Dual Biologics, Novel Peptides, and Real-World Evidence: The Expanding IBD Arsenal

Courtney Perry, DO MS

Associate Professor

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Financial Disclosures

- I have conducted advisory activities for Abbvie

Objectives

- 1. Describe updates and new pathways in therapeutic management of IBD
- 2. Identify evidence-based combination therapeutic strategies for refractory Inflammatory Bowel Disease Management

RISE
THERAPEUTICS

Orchestrating immune modulation

INNATE IMMUNE TRAINING WITH R-3750 INDUCES A TREG RESET PHENOTYPE AND COORDINATED MUCOSAL REPAIR IN ULCERATIVE COLITIS: MULTI-OMIC EVIDENCE FROM A FIRST-IN-HUMAN STUDY

Christian Furlan Freguia

Current UC therapies fail to deliver durable, off-drug remission

LIMITATIONS OF CURRENT THERAPIES

🧪 **Chronic disease requiring continuous therapy**

Relapse is common after treatment withdrawal

⚠️ **Current therapies rely on systemic immunosuppression**

Anti-TNF, anti-integrin, JAK inhibitors, S1P modulators

Associated with:

- Infection risk
- Monitoring burden
- Loss of response

WHAT IS MISSING?

🟩 **Restore Immune Tolerance**

Not just suppression

🟩 **Mucosal Barrier Repair**

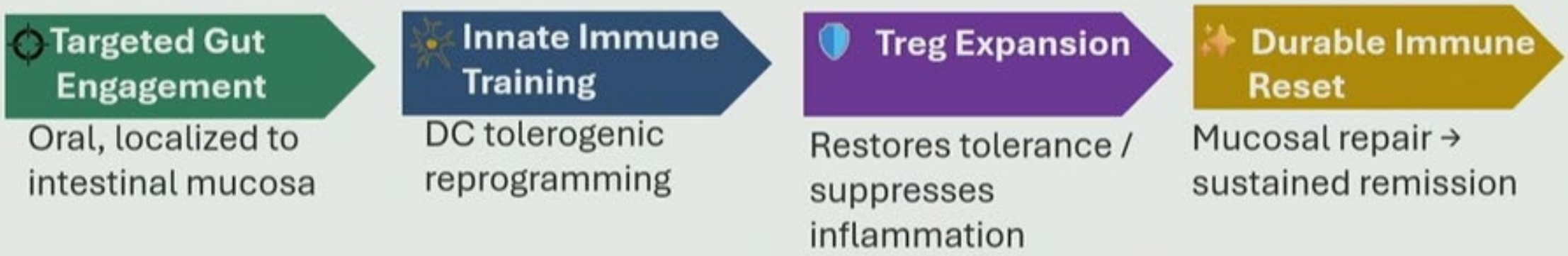
Address root cause of disease

🟩 **Durable Remission**

After short-course therapy

Can we **reset the immune system**—rather than suppress it—to achieve durable remission?

Innate immune training drives durable immune reprogramming



Short-course therapy → **durable immune reset** without systemic immunosuppression

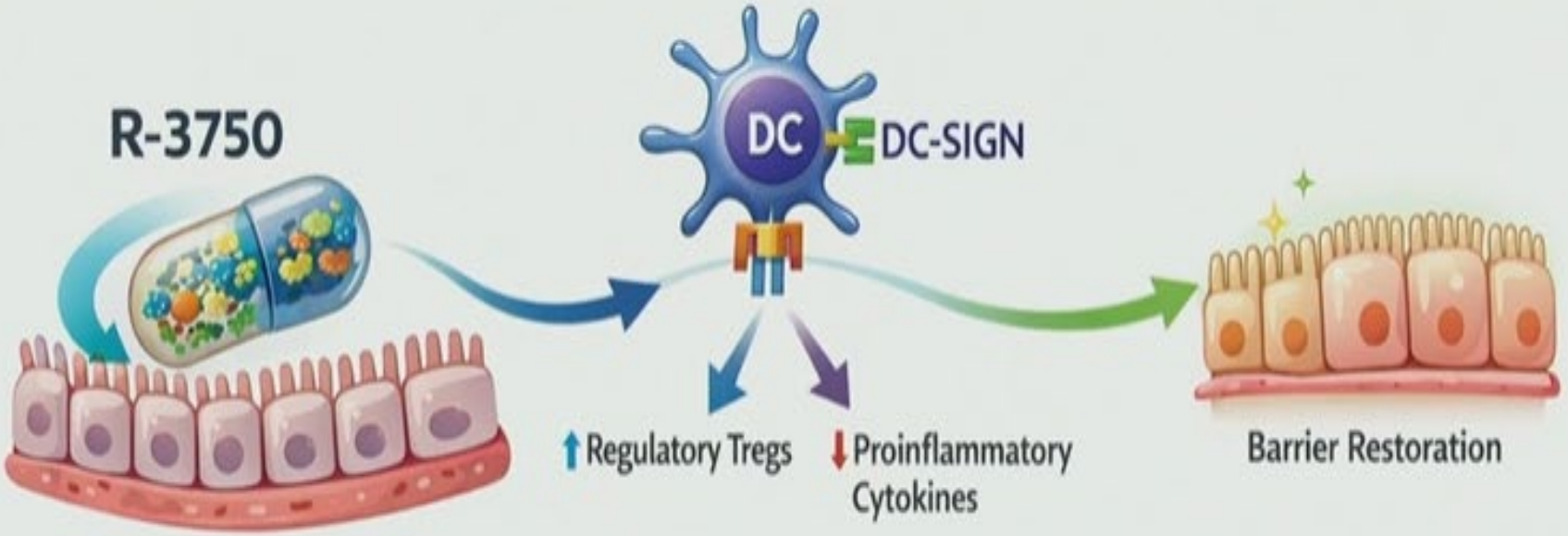
R-3750 drives innate immune training via DC-SIGN

R-3750

Engineered *L. lactis* expressing Surface Layer Protein A (SlpA)

Oral, gut-restricted

Non colonizing



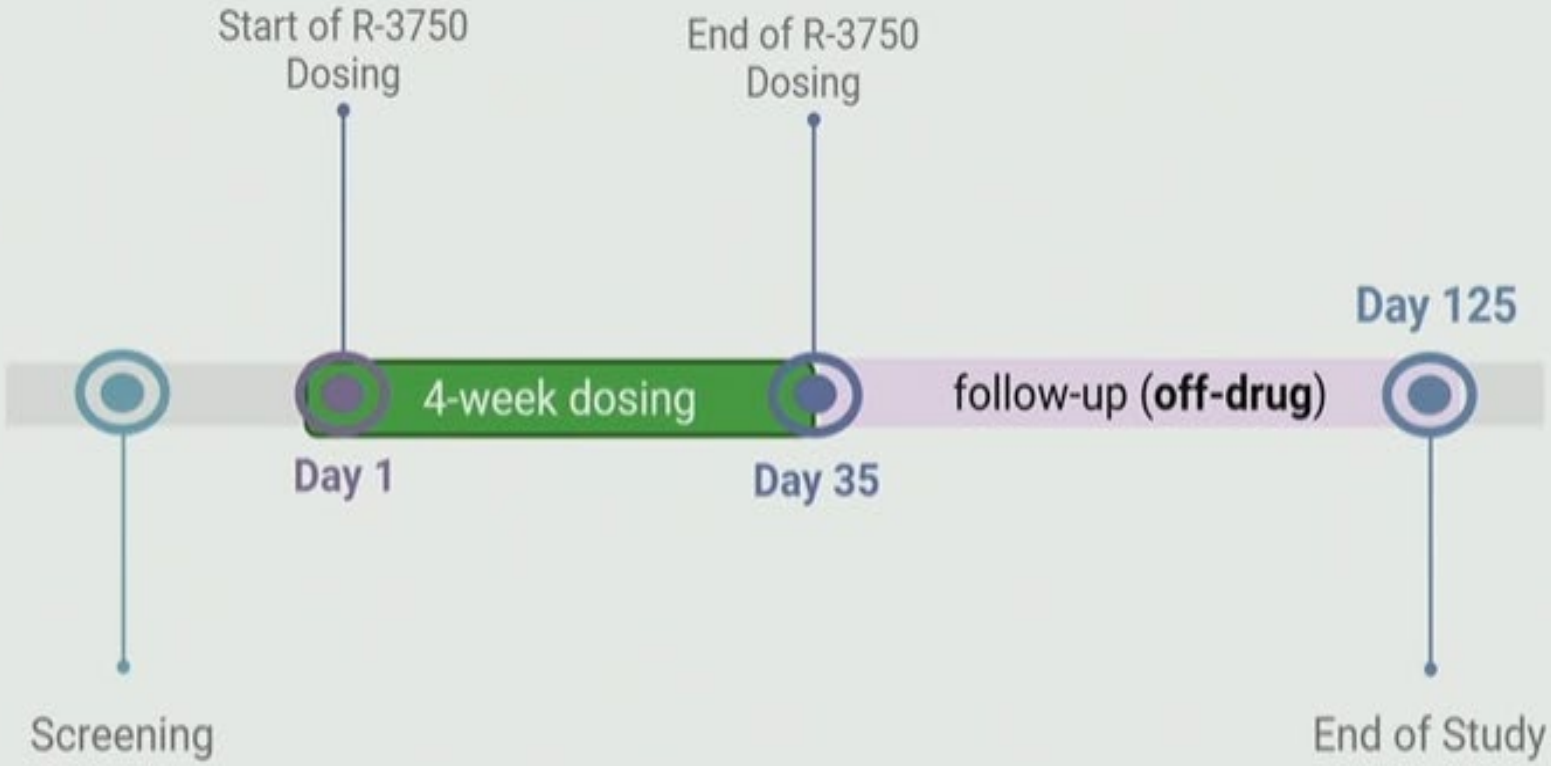
Targeted innate immune engagement → Treg induction → mucosal repair

Phase 1b study design in mild-moderate UC

Study Design
Phase 1b, open-label, multi-center
3+3 dose escalation (3 cohorts)

Dosing
Oral R-3750 once daily × 4 weeks

Population
Mild–moderate UC on stable 5-ASA
n = 9 (dose escalation)



Short-course therapy with extended **off-drug** follow-up to assess safety and **durability**

Endpoints
Primary: Safety & tolerability
Secondary: Clinical activity
Exploratory: Biomarkers (Tregs, multi-omics)

R-3750 is safe and well tolerated

Key Safety Findings

- **No serious adverse events (SAEs)**
- **No drug-related adverse events**
- All AEs were **mild and transient**

Systemic Exposure

- **No systemic exposure detected**

Clinical Labs

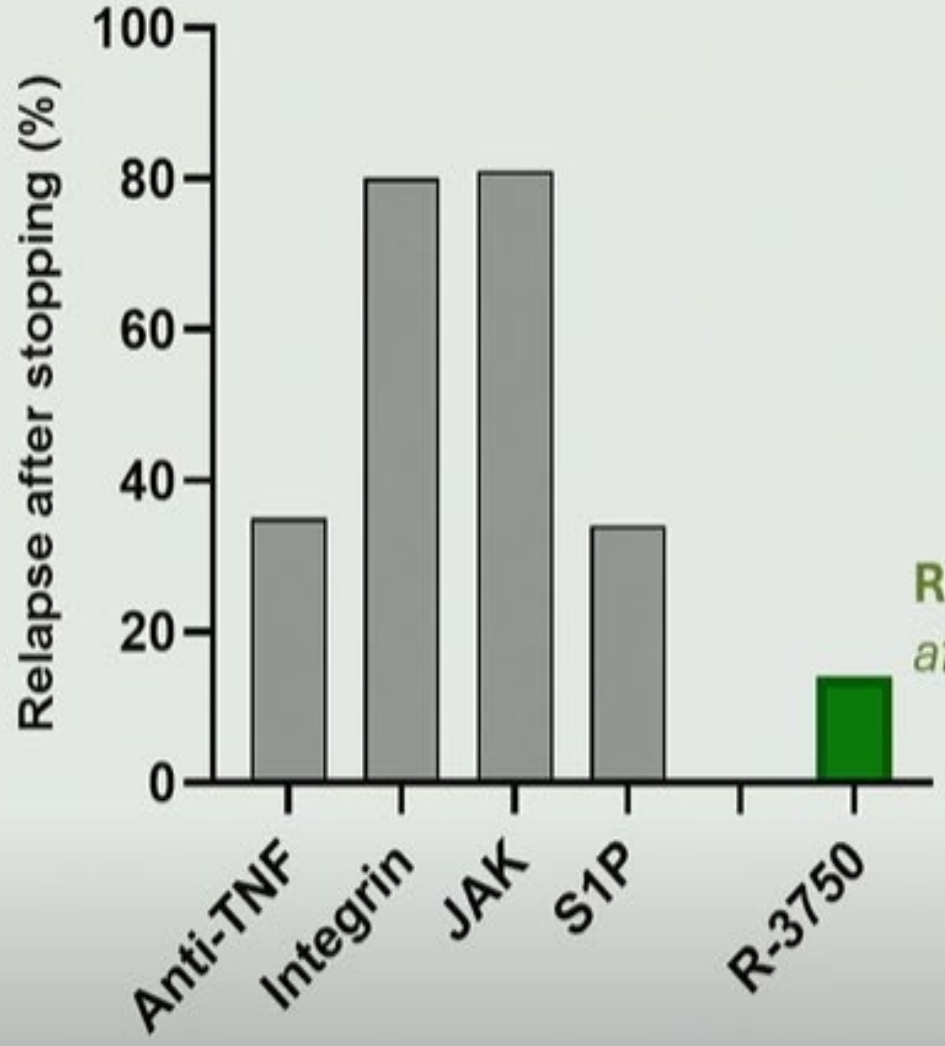
- **No clinically significant changes** in:
  - Liver function
  - Kidney function
  - Hematology

Dose	n	Drug-related AEs	SAEs
9E9 CFU	3	0	0
3E10 CFU	3	0	0
9E10 CFU	3 (+15)	1*	0

* Possibly related diarrhea; mild, transient, and resolved without intervention.

Gut-restricted therapy with **no systemic exposure**

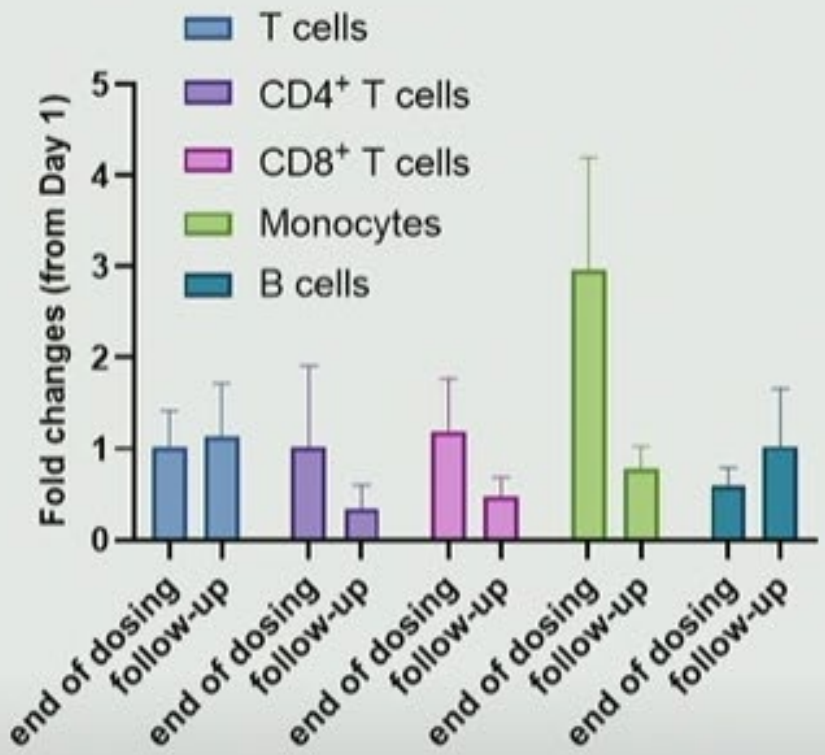
Durable off-drug remission is uncommon in UC

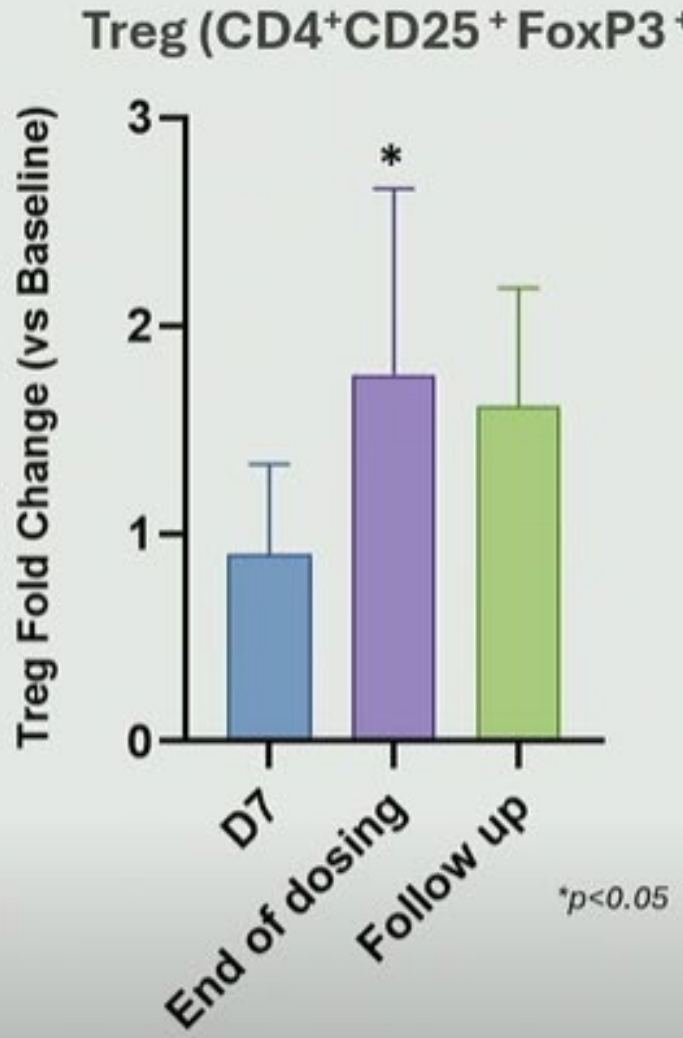


R-3750: 14% relapse
after treatment cessation

R-3750 demonstrates **durable** disease control **beyond active dosing**

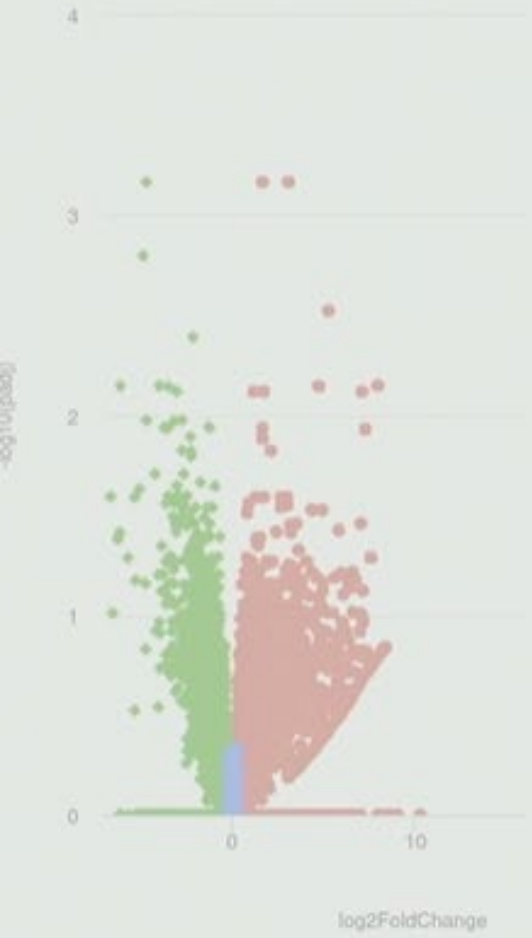
R-3750 induces Treg expansion consistent with immune reset





Targeted immune tolerance that support a **true immune reset** rather than generalized immune suppression

R-3750 drives a two-phase transcriptional program: immune resolution followed by mucosal repair

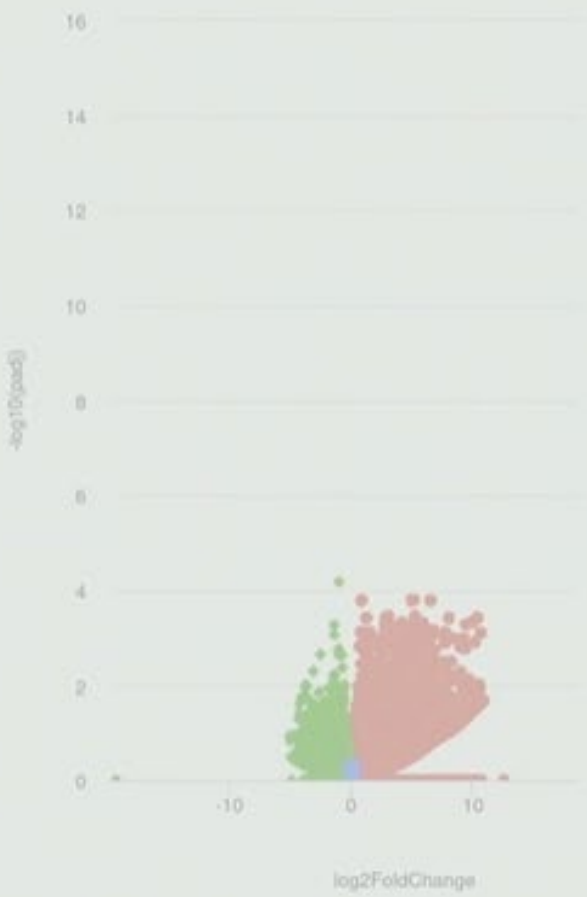


END OF DOSING:
IMMUNE RESOLUTION

↓ Inflammatory mediators

CXCL8
CCL20
TNFAIP3
NFKBIA
IL6
OSM

Inflammation OFF



FOLLOW UP (OFF-DRUG):
MUCOSAL REPAIR

↑ Barrier / repair genes

MUC13
DUOX2
PTGES
OLR1
DEFA1

Repair ON

Immune modulation enables activation of **mucosal repair**, consistent with **durable** off-drug remission

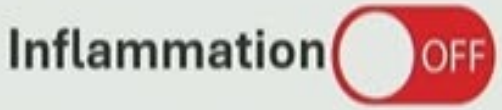
R-3750 drives a two-phase functional program: metabolic resolution followed by mucosal repair

END OF DOSING:
METABOLIC RESOLUTION

↓ Inflammatory lipid mediators
↓ Oxidative stress pathways
↑ Conjugation / detoxification pathways

FOLLOW-UP (OFF-DRUG):
METABOLIC REPAIR AND HOMEOSTASIS

↑ Lipid remodeling pathways
↑ Redox pathways
↑ Immunoregulatory and barrier-repair pathways



Metabolic reprogramming confirms **immune resolution** and enables activation of **mucosal repair**

R-3750 reprograms the gut microbiome toward a homeostatic state

END OF DOSING:
EARLY MICROBIOME REMODELING

↑ Bacteroidetes / fiber-utilizing taxa
↓ Beneficial commensals (transient)

↑ Butyrate production pathways
↑ Tryptophan metabolism

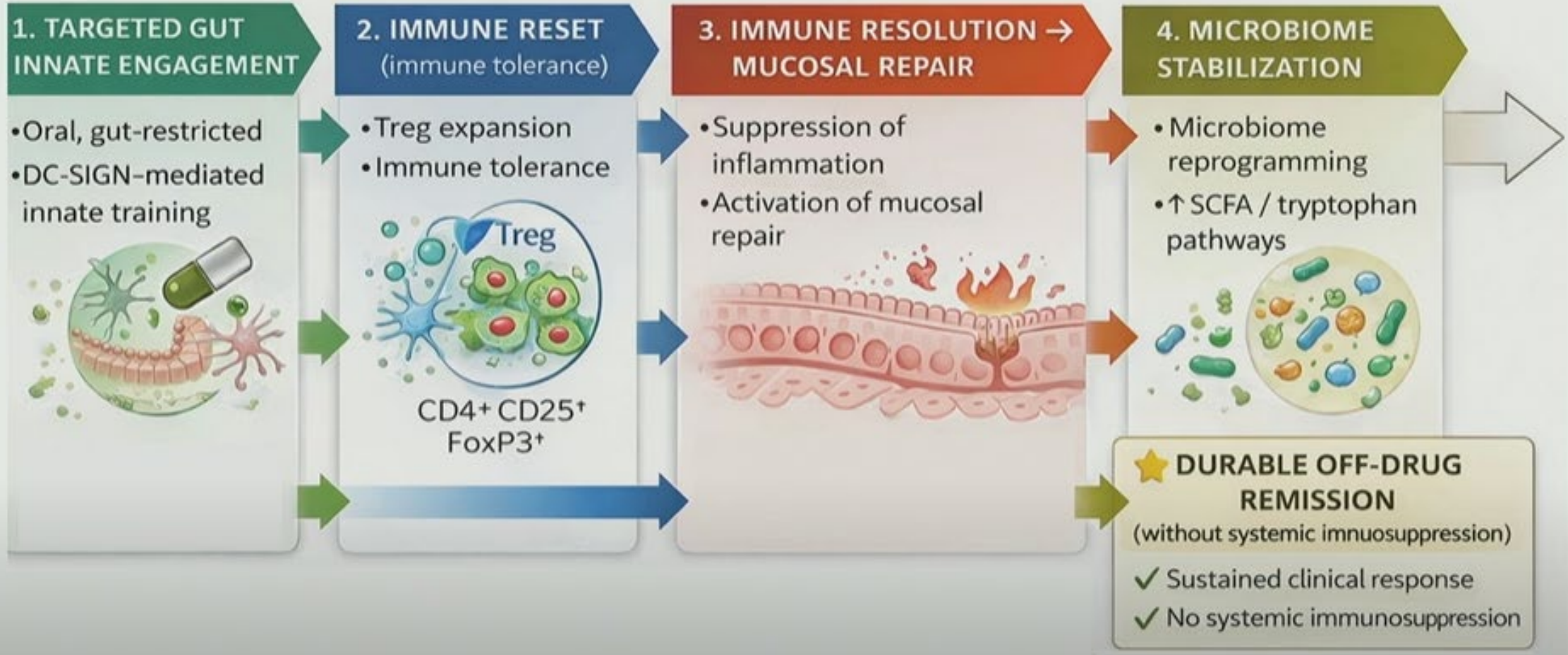
FOLLOW-UP (OFF-DRUG):
SUSTAINED SUPPORTIVE FUNCTION

↑ Butyrate-producing taxa
↑ Health-associated commensals

↑ SCFA-associated metabolism
↑ Tryptophan pathway activity

Microbiome reprogramming reinforces **immune resolution** and supports **mucosal repair**

R-3750 drives a multi-omic program resulting in durable off drug remission



Short-course therapy induces **a coordinated immune and ecosystem reset** enabling **durable remission** without immunosuppression

ICOTROKINRA, THE FIRST TARGETED ORAL PEPTIDE THAT SELECTIVELY BLOCKS THE INTERLEUKIN-23 RECEPTOR, REDUCES SYSTEMIC AND TISSUE INFLAMMATORY BURDEN IN ULCERATIVE COLITIS: RESULTS FROM THE ANTHEM-UC STUDY

Edward V. Loftus, Jr., Vipul Jairath, Britta Siegmund, Arun K. Kannan, Martha Zeeman, Amy Hart, David Strawn, Swati Venkat, Lynn Tomsho, Bradford Mcrae, Darren Ruane, Lindsey Surace, Ngozi Erondu, Joyce Zhan, Minhu Chen, Karen Chachu, Katsuyoshi Matsuoka, Jimmy Limdi, Grazyna Rydzewska, Maria T. Abreu, Edouard Louis

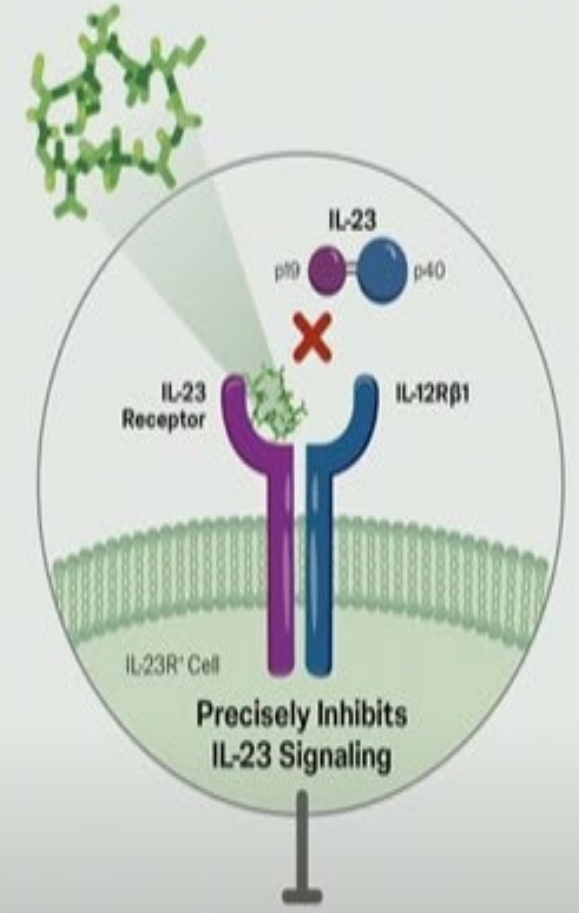
Background and Objective

Icotrokinra is a first-in-class investigational targeted oral peptide that precisely blocks the interleukin-23 (IL-23) receptor

All icotrokinra doses met the Week 12 primary endpoint[1] of ANTHEM-UC, a Phase 2b, randomized, double-blind, placebo-controlled, treat-through, dose-ranging study in adults with moderate to severe ulcerative colitis

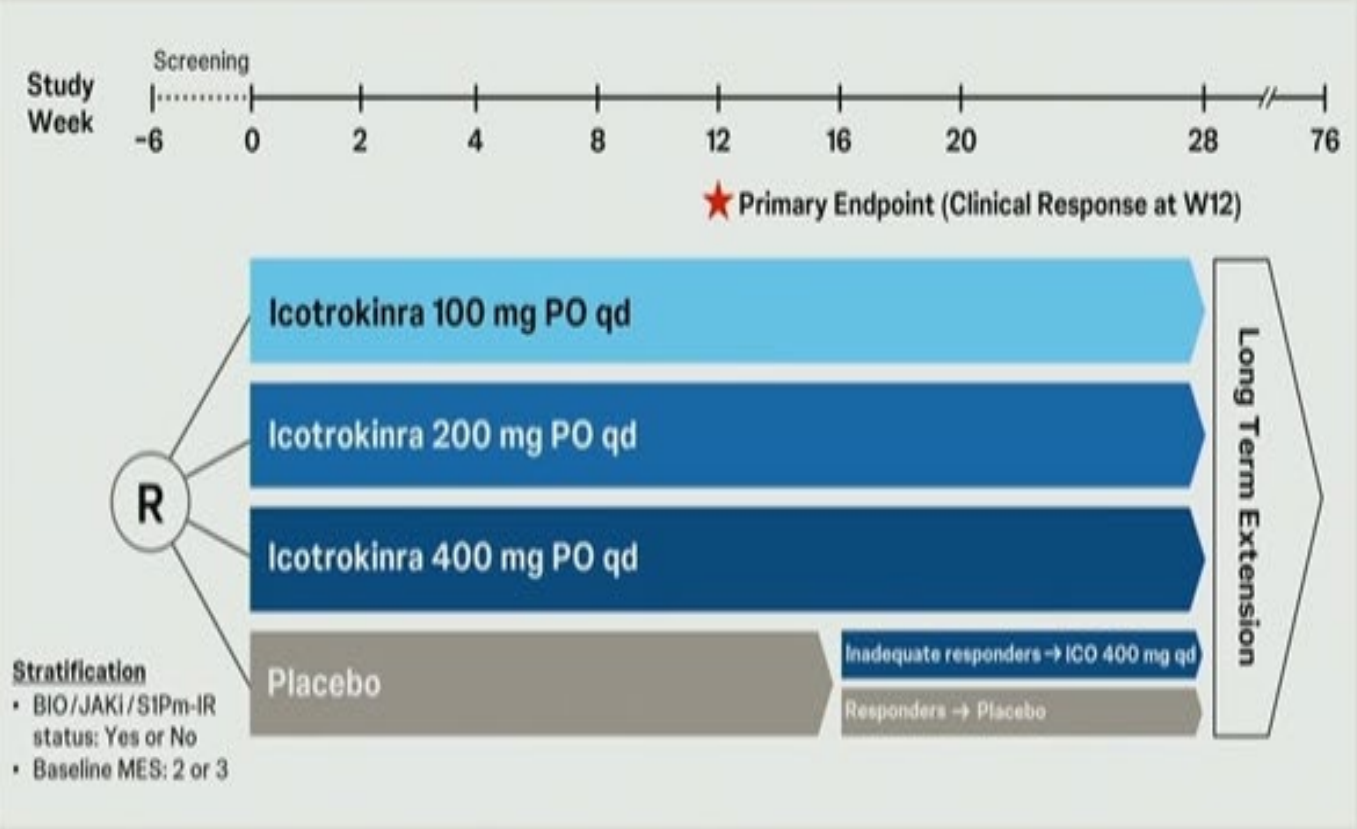
Icotrokinra also delivered clinically meaningful improvements across key secondary endpoints at Week 12, which were maintained or improved at Week 28[2]

Icotrokinra Blocks IL-23 From Binding to its Receptor



Inhibits IL-17A, IL-17F, and IL-22 Production

ANTHEM-UC Design and Methods



Key Eligibility Criteria

- Diagnosed UC of ≥12 weeks duration
- Modified Mayo score of 5–9, inclusive
- Mayo endoscopic subscore (MES) ≥2 per central review
- Inadequate response/intolerance (IR) to CS, 6-MP, or AZA **OR** CS dependence **OR** IR to TNFα antagonists, ustekinumab, vedolizumab, JAK inhibitors, or S1P receptor modulators (BIO/JAKi/S1Pm-IR)

Clinical inflammatory biomarkers: C-reactive protein and fecal calprotectin

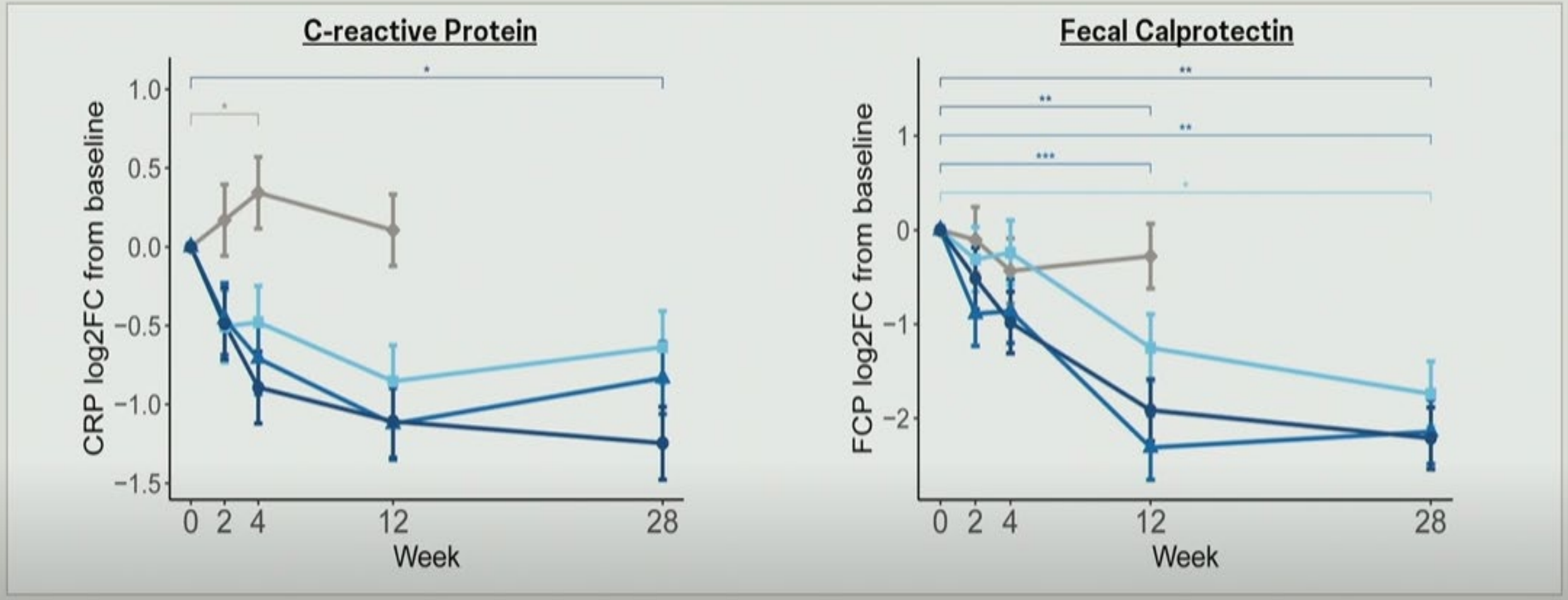
Systemic IL-23 pathway biomarkers: IL-22, IL-17A, and IL-17F

Tissue biomarkers: IL-23 pathway gene expression changes in colonic biopsies

Demographics and Baseline Disease Characteristics

	Placebo	Icotrokinra 100 mg qd	Icotrokinra 200 mg qd	Icotrokinra 400 mg qd	Total
Full analysis set, n	63	64	62	63	252
Age, years, mean (SD)	38.3 (13.8)	45.8 (14.6)	41.8 (14.6)	40.6 (14.8)	41.6 (14.7)
Sex, male, n (%)	35 (55.6%)	40 (62.5%)	32 (51.6%)	40 (63.5%)	147 (58.3%)
Race, White, n (%)	44 (69.8%)	45 (70.3%)	39 (62.9%)	42 (66.7%)	170 (67.5%)
UC disease duration, years, mean (SD)	8.3 (8.1)	7.4 (6.1)	7.8 (7.5)	7.6 (7.6)	7.8 (7.3)
Extensive disease, n (%)	27 (42.9%)	23 (35.9%)	23 (37.1%)	29 (46.0%)	102 (40.5%)
Modified Mayo score [max = 9], mean (SD)	6.75 (1.231)	6.55 (1.296)	6.75 (1.386)	6.49 (1.401)	6.63 (1.327)
Mayo endoscopic subscore of 3 (severe), n (%)	36 (57.1%)	38 (59.4%)	37 (59.7%)	37 (58.7%)	148 (58.7%)
Fecal calprotectin, mg/kg, median [IQR]	1467.0 [420.5; 3622.0]	1433.3 [698.0; 3121.2]	2467.0 [646.4; 4599.6]	1421.3 [584.6; 4978.6]	1523.0 [587.0; 3816.7]
CRP, mg/L, median [IQR]	3.0 [0.9; 7.0]	3.0 [1.1; 6.7]	5.3 [1.5; 11.3]	4.0 [1.5; 8.1]	3.6 [1.3; 8.1]

Clinical Inflammatory Biomarkers



Placebo
n = 63

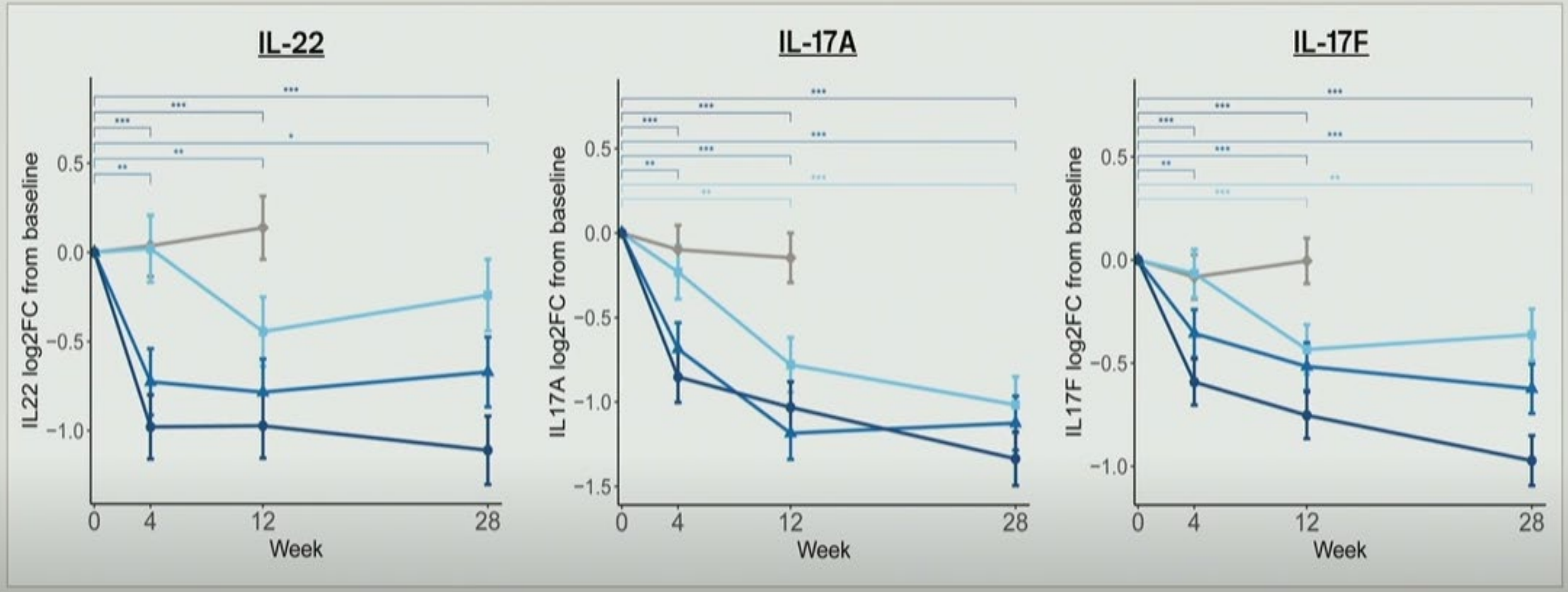
Icotrokinra 100 mg qd
n = 64

Icotrokinra 200 mg qd
n = 62

Icotrokinra 400 mg qd
n = 63

Nominal *p < 0.05, **p<0.001, ***p<0.001 for log2 fold change from baseline

Systemic IL-23 Pathway Biomarkers



Placebo
n = 44–58

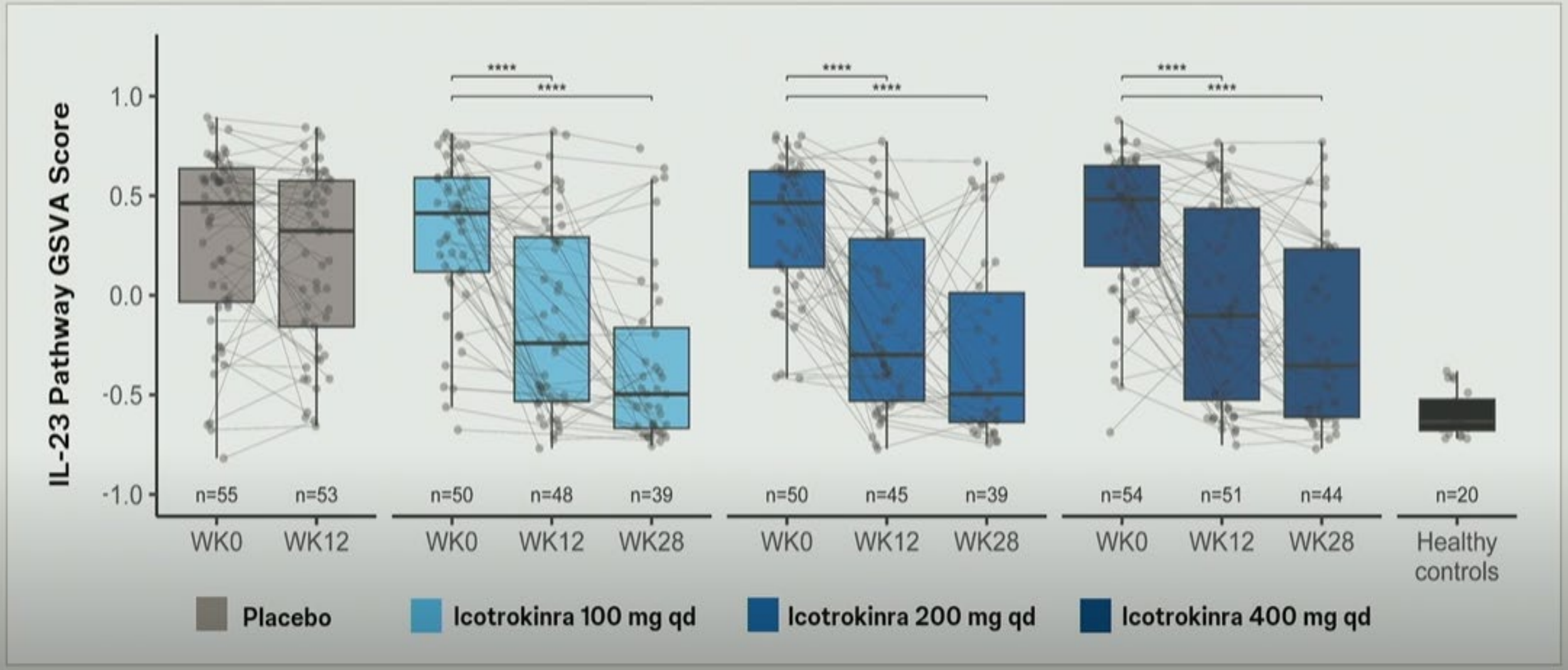
Icotrokinra 100 mg qd
n = 44–50

Icotrokinra 200 mg qd
n = 44–49

Icotrokinra 400 mg qd
n = 46–53

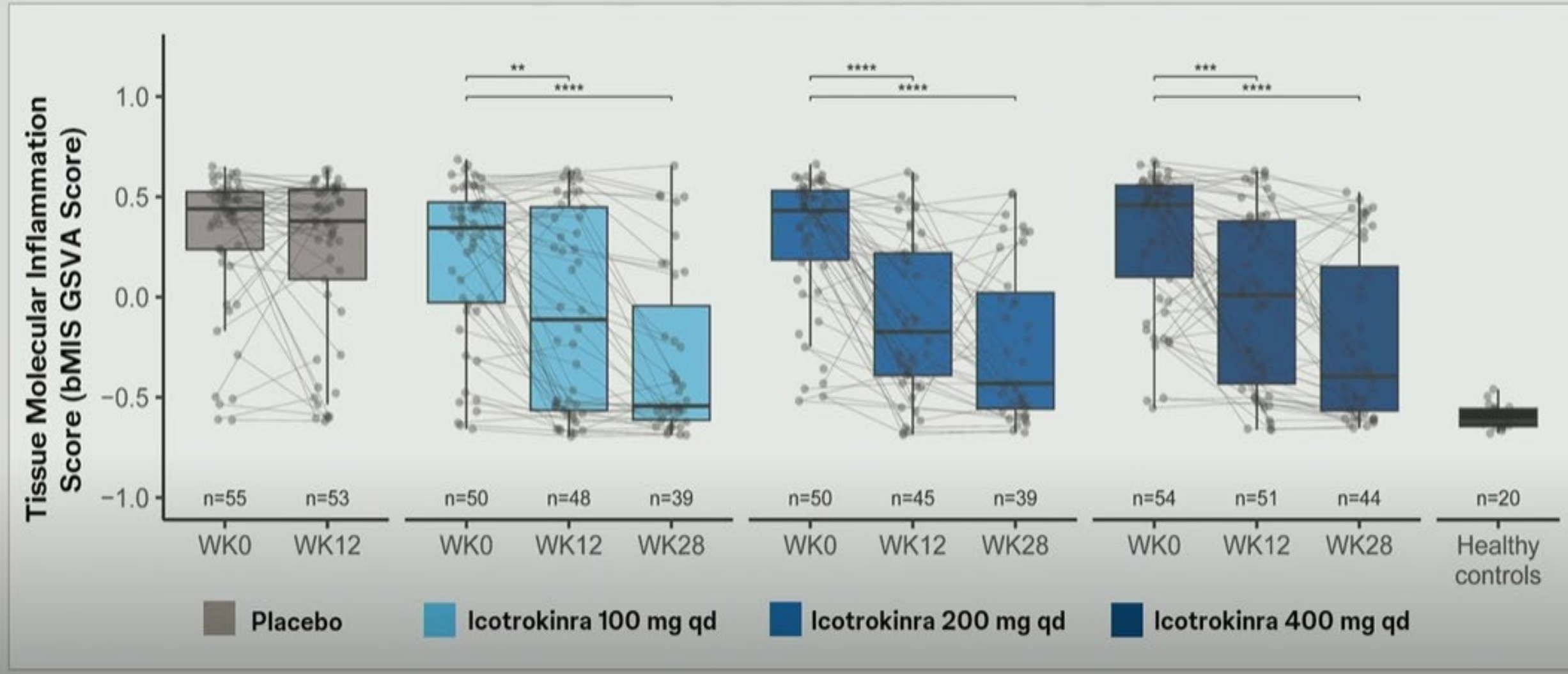
Nominal *p < 0.05, **p<0.001, ***p<0.001, ****p<0.0001 for log2 fold change from baseline

Tissue IL-23 Pathway Activation



Nominal ****p<0.0001

Tissue Inflammatory Burden



Nominal **p<0.01, ***p<0.001, ****p<0.0001

Conclusions

- Precisely blocking the IL-23 receptor with once-daily icotrokinra reduced IL-23–mediated inflammatory burden in the systemic circulation and in tissue of patients with ulcerative colitis
- Icotrokinra induced transcriptional changes that are consistent with dampening of IL-23–driven inflammation and normalization of the tissue transcriptome
- All once-daily doses of icotrokinra attenuated systemic and tissue inflammation; greater reduction of systemic inflammatory burden was observed with the 200 mg and 400 mg doses

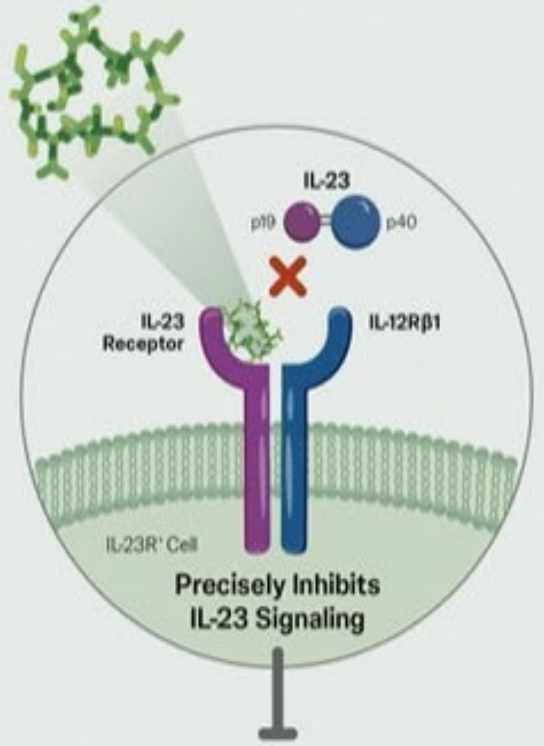
Background and Objective

Icotrokinra is a first-in-class investigational targeted oral peptide that precisely blocks the interleukin-23 (IL-23) receptor

All icotrokinra doses met the Week 12 primary endpoint[1] of ANTHEM-UC, a Phase 2b, randomized, double-blind, placebo-controlled, treat-through, dose-ranging study in adults with moderate to severe ulcerative colitis

Icotrokinra also delivered clinically meaningful improvements in clinical, endoscopic, and histologic endpoints at Week 12, which were maintained or improved at Week 28[2]

Icotrokinra Blocks IL-23 From Binding to its Receptor



Inhibits IL-17A, IL-17F, and IL-22 Production

Here, we report the efficacy of icotrokinra in ANTHEM-UC participants with and without prior inadequate response or intolerance to advanced therapies for UC

Endpoints and Statistical Considerations

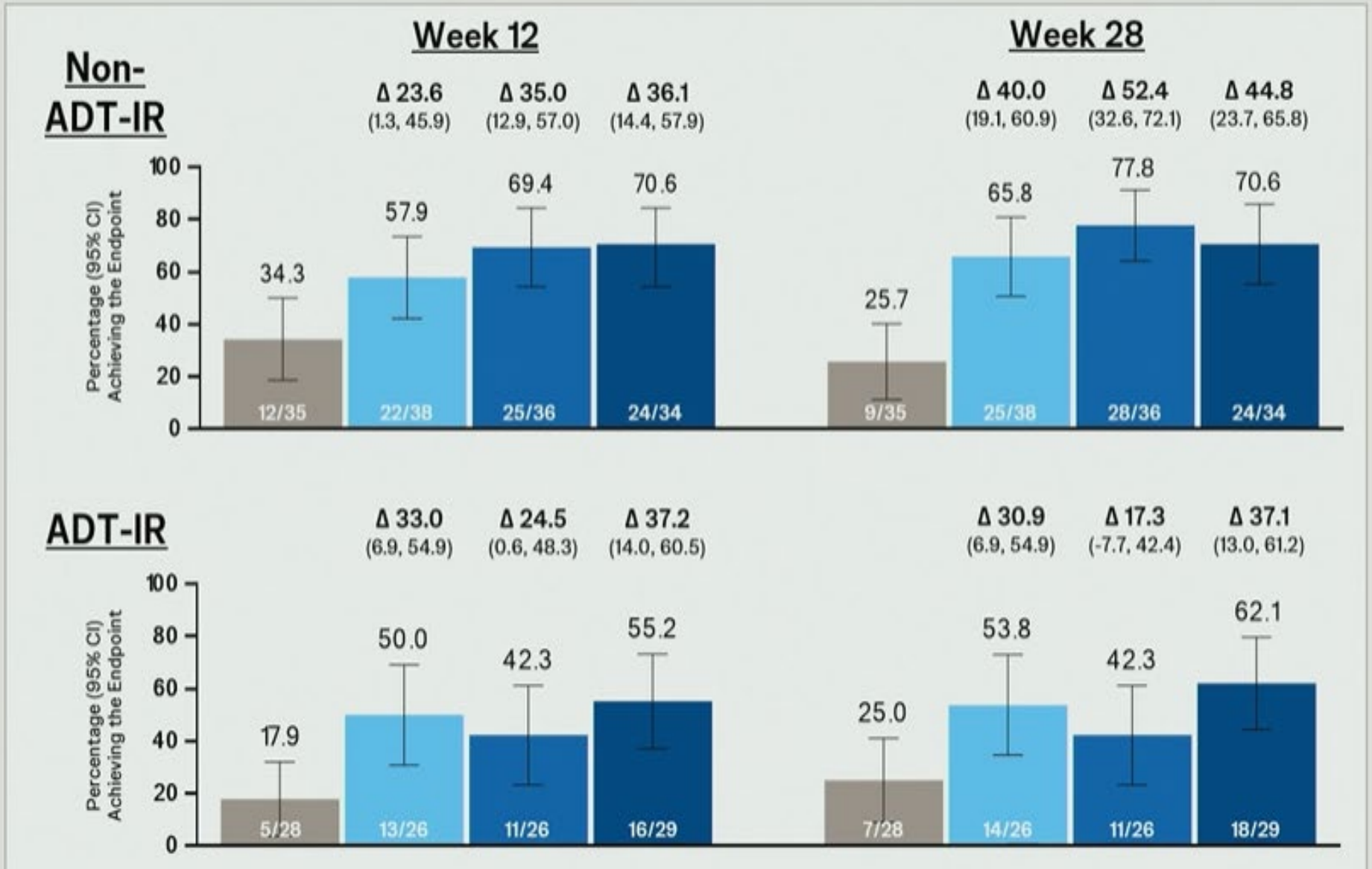
- **Key Endpoints** (Week 12)
  - Primary: clinical response
  - Secondary: clinical remission, symptomatic remission, endoscopic improvement, histologic-endoscopic mucosal improvement (HEMI)
  - Analyses were controlled for multiple comparisons (overall population only)
- Analyses in subpopulations by ADT-IR history were prespecified and exploratory (not controlled for multiple comparisons)
- Analyses at Week 28 were prespecified and exploratory (not controlled for multiple comparisons)

- Participants meeting inadequate response criteria at Week 16 received a treatment adjustment (placebo to icotrokinra 400 mg; sham adjustment for icotrokinra participants) and were considered non-responders at Week 28
- Participants with intercurrent events of ostomy or colectomy, prohibited changes in UC medication, or discontinuation of study intervention for any reason except those due to major disruptions (e.g., COVID-19–related reasons or regional crisis, excluding COVID-19 infection) were considered non-responders

Demographics and Baseline Disease Characteristics

	Placebo		Icotrokinra 100 mg qd		Icotrokinra 200 mg qd		Icotrokinra 400 mg qd	
	Non-ADT-IR N=35	ADT-IR N=28	Non-ADT-IR N=38	ADT-IR N=26	Non-ADT-IR N=36	ADT-IR N=26	Non-ADT-IR N=34	ADT-IR N=29
UC disease duration (years), mean (SD)	8.7 (9.4)	7.7 (6.3)	5.8 (5.8)	9.8 (5.8)	6.9 (7.6)	9.0 (7.5)	6.6 (6.5)	8.7 (8.6)
Extensive disease on screening endoscopy, n (%)	15 (42.9%)	12 (42.9%)	13 (34.2%)	10 (38.5%)	14 (38.9%)	9 (34.6%)	16 (47.1%)	13 (44.8%)
Modified Mayo score, mean (SD)	6.66 (1.41)	6.86 (0.97)	6.32 (1.21)	6.88 (1.37)	6.83 (1.18)	6.65 (1.65)	6.44 (1.48)	6.55 (1.33)
Mayo endoscopic subscore = 3 [severe], n (%)	20 (57.1%)	16 (57.1%)	21 (55.3%)	17 (65.4%)	22 (61.1%)	15 (57.7%)	19 (55.9%)	18 (62.1%)
Fecal calprotectin >250 mg/kg, n/N (%)	26/29 (89.7%)	20/23 (87.0%)	28/33 (84.8%)	19/21 (90.5%)	29/31 (93.5%)	20/22 (90.9%)	27/31 (87.1%)	25/27 (92.6%)
CRP >3 mg/L, n (%)	16 (45.7%)	14 (50.0%)	18 (47.4%)	13 (52.0%)	18 (50.0%)	20 (76.9%)	17 (51.5%)	16 (55.2%)
Exposed to ADT without IR, n (%)	3 (8.6%)	---	4 (10.5%)	---	5 (13.9%)	---	3 (8.8%)	---
Prior ADT-IR, n (%)								
1 ADT class	---	22 (78.6%)	---	19 (73.1%)	---	21 (80.8%)	---	15 (51.7%)
2 ADT classes	---	6 (21.4%)	---	6 (23.1%)	---	5 (19.2%)	---	14 (48.3%)
>2 ADT classes	---	0	---	1 (3.8%)	---	0	---	0

Clinical Response (Primary Endpoint at Week 12)



Placebo

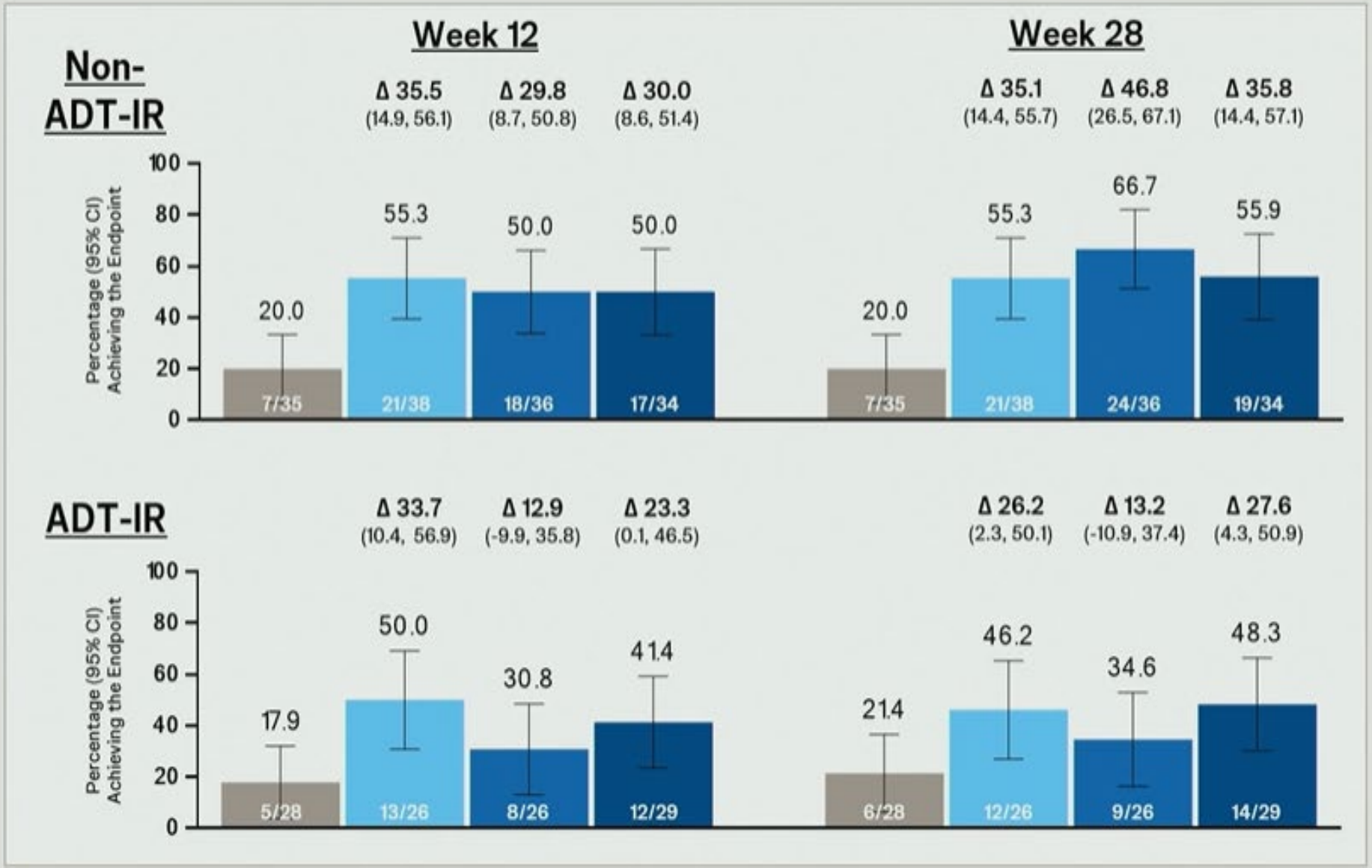
Icotrokinra 100 mg qd

Icotrokinra 200 mg qd

Icotrokinra 400 mg qd

Clinical response: a decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1

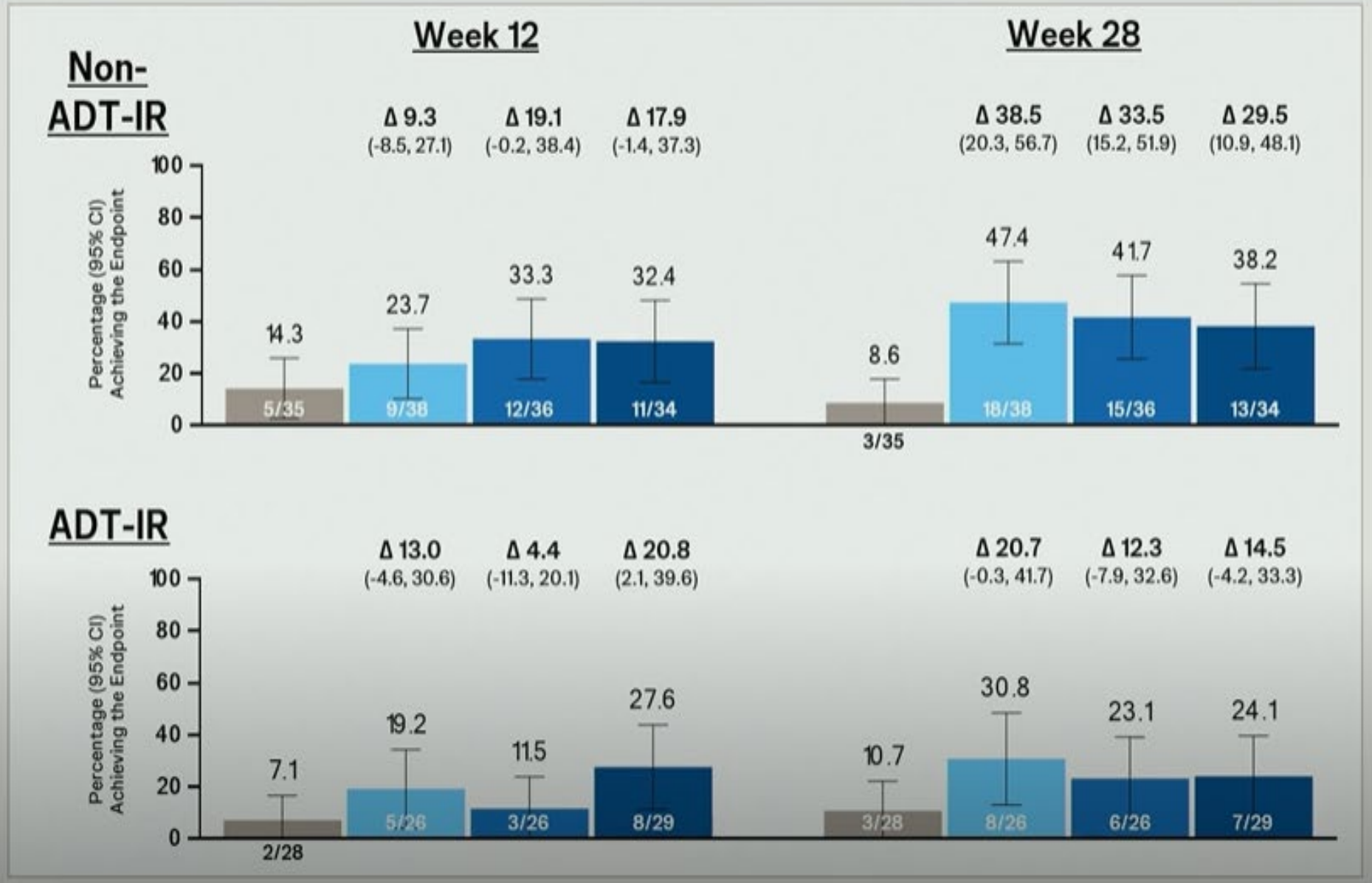
Symptomatic Remission



- Placebo
- Icotrokinra 100 mg qd
- Icotrokinra 200 mg qd
- Icotrokinra 400 mg qd

Symptomatic remission: stool frequency subscore of 0 or 1 and rectal bleeding subscore of 0

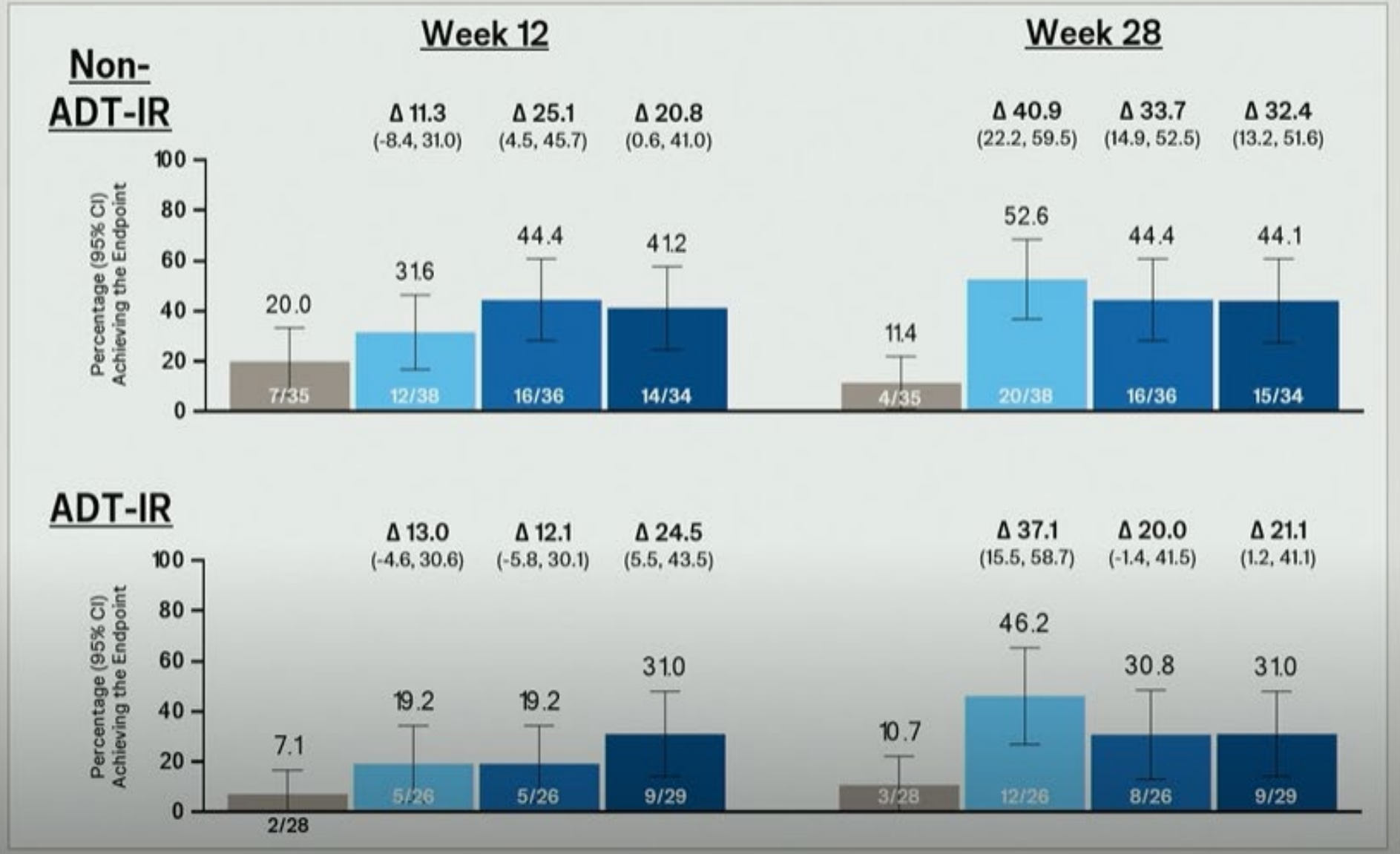
Clinical Remission



- Placebo
- Icotrokinra 100 mg qd
- Icotrokinra 200 mg qd
- Icotrokinra 400 mg qd

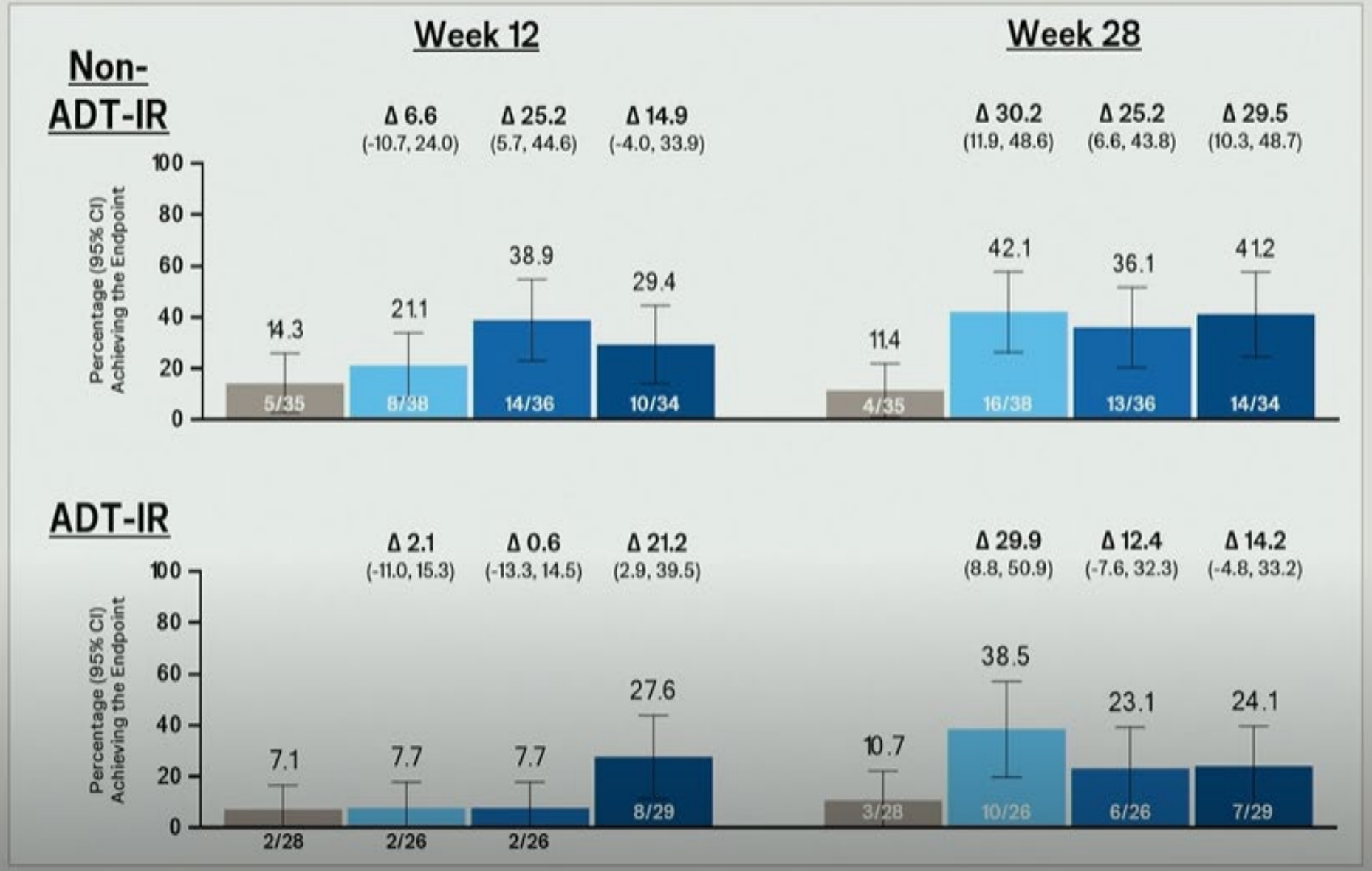
Clinical remission: stool frequency subscore of 0 or 1, rectal bleeding subscore of 0, and Mayo endoscopic subscore of 0 or 1

Endoscopic Improvement



Endoscopic improvement: Mayo endoscopic subscore of 0 or 1

Histologic-Endoscopic Mucosal Improvement (HEMI)



Histologic-endoscopic mucosal improvement: histologic remission (absence of neutrophils from the mucosa in both lamina propria and epithelium, no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system) AND endoscopic improvement

Conclusions

- Once-daily icotrokinra demonstrated efficacy in participants with moderately to severely active ulcerative colitis at Week 12 and Week 28, irrespective of prior ADT history
- Within the active treatment groups clinical and endoscopic outcomes (clinical response, symptomatic remission, clinical remission, endoscopic improvement, and HEMI) were generally maintained or improved in both subpopulations from Week 12 to Week 28
- Proportions of participants who met these endpoints were greater in the Non-ADT-IR subpopulation compared with the ADT-IR subpopulation

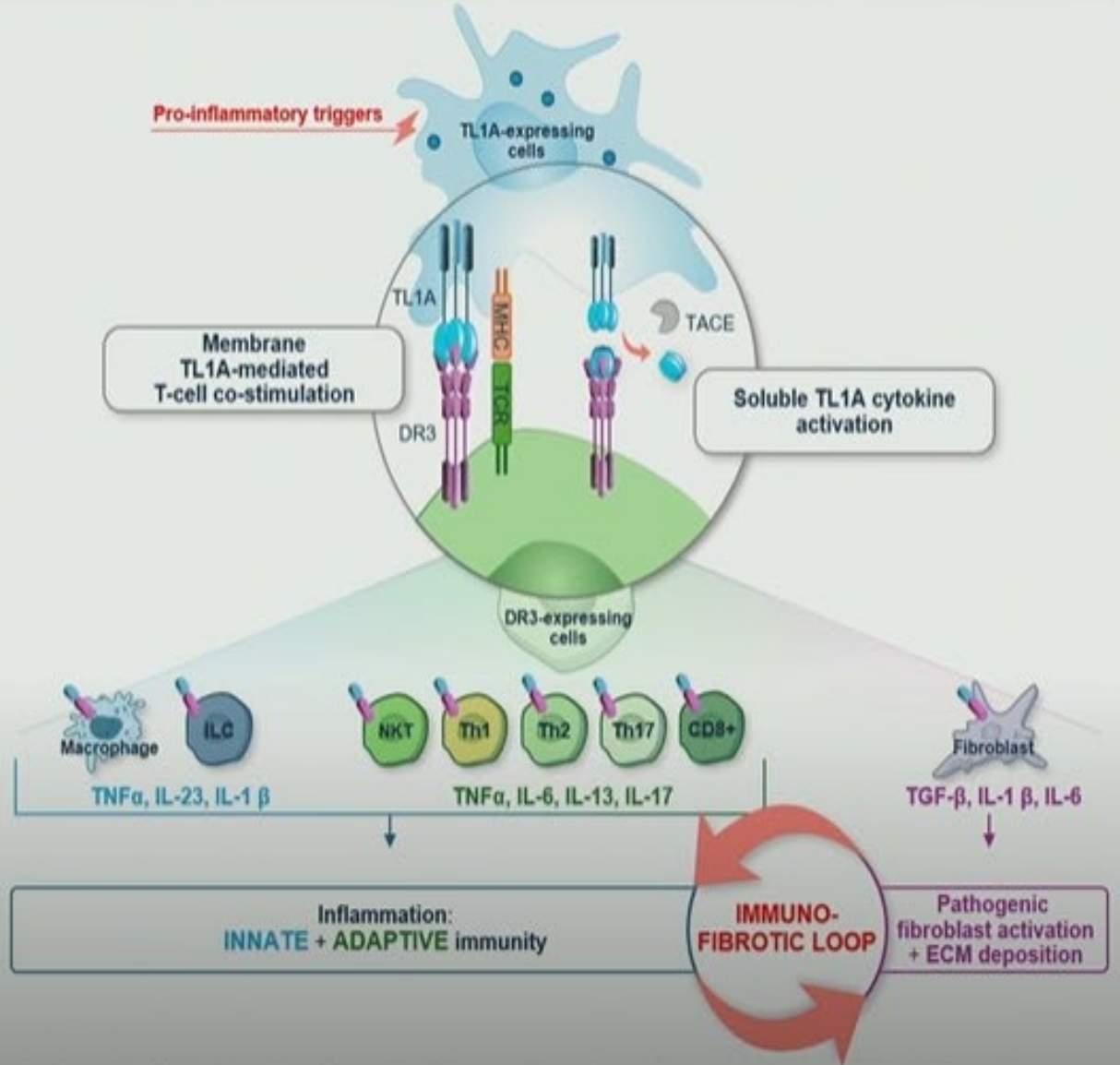
The Anti-TL1A Monoclonal Antibody Tulisokibart Inhibits Inflammatory and Fibrosis Pathways: Results From a Phase 2 Ulcerative Colitis Study

[1]Florian Rieder, [2]Richard Wnek, [2]Shiuli Agarwal, [2]Heather Llewellyn, [2]John Kang, [2]Peining Tao, [2]Wen Zhou, [2]Justin Klaff, [2]In Sock Jang, [2]Ernesto J. Muñoz-Elias, [3]Jean-Frederic Colombel

[1]Department of Gastroenterology, Hepatology and Nutrition, Digestive Diseases Institute, Cleveland Clinic Foundation, Cleveland, Ohio, USA; [2]Merck & Co., Inc., Rahway, New Jersey, USA; [3]Department of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Tulisokibart Inhibits TL1A, a Central Amplifier of Inflammatory and Fibrotic Pathways in IBD Pathogenesis

- Preclinical and translational data supported targeting TL1A for the treatment of IBD[1-7]
- Tulisokibart is a humanized monoclonal antibody that binds membrane and soluble TL1A and inhibits signaling through DR3 leading to reduction of inflammatory and fibrosis pathways[8,9,10]
- Phase 2 ARTEMIS-UC in moderately to severely active ulcerative colitis: tulisokibart induction treatment significantly improved clinical, endoscopic, and patient-reported outcomes vs placebo at week 12[11]; responses were maintained through week 50[12]



1. Bamias G, et al. *Gut*. 2025;74(4):652-668. 2. Lusetti F, et al. *Expert Rev Gastroenterol Hepatol*. 2025;19(1):15-25. 3. Sellheyer V, et al. *BioDrugs*. 2025;39(2):171-193. 4. Siakavellas SI, et al. *Inflamm Bowel Dis*. 2015;21(10):2441-2452. 5. Bamias G, et al.

ARTEMIS-UC Study Design

A phase 2, multicenter, double-blind study of tulisokibart in participants with moderately to severely active UC

Double-Blind Induction Period[a]

Cohort 1: Demonstrate Efficacy of Tulisokibart

- Tulisokibart, N=68[b]
- Placebo, N=67[b]

Day 1	Week 2	Week 6	Week 10	Week 12
1000 mg IV	500 mg IV	500 mg IV	500 mg IV	Endoscopy

Cohort 2: Dx+ only

- Tulisokibart, N=22[b]
- Placebo, N=21[b]

Day 1	Week 2	Week 6	Week 10	Week 12
1000 mg IV	500 mg IV	500 mg IV	500 mg IV	Endoscopy

Tulisokibart Clinical Responders[c]
Randomization stratified by Dx status (+/-)

Open-Label Extension

- Tulisokibart 100 mg IV Q4W (cohort 1 N=22, cohort 2 N=7)
- Tulisokibart 250 mg IV Q4W (cohort 1 N=25, cohort 2 N=7)

Inclusion Criteria:

- Moderately to severely active UC
- No/insufficient response and/or intolerance to conventional or advanced therapy
- Additional criteria for Cohort 2 — must be Dx+

Cohort 1 Stratification Factors:

- Dx status (+/-)
- Prior biologic (yes/no)

Cohort 2 Stratification Factor:

- Prior biologic (yes/no)

Primary Endpoint

- Clinical remission at week 12 per modified Mayo Score

Secondary Endpoints evaluated at Week 12 (α-controlled)

- Endoscopic improvement
- Clinical response
- Symptomatic remission
- Mucosal healing
- Histologic improvement
- Histologic-endoscopic mucosal improvement
- IBDQ response

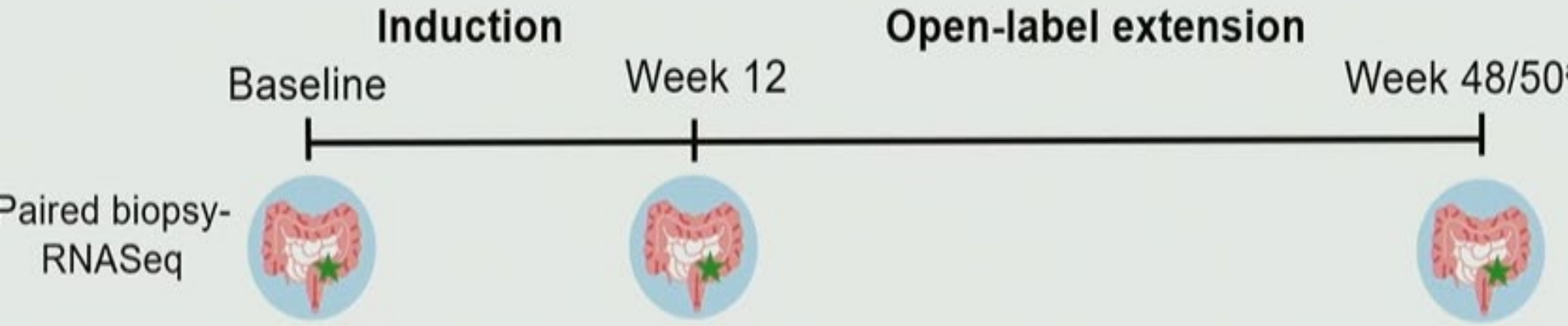
Objectives

This post hoc analysis of ARTEMIS-UC combined cohorts 1 and 2 used serial biopsy RNA sequencing data to:

- Investigate the effects of tulisokibart on mucosal immuno-inflammatory, TL1A-related, and fibroblast/extracellular matrix remodeling-related gene signatures

- Explore the association of these pharmacodynamic readouts with efficacy at weeks 12 and 50

Gene Expression Analysis of Mucosal Inflammatory and Fibrosis Pathways



Biomarker Samples

(Cohorts 1+2):

Week 12	N
Placebo	73
Tulisokibart	77

Week 50	N
Tulisokibart 100 mg	13
Tulisokibart 250 mg	25

Mucosal transcriptomic signatures analyzed by GSVA[b,1]

Inflammatory pathways

T-helper 1
Th1 biology

T-helper 17
Th17 biology

Inflammatory monocytes
Produce IL23, IL1b, TNF

TL1A pathway

TL1A Th1
TL1A-induced genes in Th1 cells

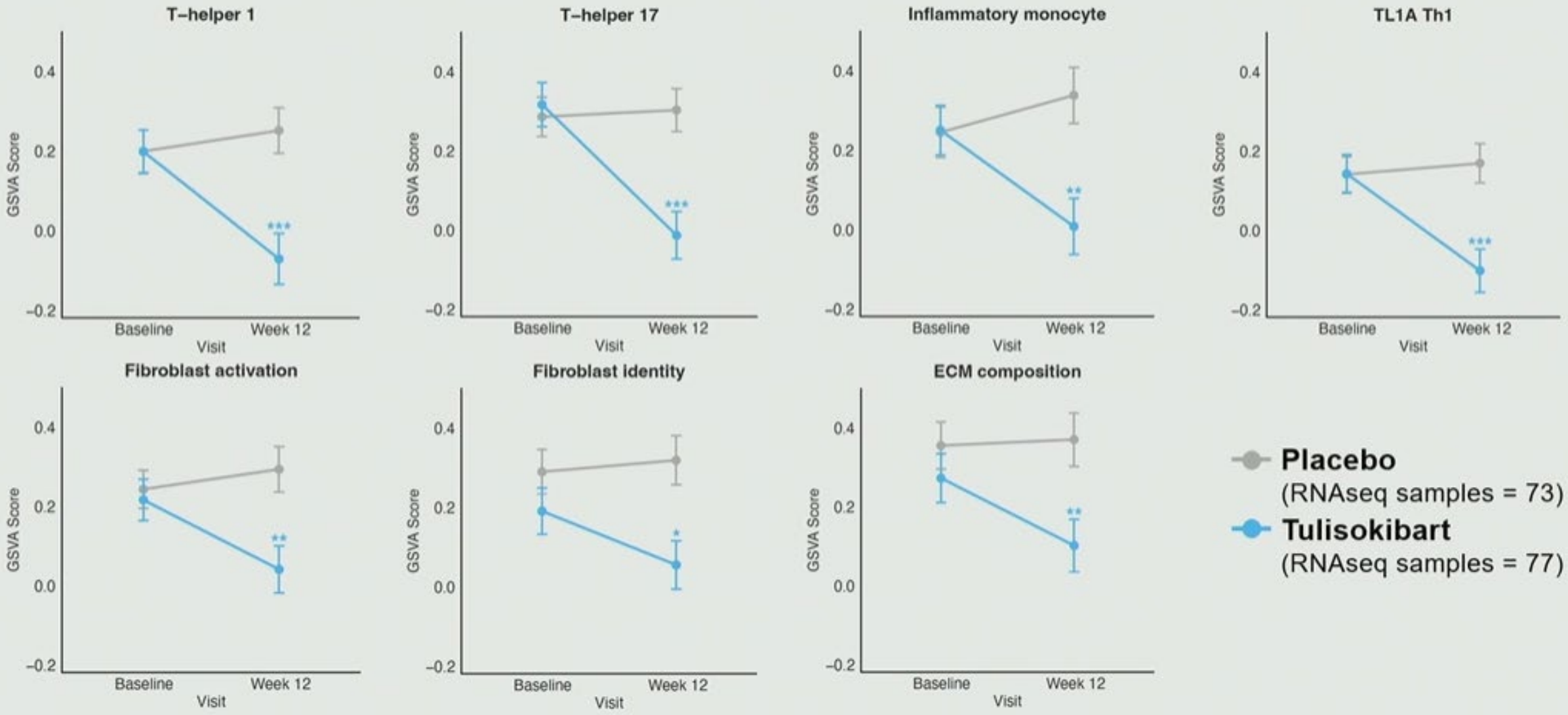
Profibrotic cell types

Fibroblast activation
IBD-activated fibroblasts

Fibroblast identity
Creeping-fat fibroblast

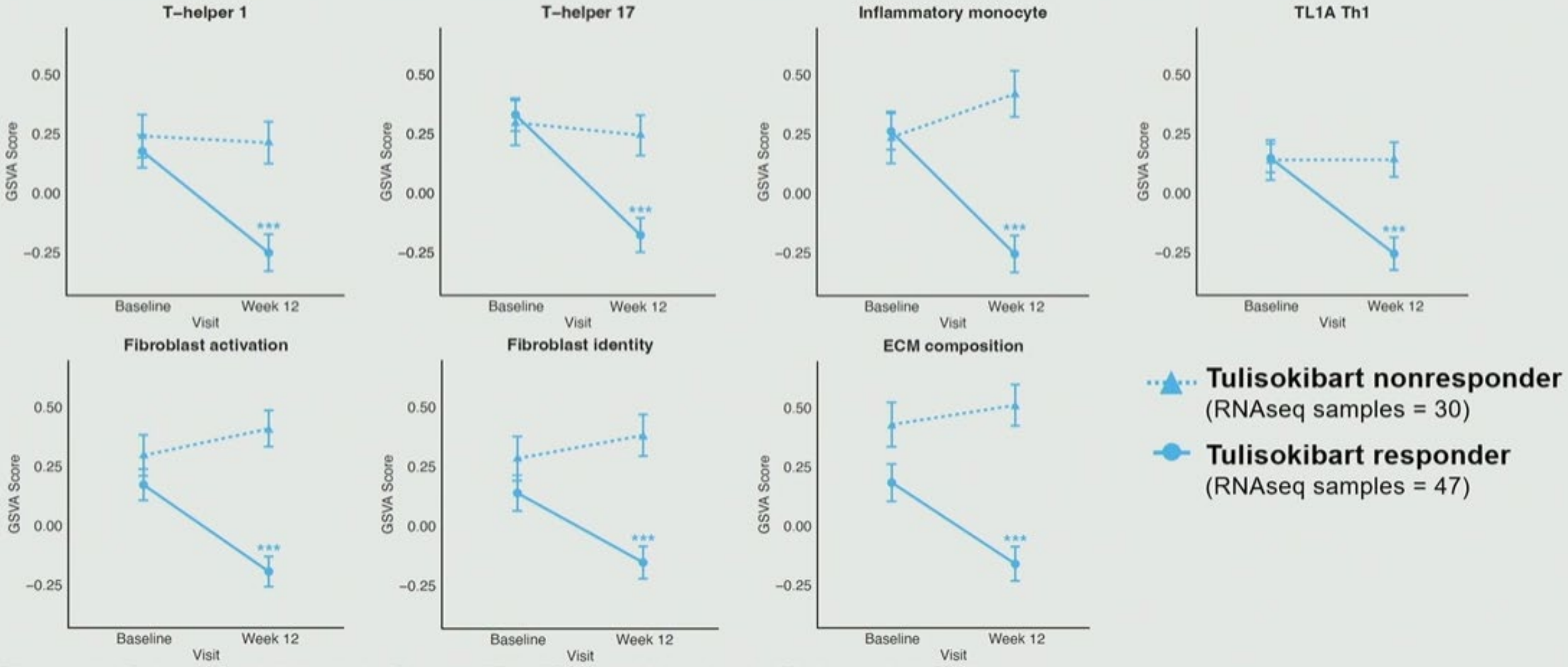
ECM composition
ECM[c] fibroblast

Tulisokibart Decreased Inflammation and Fibrosis Pathways at Week 12



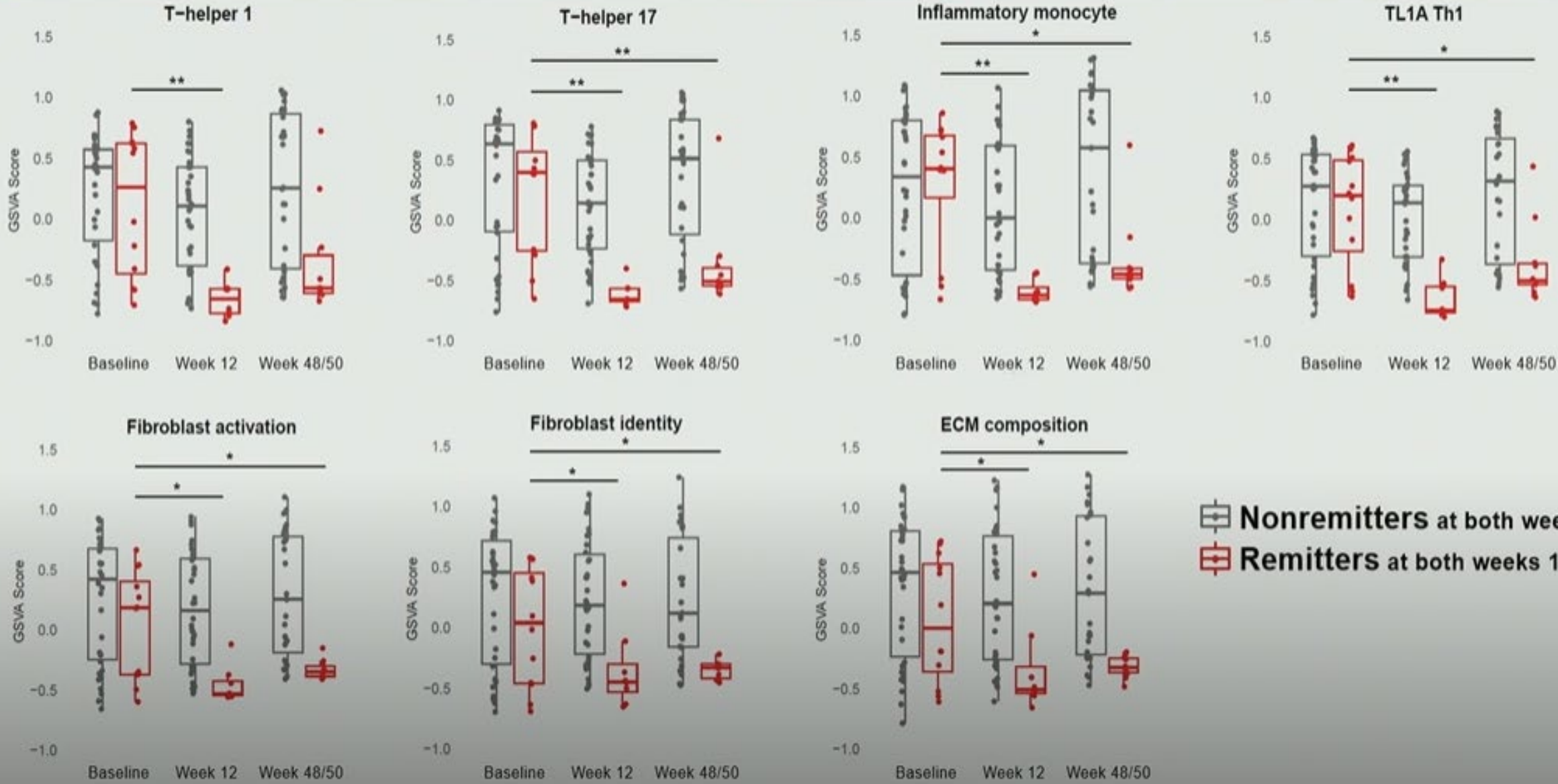
P values are for week 12 versus baseline; one-sided significance levels: **P* < 0.05; ** *P* < 0.01; *** *P* < 0.001. Paired analysis.
ECM, extracellular matrix; GSVA, gene set variation analysis; RNAseq, RNA sequencing; Th1, T-helper 1.

Tulisokibart Markedly Decreased Inflammation and Fibrosis Pathways at Week 12 in Clinical Responders[a]

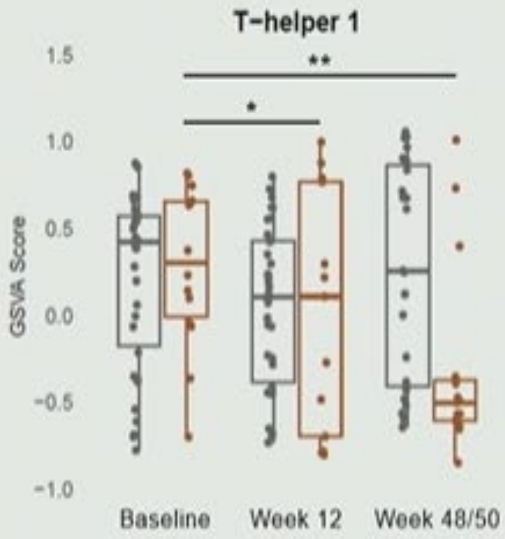


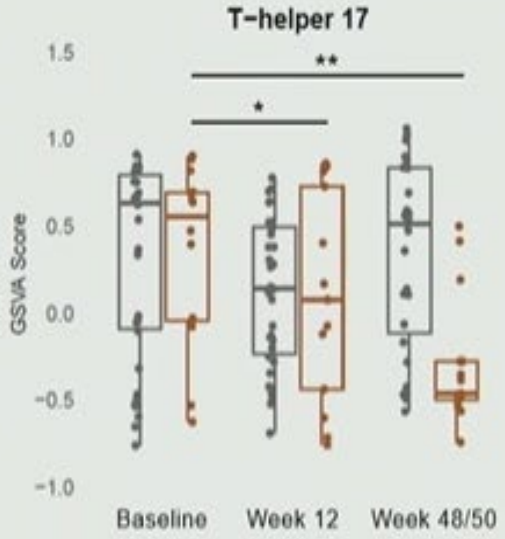
[a]Clinical responder defined per mMS as reduction from baseline ≥2 points and ≥30% in mMS, accompanied by a reduction ≥1 in RB subscore or absolute RB subscore ≤1.
P values are for week 12 versus baseline; one-sided significance levels: **P* < 0.05; ** *P* < 0.01; *** *P* < 0.001. Paired analysis.
ECM, extracellular matrix; GSVA, gene set variation analysis; mMS, 3-component modified Mayo Score; RB, rectal bleeding; RNAseq, RNA sequencing; Th1, T-helper 1.

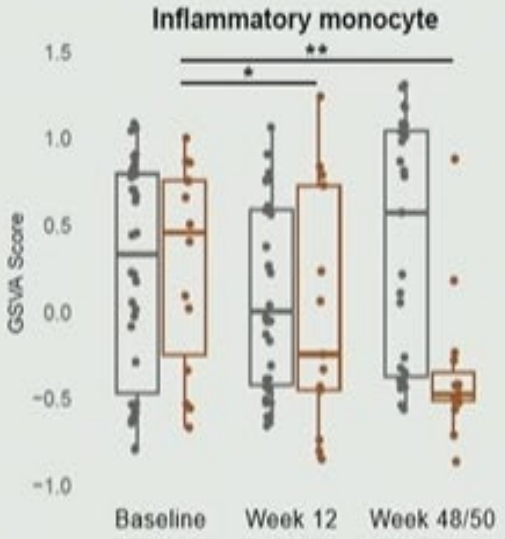
Patients Achieving Sustained Clinical Remission[a] Showed Suppression of Inflammation and Fibrosis Pathways Through Week 50

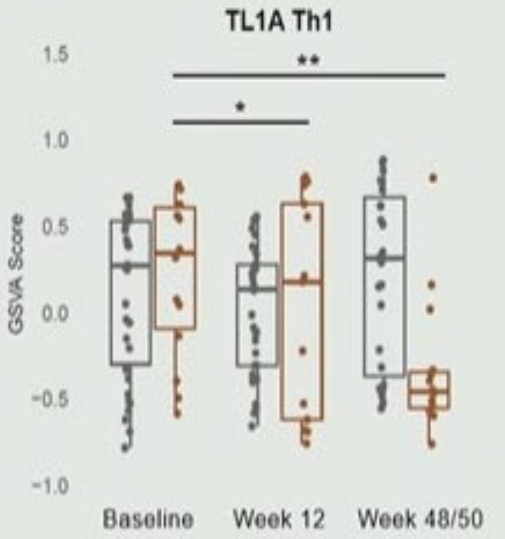


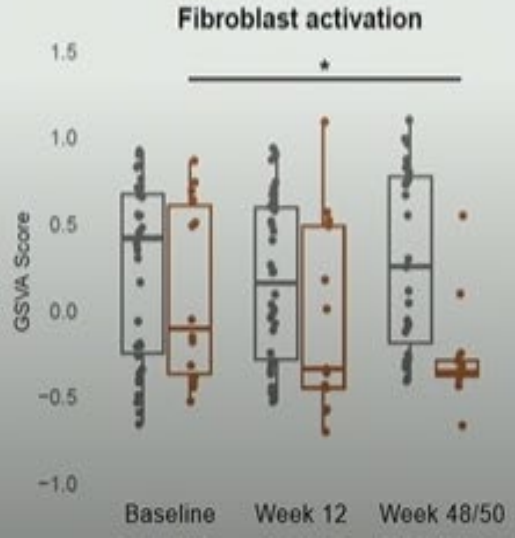
Week 12 Nonremitters Who Achieved Remission[a] by Week 50 Showed Greater Suppression in Inflammatory and Fibrosis Pathways

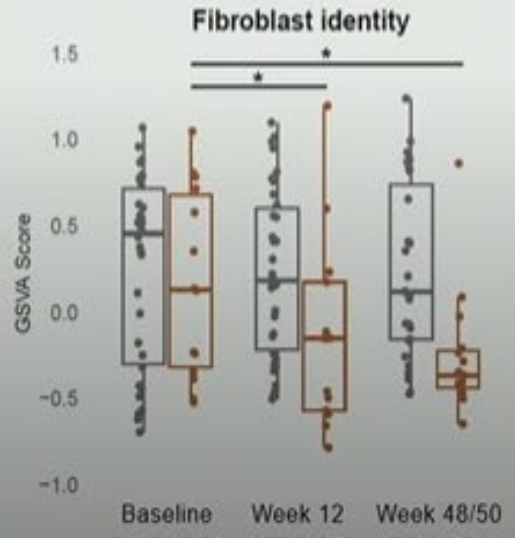


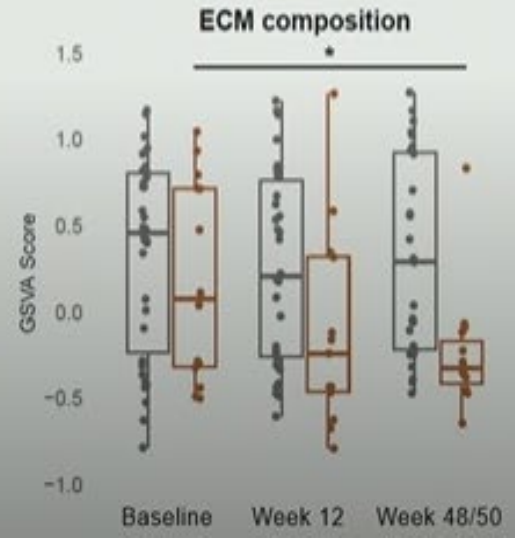












Nonremitters at both weeks 12 and 50

Nonremitters (week 12) → **Remitters** (week 50)

Conclusions

- Molecular pathways modulated by tulisokibart treatment in intestinal mucosal biopsies of UC patients support a pleiotropic role for TL1A dysregulation in driving inflammatory and fibrotic pathways
  - Tulisokibart suppressed Th1, Th17, TL1A-Th1, and fibrosis gene expression pathways
  - Tulisokibart also suppressed gene expression pathways associated with inflammatory monocytes, which are known to produce TNFα, IL-1b, and IL-23
- Tulisokibart-mediated suppression of inflammatory and fibrosis pathways was more pronounced in responders than nonresponders, was achieved by week 12, and was sustained through week 50
- These exploratory biomarker findings in a limited number of patients will be confirmed in larger phase 3 studies

Efficacy of Anti-TNF Agents for the Treatment of Anoperineal Fistulas Without Luminal Crohn's Disease: A Multicenter Cohort Study.

Abla Idrissi[1], Nadia Fathallath[2], Romain Altwegg[3], Guillaume Savoye[1], Vincent de Parades[2], Maria Nachury[4], Aurélien Amiot[2], Laurent Abramowitz[2], Ludovic Caillo[5], Cléa Rouillon[6], David Laharie[7], Mathurin Fumery[8], **Nicolas Richard**[1].

[1] Rouen, France; [2] Paris, France. [3] Montpellier, France. [4] Lille, France.[5] Nîmes, France.[6] Caen, France.[7] Bordeaux, France.[8] Amiens, France

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BACKGROUND

Perianal fistulas

Cryptoglandular Fistulas

Associated with luminal CD

Isolated Perianal CD

TOpClass consensus definition[1]:

Epithelioid granuloma in fistula

or

Anorectal stricturing or inflammatory fissure(s) evident on examination

or

Score ≥ 5

3 points	*1 point*
>1 internal opening, or >1 fistula, or organ fistulation	Potential EIM
-	-
Family history of IBD	Suspected oral CD
-	-
Confirmed classic EIM	Suspected genital CD
	-
	Coexistent HS
	-
	Minor associated perianal disease
	-
	Recurrence following fistula repair

BACKGROUND

Anti-TNF therapy for perianal fistulas **without** luminal CD:

- Reasoning by analogy with luminal CD
- Combined medical–surgical strategy

Limited literature:

- 3 clinical series[1] with fewer than 40 patients, plus case reports
- Remission rates of 20% to 48%
- Marked heterogeneity

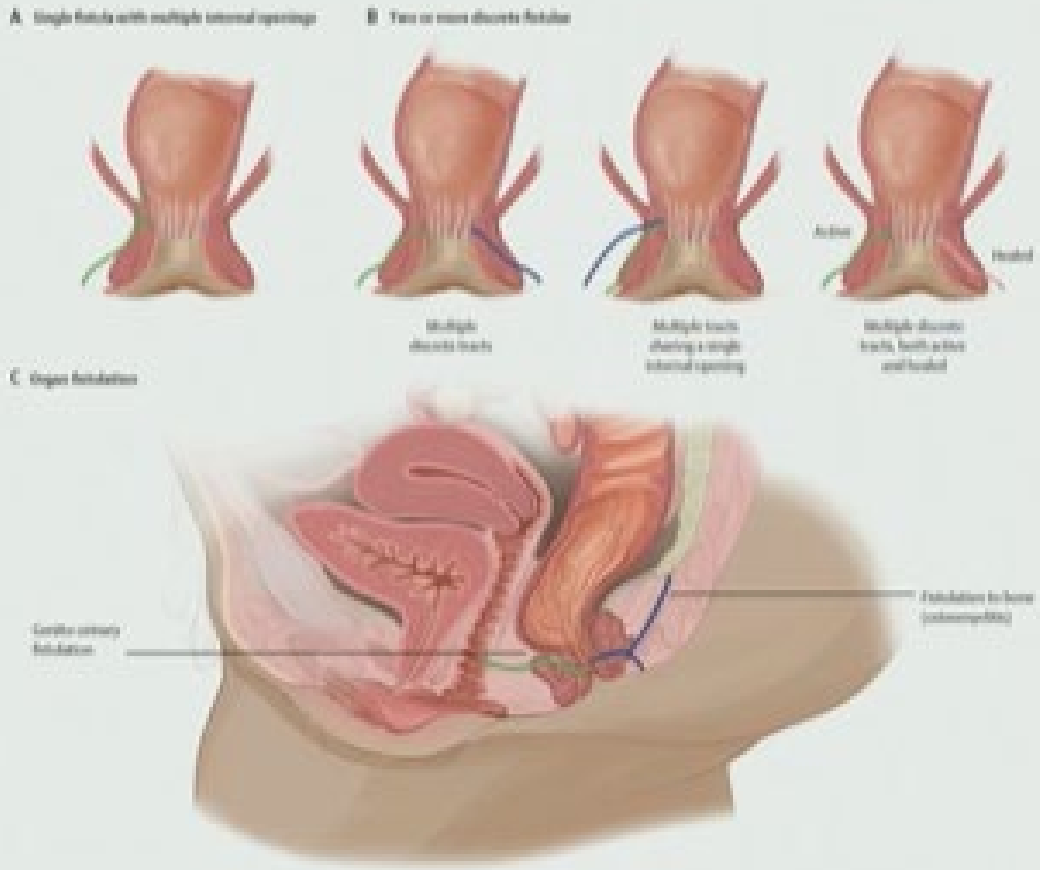
PATIENTS AND METHODS

- Retrospective multicenter observational study: **10 expert centers**
- Consecutive patients (>18 years) with a **recurrent perianal fistula without luminal CD*** treated with **anti-TNF** therapy (infliximab or adalimumab)
- Minimal follow-up of 3 months

DATA COLLECTION AND TREATMENT

Data collection by reviewing medical charts:

- Demographics (age, sex) and tabacco use
- Perianal fistula characteristics: Park's classification[1], criteria for ipCD and advanced fistulas according to TOpClass consensus[2]



CD: Crohn's disease.

[1] Parks AG *et al.*, Br J Surg, 1976; [2] Hanna LN et al. Lancet Gastroenterol Hepatol. 2025.

DATA COLLECTION AND TREATMENT

Data collection by reviewing medical charts:

- Demographics (age, sex) and tabacco use
- Perianal fistula characteristics: Park's classification[1], criteria for ipCD and advanced fistulas according to TopClass consensus[2]
- Surgical history
- After anti-TNF initiation : clinical and MRI follow-up, need for surgery, antibiotics, adverse events.

Anti-TNF treatment:

- Standard induction
- Maintenance regimen at the discretion of the physician

OUTCOMES

Primary outcome:

- **Clinical remission** 12 months after initiation of anti-TNF

Secondary outcomes:

- **Clinical response and remission** at M3, M12, and M36
- **Radiological response and remission** at M12, and M36
- **Luminal CD onset**
- **Safety**

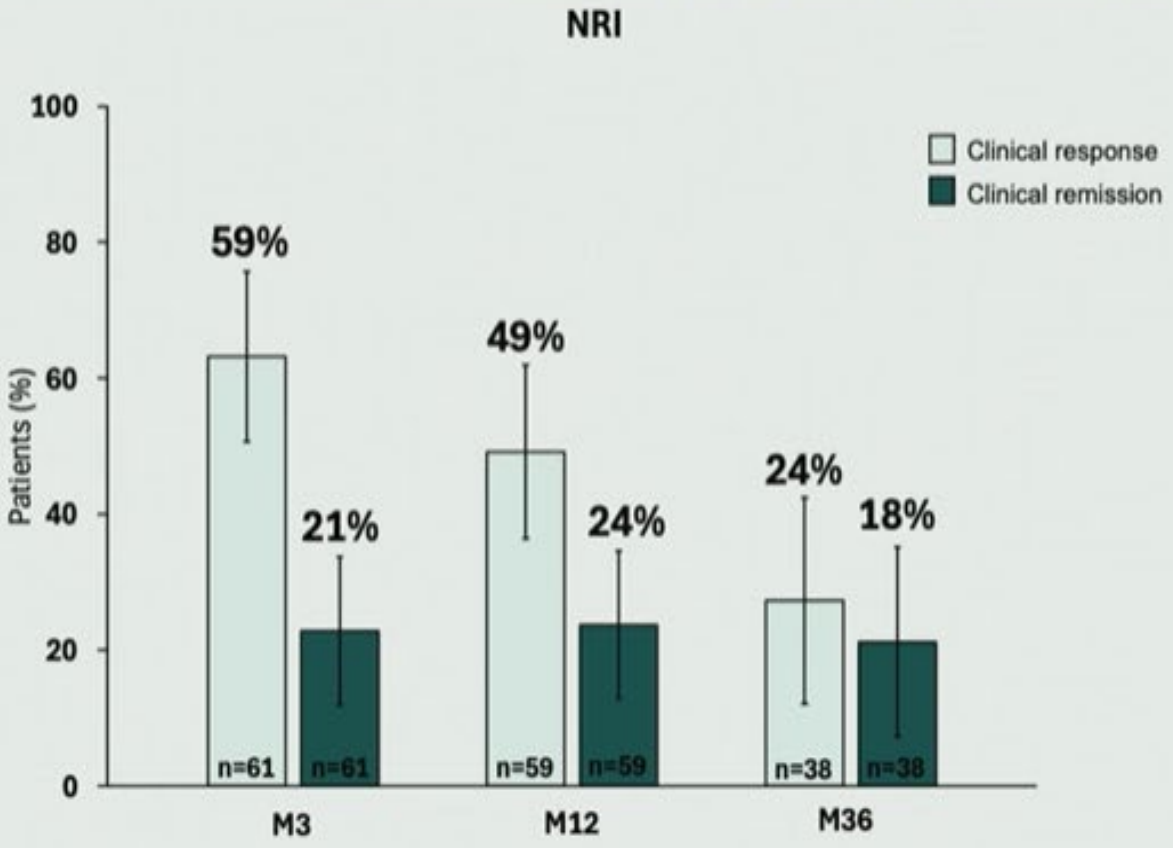
CD: Crohn's disease; M3-12-36: months 3-12-36.

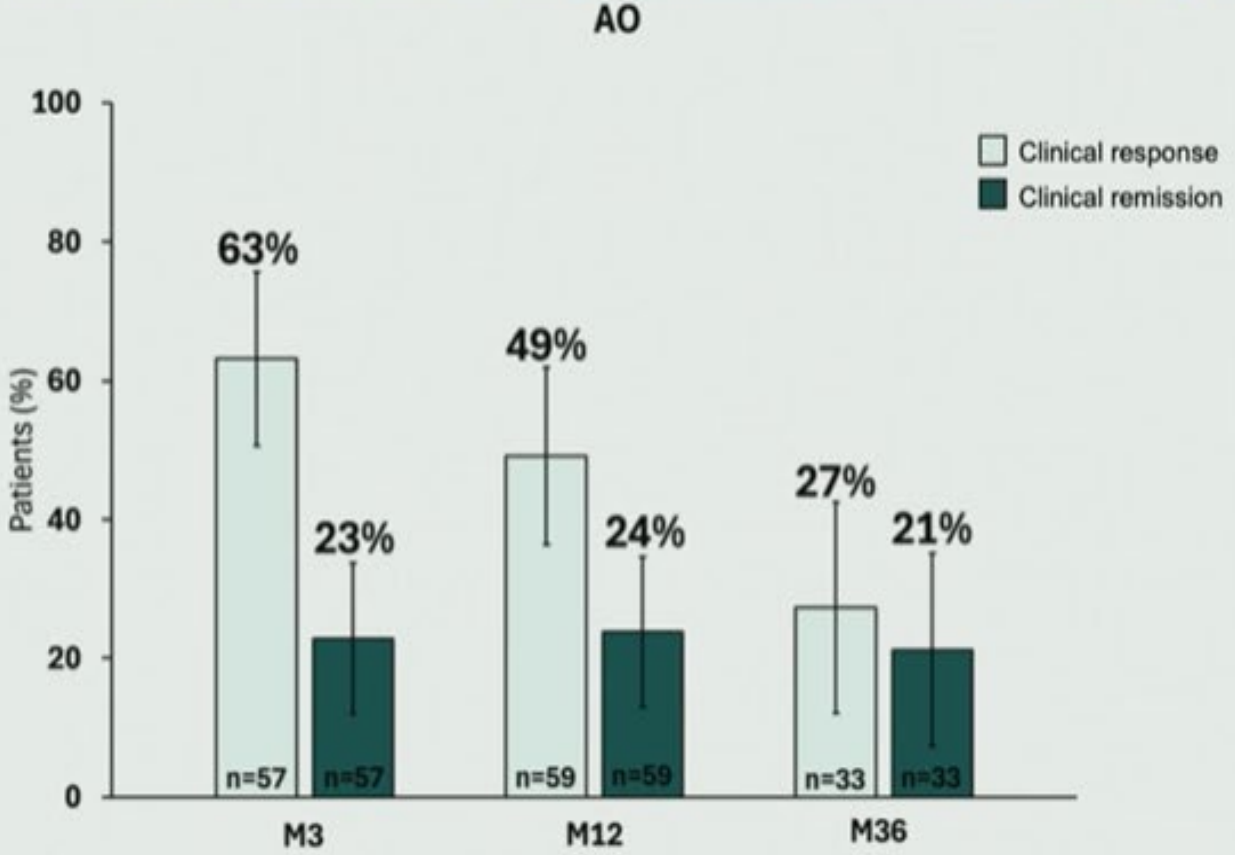
RESULTS

- 61 patients
- Median age : 37 yr [IQR29-44]
- 56% male
- Median duration since fistula onset: 16 months [7-26]
- Median number of prior perianal surgeries: 3 [IQR:2-4]
- Diagnostic ipCD* : 43%
- Complex fistula : 93%

* according to TopClass criteria
ipCD: isolated perianal Crohn's disease; IQR: interquartile range; yr: year.

RESULTS

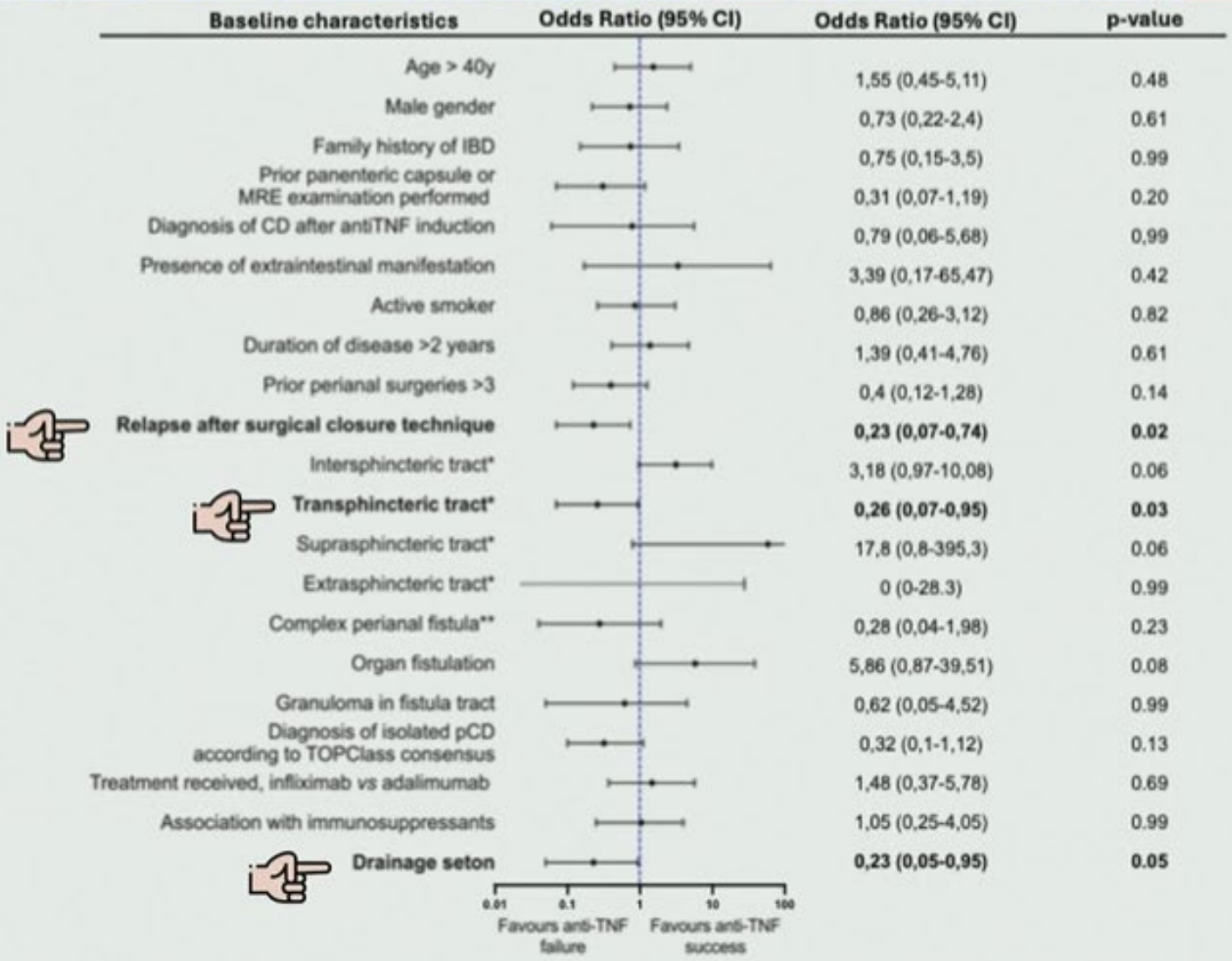




Clinical response = Improvement in clinical signs related to the fistula, as assessed by the clinician, in the absence of antibiotic therapy or any intervening surgical treatment.

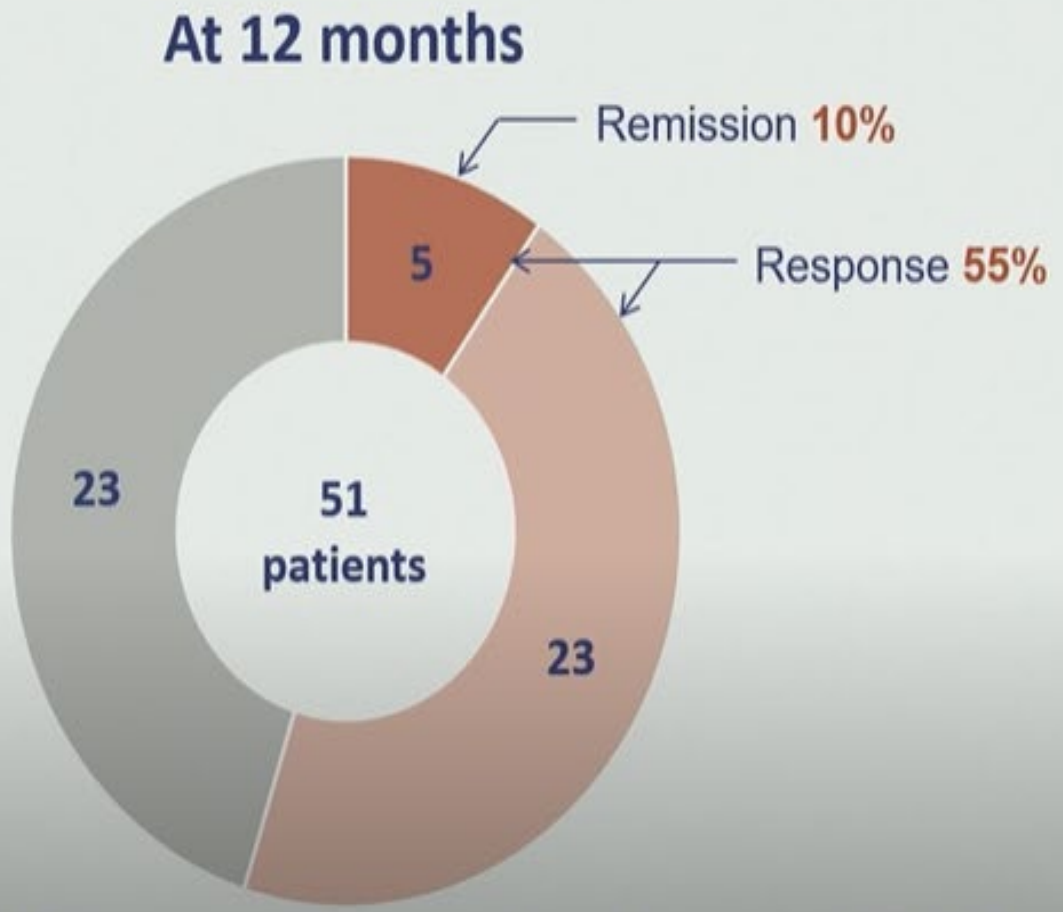
Clinical remission = Absence of discharge, in the absence of antibiotic therapy or any intervening surgical treatment.

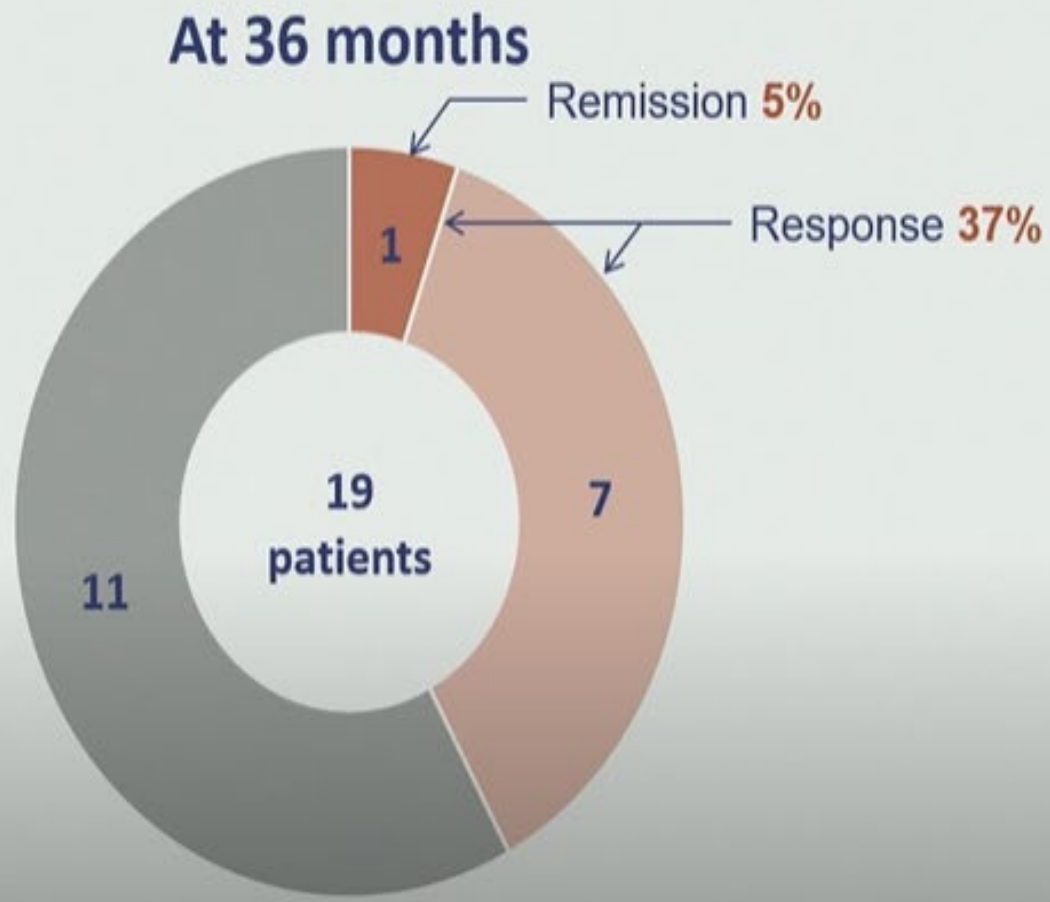
PREDICTORS OF CLINICAL REMISSION AT M12



M12: month 12.

RADIOLOGICAL OUTCOMES





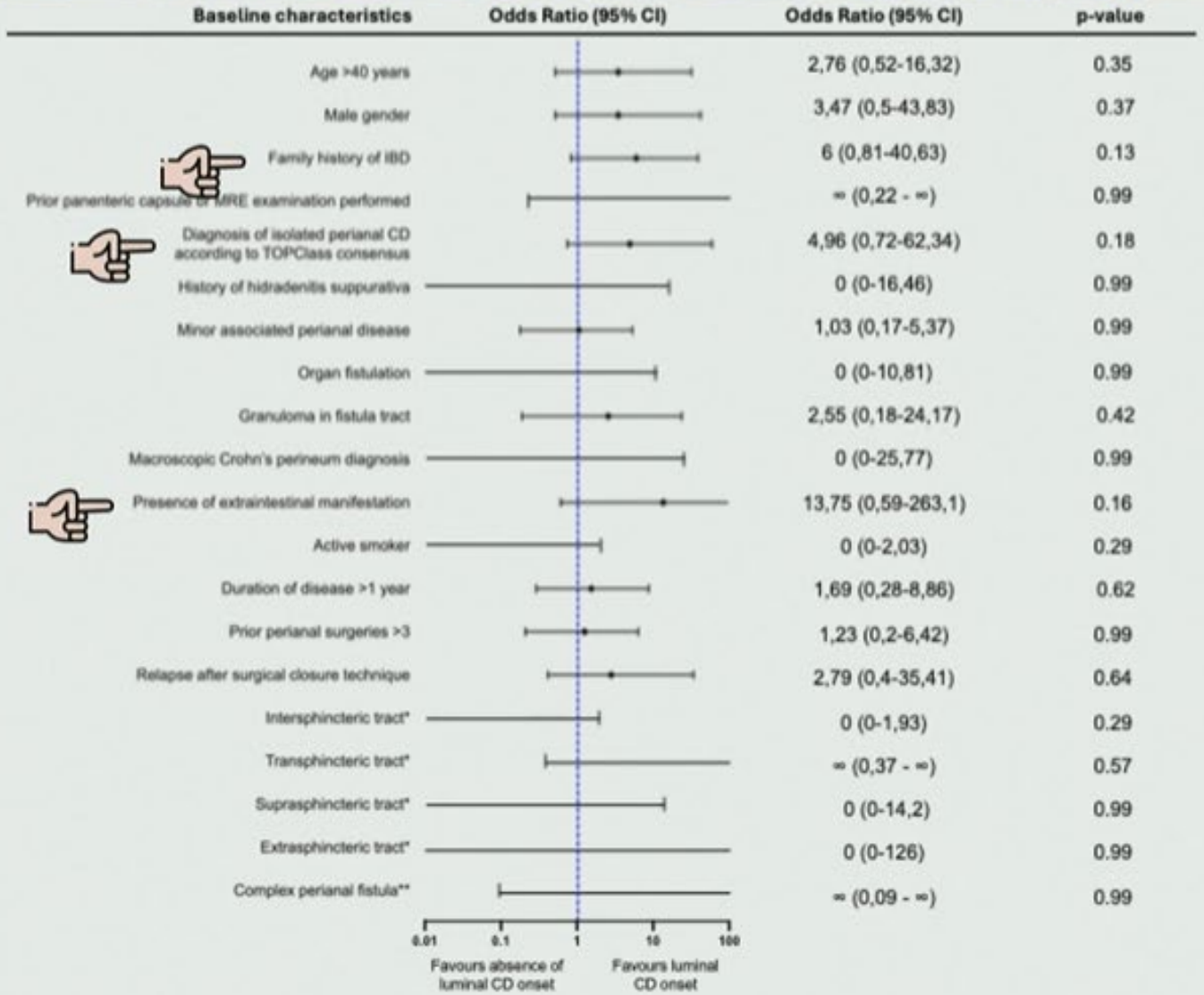
Radiological response = Absence of a collection on MRI > 3 mm and decrease in T2 or post-contrast T1 hyperintensity.

Radiological remission = Absence of a collection > 3 mm and absence of hyperintense fistulous tract on T2 or post-

CLINICAL EVOLUTION

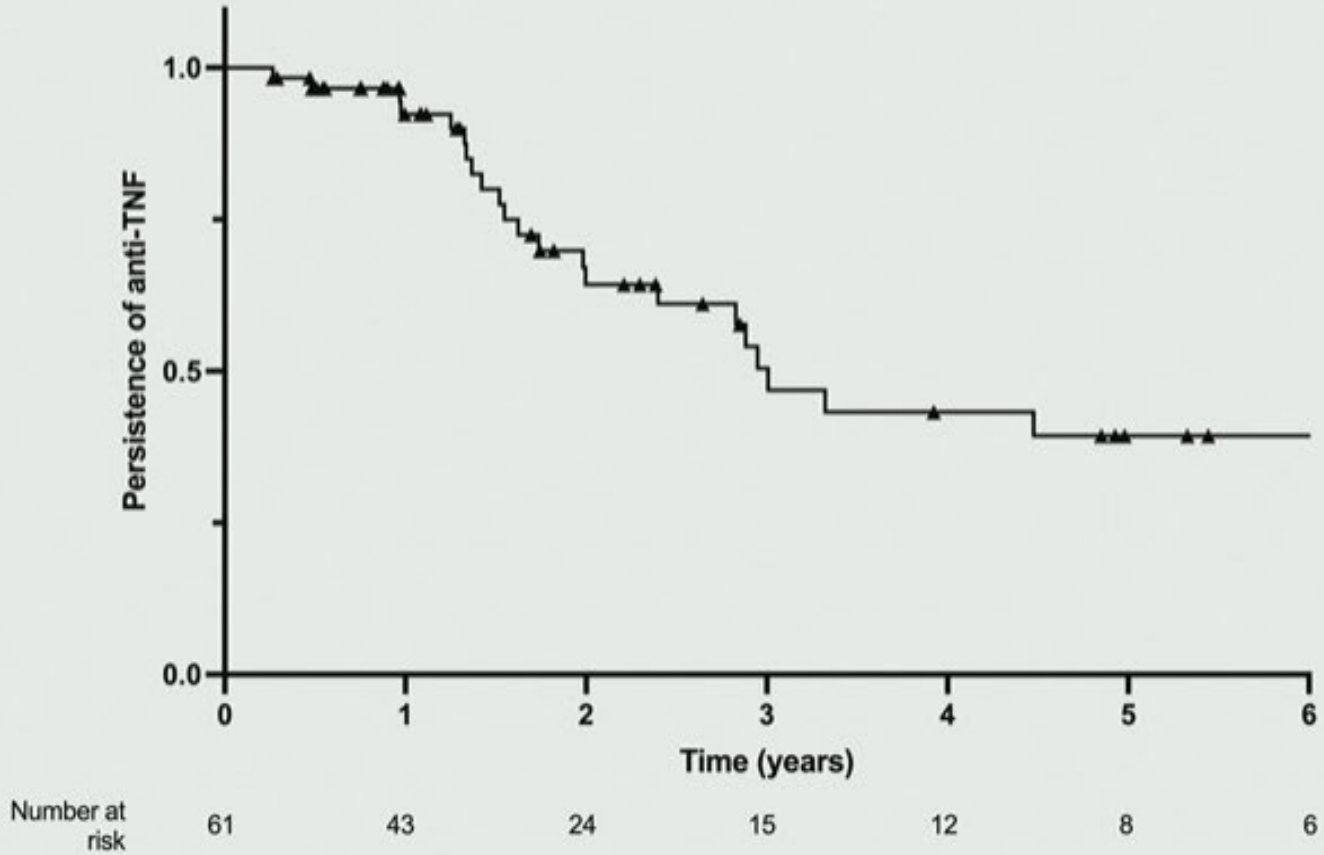
- **5 patients** (8%) developped **luminal Crohn's disease** after a median delay of **17**[12–23] **months** after anti-TNF initiation
- **1 patient** developped **disseminated tuberculosis** 5 months after anti-TNF initiation
- **32 patients (53%)** had **perianal drainage** during follow-up

PREDICTORS OF LUMINAL CD



CD: Crohn's disease.

TREATMENT PERSISTANCE AND SAFETY



- **22 patients** stopped anti-TNF (13 failures, 5 AE, 4 other)

- **6 AE:**
  - Psoriasis (2)
  - Allergy (1)
  - Tuberculosis (1)
  - Melanoma (1)
  - Collected sinusitis (1)

AE: adverse event.

DISCUSSION

Limitations

- Retrospective cohort without a control group
- No data on drug trough levels and calprotectin levels
- Heterogenous clinical management

Strengths

- Largest cohort on this topic
- First cohort to integrate the TOpClass definition
- Long follow-up period
- Objective radiological data

DISCUSSION

- **Remission rate consistant** with existing literature[1].
- **8% of patients** were subsequently diagnosed with **luminal Crohn's disease**.

CONCLUSION

- Anti-TNF therapy achieved clinical remission in **24% of patients** with perianal fistula without luminal Crohn's disease, at one year.

- In this cohort, **TOpClass criteria of isolated perianal Crohn's disease** were **not predictors** of anti-TNF success.

Sustained Symptomatic Relief and Disease Clearance Through 50 Weeks of Treatment With Tulisokibart in Participants With Moderately to Severely Active Ulcerative Colitis in the Phase 2 ARTEMIS-UC Study

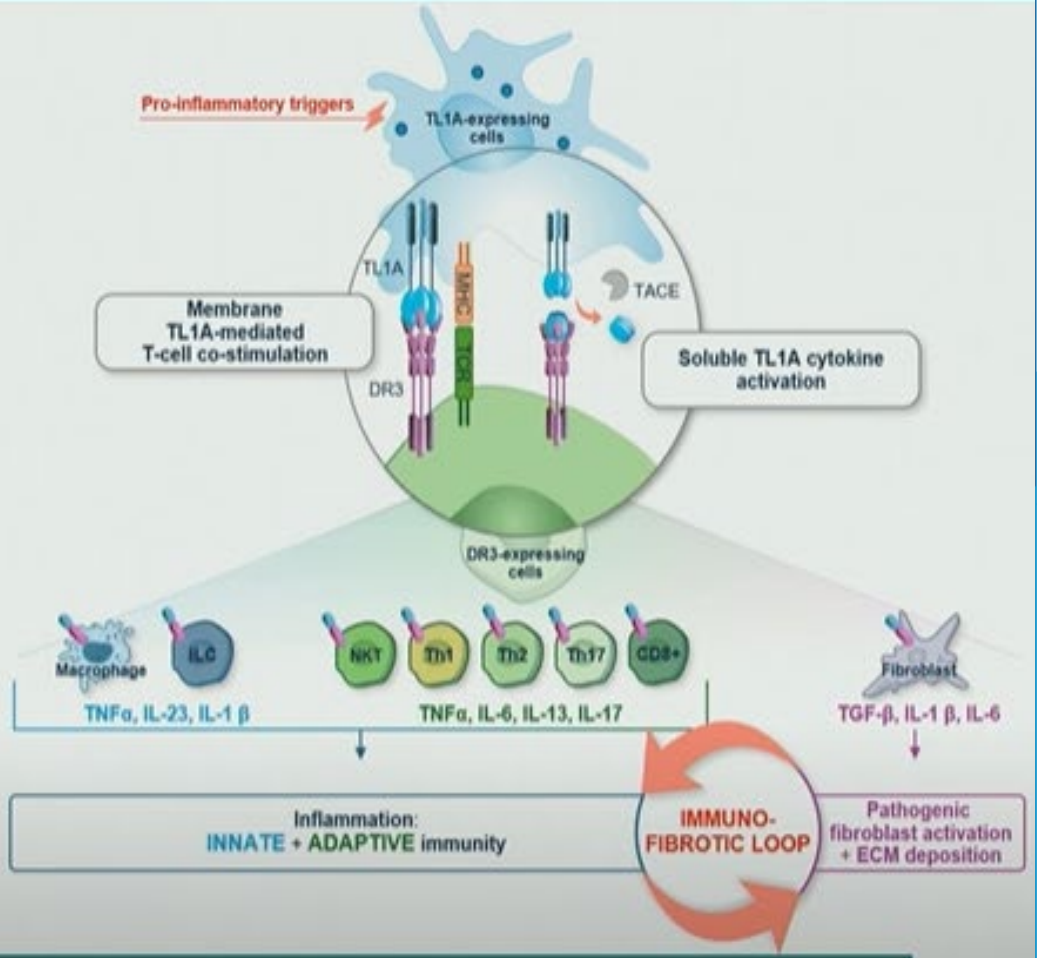
Christopher Ma,[1] Brigid S. Boland,[2] Jaroslaw Leszczyszyn,[3] Zhi Jin Xu,[4] Jeremy Shao,[4] Brian G. Feagan[5†]

[1]Division of Gastroenterology & Hepatology, Departments of Medicine and Community Health Sciences, University of Calgary, Calgary, AB, Canada; [2]Division of Gastroenterology, University of California-San Diego, La Jolla, CA, USA; [3]Department of Gastroenterology, Melita Medical, Wroclaw, Poland; [4]Merck & Co., Inc., Rahway, NJ, USA; [5]Departments of Medicine, Epidemiology, and Biostatistics, Western University, London, ON, Canada

†In memoriam (November 23, 2025).

Background

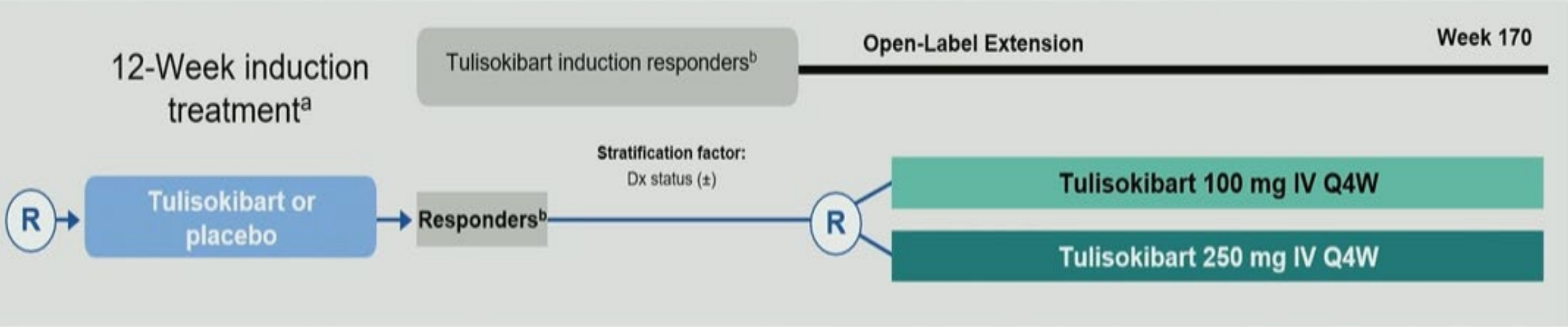
- TL1A is an amplifier of mucosal inflammation and fibrotic pathways in inflammatory bowel disease[1-3]
- Tulisokibart, a humanized monoclonal antibody, binds TL1A with high affinity and specificity and inhibits TL1A-death receptor 3 signaling, downregulating Th1, Th2, and Th17 activation and reducing fibroblast activation, thereby inhibiting inflammation and potentially fibrosis[4-6]
- In the phase 2 ARTEMIS-UC study, induction treatment with tulisokibart significantly improved clinical, endoscopic, and patient-reported outcomes vs placebo in participants with moderately to severely active UC at week 12[7]; responses were maintained through week 50 in the open-label extension study



Objectives

To assess symptomatic relief with tulisokibart treatment through changes in stool frequency and rectal bleeding subscores and evaluate the novel composite endpoint of disease clearance through 50 weeks

Phase 2 ARTEMIS-UC Study Design



Key Inclusion Criteria

- Moderately to severely active UC (mMS 4−9)
- Centrally read endoscopy subscore ≥2
- Rectal bleeding subscore ≥1
- History of insufficient response, loss of response, and/or intolerance to conventional and/or advanced therapies

Outcomes evaluated at week 50

- Stool frequency normalization: stool frequency subscore of 0 or 1 and no greater than baseline
- Resolution of rectal bleeding: rectal bleeding subscore of 0
- Symptomatic remission: achievement of both stool frequency normalization and resolution of rectal bleeding
- Disease clearance: symptomatic remission and mucosal healing (Geboes score ≤2B.1 [absence of neutrophilic inflammation in the mucosa[1]] and endoscopy subscore ≤1)

Disease Clearance

- Disease clearance has emerged as a potential new standard of treatment success in the management of UC; it represents a deep multilayered state of disease control inclusive of symptoms, mucosal appearance, and histologic findings[1]
- Real-world studies have shown that patients with UC who achieve disease clearance have both an improved disease course and lower rates of HCRU and surgery[2]

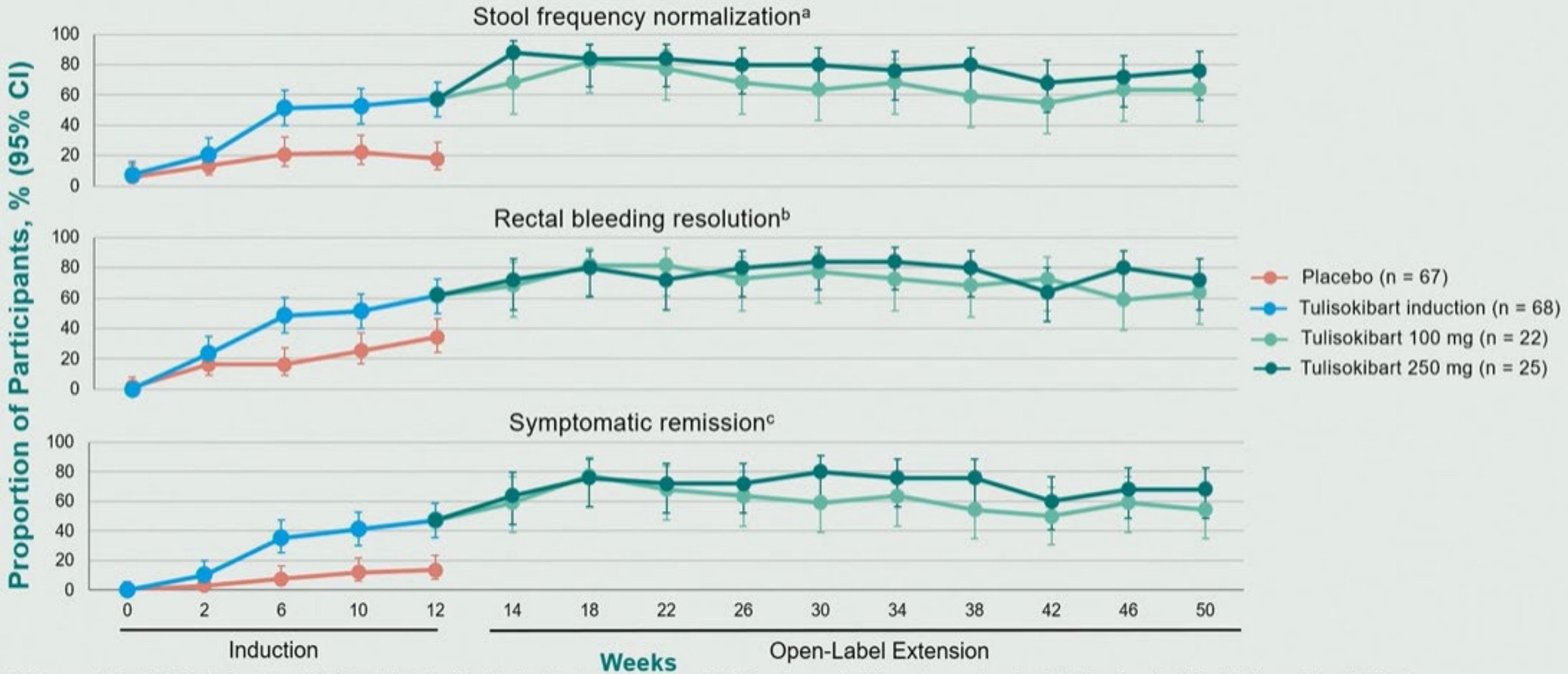
Definition of disease clearance for ARTEMIS-UC (includes all components)	
Symptomatic remission	Stool frequency subscore of 0 or 1 and no greater than baseline; rectal bleeding subscore of 0
Mucosal healing	Endoscopic improvement: Endoscopy subscore ≤1
	Histologic remission: Geboes score ≤2B.1

Baseline demographics and disease characteristics

- Baseline characteristics were similar between the placebo and tulisokibart groups and were consistent with those of patients with moderately to severely active UC with high disease burden

	Induction		Open-label extension	
	Placebo (n = 67)	Tulisokibart (n = 68)	Tulisokibart 100 mg (n = 22)	Tulisokibart 250 mg (n = 25)
Age, mean (SD), y	42.2 (16.3)	40.4 (14.4)	40.7 (17.4)	40.2 (14.2)
Female, n (%)	29 (43)	34 (50)	15 (68)	11 (44)
Duration of disease, mean (SD), y	6.3 (6.2)	6.7 (6.4)	3.9 (3.3)	6.1 (4.0)
Extent of disease, n (%)				
Proctosigmoiditis	7 (10)	2 (3)	0	1 (4)
Left-sided colon	28 (42)	35 (51)	12 (55)	11 (44)
Pancolitis	32 (48)	31 (46)	10 (46)	13 (52)
mMS, mean (SD)	7.1 (1.1)	6.9 (1.2)	6.4 (1.3)	7.0 (1.2)
Mayo endoscopic subscore, n (%)				
2	14 (21)	22 (32)	10 (46)	8 (32)
3	53 (79)	46 (68)	12 (55)	17 (68)
Concomitant immunosuppressant use, n (%)	11 (16)	8 (12)	3 (14)	3 (12)
Concomitant corticosteroid use, n (%)	38 (57)	35 (51)	8 (36)	13 (52)
Prior advanced therapy use, n (%)				
0	35 (52)	36 (53)	14 (63.6)	12 (48)
1	8 (12)	12 (18)	4 (18.2)	5 (20)
2	12 (18)	14 (21)	3 (13.6)	4 (16)
≥3	12 (18)	6 (9)	1 (4.5)	4 (16)

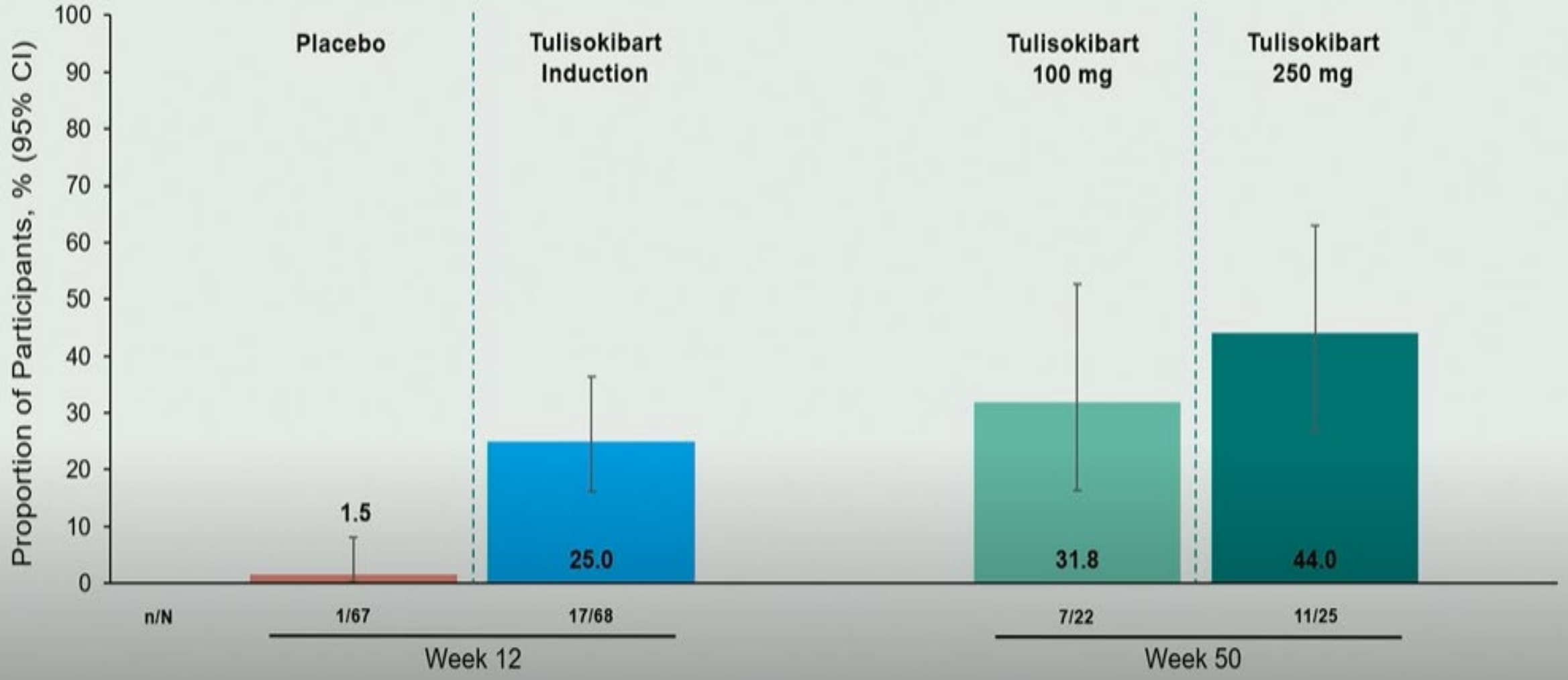
Symptomatic Outcomes Through Week 50



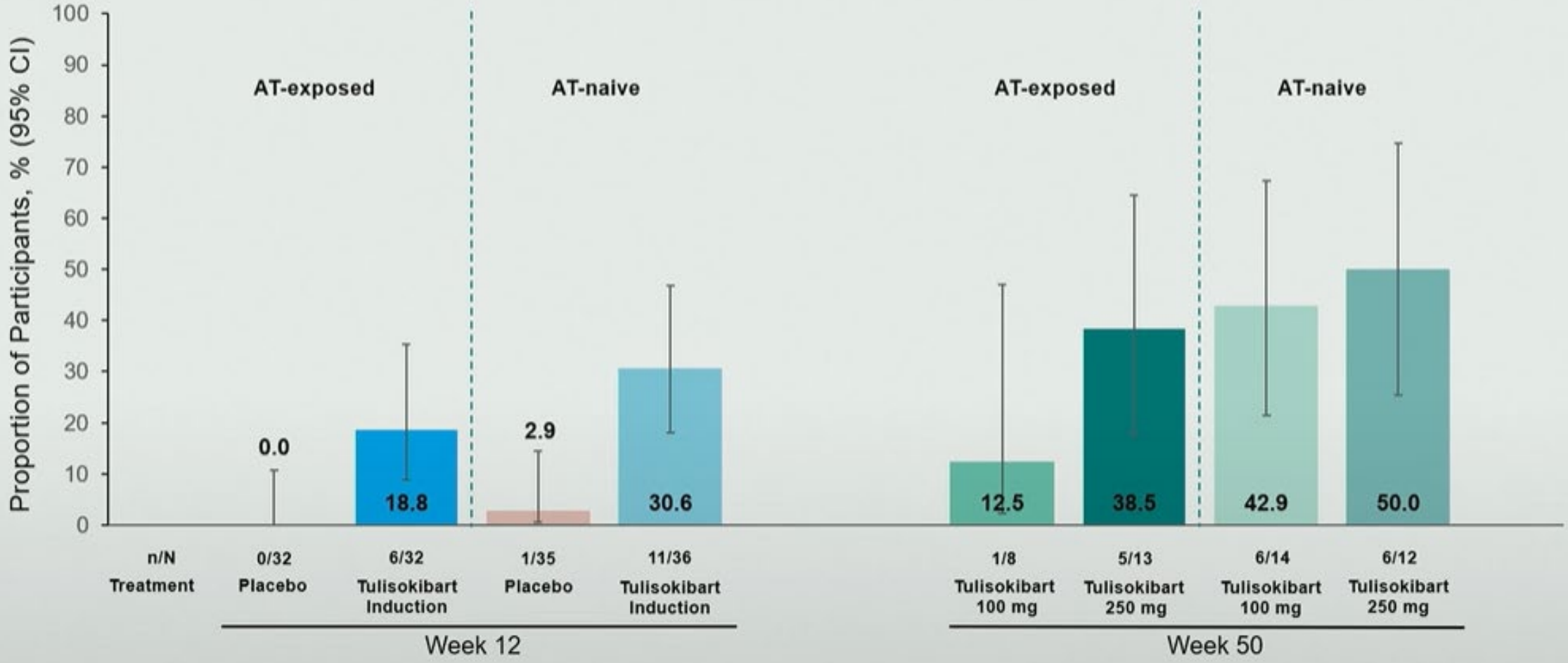
Endpoint assessed using the full analysis set at week 12 (all participants) and the intention-to-treat analysis set at week 50 (12-week responders). Percentages are based on the total number of participants in the population. Participants with missing responses were imputed as nonresponders. CIs based on the Wilson method for binomial proportion.

[a]Stool frequency normalization is defined as a score of 0 or 1 and no greater than baseline. [b]Resolution of rectal bleeding is defined as a score of 0. [c]Symptomatic remission is defined as achievement of both stool frequency normalization and rectal bleeding resolution.

Disease Clearance Rates at Weeks 12 and 50

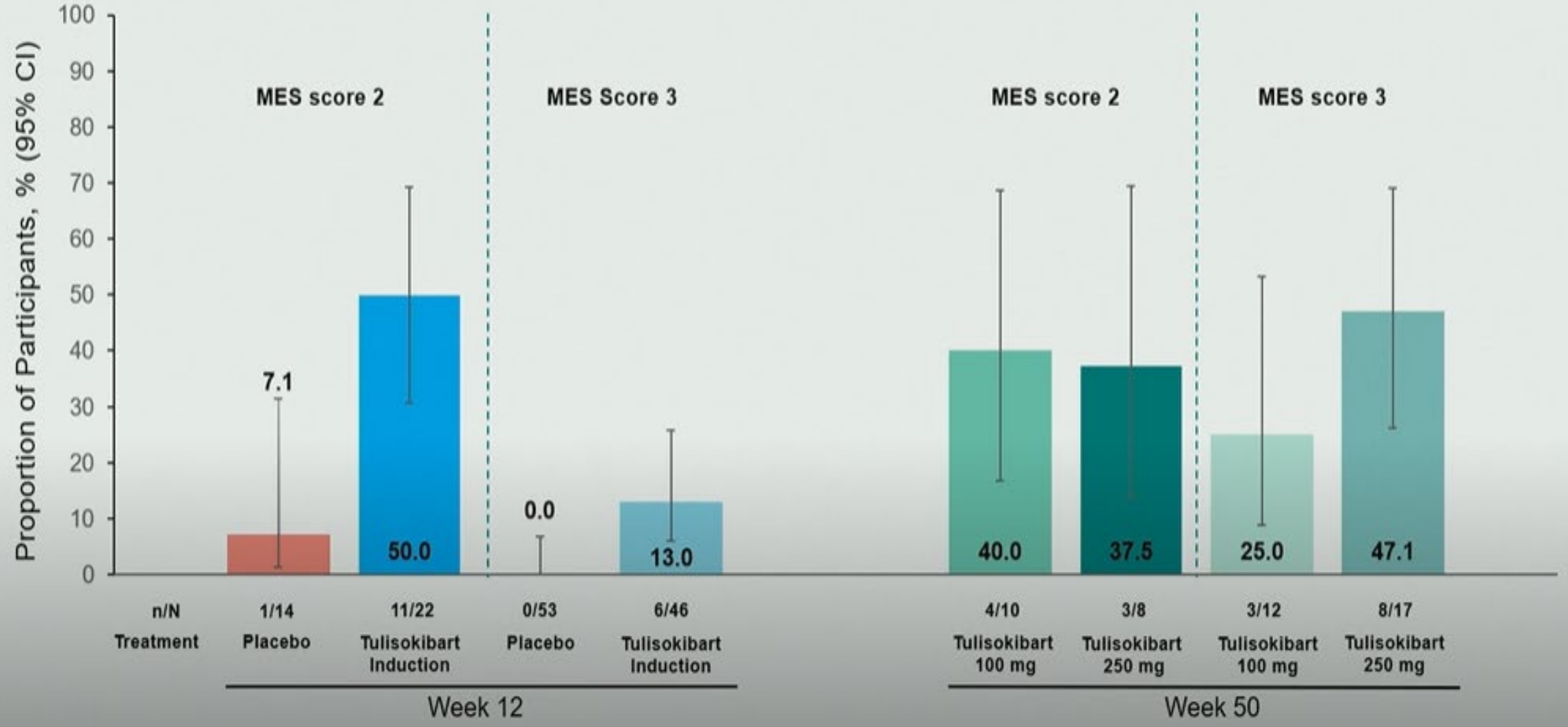


Disease Clearance Rates at Weeks 12 and 50 by Prior Advanced Therapy Use

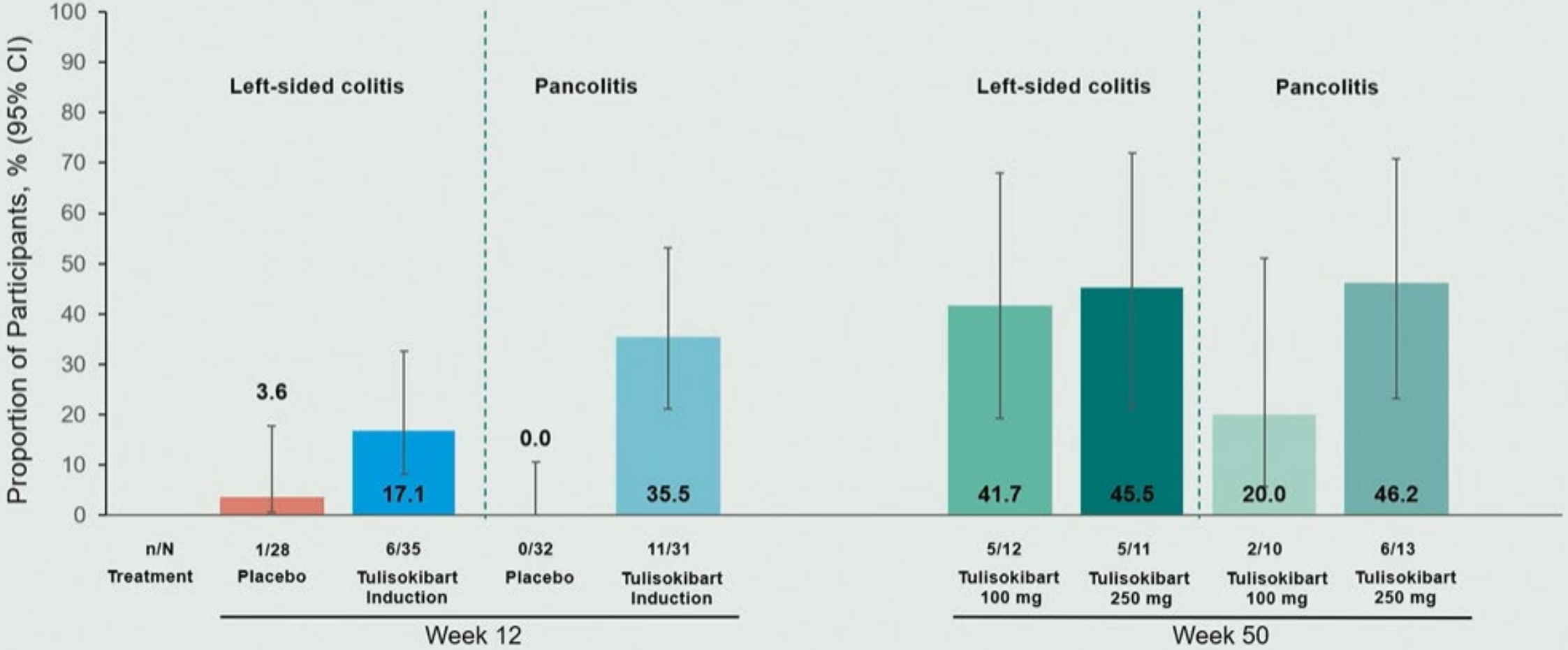


Disease clearance is defined as symptomatic remission (score of 0 or 1 and no greater than baseline for stool frequency and a score of 0 for rectal bleeding) plus mucosal healing (Geboes score ≤2B.1 and endoscopy subscore ≤1). Endpoint assessed using the full analysis set at week 12 (all participants) and the intention-to-treat analysis set at week 50 (12-week responders). Percentages are based on the total number of participants in the population. Participants with missing responses were imputed as nonresponders. CIs based on the Wilson method for binomial proportion.
AT, advanced therapy; CI, confidence interval; UC, ulcerative colitis.

Disease Clearance Rates at Weeks 12 and 50 by Baseline Mayo Endoscopic Subscore



Disease Clearance Rates at Weeks 12 and 50 by Extent of Disease[a]



Disease clearance is defined as symptomatic remission (score of 0 or 1 and no greater than baseline for stool frequency and a score of 0 for rectal bleeding) plus mucosal healing (Geboes score ≤2B.1 and endoscopy subscore ≤1). Endpoint assessed using the full analysis set at week 12 (all participants) and the intention-to-treat analysis set at week 50 (12-week responders). Percentages are based on the total number of participants in the population. Participants with missing responses were imputed as nonresponders. CIs based on the Wilson method for binomial proportion.

[a]Data on patients with proctosigmoiditis were not included due to the small sample size (placebo n = 7; tulisokibart, n = 2), with only 1 participant with proctosigmoiditis having data through week 50.

CI, confidence interval; UC, ulcerative colitis.

Conclusions

- Participants treated with tulisokibart achieved higher rates of stool frequency normalization, resolution of rectal bleeding, symptomatic remission, and disease clearance compared with those given placebo at week 12
- Among participants who responded to tulisokibart at week 12, efficacy was sustained or continued to increase through week 50, with approximately two-thirds of the participants achieving symptomatic remission
- By week 50 in participants treated with the 250-mg tulisokibart maintenance regimen, disease clearance was achieved in 47% of patients with severe baseline endoscopic disease (Mayo endoscopic subscore of 3) and in 46% of patients with pancolitis at baseline
- A phase 3 trial to confirm these findings is underway

O1058b

GUSELKUMAB FOR PERIANAL FISTULIZING CROHN'S DISEASE: WEEK 24 RESULTS FROM THE PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER FUZION STUDY

Laurent Peyrin-Biroulet, Vipul Jairath, Ailsa Hart, Geert D'Haens, Axel Dignass, Silvio Danese, Julian Panés, Susan J. Connor, Walter Reinisch, David A. Schwartz, Tadakazu Hisamatsu, Bram Verstockt, Antonino Spinelli, Anton Stift, André D'Hoore, Maciej Nazar, Jacqueline van Denderen, Talia Gramiccia, Takehiko Sakamoto, Stephen Xu, Ivana Bravatà, and Bruce E. Sands on behalf of the FUZION Study Group

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Perianal Fistulizing Crohn's Disease

Severe and **complex manifestation of CD** characterized by the development of abnormal epithelial connections between the anorectal canal and perianal skin[1,2]

PFCD affects ~**1/4th** of patients and presence at diagnosis may indicate a more severe clinical course of CD[3]

PFCD is often accompanied by[1,2,4]

- Perianal abscesses
- Pain and persistent drainage/discharge
- Fecal incontinence
- Impaired QoL

Background and Objective

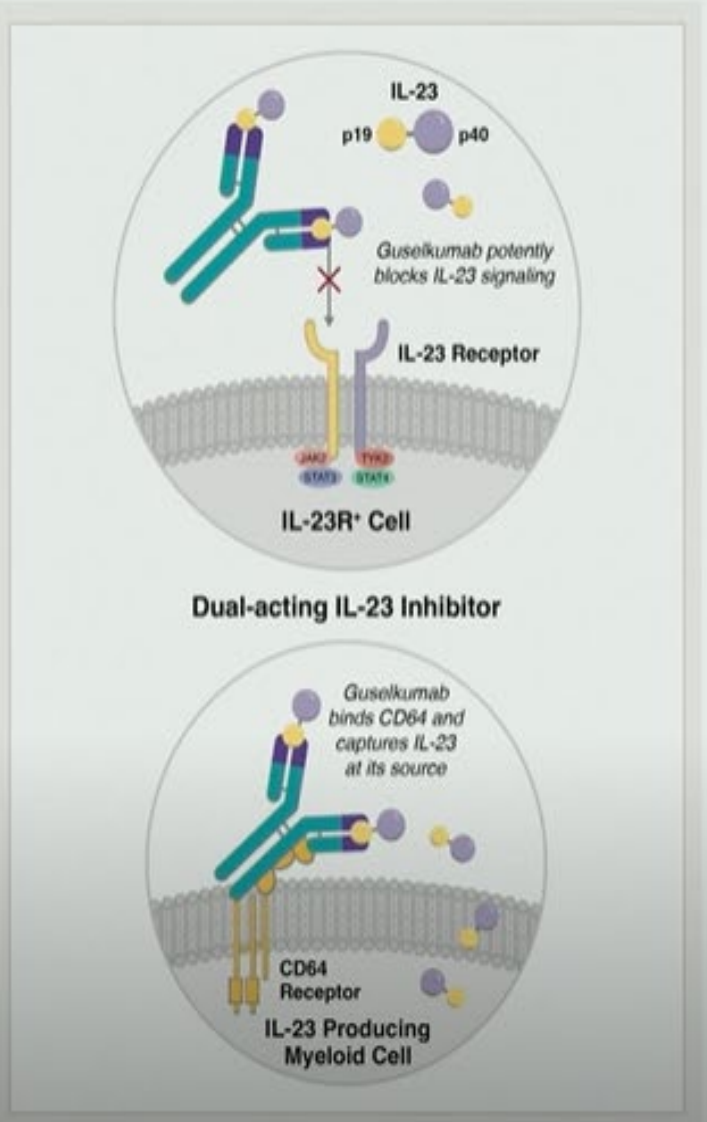
Despite combined medical-surgical management, durable fistula healing remains challenging

The last successful international, randomized, placebo-controlled trial of an advanced therapy dedicated to evaluating fistulizing Crohn's disease was the ACCENT 2 trial of infliximab, which was published in 2004[1]

Guselkumab:

- Fully human, dual-acting monoclonal antibody that selectively inhibits interleukin (IL)-23 by targeting its p19 subunit and binds to CD64, a receptor on immune cells that produces IL-23[2]
- Approved for adults with moderately-to-severely active Crohn's disease[2]

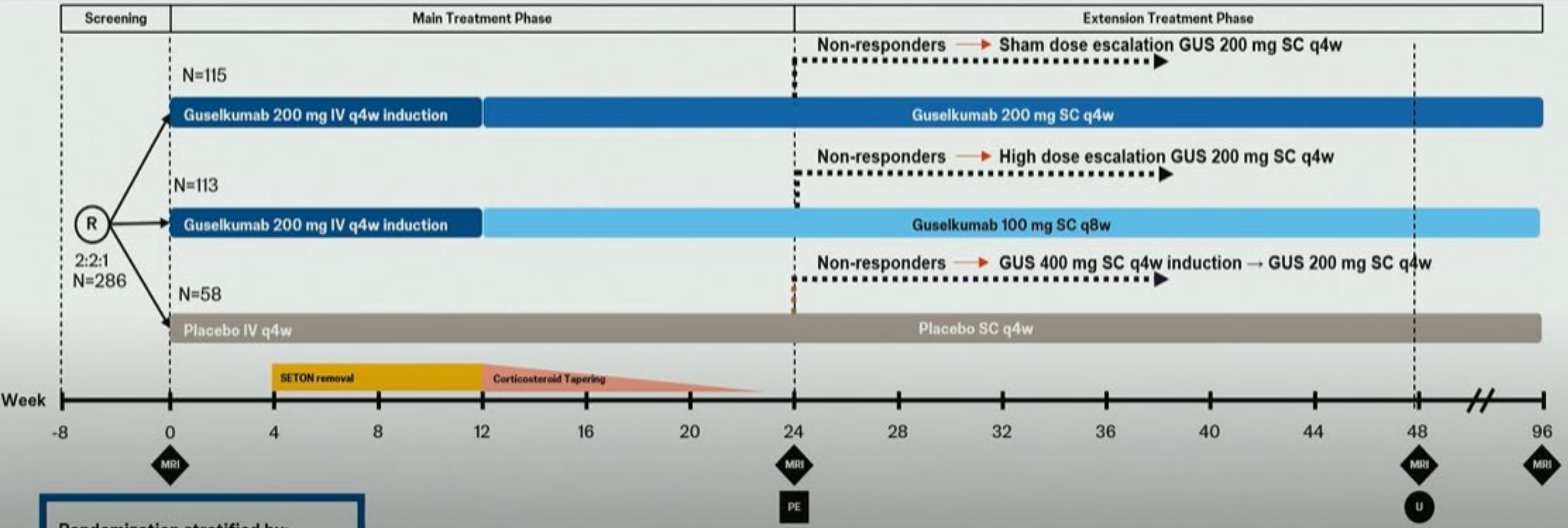
Objective: In the FUZION study (NCT05347095), a Phase 3, randomized, placebo-controlled, double-blind, international study, we evaluated the efficacy and safety of guselkumab in adults with active perianal fistulizing Crohn's disease



Phase 3, Double-Blind, Treat-Through Study

Key Eligibility Criteria

- Adults with at least 1 active draining perianal fistula confirmed by blinded central MRI review
- Active Crohn's disease (CDAI score <350)
- Inadequate response or intolerance to oral corticosteroids, azathioprine, 6-mercaptopurine, methotrexate or up to 2 advanced therapy classes (anti-TNF, vedolizumab, JAK inhibitors) and be refractory to antibiotics (ie, ciprofloxacin, metronidazole)



Randomization stratified by:

- Proctitis (Y/N), assessed by MRI
- Prior bionaive status (Y/N)

Fistula-related surgery and the use of antibiotics were allowed, according to local practice, during screening

Endpoints through Week 24*

Primary Endpoint*

Combined fistula **remission** at week 24 (clinically and radiologically assessed)

Multiplicity-Controlled Secondary Endpoints*

- Clinically assessed fistula **remission** at week 24
- Clinically assessed fistula **response** at week 24

Key Secondary Endpoints

- Clinically assessed fistula **response** at week 12

Assessment Type	Outcome	Definition
Clinical	Clinically assessed fistula **remission**	100% closure of all treated external openings, without development of new fistulas or abscesses and without any drainage by the external openings, occurring spontaneously or after gentle finger compression
	Clinically assessed fistula **response**	≥50% reduction from baseline in number of open or draining perianal fistulas
Radiological	Absence of collections >2cm	Absence of collections >2 cm of the perianal fistulas, confirmed by a blinded central review of the MRI results

*In the statistical testing procedure, guselkumab 200 mg q4w dose then the 100 mg q8w dose were sequentially tested versus placebo for the primary endpoint then for the multiplicity-controlled secondary endpoints.

Combined fistula remission definition was previously used in Panés, J. *Lancet.* 2016: 388: 1281-90. **MRI**=Magnetic Resonance Imaging, **q4w**=every 4 weeks, **q8w**=every 8 weeks.

Demographics and Baseline Disease Characteristics

	100 mg SC q8w (N=113)	200 mg SC q4w (N=115)	Combined (N=228)	Placebo (N=58)	Total (N=286)
Age, mean (SD) (years)	36.2 (12.67)	36.0 (13.02)	36.1 (12.82)	38.0 (12.93)	36.5 (12.84)
Male, n (%)	79 (69.9%)	85 (73.9%)	164 (71.9%)	41 (70.7%)	205 (71.7%)
Crohn's disease duration (years)					
Median	5.56	6.77	6.08	7.75	6.29
IQ range	(1.90; 15.64)	(2.07; 15.93)	(1.94; 15.75)	(3.41; 17.59)	(2.07; 15.93)
CDAI Score, N	113	108	221	56	277
Mean (SD)	154.6 (97.57)	143.2 (84.60)	149.0 (91.43)	147.6 (104.26)	148.7 (93.97)
> 220	25 (22.1%)	23 (21.3%)	48 (21.7%)	10 (17.9%)	58 (20.9%)
≤ 220	88 (77.9%)	85 (78.7%)	173 (78.3%)	46 (82.1%)	219 (79.1%)
Participants with open or draining fistula, n (%)					
1 fistula	73 (64.6%)	60 (52.2%)	133 (58.3%)	33 (56.9%)	166 (58.0%)
>1 fistulas	40 (35.4%)	55 (47.8%)	95 (41.7%)	25 (43.1%)	120 (42.0%)
Previous biologic exposure, n (%)					
Bio-naive	43 (38.1%)	38 (33.0%)	81 (35.5%)	16 (27.6%)	97 (33.9%)
Bio-exposed	70 (61.9%)	77 (67.0%)	147 (64.5%)	42 (72.4%)	189 (66.1%)
Proctitis at baseline, n (%)	31 (27.4%)	37 (32.2%)	68 (29.8%)	16 (27.6%)	84 (29.4%)
Seton present at baseline, n (%)	23 (20.4%)	21 (18.3%)	44 (19.3%)	10 (17.2%)	54 (18.9%)
≥1 fistula-related surgery during screening, n (%)	31 (27.4%)	30 (26.1%)	61 (26.8%)	13 (22.4%)	74 (25.9%)
Patients with collections >2 cm at baseline, n(%)	0	4 (3.5%)	4 (1.8%)	2 (3.4%)	6 (2.1%)

CDAI=Crohn's disease activity index, **IQ**=interquartile range, **q4w**=every 4 weeks, **q8w**=every 8 weeks, **SC**=subcutaneous, **SD**=standard deviation.

Prior and Concomitant Medications for Crohn's Disease

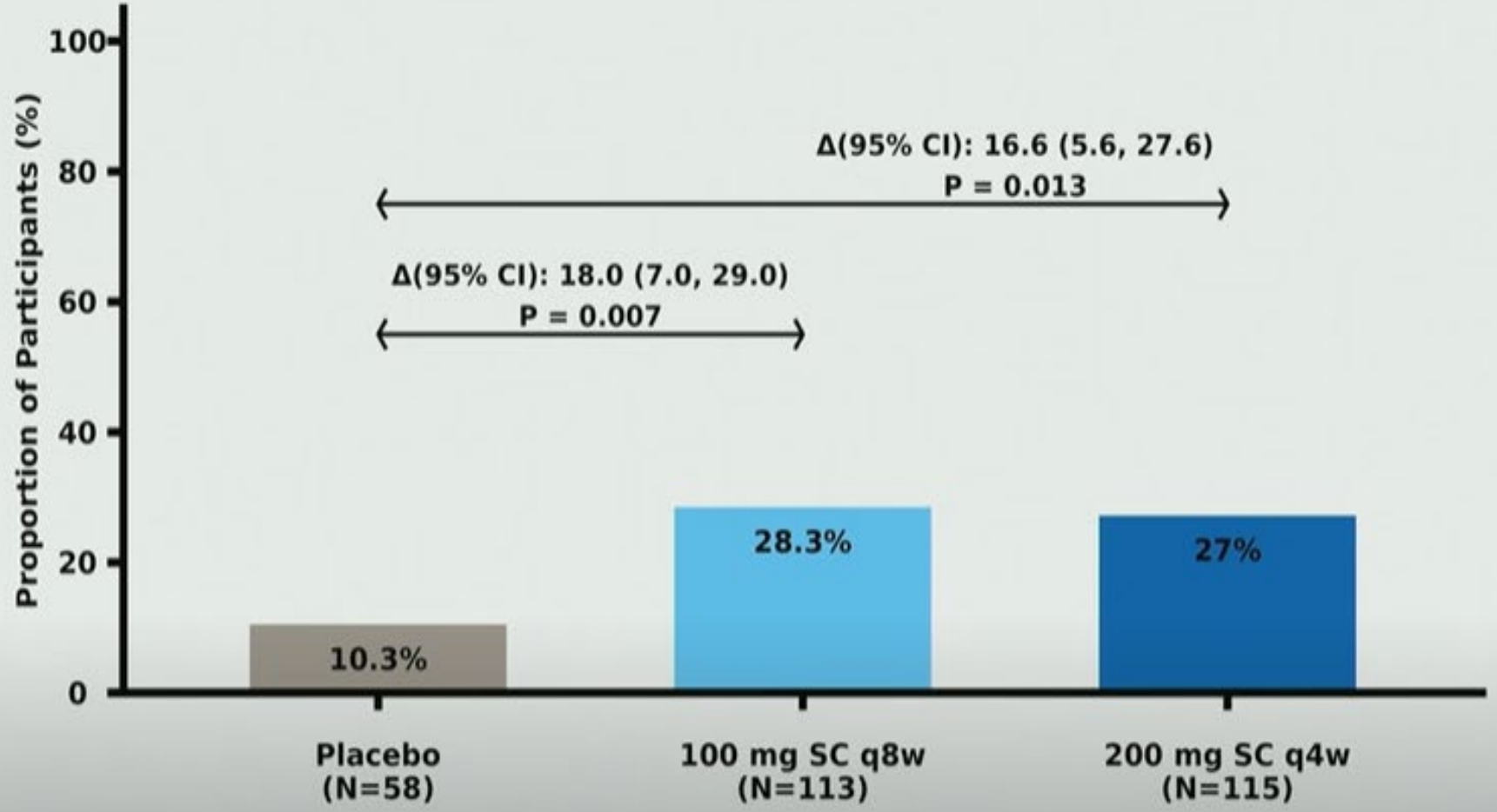
	100 mg SC q8w (N=113)	200 mg SC q4w (N=115)	Combined (N=228)	Placebo (N=58)	Total (N=286)
Inadequate response or intolerance, n (%)	70 (61.9%)	77 (67.0%)	147 (64.5%)	42 (72.4%)	189 (66.1%)
Infliximab	52 (46.0%)	58 (50.4%)	110 (48.2%)	32 (55.2%)	142 (49.7%)
Adalimumab	38 (33.6%)	42 (36.5%)	80 (35.1%)	23 (39.7%)	103 (36.0%)
Certolizumab	1 (0.9%)	2 (1.7%)	3 (1.3%)	1 (1.7%)	4 (1.4%)
Vedolizumab	8 (7.1%)	6 (5.2%)	14 (6.1%)	3 (5.2%)	17 (5.9%)
Ustekinumab*	4 (3.5%)	3 (2.6%)	7 (3.1%)	5 (8.6%)	12 (4.2%)
Only 1 anti-TNF agent	43 (38.1%)	51 (44.3%)	94 (41.2%)	27 (46.6%)	121 (42.3%)
>1 anti-TNF agent	24 (21.2%)	25 (21.7%)	49 (21.5%)	14 (24.1%)	63 (22.0%)
Only one mechanism of action	62 (54.9%)	69 (60.0%)	131 (57.5%)	35 (60.3%)	166 (58.0%)
Concomitant medications for CD at baseline, n (%)					
5-ASA	27 (23.9%)	27 (23.5%)	54 (23.7%)	19 (32.8%)	73 (25.5%)
Corticosteroids	10 (8.8%)	9 (7.8%)	19 (8.3%)	3 (5.2%)	22 (7.7%)
Immunosuppressants (AZA, 6-MP, MTX)	34 (30.1%)	35 (30.4%)	69 (30.3%)	16 (27.6%)	85 (29.7%)

Discontinuation of Study Agent Before Week 24

	100 mg SC q8w (N=113)	200 mg SC q4w (N=115)	Combined (N=228)	Placebo (N=58)	Total (N=286)
Completed 24 weeks of treatment, n (%)	100 (88.5%)	111 (96.5%)	211 (92.5%)	50 (86.2%)	261 (91.3%)
Discontinued study treatment, n (%)	13 (11.5%)	4 (3.5%)	17 (7.5%)	8 (13.8%)	25 (8.7%)
Reason for discontinuing study treatment, n (%)					
Discontinued due to AE	9 (8.0%)	3 (2.6%)	12 (5.3%)	4 (6.9%)	16 (5.6%)
Adverse event - Other	4 (3.5%)	3 (2.6%)	7 (3.1%)	0	7 (2.4%)
Adverse event - Worsening of Crohn's disease	5 (4.4%)	0	5 (2.2%)	4 (6.9%)	9 (3.1%)
Death	0	0	0	0	0
Lack of efficacy	0	0	0	1 (1.7%)	1 (0.3%)
Lost to follow-up	1 (0.9%)	0	1 (0.4%)	0	1 (0.3%)
Physician Decision	1 (0.9%)	0	1 (0.4%)	0	1 (0.3%)
Protocol deviation	0	0	0	0	0
Pregnancy	0	0	0	0	0
Subject refused further study treatment	0	0	0	1 (1.7%)	1 (0.3%)
Withdrawal of consent	2 (1.8%)	0	2 (0.9%)	0	2 (0.7%)
Prohibited Crohn's Disease related surgery	0	0	0	0	0
Other	0	1 (0.9%)	1 (0.4%)	2 (3.4%)	3 (1.0%)

Combined Fistula Remission at Week 24

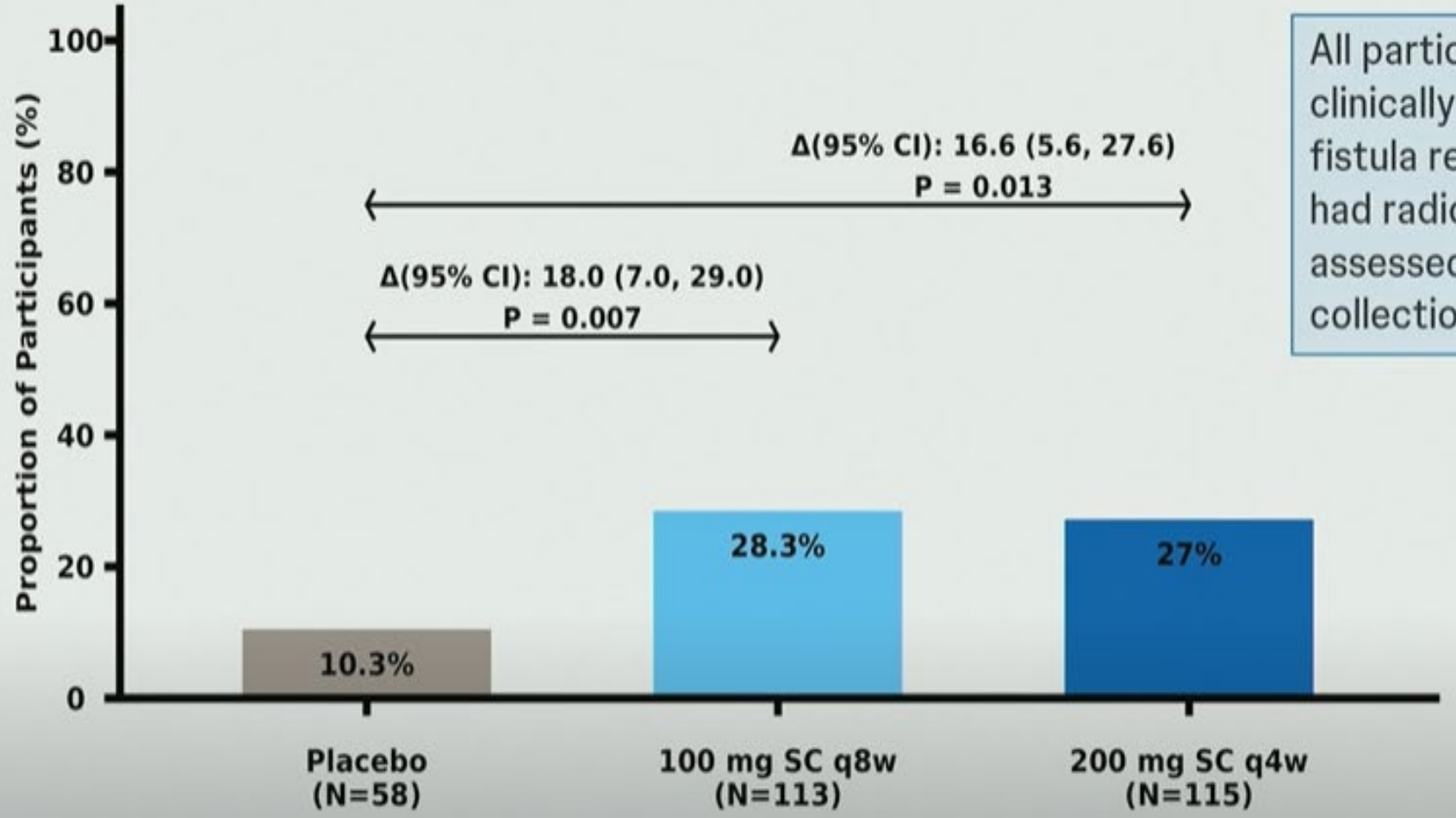
Primary Endpoint



Combined Fistula Remission: 100% closure of all treated external openings, without development of new fistulas or abscesses and without any drainage by the external openings, occurring spontaneously or after gentle finger compression AND absence of collections >2 cm of the perianal fistulas, confirmed by a blinded central review of the MRI results

Clinically Assessed Fistula Remission at Week 24

Multiplicity-Controlled Secondary Endpoint

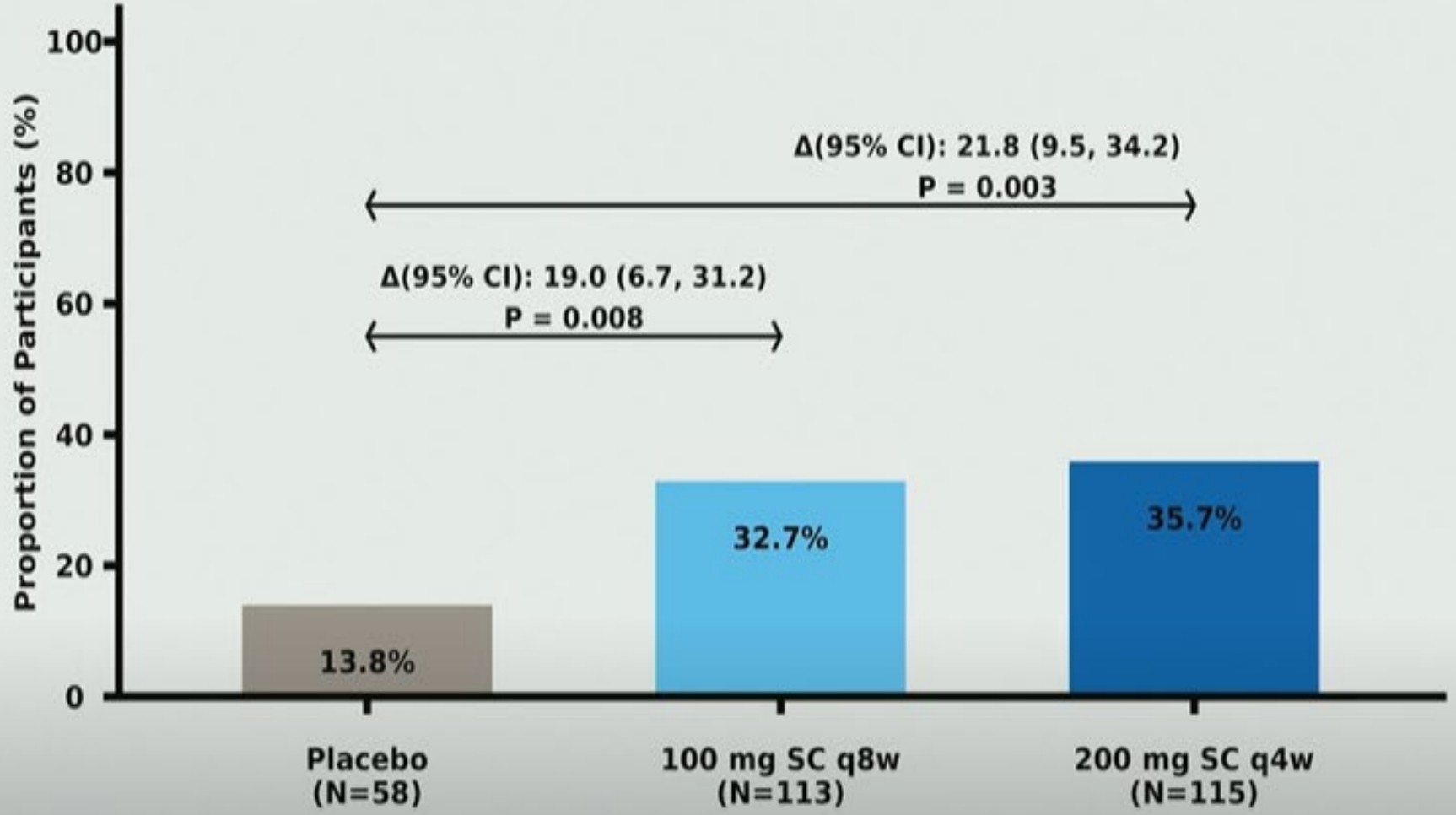


All participants who had clinically assessed fistula remission also had radiologically assessed absence of collections >2cm

Clinically Assessed Fistula Remission: 100% closure of all treated external openings, without development of new fistulas or abscesses and without any drainage by the external openings, occurring spontaneously or after gentle finger compression

Clinically Assessed Fistula Response at Week 24

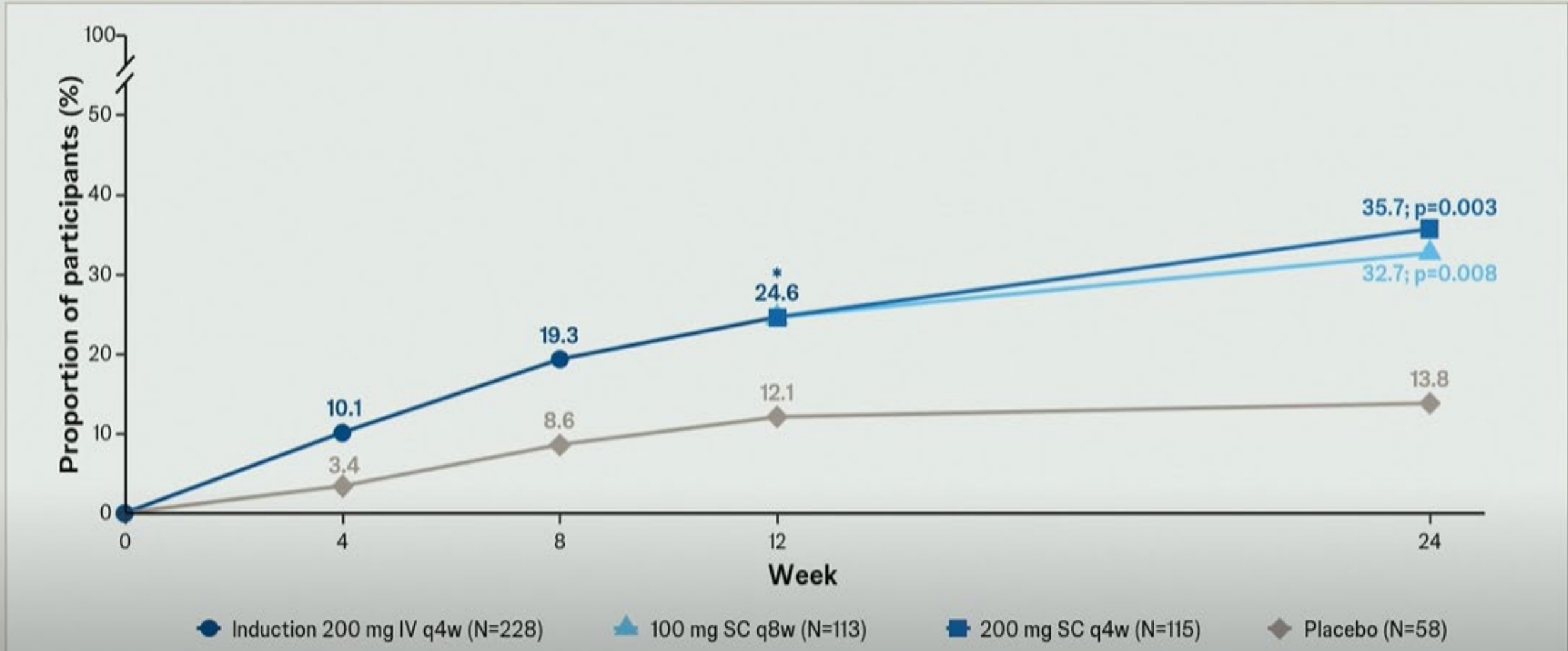
Multiplicity-Controlled Secondary Endpoint



Clinically Assessed Fistula Response: ≥50% reduction from baseline in number of open or draining perianal fistulas

Clinically Assessed Fistula Response through Week 24

Guselkumab showed meaningful difference versus placebo during induction



Clinically Assessed Fistula Response: ≥50% reduction from baseline in number of open or draining perianal fistulas

Adverse Events through Week 24

	100 mg SC q8w (N=113)	200 mg SC q4w (N=115)	Combined (N=228)	Placebo (N=58)
Mean duration of follow-up (weeks)	24.0	24.0	24.0	23.8
Mean exposure (number of study agent administrations)	5.7	5.8	5.8	5.6
Subjects with ≥1 adverse event	76 (67.3%)	80 (69.6%)	156 (68.4%)	48 (82.8%)
Subjects with ≥1 serious adverse event	12 (10.6%)	7 (6.1%)	19 (8.3%)	8 (13.8%)
Subjects with ≥1 adverse event leading to discontinuation of study agent	8 (7.1%)	3 (2.6%)	11 (4.8%)	5 (8.6%)
Subjects with ≥1 infection	45 (39.8%)	31 (27.0%)	76 (33.3%)	27 (46.6%)
Subjects with ≥1 serious infection	8 (7.1%)	2 (1.7%)	10 (4.4%)	2 (3.4%)

- No opportunistic infection, anaphylactic reactions or serum sickness reactions, MACE, clinically important hepatic disorders and VTE or deaths were reported
- **1 malignancy** a B-cell lymphoma was reported through Week 24 **(not related to study drug as assessed by investigator)**
- Injection-site reactions were **mild** and did not lead to discontinuation

Conclusions

- FUZION is the first successful international phase 3 study that assessed a combined clinical and MRI primary endpoint and the first in more than two decades that showed efficacy of an advanced therapy in perianal fistulizing Crohn's disease

- Guselkumab was efficacious through Week 24 in a study population with bio-naïve and bio-exposed patients with perianal fistulizing Crohn's disease
  - ✓ Guselkumab showed clinically meaningful difference versus placebo during induction
  - ✓ Both guselkumab maintenance doses showed statistically significant and clinically meaningful benefit compared with placebo

- The guselkumab benefit-risk profile was favorable, with no new safety signals identified

MUFEMILAST (ORAL PDE4 INHIBITOR) FOR ULCERATIVE COLITIS: OPEN-LABEL EXTENSION RESULTS AT 24 WEEKS FROM A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PARALLEL GROUP INDUCTION PHASE II CLINICAL TRIAL

L.Peyrin-Biroulet, C.R. Jones , S. T. Zhang, C.Q. Zheng, B.R. Liu, X.L. Zuo, S.G. Ding, X.Y. Ding, L. P. Li, Y.X. Chen, X. Ren, C.X. Liu, X.W. Liu, B.M. Wang, C. D. Wang, H. Guo, B.H. Xu, R.M. Yu, F. Tian, X.H. Hou, H. Yang, Z. H. Yu, X.P. Hu, Z.H.Wang, Y.Y. Zhen, H. Hai, A.H. Huo, H.S. Zhang

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Background

A Novel Oral Differentiated PDE4B Inhibitor: Approved for Plaque Psoriasis, National Medical Products Administration China (NMPA 2025)

- >1,500 subjects treated with mufemilast across multiple trials

Differentiation From First Generation PDE4 Inhibitor Apremilast

- Differentiated Pharmacokinetics:
  - Free from drug interactions, no dose adjustment required in renal impairment.
  - Reduced CNS liability (depression and suicide) no penetration of BBB.
- No dose titration, more rapid Css rapid onset of action.
- GI selective PK targeting (AUC GI/ Plasma Ratio >100).
- Improved tolerability for PDE4 related side effects (PDE4D lower affinity).
- Novel action on selective PDE4B expression inhibition (8nM vs 43 nM Apremilast) linked to inhibition of fibrosis

Differentiation From Local Approach

- Differentiated as inhibition of neutrophil trafficking requires systemic exposure

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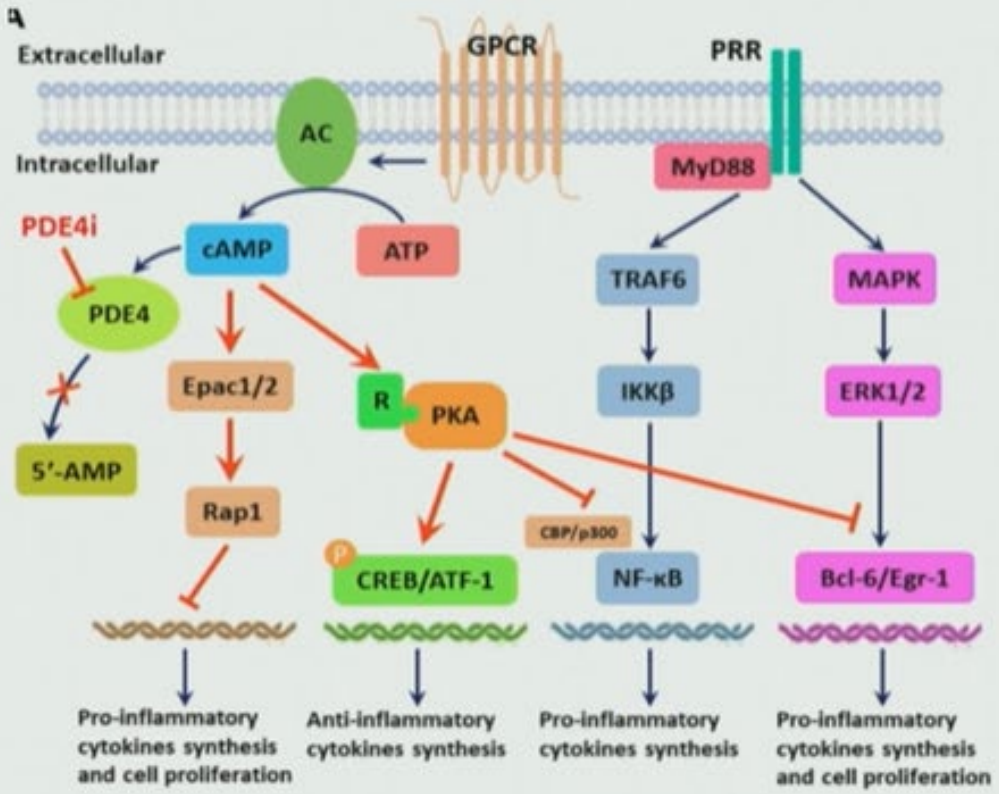
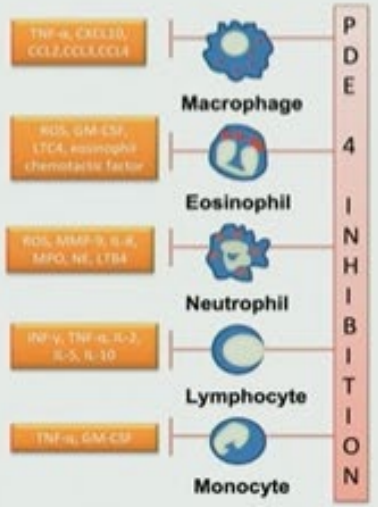
Mufemilast Targets Multiple Inflammatory Pathways



Mufemilast works beyond the axis of specific cytokines blocked by biologics (IL12/23; IL17) without additional safety concerns. This includes targeting NF-κB, MAPK, neutrophil trafficking, and PDE4b expression inhibition



Multiple target cells

DOI:10.3389/fphar.2018.01048 Corpus ID: 53167673
Phosphodiesterase-4 Inhibitors for the Treatment of Inflammatory Diseases

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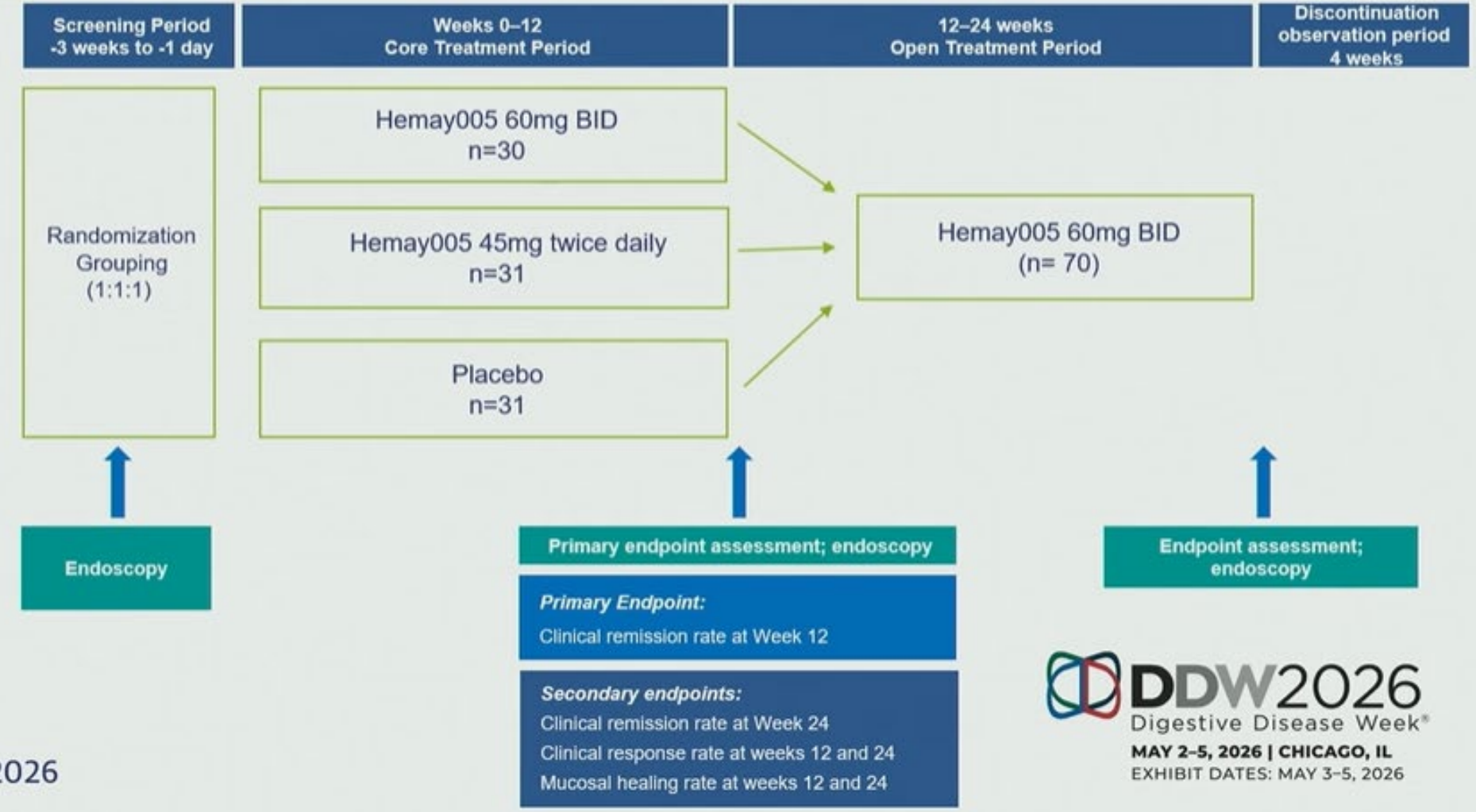
Mufemilast Phase II UC Clinical Trial Design

Key Inclusion Criteria

- Moderate to severe active UC (mMS* ≥ 4 and ≤ 9, ES ≥ 2, SF ≥ 1).
- Inadequate response, non-response, or intolerance to at least one prior conventional or advanced therapy.



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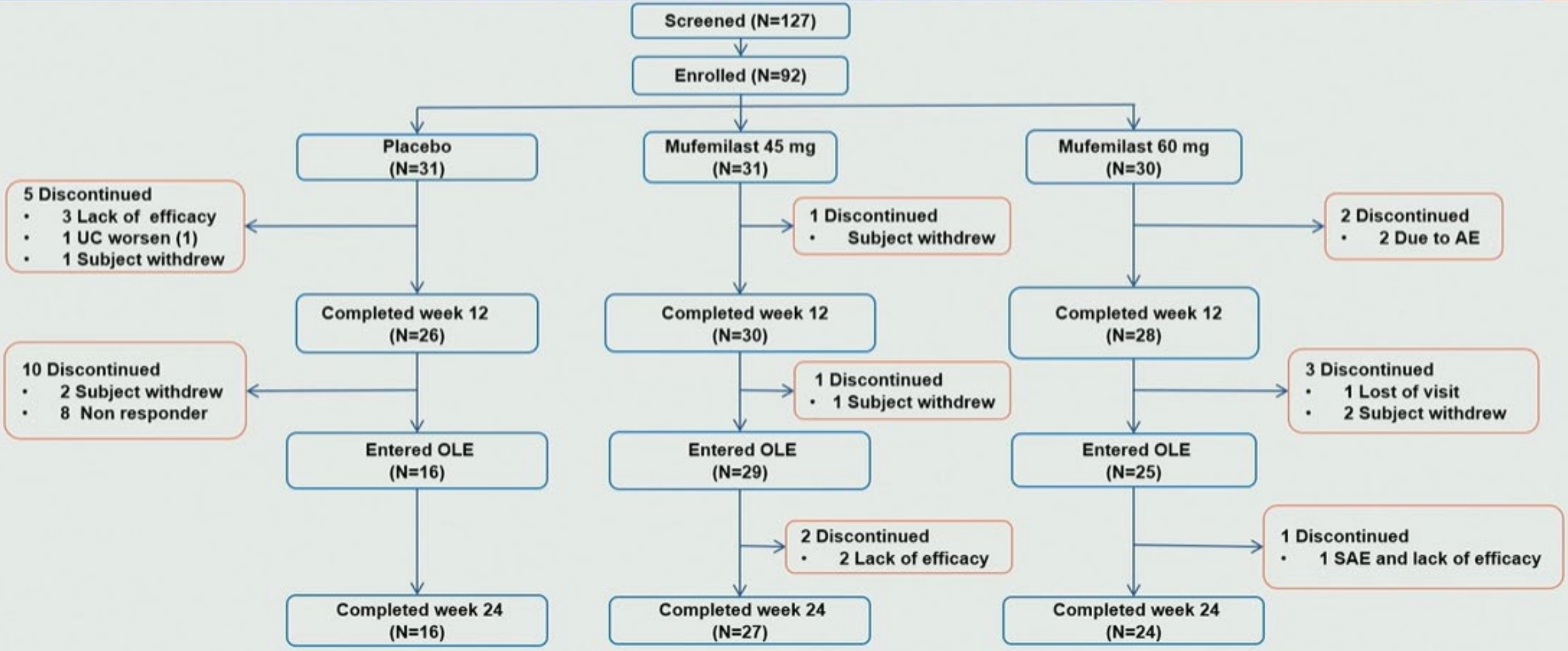
Baseline Demographics and Disease Characteristics

	Placebo Group (N=31)	45mg BID (N=31)	60 mg BID (N=30)
Age (Mean±SD), years	46.5±13.3	44.2±13.2	46.6±13.7
Male, n (%)	21 (67.6)	24 (77.4)	19 (63.3)
BMI (Mean±SD)	23.4±3.9	23.6±3.7	23.3±3.9
UC disease duration (Mean±SD), years	7.9±6.6	7.6 ± 6.8	4.0±3.1
Disease Type			
E2 (Left-sided colitis), n (%)	8 (25.8)	15 (48.4)	15 (50.0)
E3 (Extensive Colitis), n (%)	23 (74.2)	16 (51.6)	15 (50.0)
Modified Mayo score			
Moderate (4–6 points [inclusive]), n (%)	14 (45.2)	16 (51.6)	15 (50.0)
Severe (7–9 points, inclusive of both ends), n (%)	17 (54.8)	15 (48.4)	15 (50.0)
Endoscopic score (Mean±SD)	2.6±0.5	2.5±0.5	2.5±0.5
Endoscopic score = 2 points, n (%)	12 (38.7)	16 (51.6)	16 (53.3)
Endoscopic score = 3 points, n (%)	19 (61.3)	15 (48.4)	14 (46.7)

Patient Flow



Note Only Clinical responders entered the OLE (i.e. 8 non responders in the placebo group did not progress)

Primary Endpoint: Clinical Remission Rate At Weeks 12 and 24 (FAS)

- The 60mg BID group achieved a *57%* improvement vs placebo *13%* at Week 12 ($p<0.001$).
- The 60mg BID group demonstrated a trend toward higher efficacy vs the 45 mg dose.
- Responses were maintained at 24 weeks in 60mg group; 45mg and placebo switched subjects to 60mg increased responses after switching.
- Results were consistent between the Full Analysis Set (FAS) and the Per Protocol Set (PPS)

Definition of Clinical Remission (FDA Criteria)

1) Modified Mayo score (mMS) stool frequency (SF) subscore of 0 or 1, no greater than baseline
2) mMS rectal bleeding (RB) subscore of 0
3) mMS endoscopy (ES) subscore of 0 or 1 (without friability)

Secondary Endpoint: Clinical Response Rates At Weeks 12 and 24 (FAS)

- The 60mg treatment group achieved *80%* improvement vs placebo *42%* at Week 12 (p< 0.001).
- Responses were maintained through to week 24.
- Results were consistent between the full analysis set (FAS) and the per-protocol set (PPS).

Definition of Clinical Response

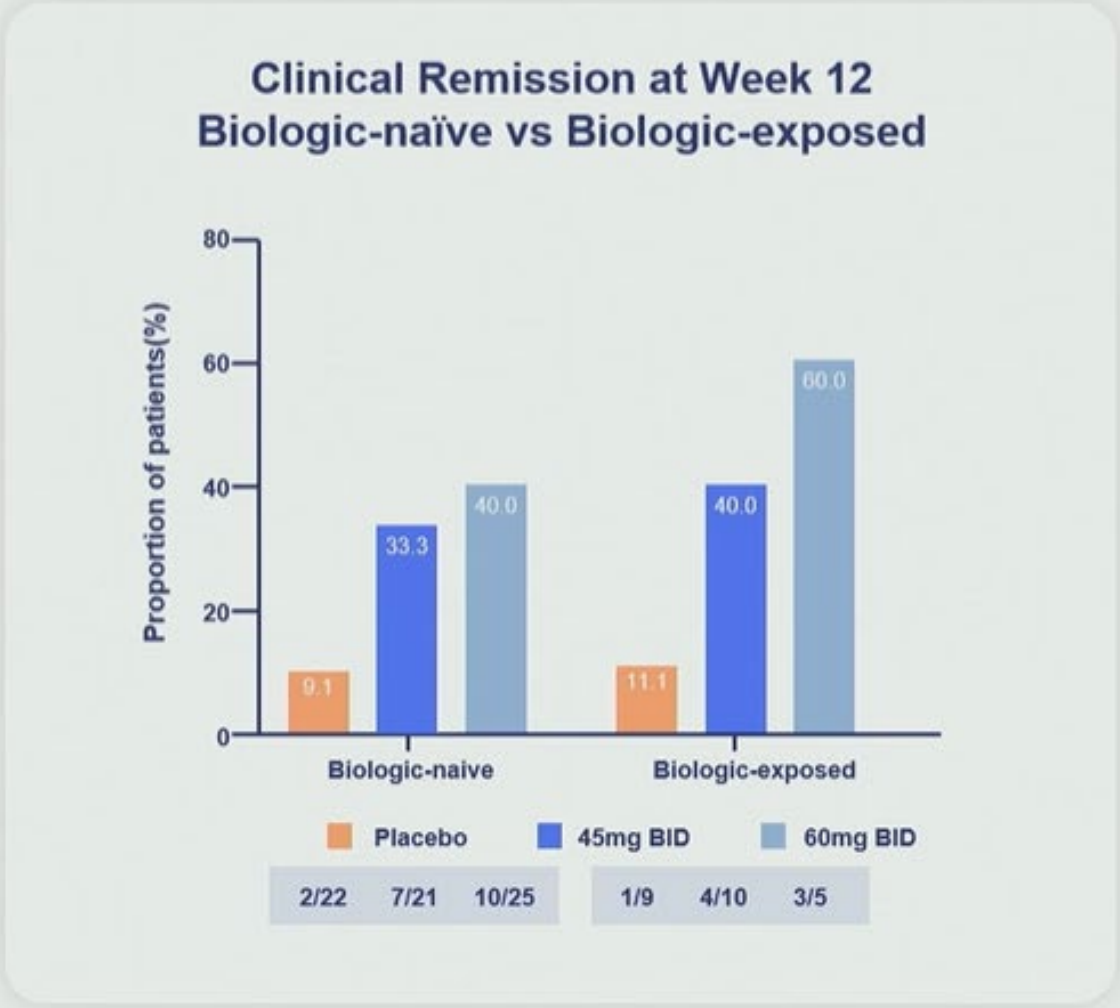
1) a reduction from baseline in mMS of ≥ 2 points and ≥ 30% from baseline.
2) a decrease from baseline in RB subscore of ≥ 1 point or an absolute RB subscore of ≤ 1 point.

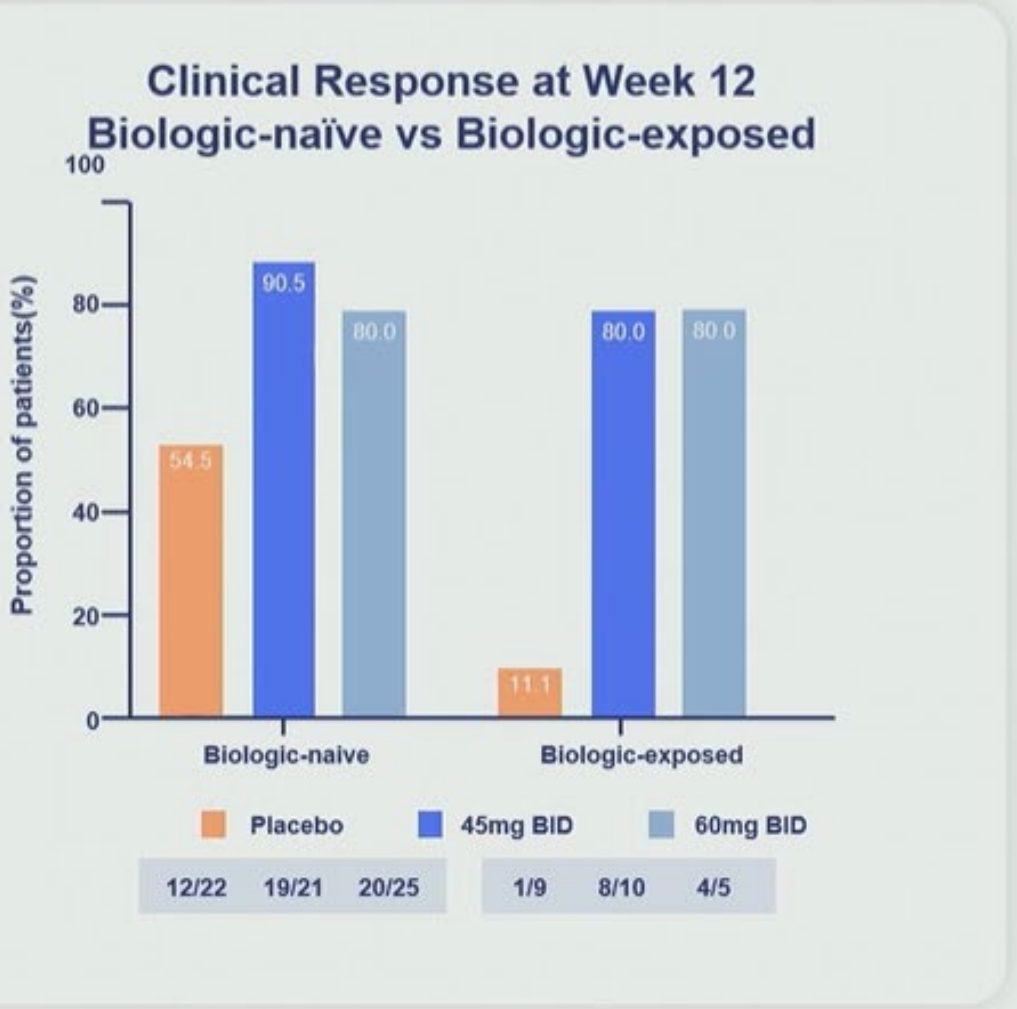
Secondary Endpoint: Endoscopic Improvement At Weeks 12 and 24

- The 60mg BID group achieved **67%** improvement vs placebo **16%** at Week 12 ($p<0.001$).
- The 60mg BID group demonstrated a trend toward higher efficacy vs the 45 mg dose.
- Responses were maintained at 24 weeks in 60mg group; 45mg and placebo switched subjects to 60mg increased responses.
- Results were consistent between the Full Analysis Set (FAS) and the Per Protocol Set (PPS).

Definition of Endoscopic Improvement: Modified Mayo score endoscopic subscore ≤ 1

Similar Efficacy in Biologic-exposed and Naïve Patients at 12 Weeks





Safety Summary at 12 and 24 Weeks

No Severe Infections or Malignancy

	Placebo-controlled Period			Open Treatment Period
	Placebo N=31	45mg BID N=31	60 mg BID N=30	60mg BID N=70
	Number of patients (%)			
At least 1 subject experienced TEAE	23 (74.2)	20 (64.5)	26 (86.7)	42 (60.0)
At least 1 subject experienced a study drug-related TEAE	13 (41.9)	14 (45.2)	18 (60.0)	26 (37.1)
SAE	0	0	2 *#(6.7)	3 (4.3)
Study drug-related adverse events leading to withdrawal	0	0	2** (6.7)	0
Adverse events leading to death	0	0	0	0

- * 1 SAE unrelated; Placebo group exacerbation of UC
- # 1 SAE varicose phlebitis patient had preexisting condition and history of phlebitis
- ** Two subjects discontinued due to AEs: one experienced moderate headache, dizziness, nausea, and restlessness; the other reported moderate bilateral lower limb pain. Both recovered after treatment.
- Seventeen TB-positive subjects received mufemilast, with no cases of tuberculosis reactivation observed.

Note: Incidence rates (%) were calculated based on the number of patients in each treatment group within the safety analysis set (SS).

Reduced PDE4 Class-related AEs With Mufemilast at 24 compared to 12 weeks

	Placebo	45mg BID	60mg BID	60mg BID OLE
Headache	**9.68% (3/31) Mild**	**9.68% (3/31) Mild**	**10.0% (3/30) 2 Mild 1 Moderate***	**2.86% (2/70) 2 Moderate**
Dizziness	6.45% (2/31) Mild	6.45% (2/31) Mild	6.67% (2/30) 2 Mild 1 Moderate	0
Nausea	3.23 (1/31) Mild	6.45% (2/31) Mild	10.0% (3/30) 2 Mild 1 Moderate	0

- All events were mild and moderate
- Tolerability increases with time
- Headache and dizziness resolve spontaneously

** 1 Moderate withdrew*

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Extensive Clinical Exposure Supports A De-risked Safety Profile

Total subjects exposed in each trial			
Trial number	**Hemay005**	**Placebo**	**Trial**
HM005PS1S01	52	0	Single administration trial
HM005PS1S02	12	0	Food Influence Crossover Dosing Trial
HM005PS1S03	18	0	Multiple dosing trial
HM005PS1S04	12	0	Multiple Dose Extension Test
HM005PS1S05	12	0	Multiple Dose Administration Trial in Australian Population
HM005PS1S06	13	0	Hepatic Impairment Special Population Trial
HM005PS1S07	24	0	Renal Impairment Special Population Trial
HM005PS1S08	20	0	Drug Interaction Trial
HM005PS1S09	28	0	Bioequivalence cross-delivery test
hm005mb1s01/crc-c2209	6	0	Substance balance test
HM005PS2S01	162	41	Psoriasis Phase II Trial
HM005PS3S01	211	85	Psoriasis Phase III Trial
HM005BD2S01	60	21	Behçets Phase II Trial
HM005AS2S01	60	0	Ankylosing Spondylitis II Trial
HM005AD2S01	53	0	Atopic Dermatitis Phase II Trial
HM005CO1S01	432	35	Titration/non-titration test
HM005UC2S01	61	16	Ulcerative Colitis Phase II Trial
HM005BD3S01	Core prognostic number on Hemay005 23, number entering extension 105, total 128		Behçets disease Phase III trial
Total number of patients	***1562***		

>1,500 subjects treated with mufemilast across multiple trials

Summary of Hemay005 exposure		
Duration of exposure ≥6 months (N)	Exposure time ≥1 year (N)	Exposure (patient-years)
Approx. >521	Approx. >373	Approx. 647.67

Mufemilast, is an oral PDE4b expression inhibitor with a favorable risk-benefit profile in UC

Improved Efficacy

- **Significant treatment effects for clinical remission (44%) and endoscopic improvement (51%) at 12 weeks.**
  - **A dose-response was observed, with 60mg bd being the optimal dose (safety and efficacy) for both clinical remission and endoscopic improvement.**
  - **Sustained Remission:** Clinical remission rates were maintained at 24 weeks.
  - **Rapid Dose Response:** When patients switched from placebo or 45mg to 60mg, responses increased rapidly for all endpoints (clinical remission, endoscopic improvement, and clinical response).
  - **Biologically naïve and exposed:** Patients showed similar magnitudes of clinical response.

Favorable safety

- **Minimal SAEs:** Only one possibly related SAE (pre-existing thrombophlebitis) was reported over 24 weeks.
- **Improved Tolerability Over Time:** The frequency of the common PDE4 side effects, such as headaches, decreased during the extension period (from 10% to 3% at the 60mg dose), and the drug-related discontinuation rates were low.
- **Clean Lab Data:** There were no clinically relevant changes in vital signs, ECGs, or laboratory values.
- **Safe in QuantiFERON Positive Patients**

EFFICACY AND SAFETY OF THE FIRST CO-ANTIBODY THERAPY, JNJ-78934804, IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS REFRACTORY TO SYSTEMIC THERAPIES

Maria T. Abreu,[1] Bruce E. Sands,[2] Séverine Vermeire,[3] Remo Panaccione,[4] Gregory T Moore,[5] Raja Atreya,[6] John Lynch,[7] Melissa G. Marko,[7] Eun Suk Jung,[7] Siyka Alexandrova,[7] Hayley Perry,[8] Marion L. Vetter,[7] Julián Panés[9]

[1]Cedars-Sinai, Los Angeles, CA, USA; [2]Dr. Henry D Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [3]University Hospitals Leuven, Leuven, Belgium; [4]Inflammatory Bowel Disease Unit, Division of Gastroenterology and Hepatology, University of Calgary, Calgary, AB, Canada; [5]Monash Health, and Monash University, Melbourne, Australia; [6]Department of Medicine 1, Erlangen University Hospital, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; [7]Johnson & Johnson, Spring House, PA, USA; [8]Johnson & Johnson Innovative Medicine UK, High Wycombe, England; [9]Hospital Clínic de Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain

DDW2026
Digestive Disease Week®
MAY 2–5, 2026 | CHICAGO, IL
EXHIBIT DATES: MAY 3–5, 2026

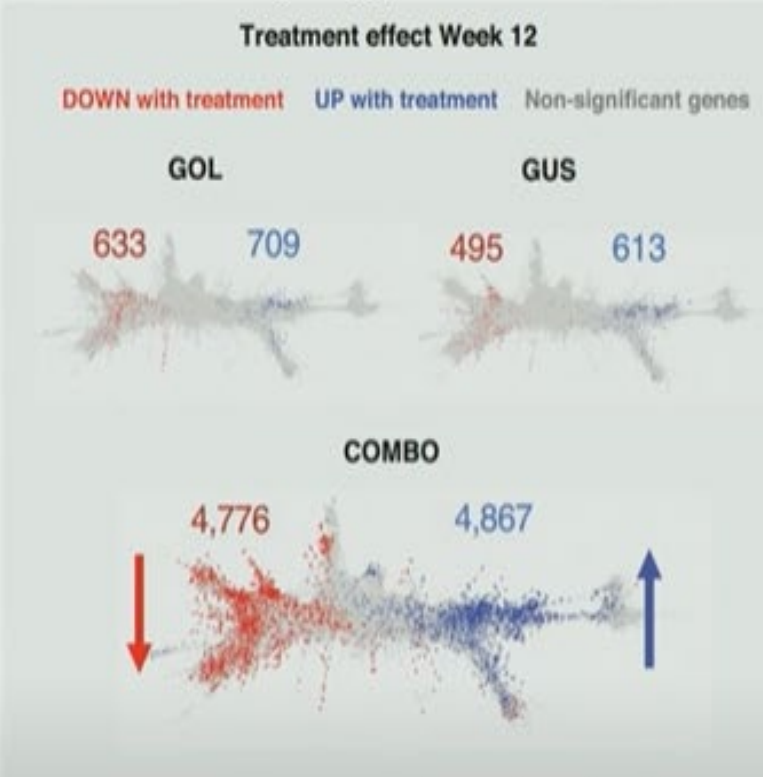
Background

In the Phase 2a VEGA study in ulcerative colitis,[1,2] guselkumab and golimumab combination therapy showed higher efficacy over either monotherapy

This combination was informed by preclinical evidence of complementary and distinct IL-23 and TNF-α activity, with molecular synergy demonstrated in VEGA

JNJ-4804 (JNJ-78934804; guselkumab and golimumab fixed-dose combination), the first co-antibody therapy in IBD, aims to address the high unmet need in patients with disease refractory to current systemic therapies

Molecular synergy observed in VEGA



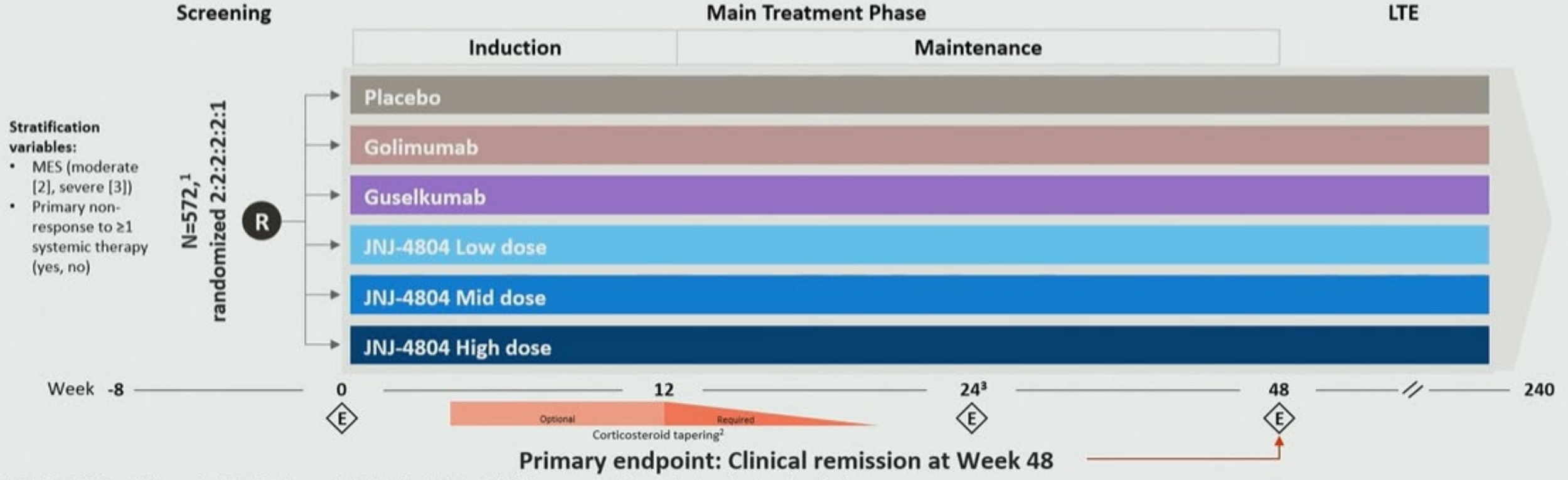
Combination associated with reduced inflammation and restoration of epithelial repair[3]

Objective

The Phase 2b DUET-UC trial (NCT05242484) evaluated the efficacy and safety of **JNJ-4804** compared with the component monotherapies in patients with moderately to severely active ulcerative colitis refractory to systemic therapies

DUET-UC: Phase 2b Randomized, Double-Blind, Active- and Placebo-Controlled Treat-Through Study in a Refractory Population

- Moderately to severely active UC
- Inadequate response or intolerance to ≥1 systemic therapy mechanism (anti-TNF, IL-12/23, IL-23p19, integrin, JAK inhibitor, or S1PR modulator)
- Caps for prior systemic therapy mechanisms: 1 (50%), 2 (35%), >2 (15%)
- All study medications were administered subcutaneously



[1]Full Analysis Set; 559 were included in the modified Full Analysis Set (13 did not meet mMayo inclusion criteria at baseline).
[2]Participants taking corticosteroids at Week 0 could begin tapering as early as Week 4 but no later than Week 12.
[3]Participants who met inadequate response criteria at Week 24 received a JNJ-4804 regimen (regardless of treatment assignment).
***E**=endoscopy, **IL**=interleukin, **JAK**=Janus kinase, **LTE**=long-term extension, **MES**=Mayo Endoscopic Score, **mMayo**=modified Mayo, **R**=randomization, **S1PR**=sphingosine-1-phosphate receptor, **TNF**=tumor necrosis factor, **UC**=ulcerative colitis.*

Endpoints and Statistical Considerations

Primary endpoint

- Clinical remission at Week 48

Other key endpoints

- Endoscopic improvement
- Histologic remission AND endoscopic improvement
- Corticosteroid-free clinical remission

Statistical considerations

- Participants who met prespecified treatment failure rules or had missing data were considered not to have met endpoints[1]
- Participants who met rescue criteria were considered treatment failures at Week 48[1]
- Analyses of subpopulations by systemic therapy history were prespecified[2] but not multiplicity controlled

[1]Participants were considered not to have met the Week 48 endpoint if any of the following occurred prior to Week 48: An ostomy or colectomy (partial or total); prohibited change in UC medication; treatment escalation due to inadequate response at Week 24; discontinuation of study treatment due to lack of efficacy or an AE of worsening UC; discontinuation of study treatment due to COVID-19 infection or any other reason. Participants who discontinued study treatment for COVID-19-related reasons (excluding COVID-19 infection) had their observed data used, if available. Missing data imputation: After accounting for these conditions, participants with missing Mayo subscores (any or all) at Week 48 (for clinical remission and corticosteroid-free clinical remission), missing endoscopy subscores at Week 48 (for endoscopic improvement and HREI), or missing histology data at Week 48 (for HREI) were considered not to have met the endpoint at Week 48.

[2]Analyses of subpopulations with 1, 2, and >2 prior systemic therapy mechanisms-IR were prespecified; the combined ≥2 systemic therapy mechanisms-IR subpopulation was evaluated based on these results.

***AE**=adverse event, **HREI**=histologic remission AND endoscopic improvement, **IR**=inadequate response or intolerance, **UC**=ulcerative colitis.*

Baseline Demographics, Disease Characteristics, and Concomitant Medications

		Placebo	Golimumab	Guselkumab	JNJ-4804 Low dose	JNJ-4804 Mid dose	JNJ-4804 High dose	Total
Full analysis set		52	104	103	103	105	105	572
Age in years, mean (SD)		38.6 (11.51)	38.5 (12.86)	40.3 (12.32)	39.8 (13.44)	39.6 (13.27)	38.0 (12.05)	39.2 (12.66)
Sex, n (%)	Male	33 (63.5%)	59 (56.7%)	54 (52.4%)	57 (55.3%)	61 (58.1%)	62 (59.0%)	326 (57.0%)
UC disease duration, years	Mean (SD)	9.3 (6.95)	8.5 (7.40)	9.4 (6.81)	9.7 (8.21)	8.9 (7.23)	8.9 (8.24)	9.1 (7.52)
Extent of disease, n (%)	Extensive	22 (42.3%)	50 (48.1%)	56 (54.4%)	52 (50.5%)	48 (45.7%)	49 (46.7%)	277 (48.4%)
mMayo Score[1]	Mean (SD)	7.0 (1.24)	7.1 (1.02)	7.0 (1.28)	7.0 (1.09)	7.2 (1.30)	7.1 (1.13)	7.1 (1.17)
Severity of UC disease, n (%)[1]	Severe (mMayo Score 7–9)	37 (71.2%)	71 (68.9%)	69 (67.6%)	74 (72.5%)	72 (69.2%)	75 (72.1%)	398 (70.2%)
Mayo Endoscopy Subscore, n (%)	Subscore of 3 (severe)	37 (71.2%)	78 (75.0%)	73 (70.9%)	73 (70.9%)	76 (72.4%)	73 (69.5%)	410 (71.7%)
Abnormal fecal calprotectin (>250 mg/kg)[2]	n (%)	41 (85.4%)	92 (95.8%)	83 (89.2%)	86 (91.5%)	80 (89.9%)	81 (91.0%)	463 (91.0%)
Fecal calprotectin (mg/kg)[2]	Median	1551.7	1689.5	1789.8	2220.4	1798.3	1634.0	1744.0
Concomitant medications at baseline								
Immunomodulators		5 (9.6%)	16 (15.4%)	14 (13.6%)	20 (19.4%)	17 (16.2%)	11 (10.5%)	83 (14.5%)
Oral corticosteroids		20 (38.5%)	38 (36.5%)	45 (43.7%)	36 (35.0%)	52 (49.5%)	51 (48.6%)	242 (42.3%)

[1]Means or percentages are based on the following numbers of participants with non-missing data: 52 (placebo), 103 (golimumab), 102 (guselkumab), 102 (JNJ-4804 low dose), 104 (JNJ-4804 mid dose), 104 (JNJ-4804 high dose), 567 (total).

[2]Medians or percentages are based on the following numbers of participants with non-missing data: 48 (placebo), 96 (golimumab), 93 (guselkumab), 94 (JNJ-4804 low dose), 89 (JNJ-4804 mid dose), 89 (JNJ-4804 high dose), 509 (total).

mMayo, modified Mayo; UC, ulcerative colitis

Highly Treatment-Refractory Population With Inadequate Response or Intolerance to Systemic Therapies

		Placebo	Golimumab	Guselkumab	JNJ-4804 Low dose	JNJ-4804 Mid dose	JNJ-4804 High dose	Total
Full analysis set		52	104	103	103	105	105	572
Participants with inadequate response to 1 or more systemic therapy mechanisms[1]								
Number of systemic therapy mechanisms - inadequate responders, n (%)[2]	**1**	30 (58.8%)	56 (53.8%)	51 (49.5%)	63 (61.2%)	58 (55.2%)	58 (55.8%)	316 (55.4%)
	≥2	21 (41.2%)	48 (46.2%)	52 (50.5%)	40 (38.8%)	47 (44.8%)	46 (44.2%)	254 (44.6%)

44.6% were refractory to 2 or more systemic therapy mechanisms

History of inadequate response or intolerance by system therapy mechanism in the overall population

- Anti-TNF: 74%
- Anti-integrin: 44%
- JAK inhibitor: 26%
- Ustekinumab: 19%
- S1PR modulator: 4%
- Anti-IL-23: 1%

60% of participants with disease refractory to 1 systemic therapy had inadequate response to an anti-TNF only

[1]Anti-TNF, anti-IL-12/23, anti-IL-23p19, anti-integrin, JAK inhibitor, and S1PR modulator
[2]Denominators are the numbers of participants with inadequate response to 1 or more systemic therapy mechanisms.
***JAK**=Janus kinase, **S1PR**=sphingosine-1-phosphate receptor, **TNF**=tumor necrosis factor, **UC**=ulcerative colitis.*

Treatment Disposition Through Week 48

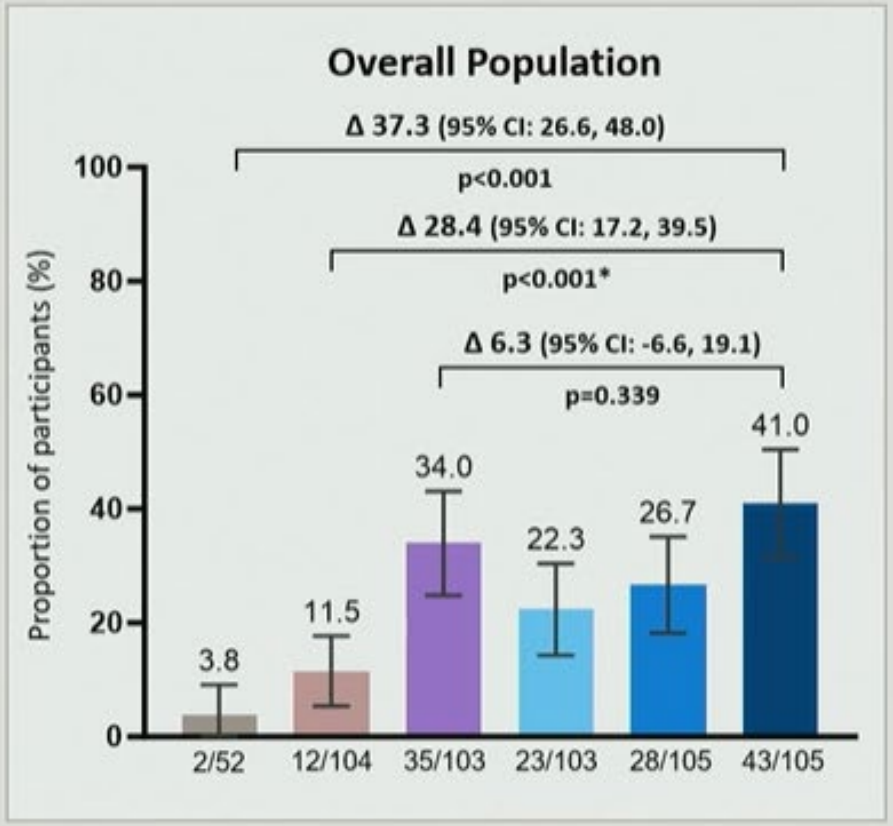
Lowest Discontinuation Rates Observed in JNJ-4804 High-Dose Group

	Placebo	Golimumab	Guselkumab	JNJ-4804 Low dose	JNJ-4804 Mid dose	JNJ-4804 High dose	Total
Full analysis set	52	104	103	103	105	105	572
Number of participants who:							
Discontinued study treatment before Week 48	17 (32.7%)	32 (30.8%)	23 (22.3%)	24 (23.3%)	23 (21.9%)	14 (13.3%)	133 (23.3%)
Most common reasons for discontinuation							
Lack of efficacy	3 (5.8%)	6 (5.8%)	13 (12.6%)	5 (4.9%)	7 (6.7%)	5 (4.8%)	39 (6.8%)
Withdrawal by participant	5 (9.6%)	11 (10.6%)	4 (3.9%)	6 (5.8%)	6 (5.7%)	2 (1.9%)	34 (5.9%)
Adverse event - worsening of UC	7 (13.5%)	11 (10.6%)	3 (2.9%)	5 (4.9%)	3 (2.9%)	5 (4.8%)	34 (5.9%)
Adverse event - other	0	2 (1.9%)	1 (1.0%)	4 (3.9%)	3 (2.9%)	0	10 (1.7%)
Initiated prohibited medication	1 (1.9%)	0	2 (1.9%)	1 (1.0%)	0	0	4 (0.7%)

Note: Final dosing for the main treatment period was received 4 weeks prior to Week 48. Participants are presented in the treatment group assigned at Week 0.

***UC**=ulcerative colitis.*

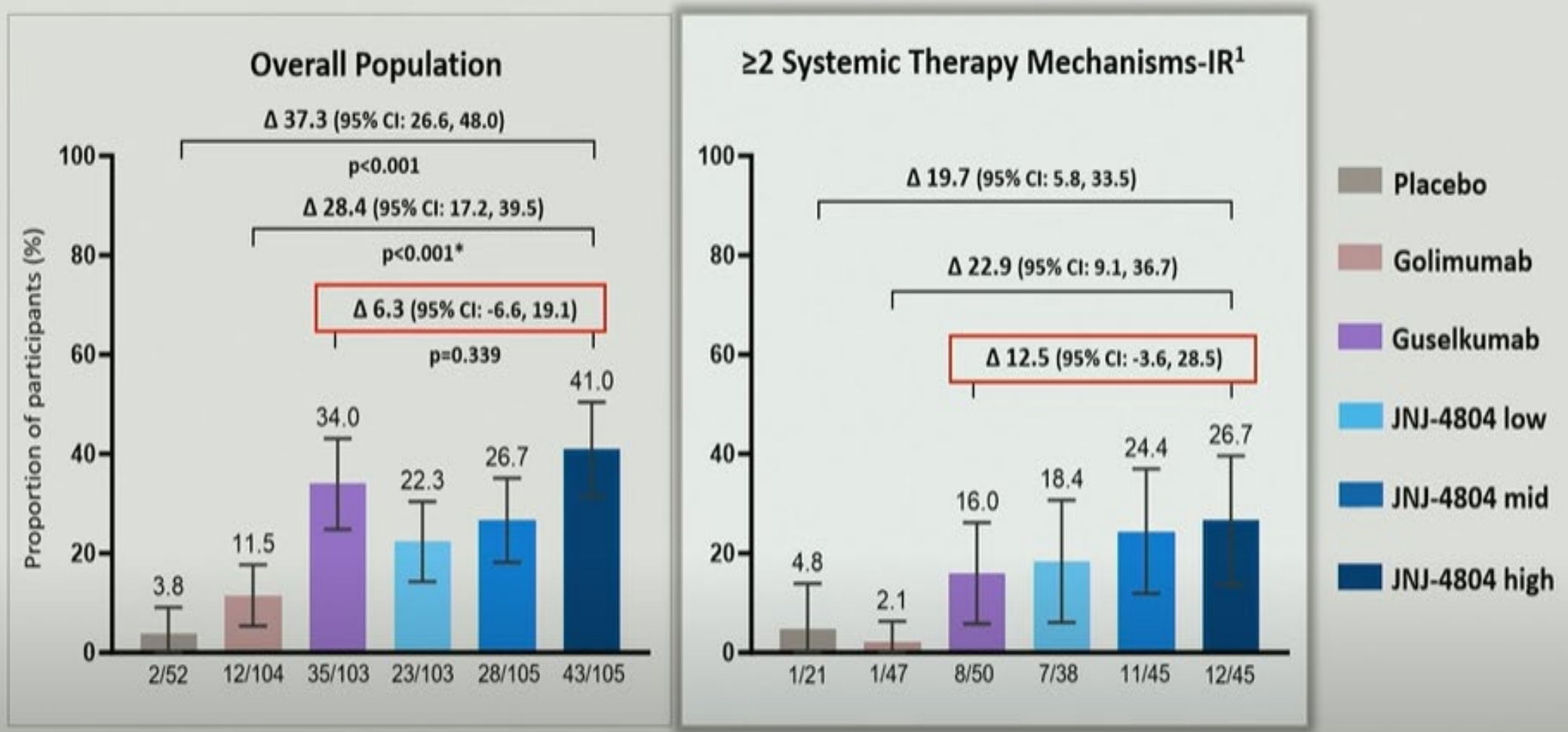
Primary Endpoint: Clinical Remission at Week 48



Clinical remission: stool frequency subscore of 0 or 1, rectal bleeding subscore of 0, and endoscopy subscore of 0 or 1 per central review of the video endoscopy

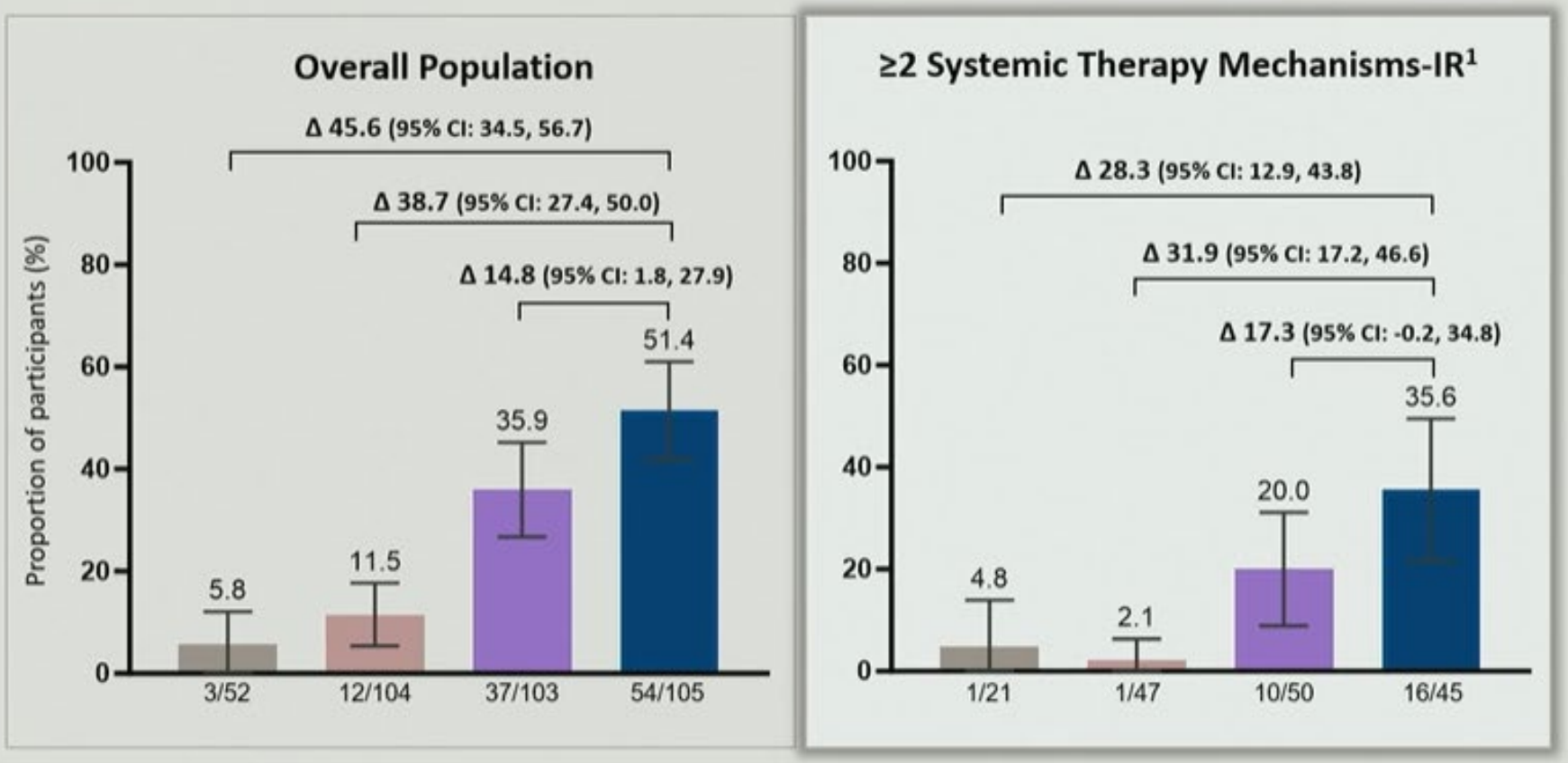
*Statistically significant. All other p-values are nominal.
CI=confidence interval.

Primary Endpoint: Clinical Remission at Week 48



Clinical remission: stool frequency subscore of 0 or 1, rectal bleeding subscore of 0, and endoscopy subscore of 0 or 1 per central review of the video endoscopy

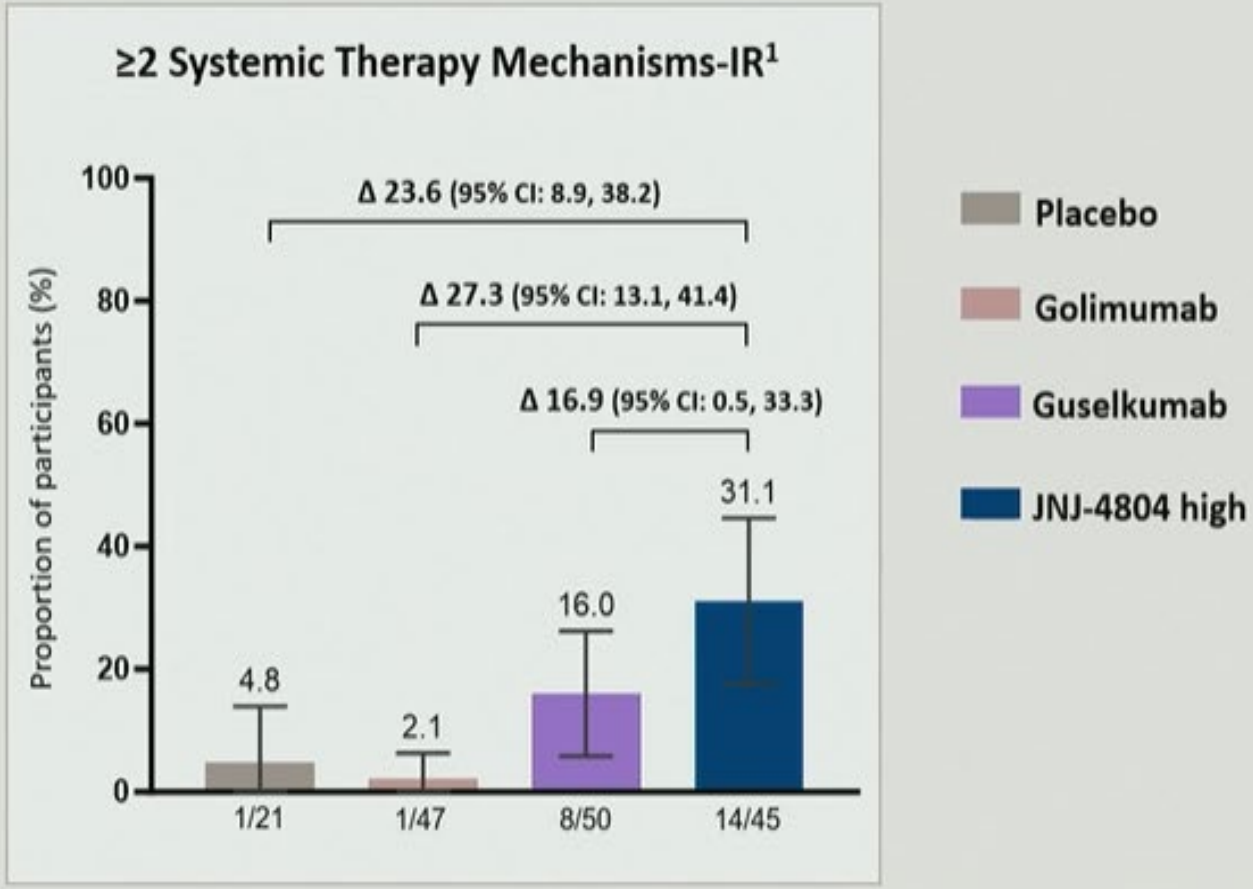
Key Secondary Endpoint: Endoscopic Improvement at Week 48



Endoscopic improvement: endoscopy subscore of 0 or 1 per central review of the video endoscopy

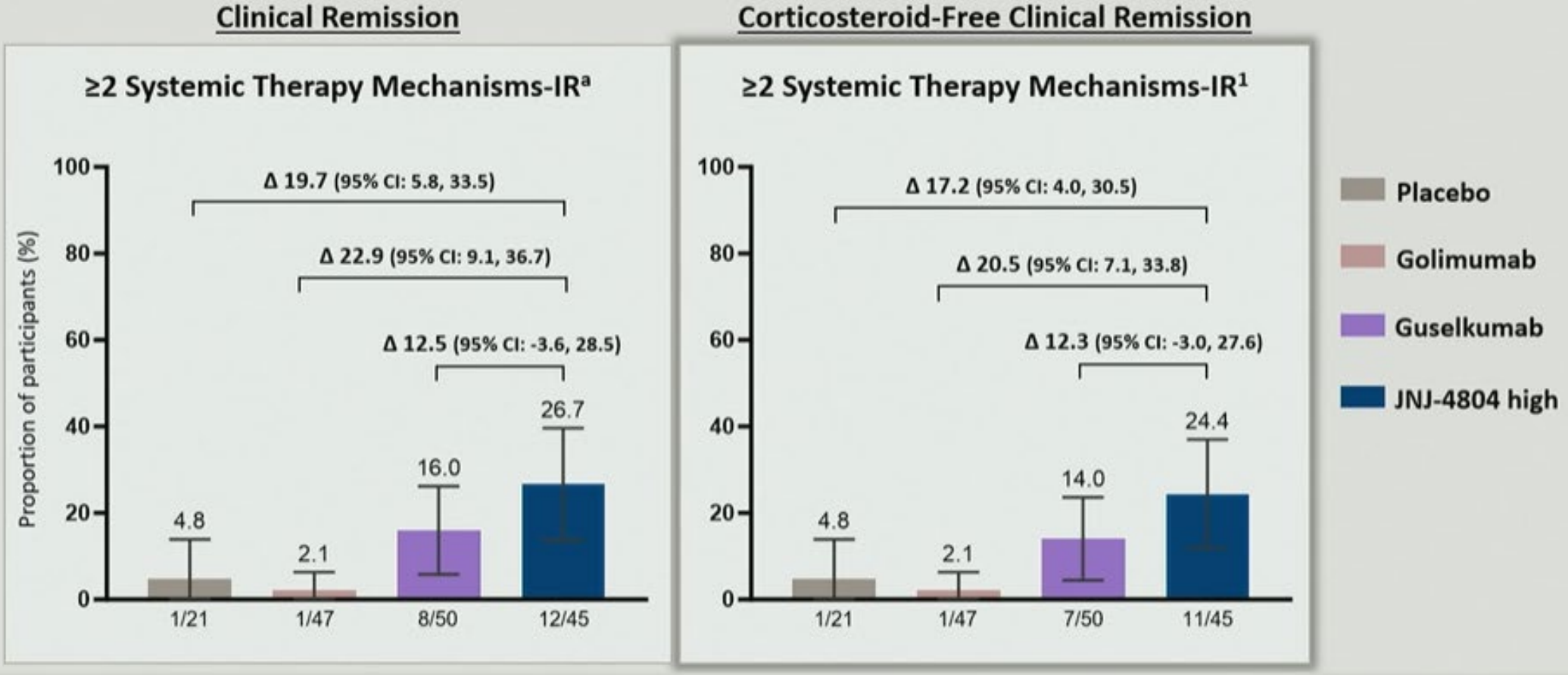
[1]Patients who were inadequate responders to two or more mechanisms of systemic therapies. Modified Full analysis set (Full analysis set excluding participants with a modified Mayo <5 or missing at baseline).
***CI**=confidence interval, **IR**=inadequate response or intolerance.*

Key Secondary Endpoint: Histologic Remission AND Endoscopic Improvement at Week 48 (≥2 Systemic Therapy Mechanisms-IR Population)



Histologic remission AND endoscopic improvement: absence of neutrophils from the mucosa (both lamina propria and epithelium), no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system, and an endoscopy subscore of 0 or 1 per central review of the video endoscopy

Key Secondary Endpoint: Corticosteroid-Free Clinical Remission at Week 48 (≥2 Systemic Therapy Mechanisms-IR Population)



Corticosteroid-free clinical remission: a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 per central review of the video endoscopy, with no corticosteroids received for at least 60 days

Of the participants in clinical remission at Week 48 in the JNJ-4804 high dose group, 11/12 (91.7%) were corticosteroid-free

[1]Patients who were inadequate responders to two or more mechanisms of systemic therapies. Modified Full analysis set (Full analysis set excluding participants with a modified Mayo <5 or missing at baseline).

***CI**=confidence interval, **IR**=inadequate response or intolerance.*

Summary of Exposure-Adjusted Adverse Events Through Week 48[1] (Overall Population)

	Placebo	Golimumab	Guselkumab	JNJ-4804 Low dose	JNJ-4804 Mid dose	JNJ-4804 High dose	JNJ-4804 Combined
Safety analysis set	52	104	103	103	105	105	313
Total patient-years of follow-up	25.5	65.0	73.0	72.2	76.1	85.1	233.4
Events per hundred patient-years [number of events]							
AEs	490.2 [125]	449.2 [292]	419.0 [306]	405.7 [293]	385.1 [293]	490.1 [417]	429.7 [1003]
SAEs	27.5 [7]	21.5 [14]	9.6 [7]	19.4 [14]	11.8 [9]	10.6 [9]	13.7 [32]
AEs leading to discontinuation of study treatment	27.5 [7]	18.5 [12]	5.5 [4]	12.5 [9]	6.6 [5]	3.5 [3]	7.3 [17]
Infections	109.8 [28]	100.0 [65]	98.6 [72]	98.3 [71]	93.3 [71]	82.3 [70]	90.8 [212]
Serious infections	3.9 [1]	7.7 [5]	0.0 [0]	1.4 [1]	3.9 [3]	3.5 [3]	3.0 [7]
Deaths	0.0 [0]	0.0 [0]	0.0 [0]	0.0 [0]	0.0 [0]	0.0 [0]	0.0 [0]

Most infections were mild or moderate and did not result in treatment discontinuation

The most frequently reported treatment-emergent AEs (reported in ≥5% of participants for all groups) were ulcerative colitis and nasopharyngitis

[1]Excludes inadequate responder events after treatment escalation at Week 24.
***AE**=adverse event, **SAE**=serious adverse event.*

Treatment-Emergent AEs of Interest Through Week 48[1]

	Placebo	Golimumab	Guselkumab	JNJ-4804 Low dose	JNJ-4804 Mid dose	JNJ-4804 High dose
Safety analysis set	52	104	103	103	105	105
Major adverse cardiovascular events	0	1 (1.0%)	0	1 (1.0%)	0	0
Venous thromboembolism	0	3 (2.9%)	0	0	0	1 (1.0%)
Clinically important hepatic disorders	0	0	0	0	0	0
Opportunistic infection	0	0	1 (1.0%)	0	1 (1.0%)	0
Participants with ≥1 AE of special interest						
Invasive fungal infection	0	0	0	0	0	0
Hepatitis B reactivation	0	0	0	0	0	0
Tuberculosis	0	0	0	0	1 (1.0%)	0
Malignancy	0	0	1 (1.0%)	1 (1.0%)	1 (1.0%)	0
Hypersensitivity reaction	0	0	0	1 (1.0%)	0	0
Congestive heart failure	0	0	0	1 (1.0%)	0	0
Demyelinating disorders	0	0	0	0	0	0
Lupus-like syndrome	0	0	0	0	0	0

1 case of active tuberculosis (JNJ-4804 mid-dose), and 1 other opportunistic infection of esophageal candidiasis (GUS)

3 malignancies, all basal cell carcinomas, in participants with no prior history; all continued in study after excision

Conclusions

- JNJ-4804, the first co-antibody therapy in development for IBD, delivered clinically meaningful efficacy exceeding that of the monotherapies in patients with treatment-refractory disease
- In the overall population, efficacy of high-dose JNJ-4804 was superior to golimumab and numerically greater than guselkumab
- In patients with disease refractory to two or more systemic therapy mechanisms, high-dose JNJ-4804 exceeded the additive effects of golimumab and guselkumab across all key clinical, endoscopic, and histologic-endoscopic endpoints
- The safety profile of JNJ-4804 through 48 weeks was consistent with the well-established safety profiles of the component monotherapies
- Building on the molecular synergy seen in VEGA, the DUET-UC results support advancement to Phase 3 in patients with disease refractory to systemic therapies, a population with high unmet need

Novel Therapies and Therapeutic Strategies Reaching the Clinic in the Coming Years

Bruce E. Sands, MD, MS

Chief of the Dr. Henry D. Janowitz Division of Gastroenterology

Dr. Burrill B. Crohn Professor of Medicine

Icahn School of Medicine at Mount Sinai

Mount Sinai Hospital

Mount Sinai Health System

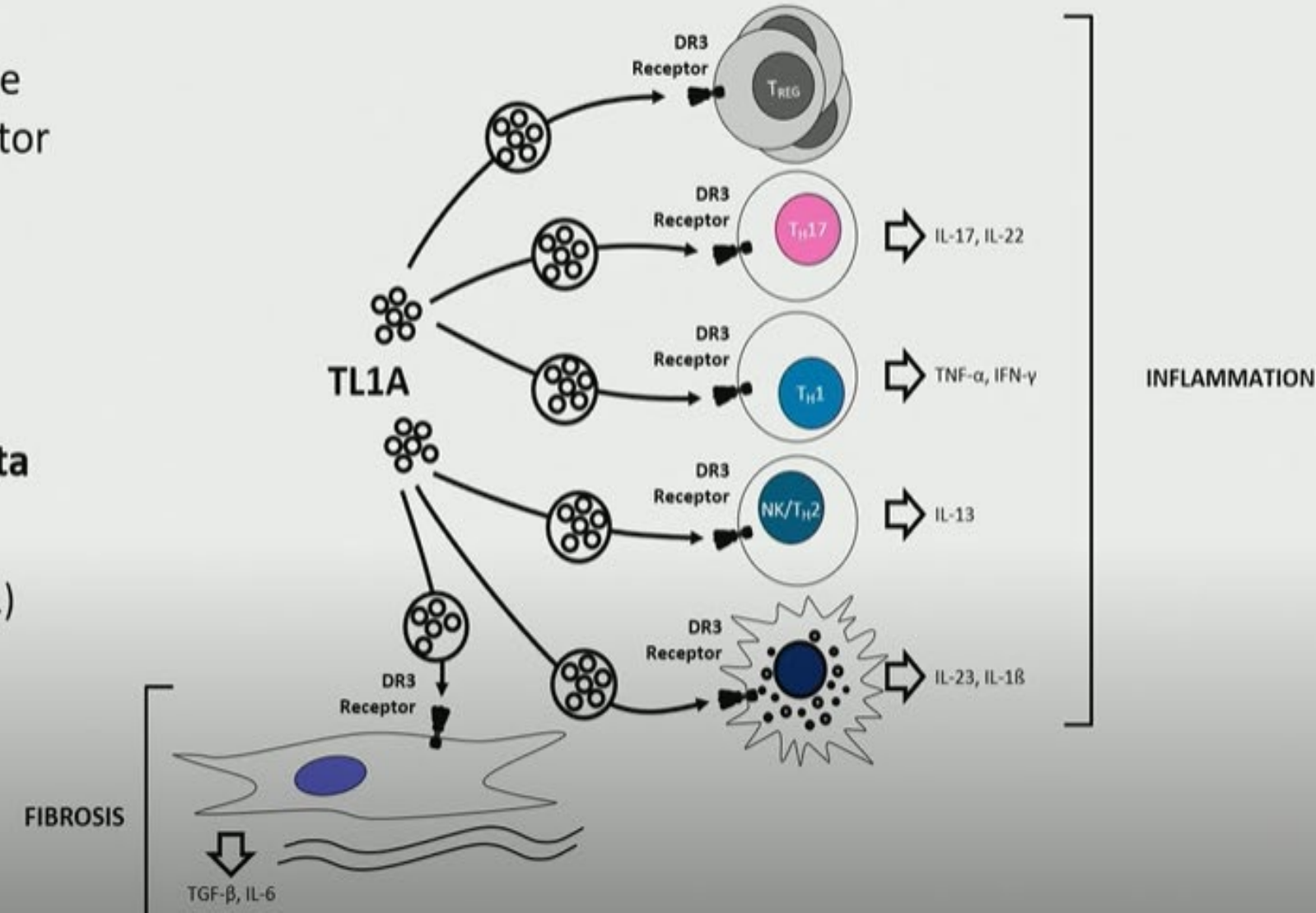
New York, USA

Mount Sinai

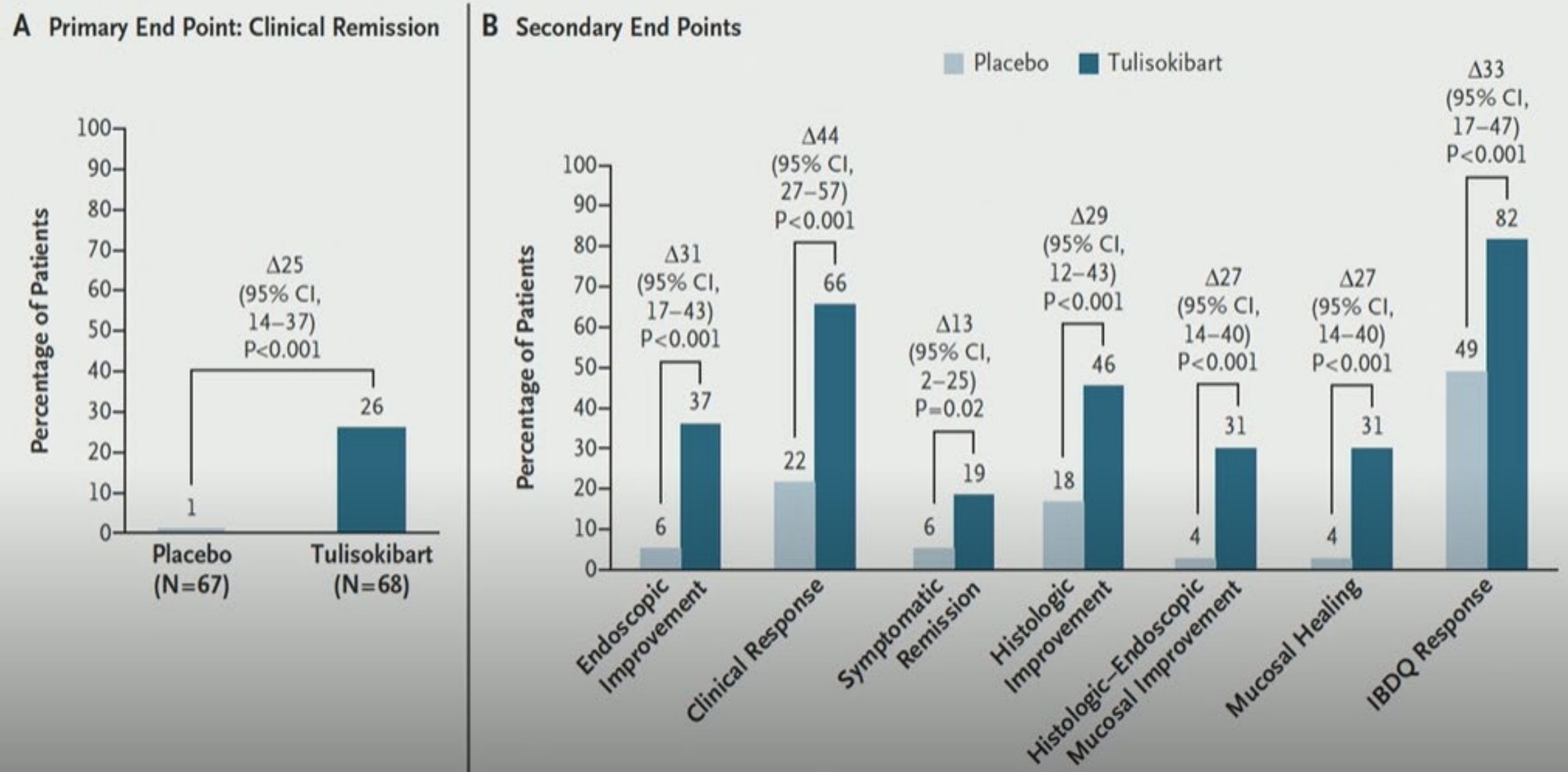
TL1A Inhibitors:

Tulisokibart (PRA-023), Afimkibart (RVT-3101), Duvakitug (TEV-48574)

- TL1A activates innate, adaptive immune pathways through binding death receptor 3 (DR3)[1,3]
- Proinflammatory effects include T-cell activation and enhanced fibrosis[1,3]
- **Three TL1A inhibitors with Phase 2 data**
  - Merck: Tulisokibart (PRA-023)
  - Genentech/Roche: Afimkibart (RVT-3101)
  - Teva/Sanofi: Duvakitug (TEV-48574)[1,2]

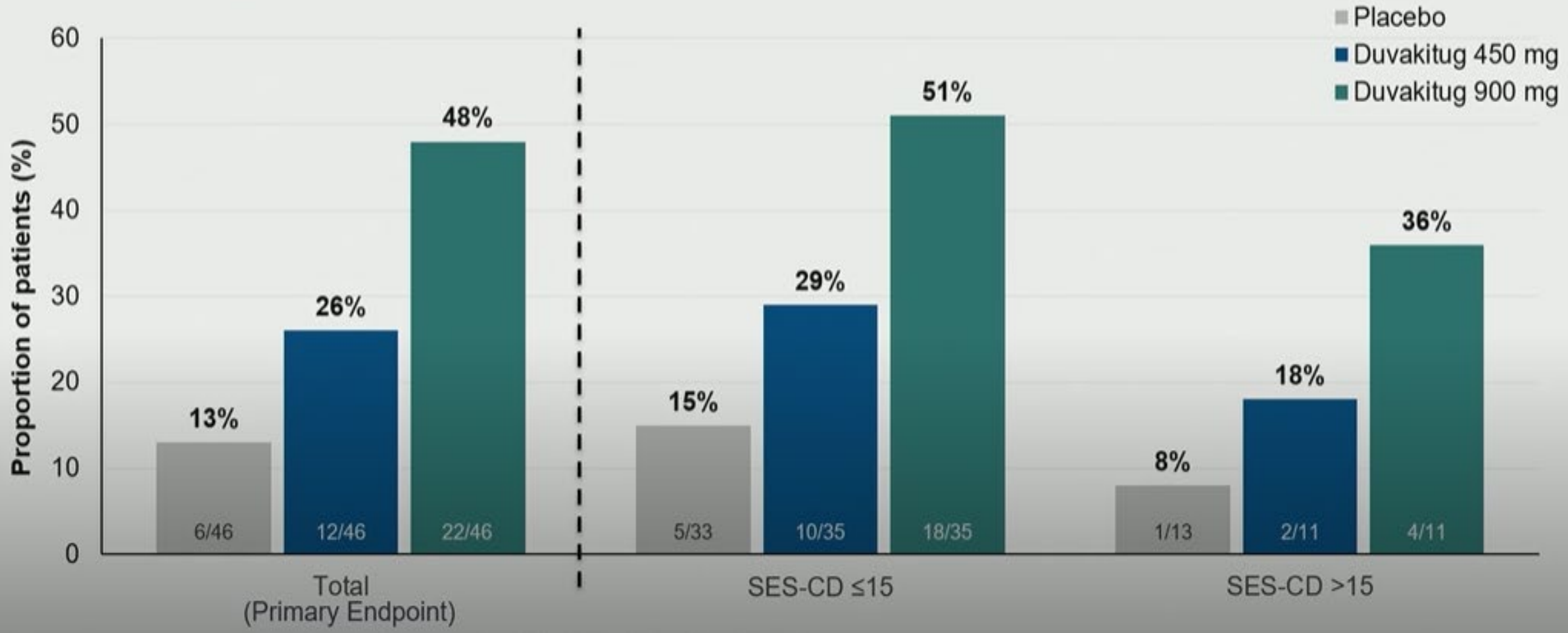


Tulisokibart (anti-TL1A antibody) in UC: Cohort 1



Duvakitug (anti-TL1A antibody) in Crohn's Disease:

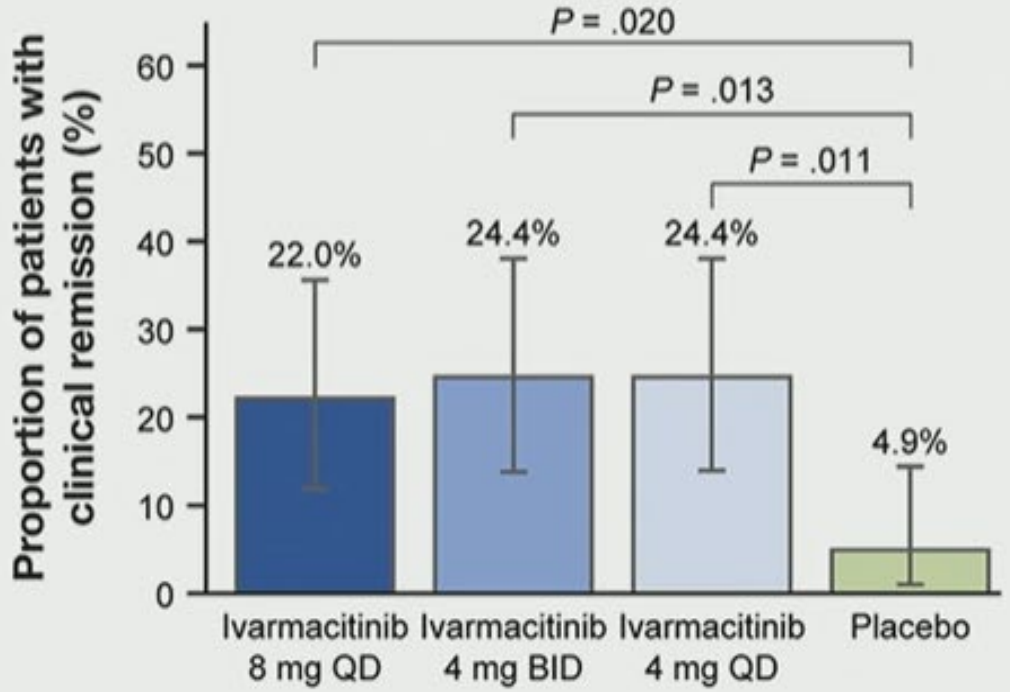
Endoscopic response at Week 14 in patients with baseline SES-CD score of ≤15 or >15

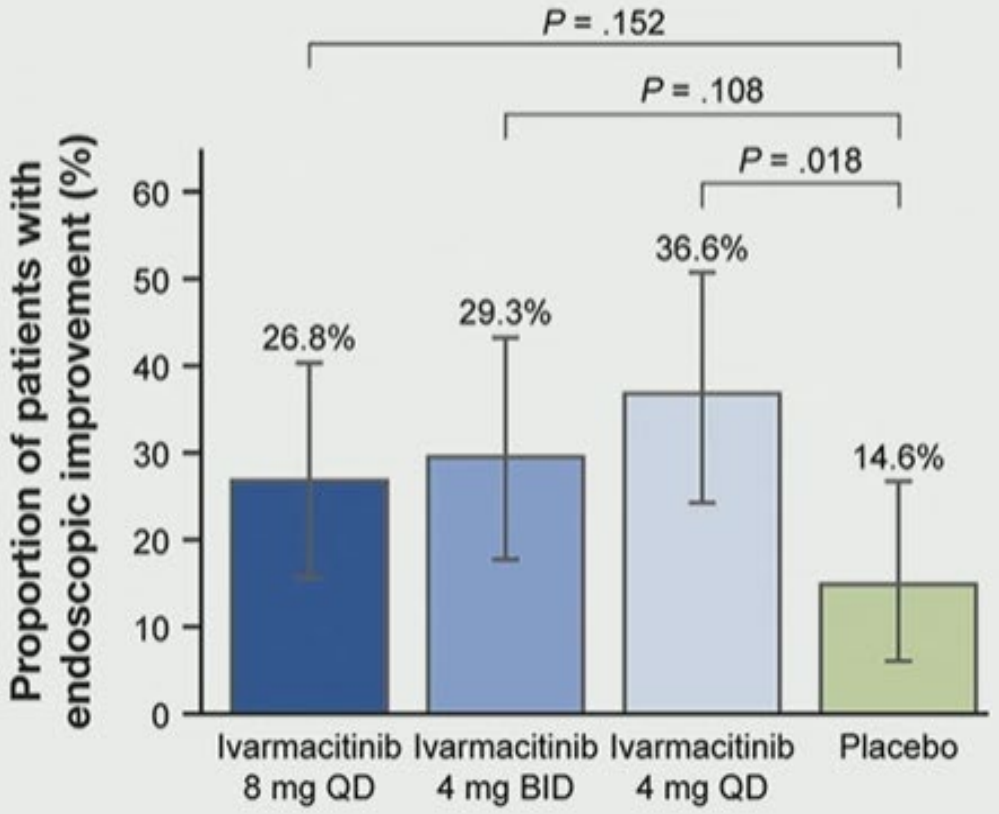


What new targets are on the radar screen?

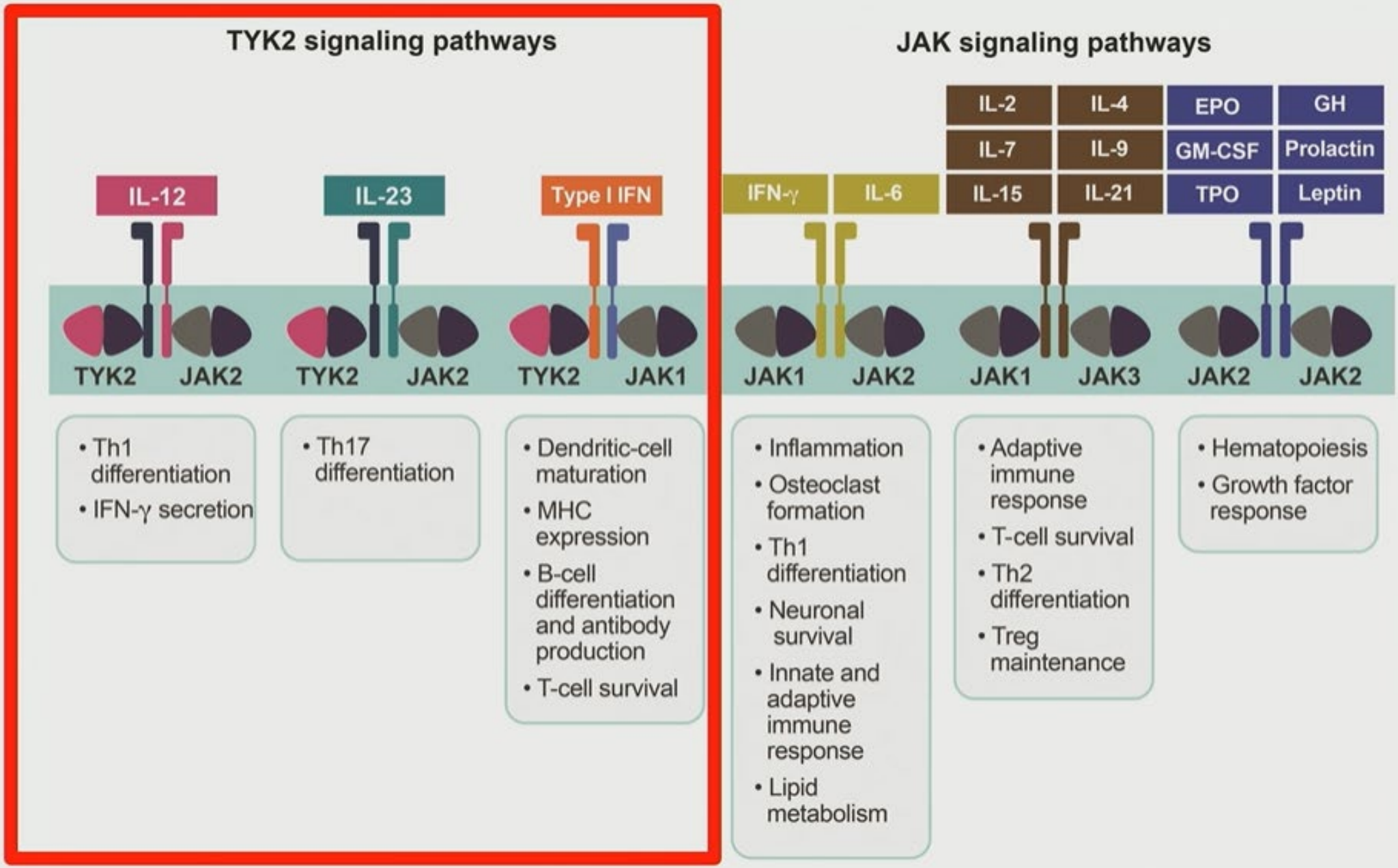
Agent	Class/Target	Sponsor	Status	Indication
VTX-002	S1P modulator	Ventyx Biosciences	Phase 2 reported	UC
Amiselimod	S1P modulator	Mitsubishi Tanabe/Bausch Health	Phase 2 reported	UC
PL8177	Melanocortin-1 agonist	Palatin Technologies	Active Phase 2	UC
Vidofludimus	Oral dihydroorotate dehydrogenase inhibitor	Immunic	Ongoing Phase 2	UC & CD
Ivarmacitinib (SHR0302)	JAK1 inhibitor	Reistone Biopharma	Phase 2 reported; in Phase 3	UC
Zasocitinib (TAK-279)	TYK2 inhibitor	Takeda	Active Phase 2	UC
Olamkicept	IL-6 trans-signaling blocker	Ferring Pharmaceuticals/ I-Mab Biopharma	Phase 2 reported	UC, CD
Lusvertikimab	Anti-IL-7R monoclonal antibody	OSE Immunotherapeutics	Phase 2 reported	UC

Ivarmacitinib (SHR0302):
Phase 2 JAK1 Selective Inhibitor for Moderate-to-Severely Active UC





Chen B, et al. Gastroenterology 2022;163:1555–1568



Danese S, Peyrin-Biroulet L. Inflammatory Bowel Diseases, 2021;27:2023–30

Zasocitinib (TAK-279) Selectivity for TYK2 Over JAK1 is Due to a Single Amino Acid Difference in the Allosteric Binding Sites

LATITUDE UC
NCT06254950

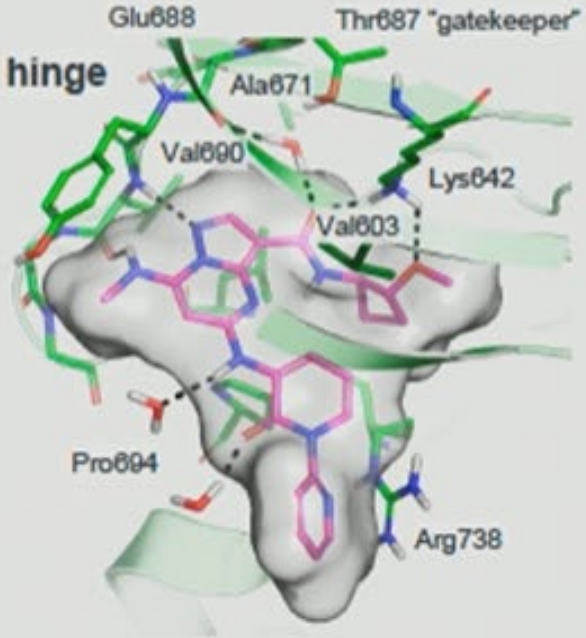
- Zasocitinib is an investigational TYK2 inhibitor with more than 1.3 million-fold greater selectivity for TYK2 as compared with JAK1, JAK2, and JAK3[1]
- The dissociation constant, K_D, describes binding affinity; lower K_D indicates greater binding affinity[2]

Zasocitinib binding to JH2 domain of TYK2[1]

Zasocitinib TYK2 JH2 K_D = 0.0038 nM

TYK2 JH2 pseudokinase domain exhibits a canonical kinase bilobal fold connected by a conserved hinge region[2,3]

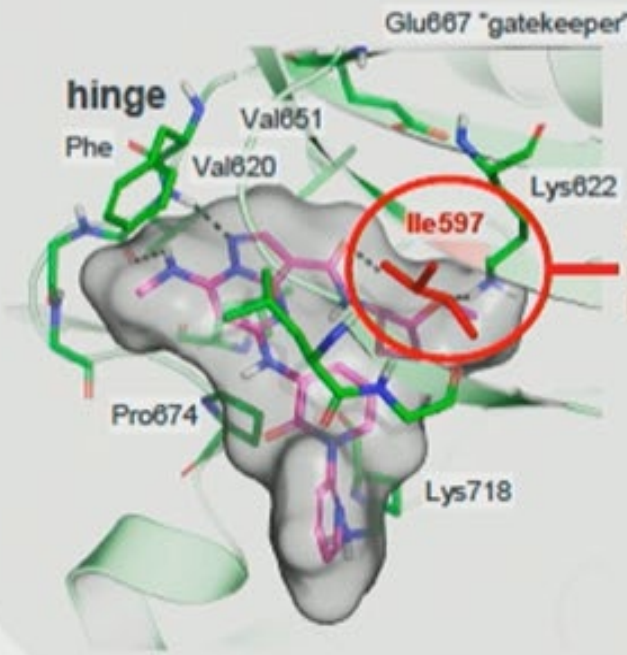
This hinge region is involved in ATP binding, which is important for TYK2 structural stabilization and controlled cytokine signaling[2]



Zasocitinib exhibits a strong steric fit into the binding pocket defined by Val603 and Lys642[1]

Zasocitinib binding to JH2 domain of JAK1[1]

Zasocitinib JAK1 JH2 K_D = 4975 nM



Steric clash with non-conserved Ile597

Ile597 of JAK1 JH2 provides increased steric occlusion of the binding pocket, leading to weak binding affinity of zasocitinib to the JAK1 JH2 domain[1]

Used with permission from Leit et al, 2023.

Zasocitinib has not been approved by any regulatory body nor has the safety or effectiveness been established. There is no guarantee that the product will receive regulatory approval and become commercially available for the use(s) being investigated.

ATP, adenosine triphosphate; JAK, Janus kinase; JH, JAK homology; K_D, dissociation constant; TYK2, tyrosine kinase 2.

1. Leit S, et al. *J Med Chem*. 2023;66:10473-10496. 2. Min X, et al. *J Biol Chem*. 2015;290:27261-27270. 3. Sik MF, et al. *ACS Omega*. 2022;9:6195-6209.

Olamkicept:
IV selective inhibitor of soluble interleukin-6 (sIL-6R)/IL-6 complex in UC

CONCLUSION In patients with active ulcerative colitis, biweekly infusion of olamkicept 600 mg, but not 300 mg, resulted in greater likelihood of clinical response at 12 weeks vs placebo. More research is needed for replication and to assess longer-term efficacy and safety.

© AMA

POPULATION

66 Men
25 Women

Adults with active ulcerative colitis and an inadequate response to conventional therapy

Mean age: 41 years

LOCATION

22
Clinical sites in mainland China, Taiwan, and South Korea

INTERVENTION

91 Patients randomized
88 Patients analyzed

30 Olamkicept, 600 mg Intravenous olamkicept

31 Olamkicept, 300 mg Intravenous olamkicept

30 Placebo Intravenous placebo

All groups received infusions on days 0, 14, 28, 42, 56, and 70 plus concomitant corticosteroids, oral immunosuppressants or 5-aminosalicylates

PRIMARY OUTCOME

Clinical response at week 12 (defined as ≥3 and ≥30% decrease from baseline total Mayo score)

FINDINGS

Rate of clinical response at week 12

Olamkicept, 600 mg 17 of 29 patients	58.6%
Olamkicept, 300 mg 13 of 30 patients	43.3%
Placebo 10 of 29 patients	34.5%

Adjusted difference:

600 mg olamkicept vs placebo, 26.6%
(90% CI, 6.2% to47.1%), *P* = .03

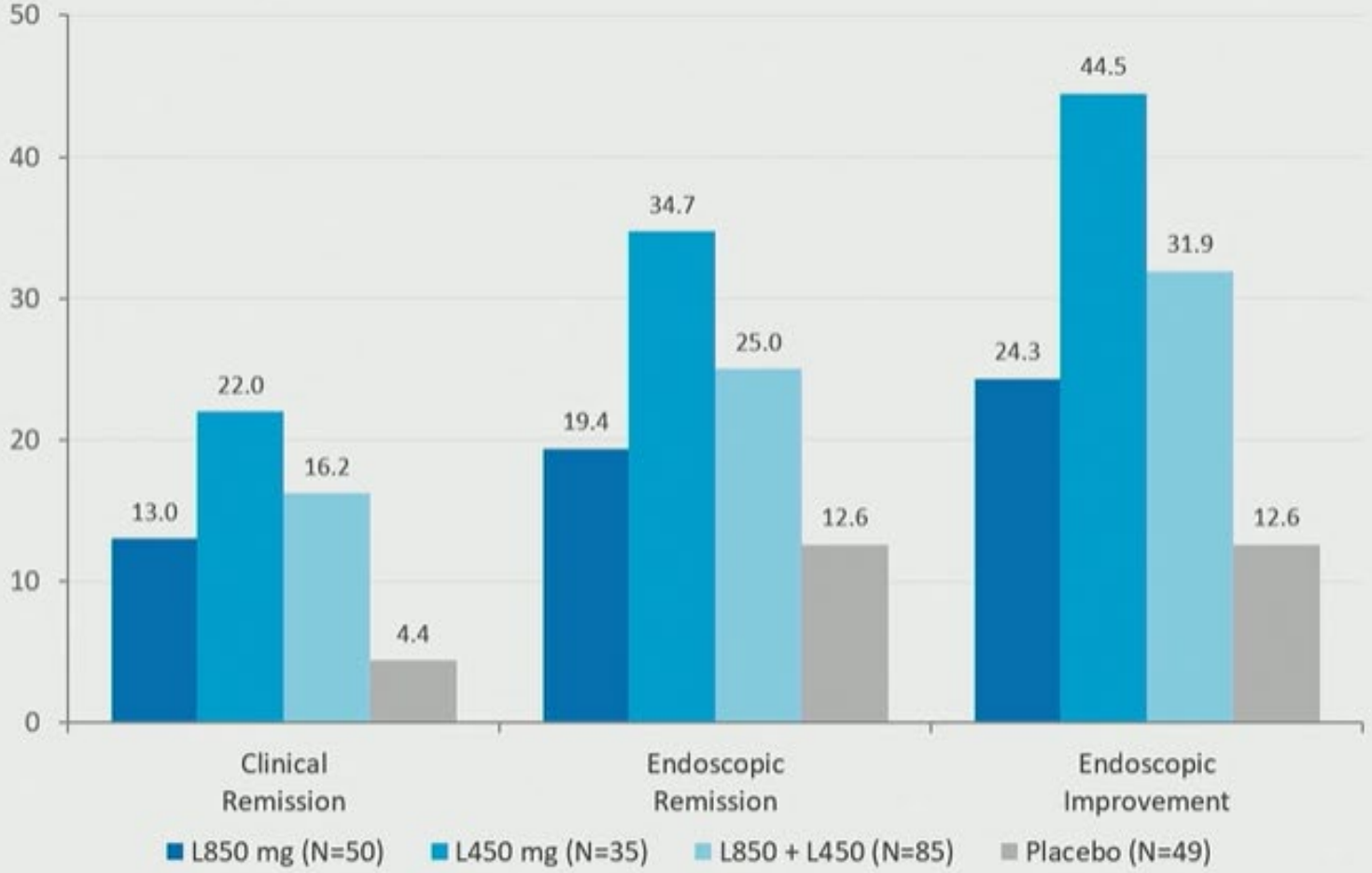
300 mg olamkicept vs placebo, 8.3%
(90% CI, −12.6% to 29.1%), *P* = .52

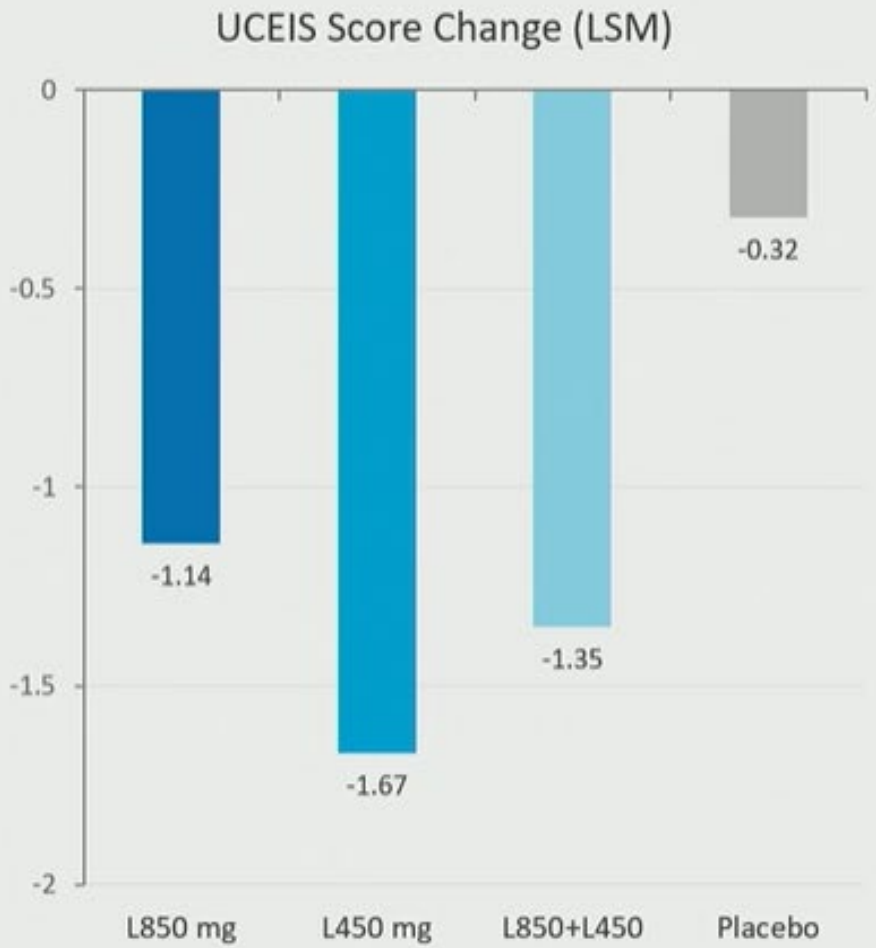
Zhang S, Chen B, Wang B, et al. Effect of induction therapy with olamkicept vs placebo on clinical response in patients with active ulcerative colitis:

Lusvertikimab (anti-IL7R antibody) in UC

Week 10 Efficacy Endpoints

- Randomized 1:1:1 to placebo, 450 mg or 850 mg IV at W0, W2 and W6
- 450mg dose dropped at a prespecified futility analysis after 58 patients but later shown not futile
- Prespecified primary endpoint was change from baseline MMS at W10





P-values vs Placebo (two-sided)

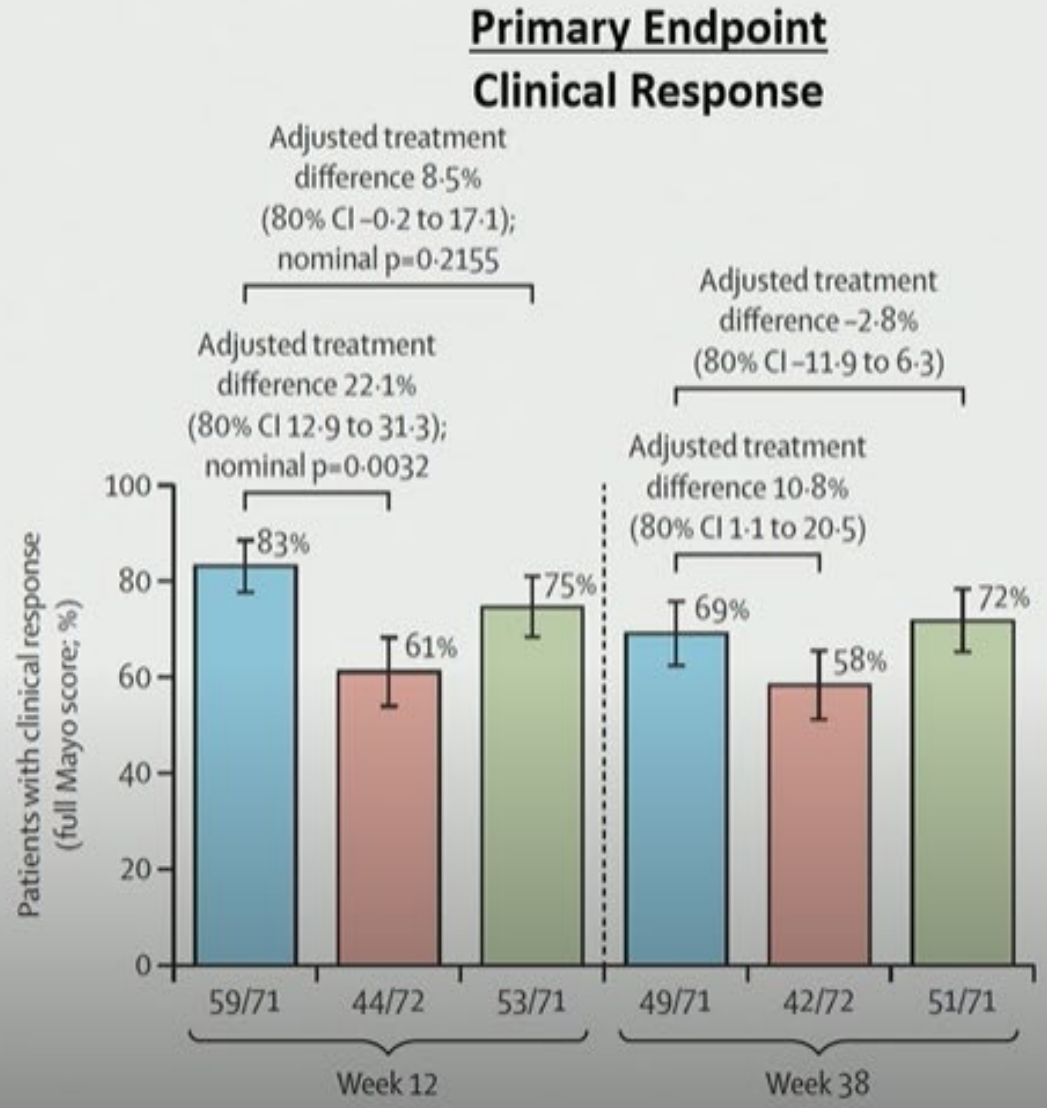
	Clinical Rem.	Endo. Rem.	Endo. Improv.	UCEIS
L850 mg	0.161	0.385	0.166	0.051
L450 mg	**0.030***	**0.032***	**0.004***	**0.006***
L850+L450	0.066	0.120	**0.027***	**0.007***

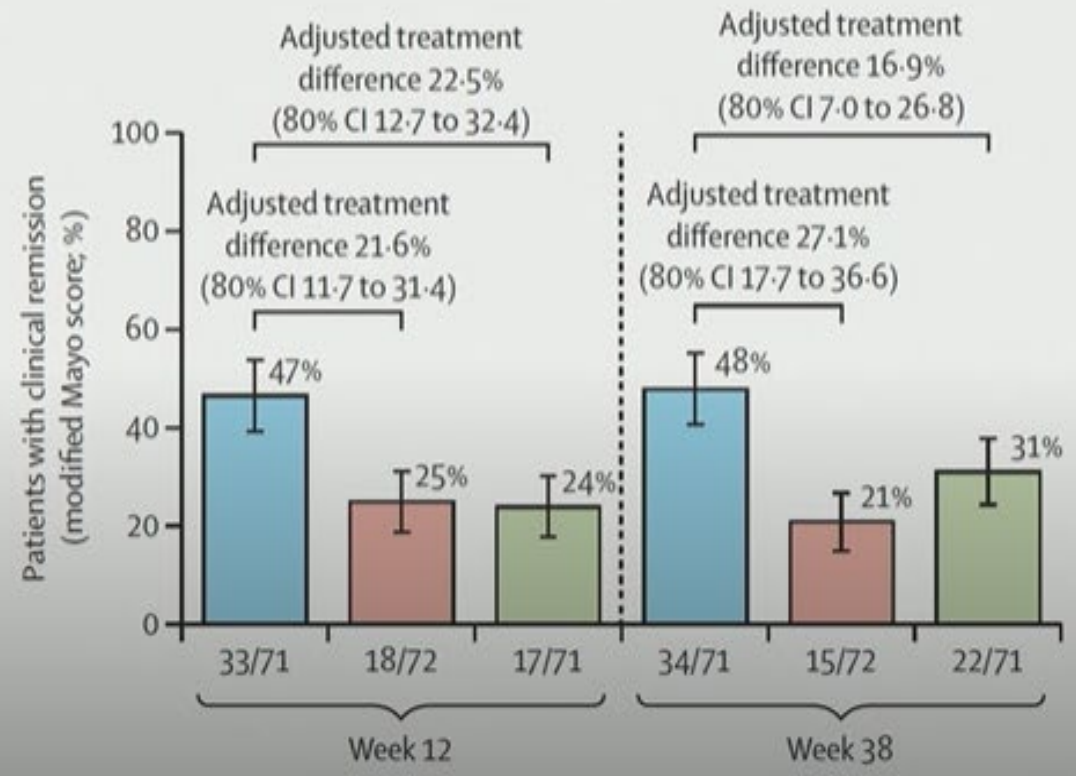
Clinical remission: MMS ≤ 2, no individual sub-score > 1, rectal bleeding = 0
Endoscopic remission: endoscopic Mayo sub-score = 0; Endoscopic improvement: endoscopic sub-score of Mayo ≤ 1

*Statistically significant vs placebo (two-sided $p < 0.05$)

Bourreille A, et al. J Crohn's Colitis. 2025;19:i71–i72

Guselkumab plus golimumab vs guselkumab or golimumab monotherapy in moderate to severe UC





Ongoing Advanced Combination Therapy Trials

DUET-UC (GOL + GUS)
NCT05242484

Tues., May 5
11:15 am-11:30 am
Location: W375c
Presentation ID: 1058d
Abreu MT, et al.

DUET-CD (GOL + GUS)
NCT05242471

Tues., May 5
9:15 am-9:30 am
Location: W180
Presentation ID: 979f
Sands B, et al.

VEDO + UPA in UC
NCT06095596

VICTRIVA (VEDO + UPA) in CD
NCT06227910

MIRI + Eltrekibart (7 ELR+ CXC chemokines) in UC
NCT06598943

COMMIT UC (MIRI + tirzepatide)
NCT06937086

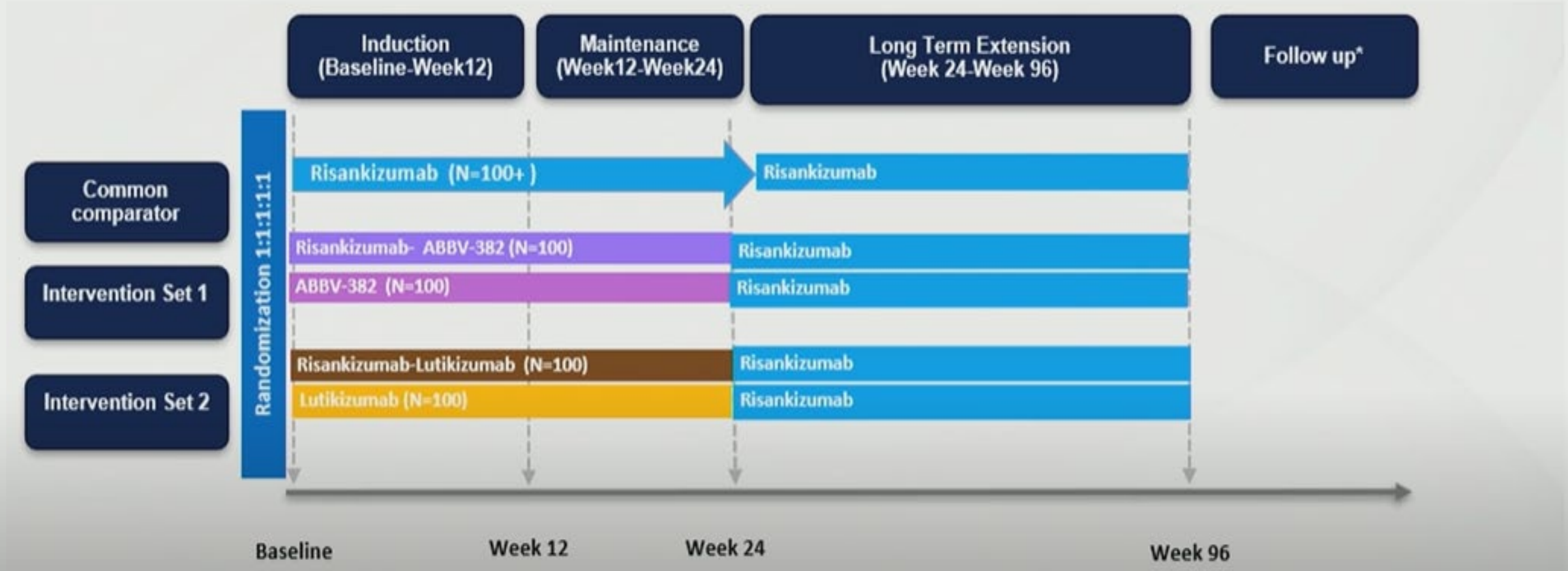
UPA + UST vs UST in CD
NCT06520397

BI706231 + ustekinumab
NCT04978493

TARGET CD (trosunilimab/lutikizumab ± RISA, ABBV-8736)
NCT06548542

SKYLINE ($\alpha4\beta7$+TL1A, $\alpha4\beta7$+IL-23, IL-23+TL1A)
NCT07012395

TARGET-CD: Risankizumab Platform Study

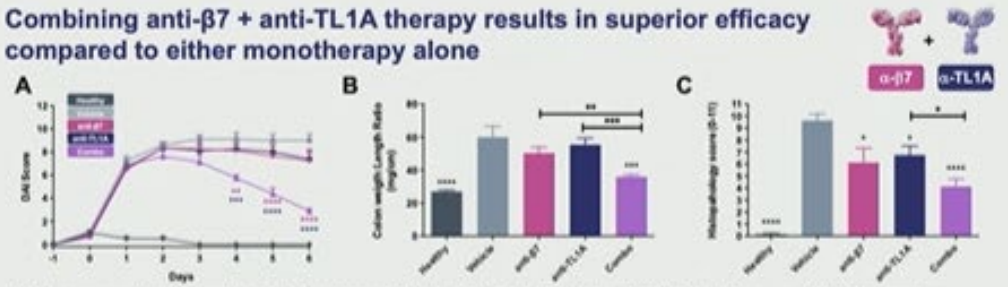


- Trosunilimab (ABBV-382) is an investigational humanized monoclonal antibody designed to bind to $\alpha 4\beta 7$ integrin
- Lutikizumab a dual variable domain IgG that neutralizes both IL-1α and IL-1β

SKYLINE: Which combination?

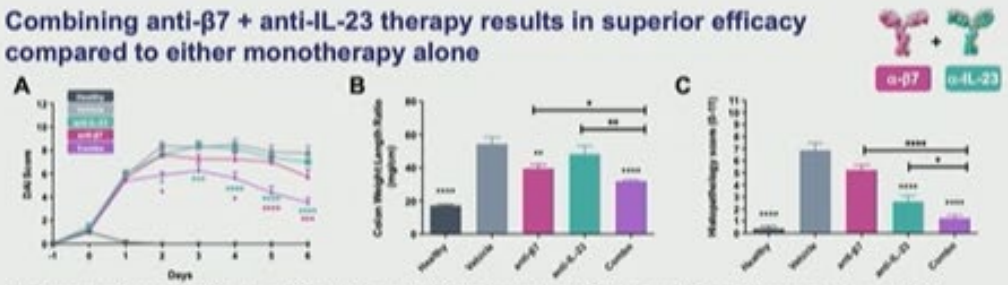
Program	Target	Phase 1	Phase 2	Phase 3	Status
SPY001	α4β7				Ph2 initiated
SPY002	TL1A				Ph2 initiated
SPY003	IL-23				Ph2 initiated
SPY120	α4β7 + TL1A				Ph2 initiation expected after Part A (mono open-label)
SPY130	α4β7 + IL-23				Ph2 initiation expected after Part A (mono open-label)
SPY230	IL-23 + TL1A				Ph2 initiation expected after Part A (mono open-label)

Combining anti-β7 + anti-TL1A therapy results in superior efficacy compared to either monotherapy alone



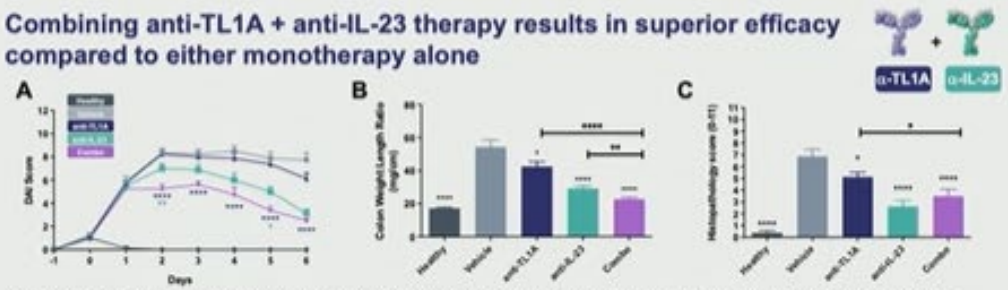
*N=8 per group, all doses were 25 mg/kg of each agent; * P<0.05, ** P<0.01, *** P< 0.001, **** P< 0.0001; two-way ANOVA for combo vs. mono using Dunnett's correction for DAI, one-way ANOVA vs. vehicle control using Dunnett's correction for colon W:L ratio and histopathology; t-test for combo vs. mono.*

Combining anti-β7 + anti-IL-23 therapy results in superior efficacy compared to either monotherapy alone



*N=8 per group; Doses were 25 mg/kg (α-β7) and 1 mg/kg (α-IL-23) in panels A and B; doses were 25 mg/kg for each agent in panel C; * P<0.05, ** P<0.01, *** P< 0.001, **** P< 0.0001; Two-way ANOVA for combo vs. mono using Dunnett's correction for DAI, One-way ANOVA vs. vehicle control using Dunnett's correction for colon W:L ratio and histopathology; t-test for combo vs. mono.*

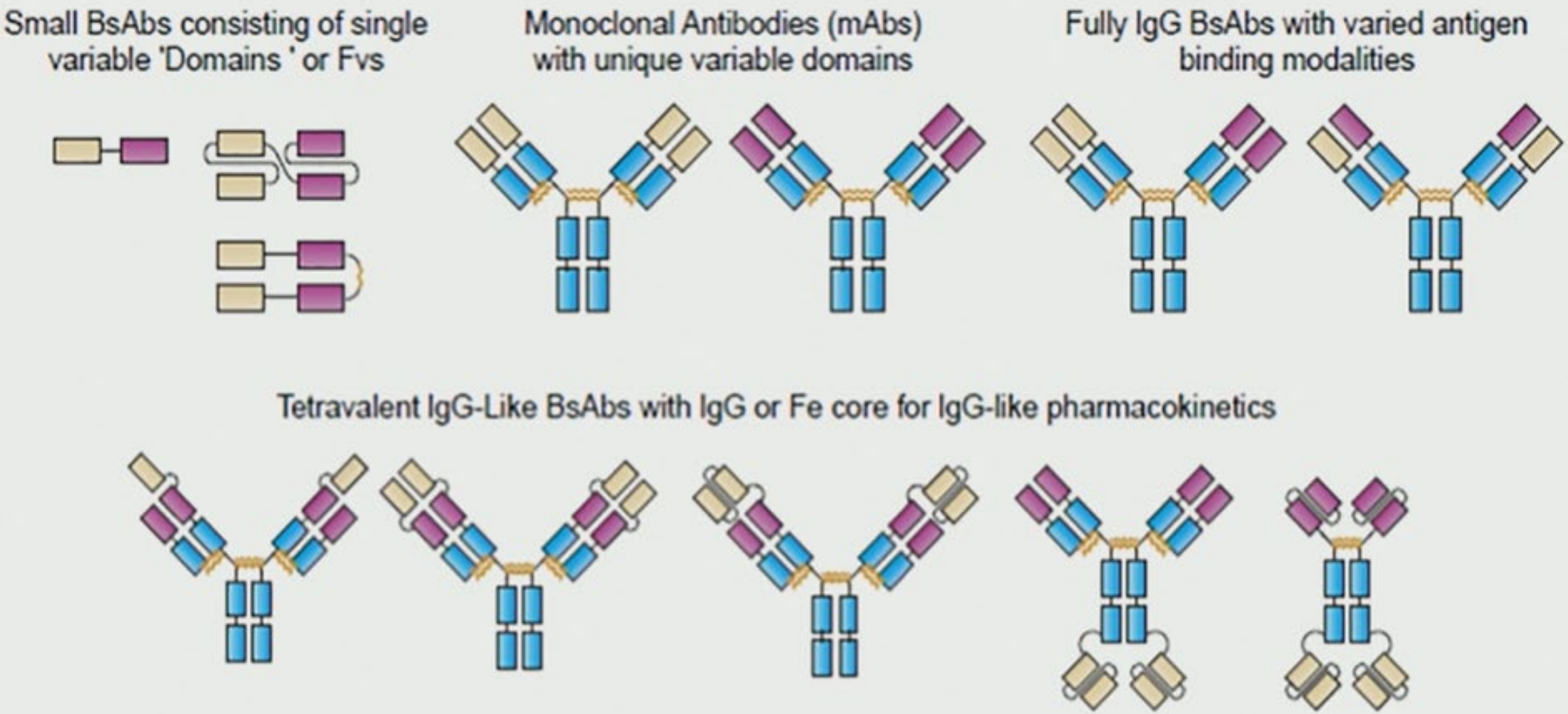
Combining anti-TL1A + anti-IL-23 therapy results in superior efficacy compared to either monotherapy alone



*N=8 per group, all doses were 25 mg/kg of each agent; * P<0.05, ** P<0.01, *** P< 0.001, **** P< 0.0001; Two-way ANOVA for combo vs. mono using Dunnett's correction for DAI; one-way ANOVA vs. vehicle control using Dunnett's correction for colon W:L ratio and histopathology; t-test for combo vs. mono.*

Siegel M et al. MP469 UEGW 2205

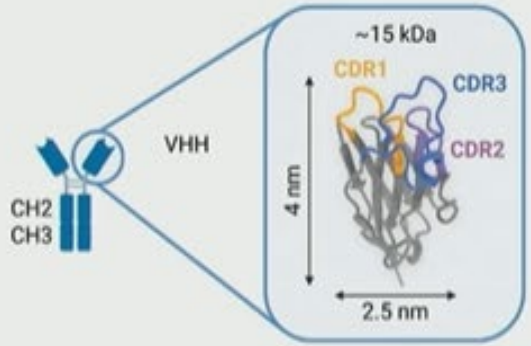
Schematic diagram of bispecific antibody structures



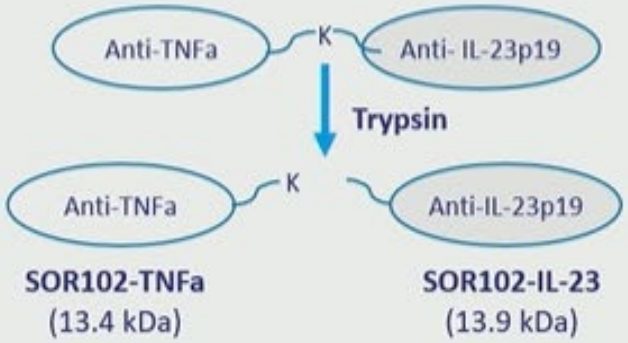
Peyrin-Biroulet L, et al. Autoimmun Rev. 2019;18:123-128.

Single Domain Oral Antibody Platform

Heavy Chain Only VHH Single Domain Antibody[1]



SOR102[2]



SOR102-TNFa (13.4 kDa)

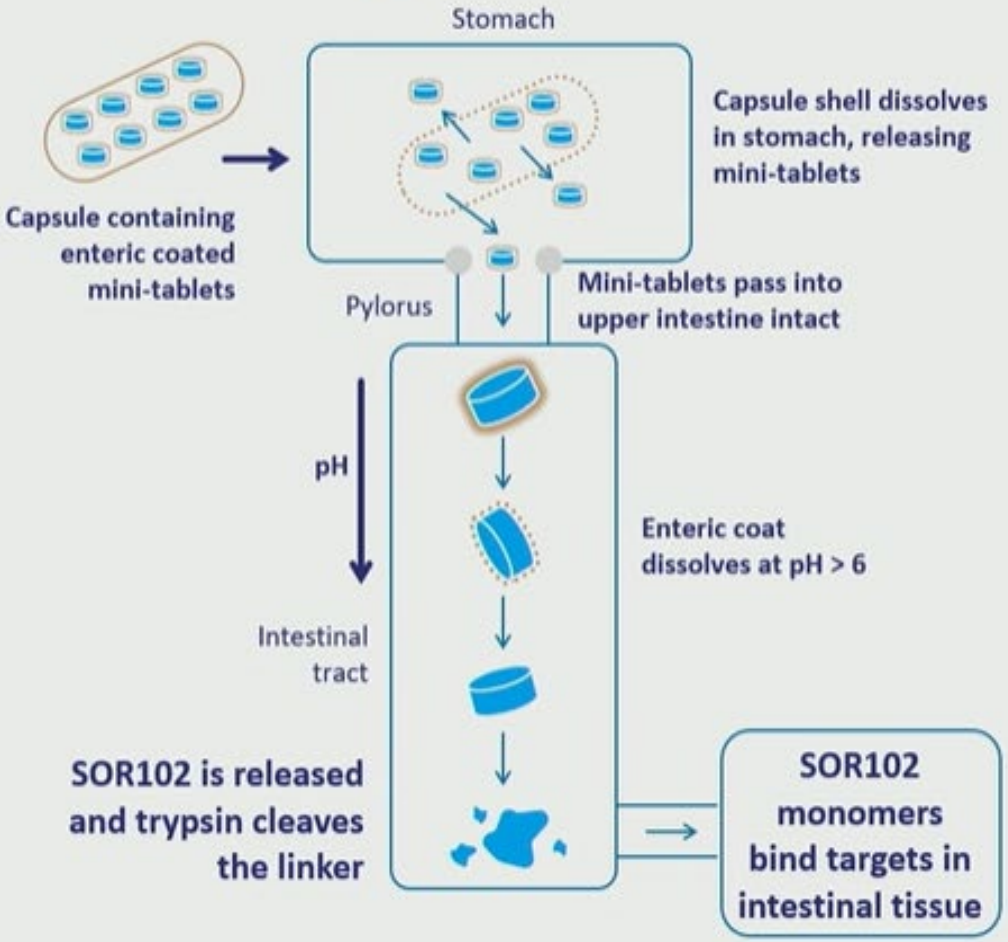
SOR102-IL-23 (13.9 kDa)

SOR102

Mechanism of Action

- Picomolar affinity to TNFa and IL-23p19
- Humanized and **GI stabile (eg protease resistant)**
- SOR102 can bind TNF and IL-23 simultaneously
- Endogenous trypsin cleaves the linker, releasing active VHH monomers to engage each target in tissue

Oral Delivery to Intestinal Tissue[3]



1.Modified from Shen et al 2022, Trends in Molecular Medicine (28) 11:1006 – 1007; 2. Roberts et al 2021, Nat Sci Rep 11 (1):19422; 3. Crowe et al 2019, Drug Dev Ind Pharm, 45 (3):387-394.

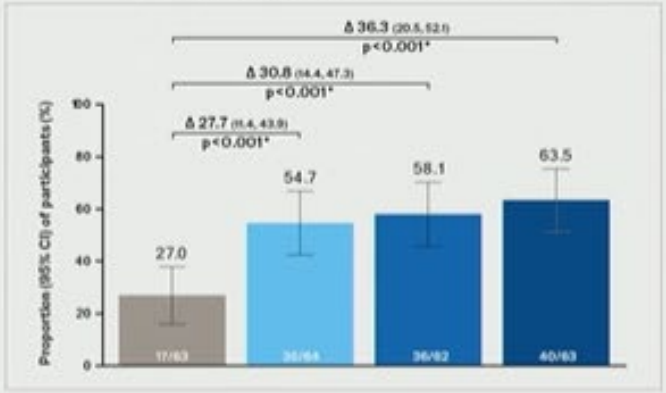
The allure of oral therapies

Drug	Target	Modality	Sponsor	Status
Izencitinib	JAK inhibition	Small Molecule	Theravance	Terminated
GB004	HIF1a stabilizer	Small Molecule	Gossamer Bio	Terminated
BT-11 (omilancor)	LANCL2 activation	Small Molecule	Nimmune Biopharma	Terminated
BBT-401	Pellino-1 inhibition	Small Molecule	Bridge Biotherapeutics	Terminated
PN-943	$\alpha 4\beta 7$	Peptide	Protagonist Therapeutics	Terminated
EB-8018 / TAK018 (sibofimloc)	*FimH* inhibition	Small Molecule	Enterome/Takeda	Terminated
AMT-101	IL-10	Biologic	Applied Molecular Transport	Terminated
NX-13/ABBV-113 (Amelenodor)	NLRX1	Small Molecule	Landos Biopharma/AbbVie	Phase 2
AGB-129	ALK5 (TGFβR1) inhibitor	Small Molecule (Gut-Restricted)	Agomab Therapeutics	Phase 2 for stricturing CD
JNJ-67864238 (Icotrokinra)	IL-23 receptor inhibitor	Peptide	Protagonist Therapeutics/J&J	Phase 3
Obefazimod	miR-124 enhancer	Small Molecule	Abivax	Phase 3 in UC
PALI-2108	PDE4 inhibitor prodrug	Small Molecule	Palisade Bio	Phase 1

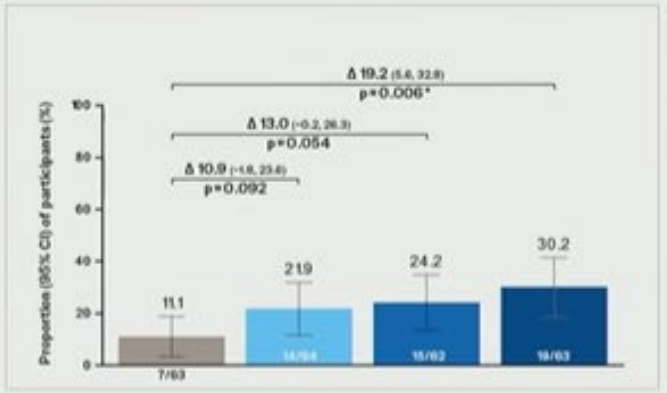
Adapted from Malti P, Sharma R, Maiti and Sharma. Clin Pharmacol Biopharm 2020;9:6

Icotrokinra in moderately to severely active UC: Week 12 results from the Phase 2b ANTHEM-UC study

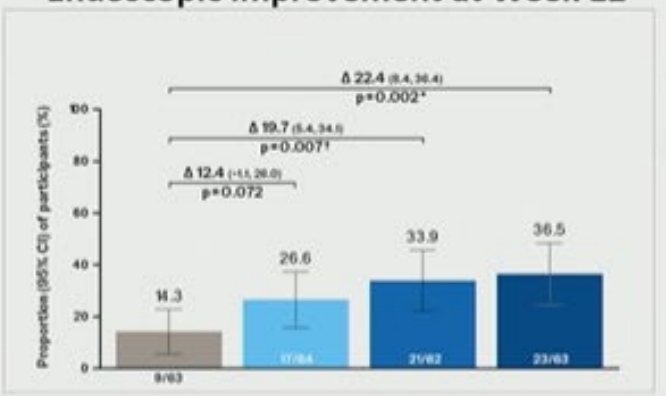
Clinical Response at Week 12



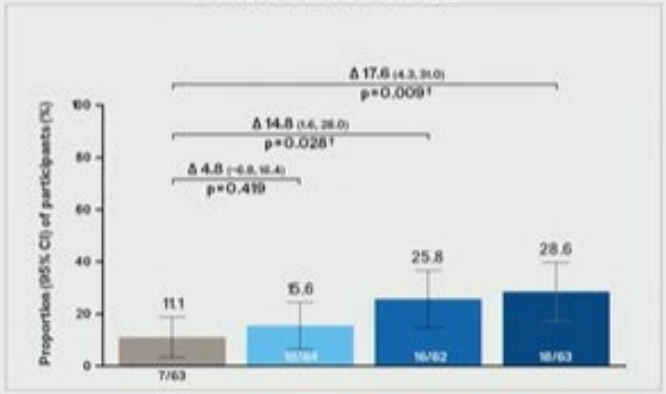
Clinical Remission at Week 12



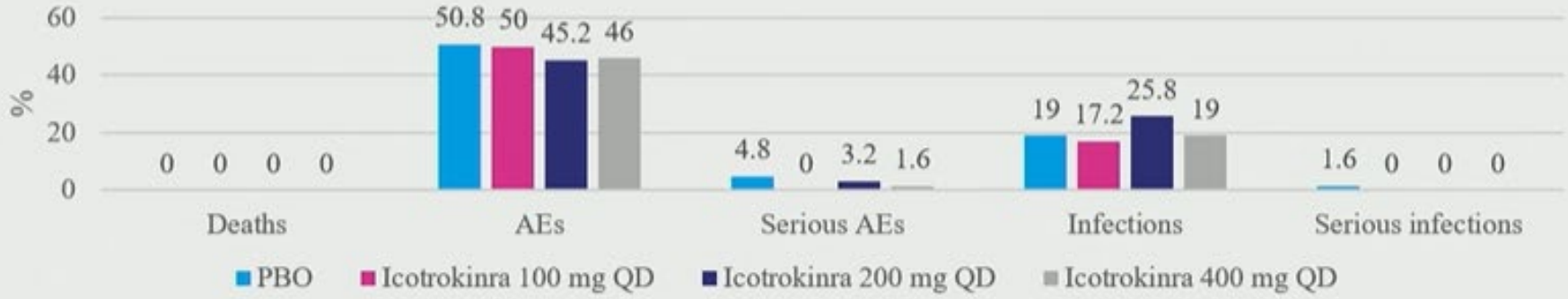
Endoscopic improvement at Week 12



HEMI at Week 12



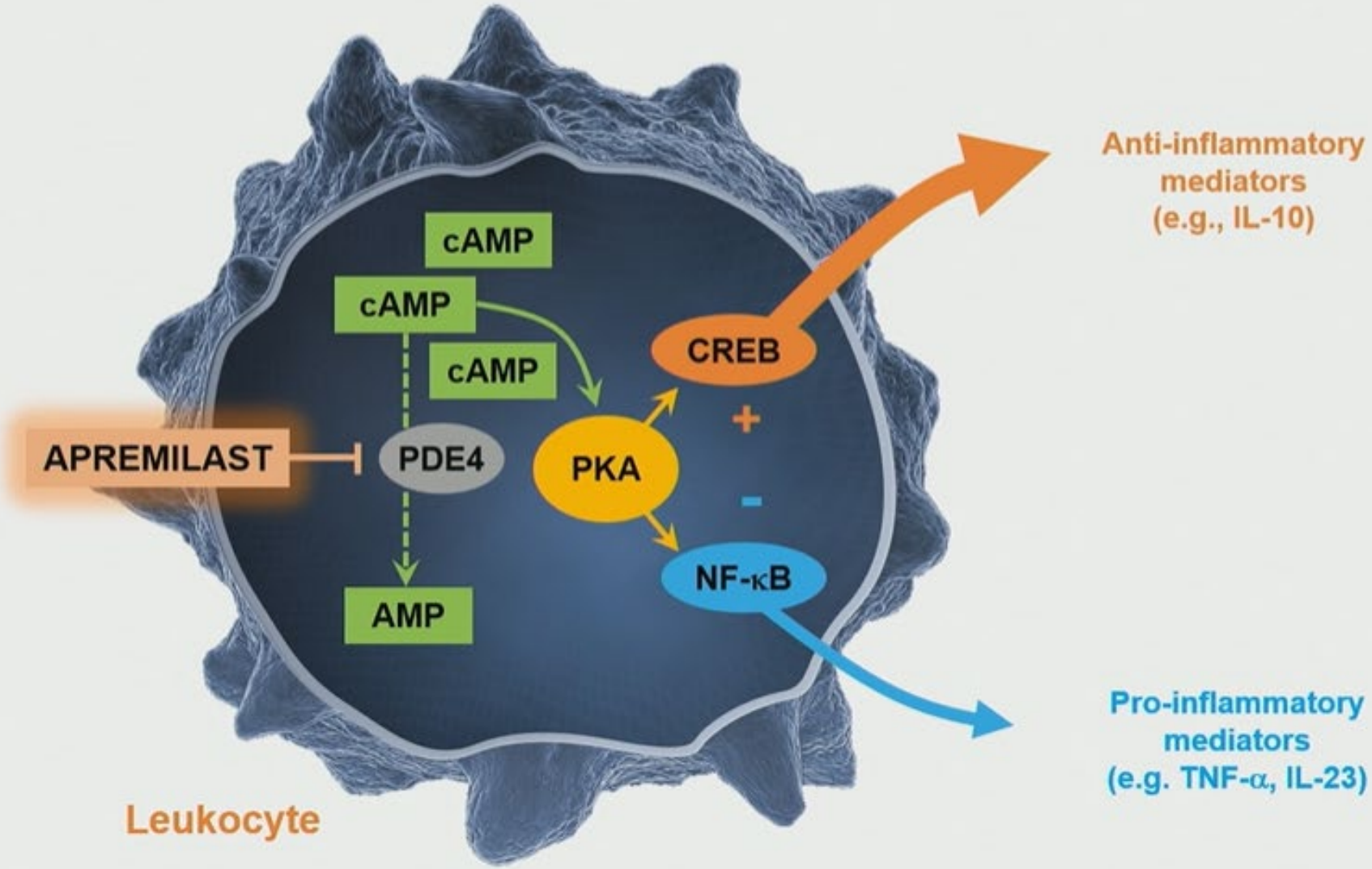
Summary of Adverse Events Through Week 12



Authors' conclusions: In adults with moderately to severely active UC, all tested doses of once-daily oral icotrokinra achieved the primary endpoint of clinical response at Week 12. Icotrokinra was well tolerated.

M. Abreu et al UEG 2025.

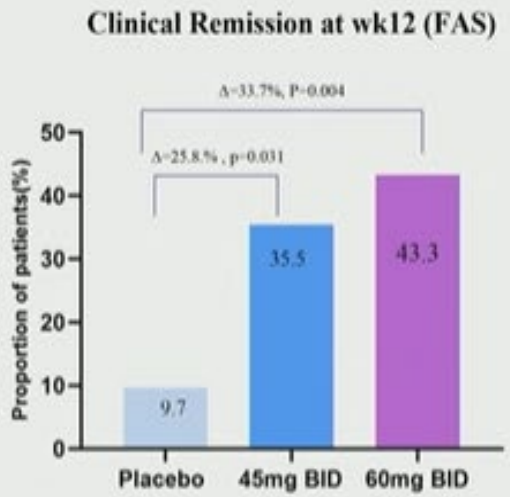
APREMILAST: An oral small molecule PDE4 inhibitor

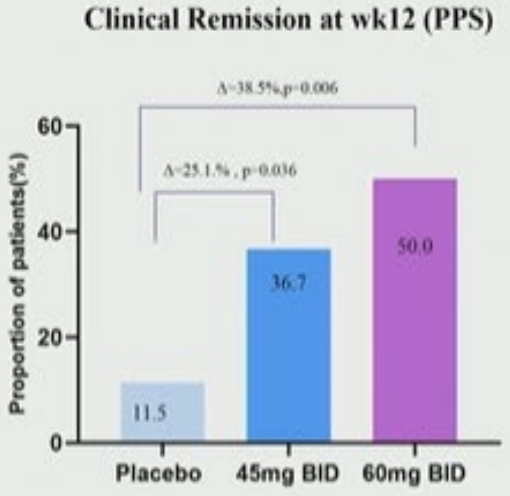


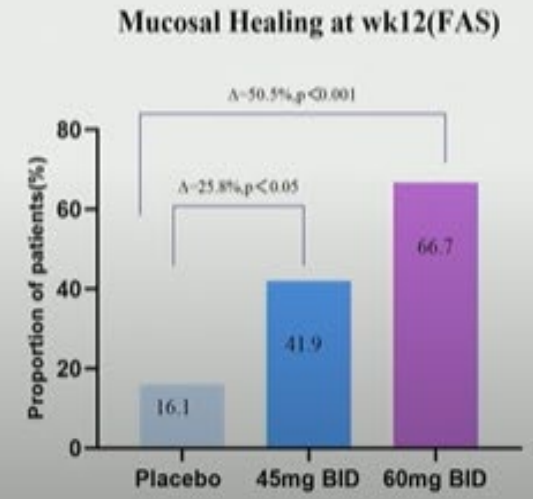
Schafer P. *Biochem Pharmacol.* 2012;83:1583-1590. Ma R, et al. *Int Immunopharmacol* 2008;10:1408–1417. Schafer, et al. *J Immunol Res.* 2015;2015:906349. Spadaccini M, et al. *Int J Mol Sci.* 2017;18:1276. doi:10.3390/ijms18061276

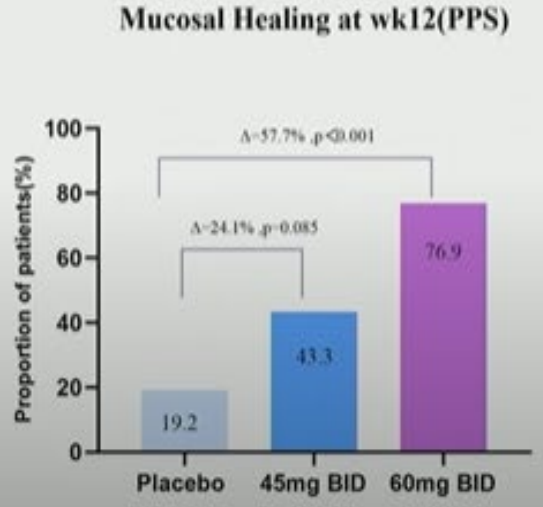
Oral Mufemilast (Selective PDE4 Inhibitor)

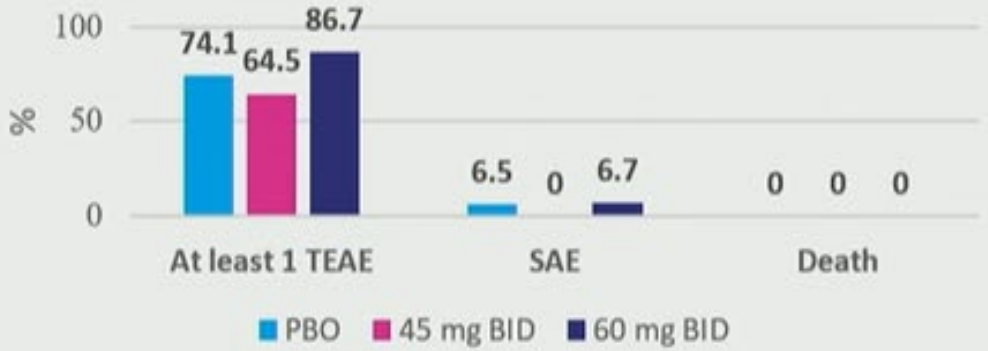
Phase II Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Trial in UC Patients in China





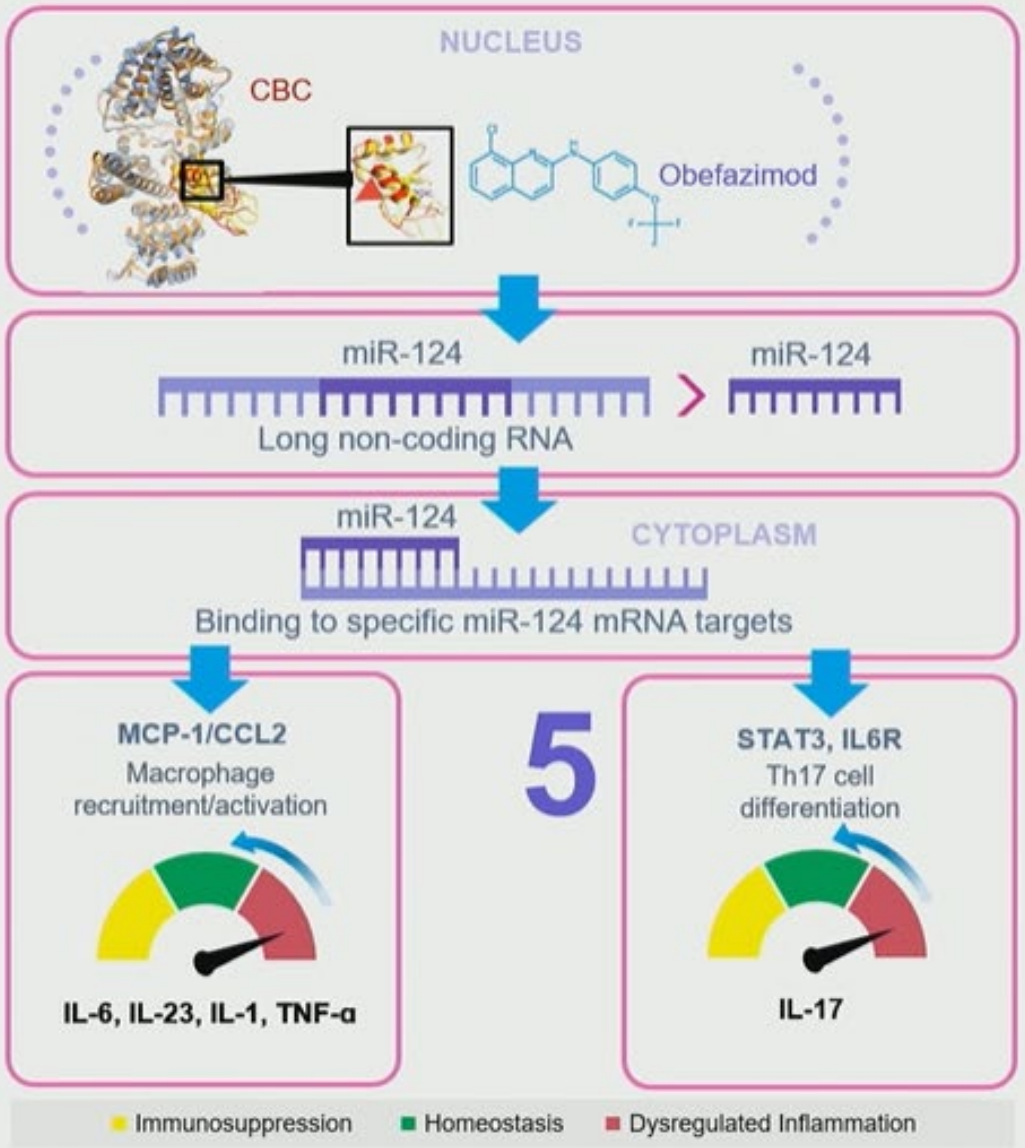






Similar response in biologically exposed and naïve (small numbers). Safe in Quantiferon positive patients. Safety database> 1500 patients in multiple indications. Phase 3 Trial in Preparation in China.

Obefazimod enhances expression of miR-124, resulting in stabilization of the dysregulated inflammatory response in UC



1 Obefazimod binds to cap binding complex (CBC) within the nucleus; demonstrated by cryo-electron microscopy* (CryoEM)

2 Induces selective splicing of a single, long, non-coding RNA, leading to enhanced expression of miR-124

3 miR124 binds to its specific mRNA targets in the cytoplasm, reducing the translation into their respective proteins

4 Reduced translation of MCP-1/CCL2 stabilizes macrophage activation and recruitment to the gut

5 Reduced translation of STAT3 and IL-6R stabilizes Th17 differentiation and related cytokines

***Cryo-electron microscopy is a technique to determine protein structure**

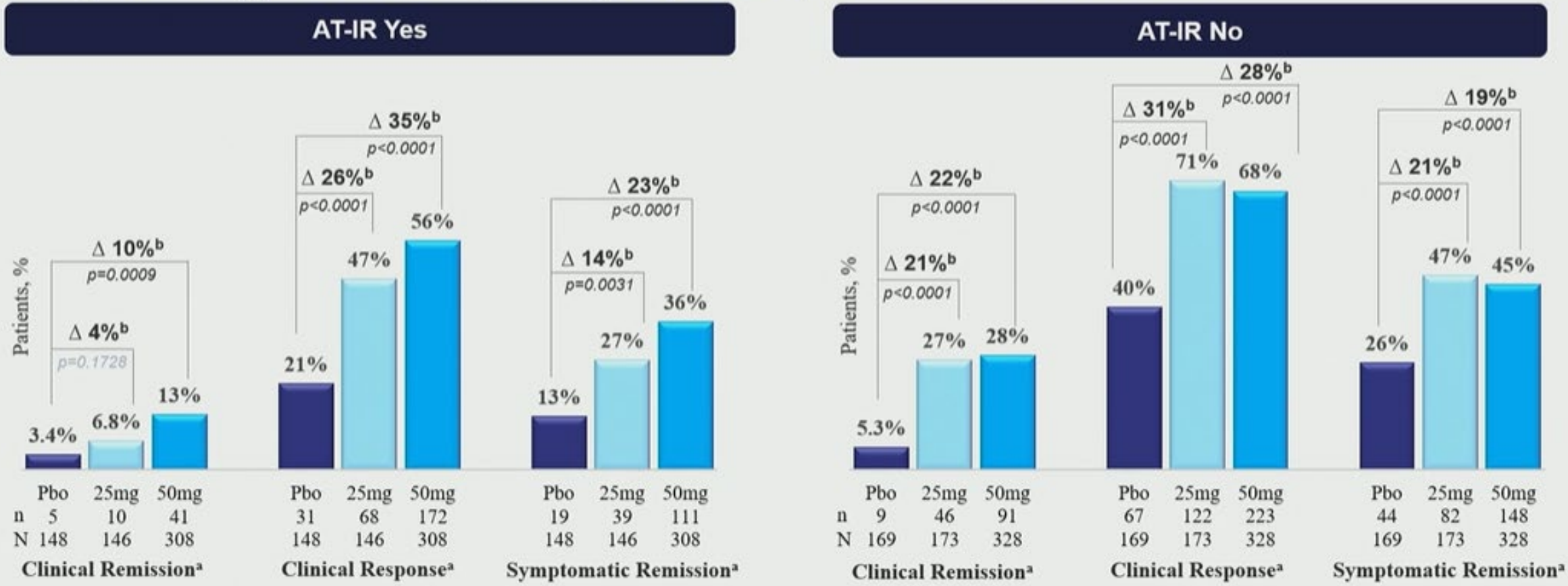
1. Vermeire S, et al. J Crohns Colitis. 2023;jjad067; Data on file. Abivax. Obefazimod is an investigational agent not approved by any health regulatory agencies.

ABTECT-1

ABTECT-2

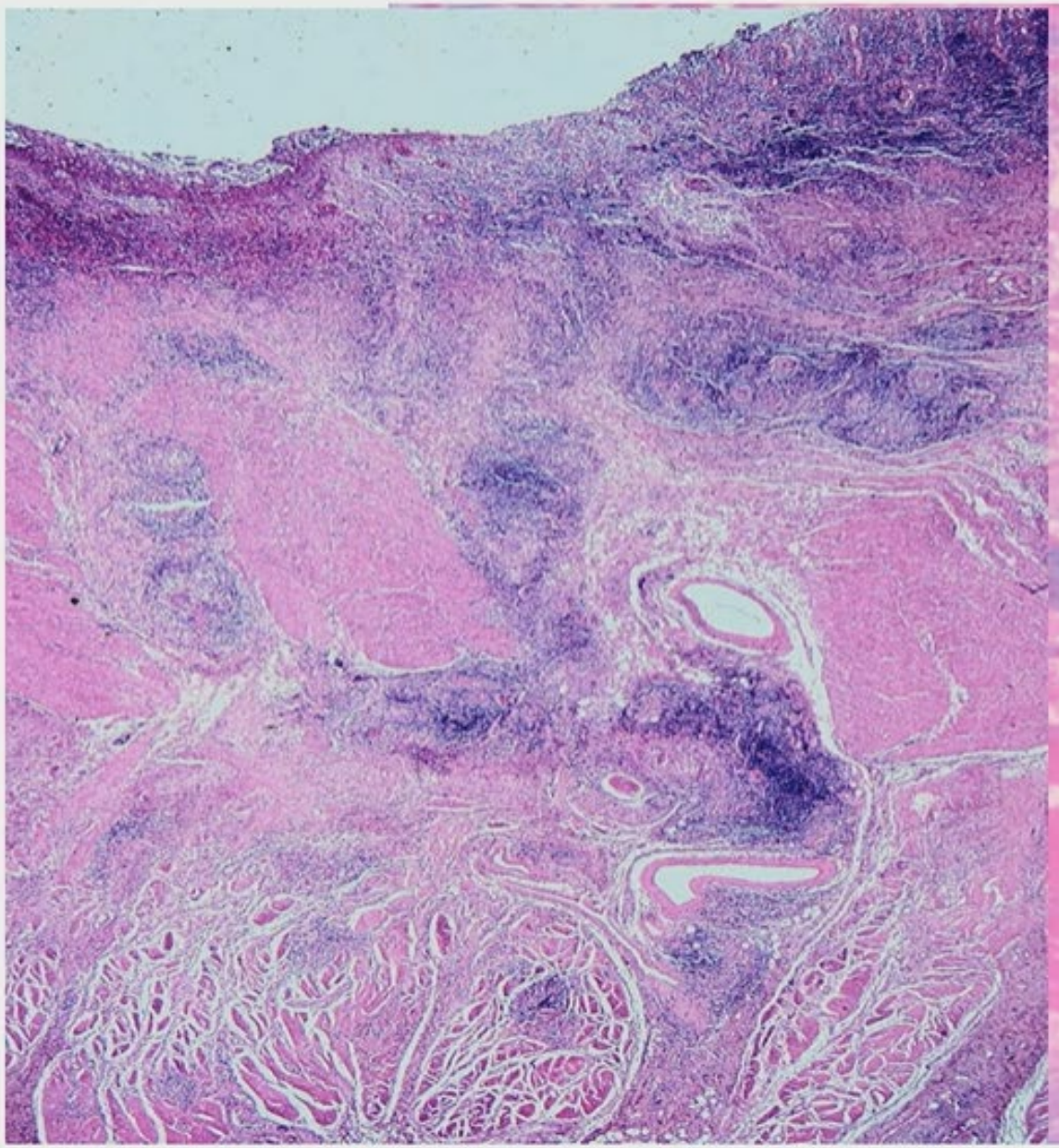
Pooled ABTECT 1 & 2: Obefazimod 50mg achieved clinically meaningful improvements in all clinical endpoints regardless of prior AT-IR

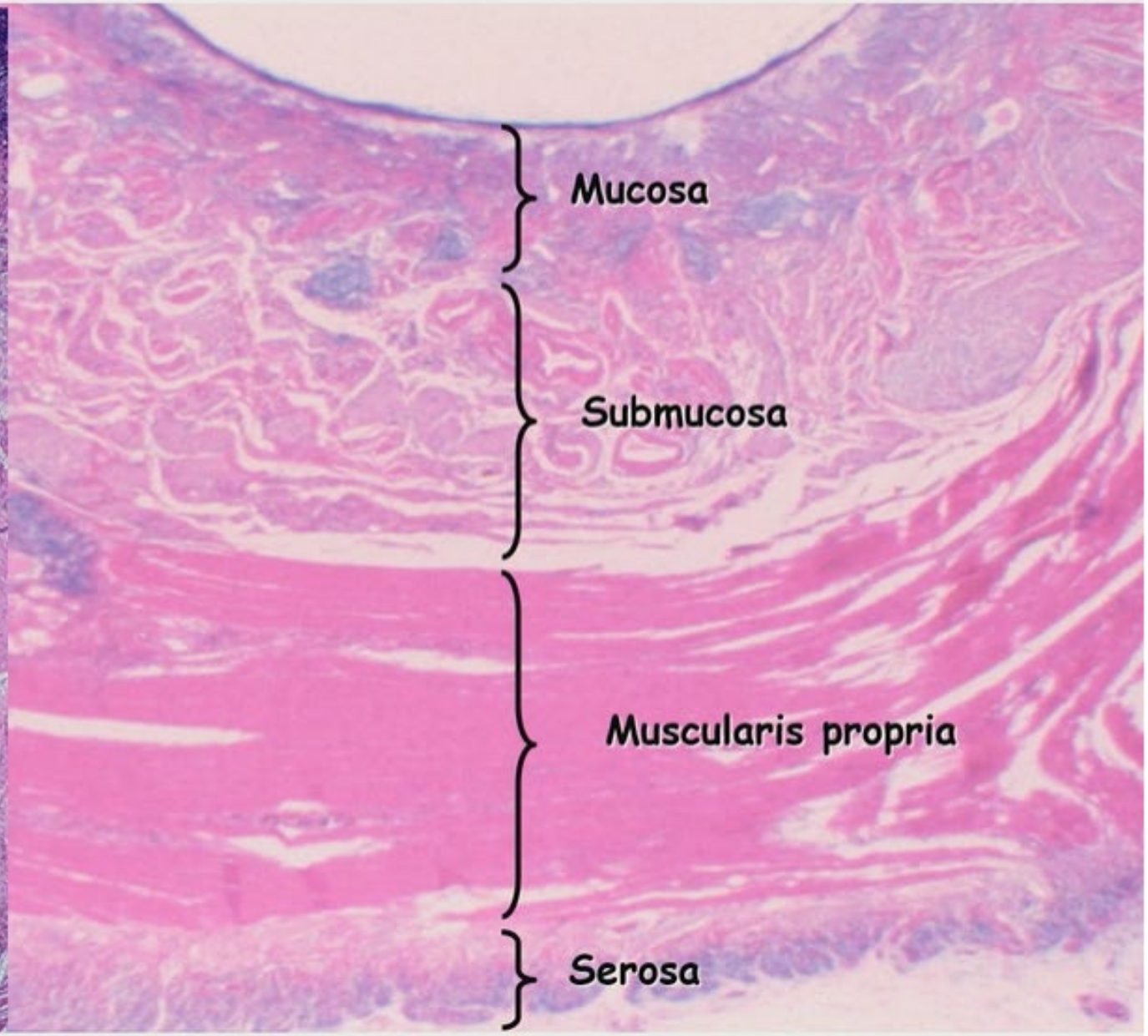
25mg and 50mg perform similarly in subgroup with no prior AT-IR in pooled data set



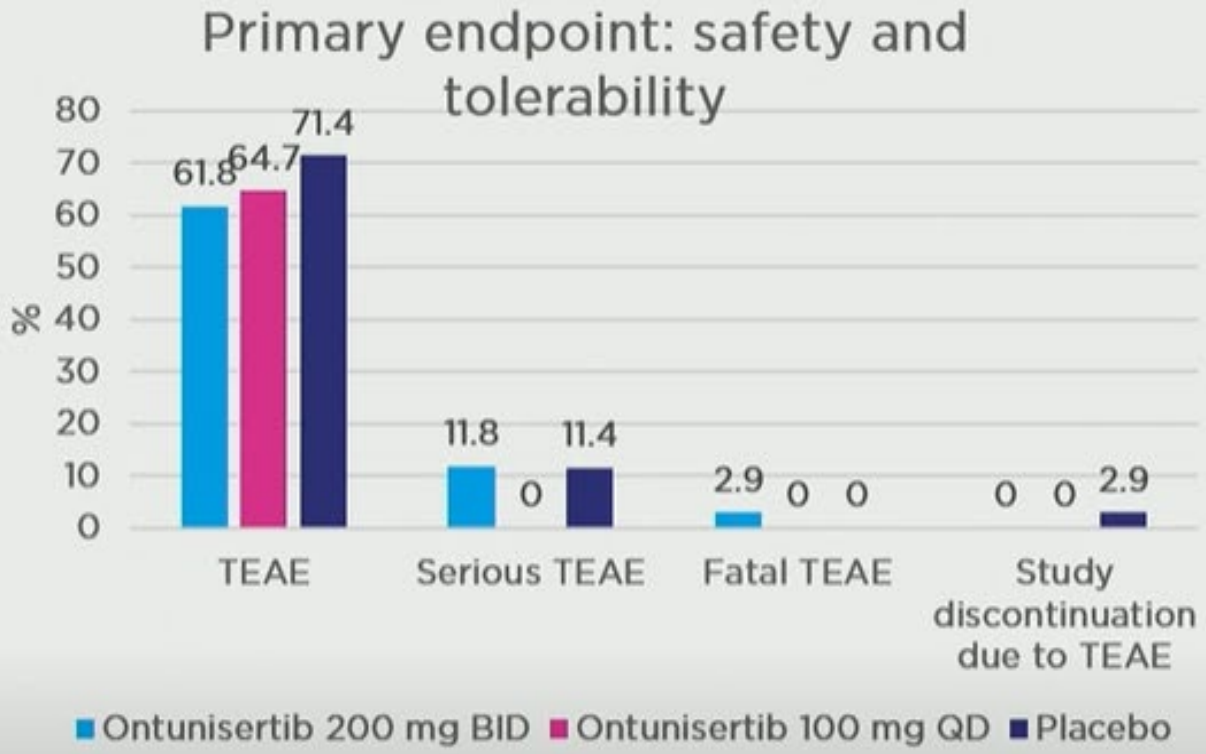
Danese S et al. Oral presentation presented at: United European Gastroenterology Week, October 4–7 2025, Berlin, Germany.
All p-values are nominal
[a] **Clinical remission** is defined as SFS = 0 or 1, and RBS = 0 and MES = 0 or 1 (MES of 1 modified to exclude friability). **Clinical response** is defined as a reduction from Baseline in MMS >= 2 points and a relative reduction from Baseline in MMS >= 30%, and a reduction from Baseline in RBS >= 1 point and/or RBS = 0 or 1. **Symptomatic remission** is defined as RBS=0 and SFS= 0 or 1
[b] % Difference is for ABX464 minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights adjusting for the randomization stratification factors: inadequate response to advanced therapies (yes/no), Baseline oral corticosteroids usage (yes/no). P-values are two sided. NRI is used for subjects with missing outcome at Week 8 and subjects reporting any IE prior to Week 8.

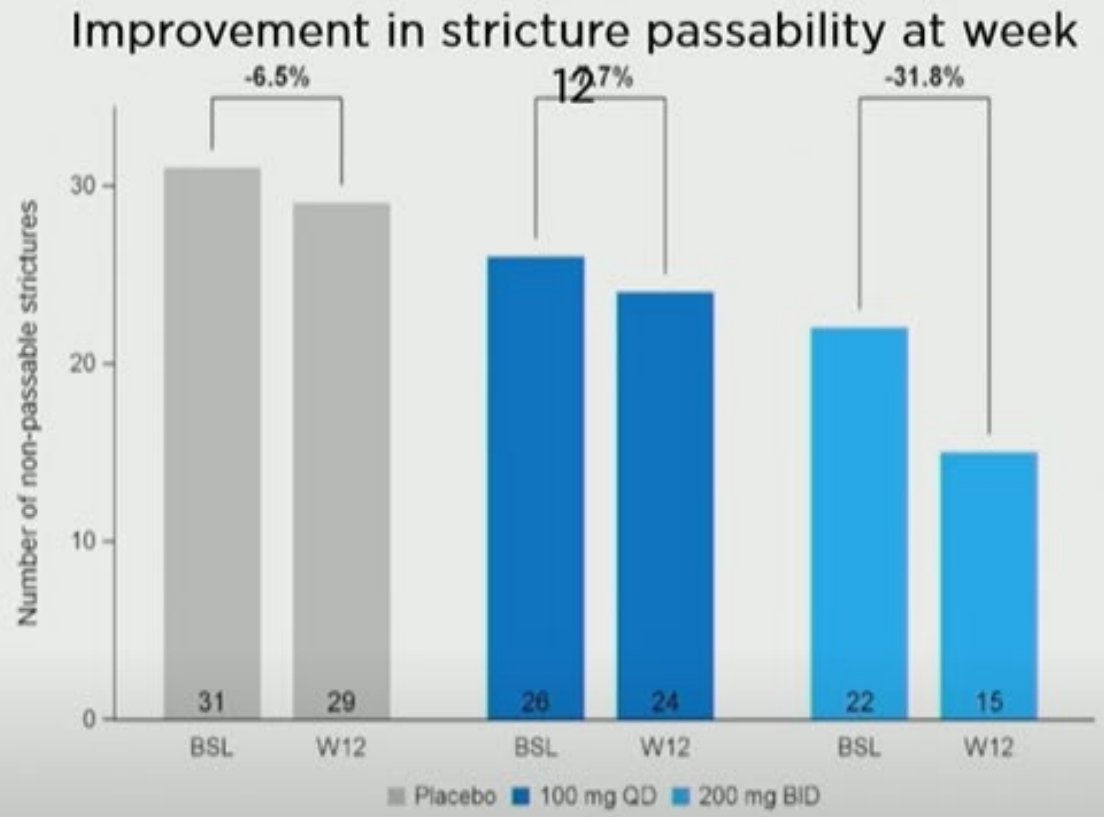
Transmural inflammation leads to fibrostenosis in Crohn's disease





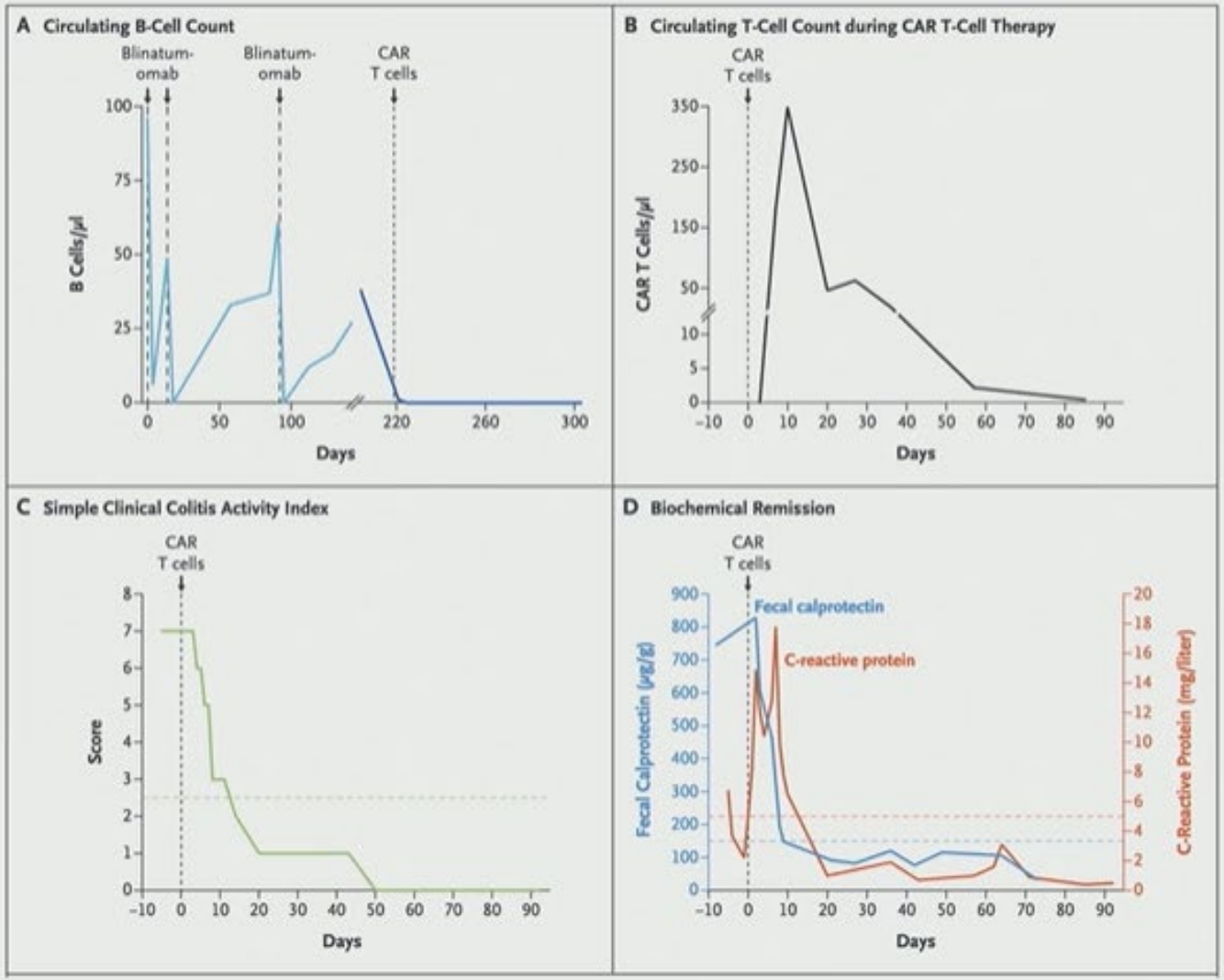
STENOVA trial: A Phase 2a, randomized, placebo-controlled, double-blind study to assess safety, PK, and pharmacodynamics of ontunisertib in fibrostenotic CD (FSCD)





Authors'conclusions: ontunisertib for 12 weeks was generally well tolerated at both doses. The GI-restricted profile of ontunisertib was confirmed. A trend of improvements in endoscopic and MRE outcomes was observed. Ontunisertib has potential to be the first ALK5 inhibitor suitable for chronic dosing in humans

B-Cells depletion: immune reset?



- Anti-CD19 CAR-T cells depleting all B cells
- 1st case of UC refractory to **all** approved medications "cured"
- Next generation **T-Cell engagers and off-the-shelf CAR-T cells**

Müller F, et al. *N Engl J Med*, 2025

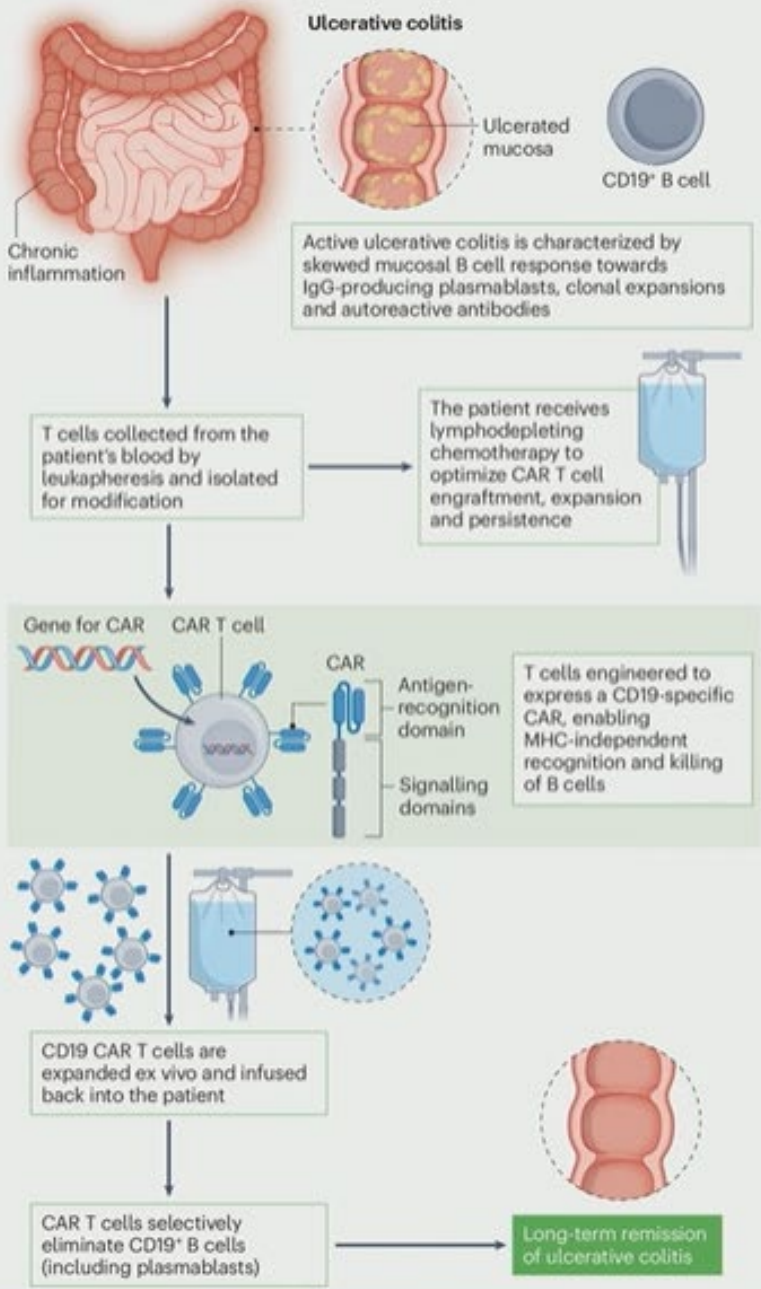
CAR-T Cells: 2nd Generation Cell Therapy

Chimeric Antigen Receptor (CAR) enables
- Antigen-specific targeting
- Enhanced persistence and expansion
- Functional reprogramming of immune responses

Theoretical advantages
- Greater selectivity vs HSCT
- Potential long-term immune reprogramming
- Moves from cytokine blockade → immune ecosystem engineering

Strategies under investigation

- CAR-Tregs[1] and Tolerance enhancement[2]
  - Antigen-specific regulatory cells
  - Aim: restore mucosal tolerance and suppress pathogenic effector responses
  - Potential for improved stability vs conventional Tregs
- B-cell depletion (anti-CD19 CAR-T)[3]
  - Target pathogenic B-cell compartments
  - Inspired by success in autoimmune diseases (e.g., SLE)
  - Hypothesis: disrupt autoantibody-driven or antigen-presentation circuits in IBD



1. Cui Y, et al. *J Crohn Colitis*, 2025 2. NCT06721962 3. Müller F, et al. *N Engl J Med*, 2025 4. Parigi TL, et al. *Nat Rev Gastro Hep*, 2026

CD19 CAR T-Cell Therapy in Multidrug-Resistant Ulcerative Colitis

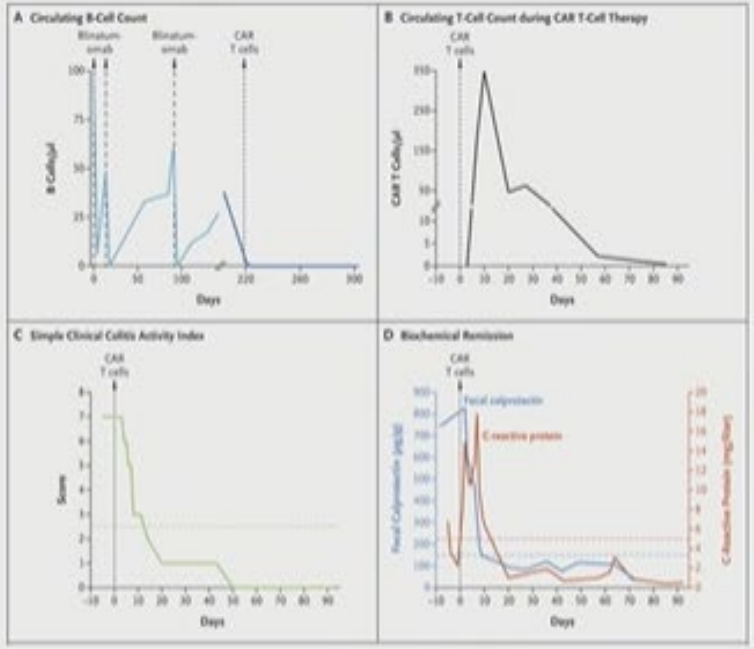
Study

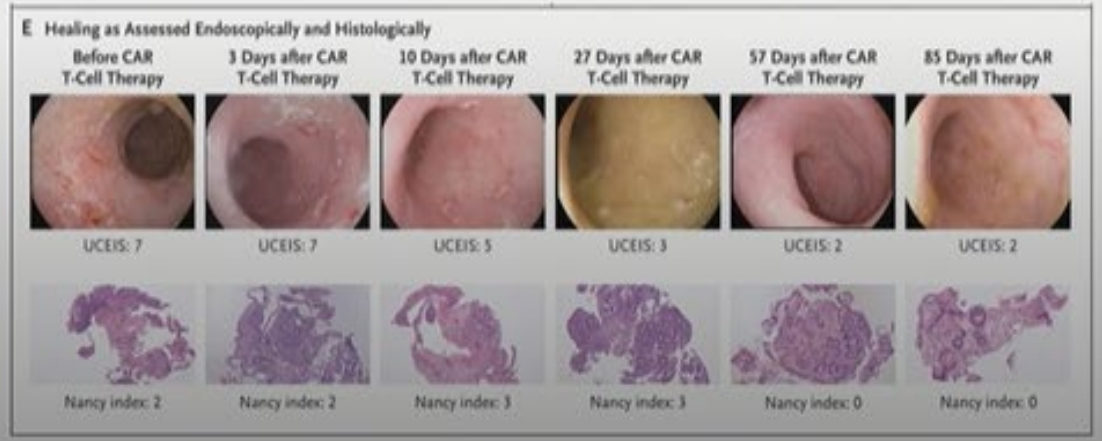
- Single patient with severe, multidrug-refractory UC who declined colectomy
- Autologous CD19-directed CAR T-cell therapy after lymphodepleting chemotherapy

Results

- Rapid clinical remission within weeks of infusion
- Biochemical remission (normalization of inflammatory markers)
- Endoscopic and histologic mucosal healing
- Sustained response during follow-up without additional UC therapy
- Profound and persistent B-cell depletion in blood and colonic tissue

CD19 CAR T-cell therapy can induce rapid drug-free remission in refractory ulcerative colitis, a disease that was previously thought to be largely B-cell–independent, given that rituximab treatment showed no efficacy.

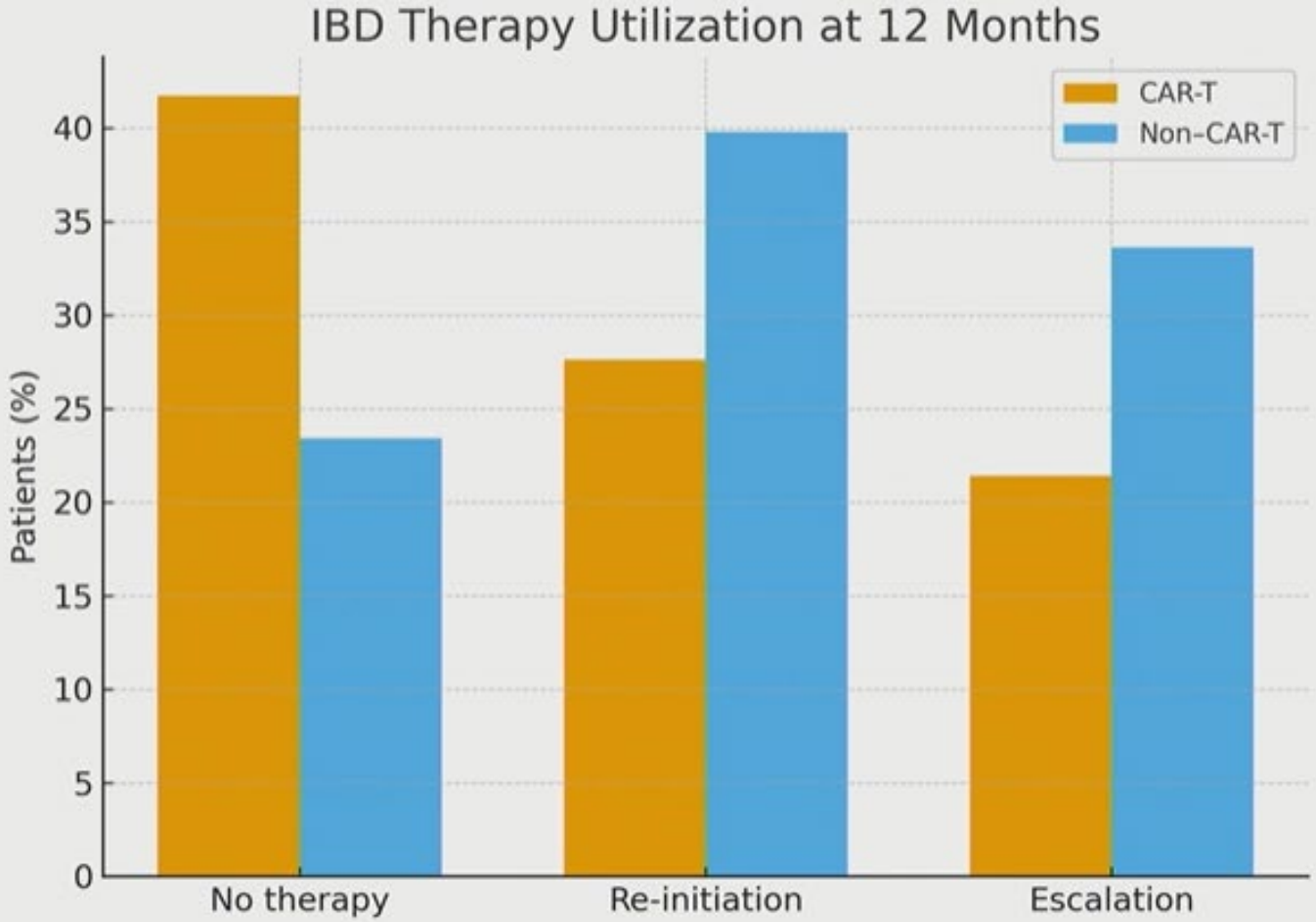




Müller F, Atreya R, Völkl S, et al. CD19 CAR T-Cell Therapy in Multidrug-Resistant Ulcerative Colitis. *N Engl J Med*. 2025;393(12):1239-1241.

CD19 CAR T-Cell Therapy in Ulcerative Colitis

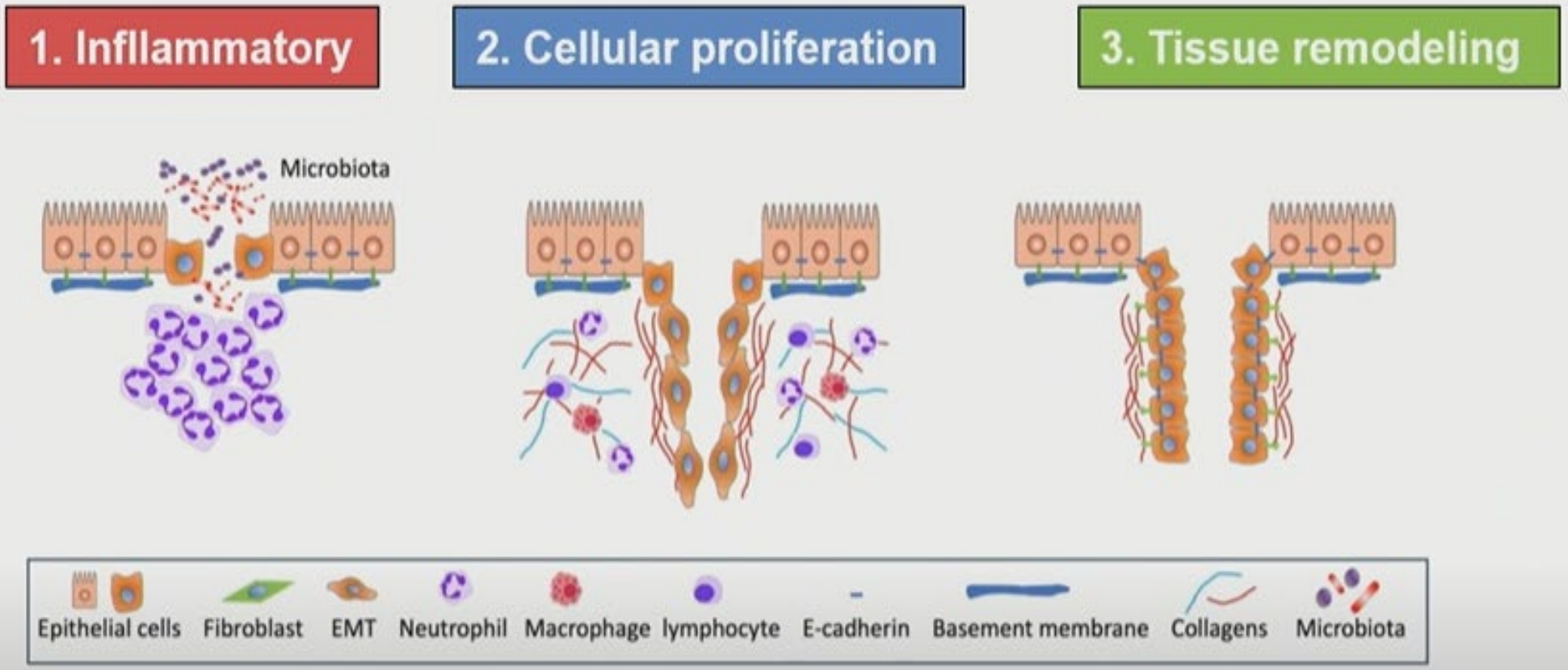
- Multicenter retrospective cohort study across a U.S. federated electronic health record network (2017–2025).
- Adults with established UC and refractory disease (≥2 advanced therapies or steroid dependence) who received CAR-T for hematologic malignancy. N= 192
  - Controls: UC patients with same cancers treated w/o CAR-T. N=384
- CAR-T associated with higher remission, fewer hospitalizations and colectomies, and substantial treatment de-escalation.
  - Infection risk was mildly higher, but mortality was unchanged



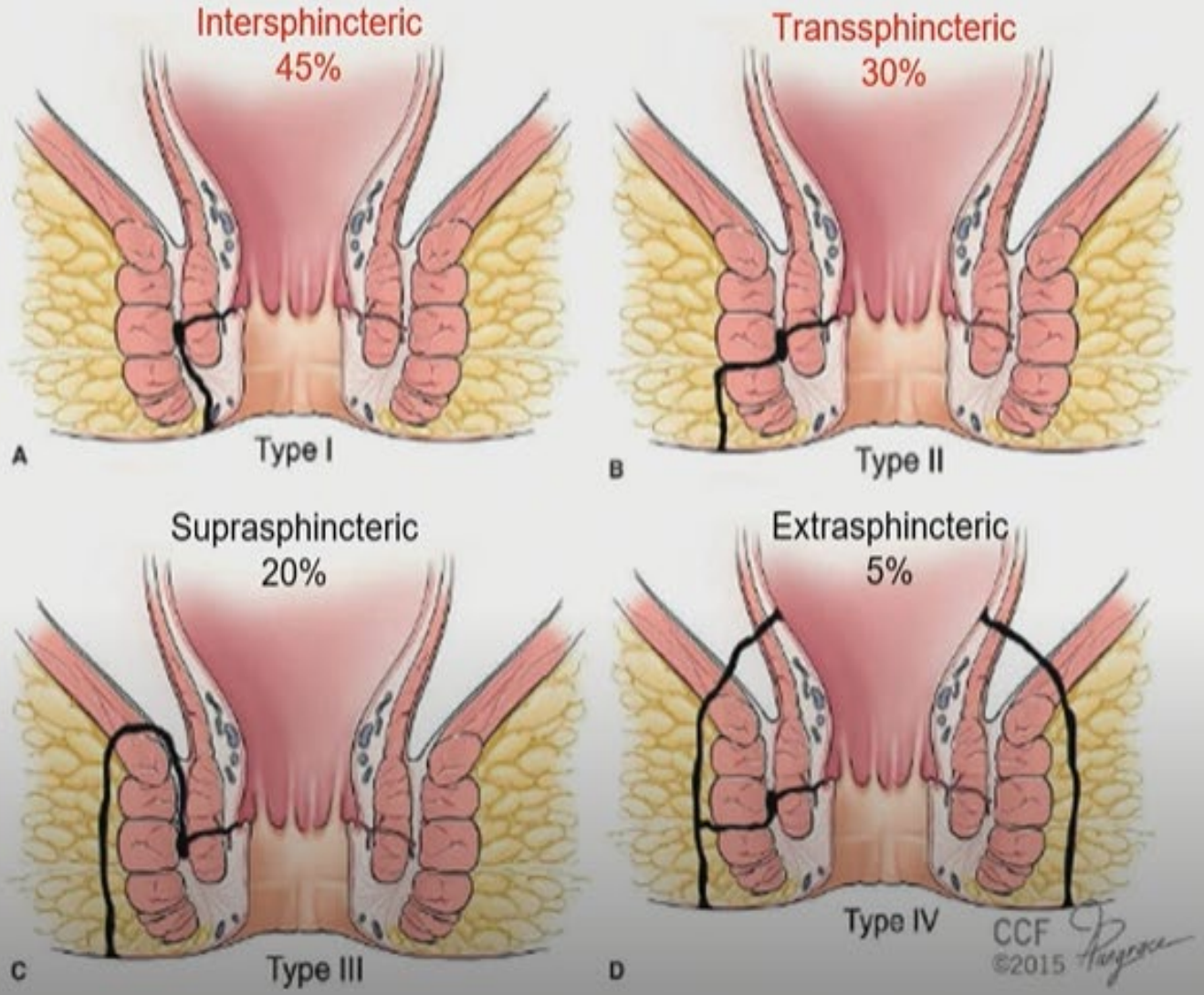
Salem et al. Abstract 33 DDW 2026

UCSF

Pathophysiology of Crohn's disease perianal fistula



Classification :
Parks Fistula Classification



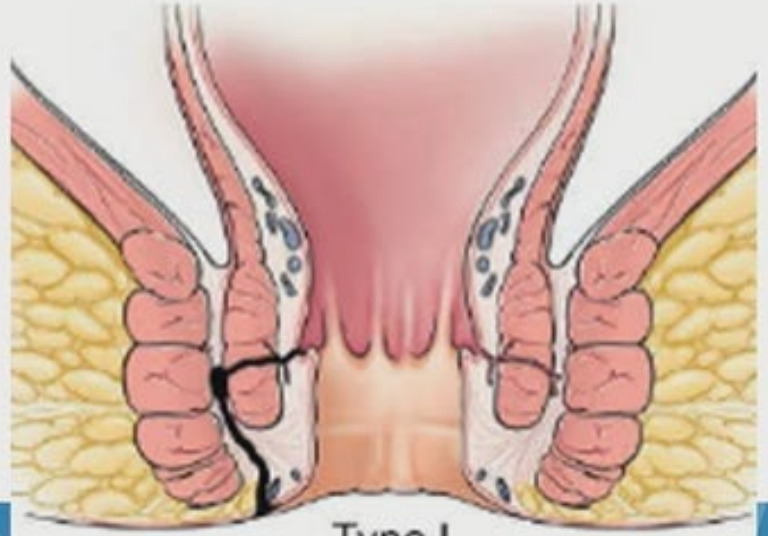
Overall, 25% of patients with Crohn's → perianal disease

However, 5% is *isolated* perianal disease

Fistula Classification #2

SIMPLE

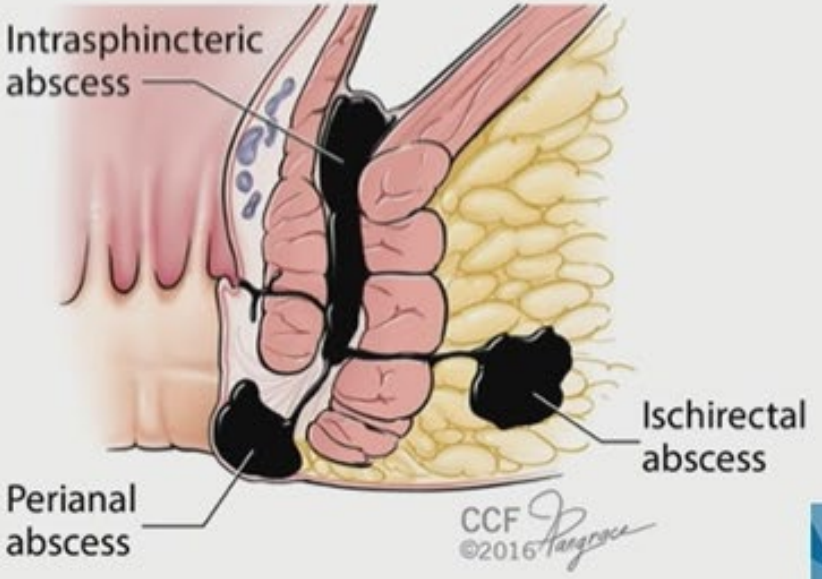
- Single track
- Low
- Single internal opening
- Single external opening (cutaneous)



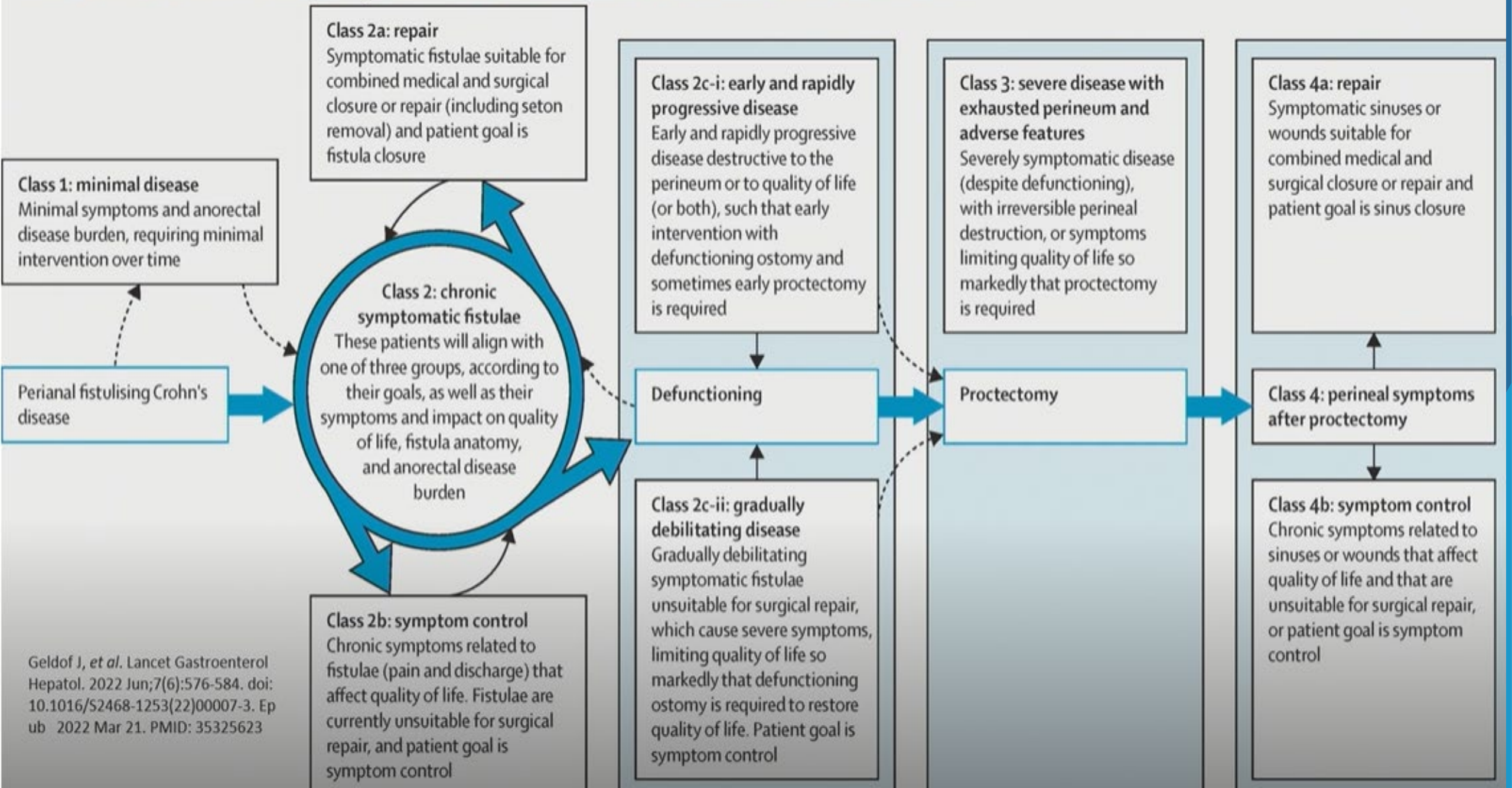
Type I

COMPLEX

- Multiple track
- High
- Multiple internal/external openings
- Anovaginal/rectovaginal
- Associated with abscess, stricture
- Recurrent
- Crohn's 80% complex vs. always complex?



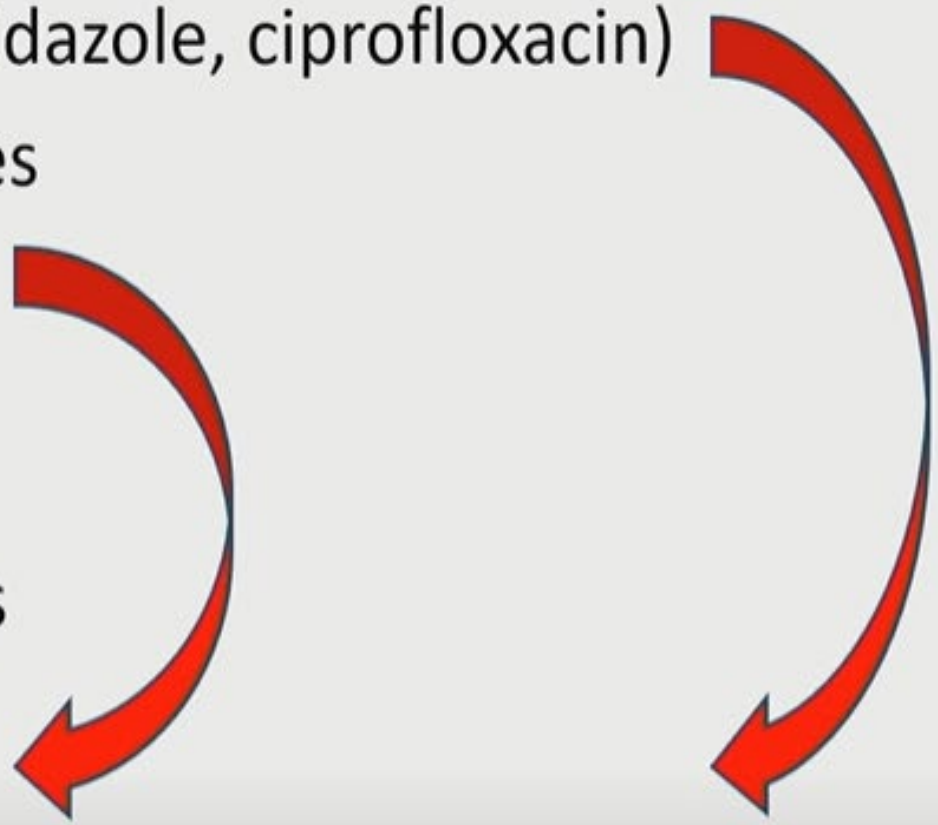
The TOPCLASS perianal fistula classification



Geldof J, *et al*. Lancet Gastroenterol Hepatol. 2022 Jun;7(6):576-584. doi: 10.1016/S2468-1253(22)00007-3. Epub 2022 Mar 21. PMID: 35325623

Medical Therapies – moving toward early advanced therapies

- Antibiotics (metronidazole, ciprofloxacin)
- Immunosuppressives
  - Azathioprine
  - 6-mercaptopurine
  - Cyclosporine
  - Tacrolimus
- Advanced Therapies
  - Infliximab
  - Adalimumab
  - Vedolizumab ?
  - Ustekinumab?
  - Upadicitinib?
- Novel Agents
  - Adipose Derive Stem Cells



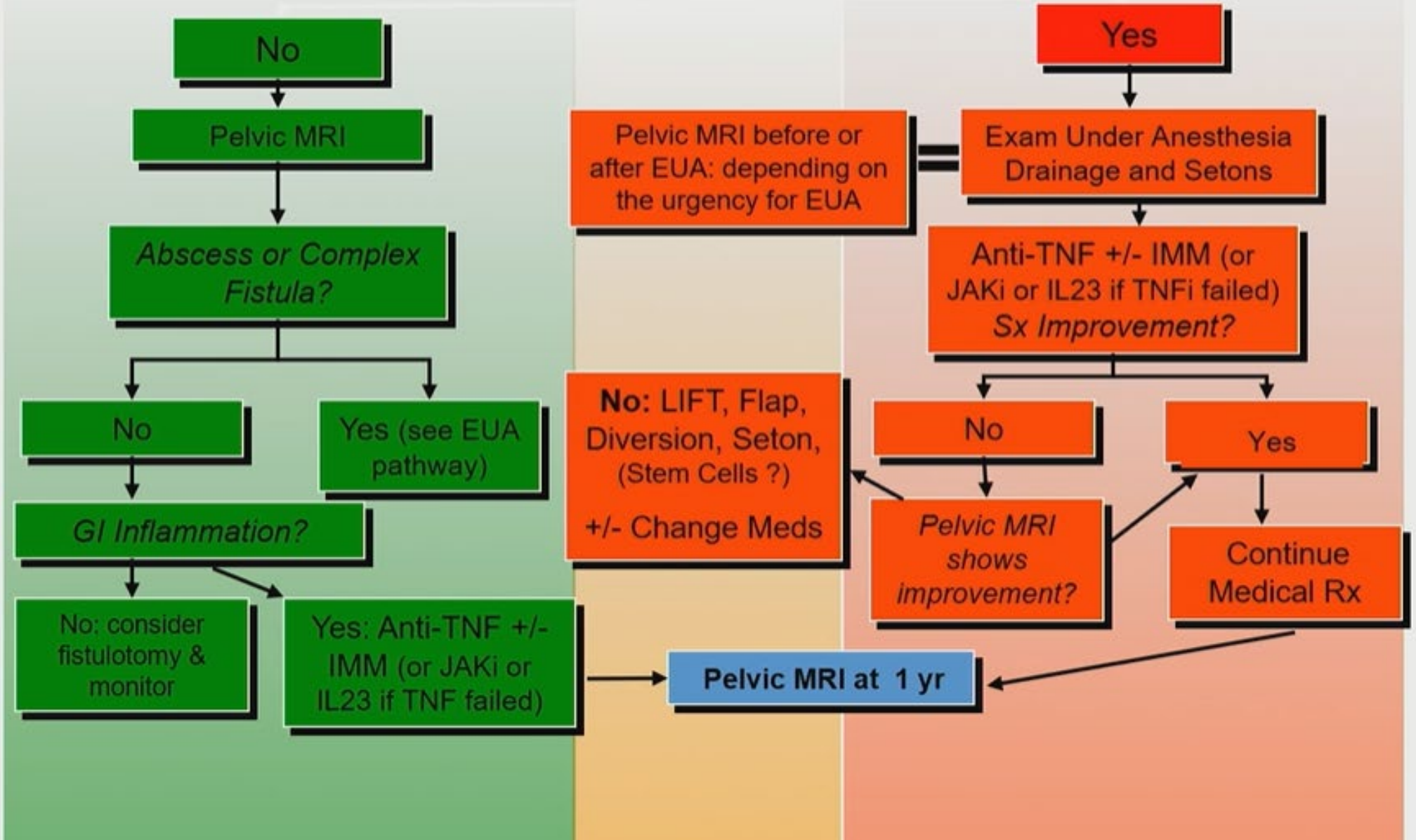
October 2023 ADMIRE – CD II Trial

did not meet primary endpoint

October 17, 2023 — Takeda (TSE:4502/NYSE: TAK) today announced that the Phase 3 ADMIRE-CD II study, assessing the efficacy and safety of Alofisel® (darvadstrocel) for the treatment of complex Crohn's Perianal Fistulas (CPF), did not meet its primary endpoint of combined remission at 24 weeks, based on topline data. The safety profile for darvadstrocel was consistent with prior studies and there were no new safety signals identified

1st Question to Answer in managing a Perianal Fistula

Pain and/or Suspected Abscess?



KEY TAKEAWAYS

- Antibiotics alone do not treat perianal fistula
- Combined medical-surgical therapy for perianal fistula with TNFi, seton drainage, and attempt at definitive closure is still best treatment
- Pelvic MRI (EUS) is important to diagnose abscesses and complex fistula, as well as monitor response to treatment
- Upadicitinib, IL23s, and Vedolizumab may be effective for fistula but, to date, data are less robust than TNFi
- Stem Cell therapy in the USA for perianal fistula is unlikely (outside of research protocols)
- Remember: fistula require a multi-disciplinary approach ***and treat anal Crohn's disease with advanced therapies at diagnosis***

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Impact of obefazimod treatment on histologic and combined histologic-endoscopic outcomes in patients with moderately to severely active ulcerative colitis: results from the ABTECT-1 and ABTECT-2 Phase 3, double-blind, placebo-controlled induction trials

Fernando Magro, Bruce E Sands, Silvio Danese, Marla Dubinsky, Fabio Cataldi, Doug Jacobstein, Christopher J Rabbat, Kevin Shan, Luciana Harlacher, Franco Scaldaferri, Geert D'Haens, Luc Biedermann, Laurent Peyrin-Biroulet

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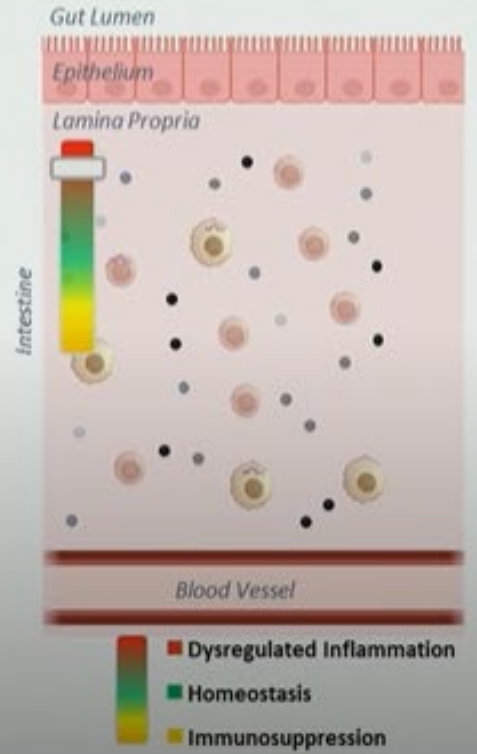
Obefazimod
Mechanism of action

Active UC

Inflammatory Th17 cells & macrophages are elevated in the mucosa: key disease drivers



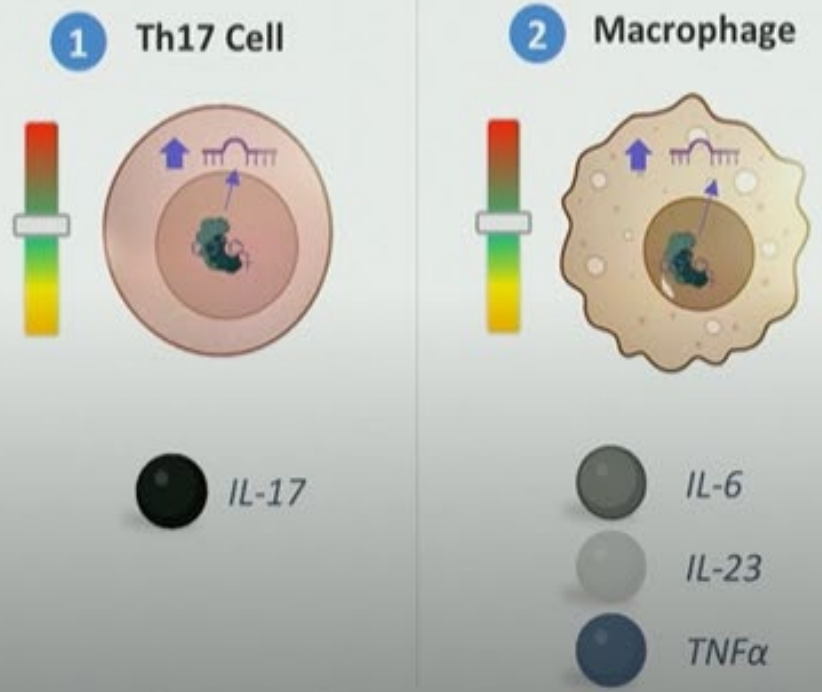
Obe ↑ miR-124

miR-124 is an endogenous regulator of cell behavior

↑ miR-124 normalizes the levels of inflammatory cells

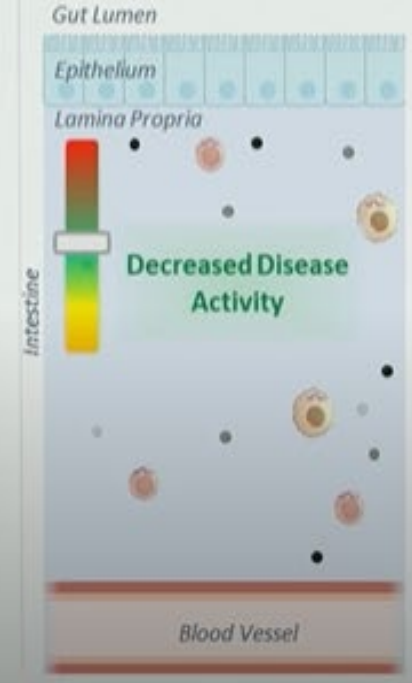
Normalizes Th17 T cells and IL-17 levels

Reduces macrophage recruitment while balancing levels of IL-23, IL-6 and TNFα



Balance restored

Restores mucosal immune balance



CBC: Cap Binding Complex - Apolit et al. Clin Transl Gastroenterol, 2023 | Vermeire et al., J Crohns Colitis, 2023 | Abivax Data on File | Images made with BioRender

Obefazimod restores mucosal immune balance in ulcerative colitis through regulation of Th17 cells and macrophages

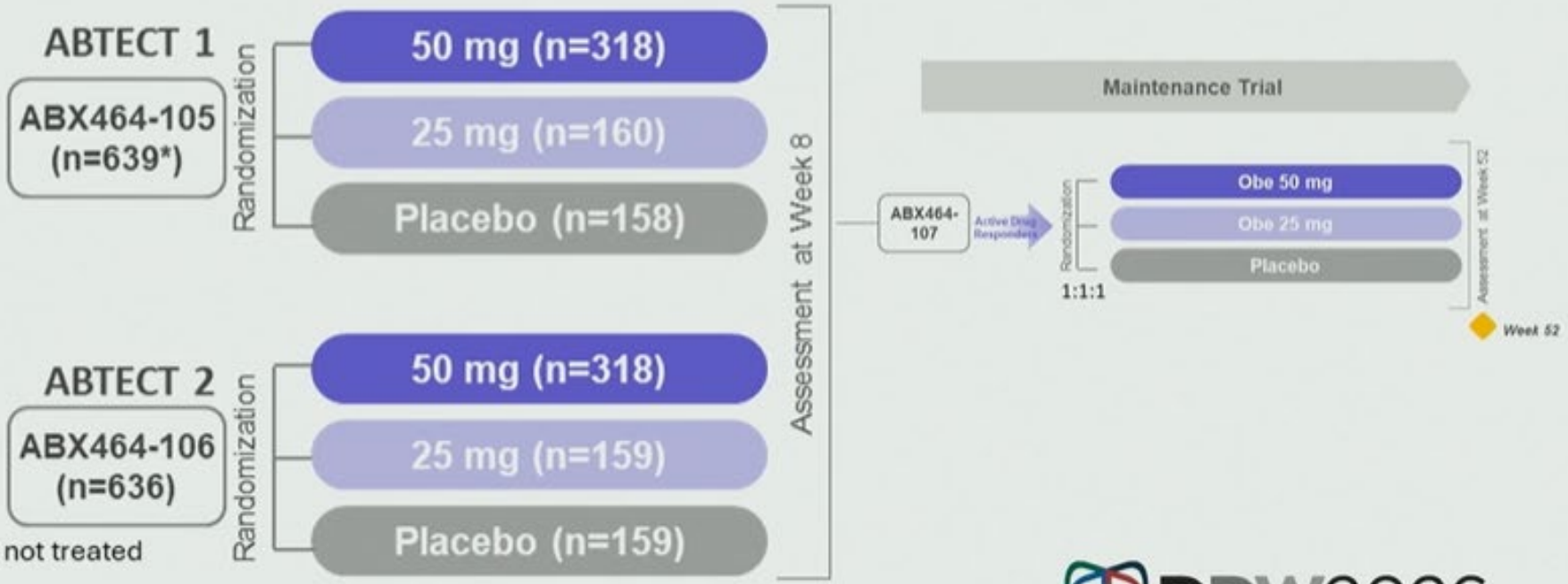
Design of ABTECT induction trials

Screening

- ❑ Moderately to severely active UC defined by:
  - MMS 5-9
  - ES≥2
  - RB≥1
- ❑ Prior failure of conventional and/or biologic/JAKi/S1P
- ❑ No limit on number of prior treatment failures

*: 3 patients in ABTECT 1 were randomized but not treated

Induction trials



Rectal or sigmoidal biopsies from the most affected segment were collected during endoscopy at screening and Week 8

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Baseline characteristics

	Pooled ABTECT 1 & 2			ABTECT 1 (105)			ABTECT 2 (106)		
	Placebo (N=317)	Obe 25 mg (N=319)	Obe 50 mg (N=636)	Placebo (N=158)	Obe 25 mg (N=160)	Obe 50 mg (N=318)	Placebo (N=159)	Obe 25 mg (N=159)	Obe 50 mg (N=318)
Age (years), mean (SD)	42.3 (14.1)	41.4 (13.2)	42.1 (14.0)	43.1 (13.6)	41.5 (13.5)	42.7 (14.3)	41.6 (14.7)	41.3 (12.8)	41.4 (13.6)
Baseline MMS, mean (SD)	6.9 (1.0)	6.9 (1.0)	6.9 (1.1)	6.9 (1.0)	6.8 (1.0)	6.9 (1.1)	6.8 (1.0)	7.0 (1.0)	6.9 (1.1)
Endoscopic subscore 3, n (%)	189 (59.6)	194 (60.8)	378 (59.4)	94 (59.5)	91 (56.9)	190 (59.7)	95 (59.7)	103 (64.8)	188 (59.1)
Extensive Colitis	130 (41.0)	131 (41.1)	236 (37.1)	59 (37.3)	63 (39.4)	110 (34.6)	71 (44.7)	68 (42.8)	126 (39.6)
Fecal Calprotectin (μg/g), median	1902	1762	1564	1969	1499	1581	1792	2041	1499
Concomitant Corticosteroids	126 (39.7)	120 (37.6)	262 (41.2)	61 (38.6)	61 (38.1)	132 (41.5)	65 (40.9)	59 (37.1)	130 (40.9)
AT-IR* Yes	148 (46.7)	146 (45.8)	308 (48.4)	69 (43.7)	70 (43.8)	149 (46.9)	79 (49.7)	76 (47.8)	159 (50.0)
Number of prior JAK-IR (% of AT-IR Yes Patients)	35 (23.6)	34 (23.3)	55 (17.9)	15 (21.7)	15 (21.4)	22 (14.8)	20 (25.3)	19 (25.0)	33 (20.8)
Number of prior AT-IR by medication name†, n (%)									
1	62 (19.6)	45 (14.1)	150 (23.6)	31 (19.6)	23 (14.4)	70 (22.0)	31 (19.5)	22 (13.8)	80 (25.2)
2	34 (10.7)	45 (14.1)	64 (10.1)	16 (10.1)	20 (12.5)	35 (11.0)	18 (11.3)	25 (15.7)	29 (9.1)
3	28 (8.8)	33 (10.3)	52 (8.2)	12 (7.6)	18 (11.3)	25 (7.9)	16 (10.1)	15 (9.4)	27 (8.5)
4+	24 (7.6)	23 (7.2)	42 (6.6)	10 (6.3)	9 (5.6)	19 (6.0)	14 (8.8)	14 (8.8)	23 (7.2)

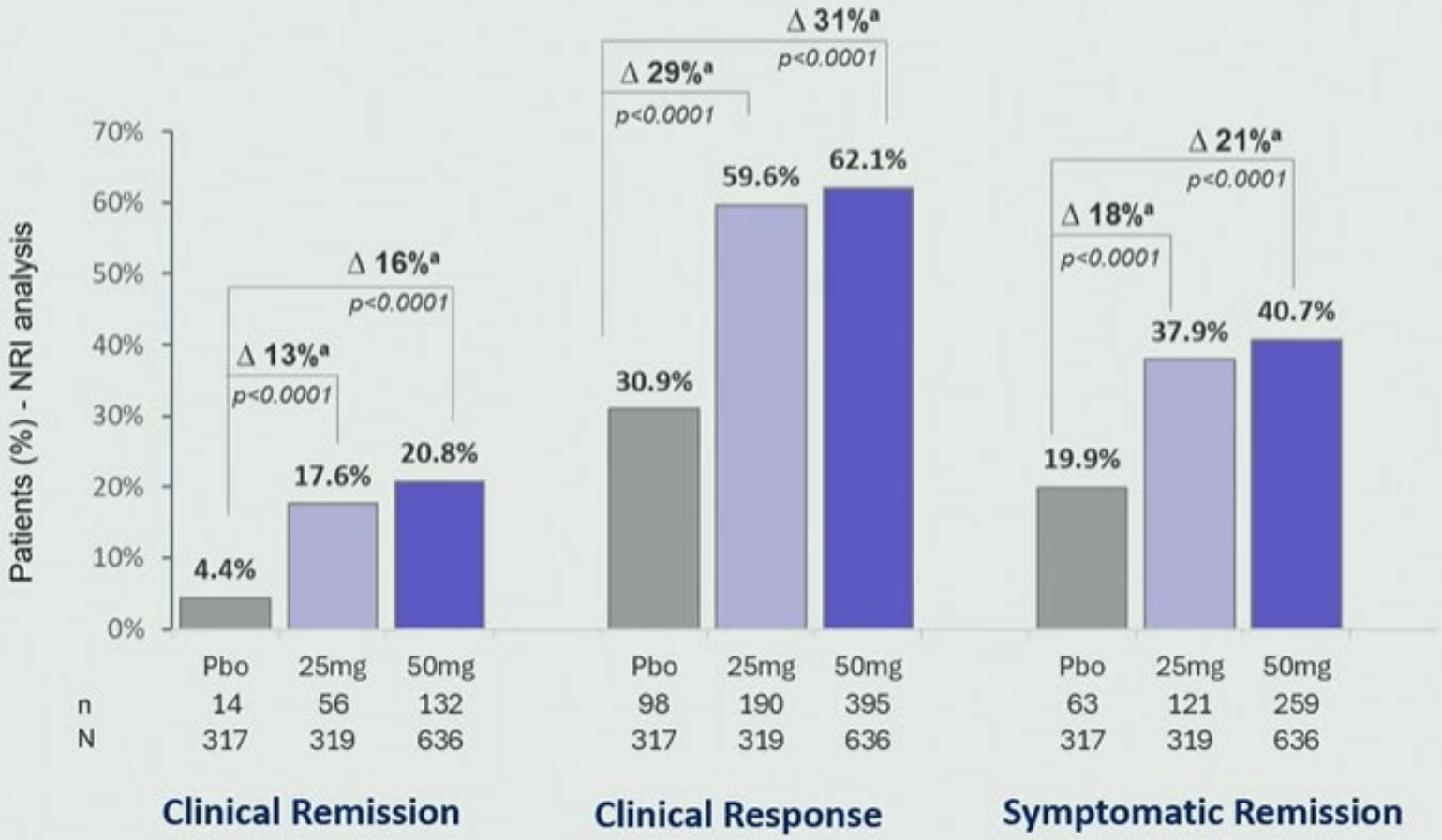
*: Inadequate Response to Advanced Therapies
†: Medication name results in each individual advanced therapy being counted as a unique medication; e.g. infliximab + adalimumab would be counted as 2

Baseline characteristics were generally well balanced in ABTECT trials, with a slightly more severe and refractory population in the 25mg group in ABTECT 2 vs. ABTECT 1

Pooled ABTECT 1 & 2

Clinical and symptomatic endpoints at Week 8

Primary Endpoint | **Key Secondary Endpoints**



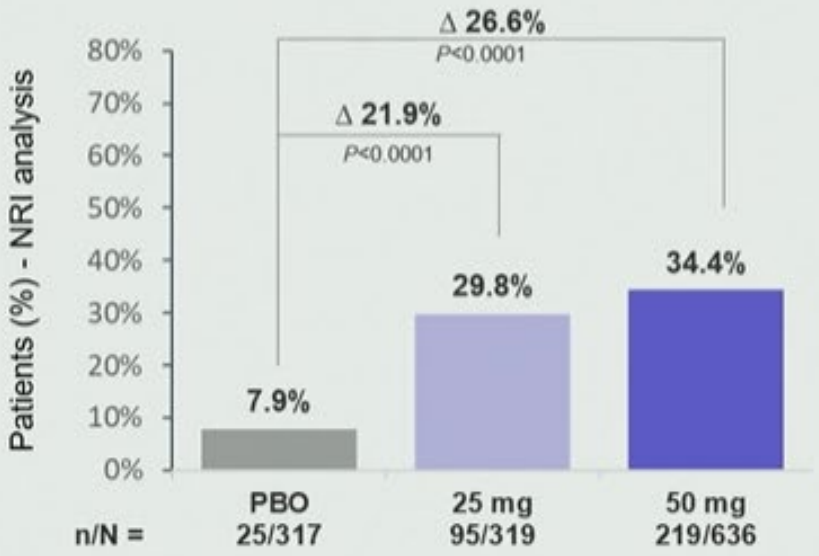
Both doses of obefazimod achieved clinically meaningful significant* improvements across clinical and symptomatic endpoints

*: All p-values are nominal

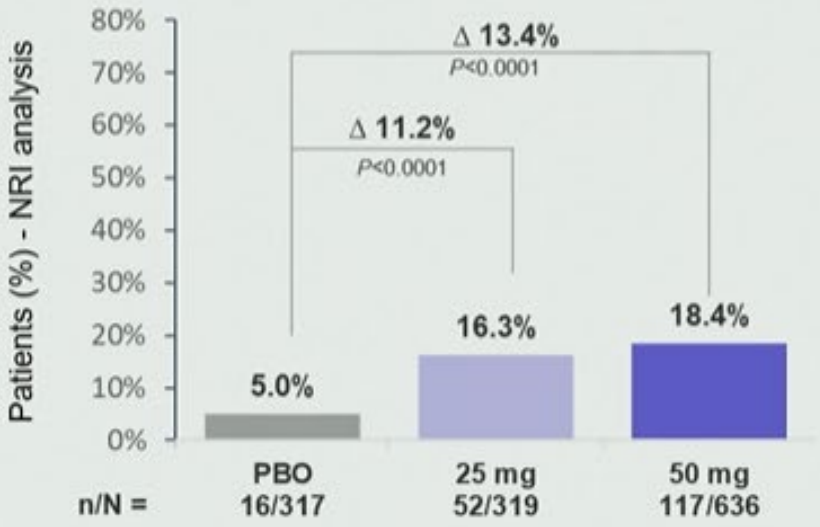
[a] % Difference is for obefazimod minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights adjusting for the randomization stratification factors: inadequate response to advanced therapies (yes/no), Baseline oral corticosteroids usage (yes/no). P-values are two sided. NRI is used for subjects with missing outcome at Week 8 and subjects reporting any IE prior to Week 8. Clinical remission is defined as SFS = 0 or 1, and RBS = 0 and MES = 0 or 1 (MES of 1 modified to exclude friability. Clinical response is defined as a reduction from Baseline in MMS >= 2 points and a relative reduction from Baseline in MMS >= 30%, and a reduction from Baseline in RBS >= 1 point and/or RBS = 0 or 1. Symptomatic remission is defined as RBS=0 and SFS= 0 or 1

Pooled ABTECT 1 & 2
Endoscopic endpoints at Week 8

Endoscopic improvement



Endoscopic remission



The pooled analysis showed significantly* higher proportions of patients treated with obefazimod 25 mg or 50 mg *versus* placebo achieving endoscopic endpoints

* All p-values are nominal

NRI is used for subjects with missing outcome at week 8 and subjects reporting any IE prior to week 8; % Difference is for Obe minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights adjusting for the randomization stratification factors: inadequate response to advanced therapies (yes/no), baseline oral corticosteroids usage (yes/no), and pivotal study (ABX464-105/ABX464-106). All P values are 2-sided. Endoscopic improvement: endoscopic subscore ≤1. Endoscopic remission: endoscopic subscore=0. IE, intercurrent event; MES, Mayo Endoscopic Subscore; NRI, non-responder imputation; Obe, obefazimod; PBO, placebo.

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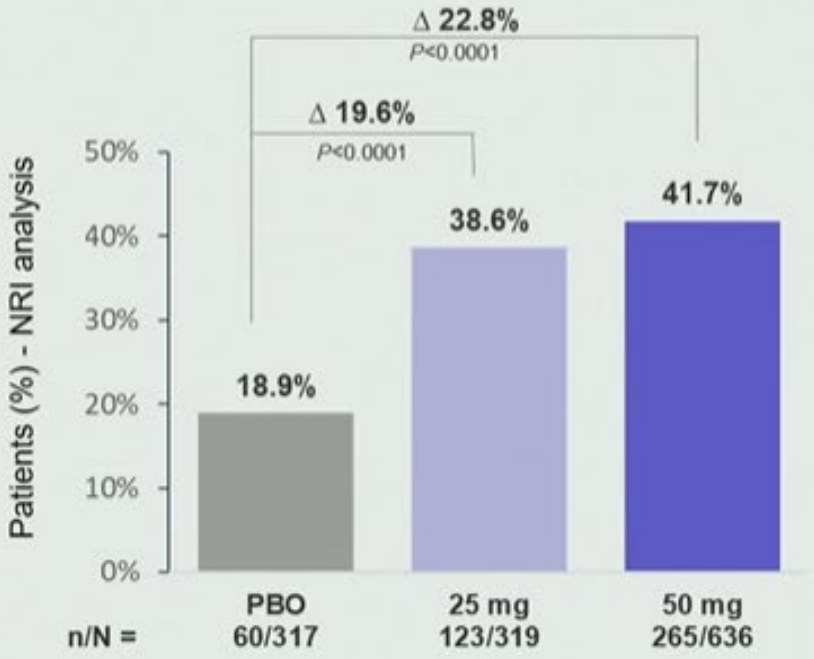
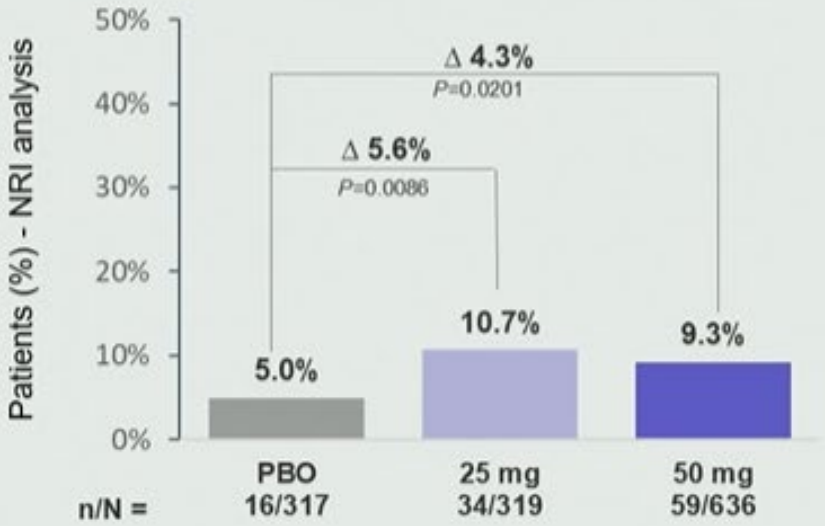
Pooled ABTECT 1 & 2
Histologic endpoints at Week 8

Histologic improvement
(Geboes histologic score ≤3.1)



Histologic remission
(Geboes histologic score <2A.0)



The pooled analysis showed significantly* higher proportions of pts receiving either obefazimod 25 mg or 50 mg *versus* placebo achieving histologic endpoints

*: All p-values are nominal; NRI is used for subjects with missing outcome at week 8 and subjects reporting any IE prior to week 8; % Difference is for Obe minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights adjusting for the randomization stratification factors: inadequate response to advanced therapies (yes/no), baseline oral corticosteroids usage (yes/no), and pivotal study (ABX464-105/ABX464-106). All P values are 2-sided. Histological improvement: neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system (ie, Geboes histologic score ≤3.1). Histological remission: absence of neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue, according to the Geboes grading system (ie, Geboes histologic score <2A.0). IE, intercurrent event; MES, Mayo Endoscopic Subscore; NRI, non-responder imputation; Obe, obefazimod; PBO, placebo.

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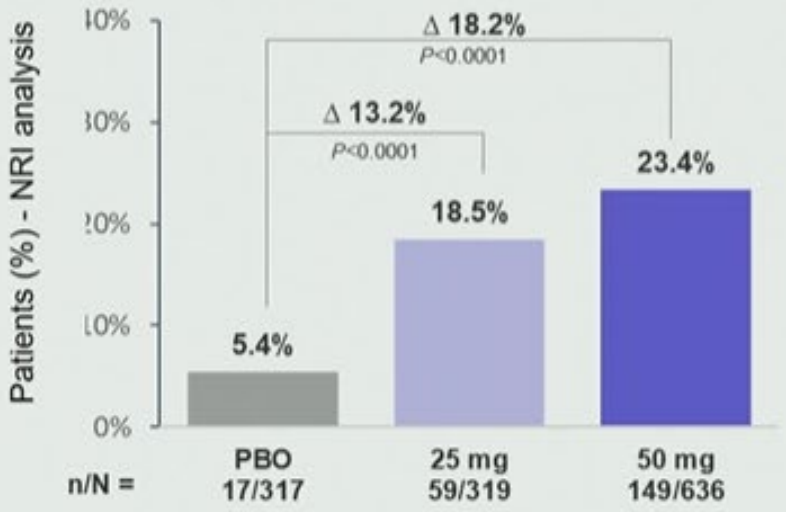
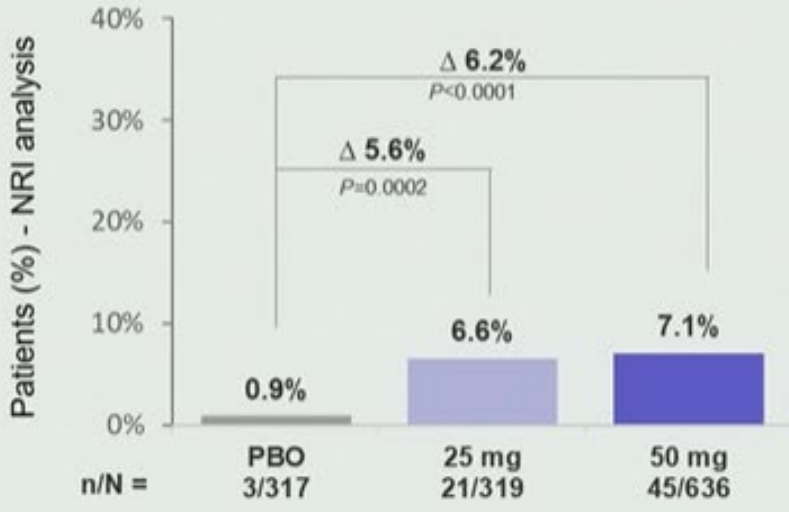
Pooled ABTECT 1 & 2
Combined histologic-endoscopic outcomes at Week 8

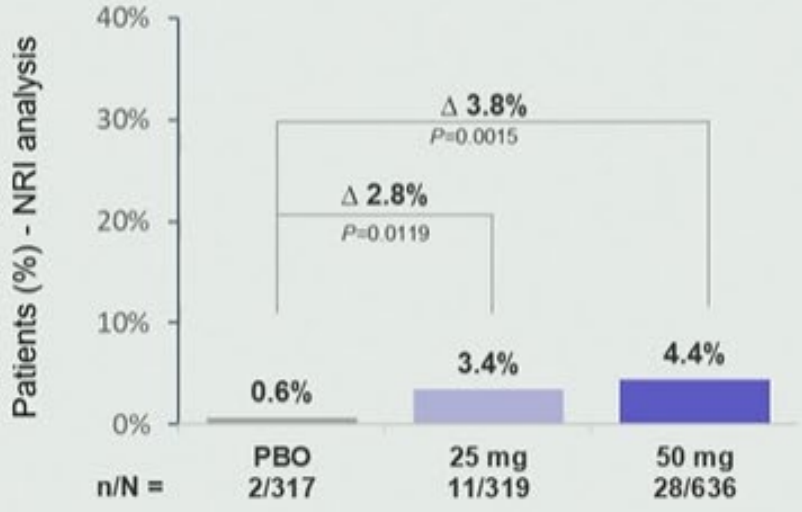
HEMI
(Endoscopic subscore ≤1 + Geboes score ≤3.1)



EIHR
(Endoscopic subscore ≤1 + Geboes score <2A.0)



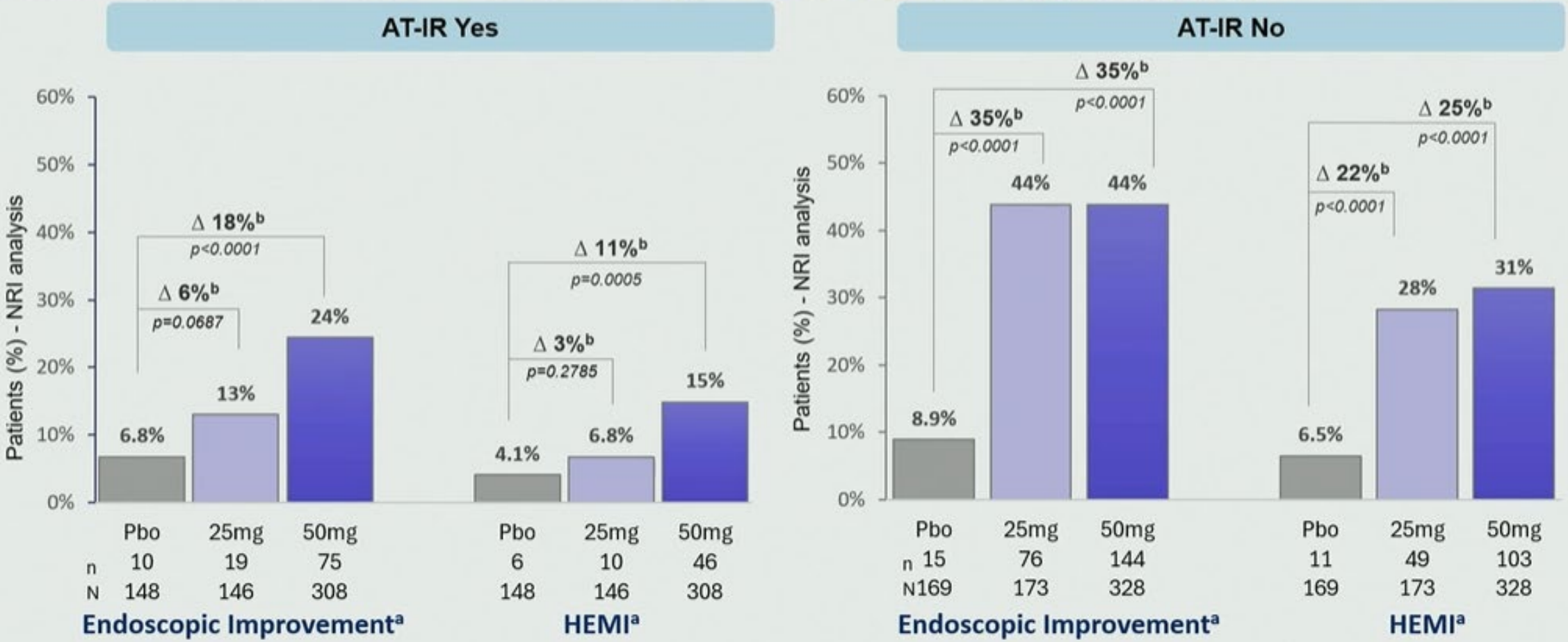
HEMR
(Endoscopic subscore =0 + Geboes score <2A.0)



All p-values are nominal; NRI is used for subjects with missing outcome at week 8 and subjects reporting any IE prior to week 8; % Difference is for Obe minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights adjusting for the randomization stratification factors: inadequate response to advanced therapies (yes/no), baseline oral corticosteroids usage (yes/no), and pivotal study (ABX464-105/ABX464-106). All P values are 2-sided. HEMI: endoscopic subscore ≤1 and Geboes Index score ≤3.1. HEMR: absence of neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue, according to the Geboes grading system (ie, Geboes histologic score <2A.0), and endoscopy subscore of 0. EIHR: endoscopic subscore ≤1 and Geboes Index score <2A.0. EIHR, Endoscopic Improvement histological remission; HEMI, Histo-endoscopic mucosal improvement; HEMR, Histo-endoscopic mucosal remission; IE, intercurrent event; MES, Mayo Endoscopic Subscore; NRI, non-responder imputation; Obe, obefazimod; PBO, placebo.

Pooled ABTECT 1 & 2

Obefazimod 50 mg improved endoscopic & histologic outcomes in both AT-IR subgroups, with stronger effects in AT-IR No patients at Week 8



AT-IR: inadequate response to advanced therapies

All p-values are nominal; [a] Endoscopic improvement is defined as MES = 0 or 1 (MES of 1 modified to exclude friability). HEMI is defined as MES = 0 or 1 and Geboes Index score ≤3.1; [b] % Difference is for obefazimod minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights adjusting for the randomization stratification factors: inadequate response to advanced therapies (yes/no), Baseline oral corticosteroids usage (yes/no). P-values are two sided. NRI is used for subjects with missing outcome at Week 8 and subjects reporting any IE prior to Week 8.

Conclusions

- Development in IBD far from over
- Next 3 to 5 years will be dominated by competing anti-TL1A development programs
- A push for oral agents
- A drive for safer agents
- Combination therapy will advance, whether by co-administration or bi-specifics
- Compelling need for combinations of agents with orthogonal MOAs (microbiome, Tregs, epithelial barrier, repair/resolution, inflammasome, etc.)
- Precision medicine lagging
- Cell-based therapies will advance, but likely for highly refractory disease