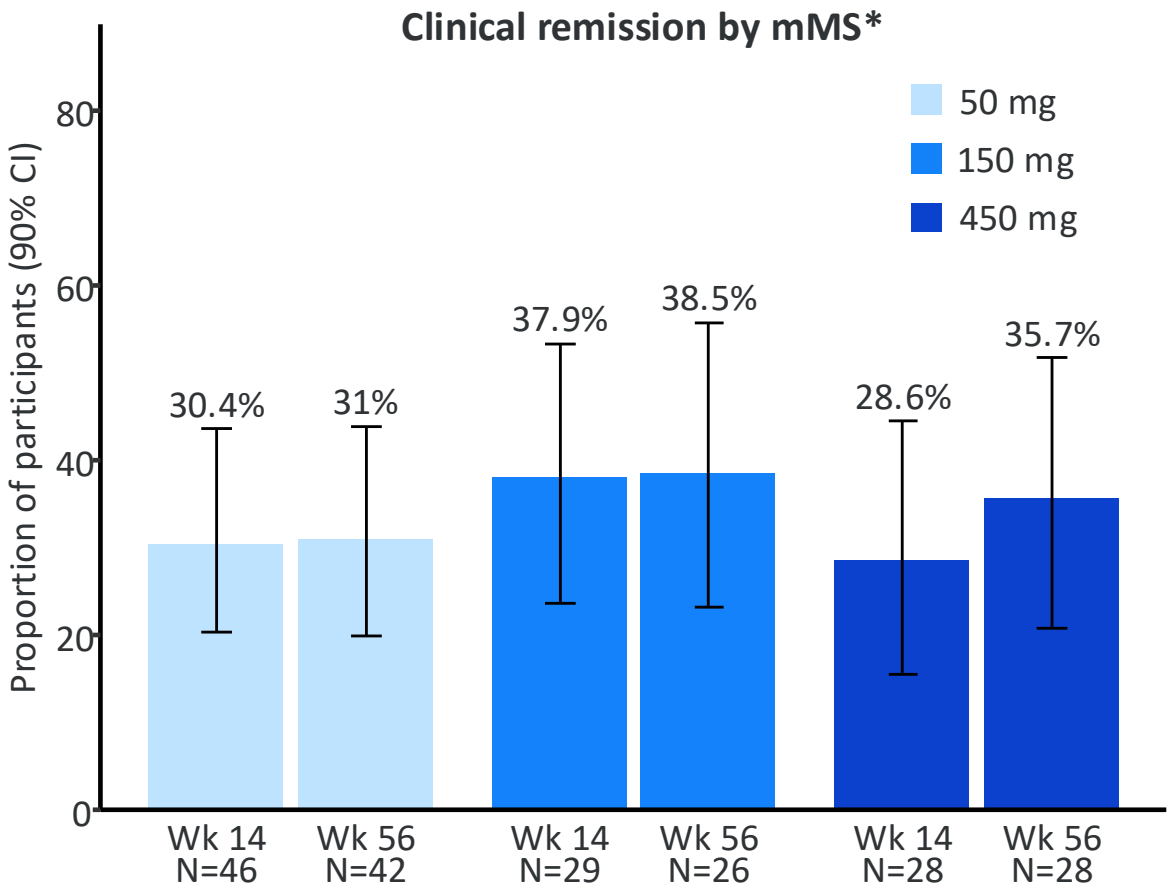
Higher proportions of patients across all RO7790121 doses experienced clinical remission vs placebo at week 14



Danese S et. al, Lancet Gastro 2024

Remission rates at week 14 were sustained through week 56 in participants treated with RO7790121



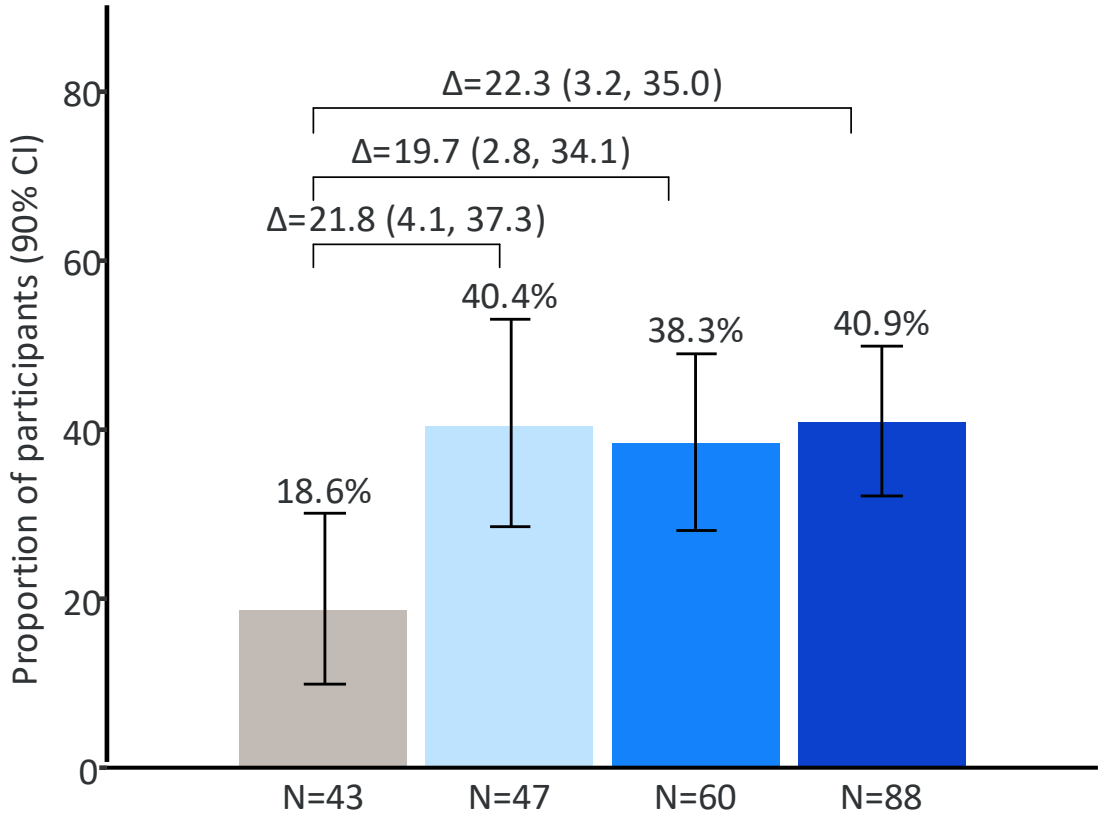


Danese S et. al, Lancet Gastro 2024

Rates of endoscopic improvement at week 14 were greater with RO7790121 vs placebo, sustained up to week 56

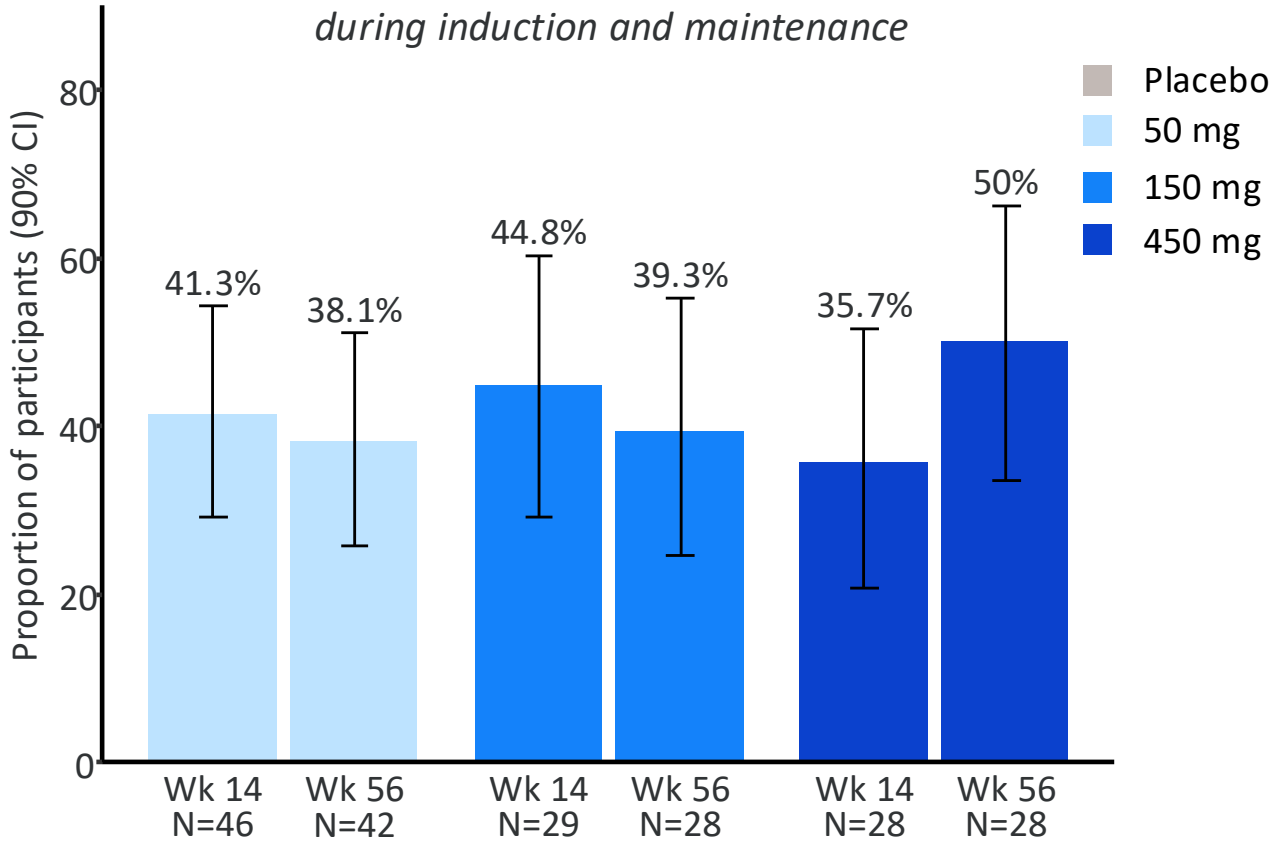
Endoscopic improvement at week 14

All participants vs placebo



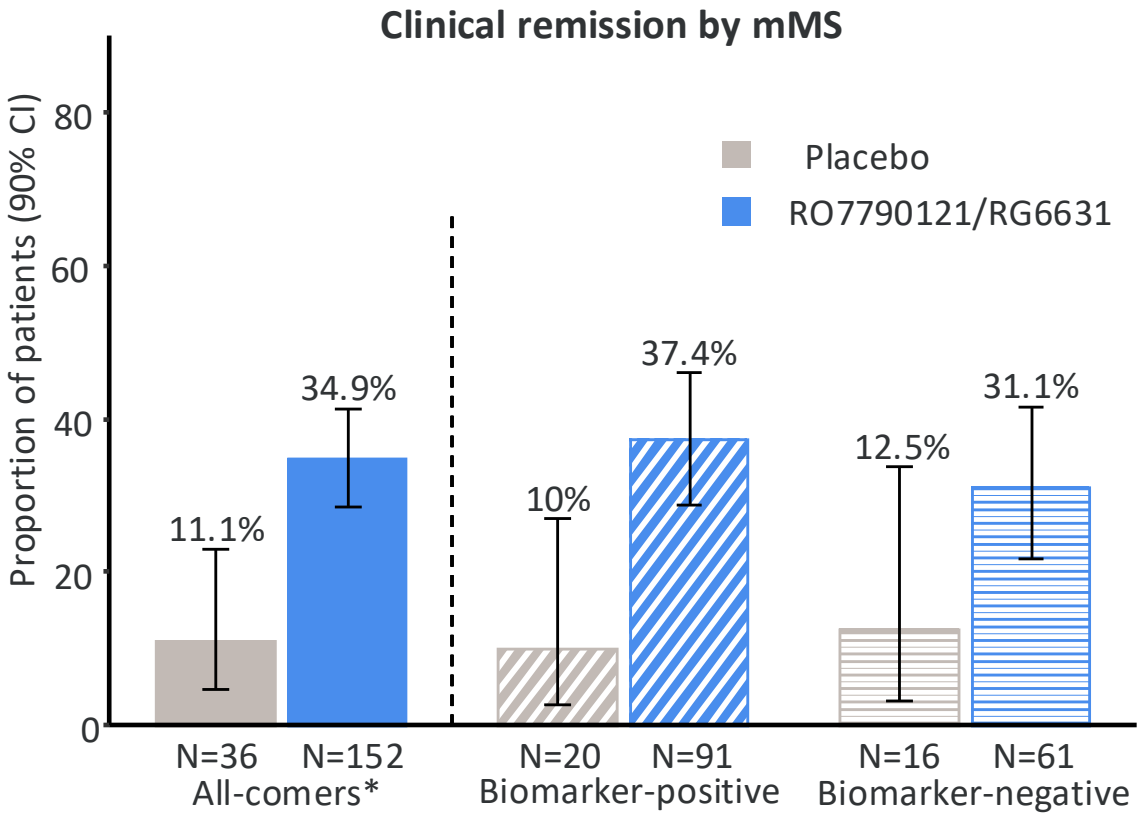
Endoscopic improvement at weeks 14 and 56*

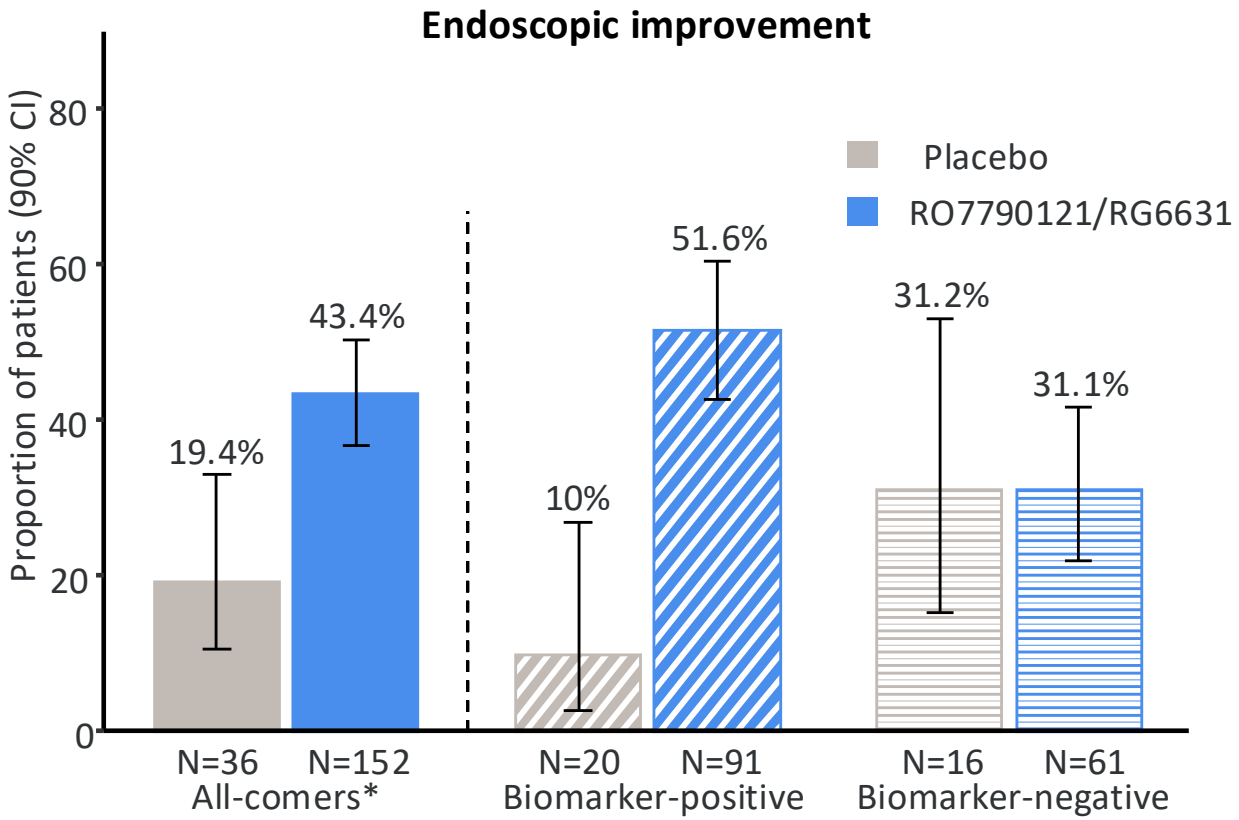
Participants receiving the same dose of RO7790121 during induction and maintenance



Danese S et. al, Lancet Gastro 2024

TUSCANY-2 trials show greater treatment signals in biomarker-positive participants relative to all-comer participants





Other potential biomarkers for anti-TL1A therapy have been investigated in other phase 2 clinical trials for UC

Western

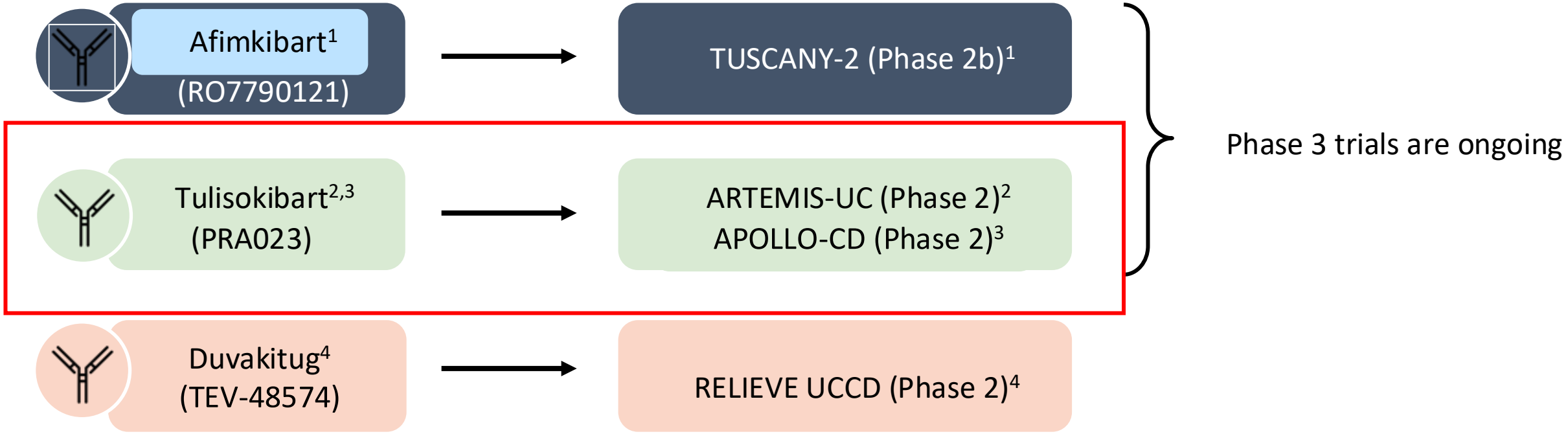
Danese S et. al, Lancet Gastro 2024

Safety Summary (Induction period)

	Placebo (N=45)	50 mg (N=47)	150 mg (N=62)	450 mg (N=91)	Total (N=245)
Treatment-emergent adverse events in ≥5% of participants in any treatment arm, n (%)					
With any adverse event	25 (55.6)	16 (34.0)	28 (45.2)	48 (52.7)	117 (47.8)
Anaemia	4 (8.9)	2 (4.3)	5 (8.1)	2 (2.2)	13 (5.3)
Headache	1 (2.2)	2 (4.3)	1 (1.6)	9 (9.9)	13 (5.3)
Ulcerative colitis	1 (2.2)	3 (6.4)	1 (1.6)	4 (4.4)	9 (3.7)
Nausea	1 (2.2)	3 (6.4)	2 (3.2)	2 (2.2)	8 (3.3)
Pyrexia	1 (2.2)	0	1 (1.6)	5 (5.5)	7 (2.9)
Fatigue	0	0	1 (1.6)	5 (5.5)	6 (2.4)
Urinary tract infection	0	3 (6.4)	0	2 (2.2)	5 (2.0)

Danese S et. al, Lancet Gastro 2024

Novel anti-TL1A treatments have reported positive phase 2 studies in IBD and transitioned to phase 3

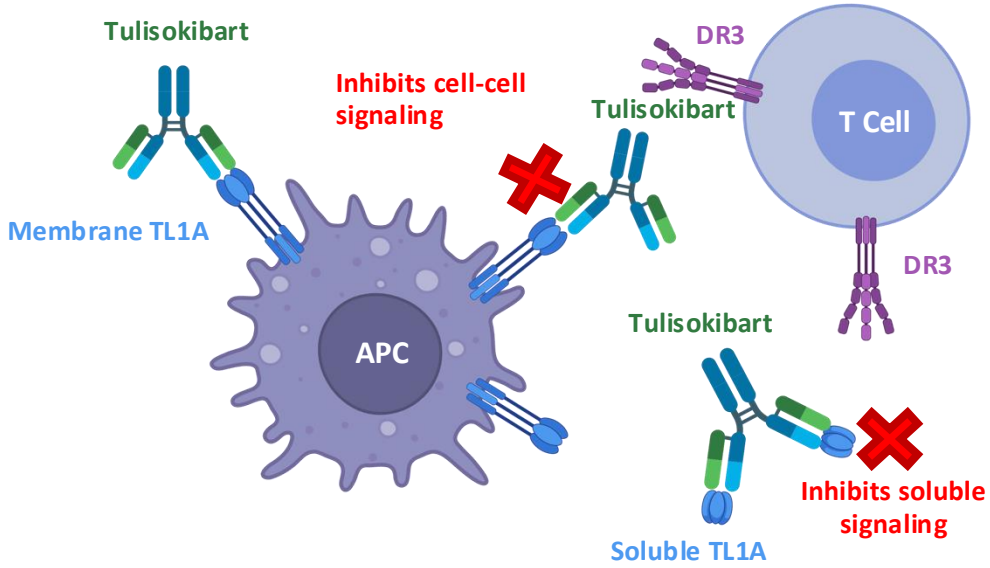


IBD, inflammatory bowel disease; CD, Crohn's disease; TL1A, tumour necrosis factor-like ligand 1A; UC, ulcerative colitis.

1. ClinicalTrials.gov identifier: NCT04090411. Accessed 4 February, 2025; 2. ClinicalTrials.gov identifier: NCT04996797. Accessed 4 February, 2025; 3. ClinicalTrials.gov identifier: NCT05013905. Accessed 4 February, 2025; 4. ClinicalTrials.gov identifier: NCT05499130. Accessed 4 February, 2025.

Tulisokibart: Proposed Mechanism of Action

- Tulisokibart is a humanized monoclonal antibody that binds to TL1A and inhibits its interaction with DR3[1]
- Tulisokibart binds both soluble and membrane-associated human TL1A with high affinity and specificity[1]
- Soluble TL1A exists in active trimeric and inactive monomeric forms that are in equilibrium
  - Tulisokibart binds to both trimer and monomer forms of TL1A[1]
- The proposed MOA of tulisokibart is inhibition of TL1A-mediated signaling[2]



Affinity (KD) and binding (EC50) of tulisokibart to soluble TL1A and membrane TL1A[1]

TL1A	Affinity/Binding
sTL1A (human)	KD = 0.06 nM
mTL1A (human)	EC50 = 17.4 nM

APC, antigen-presenting cell; DR3, death receptor 3; EC50, half-maximal effective concentration; KD, dissociation constant; MOA, mechanism of action; mTL1A, membrane-bound TL1A; sTL1A, soluble TL1A; TL1A, tumor necrosis factor–like cytokine 1A.

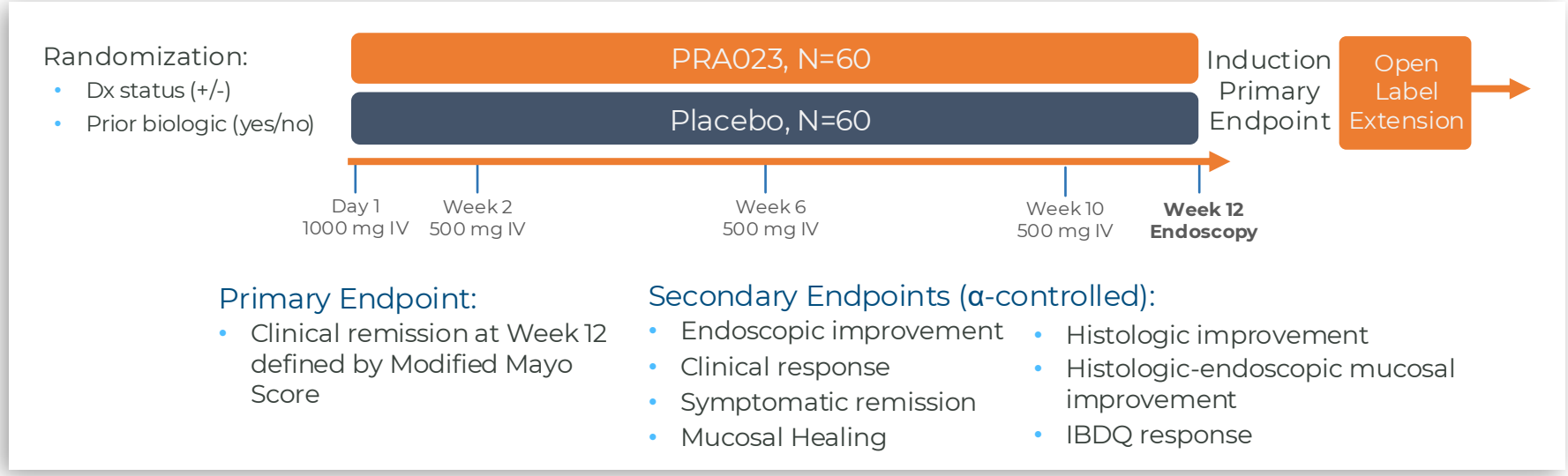
1. Fransson J, et al. Protein & Antibody Engineering Summit Lisbon, Portugal, Nov 2023. 2. Danese et al. PRA023 (MK-7240), an Anti-TL1A Inhibitory Antibody, Reduced Inflammatory and Fibrosis Associated Biomarkers in Ulcerative Colitis Patients Who Achieved Clinical Remission. Presented at UEGW 2023.

ARTEMIS-UC Phase 2 Study Design

Inclusion Criteria

- Moderately to severely active UC (modified Mayo Score 4-9)
- No/insufficient response, loss of response, and/or intolerance to conventional or advanced therapies
- Permitted prior medications
  - ≤4 approved advanced therapies (biologics & small molecule)
  - ≤3 classes of advanced therapies

Demonstrate Efficacy of PRA023



Sands B et. al, NEJM 2024

Genetic CDx Designed to Select Responders to PRA023

- Buccal swab-based PCR assay
- Validated in >400 IBD patients
- Employed in Phase 2 studies
- Patent coverage through 2040+
- Expected to drive differentiated efficacy
- Potential for front-line Rx positioning

~30% TEST-POSITIVE RATE IN IBD

>85% PPV IN IBD

Multi-Single Nucleotide Polymorphisms (SNP) signatures discovered

Big data analysis of population genetics, multi-omics from patient tissue and PBMCs, and 20 years of matching longitudinal clinical data

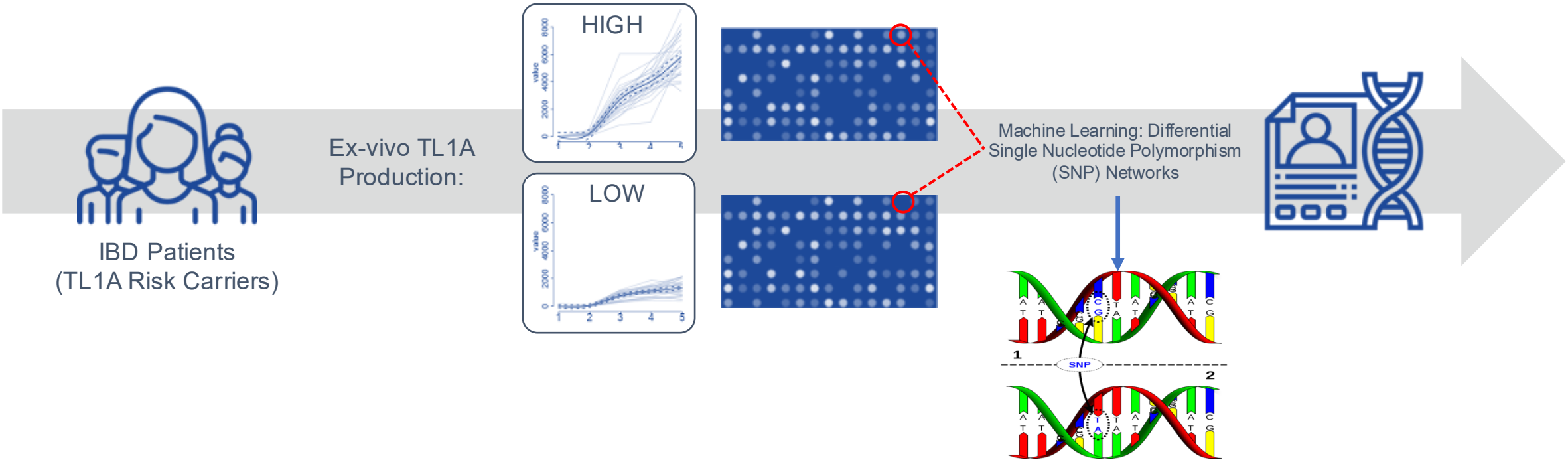
Optimized for PRA023 efficacy while ensuring a significant population can benefit

Our SNP interpretation algorithm is tuned for a 30% test-positive rate while maintaining >85% positive predictive value to enrich for responders

Validated in four independent CD and UC patient cohorts across >400 individuals

Proprietary interpretation of SNP networks reliably predicts *ex vivo* TL1A over production capacity of immune cells from IBD patients

Functional Genomics Underpins TL1A CDx Discovery

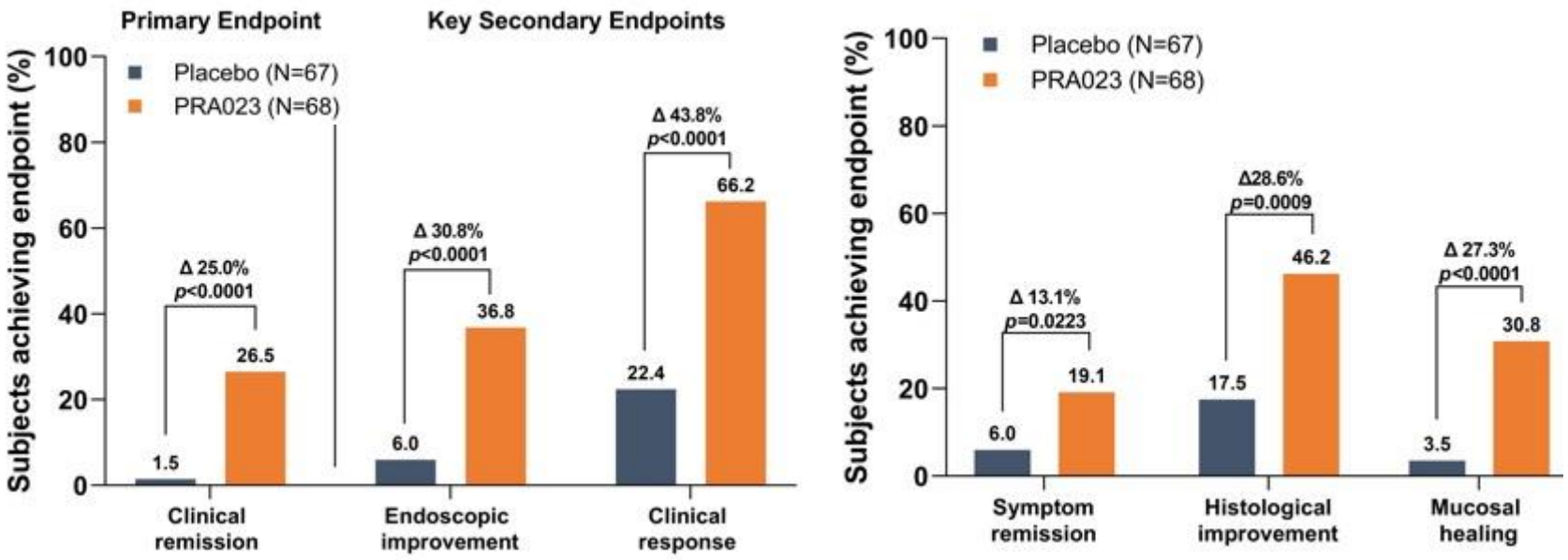


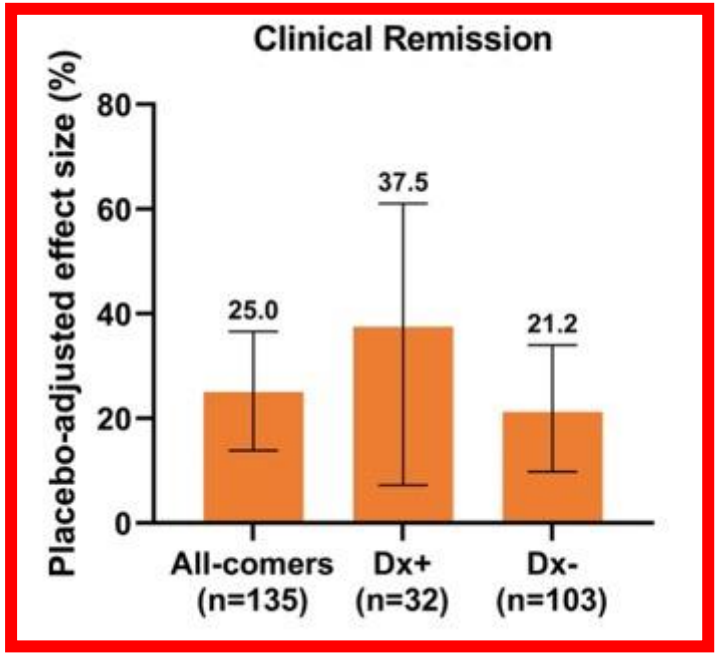
Combined genetic and clinical data with TL1A functional assays on biorepository material.

Advanced machine-learning algorithms utilized to identify *genetic networks* that drive a stronger functional separation than single TL1A variants alone.

The result: a set of genetic markers that identifies IBD patients with enhanced TL1A pathway capacity.

Anti-TNF-Like Ligand 1a (TL1A) for Moderate-Severe UC: ARTEMIS-UC Phase 2 PRA023





Conclusion

- PRA023 induction in UC was safe and improved clinical remission, endoscopic improvement & mucosal healing
- Efficacy was consistent irrespective of prior advanced therapy use, concomitant IMM or presence of ADA
- A positive genetically-based diagnostic test moderately increases likelihood of response

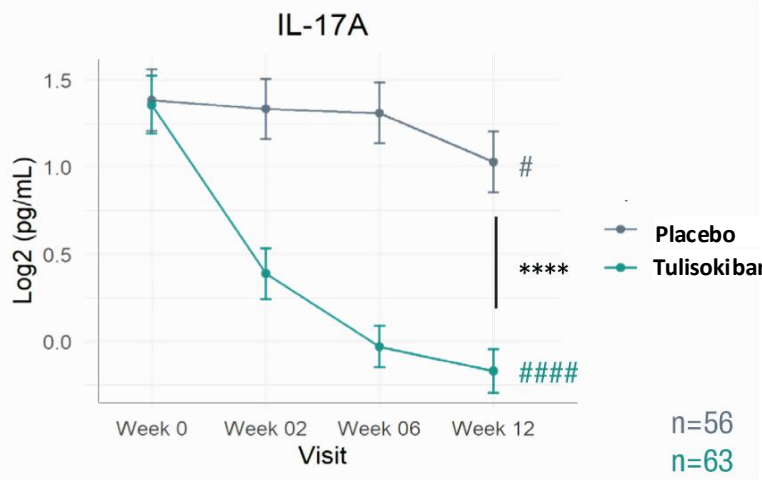
Sands B et. al, NEJM 2024

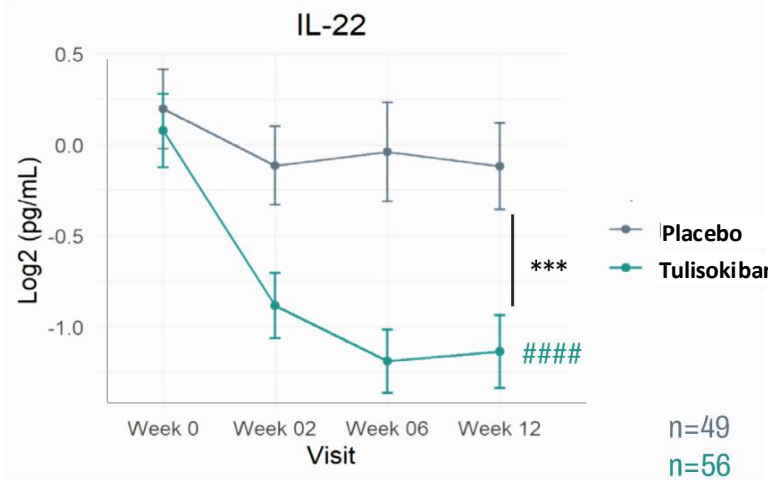
ARTEMIS-UC (Cohort 1): Serum Cytokines

Tulisokibart Reduced T_H17 and Monocyte-Derived Cytokines[a]

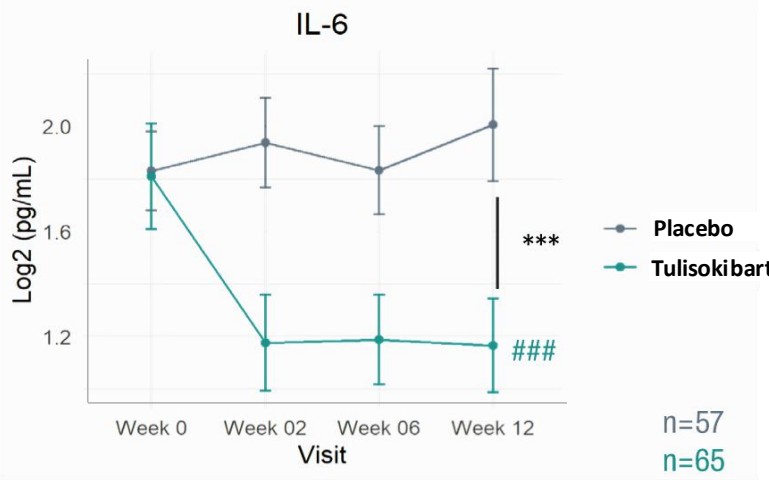
- TL1A promotes T_H17 cytokine production[1]
- TL1A synergizes with other cytokines to produce IL-6 in gut T cells[2] and PBMCs[3]

T_H17-Derived Cytokines[4]





Monocyte-Derived Cytokine[4]

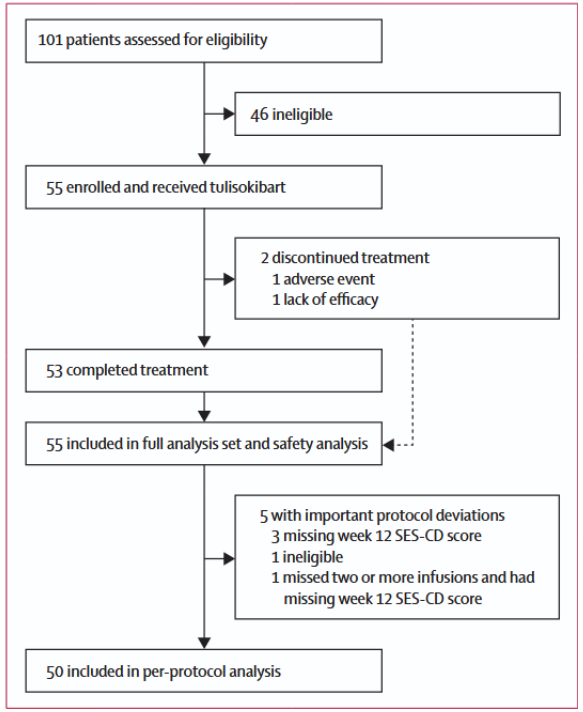


Week 12 tulisokibart vs week 12 placebo:
***P<0.001, ****P<0.0001

Week 12 treatment vs baseline:
#P<0.05, ###P<0.001, ####P<0.0001

IL, interleukin; LOQ, limit of quantification; MSD, Meso Scale Discovery; T_H, helper T cell; UC, ulcerative colitis.
1. Thomas et al. *JLB*. 2017. 2. Jin et al. *Muc Immunol.* 2013. 3. Reichwald et al. *PLoS One.* 2014. 4. Danese S, et al. United European Gastroenterology Week, Copenhagen, Denmark, Oct 2023.

APOLLO-CD: Phase 2a, Open-Label, Single Arm Study

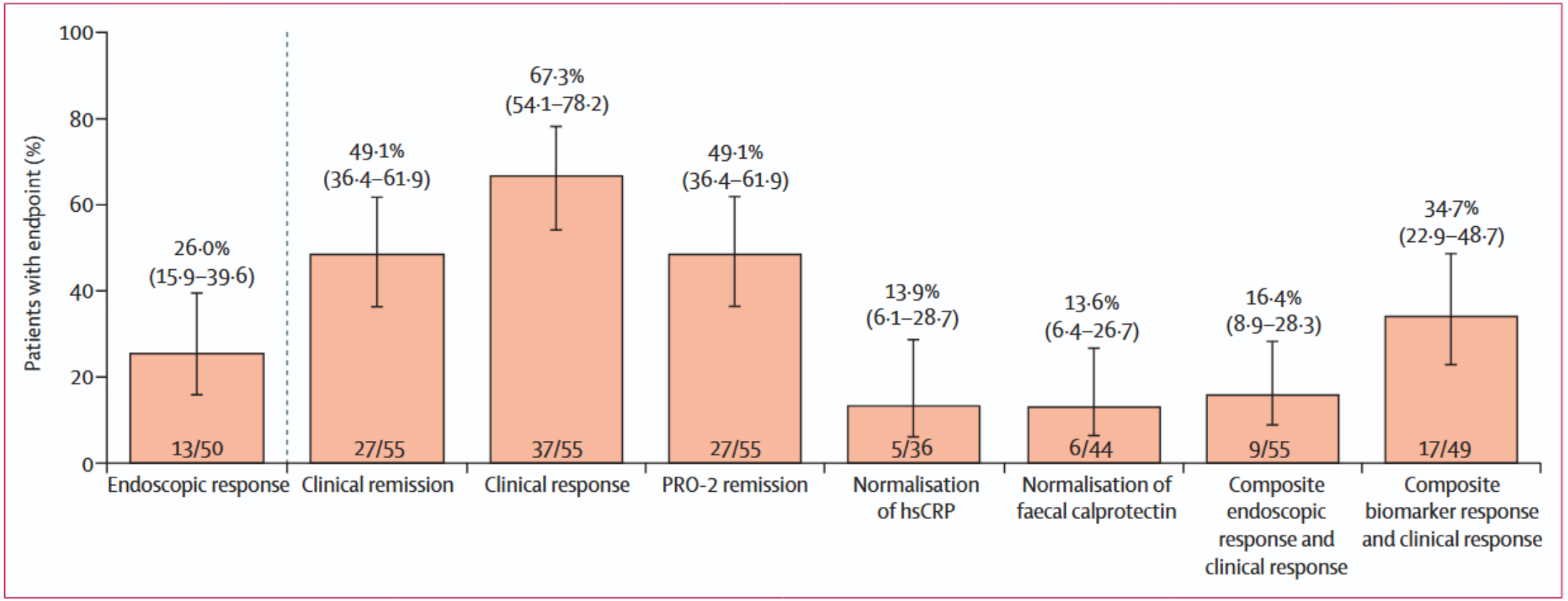


Duration of disease, years	10·3 (9·3)
Extent of disease (as reported in the medical history log)	
Ileal	8 (15%)
Colonic	15 (27%)
Ileocolonic	32 (58%)
Crohn's disease activity index	317·9 (67·2)
SES-CD score	13·4 (6·7)
Concomitant medication use	
Corticosteroid	22 (40%)
Immunosuppressant	8 (15%)
Aminosalicylate	10 (18%)
Previous biological therapies*	
0	16 (29%)
1	10 (18%)
2	10 (18%)
≥3	19 (35%)

	Participants (n=55)
Any adverse event	43 (78%)
Severe adverse event	3 (5%)
Treatment-related adverse event	3 (5%)
Any serious adverse event	8 (15%)
Any treatment-related serious adverse event	0
Adverse event leading to drug discontinuation	2 (4%)
Death	0
Adverse events of special interest	
Acute infusion reaction*	0
Peri-infusion reaction†	0
Infection	25 (45%)
Most common adverse events‡	
COVID-19	6 (11%)
Urinary tract infection	5 (9%)
Crohn's disease	5 (9%)
Anaemia	4 (7%)
Nasopharyngitis	3 (5%)
Fatigue	3 (5%)

Feagan B. et al, LGH, 2025

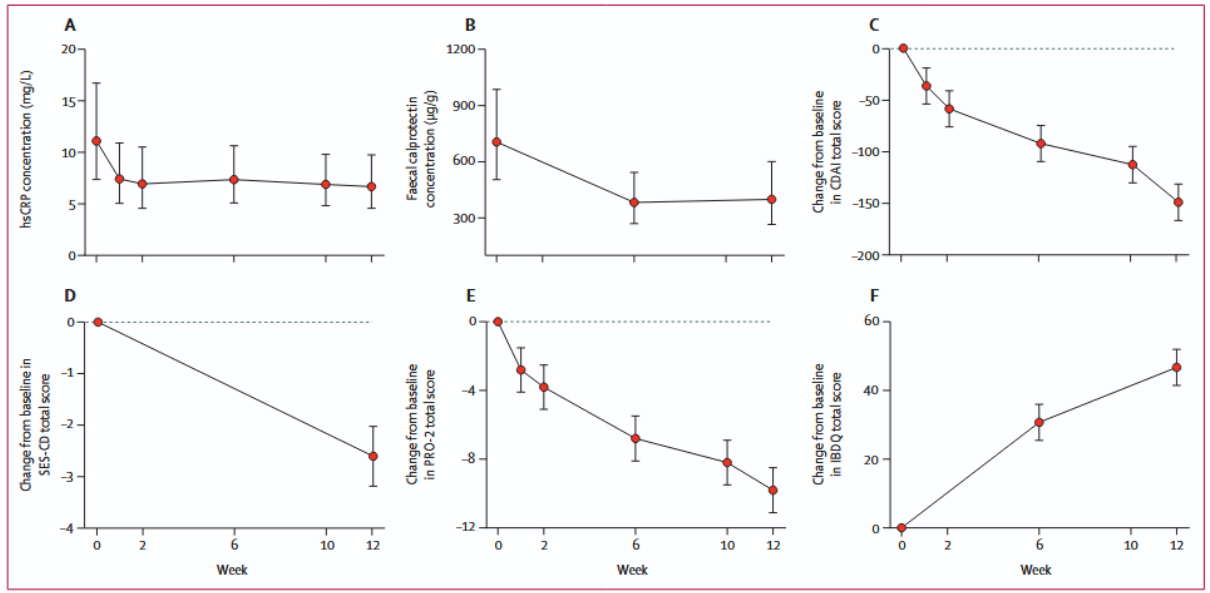
APOLLO-CD: Phase 2a, Open-Label, Single Arm Study



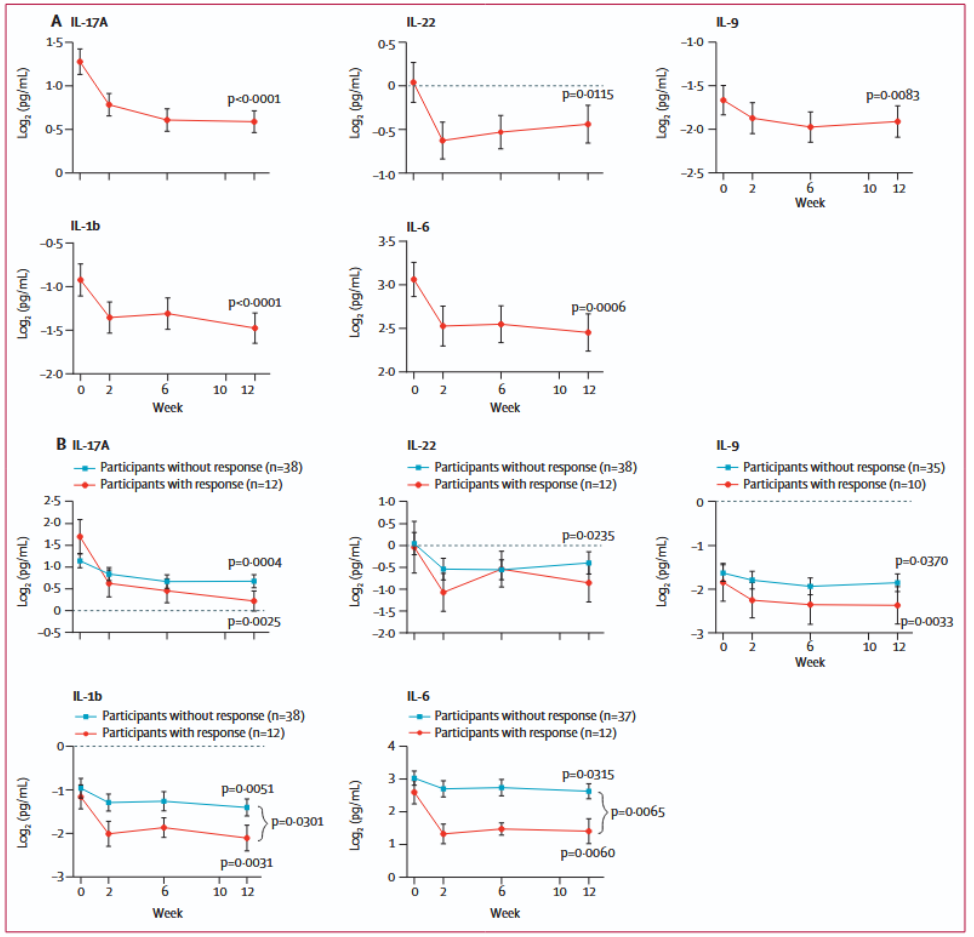
Feagan B. et al, LGH, 2025

APOLLO-CD: Phase 2a, Open-Label, Single Arm Study

Change in Biomarkers

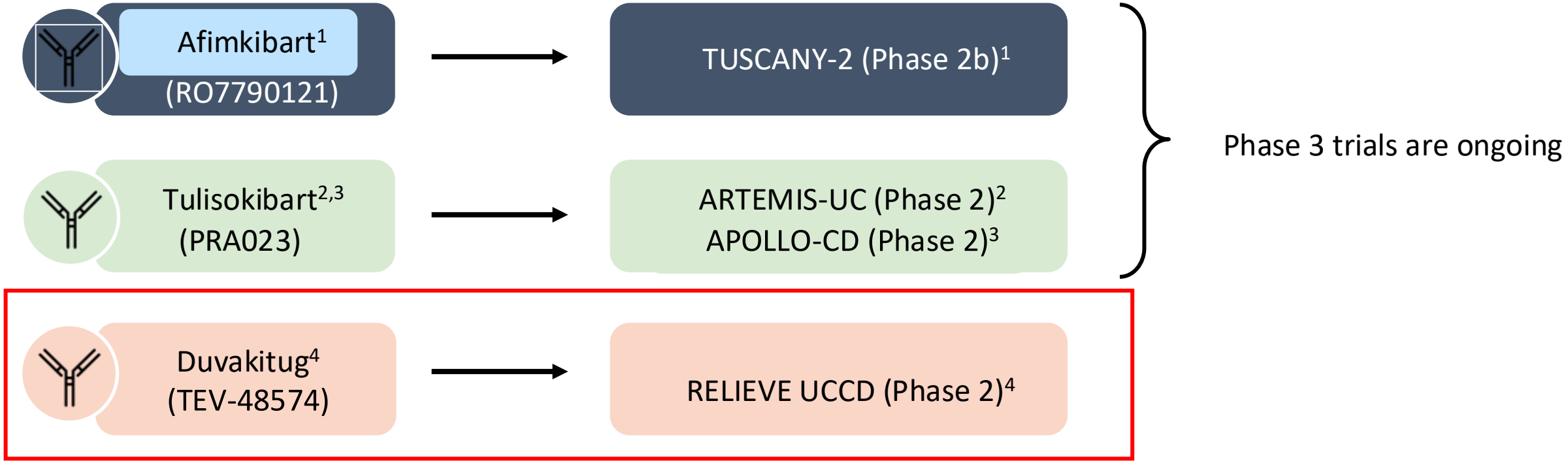


Change in Cytokines



Feagan B. et al, LGH, 2025

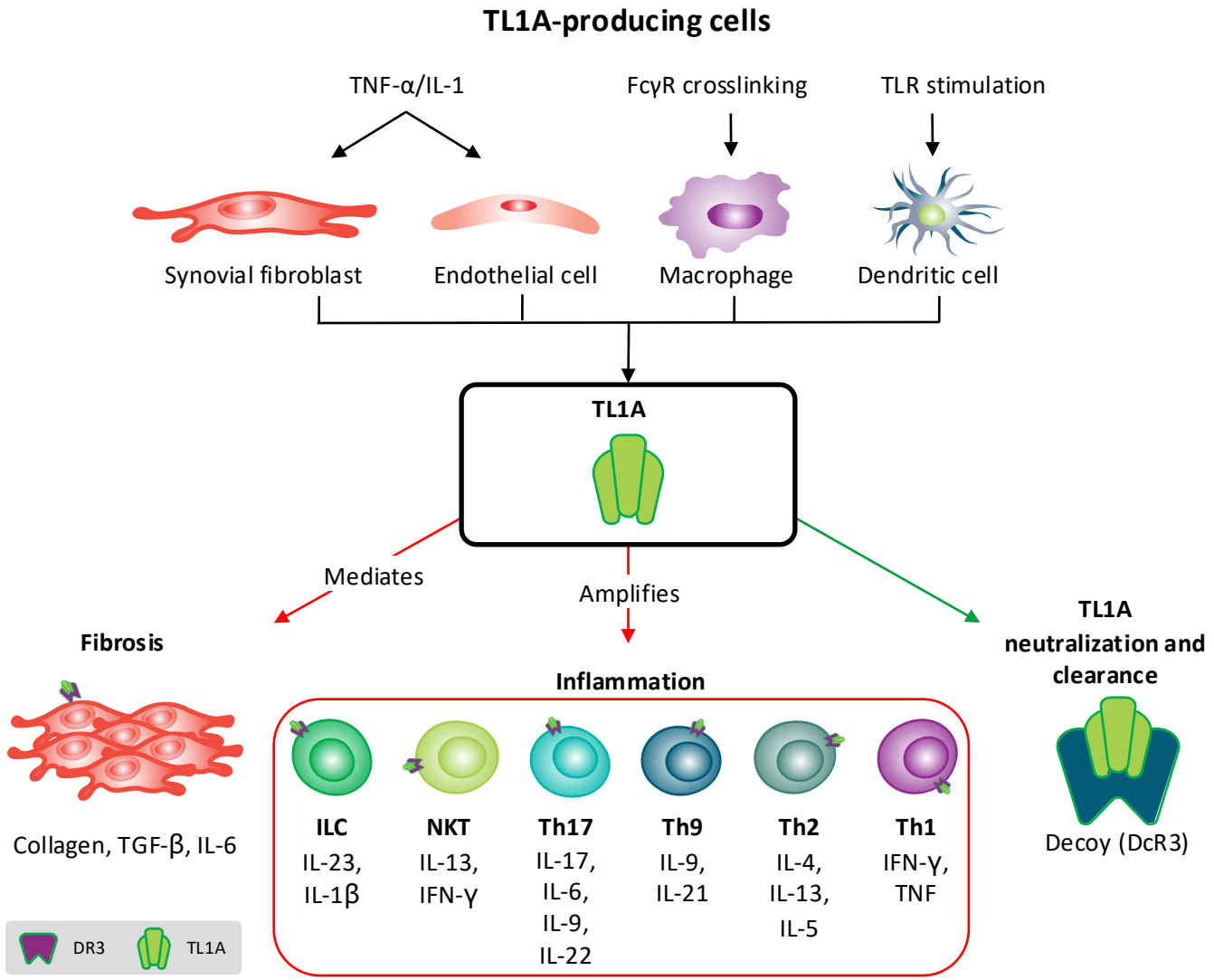
Novel anti-TL1A treatments have reported positive phase 2 studies in IBD and transitioned to phase 3



IBD, inflammatory bowel disease; CD, Crohn's disease; TL1A, tumour necrosis factor-like ligand 1A; UC, ulcerative colitis.

1. ClinicalTrials.gov identifier: NCT04090411. Accessed 4 February, 2025; 2. ClinicalTrials.gov identifier: NCT04996797. Accessed 4 February, 2025;
3. ClinicalTrials.gov identifier: NCT05013905. Accessed 4 February, 2025; 4. ClinicalTrials.gov identifier: NCT05499130. Accessed 4 February, 2025.

Duvakitug MOA

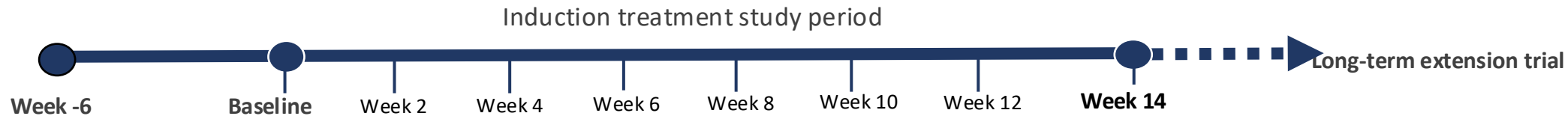


- Duvakitug is a human IgG1 monoclonal antibody uniquely designed to inhibit preferential TL1A signaling via DR3, with the potential advantage of reduced TL1A-DcR3 inhibition[1,2]
- Duvakitug has demonstrated:
  - Reduced inflammation and fibrosis in colitis animal models[1]
  - Target engagement through profound, rapid and sustained reduction in free serum TL1A levels, which persisted for weeks after the last dose[2]

DcR3: decoy receptor 3; DR3: death receptor 3; TL1A: tumour necrosis factor-like ligand 1A.

1. Clarke AW, et al. *MAbs* 2018;10(4):664-677. 2. Angeles T, et al. UEGW 2024.

RELIEVE UCCD: Induction basket trial, Bayesian Design



Randomized

UC **CD**

N~120 each

Stratified by diagnosis and prior advanced therapy

SC loading dose*

Duvakitug 900 mg SC Q2W N~40 each
Duvakitug 450 mg SC Q2W N~40 each
Placebo (PBO) SC Q2W N~40 each

Primary endpoint at week 14

Endoscopic response at week 14: ≥50% decrease in SES-CD from baseline

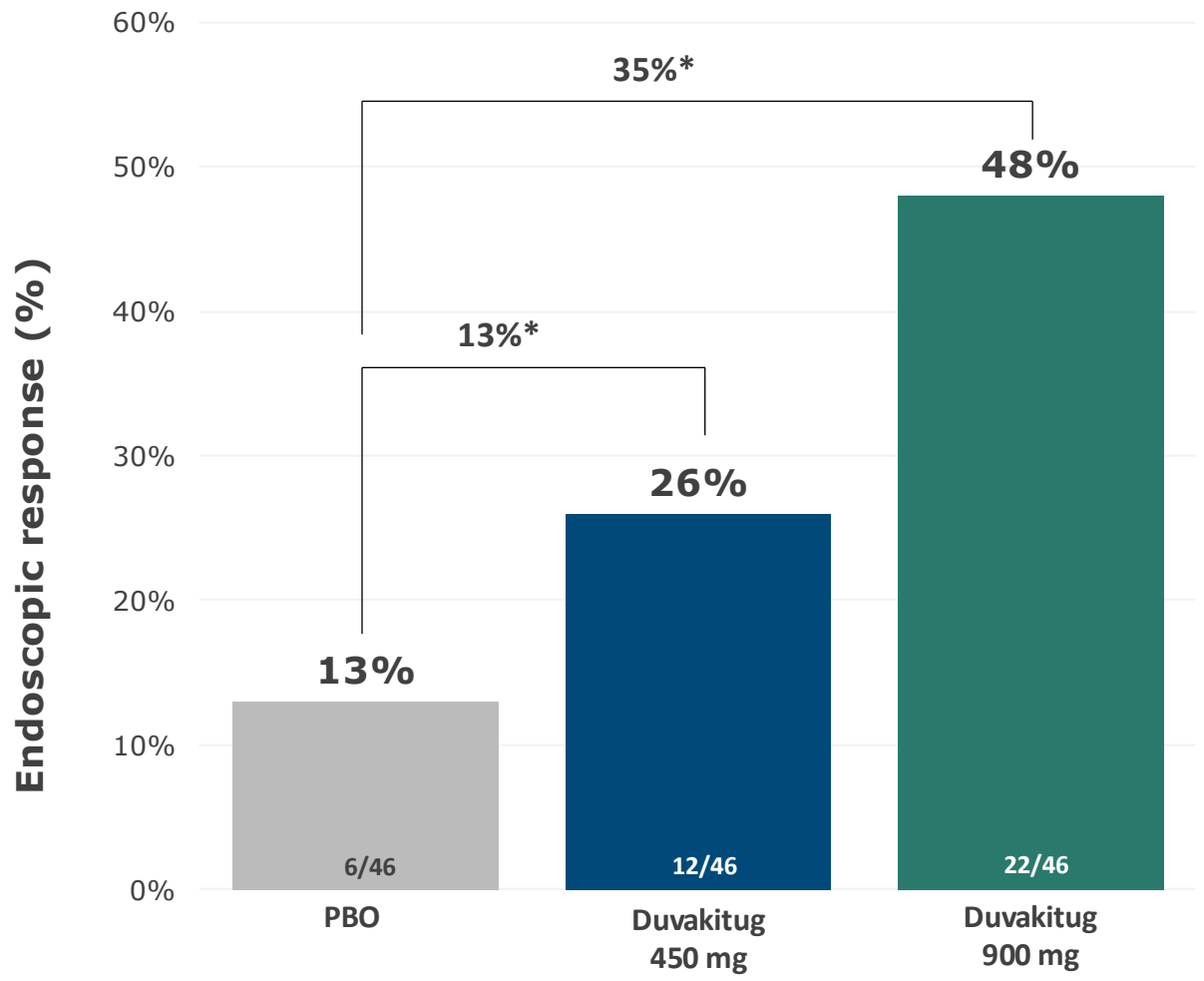
Study population

- Adults (18–75 years) with moderately to severely active CD (CDAI score ≥220 and ≤450); SES-CD score of ≥6 (≥4 for isolated ileal disease)
- Previous experience with conventional and/or advanced therapies (AT)† permitted, irrespective of the number of advanced therapies within the same class
- Concomitant medications allowed
  - Stable doses of corticosteroids (prednisone equivalent of up to 20 mg/day), 5-ASA, and immunosuppressants (6-MP, AZA, MTX)

Baseline characteristics: CD

	Placebo N=46	Duvakitug 450 mg N=46	Duvakitug 900 mg N=46	Overall N=138
Age, years, mean (SD)	38.3 (15.1)	42.5 (15.1)	37.8 (13.6)	39.5 (14.7)
Male, n (%)	22 (48)	27 (59)	31 (67)	80 (58)
BMI, mean (SD)	24.9 (6.8)	24.6 (5.0)	26.2 (6.2)	25.2 (6.0)
Geographic region, n (%) North America Eastern Europe Western Europe Other	 11 (24) 30 (65) 5 (11) 0	 11 (24) 25 (54) 8 (17) 2 (4)	 12 (26) 23 (50) 9 (20) 2 (4)	 34 (25) 78 (57) 22 (16) 4 (3)
Duration of disease, years, mean (SD)	9.6 (7.6)	11.5 (10.3)	11.3 (11.2)	10.8 (9.8)
SES-CD, mean (SD)	12.0 (5.7)	12.7 (6.6)	12.3 (5.8)	12.3 (6.0)
CDAI score, mean (SD)	309.4 (65.8)	304.7 (56.8)	294.1 (63.6)	302.7 (62.0)
Concomitant immunomodulator use, n (%)	7 (15)	5 (11)	8 (17)	20 (14)
Concomitant corticosteroid use, n (%)	20 (43)	15 (33)	12 (26)	47 (34)
Prior advanced therapies, n (%) Including investigational drugs Excluding investigational drugs	 29 (63) 24 (52)	 27 (59) 27 (59)	 31 (67) 27 (59)	 87 (63) 78 (57)
Prior approved advanced therapies, n (%) 0 1 2 ≥3	 22 (48) 10 (22) 7 (15) 7 (15)	 19 (41) 12 (26) 8 (17) 7 (15)	 19 (41) 14 (30) 7 (15) 6 (13)	 60 (43) 36 (26) 22 (16) 20 (14)

Primary endpoint: Endoscopic response at week 14

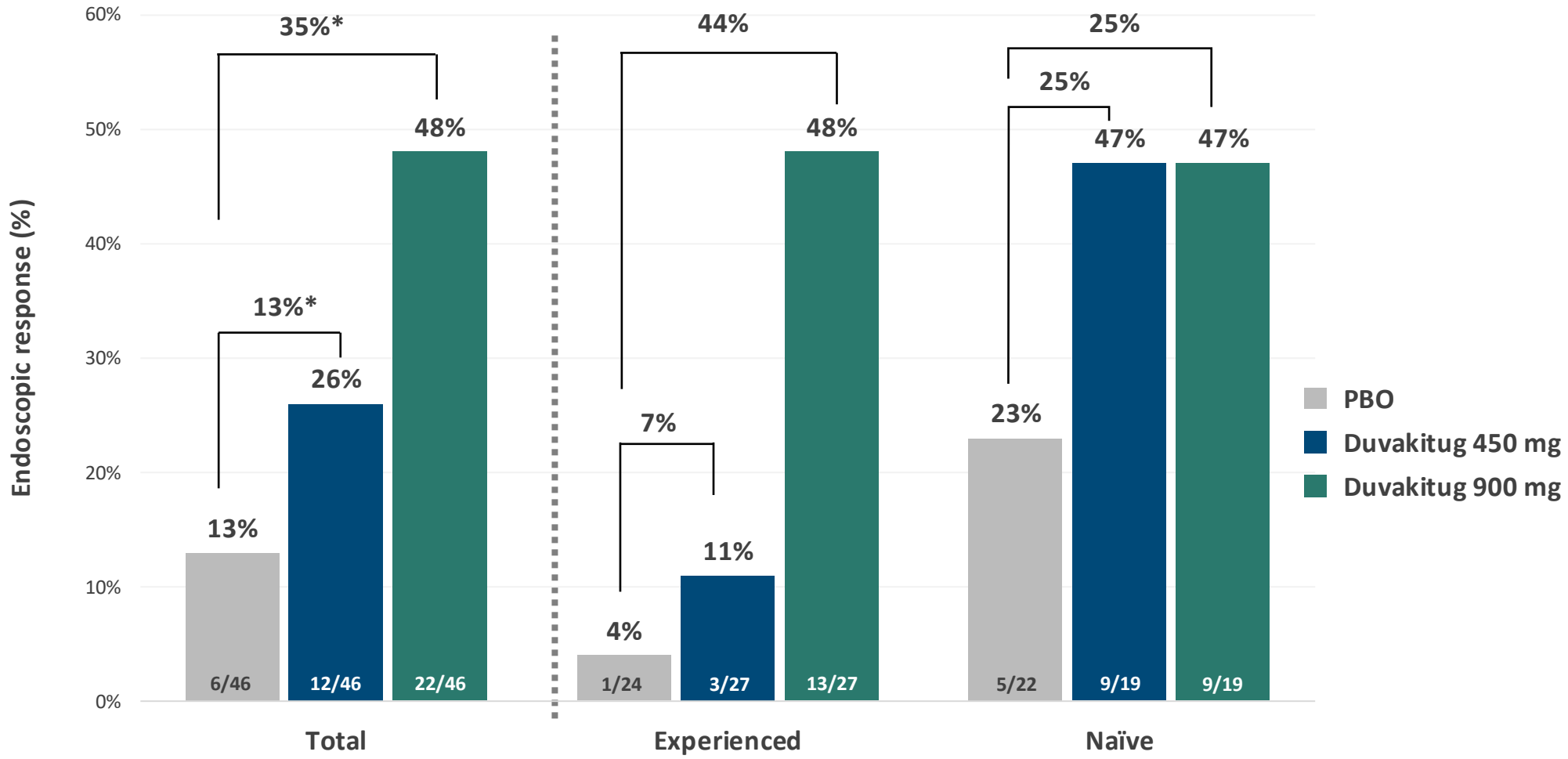


	Duvakitug 450 mg vs. PBO	Duvakitug 900 mg vs. PBO
Posterior probability†	0.94*	>0.99*
Odds ratio‡	3.0 p-value=0.031	6.4 p-value<0.001

Jairath V et al, ECCO 2025

Endoscopic response by prior advanced therapy (AT)

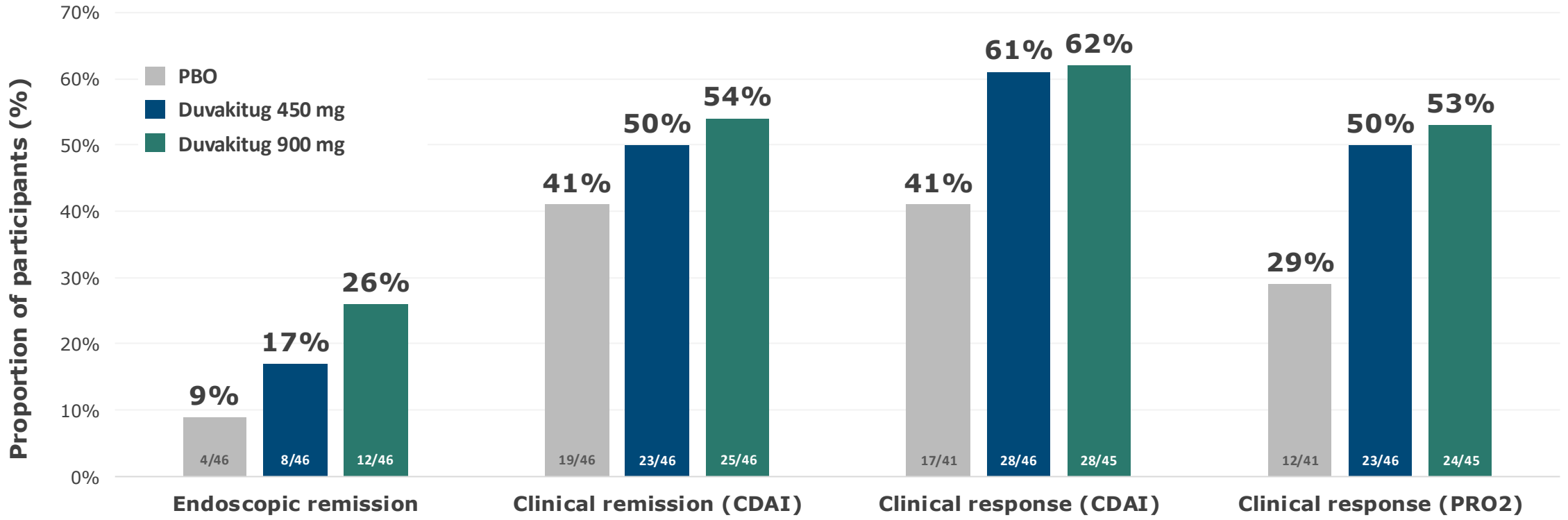
Endoscopic response was achieved for both duvakitug doses versus placebo irrespective of prior AT experience



Jairath V et al, ECCO 2025

Additional endpoints at week 14

Higher responses across additional clinical and endoscopic endpoints were achieved with both duvakitug doses versus placebo



Endpoint	Definition
Endoscopic remission	SES-CD score of ≤2
Clinical remission (CDAI)	CDAI score <150
Clinical response (CDAI)	CDAI score ≥100-point decrease from baseline
Clinical response (PRO2)	Decrease from baseline of ≥50% in PRO2 (daily average abdominal pain and daily average stool frequency scores)

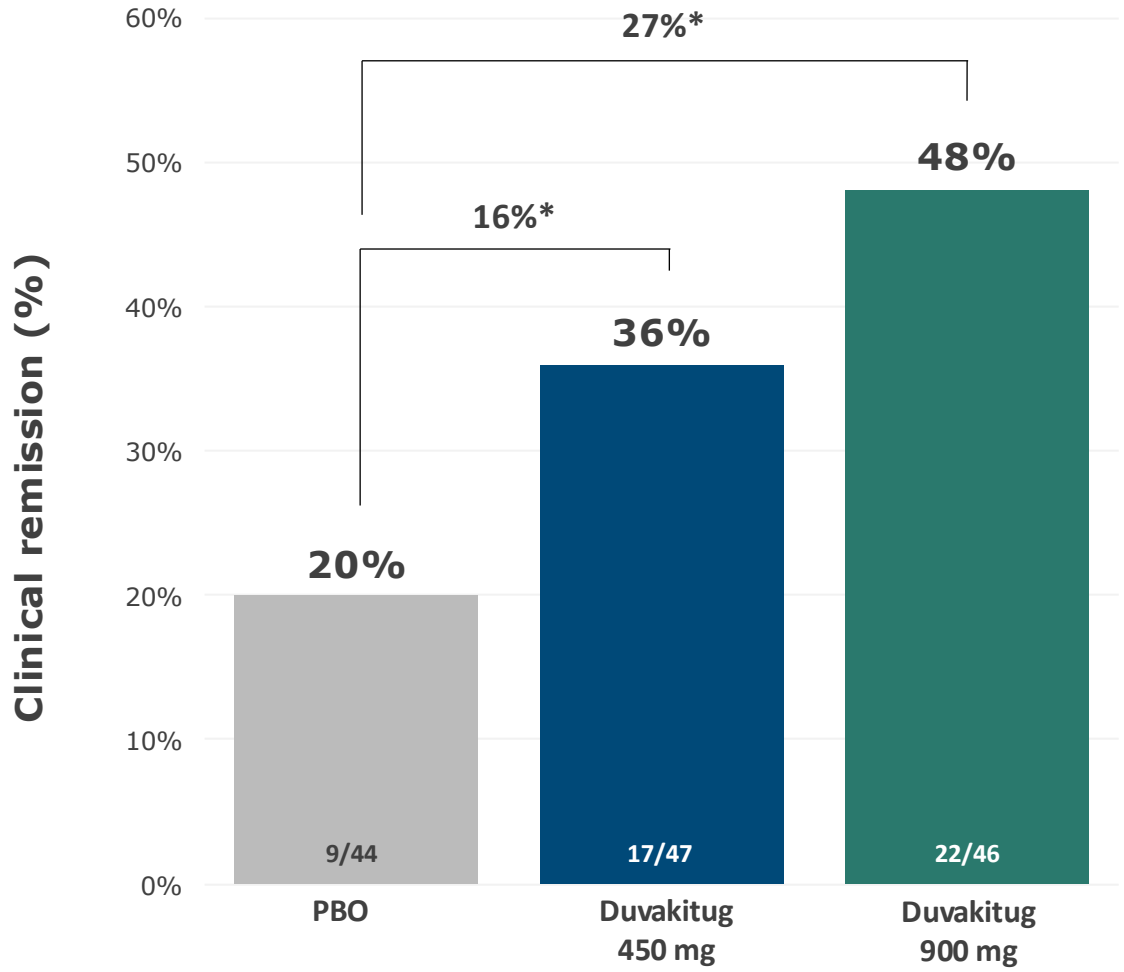
Jairath V et al, ECCO 2025

Baseline characteristics: UC

	Placebo N=44	Duvakitug 450 mg N=47	Duvakitug 900 mg N=46	Overall N=137
Age, years, mean (SD)	42.2 (13.1)	38.7 (13.0)	42.1 (13.2)	41.0 (13.1)
Male, n (%)	30 (68)	29 (62)	27 (59)	86 (63)
BMI, mean (SD)	26.4 (6.3)	25.4 (5.7)	24.8 (3.9)	25.6 (5.4)
Geographic region, n (%)				
North America	3 (7)	4 (9)	2 (4)	9 (7)
Eastern Europe	37 (84)	41 (87)	39 (85)	117 (85)
Western Europe	2 (5)	1 (2)	4 (9)	7 (5)
Other	2 (5)	1 (2)	1 (2)	4 (3)
Duration of disease, years, mean (SD)	6.2 (4.2)	9.0 (6.2)	7.8 (6.0)	7.7 (5.6)
Modified Mayo Score, mean (SD)	6.8 (1.2)	6.6 (1.2)	6.8 (1.1)	6.8 (1.1)
Mayo Endoscopy Score, n (%)				
2	17 (39)	24 (51)	19 (41)	60 (44)
3	27 (61)	23 (49)	27 (59)	77 (56)
Concomitant immunomodulator use, n (%)	5 (11)	4 (9)	4 (9)	13 (9)
Concomitant corticosteroid use, n (%)	15 (34)	22 (47)	20 (43)	57 (42)
Prior advanced therapies, n (%)				
Including investigational drugs	17 (39)	19 (40)	18 (39)	54 (39)
Excluding investigational drugs	15 (34)	14 (30)	14 (30)	43 (31)
Prior approved advanced therapies, n (%)				
0	29 (66)	33 (70)	32 (70)	94 (69)
1	11 (25)	10 (21)	6 (13)	27 (20)
2	1 (2)	2 (4)	3 (7)	6 (4)
≥3	3 (7)	2 (4)	5 (11)	10 (7)

Primary endpoint: Clinical remission at week 14

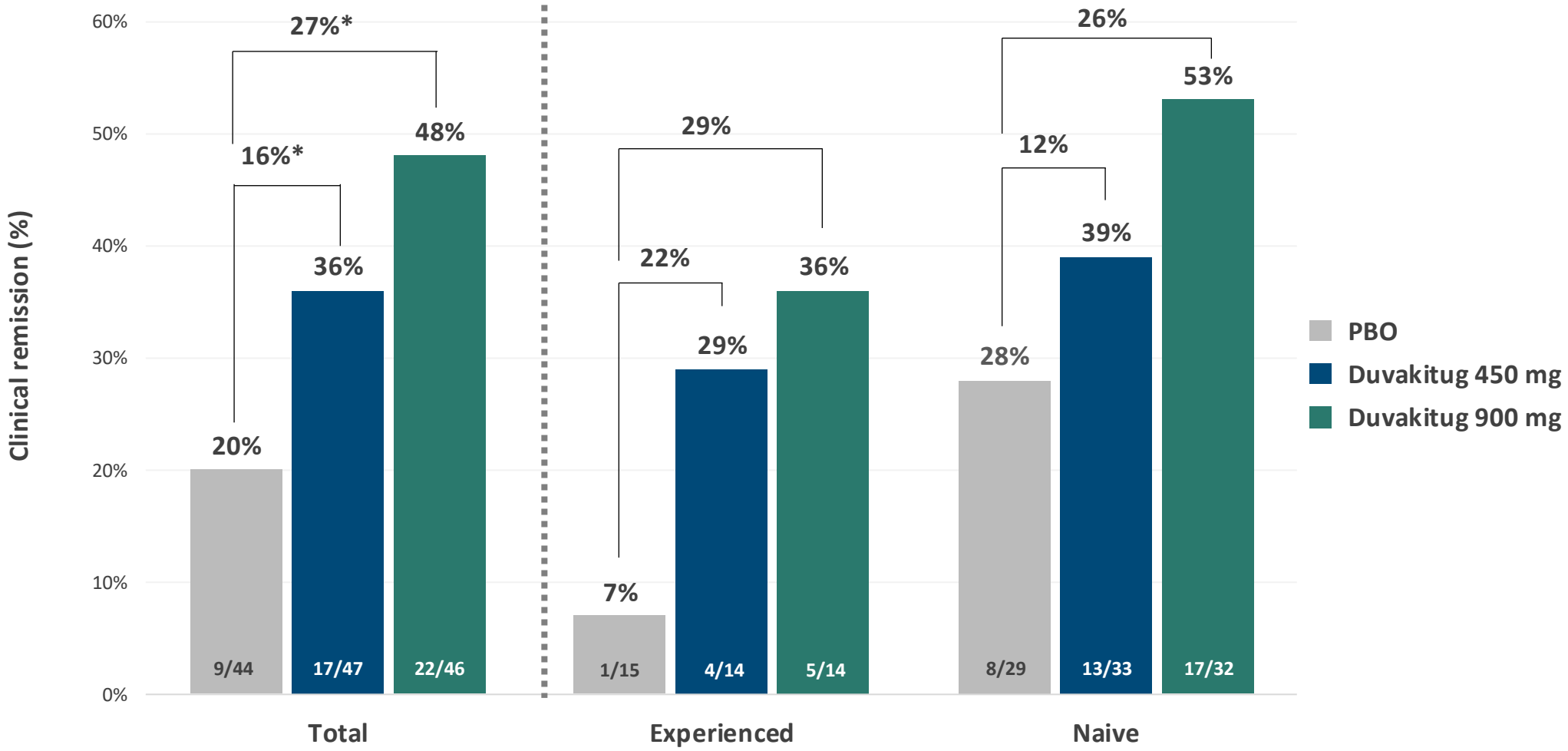
Significantly higher proportion of participants in both duvakitug doses achieved clinical remission



	Duvakitug 450 mg vs. PBO	Duvakitug 900 mg vs. PBO
Posterior probability†	0.95*	0.99*
Odds ratio‡	2.2 p-value=0.056	3.6 p-value=0.004

Clinical remission by prior advanced therapy (AT)

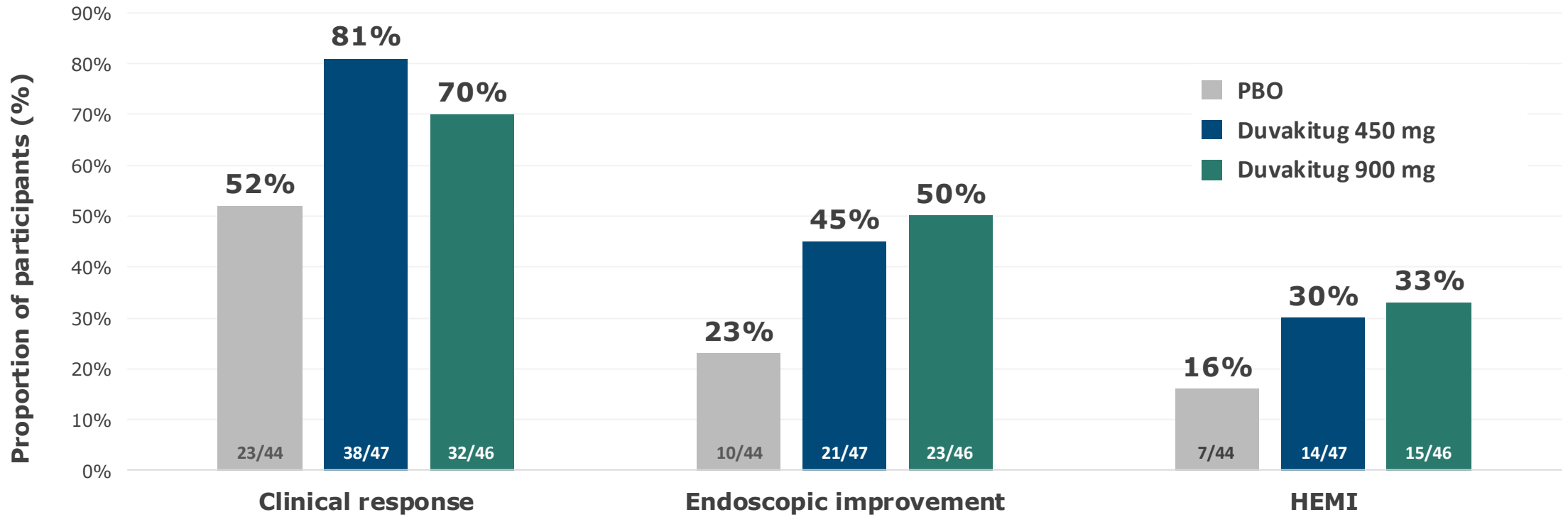
Clinical remission was consistent for both duvakitug doses versus placebo irrespective of prior AT experience



Reinisch et al, ECCO 2025

Additional endpoints at week 14

Higher responses across additional clinical, endoscopic and histological endpoints were achieved with both doses of duvakitug versus placebo



Endpoint	Definition
Clinical response	Decrease from baseline in the mMS of at least 2 points and at least a 30% reduction from baseline with either a decrease in rectal bleeding subscore of at least 1 or an absolute rectal bleeding subscore of ≤1
Endoscopic improvement	Mayo endoscopic subscore of 0 or 1 (where a score of 1 does not include 'friability')
Histological endoscopic mucosal improvement (HEMI)	Mayo endoscopic subscore of 0 or 1 (where a score of 1 does not include 'friability') and Geboes score ≤3.1

The TL1A Pipeline

	VIAL	MERCK	Roche / roivant	SANOFI teva	xencor	SPYRE THERAPEUTICS	absci
PROGRAM	BB-TL1A-VIAL-HLE	MK-7240 / PRA023	RVT-3101	TEV'574	XMAB942	SPY002	ABS-101
Q6M Dosing	✓ Q9M-Q12M**	✗ Q4W	✗ Q4W#	✗ Q2W-Q4W##	✗ Q12W%	✓ Q3M - Q6M***	✗ Q8W - Q12W&
Low Immunogenicity	✓	✓	✗	✓	✓	✓	✓
High Potency	✓	✗	✓	✓	✓	✓	✓
SubQ	✓	✓	✓	✓	✓	✓	✓
Development Stage	PHASE I	PHASE III	PHASE III	PHASE III	PHASE I/II	PHASE I	PHASE I

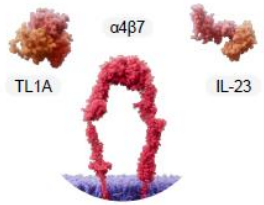
Disclaimer: Graphic is for informative purposes only and based on public company materials

Sources: Public company materials

The TL1A Pipeline: SPYRE Therapeutics

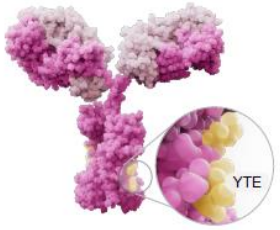
Validated targets

MOAs rationally chosen based on attractive risk-benefit profiles



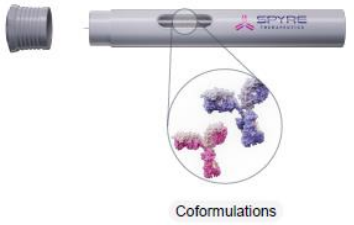
Half-life extension

Engineered for prolonged activity to enable infrequent administration

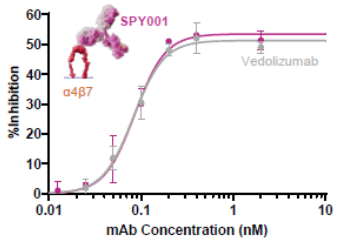


Fixed-dose combinations

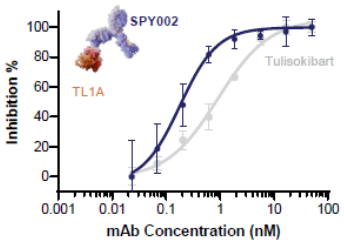
Rational combinations to address distinct disease drivers



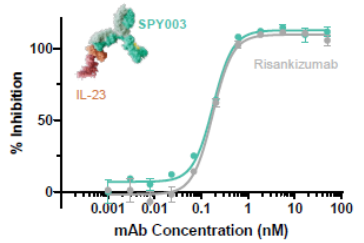
SPY001 (α4β7) potency



SPY002 (TL1A) potency

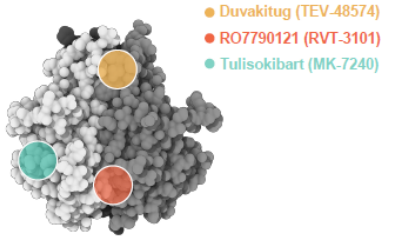


SPY003 (IL-23) potency



Single TL1A subunit epitope

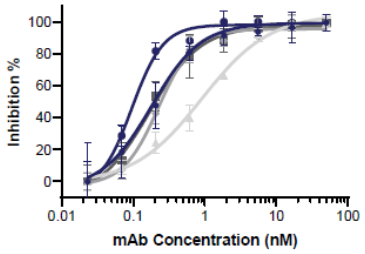
SPY002 and SPY072 each target a distinct epitope on a single TL1A monomer



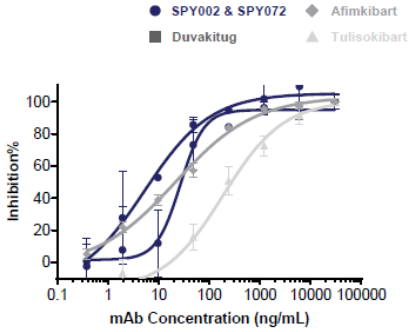
- Epitope locations were resolved by CryoEM
- Illustrative locations are overlayed with the crystal structure of trimeric TL1A

Superior or comparable potency in multiple assays

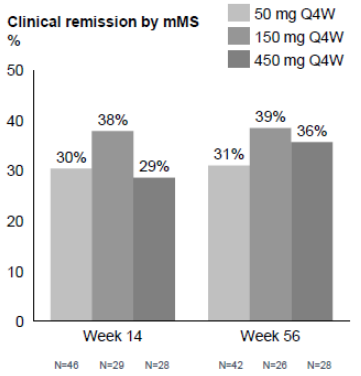
Superior or comparable inhibition of TF-1 apoptosis



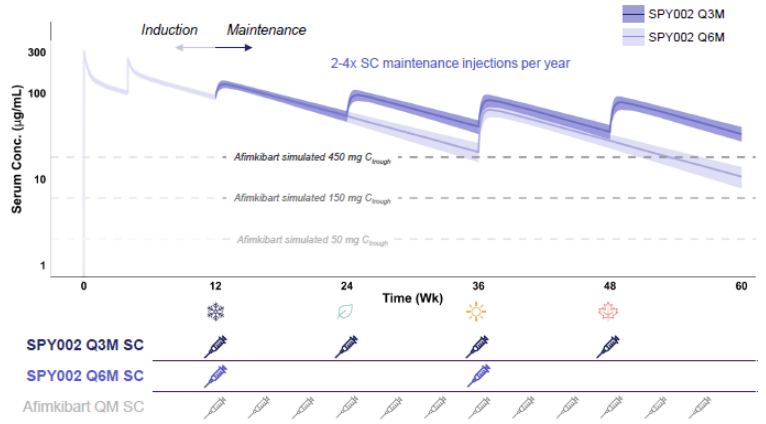
Superior or comparable inhibition of IFNγ secretion



Afimkibart Ph2 UC results



SPY002 simulated PK profile

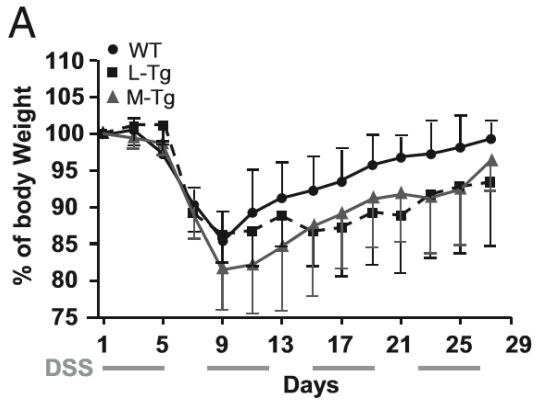


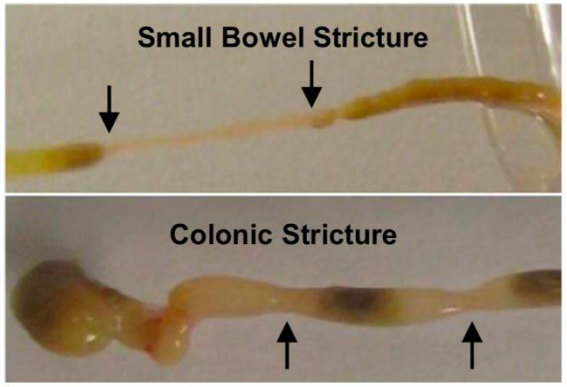
Western

Bispecific Antibodies in Development (June 2025)

Company / Developer	Bispecific Target(s) / Name	Status
Sanofi / Helixon	α4β7 × TL1A (HXN-1002) TL1A × IL-23 (tetravalent; HXN-1003)	Early clinical/private
Xencor	TL1A × IL-23p19 (XmAb)	Lead selection
Sorriso Therapeutics	TNFα × IL-23p19	Phase 1b (oral)
Generate Biomedicines	TL1A x IL-23p19	Pre-clinical
Elpiscience	TL1A x IL-23p19	Pre-clinical
Novamab	TL1A x IL-23p19 (LQ080)	Pre-clinical
Pfizer (with acquisition rights by Roche)	TL1A x IL-12/23p40 (PF-07261271)	Ph1 completed

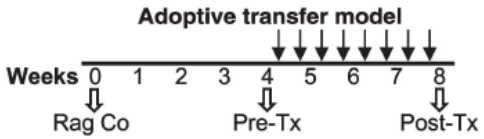
TL1A Signaling is a Driver of Gut Inflammation and Fibrosis in Mouse Models of IBD

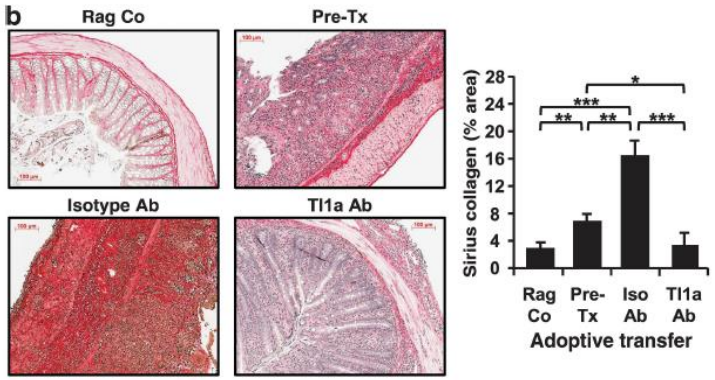




TL1A transgenic mouse models resemble a complicated form of severe human CD

- Sustained TL1A overexpression causes stricturing disease that is caused by increased collagen deposition





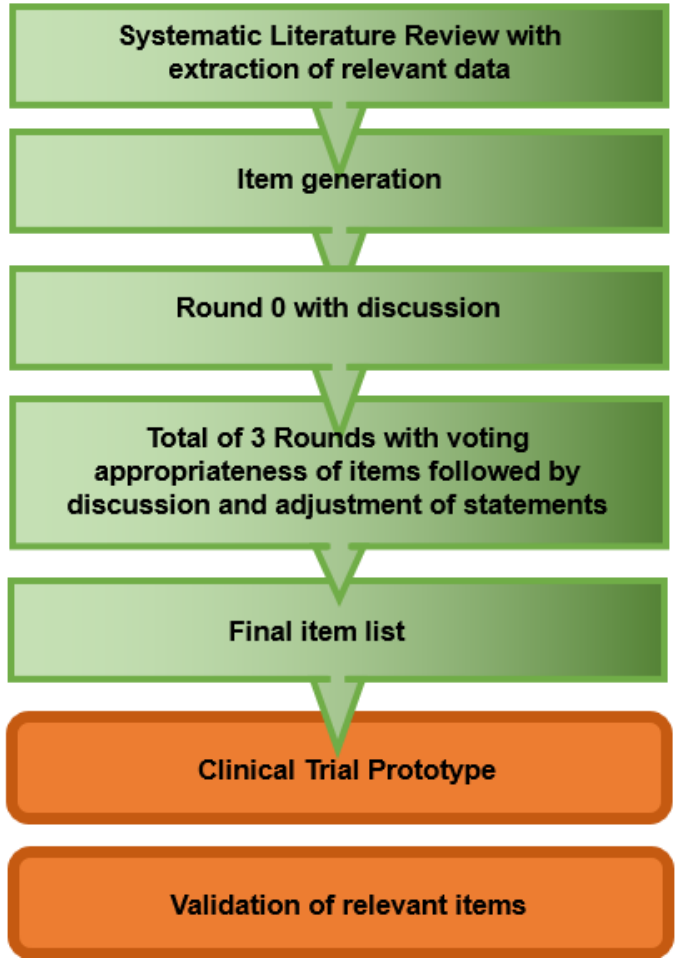
TL1A antibody treatment reverses established fibrosis in murine colitis

- This was observed in two different mouse models of chronic colitis in a study conducted by Cedars-Sinai

Barrett R, Zhang X, Koon HW,et al. Constitutive TL1A expression under colitogenic conditions modulates the severity and location of gut mucosal inflammation and induces fibrostenosis. Am J Pathol. 2012 Feb
Shih D, Zheng L, Zhang X, et al. Inhibition of a novel fibrogenic factor TL1A reveres established colonic fibrosis. Mucosal Immunol. 2014 Nov

An expert consensus to standardize definitions, diagnosis and treatment targets for anti-fibrotic stricture therapies in Crohn's disease

Florian Rieder[1], Dominik Bettenworth[2], Christopher Ma[3,4], Claire E. Parker[4], Lee A. Williamson[4], Sigrid A. Nelson[4], Gert van Assche[5], Antonio Di Sabatino[6], Yoram Bouhnik[7], Ryan W. Stidham[8], Axel Dignass[9], Gerhard Rogler[10], Stuart A. Taylor[11], Jaap Stoker[12], Jordi Rimola[13], Mark E. Baker[14], Joel G. Fletcher[15], Julian Panes[16], William J. Sandborn[4,17], Brian G. Feagan[4,18,19], and Vipul Jairath[4,18,19]



Rieder et al. Aliment Pharmacol Ther 2018

Stricture radiology index and S-PRO

Imaging Endpoints

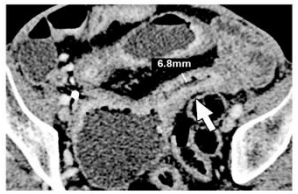
Radiology

ORIGINAL RESEARCH • GASTROINTESTINAL IMAGING

Reliability of CT Enterography for Describing Fibrostenosing Crohn Disease

Florian Rieder, MD • Christopher Ma, MD* • Jurij Hanzel, MD • Joel G. Fletcher, MD • Mark E. Baker, MD • Zhongya Wang, MS • Leonardo Guizzetti, PhD • Lisa M. Shackelton, PhD • Julie Rémillard, MS • Mihir Patel, MD • Jiafei Niu, MD • Ronald Ottichilo, MS • Cynthia S. Santillan, MD • Nunzia Capozzi, MD • Stuart A. Taylor, MD • David H. Bruining, MD • Guangyong Zou, PhD • Brian G. Feagan, MD • Vipul Jairath, MD** • Jordi Rimola, MD** • for the Stenosis Therapy and Anti-Fibrotic Research (STAR) Consortium*

CT Enterography Reliability for Describing Fibrostenosing Crohn Disease



- Retrospective study of CT enterography in 43 patients with Crohn disease and terminal ileal strictures.
- Five measurements and six observations had at least moderate interrater reliability (ICC ≥ 0.41) when assessed by four blinded abdominal radiologists.
- Stricture length, maximal stricture wall thickness, and maximal associated small bowel dilation were independently associated with stricture severity.

Rieder F and Ma C et al. Published: August 6, 2024
https://doi.org/10.1148/radiol.233038

Radiology

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ORIGINAL RESEARCH • GASTROINTESTINAL IMAGING

Reliability of MR Enterography Features for Describing Fibrostenosing Crohn Disease

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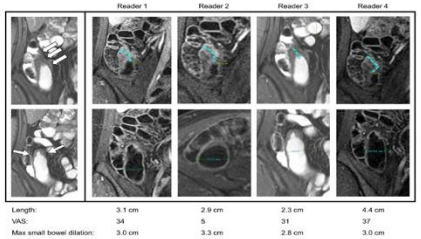
Reliability of MR Enterography Features for Fibrostenosing Crohn Disease



- Retrospective study of MR enterography from two independent samples of patients (99 development and 51 validation) with symptomatic terminal ileum Crohn disease strictures.
- Ten features had at least moderate interrater reliability (ICC ≥0.41).
- Stricture length, maximum wall thickness, and maximum small bowel dilation were associated with stricture severity (regression coefficients, 0.09–3.97).

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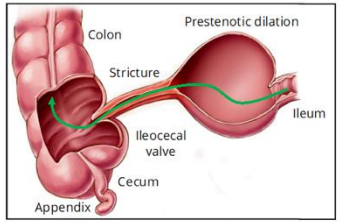
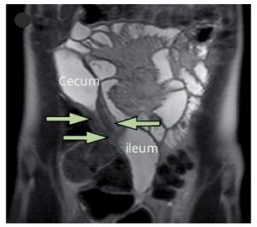
Co-Primary Endpoint

- **Symptoms: patient reported outcome instrument**
  - S-PRO: 16 questions addressing specific symptoms:
    - Pain, cramping, nausea, and vomiting after meals
    - Need to modify diet (volume and type of food)
    - Difficulty to maintain body weight
- **Imaging: Magnetic resonance enterography (MRE)**
  - SRI: Stricture radiology index evaluates:
    - Increased bowel wall thickness
    - Reduced luminal diameter
    - Prestenotic dilation





S-PRO

Stricturing Crohn's Disease Questionnaire

For each of the following questions, please choose the one response that best describes your experience with stricturing Crohn's disease during the last 24 hours.

1. How severe was your worst **abdominal pain** during the last 24 hours?
   - ☐ No pain at all
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe
2. During the last 24 hours, how often did you experience **abdominal pain after eating**?
   - ☐ Never
   - ☐ Sometimes
   - ☐ Often
   - ☐ Every time I ate
   - ☐ Not Applicable: I could not eat in the last 24 hours because of my Crohn's symptoms
   - ☐ Not Applicable: I did not eat in the last 24 hours for other reasons
3. How severe was your worst **abdominal cramping** during the last 24 hours?
   - ☐ No cramping at all
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe

Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

Looking to the future: TL1As

- TL1A likely to be next approved monoclonal antibody for CD & UC with on-going phase 3 trials
  - +/- Predictive Biomarker
- Long-term safety remains to be determined so far limited read-outs
- Being assessed as a co-formulation and bipsecific antibody
- ? Impact on fibrosis but very challenging to design trials and measure this
- ? Ability to treat disease subtypes (pCD) and EIMs