

## Gut Check: A Primer on the Evolving IBD Landscape

March 17, 2025

- **Bottom Line:** The inflammatory bowel disease (IBD) treatment landscape is undergoing rapid transformation, with a variety of novel treatment strategies and approaches in development. In this report, part of our [5 for '25 series](#), we provide a two-part primer on IBD, which includes ulcerative colitis (UC) and Crohn's disease (CD). We believe this report will be helpful for investors new to the space, in addition to those interested in how the space is evolving, including what to expect throughout the remainder of 2025.
- Part one includes an overview of both diseases, including underlying causes, how each is evaluated in clinical trials, the current treatment landscape, future unmet needs, and epidemiology. To provide a well-rounded perspective, we incorporate insights from two MEDACorp KOLs, one from an academic center and another from a high-volume private practice. Our takeaways from the section are that there are numerous treatment options for patients, but none have been able to break through an “efficacy ceiling,” and most of the approved options fail to provide durable benefit in more than 30-40% of patients. Additionally, beyond efficacy shortfalls, patients are increasingly interested in more convenient dosing options and schedules, with oral and half-life extension now heavily factored in development considerations. Lastly, we view the IBD market as considerable, with room for new entrants, with global revenues expected to eclipse \$30B in 2030.
- Part two focuses on what's next in the field, including four sections focusing on the following topics:
  - Interest in targeting the TL1A:DR3 axis has grown and driven strategic interest in recent years. TL1A is emerging as a key inflammatory driver in UC and CD, influencing fibrosis, epithelial repair, and inflammation. Multiple Phase 3 trials are ongoing following strong Phase 2 efficacy. Emerging competitors are seeking to differentiate with improvements such as half-life extension (HLE), while STTK (OP, Khurshid) is uniquely targeting DR3, the other side of the axis.
  - Companies are evaluating novel targets to provide alternatives to existing options, with ABVX (OP, Smith) close to the finish line. Companies are expanding beyond well-known cytokine pathways, with programs going after novel targets. Notable among these are ABVX's obefazimod, an orally delivered miRNA-124 inducer, with topline induction data from the Phase 3 ABTECT program in UC expected in 3Q25. Numerous other novel targets are in development, which we highlight within.
  - Combination and bispecific approaches hope to break the efficacy ceiling. Proof-of-concept studies in UC (VEGA) and

Reason for report:

**PROPRIETARY INSIGHTS**

S&P 500 Health Care Index:

1,704.96

### Companies Highlighted

**ABBV, ABVX, AMGN, BMY, JNJ, LLY, MRK, PFE, SAN FP, STTK, XNCR**

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CD (EXPLORER) have spurred development of multi-targeting advanced therapies that seek to improve on the limitations of monotherapy. A key readout this year will be Phase 2b data from JNJ (OP, Risiinger) evaluating JNJ-4804 (guselkumab [Tremfya] + golimumab [Simponi]) in the DUET studies in CD and CD. These data will likely serve as a barometer for other combination approaches in the field. Notably, SYRE (Not Rated) is focused on developing potentially best-in-class co-formulations of its own half-life extended versions of approved drugs.

- **Oral formulations provide added convenience.** Rinvoq (upadacitinib) has emerged as a leading IBD drug given its convenient oral dosing and strong efficacy. Data suggest patients are interested, or would even prefer, oral options, and the field has responded with development of several oral options against known and novel targets. Recently JNJ and PTGX (Not Rated) disclosed encouraging topline data for icotrokinra (oral IL-23R inhibitor) from the Phase 2b ANTHEM study in UC, and later-stage studies in both UC and CD are planned. LLY (OP, Risiinger) plans to disclose data from the Phase 2b EMERALD-2 study evaluating its oral  $\alpha 4\beta 7$  inhibitor, MORF-057 (which it acquired from its \$3.2B acquisition of Morphic) in 1H25.

- See within for our comprehensive review of the current state and future outlook of IBD.

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**Oral formulations ([LINK](#))**

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# SUMMARY: The report contains an IBD primer and a look at what's next

## IBD includes ulcerative colitis and Crohn's disease and is a rapidly evolving area of medicine

### IBD Primer

- Inflammatory bowel disease (IBD) is made up of two related, but distinct diseases: ulcerative colitis (UC) and Crohn's disease (CD)
- Both are chronic, relapsing conditions driven by immune dysregulation
- Patients with moderate to severe disease are typically treated with a range of approved biologic agents. Although several classes of agents are available, there is an "efficacy ceiling" (remission rates of around 30-40%) and many patients still experience relapse
- Strategies are evolving to improve durability, efficacy, and patient experience

### TL1A/DR3 programs

- The TL1A/DR3 pathway impacts fibrosis, epithelial repair, and inflammation. TL1A has attracted significant strategic interest from biopharma
- Emerging Ph 2 data support TL1A's promise, and multiple Ph 3 trials are now underway
- Emerging programs seek to differentiate, with improvements such as half-life extension, while STTK is uniquely pursuing DR3, the opposite side of the axis

### Combination/bispecifics

- Combination approaches aim to break the efficacy ceiling in IBD therapy
- Proof-of-concept data from the VEGA and EXPLORER studies have led to significant interest in the approach, including the ongoing Ph 2 DUET studies of JNJ-4804 (coformulation of guselkumab [Tremfya] and golimumab [Simponi]) by JNJ, which could have data this year. SYRE (Not Rated) is combining its own potentially best-in-class programs against validated targets (e.g., TL1A, α4β7, and IL-23p19)
- Bispecific antibody approaches are also being explored, and are aiming to improve efficacy with more comprehensive immune modulation in a single molecule

### Emerging targets

- ABVX (OP, Smith) expects topline data from its Ph 3 ABTECT program evaluating its miRNA-124 targeting program, obefazimod, in 3Q25
- An array of programs against other novel targets are in development, seeking to expand the IBD therapeutic toolbox

### Oral formulations

- JAK inhibitors, namely Rinvoq (upadacitinib), are gaining traction in IBD, providing high efficacy in an oral formulation, affording better adherence and patient convenience
- Ongoing studies are exploring oral formulations of drugs against approved targets such as IL-23 and α4β7, while others, such as ABVX, are developing oral drugs against novel targets
- Data from LLY's MORF-057, which targets α4β7, are expected in 1H25

# Advanced therapies approved in IBD

**The list of advanced treatments for IBD has grown rapidly over recent years to include new targets (e.g., IL-23 and S1PR) and new formulations (e.g., SC and oral)**

Brand	Drug	Company	Molecule	ROA-induction	ROA-maintenance	Target	UC	Status	CD
Cimzia	certolizumab pegol	UCB (Not Rated)	biologic	SC	SC	TNFα	--	Approved (2008)	
Humira	adalimumab	ABBV (OP, Berens)	biologic	SC	SC	TNFα	Approved (2008)	Approved (2007)	
Remicade	infliximab	JNJ	biologic	IV	IV/SC	TNFα	Approved (2005)	Approved (1998)	
Simponi*	golimumab	JNJ	biologic	SC	SC	TNFα	Approved (2013)	--	
Entyvio	vedolizumab	TAK (Not Rated)	biologic	IV	IV/SC	α4β7	Approved (2014)	Approved (2014)	
Tysabri	natalizumab	BIIB (OP, Goodman)	biologic	IV	IV	α4β1/α4β7	--	Approved (2008)	
Rinvoq	upadacitinib	ABBV	small molecule	Oral	Oral	JAK	Approved (2022)	Approved (2023)	
Xeljanz	tofacitinib	PFE (MP, Risinger)	small molecule	Oral	Oral	JAK	Approved (2018)	--	
Omvooh	mirikizumab	LLY	biologic	IV	IV/SC	IL-23p19	Approved (2023)	Approved (2025)	
Skyrizi	risankizumab	ABBV	biologic	IV	SC	IL-23p19	Approved (2024)	Approved (2022)	
Stelara	ustekinumab	JNJ	biologic	IV	IV/SC	IL-12/IL-23	Approved (2019)	Approved (2016)	
Tremfya	guselkumab	JNJ	biologic	IV/SC**	IV/SC	IL-23p19/CD64	Approved (2024)	sBLA	
Velsipity	etrasimod	PFE	small molecule	Oral	Oral	S1PR	Approved (2023)	II/III	
Zeposia	ozanimod	BMY (OP, Risinger)	small molecule	Oral	Oral	S1PR	Approved (2021)	--	

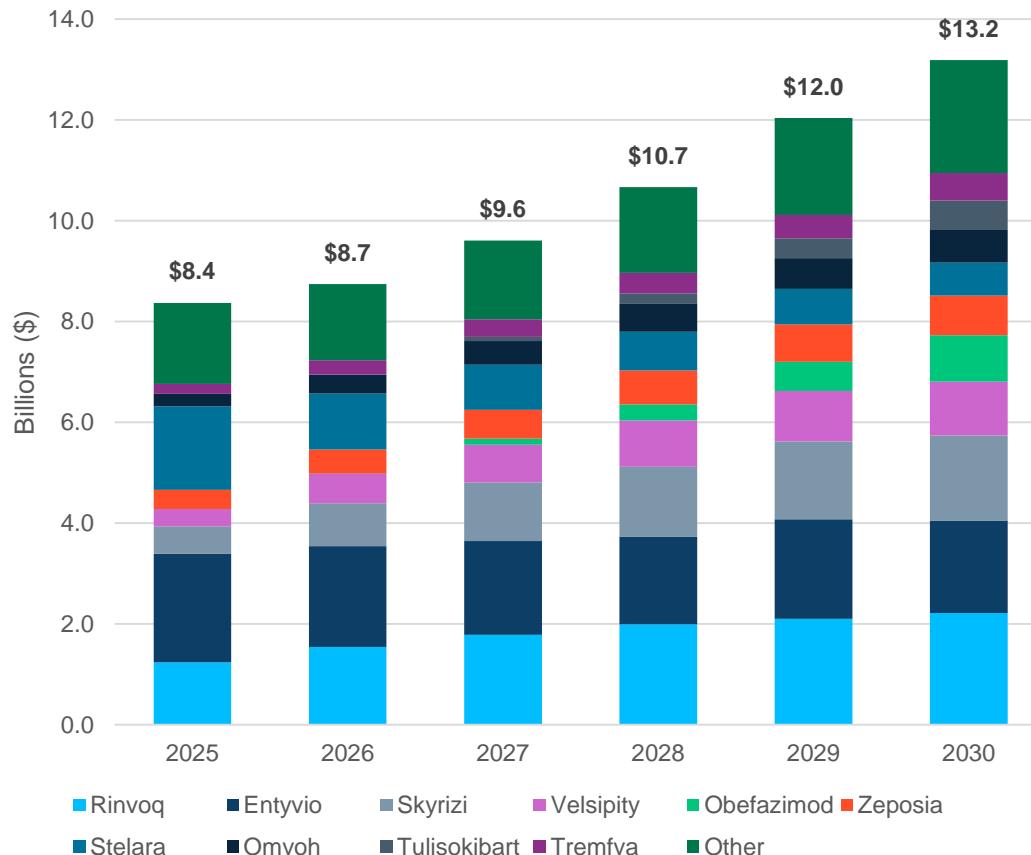
Source: Company disclosures; Leerink Partners Research. \*Simponi Aria is given IV in other indications; \*\*Following positive results in the ASTRO study, we expect SC induction to be approved in UC, data from SC induction in CD from the GALAXI study are expected in 2025 and could also support SC induction.

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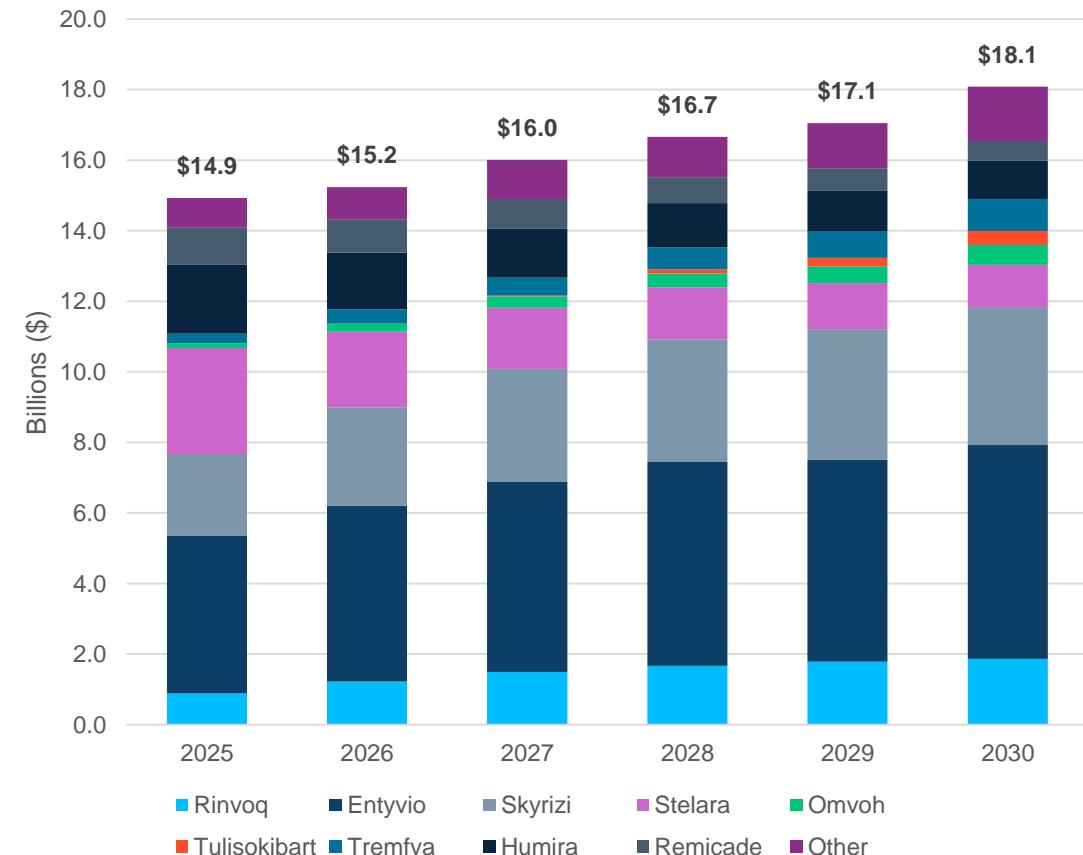
# IBD WW revenue estimates

IBD revenues are expected to eclipse >\$30B in 2031, representing a huge potential market

WW revenue estimates for UC



WW revenue estimates for CD



# Dealmaking in IBD has increased and attracted significant sums of money

An array of recent (select) transactions\* show the increasing interest in the space, highlighted by four multi-billion-dollar transactions in the last 5 years

Acquirer / Lead	Target / Partner	Deal type	Key molecule / technology	Target	Economics	Date
LLY	ONVO (Not Rated)	Acquisition	FXR314	FXR agonist	Upfront: \$10M Milestones: Up to \$50M	2.2025
LLY	MORF	Acquisition	MORF-057	α4β7 integrin	\$3.2B	7.2024
ABBV	Nimble Therapeutics	Acquisition	Preclinical asset	IL-23R, TL1A	\$200M	6.2024
ABBV	Celsius	Acquisition	CEL383	TREM1	\$250M	6.2024
ABBV	FutureGen	Collaboration	FG-M701	TL1A	Upfront: \$150M Milestones: Up to \$1.56B	6.2024
ABBV	Landos	Acquisition	NX-13	NLRX1	\$137M	3.2024
RHHBY (Not Rated)	Telavant	Acquisition	RG-6631 (RO7790121/RVT-3101/PF-06480605)	TL1A	Upfront: \$7.1B Milestones: Up to \$150M	10.2023
SAN FP (OP, Risinger)	TEVA	Collaboration	Duvakitug (TEV-48574)	TL1A	Upfront: \$500M Milestones: Up to \$1B	10.2023
MRK (OP, Graybosch)	RDXD	Acquisition	Tulisokibart (MK-7240 / PRA023)	TL1A	\$10.8B	6.2023
BMY	GentiBio	Collaboration	Treg platform	-	Milestones: Up to \$1.9B	8.2022
PFE	Arena Pharma	Acquisition	Etrasimod	S1P1	\$6.7B	12.2021
ENTO (Not Rated, formerly FWBI)	AZRX	Acquisition	Niclosamide	Various	\$229M	9.2021
Landos Biopharma (private)	LianBio	Collaboration	Omilancor	LANCL1	Milestones: Up to \$218M	5.2021

# What's next in IBD?

## An array of novel targets and approaches could disrupt the IBD landscape

### TL1A/DR3 targeting agents

- Emerging class of therapies in development that have demonstrated very encouraging data in Ph 2 studies, with first generation programs now in Ph 3. Next generation approaches, including half-life extended (HLE) versions (for added convenience), are entering the clinic
- TL1A targeting programs have attracted significant strategic interest and catalyzed several high-profile deals in recent years

### Combinations and bispecifics

- Both combinations of targeted therapies and bispecifics, which combine multiple targets in one, are in development to overcome efficacy ceilings in the space without negatively impacting safety
- JNJ's DUET Ph 2b studies of JNJ-4804, its coformulation of golimumab (Simponi) and guselkumab (Tremfya), have primary completion dates of May 2025, and data could be presented later this year

### Emerging targets

- Given the complexity of IBD and remaining unmet need, numerous novel targets are being explored for their therapeutic potential
- Notable among them is ABVX's obefazimod, a miRNA-124 inducer, that is being evaluated in the Ph 3 ABTECT program in UC, with topline induction data expected in 3Q25

### Oral formulations

- Oral formulations of approved biologics (target the same pathway) could be a disruptive innovation for IBD treatment, addressing the unmet need for more patient-friendly options
- These have also influenced notable deals in the space recently. JNJ / PTGX recently presented encouraging data from the Ph 2b ANTHEM study of icotrokinra (oral IL-23R) in UC, and data from LLY's Ph 2b EMERALD-2 study of MORF-057 (oral α4β7) in UC are expected in 1H25

# Companies are exploring other targets to differentiate in IBD

**Programs against a variety of targets implicated in IBD are in development\***

Drug	Company	Molecule	ROA	Target	UC	Status	CD
Etrasimod	PFE	small molecule	Oral	S1PR	Approved		III (CULTIVATE)
Tulisokibart	MRK	biologic	IV/SC	TL1A	III		III
RTV-3101	RHHBY	biologic	IV/SC	TL1A	III		II
Obefazimod	ABVX	small molecule	Oral	miR-124	III		II
Omilancor	Nimmune	small molecule	Oral	LANCL2	III		II
MORF-057	LLY	small molecule	Oral	$\alpha 4\beta 7$	II		II
TEV-48574	SAN FP / TEVA	biologic	SC	TL1A	II		II
Rituximab	PFE	small molecule	Oral	JAK3	II		II
ABBV-113	ABBV	small molecule	Oral	NLRX1	II		II
JNJ-2113 (PN-234)	JNJ / PTGX	small molecule	Oral	IL-23R	II	--	
GS-1427	GILD	small molecule	Oral	$\alpha 4\beta 7$	II	-	
Lutikizumab	ABBV	biologic	SC	IL-1a/1b	II		-
ABBV-668	ABBV	small molecule	Oral	RIPK1	II		-
Eclitasertib	SAN FP / DNLI	small molecule	Oral	RIPK1	II		-
OSE-127	OSE	small molecule	SC	IL-7R	II		-
ADS-051	Adiso Therapeutics	small molecule	Oral	MRP2 / FPR1	II		-
ALTB-268	AltruBio	biologic	SC	PSGL1	II		-
BBT-401	Bridge Biotherapeutics	small molecule	Oral	Pellino-1	II		-
Eltrekibart	LLY	biologic	IV/SC	CXCR1/2	II		-
Orismilast	UNION Therapeutics	small molecule	Oral	PDE4	II		-
PL8177	PTN	biologic	SC	MCR1	II		-
Rosnilimab	ANAB	biologic	IV/SC	PD-1	II		-
VE202	Vedanta Biosciences	-	Oral	microbiota	II		-
Vixarelimab	RHHBY	biologic	IV/SC	IL-31	II		-
VTX002	VTYX	small molecule	Oral	S1P1R	II		-
Tilpisertib foscemecarbil	GILD	small molecule	Oral	TPL2	II		-
CU104	Curacle Co	small molecule	Oral	IL-6	II		-
IBI112	Innovent	biologic	SC	IL-23	II		-
Dupilumab	SAN FP / REGN	biologic	SC	IL-4R $\alpha$	II		--
SPH3127	Shanghai Pharma Biotherapeutics	small molecule	Oral	renin	II*		-
Efavaleukin alfa (AMG 592)	AMGN	biologic	SC	IL-2	II		--
AZD7798	AZN	biologic	IV	CCR9	-		II
SAR441566	SAN FP	small molecule	Oral	TNFR	-		II
AGMB-129	AgomAb	small molecule	Oral	ALK5	--		II

Source: Leerink Partners Research; Company Disclosures; Biomedtracker; Clinicaltrials.gov. \*Focuses on IBD programs in later stage development (Ph 2+)

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# Select IBD catalysts in 2025

**ABVX's obefazimod Ph 3 readout will be the main event for the year, and other notable updates include potential DUET combination data**

Company	Drug	Mechanism	Event	Expected Timing
XNCR (OP, Chang)	XmAb942	Anti-TL1A	Initial Ph 1 SAD data	1H25
SAN FP / REGN	Dupixent (dupilumab)	Anti-IL-4/13	Topline data from the Ph 2 LIBERTY-UC SUCCEED study in UC	1H25
Ensho Therapeutics (private)	NSHO-101	Oral α4β7 inhibitor	Ph 2 initiation in UC	1H25
AMGN	Efavaleukin alfa (AMG 592)	IL-2 mutein fusion protein	Topline Ph 2 data	1H25
LLY	<b>MORF-057</b>	<b>Oral α4β7 inhibitor</b>	<b>Topline data from Ph 2b EMERALD-2 study in UC</b>	<b>1H25</b>
ABSI (Not Rated)	ABS-101	Anti-TL1A	IND filing / Ph 1 initiation	1H25
SYRE	SPY002	Anti-TL1A	Interim Ph 1 data	2Q25
SYRE	SPY001	Anti-α4β7	Ph 2 platform study initiation*	Mid-2025
SYRE	SPY003	Anti-IL-23	Interim Ph 1 data	2H25
STTK	SL-325	Anti-DR3	IND filing / Ph 1 initiation	3Q25
PFE	Velsipity (etrasimod)	S1PR modulator	Data from the Ph 2/3 CULTIVATE trial in CD	2H25
<b>ABVX</b>	<b>Obefazimod</b>	<b>miRNA inducer</b>	<b>Topline induction data from Ph 3 ABTECT studies in UC</b>	<b>3Q25</b>
ANAB	Rosniliimab	PD-1 depleter/agonist	Topline Ph 2 data	4Q25
JNJ	JNJ-4804	Anti-IL-23p19 + Anti-TNFα	Potential data from the Ph 2b DUET study in UC/CD	2025
ABBV	ABBV-113	Oral NLRX1 agonist	Ph 2 UC data	2025
ABBV	ABBV-8736	Oral TREM-1 agonist	Ph 2 CD initiation	2025
Vedanta Biosciences	VE202	Bacterial consortium	Ph 2b data	2025

## Disease primer

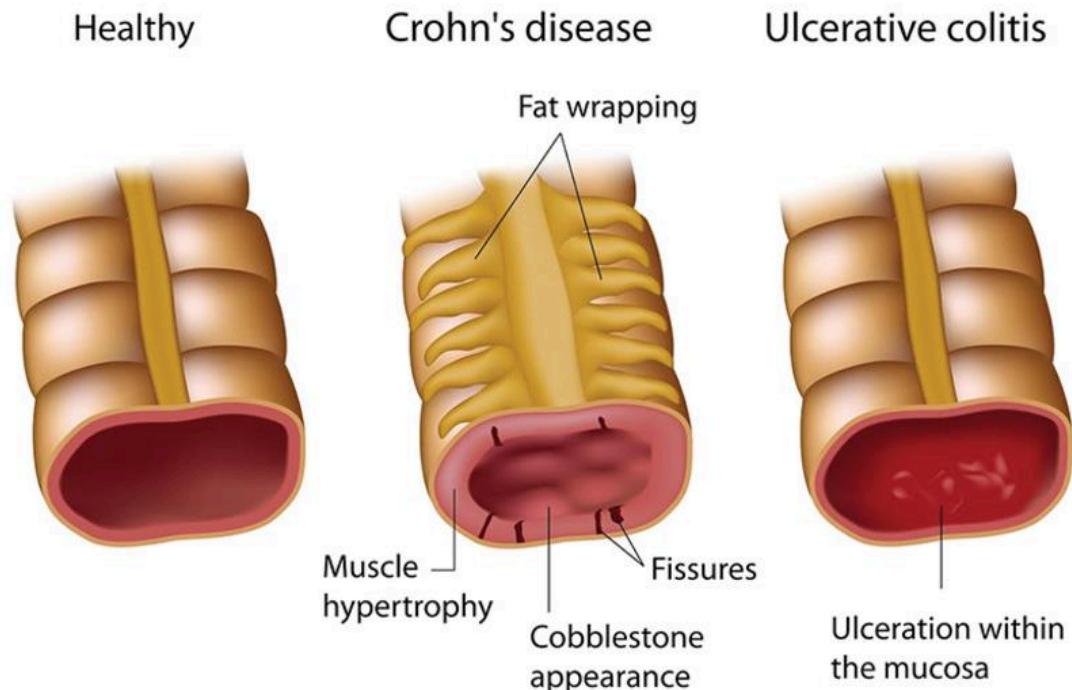
- **Inflammatory bowel disease (IBD) includes ulcerative colitis (UC) and Crohn's disease (CD):** two chronic, immune-mediated diseases affecting the gastrointestinal (GI) tract
- **Different patterns of inflammation:** UC is limited to the colon, while CD affects any part of the GI tract with transmural involvement. Both have multifactorial causes, resulting from genetic predisposition, immune dysregulation, and environmental factors
- **Clinical trials:** IBD clinical trials have varying designs and typically recruit fairly heterogeneous groups of patients. In UC studies, efficacy is typically evaluated using the Modified Mayo Score, while in CD studies, a combination of CDAI scores and endoscopy is now recommended

# Inflammatory bowel disease (IBD) overview

**IBD is an umbrella term for two common GI inflammatory diseases**

- Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal (GI) tract and is divided into ulcerative colitis (UC) and Crohn's disease (CD)
- UC and CD are alike in many ways, with both treated with similar therapeutic agents by gastroenterologists, however there are subtle differences (pathophysiology, presentation, etc.) that we explore further in this and the next section

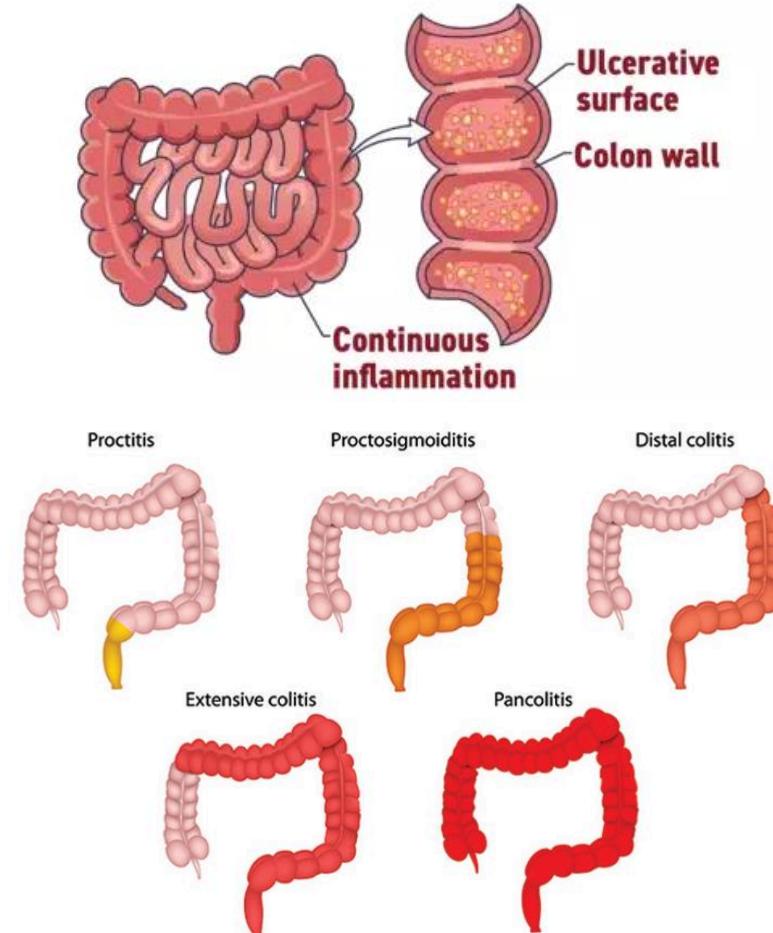
## Inflammatory Bowel Disease



# Background on ulcerative colitis (UC)

## UC is a chronic inflammatory disease of the colon

- Ulcerative colitis (UC) is a chronic inflammatory condition of the large intestine that is:
  - limited to the inner mucosal layer of the colon and almost always involves the rectum and may extend in a proximal and continuous fashion to involve other portions of the colon (see right)
- UC arises from a defective gut epithelial barrier and dysfunctional immune responses in the backdrop of genetic susceptibility (multiple genes affecting innate immunity, cytokine signaling, and epithelial function have been implicated), environmental triggers, and/or immune dysregulation
- Patients may present with rectal bleeding, increased stool frequency, and decreased stool consistency. Diagnosis can be made by clinical symptoms and endoscopy
- The natural history of the disease is characterized by periods of active inflammation alternating with periods of remission



# UC pathophysiology

A variety of processes are involved in the pathophysiology of UC and provide the basis for existing and future treatments

- Dysbiosis of gut microbiota:

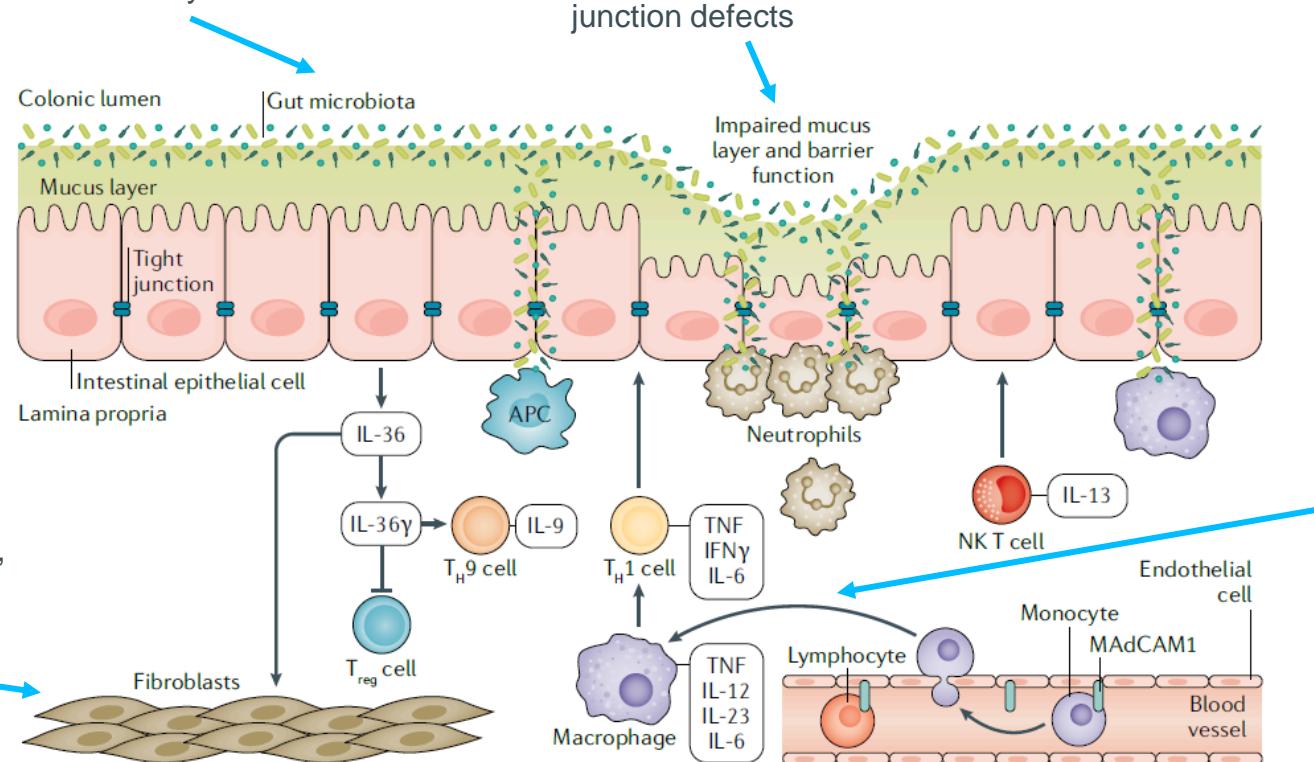
- Reduced microbial diversity
- Decreased production of short-chain fatty acids
- Altered interactions with host immune system

- Impaired intestinal barrier function:

- Decreased mucus layer thickness and altered composition
- Increased epithelial permeability and tight junction defects

- Chronic inflammation of colonic mucosa:

- Ulceration, crypt abscesses, and loss of goblet cells (mucous secreting)
- Potential progression to fibrosis and increased cancer risk



- Aberrant immune responses:

- Excessive activation of innate immune cells (neutrophils, macrophages)
- Imbalance of T cell subsets (increased Th1, Th2, Th9; decreased Tregs)
- Overproduction of pro-inflammatory cytokines (TNF, IL-13, IL-23, IL-36)
- Dysregulated intestinal homing of immune cells via adhesion molecules

# Assessing UC severity

## UC severity is loosely defined in the real world, while clinical trials use the Mayo scoring system

- UC is broadly separated and treated based on the following clinical symptoms:
  - Mild: ≤4 stools per day with or without small amounts of blood, no signs of systemic toxicity, and a normal C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR). Mild crampy abdominal pain, tenesmus, and periods of constipation are also common
  - Moderate: frequent (4 to 6 per day) loose, bloody stools, mild anemia not requiring blood transfusions, and abdominal pain that is not severe. Patients have no or minimal signs of systemic toxicity. Adequate nutrition is usually maintained
  - Severe: frequent loose bloody stools ( $\geq 6$  per day) with severe cramps and evidence of systemic toxicity as demonstrated by a fever, tachycardia, anemia, and/or an elevated CRP or ESR. Patients may have weight loss
- It is important to note that in the real-world there is no broad consensus on classification, and treatment choice can also be influenced by endoscopic findings (e.g., deep ulceration) and other considerations (e.g., age)
- **The Mayo scoring system (see right) can be used to assess disease severity and monitor patients during therapy. It is the standard assessment tool used in clinical trials (see next slide)**

### Mayo score for assessing ulcerative colitis activity in adults

#### Stool pattern

- Patient reports a normal number of daily stools (0 points)
- One to two more stools than normal (1 point)
- Three to four more stools than normal (2 points)
- Five or more stools than usual (3 points)

#### Most severe rectal bleeding of the day

- None (0 points)
- Blood streaks seen in the stool less than half the time (1 point)
- Blood in most stools (2 points)
- Pure blood passed (3 points)

#### Endoscopic findings

- Normal or inactive colitis seen (0 points)
- Mild colitis: mild friability, erythema, decrease in vascularity (1 point)
- Moderate colitis: friability, marked erythema, vascular pattern absent, erosions seen (2 points)
- Severe colitis: ulcerations and spontaneous bleeding (3 points)

#### Global assessment by clinician

- Normal (0 points)
- Mild colitis (1 point)
- Moderate colitis (2 points)
- Severe colitis (3 points)

# Primer on UC endpoints: Modified Mayo Score (MMS)

## MMS is a standard primary endpoint in UC trials, with the endoscopy score a key focus

- The Modified Mayo Score (MMS) has replaced the Total Mayo Score (TMS) as the standard endpoint in UC clinical trials
- MMS is favored vs. TMS as it focuses on non-subjective measures by excluding the physician assessment component (graded 0-3); partial Mayo is total Mayo without MES; PRO2 only includes SFS and RBS
  - MMS is a three-component score with a range of 0-9 and moderate to severe UC is typically defined as those with scores of 5-9
- Clinical remission by MMS is the gold standard endpoint**
  - Clinical remission is defined as MMS ≤2 with SFS≤1, RBS=0, and MES≤1 (without friability)**
  - Endoscopic response/improvement is defined as MES≤1
    - Endoscopic score is typically centralized reading of colonoscopy
    - Endoscopic remission is defined as MES=0
  - Clinical response is defined as MMS decrease by 30% and/or ≥3 from baseline with RBS ≤1 or RBS decrease ≥1
  - Symptomatic remission is defined as SFS=0 (or SFS=1 if baseline was 2-3) and RBS=0

### Modified Mayo Score (MMS)

#### Stool Frequency Score (SFS)

- Patient reports a normal number of daily stools (0 points)
- One to two more stools than normal (1 point)
- Three to four more stools than normal (2 points)
- Five or more stools than usual (3 points)

#### Rectal Blood Subscore (RBS)

- None (0 points)
- Blood streaks seen in the stool less than half the time (1 point)
- Blood in most stools (2 points)
- Pure blood passed (3 points)

#### Mayo Endoscopic Score (MES)

- Normal or inactive colitis seen (0 points)
- Mild colitis: mild friability, erythema, decrease in vascularity (1 point)
- Moderate colitis: friability, marked erythema, vascular pattern absent, erosions seen (2 points)
- Severe colitis: ulcerations and spontaneous bleeding (3 points)

#### Global assessment by clinician

- Normal (0 points)
- Mild colitis (1 point)
- Moderate colitis (2 points)
- Severe colitis (3 points)

Note: Mayo Score (MS) also known as Mayo Clinical Score (MCS)

Source: Leerink Partners Research; Company Disclosures; Peyrin-Biroulet, J Crohns Colitis 2023 (histopathology correlation with clinical outcomes); Peyrin-Biroulet, Gastroenterol 2021; Vespa, J Clin Med 2022; Itani, J Crohns Colitis 2018

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# Primer on UC endpoints: endoscopic response/improvement

**Aside from Mayo score, which is the gold standard holistic clinical endpoint, endoscopic outcome is considered the most important secondary outcome measure**

- An international committee has published consensus recommendations (STRIDE-II) on treatment targets in IBD in which clinical indices (i.e., Mayo scores) and endoscopic healing are emphasized as the foremost treatment goals
  - In a ranking of short-term treatment goals, clinical remission ranked the highest followed by a tie between clinical response and endoscopic response
  - In treat-to-target recommendations, the recommendation with the highest strength of recommendation for adults was “clinical response is an intermediate treatment target” followed by a tie between “clinical remission is an intermediate (i.e., medium-term) treatment target” and “endoscopic healing is a long-term target”
- Endoscopic healing is measured typically by colonoscopy or sigmoidoscopy, which are centrally read in trials; the figure at right shows case studies of MES scores ranging from 0-3
- In layman’s terms: symptomatology is important for the patient, but endoscopic results are what show true healing of disease
- STRIDE-II treatment goals are shown at right, which show that endoscopic healing is important but considered a longer-term goal

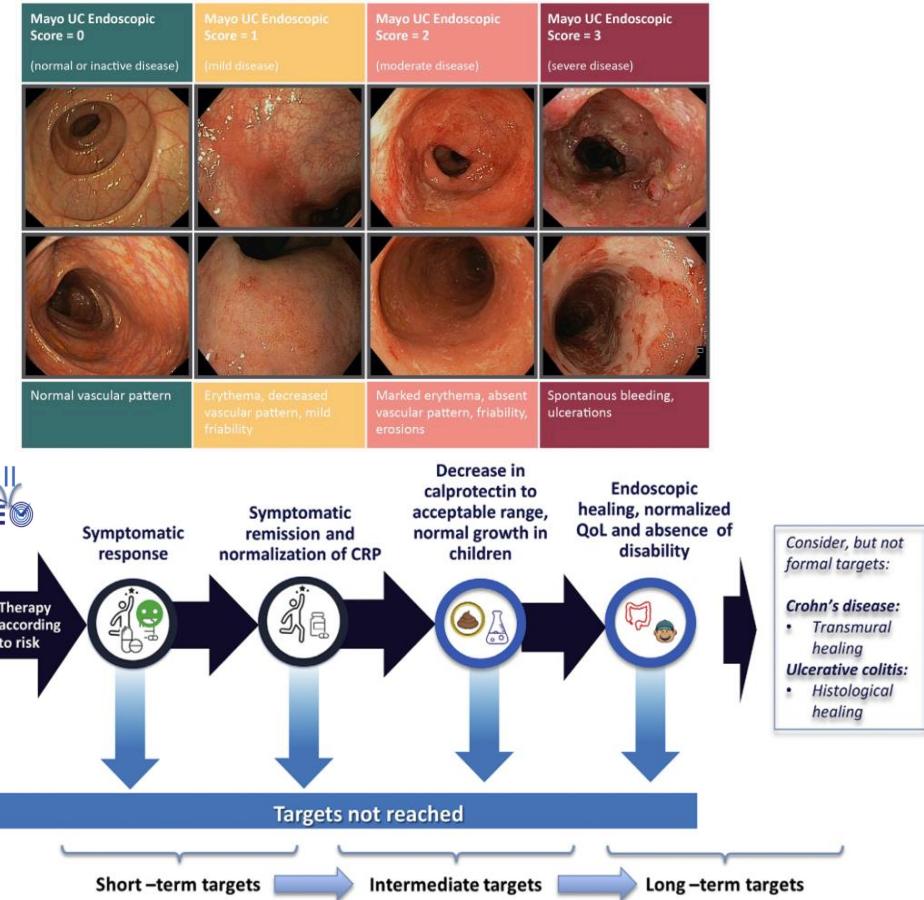


Figure 2. Treatment targets in CD and UC.

# Primer on UC endpoints: histology endpoints (1/2)

## Robarts Histopathology Index (RHI) is an emerging and potentially more sensitive measure

### Robarts Histopathology Index (RHI)

- Histopathology allows for a more precise assessment of microscopic disease characteristics and is an **emerging** clinical outcome in UC
  - There is some evidence that histopathology is correlated with Mayo score, but this isn't super well-characterized
- RHI is a clinical measure used in a few recent trials that is derived from an older more complex measure called the Geboes score (GS). Additional details on GS can be found in the citations below
  - RHI is a four-component score with a range of 0-33
  - **Remission is defined as RHI ≤3 (sometimes as ≤2) with 0 subscores for neutrophils and erosion ulcers**

$$\text{RHI} = (3 \times \text{epithelial neutrophils}) + (2 \times \text{lamina propria neutrophils score}) + (1 \times \text{chronic inflammatory infiltrate}) + (5 \times \text{erosion or ulceration})$$

#### Component

Epithelial neutrophils

0 = none

1 ≤ 5% crypts involved

2 ≤ 50% crypts involved

3 ≥ 50% crypts involved

Lamina propria neutrophils

0 = none

1 = mild but unequivocal increase

2 = moderate increase

3 = marked increase

Chronic inflammatory cell infiltrate

0 = no increase

1 = mild but unequivocal increase

2 = moderate increase

3 = marked increase

Erosion or ulceration

0 = no erosion, ulceration, or granulation tissue

1 = recovering epithelium + adjacent inflammation

1 = probable erosion—focally stripped

2 = unequivocal erosion

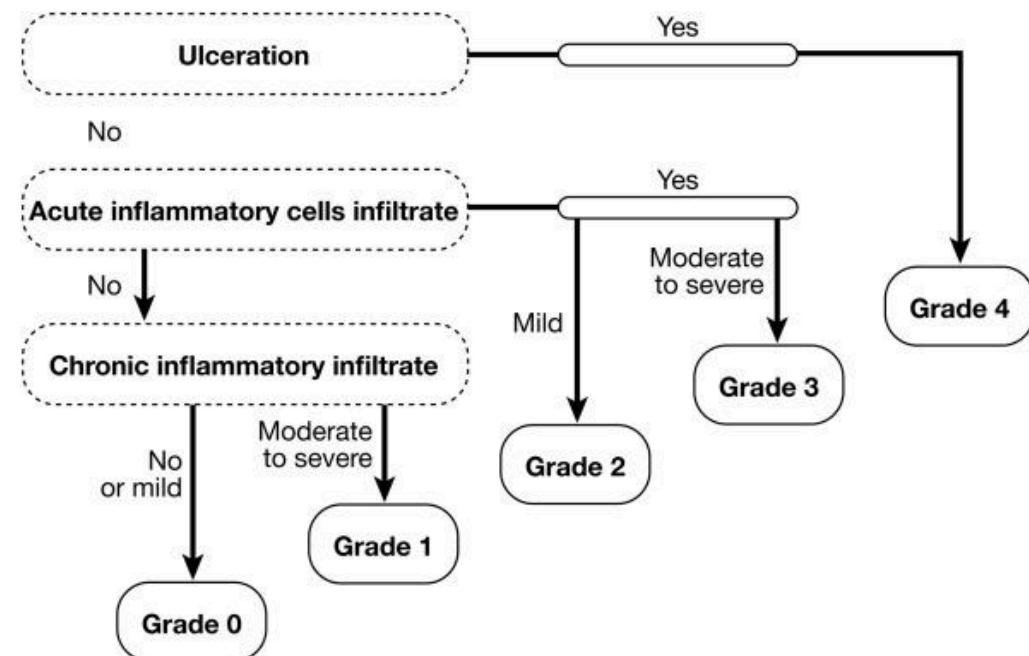
3 = ulcer or granulation tissue

# Primer on UC endpoints: history endpoints (2/2)

**Nancy Index (NI) is another histology measure, which benefits from simplicity and easy application**

## Nancy Index (NI)

- NI is a simpler assessment with fewer variables. It requires stepwise evaluation of three features, lamina propria chronic inflammation (defined as lymphocytes, plasma cells and eosinophils), neutrophilic inflammation and surface damage (erosion/ulcers), to build up a continuous 0–4 score
  - Grade 0 indicates the least severe disease, or the absence of significant histological disease and Grade 4 indicates the most severe disease. In contrast to the RHI, the worst feature present among biopsies determines the final score
  - Histological remission is defined as NI = 0 and histological response is defined as NI ≤ 1, when there are no neutrophils in the epithelium, nor erosions or ulcers
- It correlates highly with the RHI and the response to change after treatment and has the advantage of being conceptually simple
- Both RHI and NI are recommended by ECCO for use in clinical practice



# Primer on UC endpoints: steroid-free clinical remission

The FDA has flagged steroid-free remission as an emerging endpoint of interest

## Corticosteroid-free remission

- Patients with moderate to severe UC are at increased risk of long-term complications from systemic glucocorticoid use
- The FDA has identified this and has included corticosteroid-free remission as a secondary endpoint of interest for sponsors to evaluate in clinical trials, as below:

“Corticosteroid-free remission: defined as subjects who are in clinical remission at the conclusion of the controlled trial (e.g., 52 weeks) and having no corticosteroid exposure during a prespecified period (e.g., at least 8 to 12 weeks) before that assessment. The proportion of subjects achieving corticosteroid-free remission, of those who were using corticosteroids at enrollment, is of interest and should be reported”

*Expert commentary on the topic can be found in the following publication: César da Silva. Gastroenterol Hepatol 2024 ([LINK](#))*

# Primer on UC: FDA guidelines for clinical development

## Sponsors typically choose between two types of design when running UC trials

### FDA guidance on UC trial design

- The FDA recommends a randomized, double-blind, placebo-controlled trial design that would be able to demonstrate that beneficial effects observed initially with treatment are continued long term to support chronic administration. Two approaches are recommended
- Enrollment for evaluating a therapy in moderate to severe UC should include patients who have a score of 5 to 9 on the MMS, including an endoscopy subscore of  $\geq 2$ , and span the whole range of both moderately and severely active disease categories. A balanced representation of subjects who have never received treatment with a biologic and subjects who have failed prior therapy with one or more biologics or other advanced therapies is also recommended
  - For reference, in the pivotal studies for the two UC drugs approved in October 2023, mirikizumab's (Omvoh) pivotal induction study had 43% prior biologic/JAK-exposure and etrasimod's (Velsipity) pivotal studies had 30-34% prior biologic/JAK-exposure

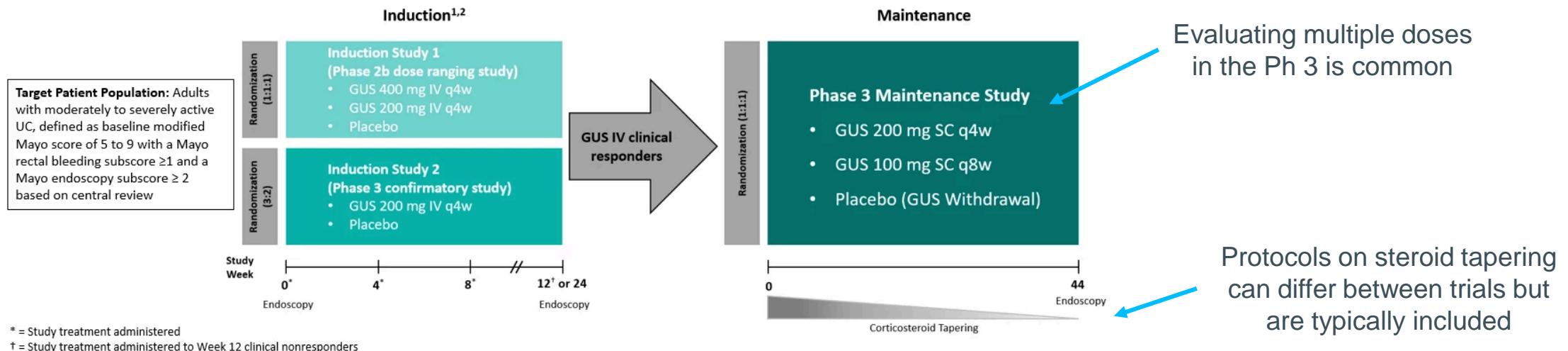
- Induction followed by randomized withdrawal maintenance** described as “a randomized, placebo-controlled induction trial to assess clinical benefit in the short term, followed by a maintenance trial in which all subjects who achieve initial clinical response to active drug at the end of induction are re-randomized to receive either active treatment or placebo, and efficacy is evaluated again at the end of the maintenance phase (e.g., 52 weeks)”
- Treat-through** design is another approach. This design “randomizes subjects once at the start of the trial to one of the treatment arms (i.e., a dosing regimen or placebo), and subjects are then treated continuously without rerandomization through 52 weeks. Sponsor should assess the primary endpoint at the end of treatment (e.g., 52 weeks). Earlier periodic assessments throughout the trial are useful to characterize the time to onset of initial clinical improvement. Early escape criteria should be incorporated to ensure that subjects who are worsening or not improving after a reasonable time frame have the opportunity to receive active treatment”

# Primer on UC: induction followed by randomized withdrawal maintenance study example

## The QUASAR program is a good example of the randomized withdrawal design in UC

### QUASAR guselkumab (Tremfya) program

- The Ph 2/3 QUASAR studies investigated the safety and efficacy of guselkumab (Tremfya) induction and maintenance therapy in patients with moderately to severe UC, and provides a useful example for thinking about late-stage UC development programs
  - Induction study:** initially patients are given either treatment or placebo and assessed at week 12 for clinical remission (by MMS), the primary endpoint of the induction portion
  - Maintenance study:** patients who are *clinical responders* (to guselkumab [Tremfya]) are then rerandomized and given maintenance therapy and assessed at week 44 for *clinical remission or response*

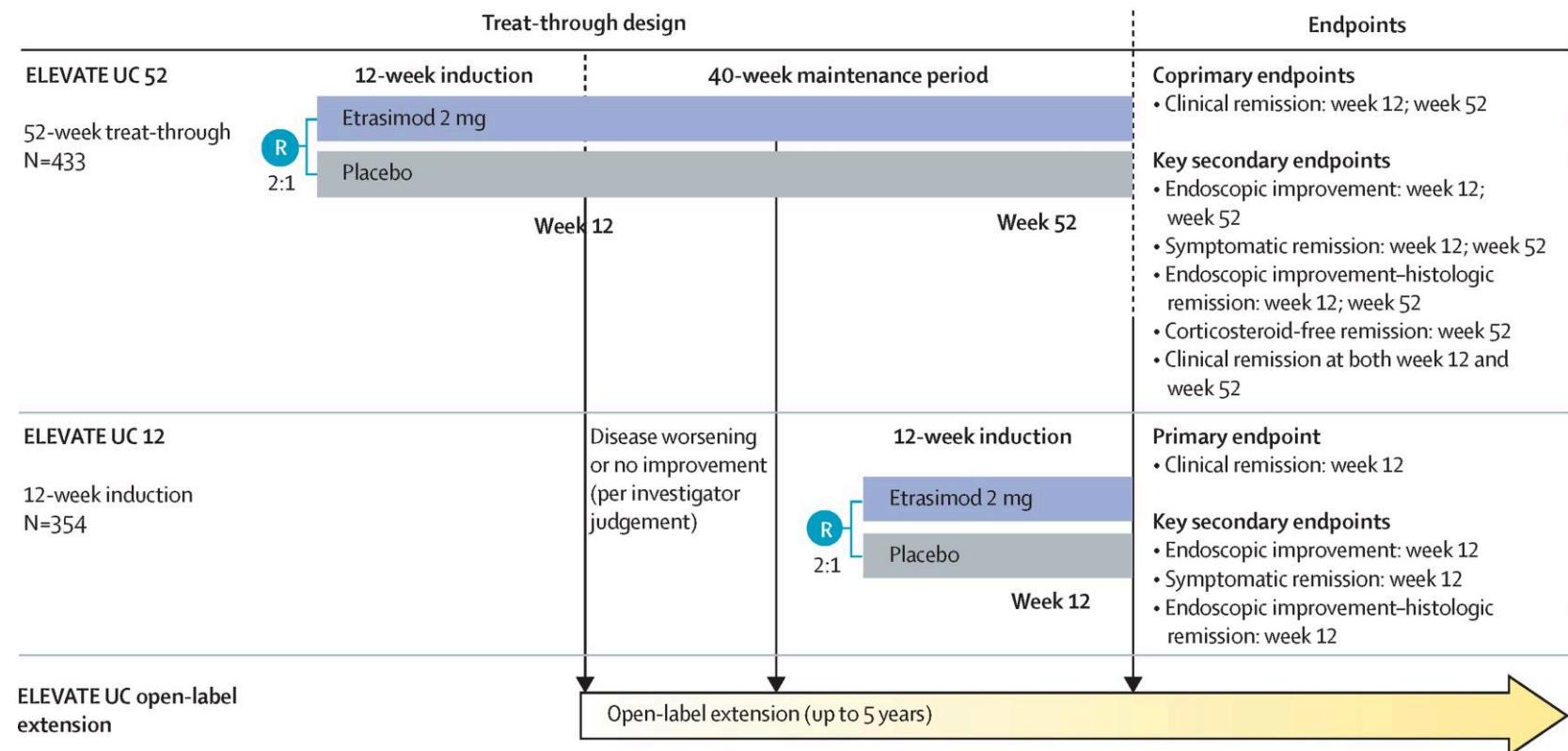


# Primer on UC: treat-through study example

Other trials use a “treat-through” approach, without rerandomization

## ELEVATE etrasimod (Velsipity) program

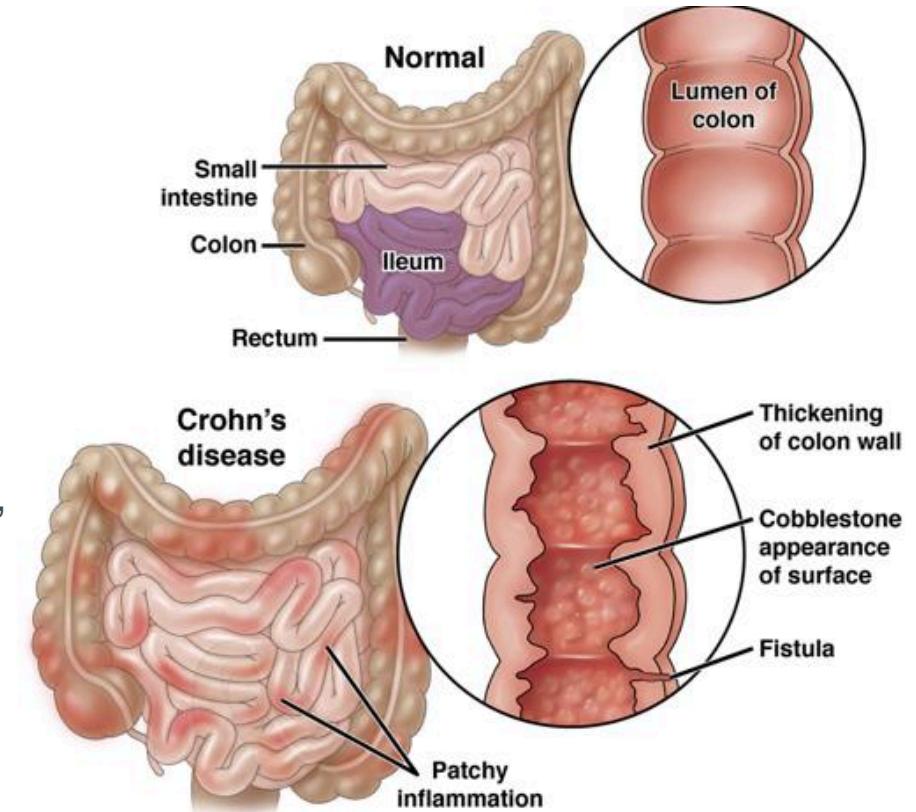
- ELEVATE UC 52 utilized a treat-through design where patients were randomized at the beginning and received either etrasimod (Velsipity) or placebo throughout



# Background on Crohn's disease (CD)

## Crohn's disease has a very different presentation and natural history than UC

- Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal (GI) tract that is:
  - Involves transmural inflammation, which can lead to complications such as strictures, fistulas, and abscesses
  - In contrast to UC, CD can affect any portion of the GI tract, from the mouth to the anus, with the most common sites being the terminal ileum and colon
- CD arises from a combination of genetic susceptibility, environmental factors, immune dysregulation, and microbial dysbiosis. Similar to UC, cytokine signaling (e.g., TNF- $\alpha$ , IL-12/23) and epithelial barrier dysfunction play central roles
- Patients may present with abdominal pain, diarrhea (often non-bloody), weight loss, fatigue, and extraintestinal symptoms (e.g., uveitis). Perianal disease, including abscesses and fistulas, is a distinguishing feature in some patient
  - In contrast to UC, rectal bleeding is less common unless the colon is involved
- The natural history of CD is characterized by a progressive disease course, with periods of flare-ups and remission. Complications such as strictures or penetrating disease may require surgical intervention



# Pathophysiology of Crohn disease (CD)

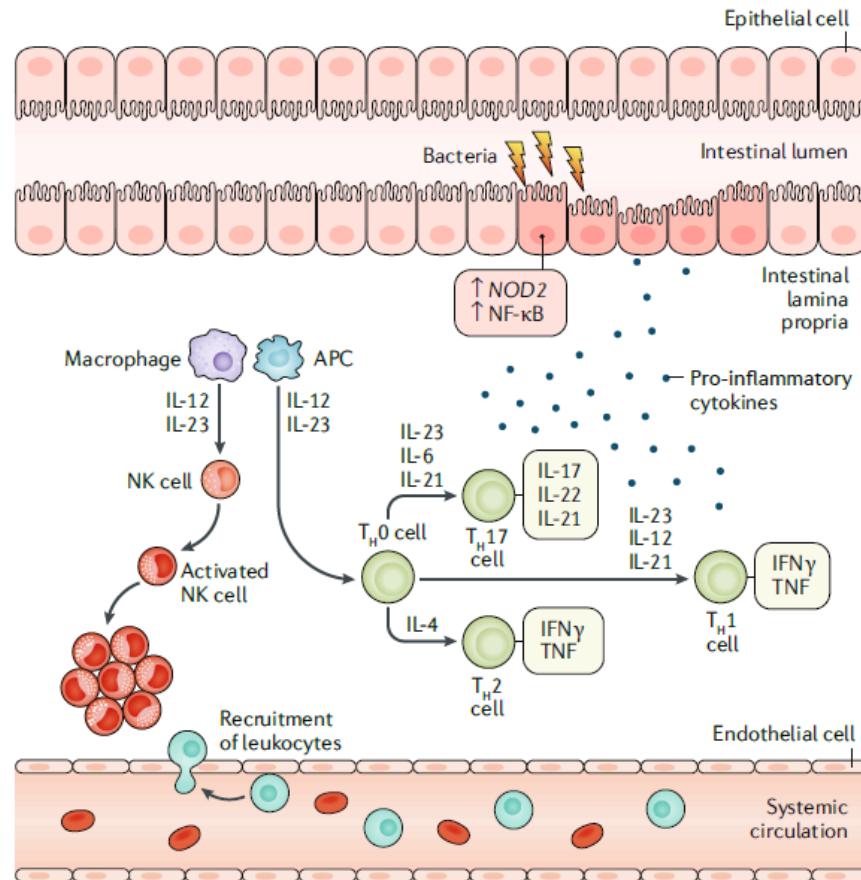
However, similar processes are involved in the pathophysiology, although inflammation is notably transmural and non-continuous within the GI tract

- Dysbiosis of gut microbiota:**

- Reduced microbial diversity
- Increased bacterial invasion of epithelial cells
- Activation of pro-inflammatory pathways
- Altered interactions with immune system

- Impaired intestinal barrier function:**

- Dysfunction of epithelial cells
- Increased permeability due to tight junction defects
- Overactivation of NF- $\kappa$ B pathway and NOD2 mutations



- Aberrant immune responses:**

- Activation of innate immune cells: macrophages and dendritic cells trigger inflammation
- T-cell imbalances: increased Th1, Th17 subsets; altered Th0 differentiation
- Overproduction of cytokines: elevated IL-12, IL-23, IFN $\gamma$ , TNF, and IL-17
- Leukocyte recruitment and chronic inflammation in the intestinal lamina propria

- Chronic inflammation in intestinal mucosa:**

- Persistent recruitment of inflammatory cells
- Increased production of cytokines leading to sustained immune activation
- Fibrosis and ulceration in severe cases

# Assessing CD severity

**CD severity is loosely defined in the real world, while clinical trials use the CDAI scoring system**

- CD symptoms differ from UC and are broadly separated and treated based on the following clinical symptoms and imaging findings:
  - **Mild:** abdominal pain, diarrhea, and fatigue with minimal impact on daily activities. No significant weight loss, dehydration, or anemia. No complications such as abscesses or fistulas
  - **Moderate:** increased abdominal pain, frequent diarrhea, and fatigue that interferes with daily activities. May involve weight loss, mild anemia, or signs of inflammation on imaging. May have localized complications like strictures or mild perianal disease
  - **Severe:** persistent and severe abdominal pain, frequent and debilitating diarrhea, significant weight loss, fever, and fatigue. May involve severe anemia, malnutrition, or systemic symptoms. Complications such as fistulas, abscesses, or intestinal obstructions are common, often requiring hospitalization or surgical intervention
- It is important to note that in the real-world there is no broad consensus on classification, and treatment choice can also be influenced by imaging and endoscopic findings (e.g., deep ulceration, fistulas) and other considerations (e.g., extraintestinal disease)
- **The Crohn's Disease Activity Index (CDAI) scoring system (see next slide) can be used to assess disease severity and monitor patients during therapy. It is the standard assessment tool used in clinical trials,** although a simplified version, the Harvey-Bradshaw Index (HBI) is commonly used in practice ([LINK](#))

# Primer on CD endpoints: Crohn's Disease Activity Index (CDAI)

**CDAI continues to serve as the gold standard primary endpoint in CD trials**

## Crohn's Disease Activity Index (CDAI)

- The Crohn's Disease Activity Index (CDAI) is often used as the standard primary endpoint in UC clinical trials
- In contrast to the MMS now used in UC clinical studies, the CDAI continues to include subjective symptoms in its score (e.g., patient well-being)
- Clinical remission by CDAI is the gold standard endpoint**
  - Clinical remission is defined as CDAI score <150
  - Clinical response is defined as CDAI decrease ≥100 (sometimes referred to as CDAI-100) and/or CDAI <150
- Note: some trials include also assess a patient reported outcome (PRO) subscore of the CDAI, known as SF-APS (stool frequency, abdominal pain score)
- Despite its historical and continued importance, CDAI has been shown to be poorly associated with intestinal inflammation in CD. This has led to an elevated role of endoscopic assessment in CD, which is now recommended by the FDA as a coprimary endpoint for trials (see next slide)

Remission	Mild	Moderate	Severe
<150	150-219	220-450	>450

Clinical or laboratory variable	Weighting factor
Number of liquid or soft stools each day for 7 days	× 2
Abdominal pain (graded from 0 to 3 based on severity) each day for 7 days	× 5
General well being, subjectively assessed from 0 (well) to 4 (terrible) each day for 7 days	× 7
Complications*	× 20
Use of diphenoxylate or opiates for diarrhea	× 30
An abdominal mass (0 for none; 2 for questionable; 5 for definite)	× 10
Absolute deviation of hematocrit from 47% in men and 42% in women	× 6
Percentage deviation from standard weight	× 1

\*One point is added for each set of complications: arthralgia or frank arthritis; inflammation of the iris or uveitis; erythema nodosum, pyoderma gangrenosum, or aphthous ulcers; anal fissures, fistulas, or abscesses; other fistulas; and fever (>100 °F) during the previous week.

# Primer on CD endpoints: simple endoscopic score for Crohn's disease (SES-CD)

## SES-CD has replaced more complex endoscopic scoring in CD

### Simple endoscopic score for Crohn's disease (SES-CD)

- As in UC, and in line with STRIDE-II, mucosal healing is a significant therapeutic goal. In CD, endoscopic assessment has been elevated to a co-primary endpoint with CDAI (e.g., the GALAXI studies of Tremfya)
  - Endoscopic findings in CD poorly correlate with CDAI, further emphasizing the need for dual-assessment to validate the efficacy of new therapeutics
- There are two commonly utilized endoscopic scoring systems in CD, the older and more complex Crohn's disease endoscopic index of severity (CDEIS, [LINK](#)) and the newer simple endoscopic score for Crohn's disease (SES-CD), which is more commonly used in clinical trials
  - Moderate to severe CD defined as SES-CD >7
- Endoscopic remission by SES-CD is now the recommended co-primary endpoint (though note most trials also response/improvement)**
  - Endoscopic remission is defined as SES-CD 0-2 or 0-4 with no subscore >1**
  - Endoscopic response/improvement is defined as SES-CD ≥50% from baseline
- Limitations of the SES-CD include
  - If all segments are showing subtle or mild disease activity, it is possible to get a higher score than in a patient with severe disease in only one segment
  - Does not take into account segments that are not visualized

Table 2. Features of the simple endoscopic score for Crohn's disease (SES-CD).

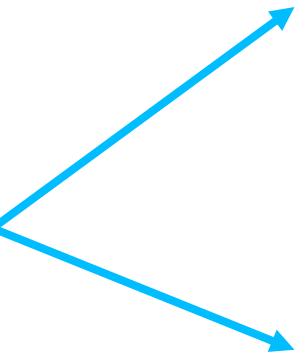
Features described in the system	Scoring	Division of the ileocolon	Definitions of disease severity
1. Size of ulcers (aphthous <0.5 cm, large 0.5–2 cm, very large >2 cm)	Total: 0–56 (all segments added together)	5 segments: terminal ileum; right colon; transverse colon; left colon; rectum	Healed: 0–2 Mild: 3–6 Moderate: 7–16 Severe: > 16
2. Surface ulcerated	Each feature has a point value of 0–3		Response to therapy: not defined
3. Surface involved in disease (affected)			
4. Presence of narrowing/stenosis			

# Primer on CD: FDA guidelines for clinical development

## Recommendations for CD are principally very similar to those for UC

### FDA guidance on CD trial design

- The FDA recommends a randomized, double-blind, placebo-controlled trial design that would be able to demonstrate that beneficial effects observed initially with treatment are continued long term to support chronic administration. Two approaches are recommended
- Enrollment for evaluating a therapy in moderate to severe CD should include patients who have a CDAI of  $\geq 220$  and SES-CD of  $\geq 6$  (or 4 if isolated ileal disease) and span the whole range of both moderately and severely active disease categories. As in UC, a balanced representation of subjects who have never received treatment with a biologic and subjects who have failed prior therapy with one or more biologics or other advanced therapies is also recommended



- Induction followed by randomized withdrawal** maintenance described as “a randomized, placebo-controlled induction trial to assess clinical benefit in the short term, followed by a maintenance trial in which all subjects who achieve initial clinical response to active drug at the end of induction are re-randomized to receive either active treatment or placebo, and efficacy is evaluated again at the end of the maintenance phase (e.g., 52 weeks)”
- Treat-through** design is another approach. This design “randomizes subjects once at the start of the trial to one of the treatment arms (i.e., a dosing regimen or placebo), and subjects are then treated continuously without rerandomization through 52 weeks. Sponsor should assess the primary endpoint at the end of treatment (e.g., 52 weeks). Earlier periodic assessments throughout the trial are useful to characterize the time to onset of initial clinical improvement. Early escape criteria should be incorporated to ensure that subjects who are worsening or not improving after a reasonable time frame have the opportunity to receive active treatment”

# Primer on CD: GALAXI provides a look at a unique trial design in CD

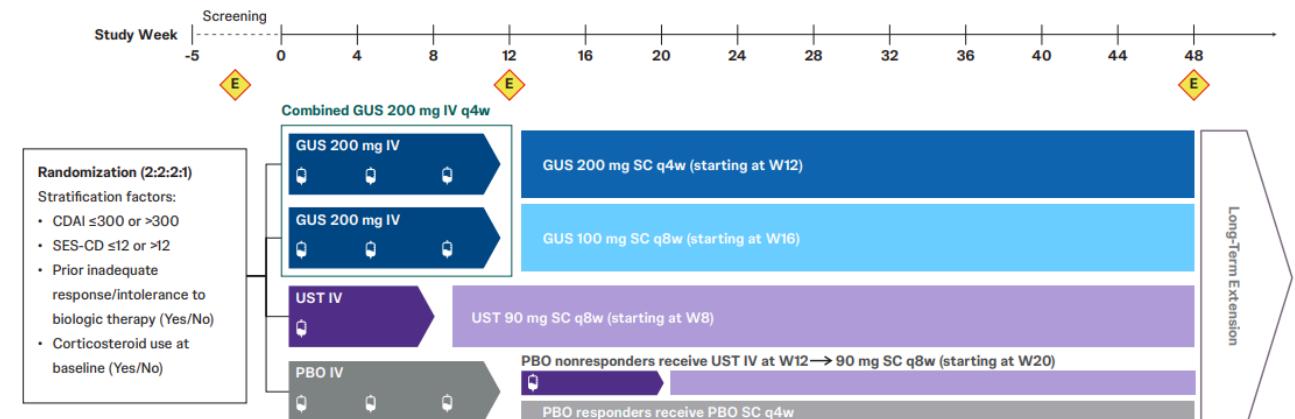
## GALAXI provides an example of an active comparator in IBD registrational studies

### GALAXI guselkumab program

- The Ph 3 GALAXI 2 and 3 studies used a treat-through design with both an inactive and active comparator arm (ustekinumab [Stelara]) and investigated the safety and efficacy of both guselkumab (Tremfya) induction and maintenance in patients with moderately to severe CD
  - Initially patients were given either treatment or placebo and assessed at week 12 for *clinical and endoscopic response* (by CDAI and SES-CD), coprimary endpoints of the induction portion
  - Patients on the active arms continued treatment until they were assessed at week 48 for *clinical remission or endoscopic response* (again by CDAI and SES-CD)
- Although unique, the trial serves an important example of the complexity (and relative flux) of IBD registrational study design. Additionally, the inclusion of an active control arm helps to facilitate comparison between biologics, which is a limitation of placebo-controlled studies

#### Eligibility Criteria

- Moderately to severely active CD (Clinical Disease Activity Index score 220–450 + mean daily Stool Frequency count >3 OR Abdominal Pain score >1) and Simple Endoscopic Score for Crohn's Disease score<sup>a</sup> ≥6 (or ≥4 for isolated ileal disease)
- Inadequate response/intolerance to oral corticosteroids or 6-mercaptopurine/azathioprine/methotrexate, or biologic therapies<sup>b</sup>



<sup>a</sup>Scored at screening by central reader with minimum scores of 1 for "size of ulcer" and "ulcerated surface". <sup>b</sup>Biologic therapies: TNF antagonists or vedolizumab. Note: To maintain treatment masking, all participants received active and/or PBO IV q4w through W12 and active and/or PBO SC q4w through W48. CDAI=Clinical Disease Activity Index; E=Endoscopy; IV=Intravenous; GUS=Guselkumab; PBO=Placebo; q4w=Every 4 weeks; q8w=Every 8 weeks; SC=Subcutaneous; SES-CD=Simple Endoscopic Score for Crohn's Disease; TNF=Tumor necrosis factor; UST=Ustekinumab; W=Week.

# Current trial design advantages and disadvantages

Ma et al. provides excellent background on current trial designs in IBD

## ① Randomized induction-only trials



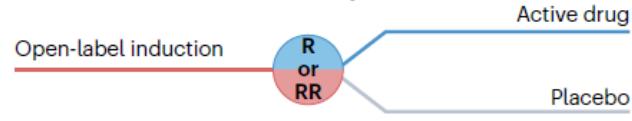
### Advantages

Rapid to recruit,  
can rapidly assess  
proof-of-concept  
for mechanism

### Disadvantages

No ability to  
evaluate long-term  
efficacy

## ② Randomized maintenance-only trials



### Advantages

All participants  
receive active  
induction therapy

### Disadvantages

Cannot evaluate  
induction efficacy

### Advantages

Only responders  
are re-randomized

### Disadvantages

Risk of immunizing  
responders with-  
drawn to placebo

## ③ Randomized treat-through trials



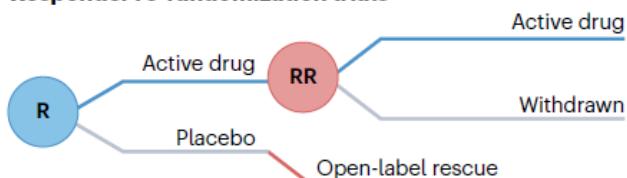
### Advantages

Easiest to interpret,  
end of trial data  
representative of  
full study  
population

### Disadvantages

Risk of higher  
dropout rates in  
patients on  
long-term placebo

## ④ Responder re-randomization trials



### Advantages

Mimics real-world  
practice wherein  
only responders  
are continued into  
maintenance  
therapy

### Disadvantages

Carry-over effects of  
induction into  
maintenance are  
possible, requires  
high patient numbers  
to ensure adequate  
maintenance  
responders are  
included

**Fig. 1 | Historical trial designs in IBD.** Historical designs for inflammatory bowel disease (IBD) trials include: (1) induction-only trials (participants randomized to intervention or placebo for 4–8 weeks; examples include CLASSIC-I, ULTRA1); (2) randomized maintenance-only trials (participants randomized to maintenance therapy after open-label induction; examples include ACCENT1, CHARM, PRECISE2); (3) treat-through trials (participants randomized to intervention or placebo, continue allocated treatment throughout the study; examples include ULTRA2, ACT1 and 2, PRECISE1); and (4) responder re-randomization trials (participants randomized to intervention or placebo, then responders to active drug are re-randomized after induction to continue active drug or withdraw to placebo; examples include GEMINI, PURSUIT, UNITI). R, randomization; RR, responder re-randomization.

*Note: this applies to both UC and CD trials,  
the second citation below provides a recent  
take on how clinical trials may evolve in IBD*

# Timeline for clinical development

**Getting an IBD drug from Ph 2a to approval can take 6+ years**

## UC clinical development timelines:

- Tremfya (JNJ) took roughly ~6 years from Ph 2a start to approval
  - Ph 2a
    - Start date: September 2018
    - Completion date: December 2020
  - Ph 2b/3 induction study (QUASAR)
    - Start date: August 2019
    - Completion date: June 2022
  - Ph 3 maintenance study (QUASAR)
    - Start date: September 2019
    - Completion Date: July 2023
    - Approval: September 2024

## CD clinical development timelines:

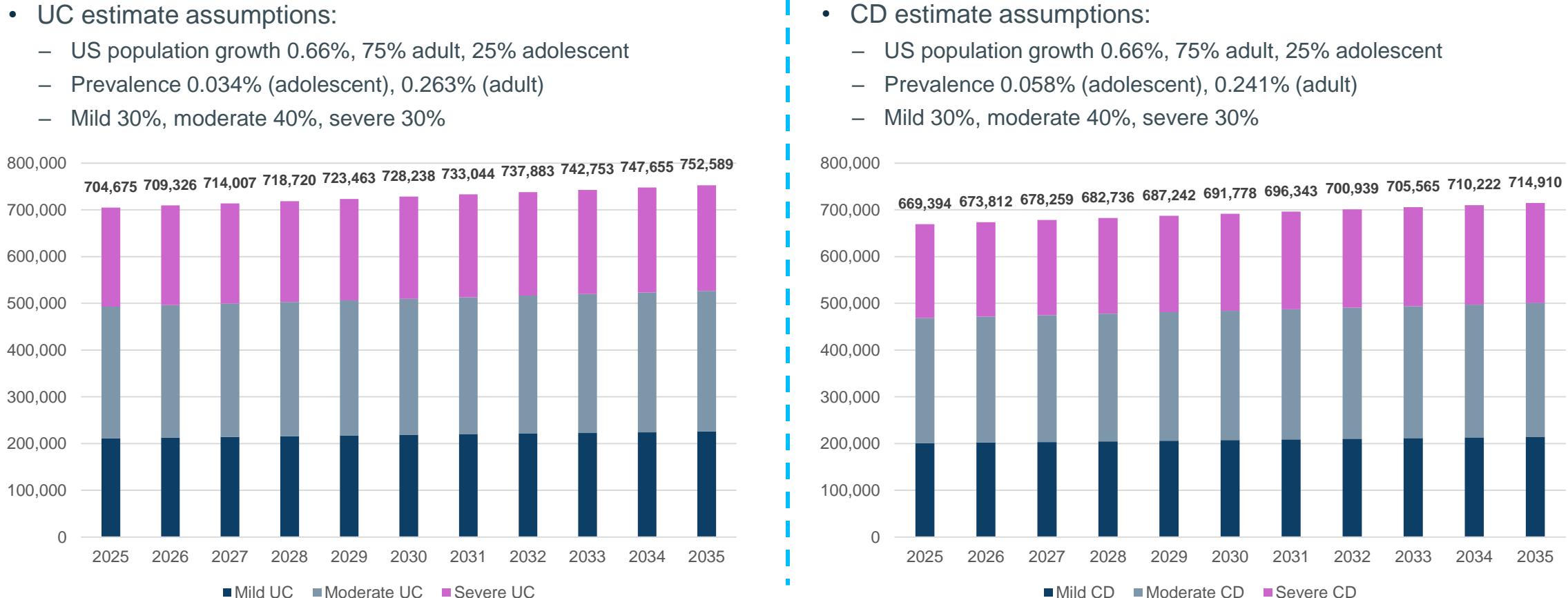
- JNJ recently submitted an sBLA for Tremfya and expects approval in 2025. This implies a timeline of ~6-7 years, slightly longer than in UC
  - Ph 2a
    - Start date: September 2018
    - Completion date: December 2020
  - Ph 2b/3 induction/maintenance study (GALAXI)
    - Start date: March 2018
    - Completion date: December 2024
  - Approval expected: 2025

**A more contemporary example: the Ph 2 ARTEMIS-UC study of MRK's TL1A, tulisokibart, initiated in July 2021, and following encouraging data, led to initiation of the Ph 3 ATLAS-UC in October 2023, which has a primary completion date of November 2026. Implying a similar timeframe of ~6 years to potential approval**

# IBD epidemiology

**IBD is a highly prevalent condition in the US, representing a sizable market of >1M patients; advanced therapies are typically reserved for moderate to severe disease**

## US IBD prevalence estimates



Source: Leerink Partners Market Model

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## Treatment primer

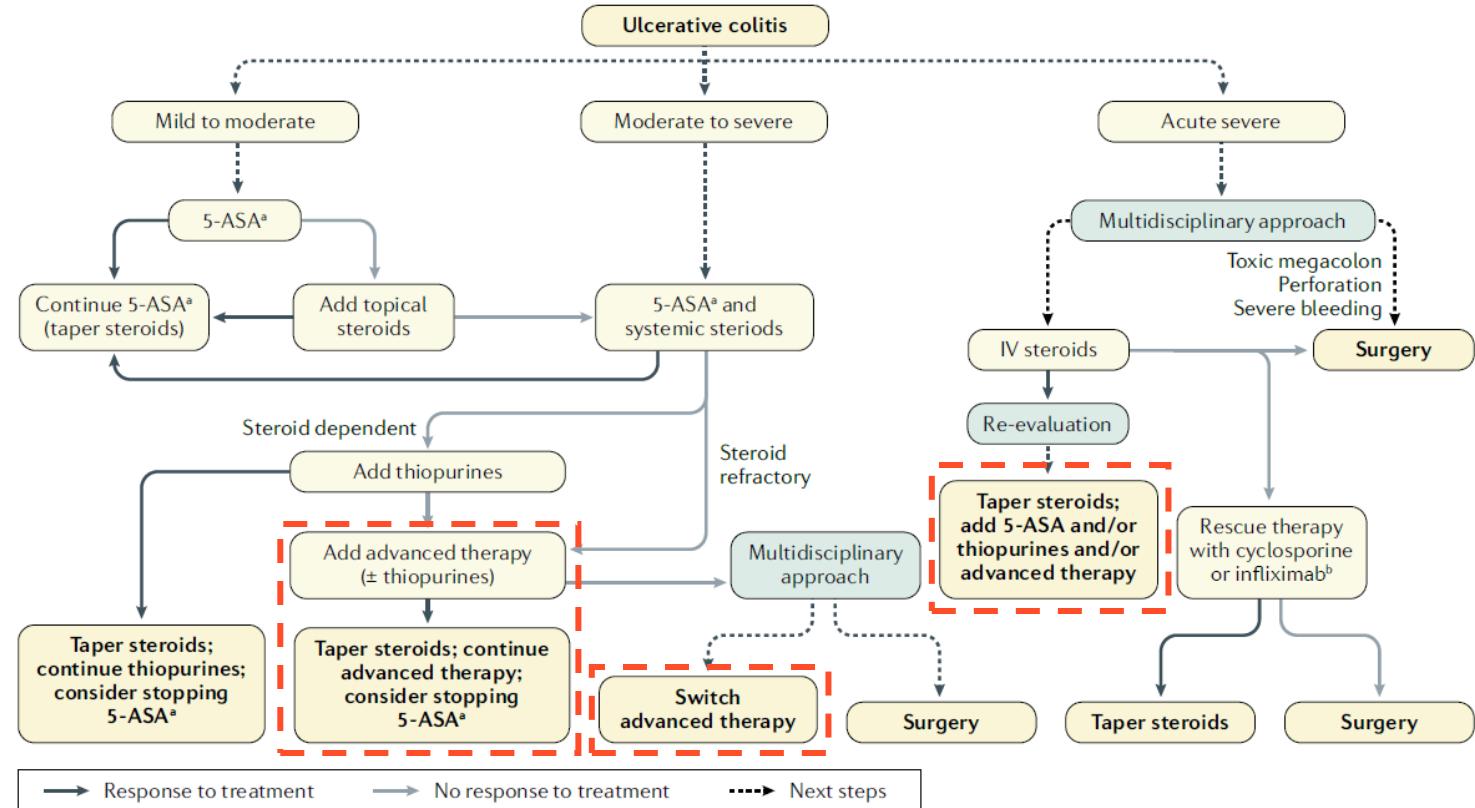
- **UC and CD treatments:** advanced therapies include IV/SC delivered biologics and oral small molecules. Key drug classes include TNF $\alpha$  inhibitors, JAK inhibitors, IL inhibitors, integrin inhibitors, and S1PR modulators
- **Current treatment:** choice of treatment in IBD is based on both physician and patient choice, with efficacy, safety, comorbidities, convenience and cost all factoring in. Vedolizumab (Entyvio), risankizumab (Skyrizi), guselkumab (Tremfya) and upadacitinib (Rinvoq) revenues are expected to rise amid growing market share in the coming years drive by strong marketing, product profile (safety, efficacy and formulation), and increasing prevalence
- **New treatments are needed:** despite the wide range of options, new treatments are needed to overcome limitations of efficacy and durability

# Treatment paradigm: UC

**Patients with moderate to severe disease receive advanced therapies after failing immunomodulators**

## Treatment paradigm

- Most patients with UC are treated with pharmacologic therapy based on disease severity, and multiple drugs are available
- Therapies can be grouped as:
  - induction therapies (i.e., relatively rapid onset of action)
  - maintenance therapies (i.e., appropriate for long-term use)
  - some therapies (e.g., biologic agents, small molecules) are used for both induction and maintenance of remission**
- This report primarily focuses on approved and emerging advanced therapies and approaches (see orange boxes)

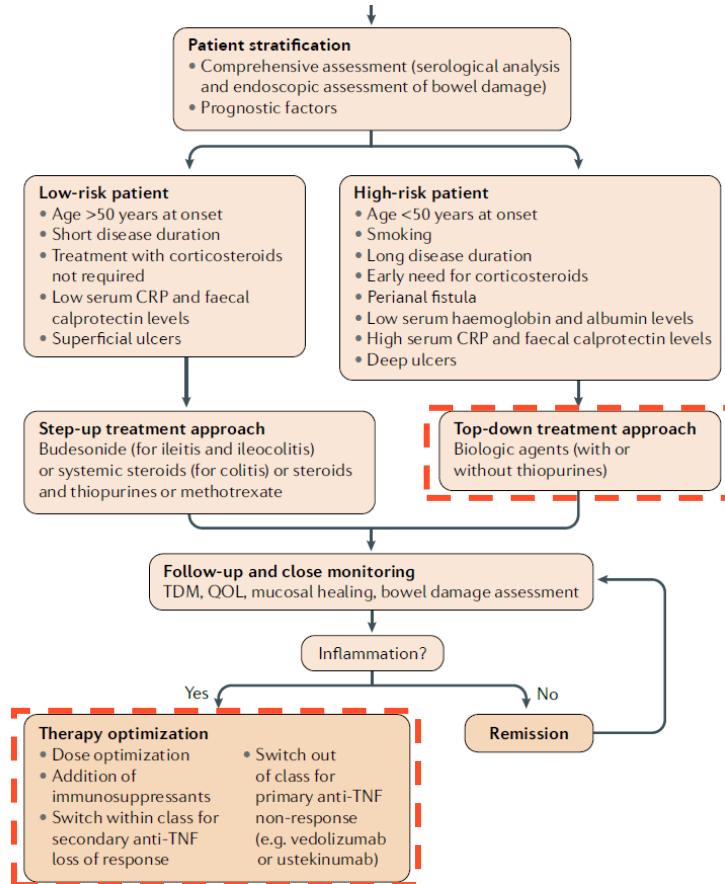


# Treatment paradigm: CD

**Patients with CD are typically treated with advanced therapies if they have high-risk features**

## Treatment paradigm

- Most patients with CD are also treated with pharmacologic therapy based on disease severity, and can similarly be divided into induction and maintenance categories
- As noted, this report primarily focuses on approved and emerging advanced therapies and approaches (see orange boxes) earmarked for use in “high-risk” patients with moderate to severe disease
- Many of the drugs approved in UC are also approved in CD (see next slide)

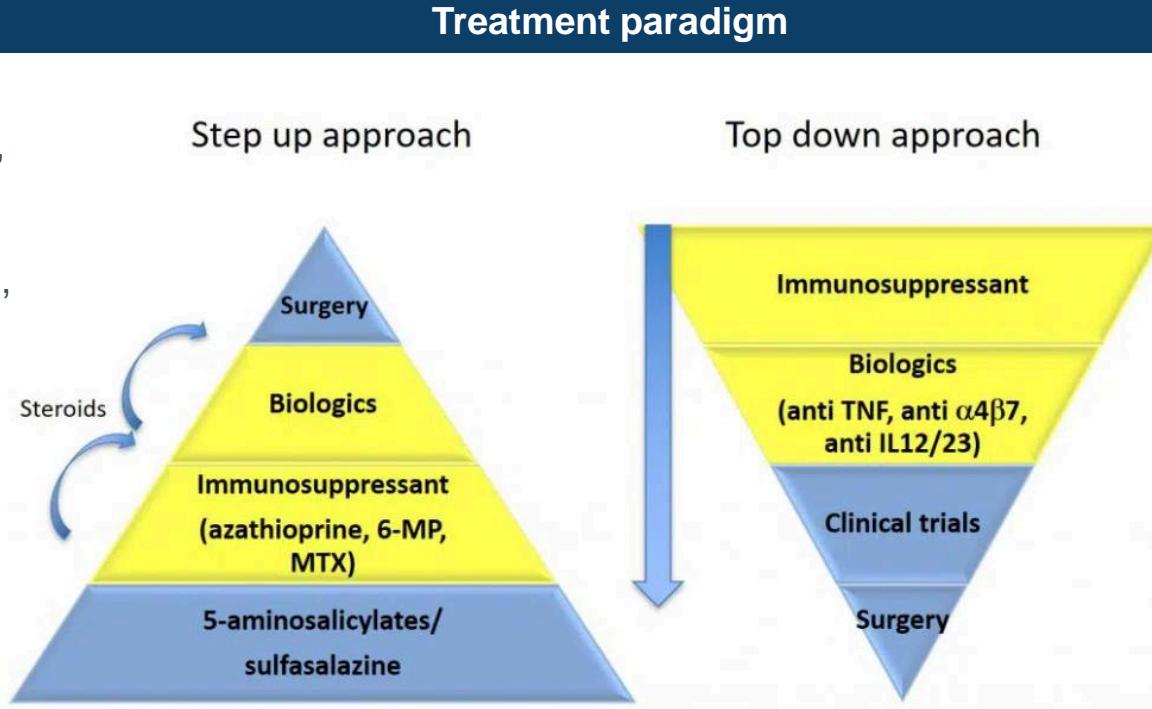


# Treatment Strategies for IBD: Step-Up vs. Top-Down

For patients with moderate to severe disease, a top-down approach is becoming more widely used

## Step up approach

- Starts with milder drugs (e.g., aminosalicylates), escalating to stronger medications (steroids, immunomodulators, biologics) as needed
- Pros: minimizes overtreatment, lower initial costs, fewer side effects
- Cons: may delay disease control, risk of complications (e.g., strictures, fistulas), steroids often required



## Top-down approach

- Begins with potent drugs (e.g., biologics, immunosuppressants) early to control inflammation aggressively
- Pros: faster remission, may prevent disease progression, reduces long-term complications
- Cons: higher initial cost, risk of overtreatment in mild cases, insurance barriers

Step up remains the standard for most patients due to cost and safety concerns, however top down is increasingly used in severe cases or high-risk patients, particularly with early biologic intervention

# Advanced therapies approved in IBD

**The list of advanced treatments for IBD has grown rapidly over recent years to include new targets (e.g., IL-23 and S1PR) and new formulations (e.g., SC and oral)**

Brand	Drug	Company	Molecule	ROA-induction	ROA-maintenance	Target	UC	Status	CD
Cimzia	certolizumab pegol	UCB	biologic	SC	SC	TNFα	--	Approved (2008)	
Humira	adalimumab	ABBV	biologic	SC	SC	TNFα	Approved (2008)	Approved (2007)	
Remicade	infliximab	JNJ	biologic	IV	IV	TNFα	Approved (2005)	Approved (1998)	
Simponi*	golimumab	JNJ	biologic	SC	SC	TNFα	Approved (2013)	--	
Entyvio	vedolizumab	TAK	biologic	IV	IV/SC	α4β7	Approved (2014)	Approved (2014)	
Tysabri	natalizumab	BIIB	biologic	IV	IV	α4β1/α4β7	--	Approved (2008)	
Rinvoq	upadacitinib	ABBV	small molecule	Oral	Oral	JAK	Approved (2022)	Approved (2023)	
Xeljanz	tofacitinib	PFE	small molecule	Oral	Oral	JAK	Approved (2018)	--	
Omvooh	mirikizumab	LLY	biologic	IV	IV/SC	IL-23p19	Approved (2023)	Approved (2025)	
Skyrizi	risankizumab	ABBV	biologic	IV	SC	IL-23p19	Approved (2024)	Approved (2022)	
Stelara	ustekinumab	JNJ	biologic	IV	IV/SC	IL-12/IL-23	Approved (2019)	Approved (2016)	
Tremfya	guselkumab	JNJ	biologic	IV/SC**	IV/SC	IL-23p19/CD64	Approved (2024)	sBLA	
Velsipity	etrasimod	PFE	small molecule	Oral	Oral	S1PR	Approved (2023)	II/III	
Zeposia	ozanimod	BMY	small molecule	Oral	Oral	S1PR	Approved (2021)	--	

Source: Company disclosures; Leerink Partners Research. \*Simponi Aria is given IV, \*\*Following positive results in the ASTRO study, we expect SC induction to be approved in UC, data from SC induction in CD from the GALAXI study are expected in 2025

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# How do the various approved advanced therapies work? (1/2)

## Several classes of approved therapies target inflammatory signaling pathways

- IBD has seen significant therapeutic advancements through the approval of biologics and small molecules targeting various inflammatory pathways. These mechanisms address specific aspects of the immune response, offering tailored options for patients based on disease severity, phenotype, and response to prior therapies. Here we note the underlying mechanisms and principles underpinning the approved advanced therapies

### TNF $\alpha$ inhibitors

- Tumor necrosis factor (TNF) inhibitors were the first biologics approved for IBD, revolutionizing treatment by targeting the pro-inflammatory cytokine TNF $\alpha$ , which plays a central role in the immune response
- Agents like infliximab (Remicade), adalimumab (Humira), and certolizumab pegol (Cimzia) reduce inflammation and promote mucosal healing, significantly improving outcomes in both UC and CD
- While effective for many, TNF inhibitors have limitations, including primary and secondary non-response rates, as well as risks of infections due to broad immunosuppression

### JAK inhibitors

- Janus Kinase (JAK) inhibitors represent an important class of oral small molecules for IBD
- Tofacitinib (Xeljanz), a pan-JAK inhibitor, was the first approved for UC, modulating multiple cytokine pathways, including those involving IL-6, IL-12, and IL-23
- More selective JAK inhibitors, such as the JAK1-specific upadacitinib (Rinvoq), aim to optimize efficacy while reducing safety concerns like thrombosis and infections observed with pan-JAK inhibition
- These agents are particularly appealing for patients seeking oral alternatives to injectable biologics

### Interleukin inhibitors

- Interleukin (IL) inhibitors target key cytokines involved in IBD pathogenesis
- Ustekinumab (Stelara), which blocks the shared p40 subunit of IL-12 and IL-23, has emerged as a critical therapy for moderate-to-severe CD and UC. Newer drugs focus on blocking IL-23 alone by targeting the p19 subunit, improving efficacy and reducing safety concerns
- By modulating Th1 and Th17 pathways, IL inhibitors address inflammation upstream of TNF, providing benefits for patients who have failed anti-TNF therapies

# How do the various approved advanced therapies work? (2/2)

## Other classes inhibit the migration of inflammatory cells to GI tissue

### Integrin inhibitors

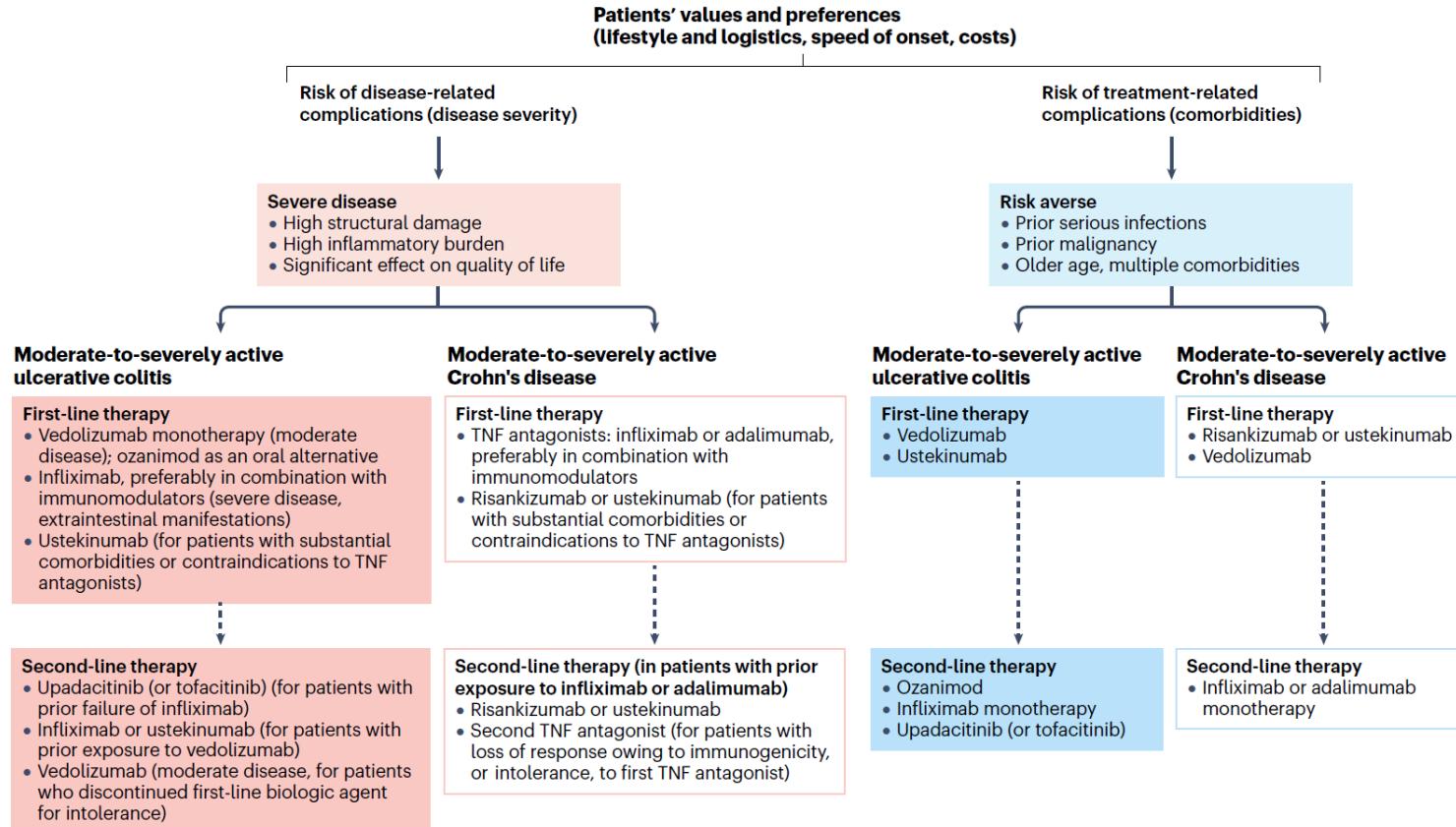
- Integrin inhibitors target cell adhesion molecules that mediate the migration of immune cells into the gastrointestinal mucosa
- Vedolizumab (Entyvio), an  $\alpha 4\beta 7$  integrin inhibitor, is gut-specific, providing localized immunosuppression
- Natalizumab (Tysabri), which targets  $\alpha 4$ , was approved first, but is now less commonly used given it can cause progressive multifocal leukoencephalopathy (PML)

### S1PR modulators

- Sphingosine-1-Phosphate (S1P) receptor modulators offer a novel mechanism of action by trapping lymphocytes in lymph nodes, thereby reducing their migration to inflamed gut tissue
- S1P is a bioactive lipid mediator that modulates lymphocyte migration by activating the cell-surface GPCRs S1P<sub>1</sub>–S1P<sub>5</sub>. S1P receptor modulators such as ozanimod (Zeposia) and etrasimod (Velsipity) cause internalization and degradation of the S1P<sub>1</sub> receptor, reducing availability on the cell surface
- S1P modulator have demonstrated efficacy in reducing inflammation while offering an oral administration route

# High level take on positioning of advanced therapies in IBD

## Various patient factors and preferences can influence choice of therapy



- Current treatment paradigms focus on patient and physician choice, but prominent first line options include vedolizumab (Entyvio), ustekinumab (Stelara\*), risankizumab (Skyrizi), and TNF inhibitor biosimilars, with upadacitinib (Rinvoq) commonly used after TNF inhibitor failure
- In the following slides we analyze the following areas to better understand why these are the prevailing choices
  - Safety
  - Efficacy
  - Convenience/cost

**Note the flow chart does not include more recent approvals (e.g., Tremfya in UC)**

# Safety profiles of the approved therapy classes

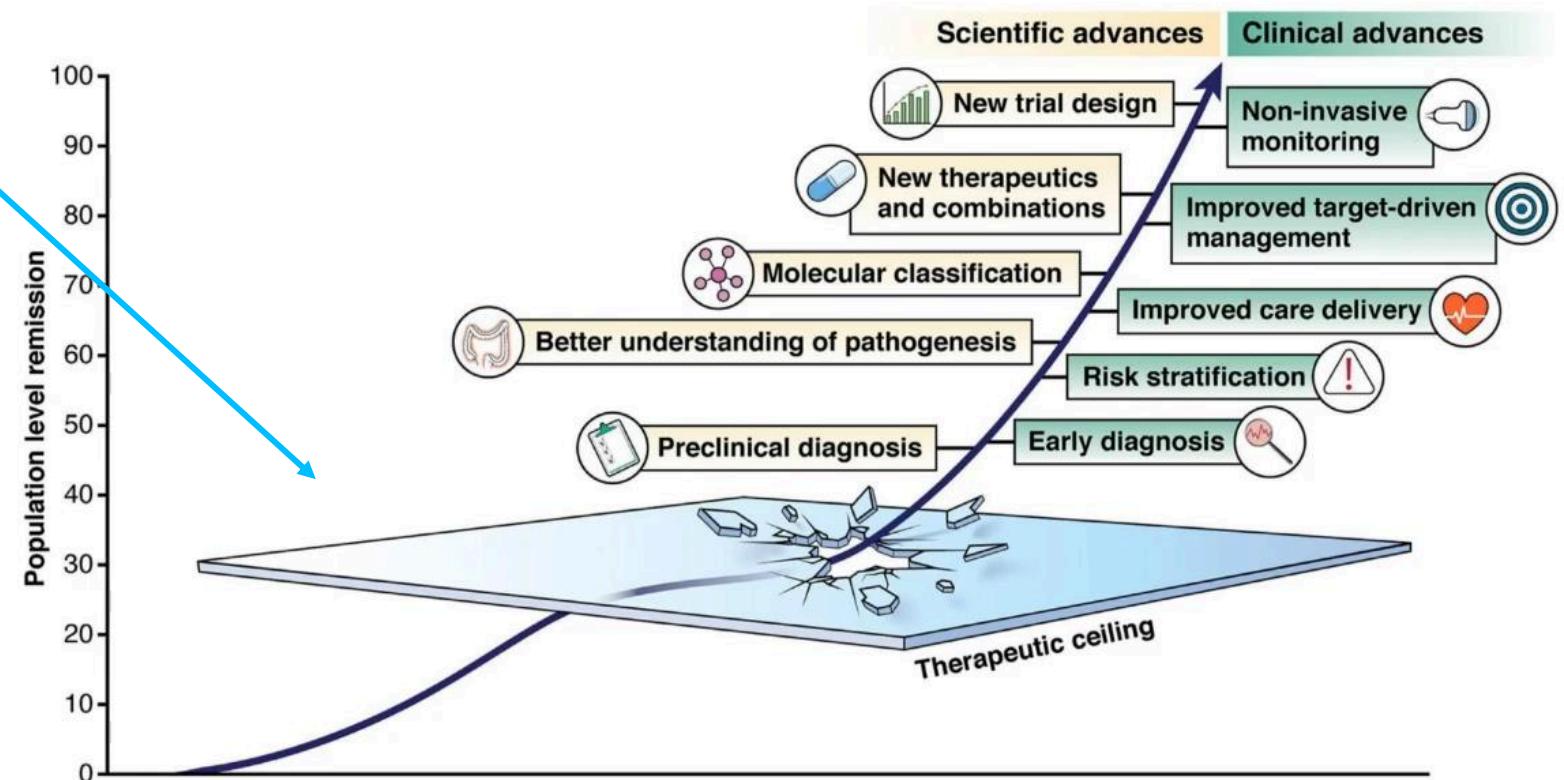
Current therapies have an array of warnings, although when discussing this with our MEDACorp KOLs, their opinion was that these were fairly overblown (e.g., Rinvoq)

Class	Route	Class warnings/safety concerns	Notable pre-administration testing and monitoring
JAK inhibitors (e.g., <a href="#">Xeljanz</a> , <a href="#">Rinvoq</a> )	Oral	<b>Boxed warning</b> for ↑ risk of serious infections, ↑ rates of hospitalization/all-cause mortality, malignancies, cardiac/thromboembolic events	Total cholesterol and high-density lipoprotein cholesterol recommended
S1P (e.g., <a href="#">Zeposia</a> , <a href="#">Velsipity</a> )	Oral	Warnings for infections, arrhythmias, liver injury, macular edema, ↑ risk of PML, immune effects upon cessation	ECG prior to treatment initiation, baseline and routine eye exams, and LFT testing are recommended
TNFα (e.g., <a href="#">Humira</a> , <a href="#">Remicade</a> , etc.)	IV/SC	<b>Boxed warnings</b> for ↑ risk of serious infections, malignancies	Therapeutic drug monitoring (checking drug levels, antidrug antibodies)
IL-12/23 (e.g., <a href="#">Stelara</a> )	IV/SC	Warnings for ↑ risk serious infections, malignancies	-
α4β7 (e.g., <a href="#">Entyvio</a> )	IV/SC	Warnings for ↑ risk serious infections	-
IL-23p19 (e.g., <a href="#">Skyrizi</a> )	IV/SC	Warnings for ↑ risk infections, hepatotoxicity	LFT testing is recommended

# There is a well-established “efficacy ceiling” for advanced therapies in IBD

Although there are differences between classes, it is widely accepted that long-term remission rates (both clinical and endoscopic) max out between 30-40% in IBD

- Remission rates for monotherapy treatment have been limited to date (usually 30-40% clinical remission)
- Existing therapies have failed to address the multiple (sometimes overlapping) pathways that drive the immune-mediated inflammatory process underlying the disease
- Mechanistic failure can develop over time for a single advanced therapy and advanced therapies used in succession tend to be less effective



Raine and Danese, Gastroenterology 2022

# The challenges of interpreting efficacy data in IBD

**IBD is a heterogenous disease further complicated by diverse trial design and recruitment**

## Disease specific considerations

- UC trials often use the MMS scoring system, which is a composite primary endpoint that include both patient-reported outcomes (stool frequency, rectal bleeding) in addition to (more) objective endoscopic measures. Historically, TMS was used, complicating cross-trial comparison
  - Baseline characteristics can vary substantially among patients with moderate to severe UC (and across trials), including initial MMS/endoscopic/histology scores and prior advanced therapies
  - Trial design variations, such as extended induction, treat-through vs. responder re-randomization, and differences in placebo response rates can further complicate direct comparisons between therapies. Responder re-randomization designs, which enrich maintenance populations with induction responders, can inflate efficacy signals
- CD trials also have a high degree of complexity, in part due to heterogeneous disease presentation (ileal vs. colonic, stricturing vs. inflammatory phenotypes) and evolving endpoint definitions. Recall coprimary endpoints are now encouraged, given CDAI includes several subjective assessments
  - Similarly, baseline characteristics of moderate to severe CD patients can differ drastically (including on disease presentation) and prior advanced therapies
  - Considerations regarding trial design variability are consistent with those in UC (see above)

**The following slides contain benchmark tables for induction and maintenance studies in UC and IBD, with additional detail on baseline characteristics found [HERE](#) and [HERE](#)**

# Reference: SOC induction clinical remission benchmarks for moderate to severe UC (1/2)

**Placebo-adjusted clinical remission rates for approved therapies in UC following induction: 7-29%**

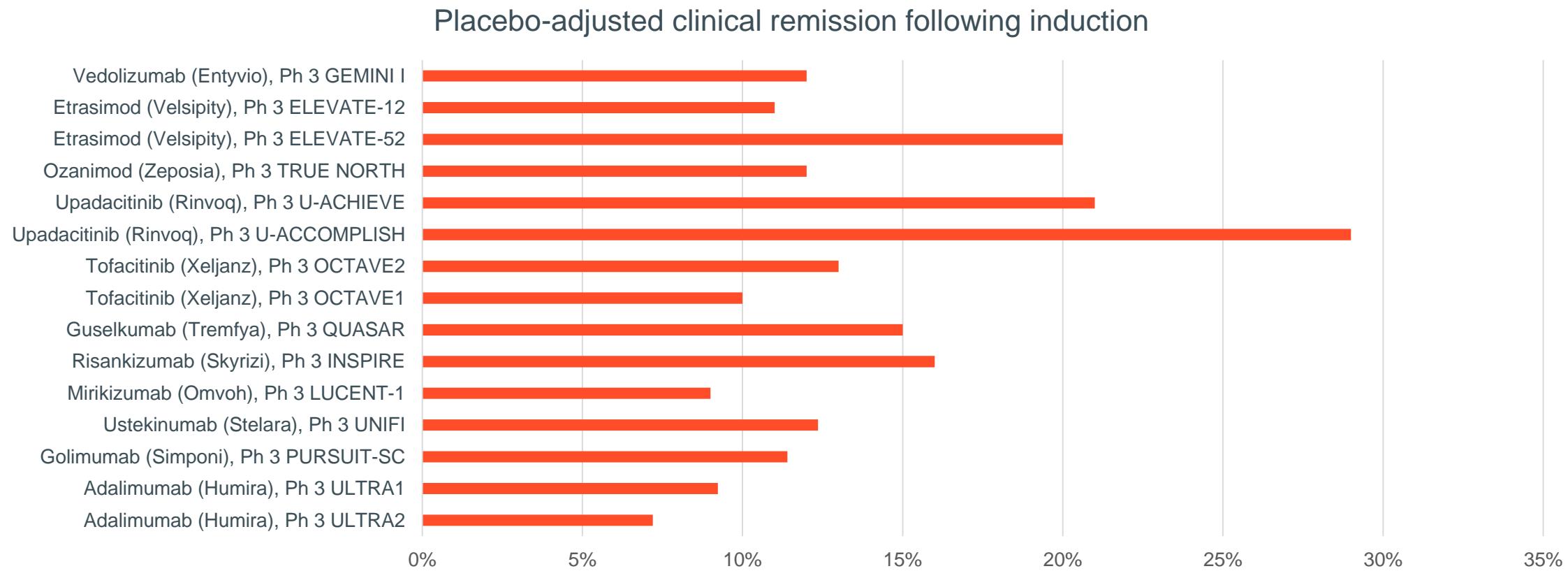
## Monotherapy (induction)

Drug	Company	Target	UC approval	ROA	Scoring	Clinical Trial	Duration	N	% Prior Adv Ther	Clin Rem			Best Remission Rate in Class	Avg Remission Rate in Class
										Abs.	PBO	PBO-Adj.		
<b>Adalimumab (Humira)</b>	ABBV	TNFα	2008	SC Q2/4W (160/80 mg)	TMS	Ph 3 ULTRA2	8 Weeks	248	39.1%	17%	9%	7%	11%	9%
						Ph 3 ULTRA1	8 Weeks	130	-	18%	9%	9%		
<b>Golimumab (Simponi)</b>	JNJ	TNFα	2013	SC Q2W (200/100mg)	TMS	Ph 3 PURSUIT-SC	6 Weeks	253	-	18%	6%	11%		
<b>Ustekinumab (Stelara)</b>	JNJ	IL-12/IL-23	2019	IV (6 mg/kg)	TMS	Ph 3 UNIFI	8 Weeks	322	51.6%	19%	7%	12%		
<b>Mirikizumab (Omwoh)</b>	LLY	IL-23p19	2023	IV Q4W	MMS	Ph 3 LUCENT-1	12 Weeks	795	41.6%	24%	15%	9%	16%	13%
<b>Risankizumab (Skyrizi)</b>	ABBV	IL-23p19	2024	IV (Q4W)	MMS	Ph 3 INSPIRE	12 Weeks	646	51.2%	24%	8%	16%		
<b>Guselkumab (Tremfya)</b>	JNJ	IL-23p19/CD64	2024	IV (Q4W)	MMS	Ph 3 QUASAR	12 Weeks	421	49.4%	23%	8%	15%		
<b>Tofacitinib (Xeljanz)</b>	PFE	Pan-JAK	2018	Oral BID (10 mg)	TMS	Ph 3 OCTAVE1	8 Weeks	476	51.1%	18%	8%	10%	29%	18%
						Ph 3 OCTAVE2	8 Weeks	429	51.7%	17%	4%	13%		
<b>Upadacitinib (Rinvoq)</b>	ABBV	JAK1	2022	Oral QD (45 mg)	MMS	Ph 3 U-ACCOMPLISH	8 Weeks	341	50.7%	33%	4%	29%	29%	18%
						Ph 3 U-ACHIEVE	8 Weeks	319	52.7%	26%	5%	21%		
<b>Ozanimod (Zeposia)</b>	BMY	S1PR	2021	Oral QD	MMS	Ph 3 TRUE NORTH	10 Weeks	429	30.3%	18%	6%	12%		
<b>Erasimod (Velsipify)</b>	PFE	S1PR	2023	Oral QD	MMS	Ph 3 ELEVATE-52	12 Weeks	274	29.2%	27%	7%	20%	20%	14%
						Ph 3 ELEVATE-12	12 Weeks	221	33.5%	26%	15%	11%		
<b>Vedolizumab (Entyvio)</b>	TAK	α4β7	2014	IV Q2W	TMS	Ph 3 GEMINI I	6 Weeks	225	-	17%	5%	12%	12%	12%

Source: Company disclosures; FDA USPI; Leerink Partners Research. Data from FDA USPI where available. TMS: total Mayo score; MMS: modified Mayo score

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# Reference: SOC induction clinical remission benchmarks for moderate to severe UC (2/2)



With regard to induction data (caveat these include both remission by TMS and MMS), Rinvoq has a rapid onset (note high rate of placebo-adjusted clinical remission), and our MEDACorp KOL noted they will frequently use it as a bridge to other agents that have longer onset of effect

# Reference: SOC induction clinical response and endoscopic improvement benchmarks for moderate to severe UC

Placebo-adjusted clinical response rates for approved therapies in UC following induction: 10-49%													Placebo-adjusted endoscopic improvement rates for approved therapies in UC following induction: 5-36%					
Drug	Company	Target	UC approval	ROA	Scoring	Clinical Trial	Duration	N	% Prior Adv Ther	Clin Res			Endo Imp			Best Endo Imp in Class	Avg Endo Imp in Class	
										Abs.	PBO	PBO-Adj.	Abs.	PBO	PBO-Adj.			
<b>Adalimumab (Humira)</b>	ABBV	TNFα	2008	SC Q2/4W (160/80 mg)	TMS	Ph 3 ULTRA2	8 Weeks	248	39.1%	50%	35%	16%	41%	32%	9%	14%	9%	
						Ph 3 ULTRA1	8 Weeks	130	-	55%	45%	10%	47%	42%	5%			
<b>Golimumab (Simponi)</b>	JNJ	TNFα	2013	SC Q2W (200/100mg)	TMS	Ph 3 PURSUIT-SC	6 Weeks	253	-	51%	30%	21%	42%	29%	14%			
<b>Ustekinumab (Stelara)</b>	JNJ	IL-12/IL-23	2019	IV (6 mg/kg)	TMS	Ph 3 UNIFI	8 Weeks	322	51.6%	58%	31%	27%	25%	13%	12%	24%	16%	
<b>Mirikizumab (Omvoh)</b>	LLY	IL-23p19	2023	IV Q4W	MMS	Ph 3 LUCENT-1	12 Weeks	795	41.6%	65%	43%	22%	34%	21%	13%			
<b>Risankizumab (Skyrizi)</b>	ABBV	IL-23p19	2024	IV (Q4W)	MMS	Ph 3 INSPIRE	12 Weeks	646	51.2%	65%	36%	29%	36%	12%	24%			
<b>Guselkumab (Tremfya)</b>	JNJ	IL-23p19/CD64	2024	IV (Q4W)	MMS	Ph 3 QUASAR	12 Weeks	421	49.4%	62%	28%	34%	27%	11%	16%			
<b>Tofacitinib (Xeljanz)</b>	PFE	Pan-JAK	2018	Oral BID (10 mg)	TMS	Ph 3 OCTAVE1	8 Weeks	476	51.1%	60%	33%	27%	31%	16%	15%	36%	24%	
						Ph 3 OCTAVE2	8 Weeks	429	51.7%	55%	29%	26%	28%	12%	16%			
<b>Upadacitinib (Rinvoq)</b>	ABBV	JAK1	2022	Oral QD (45 mg)	MMS	Ph 3 U-ACCOMPLISH	8 Weeks	341	50.7%	74%	25%	49%	44%	8%	36%			
						Ph 3 U-ACHIEVE	8 Weeks	319	52.7%	73%	27%	46%	36%	7%	29%			
<b>Ozanimod (Zeposia)</b>	BMY	S1PR	2021	Oral QD	MMS	Ph 3 TRUE NORTH	10 Weeks	429	30.3%	48%	26%	22%	27%	12%	15%	21%	16%	
<b>Etrasimod (Velsipity)</b>	PFE	S1PR	2023	Oral QD	MMS	Ph 3 ELEVATE-52	12 Weeks	274	29.2%	62%	34%	28%	35%	14%	21%			
						Ph 3 ELEVATE-12	12 Weeks	221	33.5%	62%	41%	21%	30%	19%	11%			
<b>Vedolizumab (Entyvio)</b>	Takeda	α4β7	2014	IV Q2W	TMS	Ph 3 GEMINI I	6 Weeks	225	-	47%	26%	21%	41%	25%	16%	16%	16%	

Source: Company disclosures; FDA USPI; Leerink Partners Research. Data from FDA USPI where available. TMS: total Mayo score; MMS: modified Mayo score

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# Reference: SOC maintenance clinical remission benchmarks for moderate to severe UC

Maintenance data reveal the efficacy ceiling, with Entyvio and Rinvoq demonstrating efficacy toward the top end of the range of clinical remission rates (9-40%), supporting their relatively strong revenues

Monotherapy (maintenance)

Drug	Company	Target	Study Type	ROA	Scoring	Clinical Trial	Duration	N	% Prior Adv Ther	Clin Rem			Best Remission Rate in Class	Avg Remission Rate in Class
										Abs.	PBO	PBO-Adj.		
Adalimumab (Humira)	ABBV	TNFα	TrTh	SC Q4W (40 mg)	TMS	Ph 3 ULTRA2	52 weeks	248	39.1%	17%	9%	9%	12%	11%
Golimumab (Simponi)	JNJ	TNFα	MoR	SC Q4W (100 mg)	TMS	Ph 3 PURSUIT-M	54 weeks	151	-	28%	16%	12%		
Ustekinumab (Stelara)	JNJ	IL-12/IL-23	MoR	SC Q8W	TMS	Ph 3 UNIFI	52 weeks	176	51.7%	45%	26%	19%	31%	22%
Mirikizumab (Omsovo)	LLY	IL-23p19		SC Q4W (100/200 mg)	MMS	Ph 3 LUCENT-2	52 weeks	337	35.9%	51%	27%	24%		
Risankizumab (Skyrizi)	ABBV	IL-23p19	MoR	SC Q8W (180 mg)	MMS	Ph 3 COMMAND	52 weeks	179	74.9%	45%	26%	19%		
				SC Q8W (360 mg)				186	74.7%	41%	26%	15%		
Guselkumab (Tremfya)	JNJ	IL-23p19/CD64	MoR	SC Q8W (100 mg)	MMS	Ph 3 QUASAR	56 weeks	188	41.0%	45%	19%	26%		
				SC Q4W (200 mg)				190	46.3%	50%	19%	31%		
Tofacitinib (Xeljanz)	PFE	Pan-JAK	MoR	Oral BID (5 mg)	TMS	Ph 3 OCTAVE Sustain	52 weeks	198	41.9%	41%	11%	30%	40%	31%
				Oral BID (10 mg)				197	47.2%	34%	11%	23%		
Upadacitinib (Rinvoq)	ABBV	JAK1	MoR	Oral QD (15 mg)	MMS	Ph 3 U-ACHIEVE maintenance	52 weeks	148	48.0%	42%	12%	30%		
				Oral QD (30 mg)				154	47.4%	52%	12%	40%		
Ozanimod (Zeposia)	BMY	S1P	MoR	Oral QD	MMS	Ph 3 TRUE NORTH	52 weeks	230	33.0%	37%	19%	18%	18%	17%
Etrasimod (Velsipity)	PFE	S1P	TrTh	Oral QD	MMS	Ph 3 ELEVATE-52	52 weeks	274	29.2%	18%	2%	16%		
Vedolizumab (Entyvio)	Takeda	α4β7	MoR	IV Q8W	TMS	Ph 3 GEMINI I	52 weeks	122	-	42%	16%	26%	32%	29%
			MoR	SC Q2W		Ph 3 VISIBLE 1	52 weeks	106	37.7%	46%	14%	32%		

Source: Company disclosures; FDA USPI; Leerink Partners Research. TrTh: treat-through; MoR: maintenance of response / maintenance withdrawal design

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# Reference: SOC maintenance clinical response and endoscopic improvement benchmarks for moderate to severe UC

**Placebo-adjusted clinical response rates for approved therapies in UC following maintenance: 12-42%**

Monotherapy (maintenance)

Drug	Company	Target	Study Type	ROA	Scoring	Clinical Trial	Duration	N	% Prior Adv Ther	Clin Res			Endo Imp			Best Endo Imp in Class	Avg Endo Imp in Class
										Abs.	PBO	PBO-Adj.	Abs.	PBO	PBO-Adj.		
Adalimumab (Humira)	ABBV	TNFα	TrTh	SC Q4W (40 mg)	TMS	Ph 3 ULTRA2	52 weeks	248	39.1%	30%	18%	12%	25%	15%	10%	16% 33% 48%	13% 25% 35%
Golimumab (Simponi)	JNJ	TNFα	MoR	SC Q4W (100 mg)	TMS	Ph 3 PURSUIT-M	54 weeks	151	-	50%	31%	19%	42%	27%	16%		
Ustekinumab (Stelara)	JNJ	IL-12/IL-23	MoR	SC Q8W	TMS	Ph 3 UNIFI	52 weeks	176	51.7%	74%	48%	26%	47%	27%	20%		
Mirikizumab (Omvohe)	LLY	IL-23p19	MoR	SC Q4W (100/200 mg)	MMS	Ph 3 LUCENT-2	52 weeks	337	35.9%	66%	40%	26%	58%	30%	28%		
Risankizumab (Skyrizi)	ABBV	IL-23p19	MoR	SC Q8W (180 mg)	MMS	Ph 3 COMMAND	52 weeks	179	74.9%	-	-	-	-	-	20%		
				SC Q8W (360 mg)				186	74.7%	-	-	-	-	-	18%		
Guselkumab (Tremfya)	JNJ	IL-23p19/CD64	MoR	SC Q8W (100 mg)	MMS	Ph 3 QUASAR	56 weeks	188	41.0%	61%	34%	27%	52%	19%	33%		
				SC Q4W (200 mg)				190	46.3%	72%	34%	38%	49%	19%	30%		
Tofacitinib (Xeljanz)	PFE	Pan-JAK	MoR	Oral BID (5 mg)	TMS	Ph 3 OCTAVE Sustain	52 weeks	198	41.9%	52%	20%	32%	46%	13%	33%		
				Oral BID (10 mg)				197	47.2%	62%	20%	42%	37%	13%	24%		
Upadacitinib (Rinvoq)	ABBV	JAK1	MoR	Oral QD (15 mg)	MMS	Ph 3 U-ACHIEVE maintenance	52 weeks	148	48.0%	-	-	-	49%	14%	35%		
				Oral QD (30 mg)				154	47.4%	-	-	-	62%	14%	48%		
Ozanimod (Zeposia)	BMY	S1P	MoR	Oral QD	MMS	Ph 3 TRUE NORTH	52 weeks	230	33.0%	60%	41%	19%	46%	26%	20%	27%	24%
Etrasimod (Velsipity)	PFE	S1P	TrTh	Oral QD	MMS	Ph 3 ELEVATE-52	52 weeks	274	29.2%	-	-	-	37%	10%	27%		
Vedolizumab (Entyvio)	Takeda	α4β7	MoR	IV Q8W	TMS	Ph 3 GEMINI I	52 weeks	122	-	57%	24%	33%	52%	20%	32%	36%	34%
			MoR	SC Q2W		Ph 3 VISIBLE 1	52 weeks	106	37.7%	64%	29%	35%	57%	21%	36%		

Source: Company disclosures; FDA USPI; Leerink Partners Research. TrTh= treat-through; MoR= maintenance of response / maintenance withdrawal design

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# Reference: SOC induction clinical remission benchmarks for moderate to severe CD (1/2)

**Placebo-adjusted clinical remission rates for approved therapies in CD following induction: 3-35%**

## Monotherapy (induction)

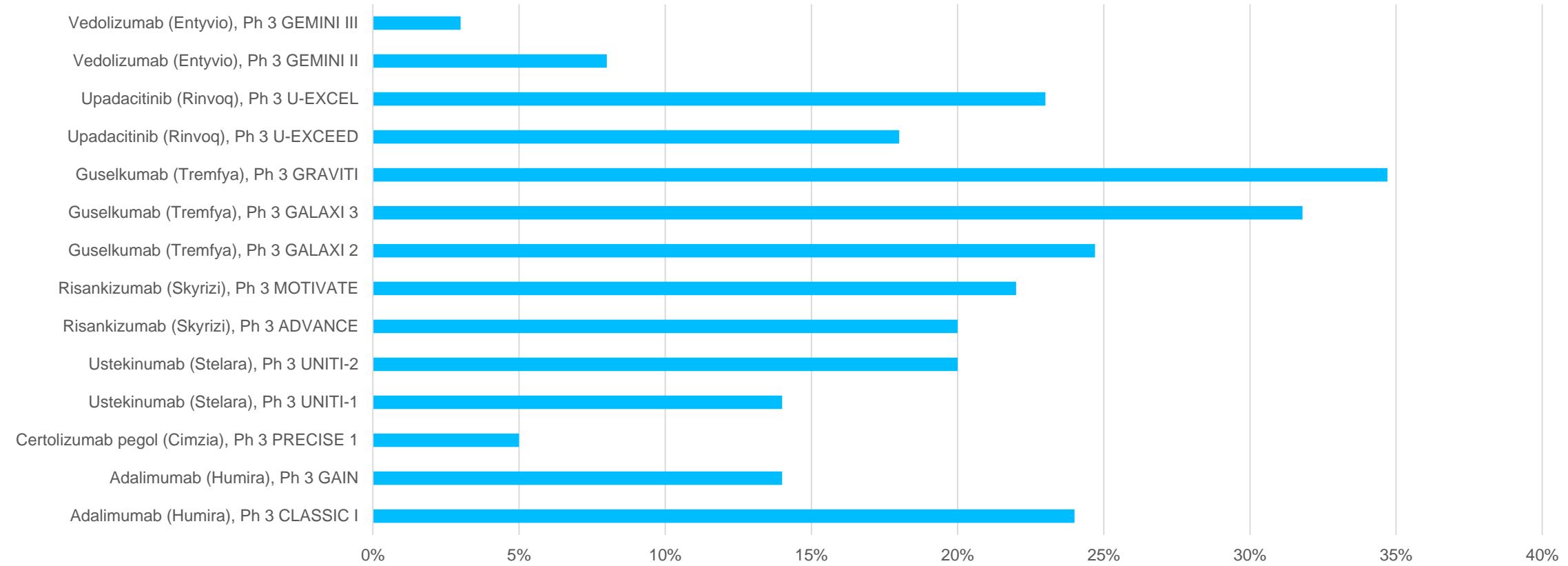
Drug	Company	Target	CD Approval	ROA	Scoring	Clinical Trial	Duration	N	% Prior Adv Ther	Clin Rem			Best Remission Rate in Class	Avg Remission Rate in Class
										Abs.	PBO	PBO-Adj.		
<b>Adalimumab (Humira)</b>	ABBV	TNF $\alpha$	2007	SC Q2W (160/80 mg)	CDAI	Ph 3 CLASSIC I	4 weeks	76	-	36%	12%	<b>24%</b>	24%	14%
						Ph 3 GAIN	4 weeks	159	-	21%	7%	<b>14%</b>		
<b>Certolizumab pegol (Cimzia)</b>	UCB	TNF $\alpha$	2008	SC Q2W	CDAI	Ph 3 PRECISE 1	6 weeks	331	30.0%	22%	17%	<b>5%</b>		
<b>Ustekinumab (Stelara)</b>	JNJ	IL-12/IL-23	2016	IV Q8W (6 mg/kg)	CDAI	Ph 3 UNITI-1	8 weeks	249	100.0%	21%	7%	<b>14%</b>	35%	24%
						Ph 3 UNITI-2	8 weeks	209	31.0%	40%	20%	<b>20%</b>		
<b>Mirikizumab (Omvooh)</b>	LLY	IL-23p19	2025	IV Q4W	CDAI	Ph 3 VIVID-1	12 weeks	511	52.4%	-	-	-		
<b>Risankizumab (Skyrizi)</b>	ABBV	IL-23p19	2022	IV (Q4W)	CDAI	Ph 3 ADVANCE	12 weeks	336	58.0%	45%	25%	<b>20%</b>	35%	24%
						Ph 3 MOTIVATE	12 weeks	191	100.0%	42%	20%	<b>22%</b>		
<b>Guselkumab (Tremfya)</b>	JNJ	IL-23p19/CD64	sBLA	IV (Q4W)	CDAI	Ph 3 GALAXI 2	12 weeks	289	52.8%	47%	22%	<b>25%</b>		
				IV (Q4W)		Ph 3 GALAXI 3	12 weeks	293	51.9%*	47%	15%	<b>32%</b>		
				SC (Q4W)		Ph 3 GRAVITI	12 weeks	230	47%*	56%	21%	<b>35%</b>		
<b>Upadacitinib (Rinvoq)</b>	ABBV	JAK1	2023	Oral QD (45 mg)	CDAI	Ph 3 U-EXCEED	12 weeks	273	100.0%	36%	18%	<b>18%</b>	23%	21%
						Ph 3 U-EXCEL	12 weeks	295	45.8%	46%	23%	<b>23%</b>		
<b>Vedolizumab (Entyvio)</b>	Takeda	$\alpha 4\beta 7$	2014	IV Q2W	CDAI	Ph 3 GEMINI II	6 weeks	220	47.7%	15%	7%	<b>8%</b>	8%	6%
					CDAI	Ph 3 GEMINI III	6 weeks	158	100.0%	15%	12%	<b>3%</b>		

Source: Company disclosures; FDA USPI; Leerink Partners Research. \*Data from FDA USPI

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# Reference: SOC induction clinical remission benchmarks for moderate to severe CD (2/2)

Placebo-adjusted clinical remission following induction



# Reference: SOC maintenance clinical remission benchmarks for moderate to severe CD

Placebo-adjusted CDAI 100 rates for approved therapies in CD following maintenance: 5-30%															Placebo-adjusted endoscopic improvement rates for approved therapies in CD following maintenance: 18-33%				
Drug	Company	Target	CD Approval	ROA	Scoring	Clinical Trial	Duration	N	% Prior Adv Ther	CDAI 100			Endo Imp			Best Endo Imp in Class	Avg Endo Imp in Class		
										Abs.	PBO	PBO-Adj.	Abs.	PBO	PBO-Adj.				
<b>Adalimumab (Humira)</b>	ABBV	TNF $\alpha$	2007	SC Q2W (160/80 mg)	CDAI	Ph 3 CLASSIC I	4 weeks	76	-	50%	25%	25%	-	-	-	-	-		
						Ph 3 GAIN	4 weeks	159	-	38%	25%	13%	-	-	-				
<b>Certolizumab pegol (Cimzia)</b>	UCB	TNF $\alpha$	2008	SC Q2W	CDAI	Ph 3 PRECISE 1	6 weeks	331	30.0%	35%	27%	8%	-	-	-				
<b>Ustekinumab (Stelara)</b>	JNJ	IL-12/IL-23	2016	IV Q8W (6 mg/kg)	CDAI	Ph 3 UNITI-1	8 weeks	249	100.0%	38%	20%	18%	-	-	-				
						Ph 3 UNITI-2	8 weeks	209	31.0%	-	-	-	-	-	-				
<b>Mirikizumab (Omvoh)</b>	LLY	IL-23p19	2025	IV Q4W	CDAI	Ph 3 VIVID-1	12 weeks	511	52.4%	-	-	-	32%	11%	21%				
<b>Risankizumab (Skyrizi)</b>	ABBV	IL-23p19	2022	IV (Q4W)	CDAI	Ph 3 ADVANCE	12 weeks	336	58.0%	60%	37%	23%	40%	12%	28%	28%	23%		
						Ph 3 MOTIVATE	12 weeks	191	100.0%	60%	30%	30%	29%	11%	18%				
<b>Guselkumab (Tremfya)</b>	JNJ	IL-23p19/CD64	sBLA	IV (Q4W)	CDAI	Ph 3 GALAXI 2	12 weeks	289	52.8%	-	-	-	38%	11%	27%				
				IV (Q4W)		Ph 3 GALAXI 3	12 weeks	293	51.9%*	-	-	-	36%	14%	22%				
				SC (Q4W)		Ph 3 GRAVITI	12 weeks	230	47%*	-	-	-	41%	21%	20%				
<b>Upadacitinib (Rinvoq)</b>	ABBV	JAK1	2023	Oral QD (45 mg)	CDAI	Ph 3 U-EXCEED	12 weeks	273	100.0%	54%	31%	23%	34%	3%	31%	33%	32%		
						Ph 3 U-EXCEL	12 weeks	295	45.8%	64%	40%	24%	46%	13%	33%				
<b>Vedolizumab (Entyvio)</b>	Takeda	$\alpha\beta\gamma$	2014	IV Q2W	CDAI	Ph 3 GEMINI II	6 weeks	220	47.7%	31%	26%	5%	-	-	-	-	-	-	
					CDAI	Ph 3 GEMINI III	6 weeks	158	100.0%	-	-	-	-	-	-	-	-	-	

Source: Company disclosures; FDA USPI; Leerink Partners Research. \*Data from FDA USPI

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# Reference: SOC maintenance clinical remission benchmarks for moderate to severe CD

Maintenance data reveal again reveal a relative efficacy ceiling, clinical remission rates of 11-49% (note: slightly higher in CD), with IL-23 inhibitors and Rinvoq demonstrating why they are commonly recommended (in addition to TNF inhibitors) in CD

## Monotherapy (maintenance)

Drug	Company	Target	Study type	ROA	Scoring	Clinical Trial	Duration	N	% Prior Adv Ther	Clin Rem			Best Remission Rate in Class	Avg Remission Rate in Class
										Abs.	PBO	PBO-Adj.		
Adalimumab (Humira)	ABBV	TNF $\alpha$	MoR	SC Q4W (40 mg)	CDAI	Ph 3 CHARM	56 weeks	172	54.5%	36%	12%	24%	24%	22%
Certolizumab pegol (Cimzia)	UCB	TNF $\alpha$	MoR	SC Q4W	CDAI	Ph 3 PRECISE 2	26 weeks	215	24.0%	48%	29%	19%		
Ustekinumab (Stelara)	JNJ	IL-12/IL-23	MoR	SC Q8W (90 mg)	CDAI	Ph 3 IM-UNITI	52 weeks	128	43.8%	53%	36%	17%	49%	25%
Mirikizumab (Omsovo)	LLY	IL-23p19	TrTh	SC Q4W (100/200 mg)	CDAI	Ph 3 VIVID-1	52 weeks	511	52.4%	53%	36%	17%		
Risankizumab (Skyrizi)	ABBV	IL-23p19	MoR	SC Q8W (180 mg)	CDAI	Ph 3 FORTIFY	52 weeks	135	70.4%	61%	46%	15%		
				SC Q8W (360 mg)				117	70.9%	57%	46%	11%		
Guselkumab (Tremfya)	JNJ	IL-23p19/CD64	TrTh	SC Q8W (100 mg)	CDAI	Pooled Ph 3 GALAXI 2/3	48 weeks	286	53.5%	65%	-	-		
				SC Q4W (200 mg)				296	49.7%	70%	-	-		
				SC Q8W (100 mg)		Ph 3 GRAVITI	48 weeks	115	47.8%	60%	17%	43%		
				SC Q4W (200 mg)				115	46.1%	66%	17%	49%		
Upadacitinib (Rinvoq)	ABBV	JAK1	MoR	Oral QD (15 mg)	CDAI	Ph 3 U-ENDURE	52 weeks	113	72.6%	42%	14%	28%	41%	35%
				Oral QD (30 mg)				119	75.6%	55%	14%	41%		
Vedolizumab (Entyvio)	Takeda	$\alpha 4\beta 7$	MoR	IV Q8W	CDAI	Ph 3 GEMINI II	52 weeks	154	55.0%	39%	22%	17%	17%	16%
			MoR	SC Q2W		Ph 3 VISIBLE 2	52 weeks	275	61.1%	48%	34%	14%		

Source: Company disclosures; FDA USPI; Leerink Partners Research. TrTh= treat-through; MoR= maintenance of response / maintenance withdrawal design

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# Reference: SOC maintenance clinical response and endoscopic improvement benchmarks for moderate to severe CD

**Placebo-adjusted CDAI 100 rates for approved therapies in CD following maintenance: 13-27%**

**Placebo-adjusted endoscopic improvement rates for approved therapies in CD following maintenance: 21-45%**

Monotherapy (maintenance)

Drug	Company	Target	Study type	ROA	Scoring	Clinical Trial	Duration	N	% Prior Adv Ther	CDAI 100			Endo Imp			Best Endo Imp in Class	Avg Endo Imp in Class
										Abs.	PBO	PBO-Adj.	Abs.	PBO	PBO-Adj.		
Adalimumab (Humira)	ABBV	TNFα	MoR	SC Q4W (40 mg)	CDAI	Ph 3 CHARM	56 weeks	172	54.5%	52%	27%	25%	-	-	-	-	-
Certolizumab pegol (Cimzia)	UCB	TNFα	MoR	SC Q4W	CDAI	Ph 3 PRECISE 2	26 weeks	215	24.0%	63%	36%	27%	-	-	-	-	-
Ustekinumab (Stelara)	JNJ	IL-12/IL-23	MoR	SC Q8W (90 mg)	CDAI	Ph 3 IM-UNITI	52 weeks	128	43.8%	59%	44%	15%	-	-	-	-	-
Mirikizumab (Omvooh)	LLY	IL-23p19	TrTh*	SC Q4W (100/200 mg)	CDAI	Ph 3 VIVID-1	52 weeks	511	52.4%	-	-	-	46%	23%	23%	-	-
Risankizumab (Skyrizi)	ABBV	IL-23p19	MoR	SC Q8W (180 mg)	CDAI	Ph 3 FORTIFY	52 weeks	135	70.4%	-	-	-	50%	22%	28%	45%	32%
				SC Q8W (360 mg)				117	70.9%	-	-	-	48%	22%	26%		
Guselkumab (Tremfya)	JNJ	IL-23p19/CD64	TrTh*	SC Q8W (100 mg)	CDAI	Pooled Ph 3 GALAXI 2/3	48 weeks	286	53.5%	-	-	-	48%	-	-	45%	32%
				SC Q4W (200 mg)				296	49.7%	-	-	-	53%	-	-		
				SC Q8W (100 mg)	CDAI	Ph 3 GRAVITI	48 weeks	115	47.8%	-	-	-	44%	7%	38%		
				SC Q4W (200 mg)				115	46.1%	-	-	-	51%	7%	45%		
Upadacitinib (Rinvoq)	ABBV	JAK1	MoR	Oral QD (15 mg)	CDAI	Ph 3 U-ENDURE	52 weeks	113	72.6%	-	-	-	28%	7%	21%	34%	28%
				Oral QD (30 mg)				119	75.6%	-	-	-	41%	7%	34%		
Vedolizumab (Entyvio)	Takeda	α4β7	MoR	IV Q8W	CDAI	Ph 3 GEMINI II	52 weeks	154	55.0%	44%	30%	13%	-	-	-	-	-
			MoR	SC Q2W		Ph 3 VISIBLE 2	52 weeks	275	61.1%	-	-	-	-	-	-	-	-

Source: Company disclosures; FDA USPI; Leerink Partners Research. TrTh= treat-through; MoR= maintenance of response / maintenance withdrawal design

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# Comparative efficacy overall

**Head-to-head studies are limited, but have informed treatment decisions and positioning**

## Head-to-head trials in IBD

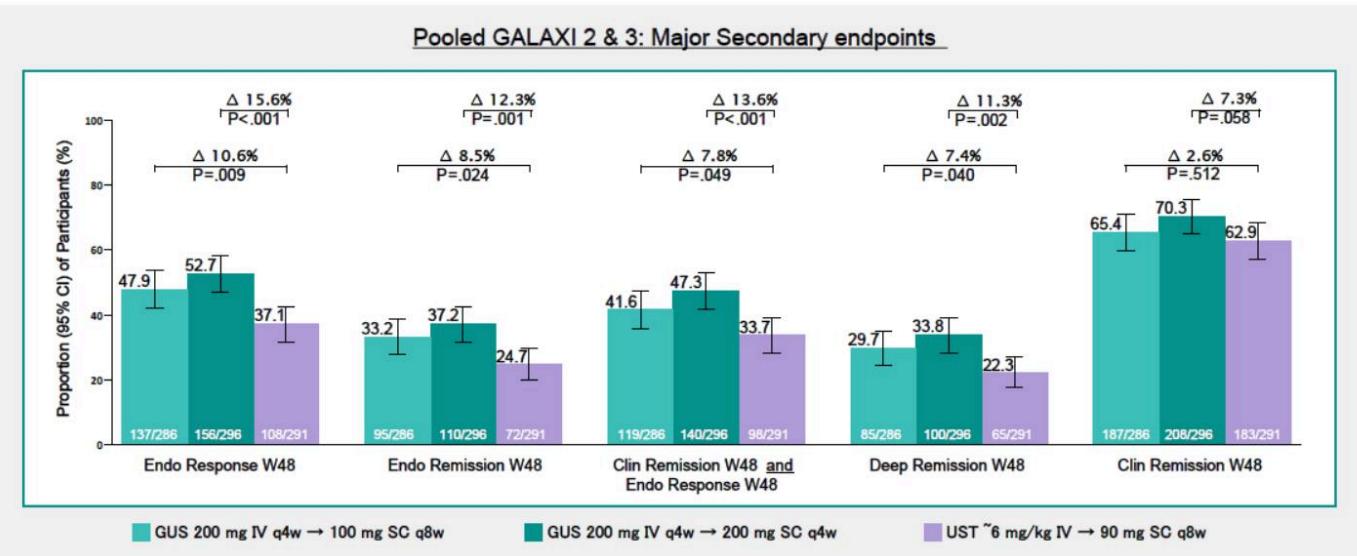
	YEAR & NAME	IBD	DRUG/Intervention	RESULTS
Original biologic vs biosimilar	2017 NOR-SWITCH	IMIDS	IFX	CTP I3 = IFX originator
	2019 PLANET CD	CD	IFX	CTP I3 = IFX originator
	2021 VOLTAIRE-CD	CD	ADA	BI 695501 = ADA originator
Biologic vs Biologic	2019 VARSITY	UC	VDZ vs ADA	VDZ > ADA
	2020 VISIBLE 1	UC	VDZ IV vs SC	VDZ SC = VDZ IV
	2021 GARDENIA	UC	ETR vs IFX	ETR = IFX
	2021 IFX SC	IBD	IFX sc vs IFX IV	IFX IV= IFX SC
	2022 SEAVUE	CD	ADA vs UST	ADA = UST
	2022 HIBISCUS	UC	ETR vs ADA	ETR = ADA
	2023 VEGA	UC	GUS+GOL vs GUS vs GOL	GUS+GOL=GUS > GOL
	SEQUENCE*	CD	UST vs RIS	RIS > UST
	VIVID 1*	CD	UST vs MIRI	MIRI = UST

- The positioning of biologics in IBD patients is an ongoing and dynamic process that will likely become even more challenging in the future with the approval of new therapies with novel modes of action (i.e., how best to sequence)
- Limited number of randomized head-to-head trials have been conducted in IBD, despite them providing useful context for treating physicians
- Three notable examples:
  - VARSITY compared vedolizumab (Entyvio) and adalimumab (Humira) in UC and showed vedolizumab to be superior to adalimumab at achieving clinical remission and endoscopic improvement at week 52
  - SEAVUE compared ustekinumab (Stelara) and adalimumab (Humira) in CD and showed similar efficacy between the at week 16, although ustekinumab was associated with fewer serious adverse events and infections
  - SEQUENCE compared risankizumab (Skyrizi) and ustekinumab (Stelara) in CD. Risankizumab demonstrated equivalence to ustekinumab in achieving clinical remission at week 24 and superiority in achieving endoscopic remission at week 48.

# Comparative efficacy within the IL-23 class

**Within the IL-23 class, prevailing sentiment is that ABBV's Skyrizi (risankizumab) will take the majority of market share given its lead and relatively strong data package**

- ABBV's Skyrizi (risankizumab) is positioned as the preferred IL-23 inhibitor in IBD, due to its stronger efficacy (compared to Stelara (ustekinumab), see right) and more convenient dosing
- Additionally, cross-trial comparison between Skyrizi and Tremfya (guselkumab) studies against Stelara reveal the following (see right):
  - Clinical remission at Week 48:
  - Skyrizi: 20% improvement vs. Stelara
  - Tremfya: 7% improvement vs. Stelara
  - Endoscopic remission at Week 48:
  - Skyrizi: 16% improvement vs. Stelara
  - Tremfya: 12% improvement vs. Stelara
- Both Ph 3 studies, COMMAND (Skyrizi) and QUASAR (Tremfya) in UC studies show similar efficacy, but Skyrizi's Q8W dosing (6 injections/year) is likely preferred over Tremfya's likely Q4W (12 injections/year) and Skyrizi is already approved in both UC and CD
- ABBV's existing leadership in immunology and aggressive market penetration strategies give Skyrizi an edge



SEQUENCE Head-to-Head Study Results <sup>1*</sup>			
		Risankizumab (n=255)	Ustekinumab (n=265)
Primary Endpoints	Clinical Remission <sup>a</sup> (Week 24; non-inferiority) (Risankizumab, n=128 <sup>†</sup> ) (Ustekinumab, n=137 <sup>†</sup> )	59 %	40 %
	Endoscopic Remission <sup>b</sup> (Week 48; superiority)	32 %	16 %
Secondary Endpoints (superiority)	Clinical Remission <sup>a</sup> (Week 48)	61 %	41 %
	Endoscopic Response <sup>c</sup> (Week 48)	45 %	22 %
	Endoscopic Response <sup>c</sup> (Week 24)	45 %	26 %
	Steroid-free Endoscopic Remission <sup>d</sup> (Week 48)	31 %	15 %
	Steroid-free Clinical Remission <sup>e</sup> (Week 48)	61 %	40 %

# Route of administration and cost considerations

**Administration and cost can impact convenience to patients and providers**

TNF $\alpha$ inhibitors	Integrin inhibitors	Interleukin inhibitors	JAK inhibitors	S1PR modulators
<b>Administration</b> <ul style="list-style-type: none"><li>Range of formulations (IV and SC)</li><li>Typically used in hospitalized patients (IV has rapid onset)</li></ul> <b>Cost</b> <ul style="list-style-type: none"><li>Biosimilars are available</li></ul>	<b>Administration</b> <ul style="list-style-type: none"><li>Range of formulations (IV and recently, SC for vedolizumab [Entyvio])</li><li>Convenient maintenance schedule for IV (Q8W), SC pen is Q2W</li></ul>	<b>Administration</b> <ul style="list-style-type: none"><li>Infrequent and convenient maintenance schedule (Q8W) available (risankizumab [Skyrizi] and ustekinumab [Stelara])</li><li>Risankizumab [Skyrizi] can be self-administered via an on-body injector Q8W</li><li>Our MEDACorp KOL noted they were initially skeptical of this approach, but was surprised that most of his patients liked the device and convenience</li><li>JNJ is expecting approval of SC induction for Tremfya</li></ul> <b>Cost</b> <ul style="list-style-type: none"><li>Biosimilar Stelara (ustekinumab) became available in 2025</li></ul>	<b>Administration</b> <ul style="list-style-type: none"><li>Oral formulation</li><li>Rapid onset of action (sometimes used as a bridge to other therapies)</li></ul>	<b>Administration</b> <ul style="list-style-type: none"><li>Oral formulation</li><li>Rapid onset of action</li><li>Ozanimod requires dose titration</li></ul>

**Additional information on ROA can be found in the appendix, [HERE](#)**

# Studies on patient preference on ROA and treatment priorities

**Data suggest oral formulations are the preferred route of administration (ROA), although this can vary, and is one of several priorities for patients**

Preference for oral	Other datapoints
<ul style="list-style-type: none"><li>J&amp;J Business Review 2023 revealed 75% of psoriatic arthritis patients would <b>switch to an oral therapy if safety and efficacy were consistent</b></li><li>Buisson et al. Inflamm Bowel Dis 2023 (<a href="#">LINK</a>): A nationwide study among IBD patients found that <b>the most preferred regimens were oral intake (QD/BID) and SC (Q8W/Q12W)</b>.</li><li>Fiorino et al. Inflamm Bowel Dis 2024 (<a href="#">LINK</a>): In a survey of UC patients across seven EU countries, <b>patients preferred oral and SC treatments</b> over IV and the most important attributes overall were:<ul style="list-style-type: none"><li>– ROA (31%) and frequency of serious adverse events (SAEs) (23%)</li></ul></li><li>Gisbert et al. J Crohns Colitis 2024 (<a href="#">LINK</a>): A survey of UC patients across five EU countries found that clinical remission was the highest priority, although patients also <b>valued the convenience of oral treatments</b>, avoiding steroids, and maintaining work/school attendance</li><li>Morishita et al. Inflamm Intest Dis 2023 (<a href="#">LINK</a>): Oral administration was preferred by 88.9% of IBD patients</li><li>Amenomori et al. Arq Gasteroenterol 2020 (<a href="#">LINK</a>): <b>87% of patients preferred oral formulations</b> in a small study in Brazil</li></ul>	<ul style="list-style-type: none"><li>Fiorino et al. 2024 Inflamm Bowel Dis 2024 (<a href="#">LINK</a>) also reported that CD patients ranked route of administration as the most important attribute (32% importance), preferring SC over IV (oral option not included in survey). All patients prioritized general well-being, energy level, and daily activities as the most important aspects for improvement through treatment</li><li>Richter et al. J Clin Med 2024 (<a href="#">LINK</a>): Patients with prior experience with IV or SC treatments were more likely to prefer those ROA. Interestingly, 37.1% of patients in one study believed that IV infusions were inherently more effective than SC injections, despite lack of evidence supporting this view</li><li>Van Deen et al. Dig Dis 2022 (<a href="#">LINK</a>): While prior SC/IV exposure was a strong predictor for SC/IV preferences, patients' preferences largely are determined by a variety of other personal factors</li></ul>

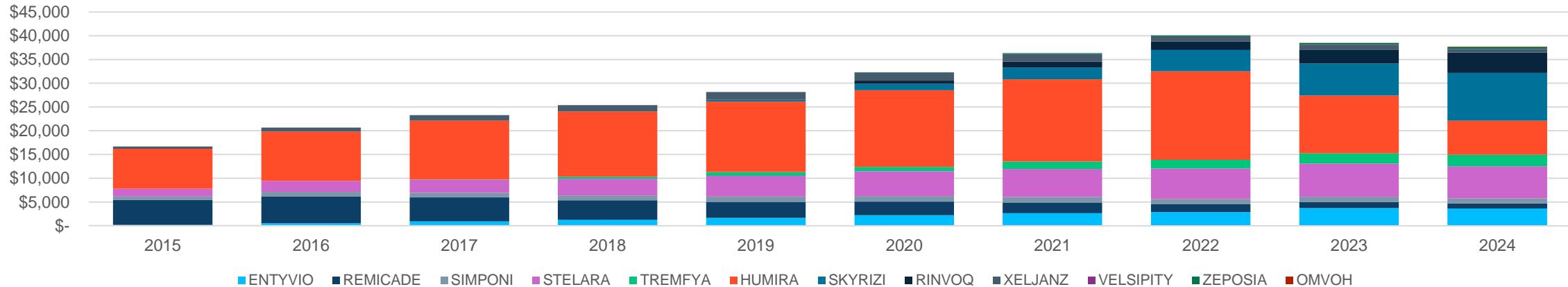
## Takeaways

- Oral therapies are highly preferred**, but preferences vary based on patient experience and perceived efficacy
- SC formulations are favored over IV in many cases, but some patients believe IV is more effective
- Convenience, efficacy, safety, and long-term quality of life are key drivers in treatment decision**

# Analysis of historic revenues of major IBD drugs

**Revenue in IBD has shifted from TNF inhibitors towards Entyvio, IL-23s, and Rinvoq**

US revenue across all approved indications



Approvals	Pre-2015	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
ENTYVIO	UC, CD									UC (SC)	CD (SC)	
REMICADE	CD, RA, AS, PsA, UC, pCD, PP, pUC											
SIMPONI	RA, PsA, AS, UC											
STELARA	PP, PsA	CD	aPP		UC	pPP		pPsA				
TREMFYA		PP				PsA				UC	CD	
HUMIRA	RA, PsA, AS, CD, PP, PJIA, h UC, pCD	HS	NIV				pUC					
SKYRIZI			PP			PsA, CD		UC				
RINVOQ				RA		PsA	AD, UC, AS	CD		PPJA, pPsA		
XELJANZ	RA		PsA	UC	PJIA	AS				UC		
VELSIPITY										UC		
ZEPOSIA					RMS	UC				UC	CD	
OMVOH												CD

Acronyms: UC: ulcerative colitis, CD: Crohn's disease, RA: rheumatoid arthritis, AS: ankylosing spondylitis, PsA: psoriatic arthritis, pCD: pediatric CD, PP: plaque psoriasis, pUC: pediatric UC, aPP: adolescent PP, pPP: pediatric PP, pPsA: pediatric PsA, PJIA: polyarticular juvenile idiopathic arthritis, NIV: non-infectious uveitis, AD: atopic dermatitis, RMS: relapsing multiple sclerosis

Source: Leerink Partners Research; Company Disclosures; Visible Alpha; MEDACorp Private Practice & Academic KOL Discussion. \*75% of Stelara revenues are from IBD

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## Takeaways

- Biosimilars of TNF inhibitors have eroded branded revenue, while a similar trend is expected for Stelara (ustekinumab)\* in 2025 onward
- Entyvio (vedolizumab), Skyrizi (risankizumab), Tremfya (guselkumab) and Rinvoq (upadacitinib) are all expected to grow in market share amid strong marketing, product profile (safety, efficacy and formulation)**
- S1PR modulator revenues have been fairly muted, with efficacy inferior to the predominant oral option, Rinvoq

# Big pharma commentary on anticipated performance in the IBD market

**There is considerable jockeying for position in the market, but we believe each of these drugs will (continue to) generate blockbuster revenues**

## TAK on Entyvio (vedolizumab) – 3Q24 Earnings Call (Jan 2025), TAK CEO Christophe Weber

"So, overall, the pattern has not changed. **Entyvio is keeping its leading position**, especially in first-line biological treatment. We have lost some market share in second and third line, **but we are growing faster than the market**, so we are pleased with the performance. And obviously, as we discussed in Japan in the past, **the launch of the Pen (SC formulation) is very much important in the life cycle of ENTYVIO**"

## ABBV on Skyrizi (risankizumab) and Rinvoq (upadacitinib) – 4Q24 Earnings Call (Jan 2025), ABBV CEO Robert Michael

"We anticipate a **substantial portion of this growth will be driven by robust performance from Skyrizi and Rinvoq**. These two assets are expected to **collectively generate nearly \$24B of revenue in 2025, reflecting growth of more than \$6B**. We are seeing strong performance across all of their **approved indications, especially in IBD**, and we see several tailwinds that will support growth into the next decade, including healthy immunology market growth; strong share capture, given best-in-class profiles; continued robust market access; and momentum from new indications, such as the recent launch of Skyrizi in UC, as well as the potential for five new indications for Rinvoq over the next few years"

## JNJ on Tremfya (guselkumab) – 4Q24 Earnings Call (Jan 2025), JNJ EVP Innovative Medicine Jennifer Taubert

"We've guided – maybe just back on STELARA, we've talked about the HUMIRA erosion curve being probably the best thing to model. Specific to your question about should there or will there be patient switches, I think there are a lot of patients in the immunology market right now that are in need of both advanced therapies or are in need of better therapies than they are on now. And so we do see across the board shifting of patients and movement into the newer and the better product. I would put Tremfya squarely in that camp. **We've got lots of reasons we focus in on IBD and the potential growth for Tremfya**. We've got a lot of reasons for great optimism there and differentiation. It's the only dual-acting IL-23 agent in IBD. Acts on both IL-23 as well as CD64. We think it's got the potential to really set the next bar in efficacy, and we know there are a lot of patients who need more and are ready for switch. And we think with our SC induction dose, we're going to have unrivaled flexibility. **So, the ability for fully SC induction and maintenance as well as the opportunity for IV. So the launch right now is going very well in UC, and we're very excited and optimistic, really looking forward to the upcoming launch in CD in SC.** Anti-IL-23s are viewed as safer long-term options compared to TNF inhibitors, which carry infection and malignancy risks, while JAK inhibitors can be restricted due to cardiovascular concerns"

# MEDACorp KOL feedback on advanced therapy positioning in IBD

Here we note some feedback from our MEDACorp KOLs on what impacts treatment choice

## Safety

- Currently approved therapies have similar efficacy ceilings, with differences in safety shaping selection for specific patient populations
- Anti-IL-23s are viewed as safer long-term options compared to TNF inhibitors, which carry infection and malignancy risks, while JAK inhibitors can be restricted due to cardiovascular concerns
- S1PR modulators have struggled with uptake due to cardiovascular monitoring requirements and hesitancy around heart-related risks

## Efficacy

- Efficacy is generally similar across advanced therapies, with all agents reaching a 40-50% clinical remission rate and ~30% steroid-free remission in trials
- Head-to-head data are limited, making cross-trial comparisons difficult, with network meta-analyses often guiding real-world decision making

## Convenience

- Route of administration matters, but preferences vary. Some patients prefer oral JAK inhibitors or S1P modulators, while others find subcutaneous IL-23 (e.g., risankizumab [Skyrizi]) appealing for less frequent dosing
- Dosing frequency plays a key role, some patients may favor quarterly injections (IL-23 inhibitors) over biweekly TNF inhibitors or daily oral therapies

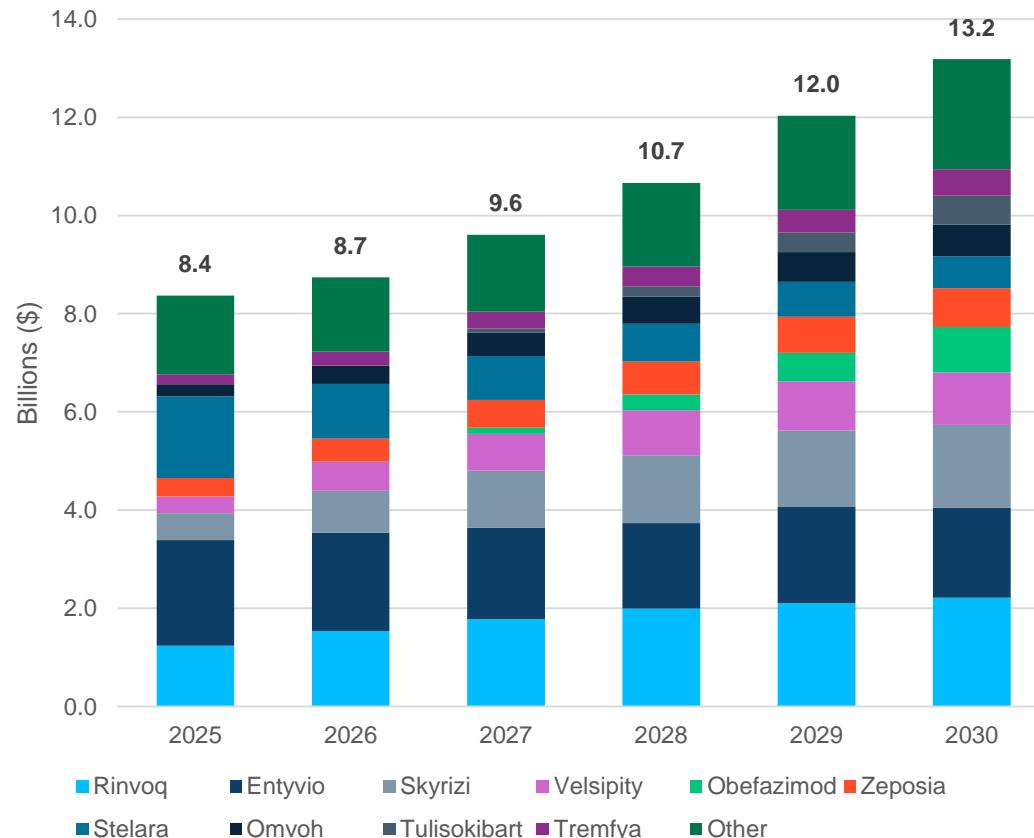
## Marketing

- Companies like ABBV and JNJ dominate due to established GI networks, while PFE and BMY have struggled with S1P adoption because of weaker marketing efforts
- Community GI influence is crucial—speaker programs and peer-to-peer education drive prescribing trends more than data alone, making KOL engagement a key strategy for new entrants

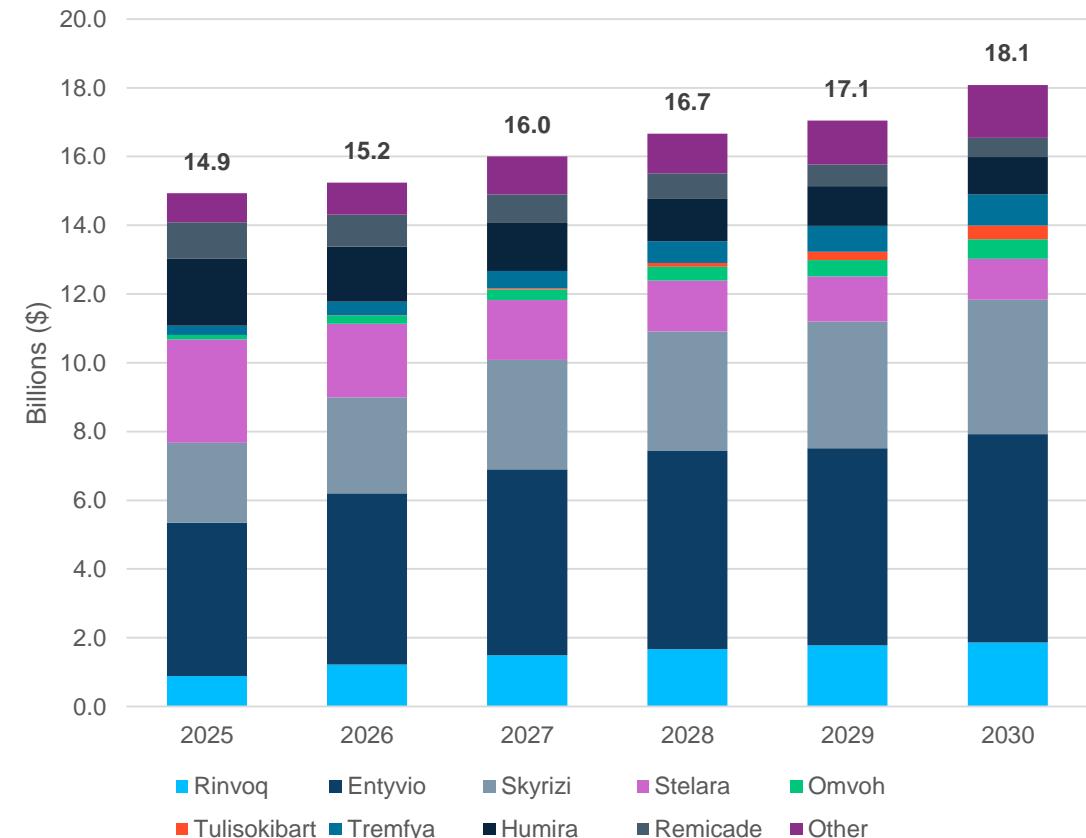
# IBD WW revenue estimates

IBD revenues are expected to eclipse >\$30B in 2031, representing a huge potential market

WW revenue estimates for UC



WW revenue estimates for CD



Source: Estimates from Evaluate Pharma; Leerink Partners Research

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# MEDACorp KOL thoughts on unmet needs in IBD

**Our MEDACorp KOLs had differing views on unmet needs, but agreed that new approaches and therapies were needed to overcome existing efficacy limitations**

## MEDACorp KOL (academic setting)

- **Therapeutic ceiling** remains a major issue. Across all advanced therapies, clinical remission rates hover around 40-50%, and steroid-free remission is ~30%, limiting differentiation and long-term success
- Diminishing returns in **sequencing** therapies. Data suggest that first-line biologic choice is critical, as response rates decline significantly when switching between TNF inhibitors and IL-23 or vice versa
- **Precision medicine** needed, there are no widely adopted biomarkers currently guide drug selection, leading to trial-and-error prescribing

## MEDACorp KOL (large, high-volume private practice)

- **Safety is not a differentiator**, most clinicians feel that current IBD drugs are generally well tolerated, with few side effects requiring intervention
- **Endoscopic healing is a key unmet need.** While symptoms improve, long-term mucosal healing rates (~30-40%) remain suboptimal, impacting disease progression
- Physicians are generally content with current options, but **marketing, drug access and payer restrictions drive decision-making** more than efficacy or safety differences
- Force rank of unmet needs:
  - More durable responses: current therapies often lose effectiveness over time
  - Oral alternatives
  - Combination therapy: “want one injection...improved endoscopic improvement rates and high durability without higher rates of side effects”

# What's next in IBD?

## An array of novel targets and approaches could disrupt the IBD landscape

### TL1A/DR3 targeting agents

- Emerging class of therapies in development that have demonstrated very encouraging data in Ph 2 studies, with first generation programs now in Ph 3. Next generation approaches, including half-life extended (HLE) versions (for added convenience), are in early clinical development
- TL1A targeting programs have attracted significant strategic interest and influenced several high-profile deals in recent years

### Combinations and bispecifics

- Both combinations of targeted therapies and bispecifics, which combine multiple targets in one, are in development aiming to overcome the “efficacy ceiling” without negatively impacting safety
- JNJ’s DUET Ph 2b studies of JNJ-4804, its coformulation of golimumab (Simponi) and guselkumab (Tremfya), have primary completion dates of May 2025, and data could be presented this year

### Emerging targets

- Given the complexity of IBD, numerous targets are being explored for their potential therapeutic potential
- Notable among them is ABVX’s obefazimod, a miRNA-124 inducer, that is being evaluated in a Ph 3 study in UC, with topline induction data expected in 3Q25

### Oral formulations

- Oral formulations of approved biologics (target the same pathway) are a disruptive innovation for IBD treatment, addressing the unmet need for more patient-friendly options
- These have also influenced notable deals in the space recently. JNJ / PTGX recently presented encouraging data from the Ph 2b ANTHEM study of icotrokinra (oral IL-23R) in UC, and data from LLY’s Ph 2b EMERALD-2 study of MORF-057 (oral α4β7) in UC are expected in 1H25

## TL1A/DR3

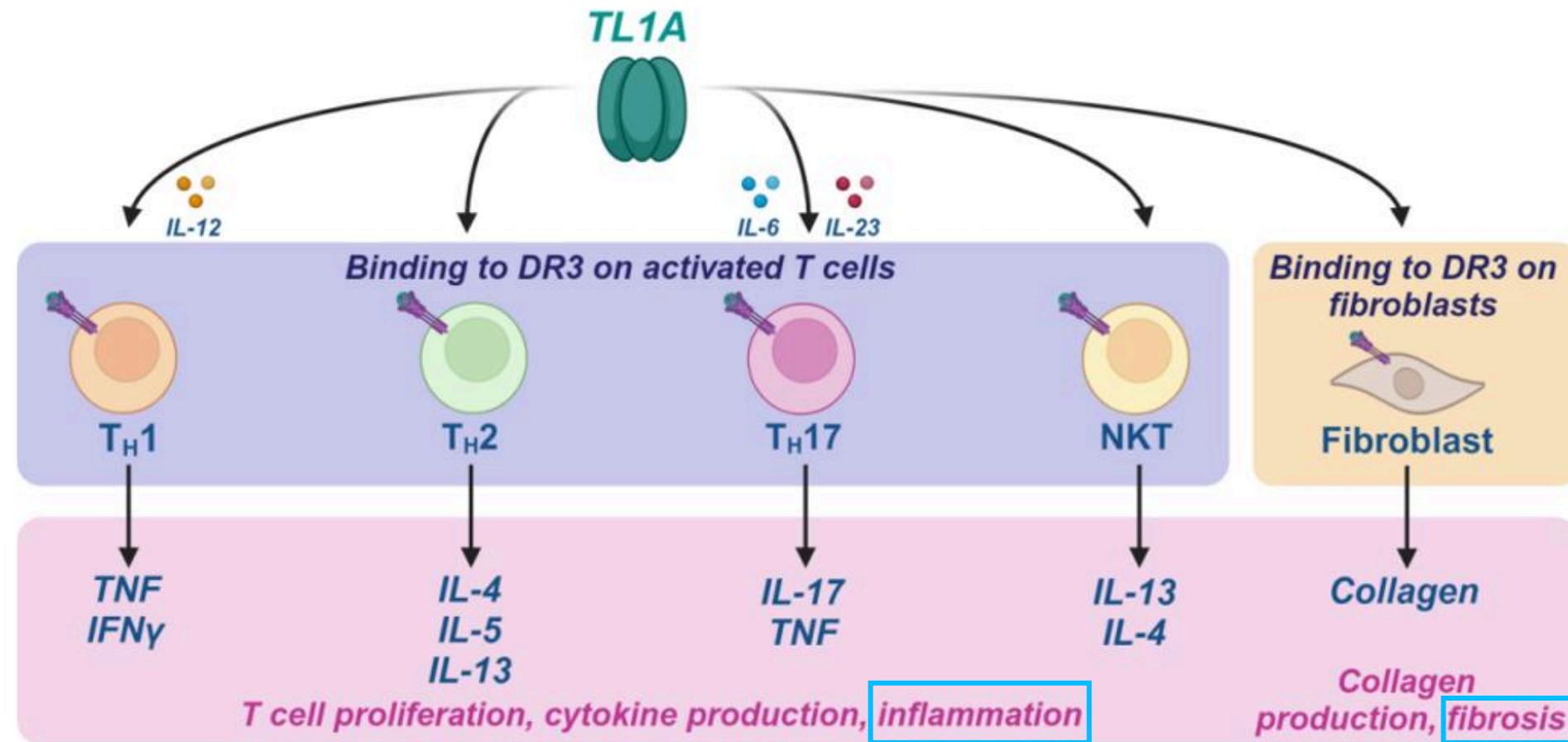
- **TL1A is a hot target:** several emerging therapies are focusing on blocking TL1A in IBD. Pharma interest is high, and TL1A programs have driven major biotech deals in recent years, including multi-billion-dollar acquisitions
- **Strong clinical data:** Ph 2 studies have shown promising efficacy, with Ph 3 trials underway
- **Next-gen improvements:** Half-life extended (HLE) and more potent versions are in development for more convenient dosing, while STTK is uniquely targeting the DR3 side of the TL1A/DR3 axis
- **Outlook:** TL1A drugs could reshape IBD treatment if Ph 3 data confirm long-term benefits

# TL1A/DR3 targeting therapies quick hits

Background	+/- considerations
<ul style="list-style-type: none"><li>• TL1A, a member of the TNF superfamily, interacts with its functional receptor DR3 to regulate immune responses and inflammation. This ligand-receptor pair plays a pivotal role in both adaptive and innate immunity, with implications in IBD pathogenesis</li><li>• Several large pharma companies have programs in later stage clinical development (RHHBY, MRK and SAN FP / TEVA) following encouraging efficacy in various Ph 2 studies</li><li>• An emerging group of players are trying to differentiate from the first generation with improved potency and half-life extension (XNCR, SYRE, and ABSI) or through combinations (SYRE and ABBV)</li><li>• STTK is aiming to differentiate by targeting the DR3 side of the axis</li></ul>	<ul style="list-style-type: none"><li>• Ph 2 datasets from clinical-stage programs show potential for best-in-class efficacy and leave the class well-positioned to disrupt the IBD treatment paradigm, possibly with biomarker selection</li><li>• Emerging players are aiming to improve on this efficacy with increased potency, combination approaches, and/or more convenient dosing</li><li>• DR3 targeting is a differentiated approach that may offer advantages over TL1A targeting</li><li>• Evaluation in other indications is underway, potentially expanding the opportunity</li></ul> <ul style="list-style-type: none"><li>• Targeting TL1A inherently predisposes patients to forming anti-drug antibodies (ADAs)</li><li>• Targeting DR3 is untested clinically</li><li>• Larger datasets will be needed to better qualify the infection and malignancy risks posed by targeting the pathway</li><li>• The field of IBD treatments is becoming increasingly crowded, with oral options emerging and biosimilars now available</li></ul>

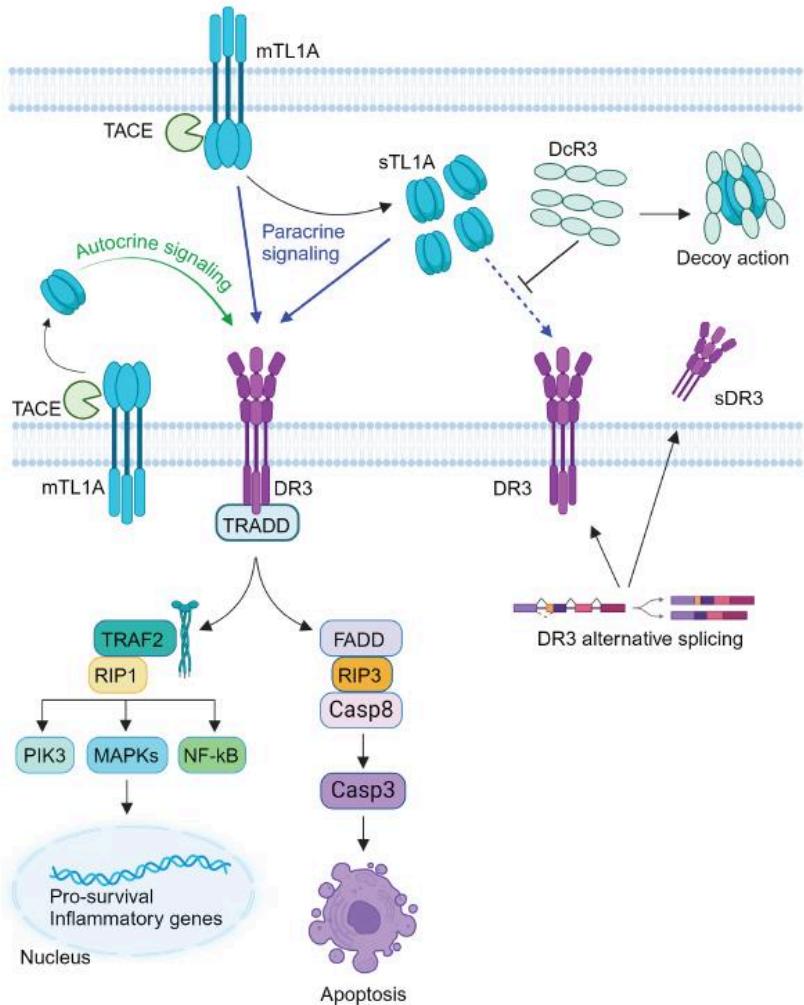
# Simplified graphic of the TL1A/DR3 axis

High level: TL1A is a ligand that interacts with DR3 on lymphocytes to induce inflammation and fibrosis



# Overview of the TL1A:DR3 axis

## The TL1A:DR3 axis is an important regulator of the GI immune system



- **TL1A (TNF-like Cytokine 1A)** is a member of the TNF superfamily and plays a pivotal role in immune regulation and inflammation. It exists as a homotrimer and has two forms: **membrane-bound (mTL1A)** and **soluble (sTL1A)**, both of which are biologically active
  - TL1A functions as a potent costimulator of adaptive immunity, amplifying effector T cell responses (Th1, Th2, Th9, and Th17) and influencing innate immune pathways, including epithelial repair (including fibrosis) and antimicrobial defenses
- Its expression is induced by inflammatory cytokines (e.g., TNF, IL-1 $\alpha$ ) and is significantly upregulated in inflammatory lesions, particularly in IBD, where it is found in dendritic cells, macrophages, lymphocytes, and stromal cells
- **DR3 (Death Domain Receptor 3)** is the functional receptor for TL1A and expressed on activated lymphocytes, including CD4+ and CD8+ T cells, NK cells, B cells, and subsets of innate lymphoid cells (ILCs). DR3 signaling amplifies immune responses, particularly in the presence of TL1A, triggering pathways that regulate T cell activation, cytokine production, and inflammation
  - Expression of DR3 is dynamically regulated, increasing during immune activation (e.g., following TCR stimulation) and in response to pro-inflammatory cytokines. In IBD, DR3 is upregulated on immune cells in intestinal lesions, highlighting its role in chronic inflammation and its potential as a therapeutic target
- sTL1A also binds to Decoy Receptor 3 (DcR3), a soluble receptor that prevents TL1A from interacting with its functional receptor, thereby downregulating inflammatory responses
- **Decoy Receptor 3 (DcR3)** is a soluble receptor that competes with DR3 for TL1A binding, serving as a key regulator of immune responses. DcR3 is predominantly expressed in inflammatory settings and cancer, where it may protect tissues from excessive damage or promote immune evasion
- This network of TL1A, DR3, and DcR3 forms a complex and tightly regulated signaling system that influences both inflammation and tissue homeostasis, particularly in diseases like IBD (see further detail [HERE](#))

Source: Bamias et al. Gut 2024 ([LINK](#))

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# Big pharma has shown strong strategic interest in TL1A

## TL1A has been the focus of numerous recent transactions in IBD

Acquirer / Lead	Target / Partner	Deal type	Key molecule / technology	Target	Economics	Date
ABBV	FutureGen	Collaboration	FG-M701	TL1A	Upfront: \$150M Milestones: Up to \$1.56B	6.2024
RHHBY	Telavant	Acquisition	RG-6631 (RO7790121/RVT-3101/PF-06480605)	TL1A	Upfront: \$7.1B Milestones: Up to \$150M	10.2023
SAN FP	TEVA	Collaboration	Duvakitug (TEV-48574)	TL1A	Upfront: \$500M Milestones: Up to \$1B	10.2023
MRK	RXDX	Acquisition	Tulisokibart (MK-7240 / PRA023)	TL1A	\$10.8B	6.2023

# Overview of TL1A/DR3 targeting landscape

**2025 catalysts mostly focus on early-stage data from emerging players**

Drug	Company	UC		CD		Next IBD catalyst	
		Clinical data?	Status	Clinical data?	Status		
TL1A	Tulisokibart (MK-7240 / PRA023)	MRK	✓	Ph 3 ongoing PC: 11.2026	✓	Ph 3 ongoing PC: 9.2029	Ph 3 UC data 2026
	Duvakitug (TEV-48574)	SAN FP / TEVA	✓	Ph 3 planning	✓	Ph 3 planning	Ph 3 initiation in 2H25
	RG6631 / RO7790121 (RVT-3101, PF 6480605)	RHHBY	✓	Ph 3 ongoing PC: 6.2027	-	Ph 2 ongoing PC: 12.2028	-
	SPY002*	SYRE	-	-	-	-	Ph 1 data and molecule selection 2Q25; initiate Ph 2 mid-2025
	XmAb942	XNCR	-	-	-	-	Ph 1 data 1H25; initiate Ph 2 2H25
	ABS-101	ABSI	-	-	-	-	Ph 1 initiation 1H25; Ph 1 data 2H25
	FG-M701	ABBV / FutureGen	-	-	-	-	Combination studies planned
DR3	SL-325	STTK	-	-	-	-	IND filing 3Q25; initial data 2026

# TL1A UC induction clinical data tables

**TL1A assets have shown strong remission and endoscopic improvement rates during the induction stage of Ph 2 UC studies**

Drug	Company	Target	ROA	Scoring	Clinical Trial	Duration	Cohort/subgroup	N	% Prior Adv Ther	Clin Rem			Best Remission Rate in Class
										Abs.	PBO	PBO-Adj.	
<b>Tulisokibart</b>	MRK	TL1A	IV Q2/4W	MMS	Ph 2 ARTEMIS-UC	12 weeks	All-comers	68	47%	26.5%	1.5%	25.0%	27.4%
							Biomarker	38	53%	32.0%	11.0%	21.0%	
<b>RG6631</b>	RHHBY	TL1A	SC Q4W	MMS	Ph 2b TUSCANY-2	12 weeks	50 mg	47	40%	29.8%	11.6%	18.2%	27.4%
							150 mg	62	34%	35.0%	11.6%	23.4%	
							450 mg	91	43%	31.8%	11.6%	20.2%	
							Biomarker	111	-	37.4%	10.0%	27.4%	
							Low dose	47	30%	36.2%	20.5%	15.8%	
<b>Duvakitug</b>	SAN FP/TEVA	TL1A	SC Q2W	MMS	Ph 2b RELIEVE UCCD	12 weeks	High dose	46	30%	47.8%	20.5%	27.4%	27.4%

Drug	Company	Target	ROA	Scoring	Clinical Trial	Duration	Cohort/subgroup	N	% Prior Adv Ther	Endo Imp			Best Endo Imp in Class
										Abs.	PBO	PBO-Adj.	
<b>Tulisokibart</b>	MRK	TL1A	IV Q2/4W	MMS	Ph 2 ARTEMIS-UC	12 weeks	All-comers	68	47%	36.8%	6.0%	30.8%	41.6%
							Biomarker	38	53%	37.0%	19.0%	18.0%	
<b>RG6631</b>	RHHBY	TL1A	SC Q4W	MMS	Ph 2b TUSCANY-2	12 weeks	50 mg	47	40%	40.4%	18.6%	21.8%	41.6%
							150 mg	62	34%	38.3%	18.6%	19.7%	
							450 mg	91	43%	40.9%	18.6%	22.3%	
							Biomarker	111	-	51.6%	10.0%	41.6%	
							Low dose	47	30%	44.6%	22.7%	22.0%	
<b>Duvakitug</b>	SAN FP/TEVA	TL1A	SC Q2W	MMS	Ph 2b RELIEVE UCCD	12 weeks	High dose	46	30%	50.0%	22.7%	27.3%	41.6%

- With the caveat of cross-trial comparison and high degree of heterogeneity in IBD trials, these findings suggest that TL1A inhibitors have significant effects on typical UC endpoints during induction and appear as good or better than SOC ([LINK](#)) with biomarker-driven stratification potentially enhancing patient response
- Within the group, parsing out which program is best at this stage is similarly limited, and we view the programs with relative equivalence**

# TL1A UC maintenance clinical data tables

Maintenance data are similarly impressive, however interpretation is somewhat limited by study design differences and the lack of placebo control (OLE)

Drug	Company	Target	Study Type	ROA	Scoring	Clinical Trial	Duration	Cohort/subgroup	N	% Prior Adv Ther	Clin Rem			Best Remission Rate in Class
											Abs.	PBO	PBO-Adj.	
Tulisokibart	MRK	TL1A	MoR	IV Q2/4W	MMS	Ph 2 ARTEMIS-UC OLE*	50 weeks	100 mg	22	36%	31.8%	-	-	-
								250 mg	25	52%	48.0%	-	-	
RG6631	RHHBY	TL1A	TrTh	SC Q4W	MMS	Ph 2b TUSCANY-2 LTE	56 weeks	50 mg	42	-	31.0%	-	-	-
								150 mg	28	-	38.5%	-	-	
								450 mg	28	-	35.7%	-	-	

# TL1A CD induction clinical data tables

**Less data have been reported on TL1A-targeting in CD, although data are compelling**

Drug	Company	Target	ROA	Scoring	Clinical Trial	Duration	Cohort/subgroup	N	% Prior Adv Ther	Clin Rem			Best Remission Rate in Class
										Abs.	PBO	PBO-Adj.	
Tulisokibart	MRK	TL1A	IV Q2/4W	CDAI/SES-CD	Ph 2 APOLLO-CD	12 weeks	All-comers	50-55	71%	49.1%	16.0%	33.1%	33.1%
Duvakitug	SAN FP/TEVA	TL1A	SC Q2W	CDAI/SES-CD	Ph 2b RELIEVE UCCD	12 weeks	Low dose	46	59%	50%	41.3%	8.7%	
							High dose	46	59%	54.3%	41.3%	13%	

Drug	Company	Target	ROA	Scoring	Clinical Trial	Duration	Cohort/subgroup	N	% Prior Adv Ther	Endo Imp			Best Endo Imp in Class
										Abs.	PBO	PBO-Adj.	
Tulisokibart	MRK	TL1A	IV Q2/4W	CDAI/SES-CD	Ph 2 APOLLO-CD	12 weeks	All-comers	50-55	71%	26.0%	12.0%	14.0%	34.8%
Duvakitug	SAN FP/TEVA	TL1A	SC Q2W	CDAI/SES-CD	Ph 2b RELIEVE UCCD	12 weeks	Low dose	46	59%	26.1%	13.0%	13.1%	
							High dose	46	59%	47.8%	13.0%	34.8%	

- Again, with the caveat of cross-trial comparison and the high degree of heterogeneity in IBD trials, these results demonstrate TL1A can have robust effects typical CD outcomes and appear as good or better than many approved therapies ([LINK](#))
- It is important to note that the tulisokibart studies were benchmarked to historical placebo control rates

# TL1A CD maintenance clinical data tables

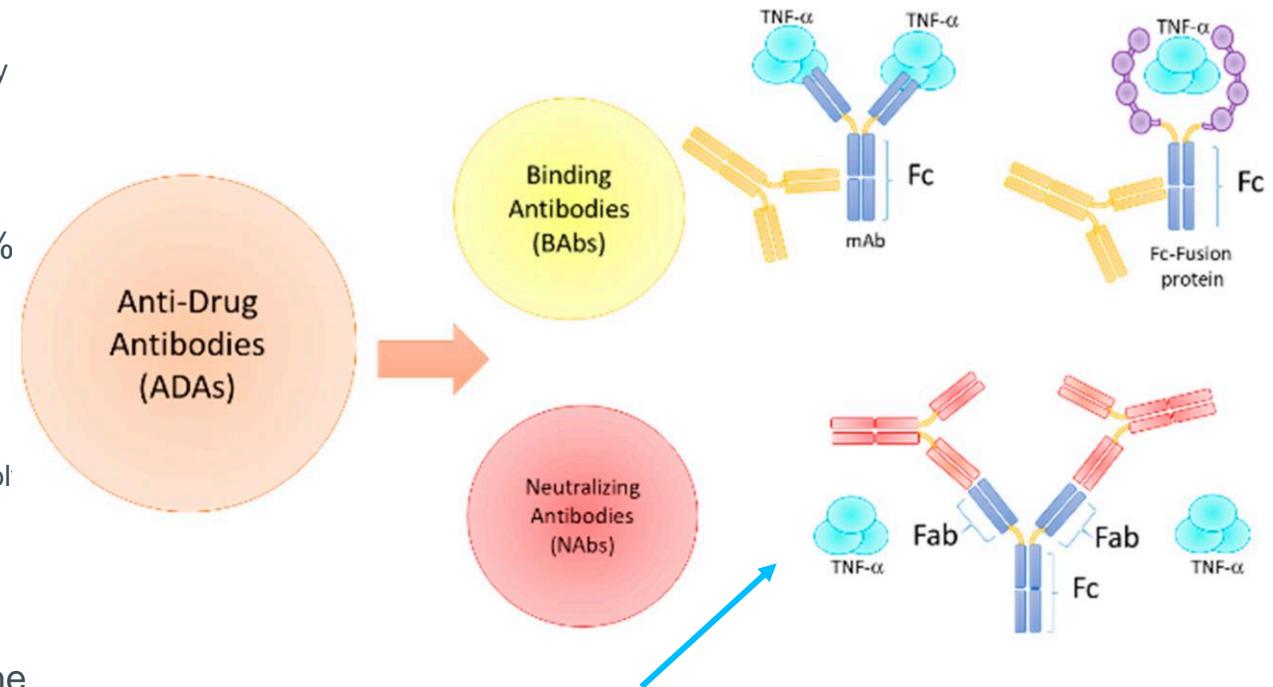
Maintenance data in CD are even more limited, and more is needed to fully interpret the longitudinal benefits of TL1A targeting in the disease

Drug	Company	Target	Study Type	ROA	Scoring	Clinical Trial	Duration	Cohort/subgroup	N	% Prior Adv Ther	Endo Imp			Best Endo Imp in Class
											Abs.	PBO	PBO-Adj.	
Tulisokibart	MRK	TL1A	MoR	IV Q2/4W	CDAI/SES-CD	Ph 2 APOLLO-CD LTE	50 weeks	100 mg	19	79.0%	27.8%	-	-	-
								250 mg	18	56.0%	15.8%	-	-	-

# Targeting TL1A could risk antidrug antibody formation

**TL1A is a soluble ligand, which increases the chance of ADA formation against a mAb that targets it- and has been observed with earlier study's of RHHBY's RG6631**

- Targeting TL1A has shown efficacy, but there are characteristics of the target that predispose therapies to immunogenicity risks
  - Internalization of mAb:TL1A complexes by macrophages etc. potentially contributes to immune activation and formation of ADA
  - Presence of T cell epitopes in the antibody structure
- An early example of TL1A therapies having an ADA risk is PF-06480605 (now RHHBY's RG6631), which showed 82% antidrug antibody (ADA) and 10% neutralizing antibody (NAb) positivity. However, it was noted that ADAs did not significantly impact safety, pharmacokinetics or efficacy at higher doses
  - Data published by ABSI show that RG6631 internalizes at a considerably greater rate than their own next-generation program, ABS-101, and MRK's tulisokibart ([LINK](#))
  - Early testing of tulisokibart was notable for an ADA-related death in an NHP (though this was “not considered relevant to humans”)
- ADAs can potentially impact drug efficacy by neutralizing the drug's ability to bind TL1A, altering the drug's PK and clearance. Optimizing the antibody structure can reduce immunogenicity risks, but ADA formation will be an important thing to monitor in upcoming TL1A clinical datasets, especially how this impacts long term efficacy



TNF targeting, particularly with infliximab (Remicade) is the prototypical example used for ADA formation in IBD

# Tulisokibart (MRK): Overview

## MRK's tulisokibart is arguably the closest to approval

### Tulisokibart program background

- Tulisokibart is humanized IgG1-k mAb
  - Binds TL1A monomers and trimers
  - SC formulation being tested
- MRK received tulisokibart from its acquisition of RXDX in 2023
  - RXDX had reported encouraging Ph 2 induction data in both UC (ARTEMIS-UC) and CD (APOLLO-CD) in Dec. 2022 and were planning Ph 3 development across both indications (which is now ongoing)
- MRK recently reported long-term maintenance data from the extension portions of these studies

### Data highlights

- ARTEMIS-UC and APOLLO-CD demonstrated robust efficacy during induction and maintenance, despite both enrolling refractory, difficult-to-treat populations
  - In both studies certain patients had buccal swabs tested by a genetic-based companion diagnostic (CDx). CDx positive patients showed promising results
- Regarding safety, infections were common, but not severe, in both trials, with rates slightly more pronounced in the OLE portion of APOLLO-CD. The rate of ADAs was low (e.g., 15% in ARTEMIS-UC) and said to have an unremarkable impact on efficacy and safety

### Next up?

- Tulisokibart is currently being evaluated in Ph 3 programs in UC (ATLAS-UC) and CD (ARES-CD). Each program consists of two trials, one that evaluates induction at week 12 and another that evaluates both induction and maintenance at week 52 with a treat-through design
  - ATLAS-UC has a primary completion date of Nov. 2026
  - ARES-CD has a primary completion date of Sept. 2029
  - CDx is being tested in both
- An ongoing Ph 2 study in SSc-ILD (ATHENA-SSc-ILD) has primary completion 2026

Source: Sands et al. N Eng J Med 2024 ([LINK](#)); MRK tulisokibart ACG 2024 Poster ([LINK](#), [LINK](#)); MRK 4Q24 Earnings Presentation ([LINK](#)); PRA023 ARTEMIS-UC Study Protocol ([LINK](#)). SSc-ILD: Systemic sclerosis interstitial lung disease. \*patients with a positive test for likelihood of response

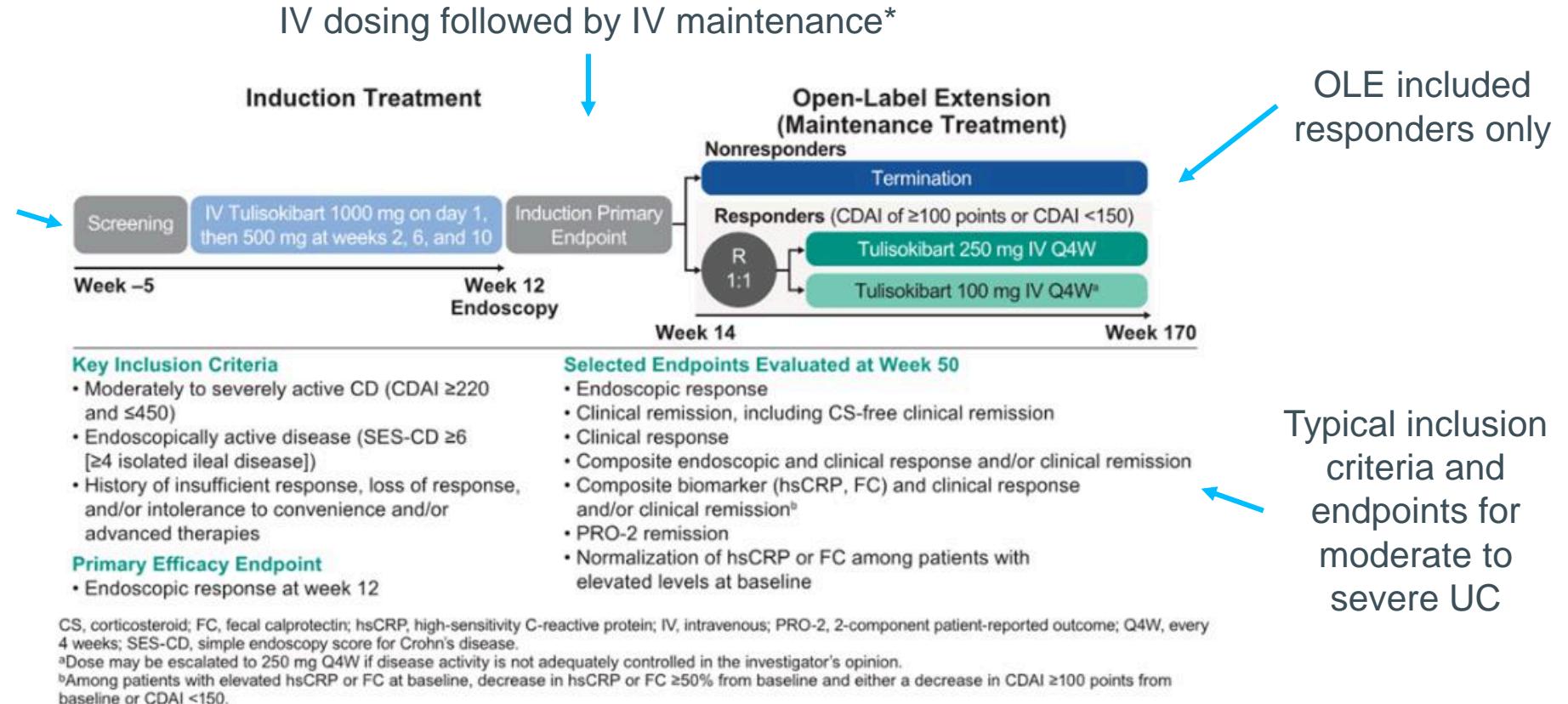
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# Tulisokibart (MRK): ARTEMIS-UC design

UC

## ARTEMIS-UC employed a typical two-part, induction-maintenance design

ARTEMIS-UC enrolled two cohorts, Cohort 1 were unselected, while Cohort 2 were positive for a biomarker test designed to predict likelihood of response



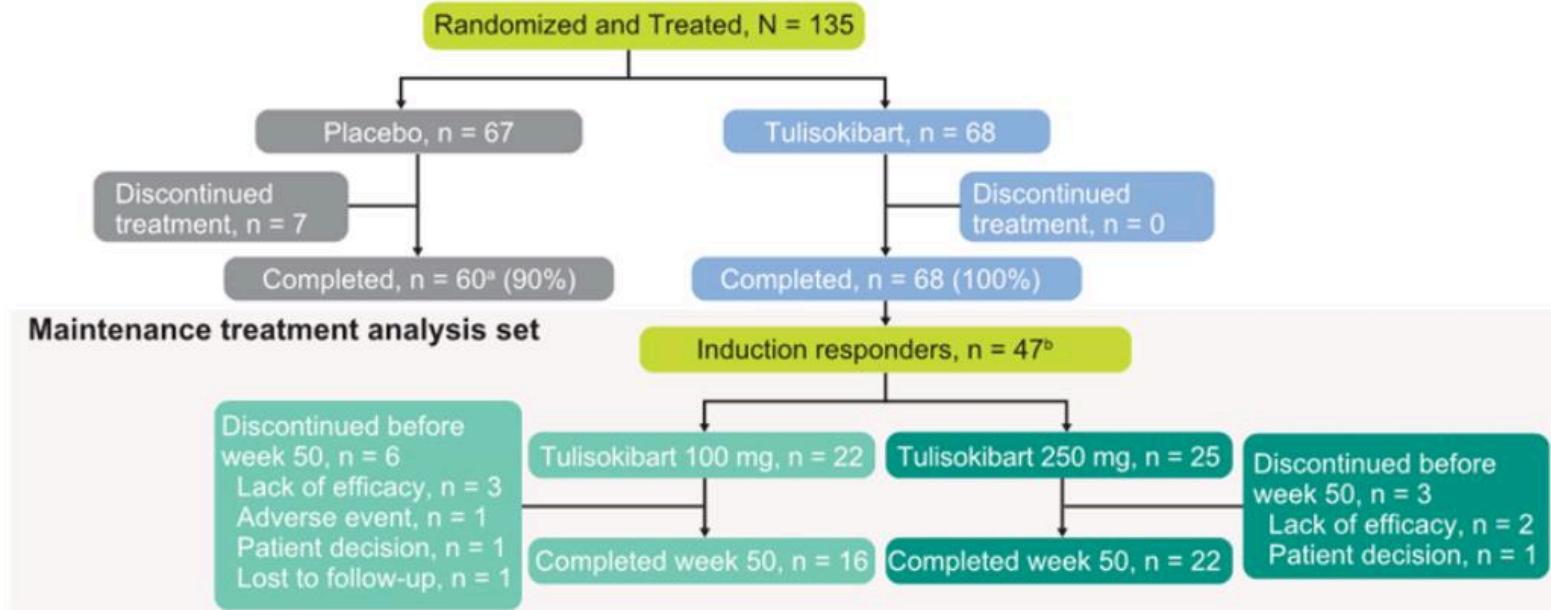
# Tulisokibart (MRK): ARTEMIS-UC design (cont.)

UC

## OLE data focused on responders from the biomarker-unselected Cohort 1

Cohort 1 included a biomarker-unselected population

→ **Figure 2. Patient disposition: cohort 1 induction responders in the tulisokibart group**



<sup>a</sup>Induction responders in the placebo group (n = 18) were randomized to receive tulisokibart 100 (n = 8) or 250 (n = 10) mg during OLE and were included in the safety population.

<sup>b</sup>OLE randomization occurred prior to final database lock; induction responders at final database lock may differ.

# Tulisokibart (MRK): ARTEMIS-UC induction baseline demographics

UC

Strong efficacy during induction was observed despite the trial enrolling difficult to treat patients

Characteristic	Cohort 1		Patients with Positive Test for Likelihood of Response†	
	Placebo (N=67)	Tulisokibart (N=68)	Placebo (N=37)	Tulisokibart (N=38)
Age — yr	42.2±16.3	40.4±14.4	38.6±13.0	37.3±15.7
Female sex — no. (%)	29 (43)	34 (50)	13 (35)	20 (53)
Race or ethnic group — no. (%)‡				
American Indian or Alaska Native	0	0	0	0
Asian	1 (1)	1 (1)	1 (3)	3 (8)
Black	2 (3)	0	0	0
White	57 (85)	65 (96)	31 (84)	32 (84)
Multiple	1 (1)	0	1 (3)	0
Not reported or patient declined to respond	6 (9)	2 (3)	4 (11)	3 (8)
Hispanic or Latino ethnic group — no. (%)‡				
Yes	2 (3)	4 (6)	1 (3)	2 (5)
No	62 (93)	60 (88)	34 (92)	34 (89)
Not reported or patient declined to respond	3 (4)	4 (6)	2 (5)	2 (5)
Weight — kg	76.6±18.5	73.9±19.7	76.4±15.2	77.6±22.6
Body-mass index§	25.5±5.0	25.7±7.0	25.6±5.1	26.7±7.8
Duration of disease — yr	6.3±6.2	6.7±6.4	7.9±6.3	5.9±3.9
Extent of disease — no. (%)				
Proctosigmoiditis	7 (10)	2 (3)	1 (3)	2 (5)
Colitis on the left side	28 (42)	35 (51)	15 (41)	19 (50)
Pancolitis	32 (48)	31 (46)	21 (57)	17 (45)
Mayo endoscopic subscore — no. (%)¶				
2	14 (21)	22 (32)	15 (41)	10 (26)
3	53 (79)	46 (68)	22 (59)	28 (74)
Modified Mayo score	7.1±1.1	6.9±1.2	6.8±1.2	6.8±1.3
Roberts Histopathology Index**	20.3±7.8	17.9±10.4	16.6±9.2	17.7±9.7
IBDQ score††	116.3±30.7	113.3±32.4	119.7±32.0	120.6±30.4
High-sensitivity C-reactive protein level — mg/liter	10.0±13.8	10.2±19.2	9.5±14.4	9.8±16.1
Fecal calprotectin level — µg/g	1395.4±1430.6	1219.1±1381.5	1257.9±1202.0	1096.4±1011.2
Concomitant medication use — no. (%)				
Oral glucocorticoids	38 (57)	35 (51)	14 (38)	16 (42)
Immunosuppressants	11 (16)	8 (12)	1 (3)	2 (5)
Aminosalicylate	44 (66)	44 (65)	24 (65)	25 (66)
Previous treatment for ulcerative colitis — no. (%)				
Glucocorticoids	58 (87)	51 (75)	30 (81)	29 (76)
Immunosuppressants	28 (42)	22 (32)	14 (38)	10 (26)
Advanced therapies	32 (48)	32 (47)	18 (49)	20 (53)

High disease activity overall with baseline endoscopic scores of 3 in the majority

Characteristic	Cohort 1		Patients with Positive Test for Likelihood of Response†	
	Placebo (N=67)	Tulisokibart (N=68)	Placebo (N=37)	Tulisokibart (N=38)
No. of previous advanced therapies — no. (%)‡‡				
0	35 (52)	36 (53)	19 (51)	18 (47)
1	8 (12)	12 (18)	4 (11)	6 (16)
2	12 (18)	14 (21)	7 (19)	5 (13)
≥3	12 (18)	6 (9)	7 (19)	9 (24)



Relatively “refractory” population with high %s of prior advanced therapies, potentially influencing the low placebo induction clinical remission rate (1%)

# Tulisokibart (MRK): ARTEMIS-UC maintenance safety

UC

## Tulisokibart's safety profile was fairly benign during the OLE

**Table 2. Summary of treatment-emergent AEs during induction (week 0 to 14 before maintenance treatment) and OLE (week 14 to 50)**

Treatment-Emergent AEs, n (%)	Induction		OLE Tulisokibart <sup>a</sup>	
	Placebo (n = 67)	Tulisokibart (n = 68)	100 mg (n = 30)	250 mg (n = 35)
<b>Patients with any AE</b>	29 (43)	31 (46)	23 (77)	22 (63)
Any severe (grade ≥ 3) AE	4 (6)	0	3 (10)	1 (3)
Any drug-related AE	1 (1)	3 (4)	2 (7)	4 (11)
AE leading to study drug discontinuation	3 (4)	1 (1)	2 (7)	1 (3)
Any SAE	6 (9)	0	2 (7)	1 (3)
Any drug-related SAE	0	0	0	0
<b>Patients with any AE of special interest</b>				
Acute infusion reaction <sup>b</sup>	0	0	0	0
Peri-infusion reaction <sup>c</sup>	1 (1)	0	0	0
Infection and infestation <sup>d</sup>	10 (15)	11 (16)	11 (37)	16 (46)

MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA queries.

<sup>a</sup>Safety population for OLE includes all cohort 1 induction responders from the tulisokibart and placebo groups who received tulisokibart 100 mg or 250 mg during OLE.

<sup>b</sup>Acute infusion reaction: events as defined by the MedDRA hypersensitivity SMQ occurring within 1 hour of completion of infusion.

<sup>c</sup>Peri-infusion reaction: events as defined by the MedDRA hypersensitivity SMQ occurring within 24 hours of completion of infusion.

<sup>d</sup>AE classification.

Data cutoff date: Induction, June 6, 2023; OLE, August 7, 2023.

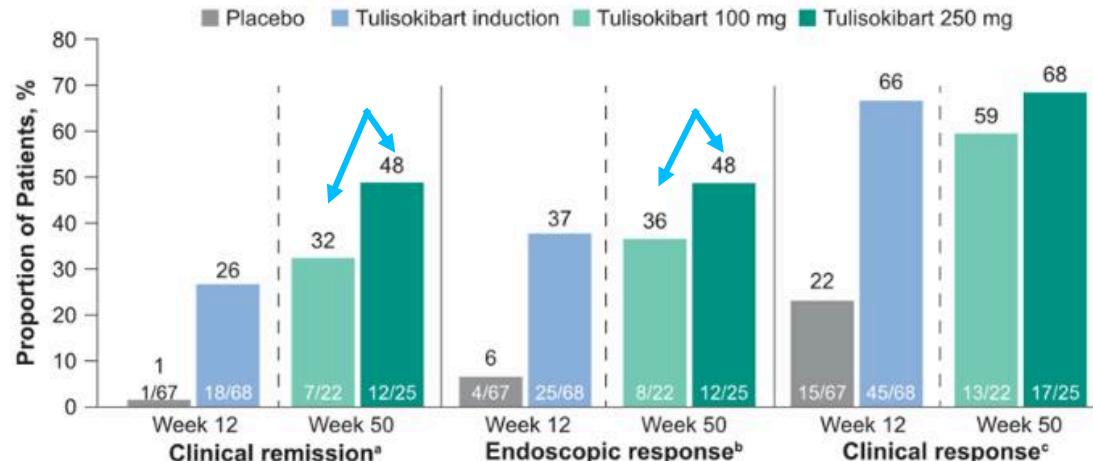
- Tulisokibart monotherapy demonstrated a manageable safety profile in both induction and maintenance setting of ARTEMIS-UC
- Given the immunosuppressive mechanism, the infection rates were important to monitor and during the maintenance phase rates did elevate to 37% in the 100 mg arm and 46% in the 250 mg arm, although it was noted that these were “predominantly upper respiratory infections” and no “serious infections or infections related to systemic immunosuppression, such as herpes zoster,” were reported
- Interpretation of the OLE is limited by the lack of a placebo comparator

# Tulisokibart (MRK): ARTEMIS-UC efficacy data

UC

## Tulisokibart maintenance data and subgroup analysis validate potential benefit of TL1A inhibition

**Figure 3. Clinical and endoscopic outcomes at week 50**



<sup>a</sup>Defined per mMS as endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and stool frequency subscore of 0 or 1 and not greater than baseline.

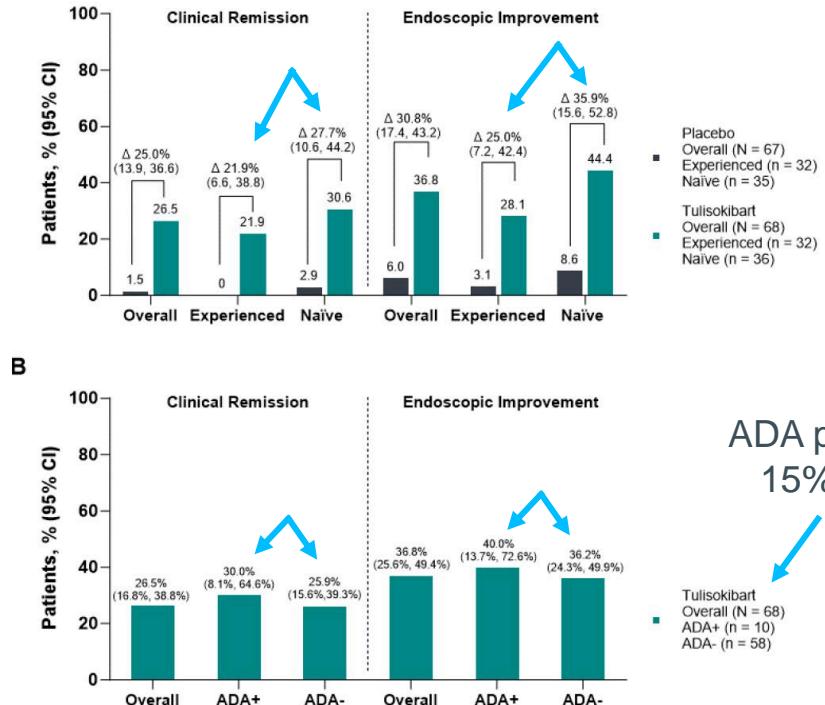
<sup>b</sup>Defined as endoscopy subscore  $\leq 1$  with no friability.

<sup>c</sup>Defined per mMS as reduction from baseline  $\geq 2$  points and  $\geq 30\%$  in mMS, accompanied by a reduction  $\geq 1$  in rectal bleeding subscore or absolute rectal bleeding subscore  $\leq 1$ .

Analyses conducted in the full analysis set at week 12 (all patients who have been randomized and treated in cohort 1) and the maintenance treatment analysis set at week 50 (tulisokibart induction responders at week 12 who have been randomized and treated in OLE).

Data cutoff date: week 12, October 28, 2022; week 50, August 7, 2023.

- Tulisokibart conferred dose-dependent improvements in clinical and endoscopic outcomes despite the small sample size



ADA positivity in 15% (10/68)

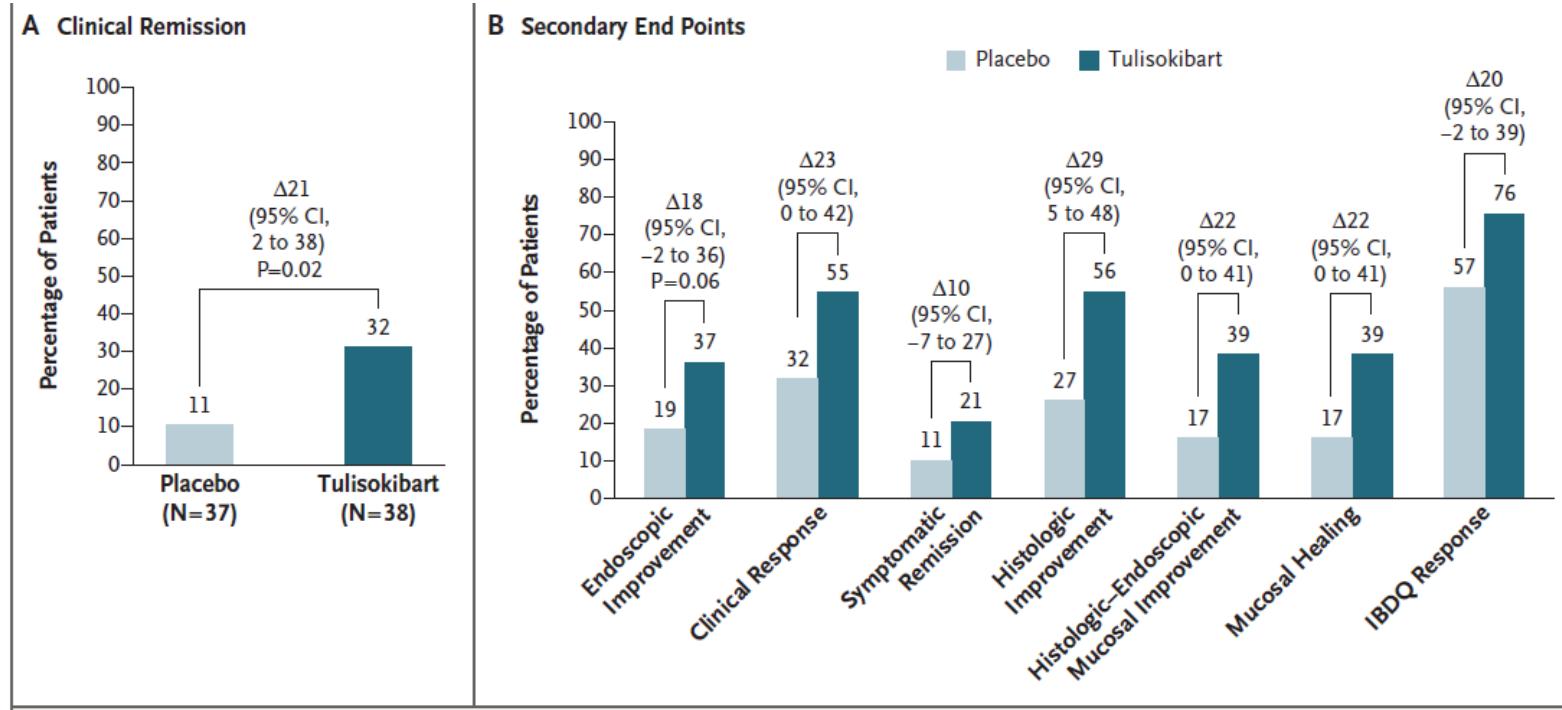
Tulisokibart  
Overall (N = 68)  
ADA+ (n = 10)  
ADA- (n = 58)

- Subgroup analysis from the induction phase showed tulisokibart was effective independent of prior therapy or ADA status. Although these were unpowered and exploratory, they are nonetheless encouraging

# Tulisokibart (MRK): ARTEMIS-UC biomarker-selected efficacy data

UC

Efficacy was generally improved in CDx positive patients compared to the total population



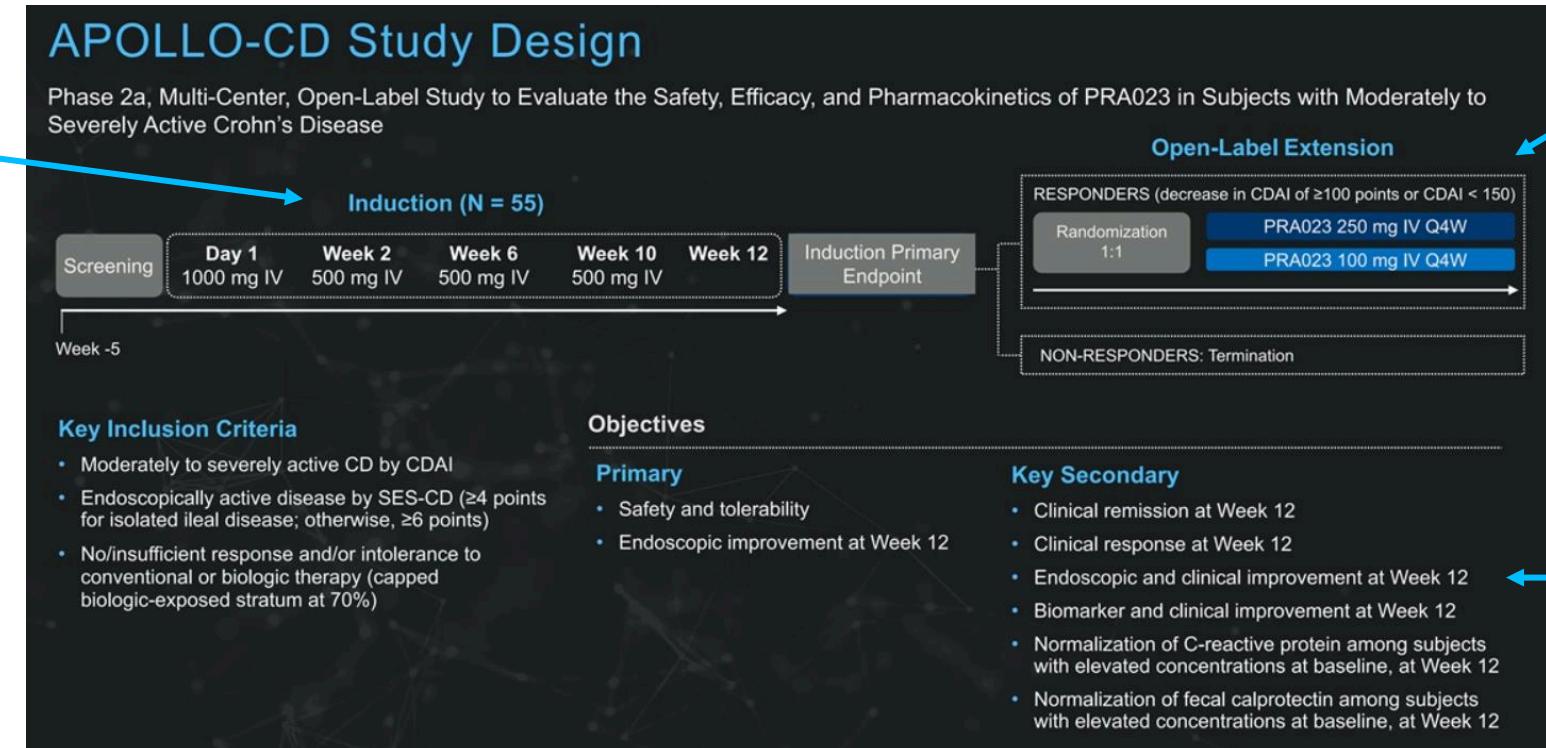
- In Cohort 2 (CDx positive patients), more patients achieved clinical remission at week 12 on tulisokibart than on placebo. Regarding secondary endpoints (see right side of figure), numerical increases were observed, although in the context of the limited sample size these were not statistically significant

# Tulisokibart (MRK): APOLLO-CD design

CD

APOLLO-CD employed an induction-maintenance design with an OLE without a placebo arm

Used historical placebo controls:  
12% endoscopic response  
16% clinical remission



OLE included responders only

Typical inclusion criteria and endpoints for moderate to severe CD

# Tulisokibart (MRK): APOLLO-CD induction baseline demographics

CD

## APOLLO-CD also enrolled a difficult-to-treat population

PRA023 (N = 55)	
Age, years, mean (SD)	39.1 (15.7)
Female, n (%)	21 (38.2%)
Weight, kg, mean (SD)	77.6 (20.6)
<b>Geographic region, n (%)</b>	
North America	33 (60%)
Eastern Europe	13 (23.6%)
Western Europe	7 (12.7%)
Rest of world (Australia)	2 (3.6%)
<b>Duration of disease, years, mean (SD)</b>	10.29 (9.27)
Extent of disease, n (%)	
Ileal	8 (14.5%)
Colonic	15 (27.3%)
Ileocolonic	32 (58.2%)
Baseline CDAI Score, mean (SD)	317.9 (67.2)
Baseline SES-CD, mean (SD)	13.4 (6.7)
Concomitant immunomodulator use, n (%)	8 (14.5%)
Concomitant corticosteroid use, n (%)	22 (40%)
<b>Number of prior exposure to biologic therapy, n (%)</b>	
0	16 (29.1%)
1	10 (18.2%)
2	10 (18.2%)
≥3	19 (34.5%)

Similar to ARTEMIS-UC, the APOLLO-CD study enrolled patients with high disease activity (extensive disease and high CDAI) and many who were refractory to ≥1 advanced therapies (70.9% with ≥1 and 52.7% with ≥2)

# Tulisokibart (MRK): APOLLO-CD maintenance safety

CD

Safety data from the OLE maintenance portion of APOLLO-CD revealed a high rate of infections, which will be an important aspect to monitor going forward

## Safety

- At week 50, adverse events (AEs) were reported in 84% and 83% of patients receiving tulisokibart 100 and 250 mg, respectively (Table 2)
- Most AEs were mild to moderate in severity, and serious AEs (SAEs) occurred in 2 patients receiving tulisokibart 100 mg and 1 patient receiving tulisokibart 250 mg
- During the OLE period, most frequent infections were urinary tract infection (16% and 11% of patients in the 100 and 250 mg groups, respectively), COVID-19 (11% of patients in each dose group), and upper respiratory tract infection (16% and 6% of patients in the 100 and 250 mg groups, respectively)

Table 2. Summary of treatment-emergent AEs during induction (week 0 to 14 before maintenance treatment) and OLE (week 14 to 50)

Treatment-emergent AEs, n (%)	Induction	OLE Tulisokibart	
	Tulisokibart (n = 55)	100 mg (n = 19)	250 mg (n = 18)
Patients with any AE	43 (78)	16 (84)	15 (83)
Any severe (grade $\geq 3$ ) AE	3 (5)	3 (16)	4 (22)
Any drug-related AE	3 (5)	3 (16)	0
AE leading to study drug discontinuation	2 (4)	4 (21)	2 (11)
Any SAE	8 (15)	2 (11)	1 (6)
Any drug-related SAE	0	0	0
Death	0	0	0
Patients with any AE of special interest			
Acute infusion reaction <sup>a</sup>	0	0	0
Peri-infusion reaction <sup>b</sup>	0	0	0
Infection and infestation <sup>c</sup>	25 (45)	12 (63)	11 (61)

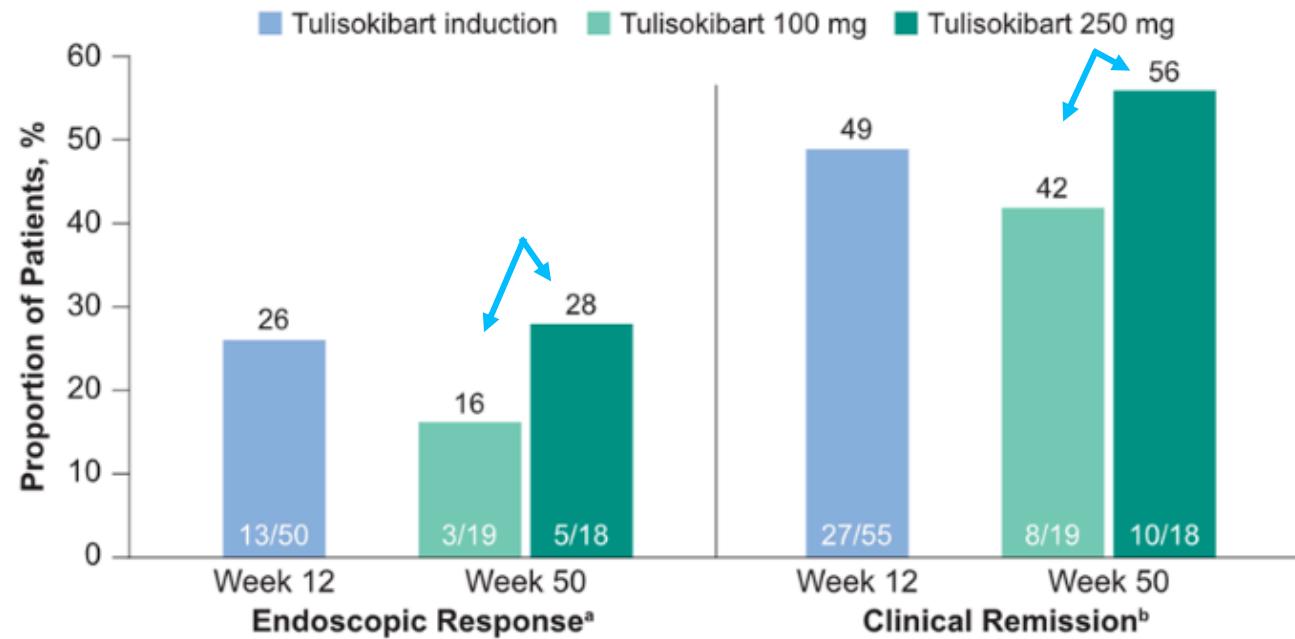
The safety profile observed in APOLLO-CD was comparatively worse, with the infections common and higher rates of SAEs (none deemed study drug-related). Although the study was conducted during the COVID-19 pandemic, it will be important to consider this signal in larger, placebo-controlled studies of TL1A inhibitors in CD and in emerging programs' data (and potential combination and bispecific applications)

# Tulisokibart (MRK): APOLLO-CD efficacy

CD

APOLLO-CD employed a typical induction design with an open-label extension

Figure 3. Endoscopic response and clinical remission at week 50



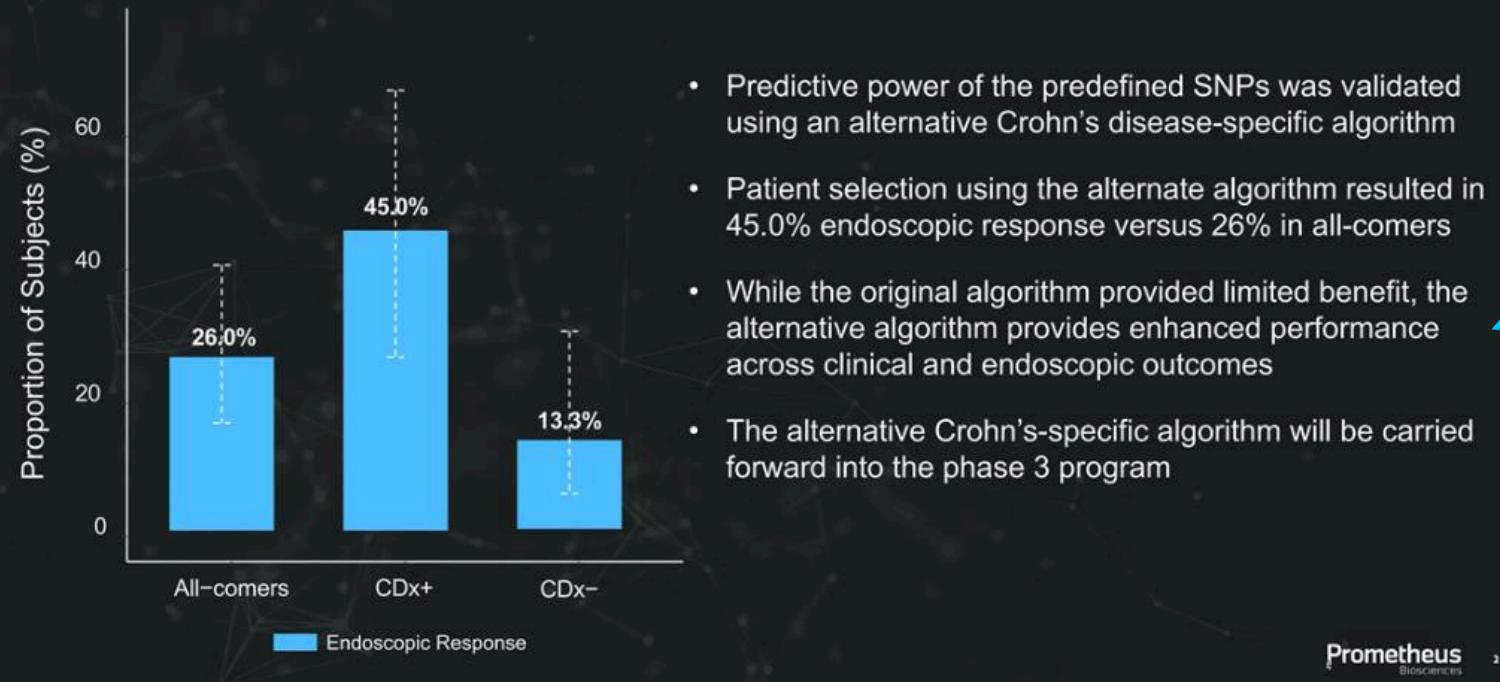
The tulisokibart OLE data are the only longer-term efficacy data published to date in CD, and overall, the data show a dose-response and compare well at this early-stage to the approved benchmarks

# Tulisokibart (MRK): APOLLO-CD biomarker efficacy

CD

Post-hoc analysis using an updated biomarker selection showed potential in CD, and the strategy is being employed in the ongoing Ph 3

## Analysis of APOLLO-CD Confirms Relevance of SNPs Used on Diagnostic Assay



An alternative biomarker-selection strategy helped segregate responses in post-hoc analysis of the APOLLO-CD data, and a diagnostic assay is being employed in the ARES-CD Ph 3

# RG6631 (RHHBY): Overview

## RHHBY is close behind following its acquisition of RG6631 from ROIV (OP, Risinger)

### RG6631 program background

- RG6631 is fully human mAb
  - Binds TL1A trimers preferentially
  - SC formulation being tested
- RHHBY received RG6631 from its acquisition of Telavant in 2023
  - Telavant was the first to publish longer-term efficacy data for a TL1A program when it announced UC data from the maintenance portion of Ph 2b TUSCANY-2 study in June 2023
  - Telavant initiated the Ph 2 TAHOE study evaluating the program in CD July 2023 shortly before the acquisition

### Data highlights

- TUSCANY-2 was a Ph 2b study that demonstrated the efficacy and safety of RG6631 in both the induction and maintenance settings in UC
  - biomarker-selected patients performed numerically better than unselected across Week 14 endpoints
- Notably the study used a treat-through design, so direct comparison with tulisokibart is limited
- To-date, no Ph 2 CD data have been reported

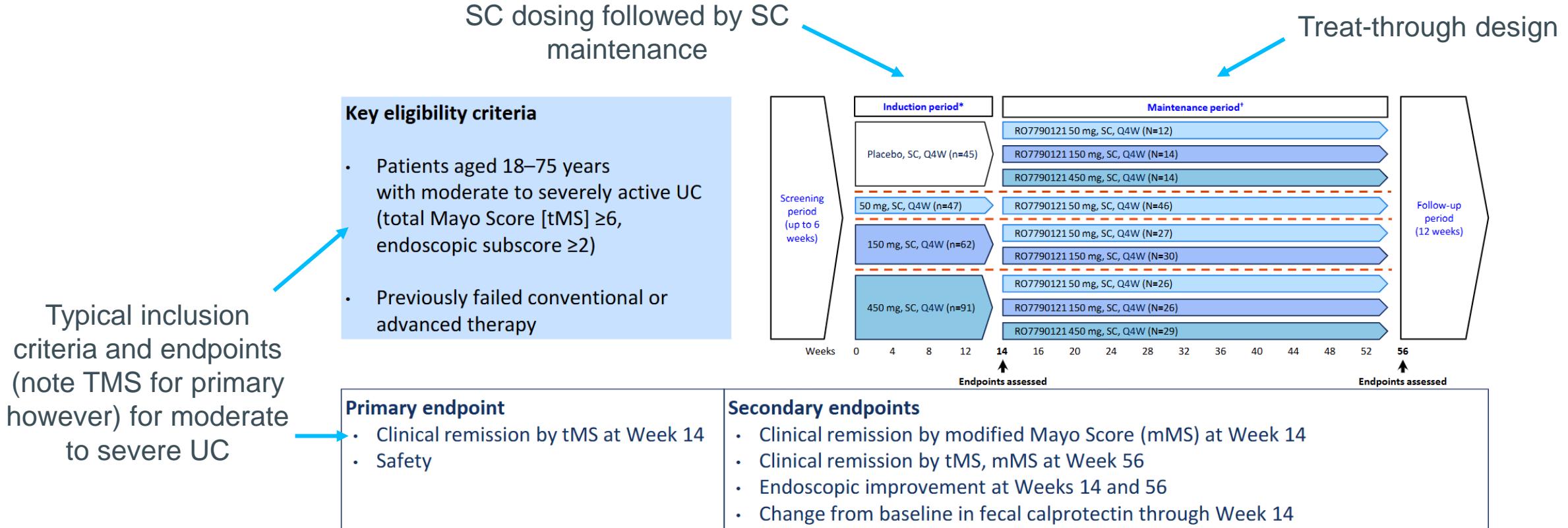
### Next up?

- RG6631 is currently being evaluated in a Ph 3 program in UC (AMETRINE-1/2), the latter evaluating IV induction up to week 12, while another uses a treat-through design with IV induction followed by SC maintenance up to week 52
  - Both AMETRINE-1/2 have primary completion dates of Jun. 2027
- The Ph 3 program in CD is expected to initiate 1Q25
- RHHBY plans to initiate a Ph 2b study in atopic dermatitis and a Ph 1b study in MASH in 1Q25

# RG6631 (RHHBY): TUSCANY-2 design

UC

TUSCANY-2 used a treat-through design and evaluated all patients for biomarker positivity



Note: prospective biomarker testing was performed based on previous Ph 2a TUSCANY results, and 60% were biomarker positive

# RG6631 (RHHBY): TUSCANY-2 baseline characteristics

UC

**TUSCANY-2 enrolled a relatively less refractory population compared to ARTEMIS-UC**

	Placebo (n=45)	50 mg (n=47)	150 mg (n=62)	450 mg (n=91)	Overall (N=245)
<b>Age (yr), mean (SD)</b>	39.9 (12.9)	37.8 (13.9)	42.2 (13.0)	41.6 (13.8)	40.7 (13.5)
<b>Sex, female, n (%)</b>	21 (46.7)	19 (40.4)	23 (37.1)	36 (39.6)	99 (40.4)
<b>BMI (kg/m<sup>2</sup>), mean (SD)</b>	24.4 (5.0)	23.6 (5.4)	24.7 (5.2)	24.6 (5.1)	24.4 (5.1)
<b>Disease duration (yr), mean (SD)</b>	7.6 (7.3)	6.8 (7.7)	7.3 (7.4)	7.5 (6.8)	7.3 (7.2)
<b>Pancolitis, n (%)</b>	19 (42.2)	16 (34.0)	23 (37.1)	38 (41.8)	96 (39.2)
<b>mMS, median (IQR)*</b>	7.0 (6.0–8.0)	6.0 (5.0–7.0)	7.0 (6.0–8.0)	7.0 (6.0–8.0)	7.0 (6.0–8.0)
<b>Endoscopy subscore, n (%)</b>					
2	22 (48.9)	28 (59.6)	23 (37.1)	44 (48.4)	117 (47.8)
3	23 (51.1)	19 (40.4)	39 (62.9)	47 (51.6)	128 (52.2)
<b>Fecal calprotectin (µg/g), median (IQR)</b>	1560.0 (927.0–4,497.0)	1354.0 (488.0–2,299.0)	2112.0 (922.0–3,972.0)	1349.5 (702.0–2,730.0)	1511.0 (738.0–3,152.0)
<b>Steroid use at baseline, n (%)</b>	11 (24.4)	19 (40.4)	32 (51.6)	41 (45.1)	103 (42.0)
<b>Number of prior advanced therapy failures†, n (%)</b>					
0	28 (62.2)	28 (59.6)	41 (66.1)	52 (57.1)	149 (60.8)
1	6 (13.3)	7 (14.9)	10 (16.1)	14 (15.4)	37 (15.1)
2	4 (8.9)	5 (10.6)	4 (6.5)	15 (16.5)	28 (11.4)
≥3	7 (15.5)	7 (14.9)	7 (11.3)	10 (11.0)	31 (12.6)

Overall, TUSCANY-2 enrolled a less refractory population compared to ARTEMIS-UC, with lower rates of advanced therapy use and fewer patients with endoscopic subscores of 3

# RG6631 (RHHBY): TUSCANY-2 safety

UC

## RG6631 appeared safe and well-tolerated throughout induction and maintenance

	Induction period*				
	Placebo (N=45)	50 mg (N=47)	150 mg (N=62)	450 mg (N=91)	Total (N=245)
<b>With any adverse event, n (%)</b>	25 (55.6)	16 (34.0)	28 (45.2)	48 (52.7)	117 (47.8)
Participants with serious adverse events	4 (8.9)	3 (6.4)	0 (0.0)	3 (3.3)	10 (4.1)
Participants discontinued study drug due to adverse events	3 (6.7)	1 (2.1)	1 (1.6)	1 (1.1)	6 (2.4)
<b>Participants with treatment-related adverse events, n (%)</b>	4 (8.9)	6 (12.8)	9 (14.5)	13 (14.3)	32 (13.1)
Participants with serious treatment-related adverse events	1 (2.2)	0 (0.0)	0 (0.0)	1 (1.1)	2 (0.8)
	Maintenance period†				
	N/A	50 mg → 50 mg (N=46)	150 mg → 150 mg (N=30)	450 mg → 450mg (N=29)	Total maintenance population (N=224)
<b>With any adverse event, n (%)</b>		28 (60.9)	15 (50.0)	19 (65.5)	132 (58.9)
Participants with serious adverse events		4 (8.7)	0 (0.0)	4 (13.8)	12 (5.4)
Participants discontinued study drug due to adverse events		3 (6.5)	0	1 (3.4)	11 (4.9)
<b>With treatment-related adverse events, n (%)</b>		5 (10.9)	2 (6.7)	2 (6.9)	30 (13.4)
Participants with serious treatment-related adverse events		0	0	1 (3.4)	1 (0.4)

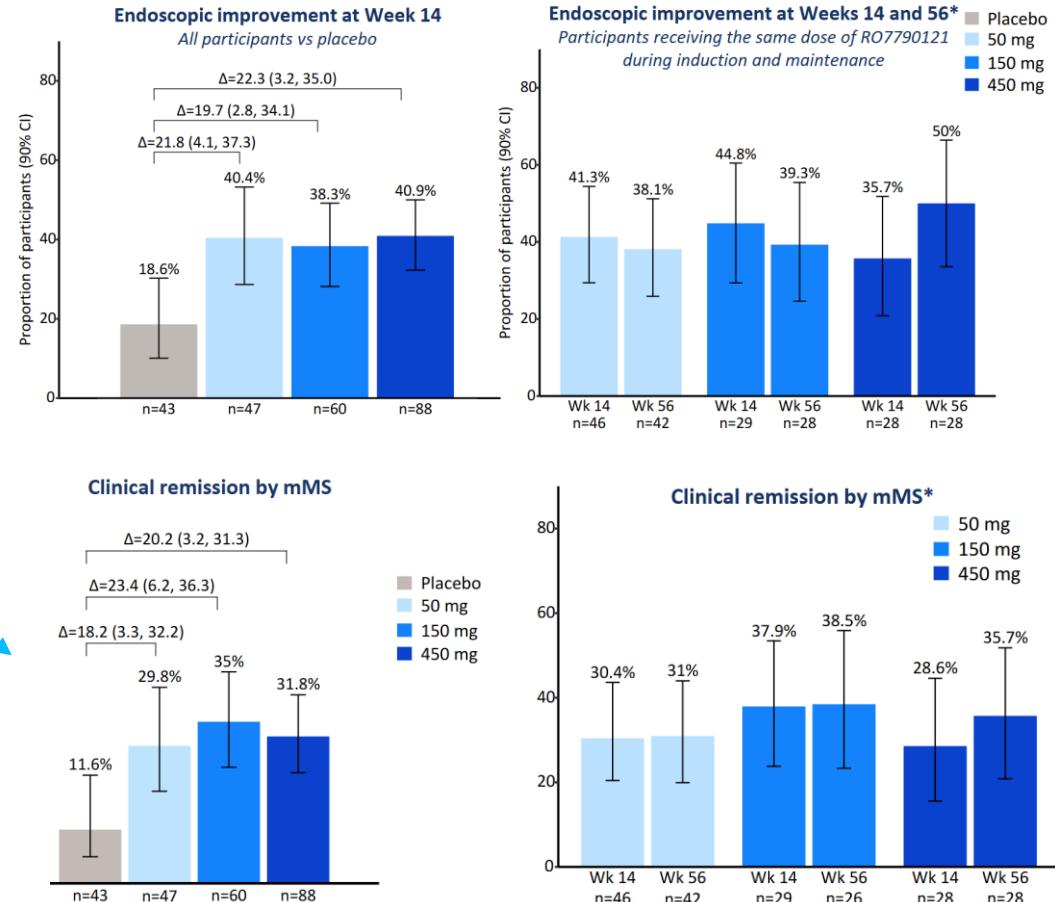
- RG6631 also demonstrated a relatively clean safety profile in both induction and maintenance
- Another notable datapoint for future consideration is that in the initial Ph 2a TUSCANY study (run by PFE), 82% of patients tested positive for anti-drug antibodies (ADAs) and 10% for neutralizing antibodies. This was not deemed to have affected safety. To our knowledge, these data have not been disclosed for TUSCANY-2

# RG6631 (RHHBY): TUSCANY-2 efficacy

UC

## Treatment with RG6631 also resulted in notable improvements in relevant efficacy endpoints

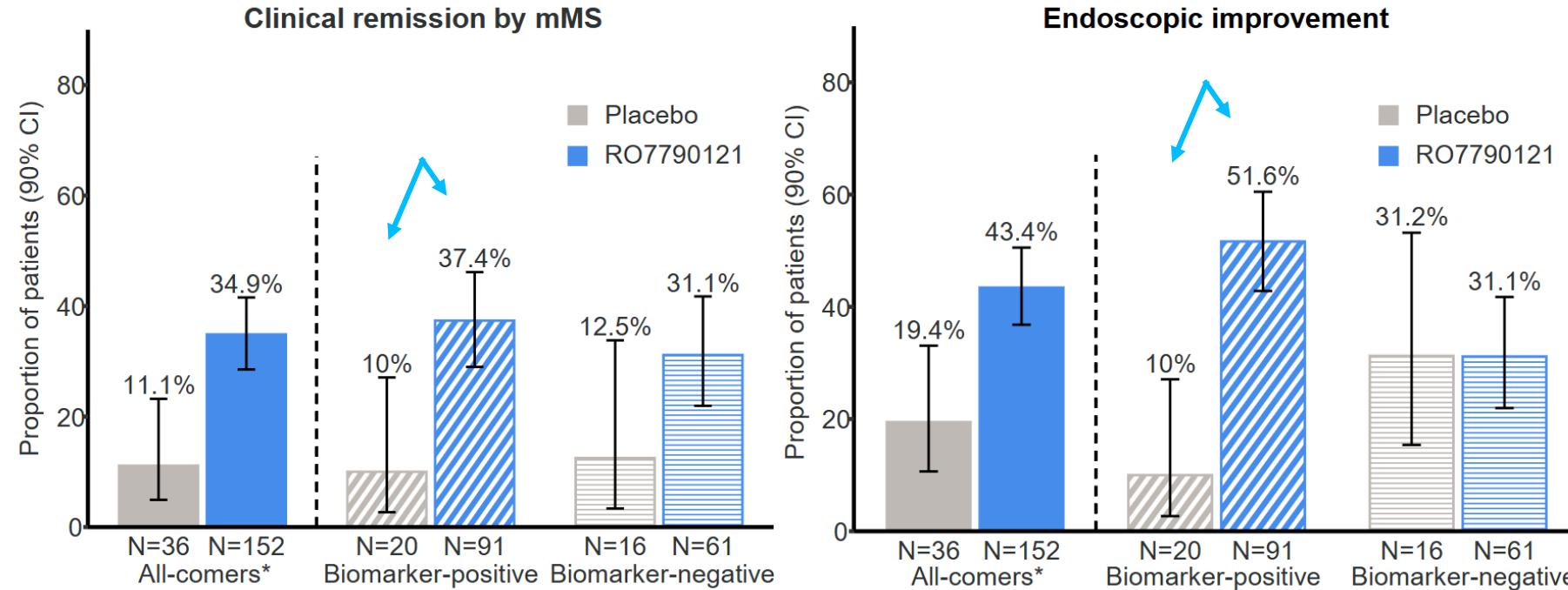
- RG6631 demonstrated meaningful, but not statistically significant, improvements on a number of important endpoints, including clinical remission by mMS and endoscopic improvements at all three doses tested (though no obvious dose response was observed)
- Early improvements in symptomatic remission compared to placebo were also reported and sustained through induction
- Improvements were maintained in patients observed during the OLE maintenance portion



# RG6631 (RHHBY): TUSCANY-2 biomarker efficacy

UC

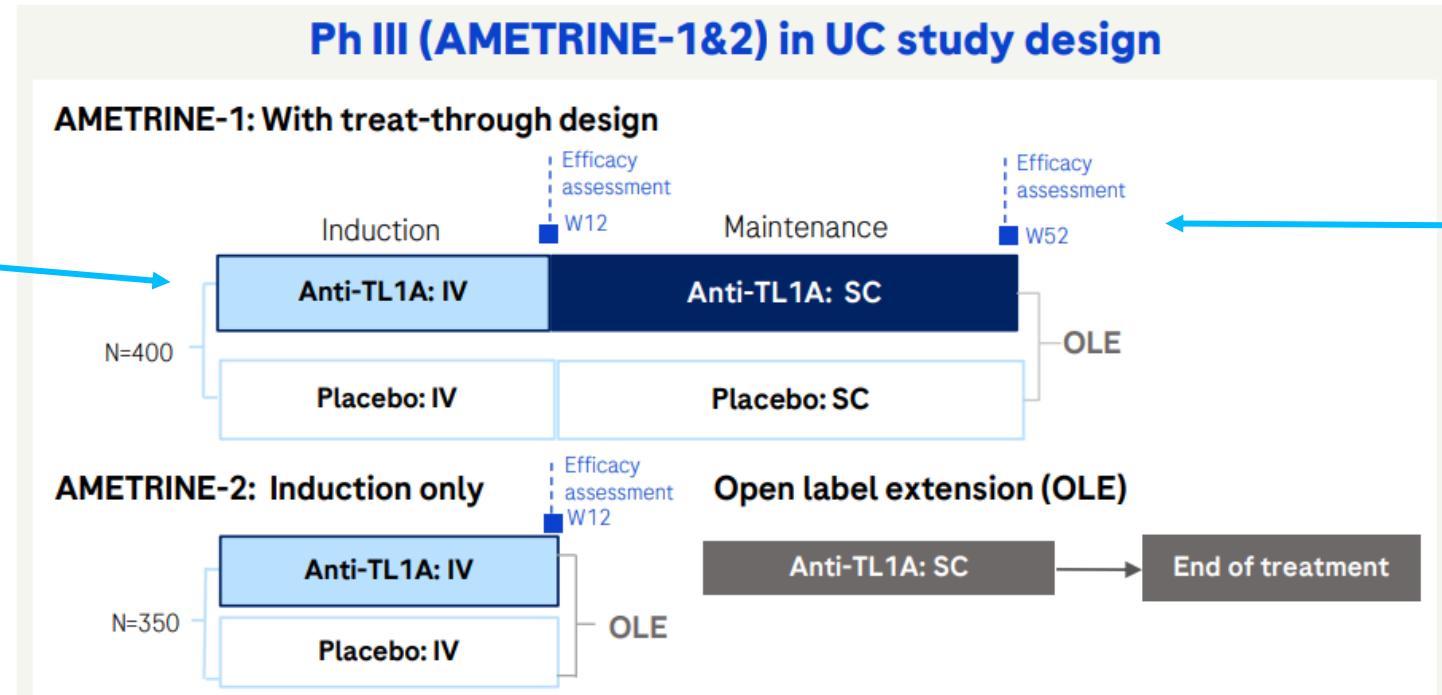
The biomarker test revealed numerical benefit, with endoscopic improvement results particularly dramatic



At week 14, numerically greater efficacy was observed in biomarker-positive participants relative to all-comer participants- this was particularly pronounced on endoscopic improvement

The AMETRINE program evaluates RG6631 in two induction studies, with AMETRINE-1 using a treat-through design for a maintenance portion

IV induction followed by SC maintenance  
(different from SC->SC in TUSCANY-2)



# Duvakitug (SAN FP / TEVA): Overview

**SAN FP and TEVA are partnering on Duvakitug, with recent data generating excitement, although dosing frequency could be a headwind**

## Duvakitug program background

- SAN FP and TEVA are collaborating (see terms, [HERE](#)) on duvakitug, a fully humanized IgG1 mAb targeting TL1A, which was being evaluated in the Ph 2b RELIEVE-UCCD study at the time of the deal
  - Binds TL1A trimers preferentially
- The companies reported initial data for the program in Dec. 2024, including the first placebo-controlled CD data for the class, with additional detail presented at ECCO 2025

## Data highlights

- RELIEVE-UCCD was a basket study that used a single protocol to evaluate UC and CD patients
- Duvakitug efficacy was encouraging in UC and CD, although the UC cohort enrolled patients with a potentially less severe phenotype than others in the class. Safety and tolerability were in line with others in the class. A low rate of ADAs (3-5%) were observed
- Duvakitug efficacy appears in line with the class, although uses a more frequent Q2W dosing schedule

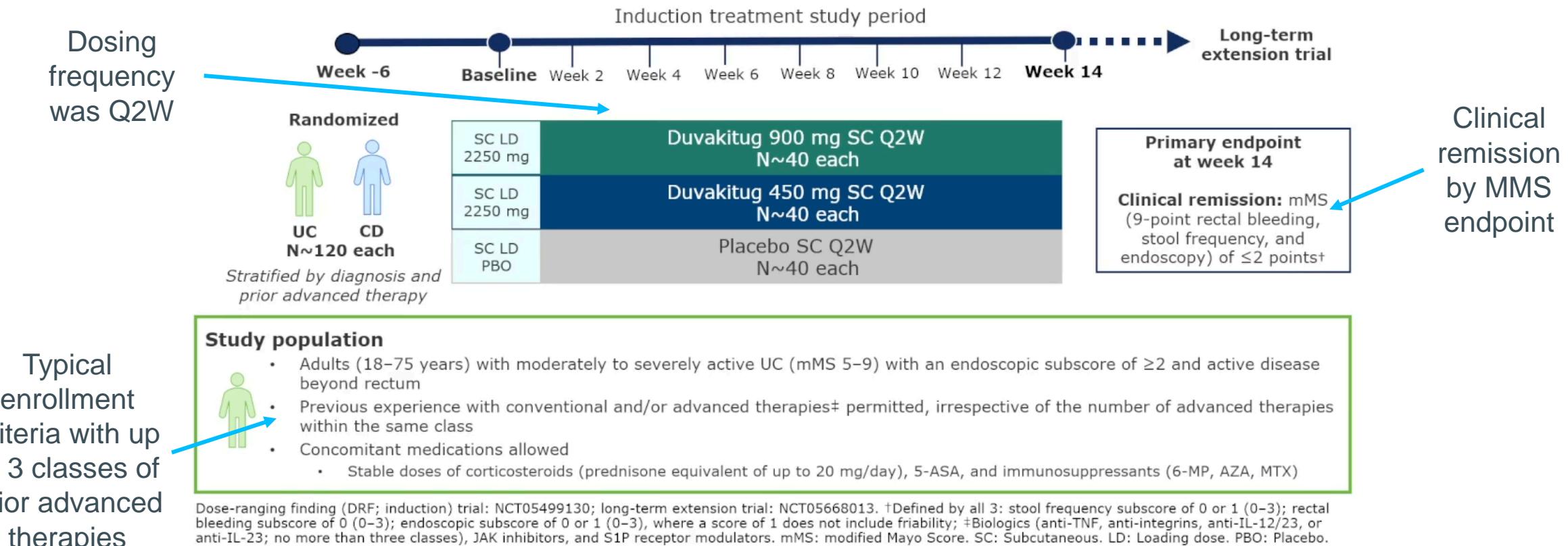
## Next up?

- SAN FP and TEVA are planning Ph 3 programs in both UC and CD, with initiation planned for 2H25

# Duvakitug (SAN FP / TEVA): RELIEVE UCCD design, UC cohort

UC

RELIEVE UCCD employed a basket design, allowing both UC and CD patients to be enrolled under a single Ph 2 protocol



# Duvakitug (SAN FP / TEVA): RELIEVE-UCCD, UC baseline characteristics

UC

The UC cohort enrolled patients with relatively less severe disease than other TL1A trials

Table 1: Demographics and baseline characteristics

	Placebo (N=44)	Duvakitug 450 mg (N=47)	Duvakitug 900 mg (N=46)	Overall (N=137)
Age, years, mean (SD)	42.2 (13.1)	38.7 (13.0)	42.1 (13.2)	41.0 (13.1)
Male, n (%)	30 (68)	29 (62)	27 (59)	86 (63)
Weight, kg, mean (SD)	80.1 (20.9)	77.7 (20.1)	74.8 (13.2)	77.5 (18.3)
BMI, kg/m <sup>2</sup> , mean (SD)	26.4 (6.3)	25.4 (5.7)	24.8 (3.9)	25.6 (5.4)
Geographic region, n (%)				
North America	3 (7)	4 (9)	2 (4)	9 (7)
Eastern Europe	37 (84)	41 (87)	39 (85)	117 (85)
Poland	18 (41)	28 (60)	20 (43)	66 (48)
Other	19 (43)	13 (28)	19 (41)	51 (37)
Western Europe	2 (5)	1 (2)	4 (9)	7 (5)
Japan	1 (2)	1 (2)	1 (2)	3 (2)
Israel	1 (2)	0	0	1 (<1)
Duration of disease, years, mean (SD)	6.2 (4.2)	9.0 (6.2)	7.8 (6.0)	7.7 (5.6)
Modified Mayo score, mean (SD)	6.8 (1.2)	6.6 (1.2)	6.8 (1.1)	6.8 (1.1)
Mayo endoscopy score, n (%)				
2	17 (39)	24 (51)	19 (41)	60 (44)
3	27 (61)	23 (49)	27 (59)	77 (56)
Concomitant immunomodulator use, n (%)	5 (11)	4 (9)	4 (9)	13 (9)
Concomitant corticosteroid use, n (%)	15 (34)	22 (47)	20 (43)	57 (42)
Prior advanced therapies, n (%)				
Including investigational drugs	17 (39)	19 (40)	18 (39)	54 (39)
Excluding investigational drugs	15 (34)	14 (30)	14 (30)	43 (31)
Prior approved advanced therapies, n (%)				
0	29 (66)	33 (70)	32 (70)	94 (69)
1	11 (25)	10 (21)	6 (13)	27 (20)
2	1 (2)	2 (4)	3 (7)	6 (4)
>3	3 (7)	2 (4)	5 (11)	10 (7)

Advanced therapies include approved therapies: biologics (TNF inhibitors, integrin inhibitors, IL-12/23 inhibitors or anti-IL-23), JAK inhibitors and S1P receptor modulators. Drugs currently in development for IBD are included in the investigational drugs category. Percentages may not add up to 100 due to rounding.

99% of patients completed the trial, with highest discontinuation rate in the placebo arm (11% vs. 0% [450 mg] and 2% [900 mg])

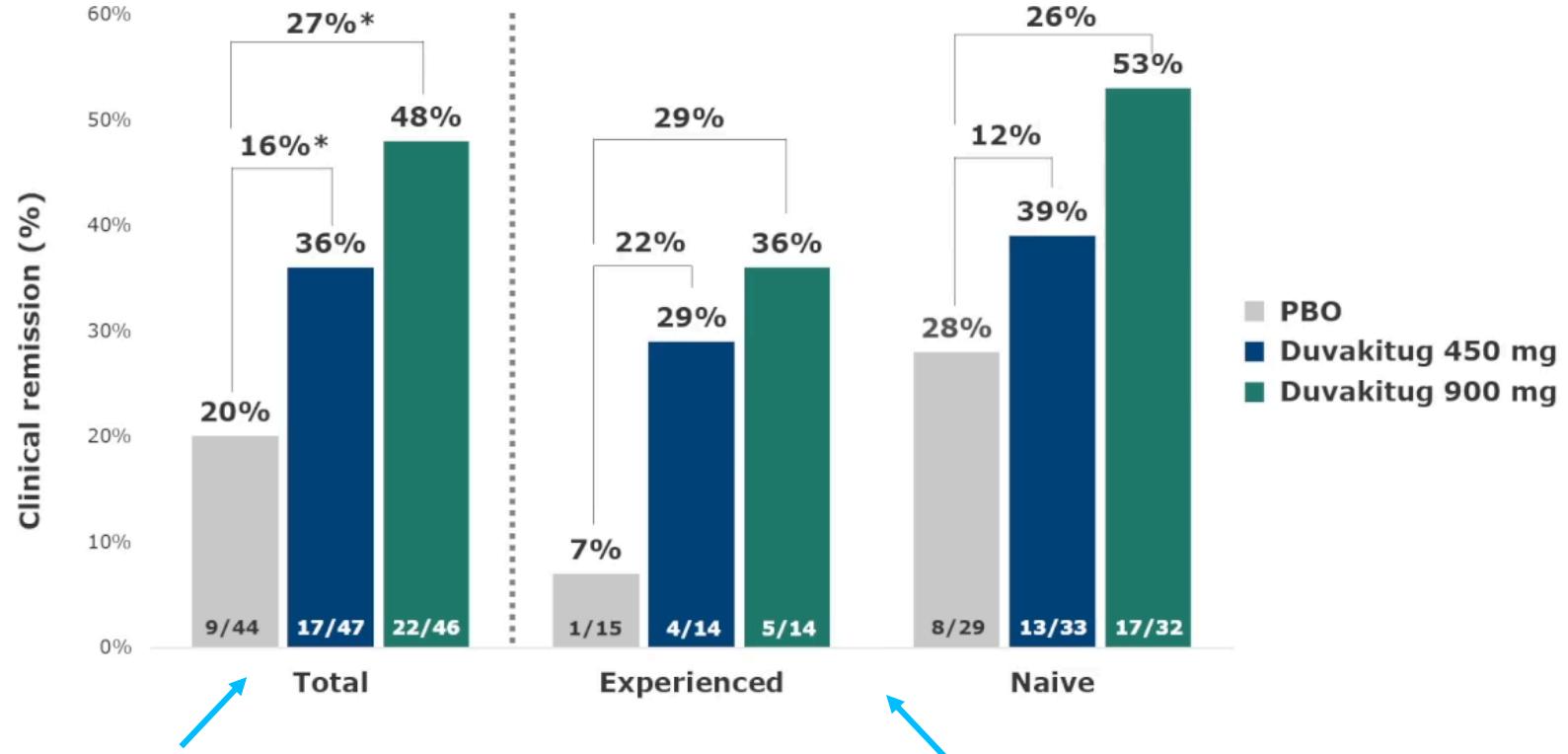
Enrollment was heavily skewed towards Poland

The majority of patients had severe disease (by endoscopy), however many had seen fewer advanced therapies relative to other trials

# Duvakitug (SAN FP / TEVA): RELIEVE-UCCD, UC efficacy

UC

However, efficacy was pronounced across both biologic naïve and experienced patients



Both doses achieved statistically significant rates of clinical remission compared to placebo. Clinical response and endoscopic endpoints were also numerically improved with duvakinug (not shown)

Encouragingly, efficacy was observed in both biologic naïve and experienced patients

# Duvakitug (SAN FP / TEVA): RELIEVE-UCCD, UC safety

UC

Although limited by follow-up, safety appears favorable at this early timepoint

Category, n (%)	Placebo N=44	Duvakitug 450 mg N=47	Duvakitug 900 mg N=46
<b>Participants with any treatment-emergent AE</b>	<b>23 (52)</b>	<b>23 (49)</b>	<b>20 (43)</b>
Treatment-related AEs	2 (5)	3 (6)	6 (13)
Serious AEs <sup>†</sup>	1 (2)	0	1 (2)
AEs leading to discontinuation <sup>‡</sup>	2 (5)	0	1 (2)
Death	0	0	0
Participants with AESI <sup>*§</sup>	2 (5)	2 (4)	2 (4)

- No dose-dependent effect and no trends were observed across safety categories
- AESIs were non-serious and transient
- No clinically meaningful changes in laboratory parameters, vital signs, or ECGs

Percentages for AEs are based on N of the treatment groups.

<sup>†</sup>PBO: hemorrhage intracranial; duvakinug 900 mg: noninfective oophoritis.

<sup>‡</sup>PBO: colitis ulcerative, hemorrhage intracranial; duvakinug 900 mg: neutropenia.

<sup>\*</sup>AESIs were defined as systemic severe reactions, opportunistic or severe and/or serious infections, malignancies, liver injury, severe haematology abnormalities.

<sup>§</sup>PBO: erysipelas, anaemia; duvakinug 450 mg: alanine aminotransferase increased, oral herpes; duvakinug 900 mg: skin papilloma, neutropenia.

AE: adverse event; AESI: adverse event of special interest.

Presented at ECCO'25 Congress

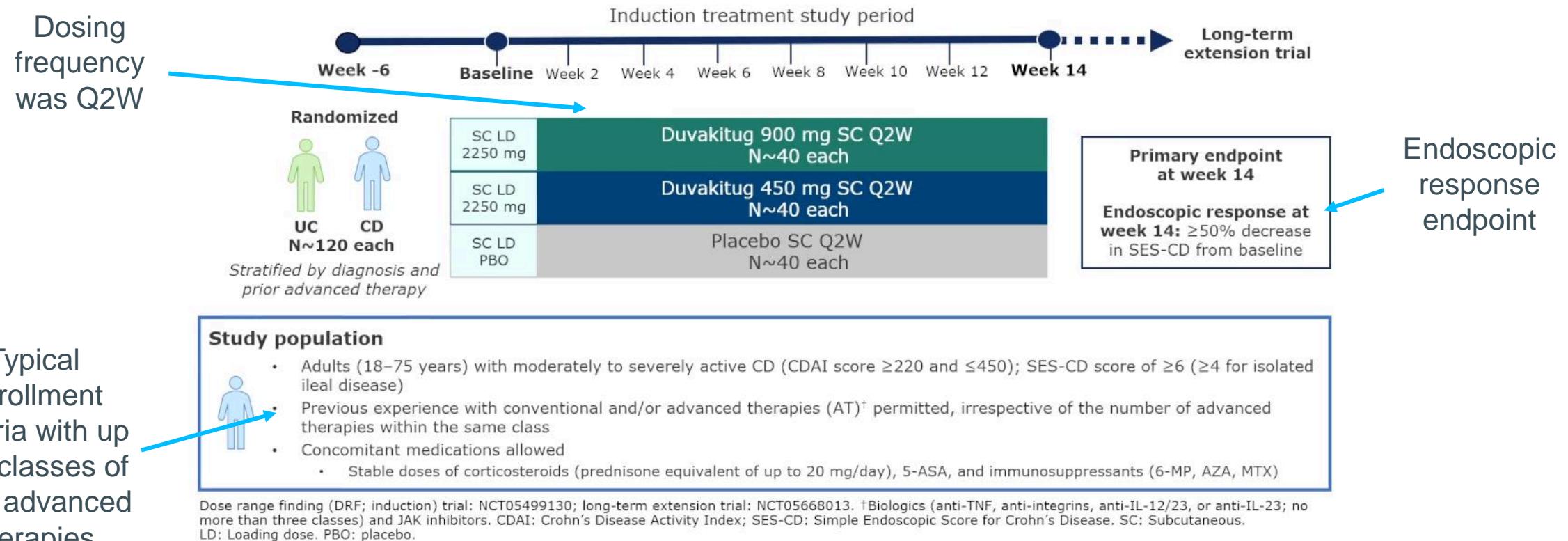
Duvakinug demonstrated a favorable safety profile, with AEs, including infections, well balanced between placebo and treatment arms.

“we actually have seen ADA rates of about 3% to 5%. So, that's a very low rate at this point. In fact, we had seen below 10% in our first asthma study, but 3% to 5% was very encouraging to see”

# Duvakitug (SAN FP / TEVA): RELIEVE UCCD design, CD cohort

CD

RELIEVE UCCD employed a basket design, allowing both UC and CD patients to be enrolled under a single Ph 2 protocol



# Duvakitug (SAN FP / TEVA): RELIEVE-UCCD, CD baseline characteristics

CD

The CD cohort, in contrast, enrolled patients with a relatively more severe phenotype

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

85% of patients completed the trial, with highest discontinuation rate in the placebo and 450 mg arms (both 20% vs. 7% [900 mg])

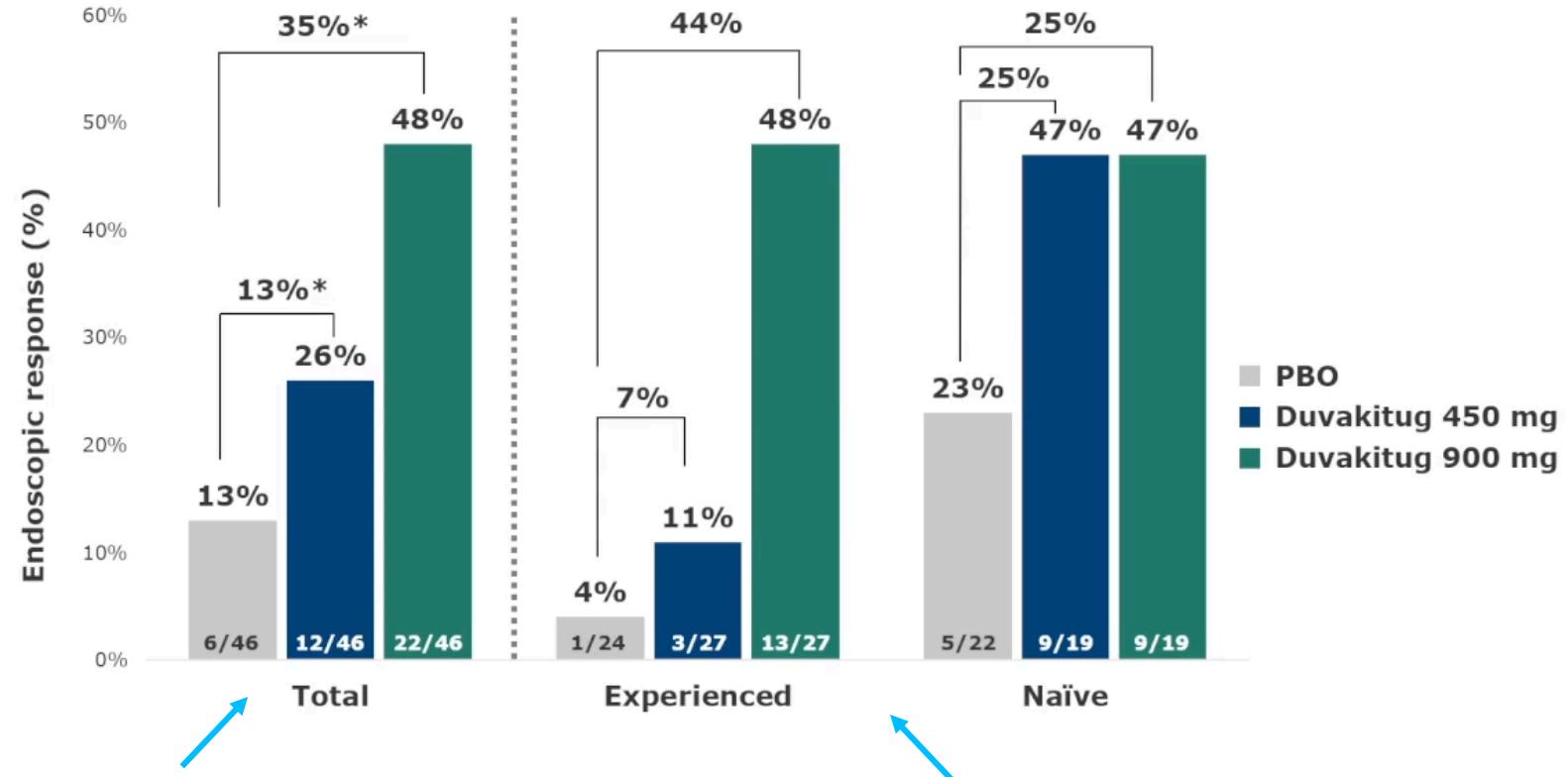
Enrollment predominantly in Eastern Europe

The majority of patients had severe disease (by CDAI), with over half advanced therapy experienced

# Duvakitug (SAN FP / TEVA): RELIEVE-UCCD, CD efficacy

CD

Again, efficacy was demonstrated across both biologic naïve and experienced patients



Both doses achieved statistically significant rates of endoscopic improvement compared to placebo. Clinical response and endoscopic/histologic endpoints were also numerically improved with duvakinug (not shown)

Endoscopic improvement was observed in almost half of advanced therapy experienced patients at the highest dose

# Duvakitug (SAN FP / TEVA): RELIEVE-UCCD, CD safety

CD

Safety data in the CD cohort was similar to those reported in the UC cohort

Category, n (%)	Placebo N=46	Duvakitug 450 mg N=46	Duvakitug 900 mg N=46
<b>Participants with any treatment-emergent AE</b>	<b>22 (48)</b>	<b>31 (67)</b>	<b>20 (43)</b>
Treatment-related AEs	2 (4)	6 (13)	6 (13)
Serious AEs	5 (11)	6 (13)	1 (2)
AEs leading to discontinuation	1 (2)	4 (9)	1 (2)
Death	0	0	0
<b>Participants with any AESI*</b>	<b>4 (9)</b>	<b>5 (11)</b>	<b>3 (7)</b>

- No dose-dependent effect and no trends were observed across safety categories
- AESIs were mostly non-serious and transient
- No clinically meaningful changes in laboratory parameters, vital signs, or ECGs

Duvakitug demonstrated a favorable safety profile, with AEs, including infections, well balanced between placebo and treatment arms.

“we actually have seen ADA rates of about 3% to 5%. So, that's a very low rate at this point. In fact, we had seen below 10% in our first asthma study, but 3% to 5% was very encouraging to see”

# Characteristics of emerging TL1A programs

	<b>FG-M701</b>	<b>SPY002 (SYRE)</b>	<b>XmAb942 (XNCR)</b>	<b>ABS-101 (ABSI)</b>
<b>Company</b>	ABBV/FutureGen	SYRE	XNCR	ABSI
<b>Overview</b>	Fully human mAb	Consists of two lead candidates, fully human IgG1 mAbs	Human IgG1 mAb	mAb developed with AI-driven de novo design
<b>Binding characteristics</b>	-	Bind TL1A monomers and trimers with sub-nanomolar potency	Bind TL1A trimers with sub-nanomolar potency	Binds both TL1A monomers and trimers with sub-nanomolar potency
<b>Projected dosing schedule and route</b>	“designed to have less frequent dosing compared to other TL1As in development (first-generation) and will be evaluated in combination with Skyrizi”	Q12W (quarterly) to twice-annual SC injection via a single autoinjector	Q8-12W dosing with a developability profile designed for high-concentration formulation suitable for SC injection	Q8-Q12W dosing with a developability profile designed for a high-concentration formulation (200mg/mL) suitable for SC injection

Source: ABBV 7/25/24 Transcript via FactSet; SYRE Corporate Presentation 1/2025 ([LINK](#)); XNCR XmAb942 UEG 2024 ([LINK](#)); XNCR Corporate Presentation 1/2024 ([LINK](#)); ABSI ABS-101 Poster ([LINK](#)); ABSI 1/2025 Healthcare Conference Presentation ([LINK](#)); ABSI 2024 R&D Day Presentation ([LINK](#))

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# FG-M701 (ABBV/FutureGen)

**ABBV in-licensed its TL1A from China and has hinted at plans to develop it using a combination approach**

## FG-M701 program background

- FG-M701 is a fully-human TL1A-targeting mAb with half-life extension
  - Per the press release “FG-M701 is uniquely engineered with potential best-in-class functional characteristics compared to first-generation TL1A antibodies with the goal to drive greater efficacy and less frequent dosing as a therapy for IBD”
- ABBV acquired a global license for the program from FutureGen in 2024 for \$150M upfront and up to \$1.56B in milestones
- ABBV also acquired a preclinical stage oral TL1A inhibitor when it acquired Nimble Therapeutics for \$200M

## Next up?

- ABBV has committed to evaluating FG-M701 in combination with Skyrizi as part of a broader platform study

“Mechanisms like TL1A, we think, are going to be important, **especially from a combination approach**, which we have one internally. We think the ulcerative colitis data are encouraging, but from a monotherapy standpoint, not differentiated, especially when you look at the Skyrizi data that I mentioned earlier and Rinvoq. And then in Crohn's, something like TL1A, we think it really does need a combo.”

—Roopal Thakkar, ABBV CSO on 10.30.24

# SPY002 (SYRE)

**SYRE is evaluating two TL1A programs, with plans to advance one into combination development**

## SPY002 program background

- Fully human IgG1 mAbs with HLE and SC enabled formulation (two molecules, lead selection in 2Q25)
- Both molecules bind to the distinct epitopes on a single TL1A monomer
- Preclinical data for both SPY002 molecules demonstrate picomolar potency and potential for quarterly or twice-yearly dosing (note: SYRE aims to develop the program in combination)

## Next up?

- Interim PK, PD, and safety data from healthy volunteers for both SPY002 molecules, which will inform lead selection, anticipated in the 2Q25

# Emerging TL1A players, with potentially improved profiles, are in early-stage development

## Other companies are developing potentially improved TL1A programs

### XmAb942 (XNCR)

- Human IgG1 mAb with HLE (potentially enabling quarterly dosing) and an SC enabled formulation
- XmAb942 binds to trimeric TL1A, and preclinical experiments demonstrate superior PK to first-generation anti-TL1A programs (SAN FP/TEVA, RHHBY, and MRK)
- The first subject was dosed with XmAb942 in a Ph 1 healthy volunteer trial in 4Q24
  - XNCR are also developing a TL1A x IL-23 bispecific, with lead selection expected in 2025

Next up?

- Initial SAD data in 1H25

### ABS-101 (ABSI)

- A TL1A-targeting mAb developed with AI-driven de novo design
- ABS-101 exhibits high affinity to both TL1A monomer and trimer (single-digit picomolar), outperforming first-generation competitors (SAN FP/TEVA, RHHBY, and MRK) in binding and functional assays
- Differentiation includes SC enabled formulation, potential efficacy benefits via monomer binding, HLE (potentially enabling quarterly dosing), and lower immunogenicity risk through targeted epitope selection

Next up?

- Ph 1 trial initiating 1H25 with interim data in 2H25

# SL-325 (STTK)

## SL-325 is a first-in-class program targeting DR3, the other side of the axis

### SL-325 program background

- SL-325 is a monoclonal antibody targeting DR3, designed to block TL1A-DR3 signaling in inflammatory diseases
- Unlike TL1A inhibitors, SL-325 directly interferes with DR3, which is constitutively expressed in both inflamed and non-inflamed tissue
- The program builds on strong preclinical validation suggesting DR3 inhibition may provide broader suppression of TL1A-driven inflammation (likened to targeting PD-1 vs. PD-L1)
- We cover the company and program in additional depth in our accompanying initiation: LINK

### Preclinical highlights

- SL-325 binds DR3 with 1.3 picomolar affinity and does not cross-bind the decoy receptor (DcR3), preserving native TL1A-DcR3 interactions
- Demonstrates superior potency in in vitro assays compared to first gen TL1A inhibitors
- Blocks TL1A-driven cytokine release and immune cell activation without receptor internalization, potentially avoiding immune complex formation seen with TL1A inhibitors

### Next up?

- IND filing planned for mid-2025, with FIH trials set to begin in 2H25
- Initial SAD data expected by YE25, with full Ph 1 readout in 2Q26

## Emerging Targets

- **New targets aim to expand IBD treatment:** beyond TL1A, novel approaches are being explored to address gaps in efficacy and durability
- **Obefazimod leads the pack:** ABVX's miRNA-124 targeting drug is in Ph 3 in UC, with topline data expected in 3Q25. If data recapitulate Ph 2 results, obefazimod could bring a new effective and safe oral option to the treatment paradigm
- **Lusvertikimab data have also been encouraging:** OSE's IL-7 targeting program has demonstrated encouraging safety and efficacy in a Ph 2 study in UC
- **Diverse mechanisms in development:** numerous other targets are being explored

# Emerging targets quick hits

Background	+/- considerations
<ul style="list-style-type: none"><li>The robust IBD market opportunity and enduring unmet medical need has spurred the development of numerous emerging development candidates with differentiated targets and mechanisms of action</li><li>One prominent agent among this new wave of therapeutics is ABVX's obefazimod<ul style="list-style-type: none"><li>Obefazimod is a first-in-class oral small molecule designed to upregulate miR-124 and suppress immune cell-mediated intestinal inflammation</li><li>Topline induction data from the Phase 3 ABTECT study of obe in UC are expected in 3Q25</li><li>Topline induction data from the Phase 2b ENHANCE-CD study are expected in 2H26</li></ul></li><li>OSE's lusvertikimab targets IL-7R, which is upstream of many inflammatory pathways in IBD, and the company recently presented encouraging Ph 2 UC data at ECCO 2025</li></ul>	<ul style="list-style-type: none"><li>Obefazimod has produced highly encouraging data, and could provide another oral option for both treatment naïve and/or refractory patients</li><li>There remains significant commercial headroom for novel agents given the enduring unmet medical need in IBD</li><li>Orthogonal mechanisms may enable additional combination regimens or novel sequencing</li><li>Novel targets like IL-7R, IL-1, TYK2, PSGL-1, ALK5 and others may provide additional options for patients</li></ul> <ul style="list-style-type: none"><li>Enrolling placebo-controlled monotherapy studies is increasingly challenging given the competitive landscape</li><li>As new entrants and clinical assets demonstrate superior clinical profiles, the efficacy bar for monotherapy treatments is increasing</li><li>The launch of additional generic/biosimilar options may lead to access and formulary headwinds for novel agents</li></ul>

# Companies are interrogating unique targets for differentiation in IBD

## Programs\* against a variety of targets implicated in IBD are in development

Drug	Company	Molecule	ROA	Target	UC	Status	CD
Etrasimod	PFE	small molecule	Oral	S1PR	Approved		III (CULTIVATE)
Tulisokibart	MRK	biologic	IV/SC	TL1A	III		III
RTV-3101	RHHBY	biologic	IV/SC	TL1A	III		II
Obefazimod	ABVX	small molecule	Oral	miR-124	III		II
Omilancor	Nimmune	small molecule	Oral	LANCL2	III		II
MORF-057	LLY	small molecule	Oral	$\alpha 4\beta 7$	II		II
TEV-48574	SAN FP / TEVA	biologic	SC	TL1A	II		II
Rituximab	PFE	small molecule	Oral	JAK3	II		II
ABBV-113	ABBV	small molecule	Oral	NLRX1	II		II
JNJ-2113 (PN-234)	JNJ / PTGX	small molecule	Oral	IL-23R	II	-	
GS-1427	GILD	small molecule	Oral	$\alpha 4\beta 7$	II	-	
Lutikizumab	ABBV	biologic	SC	IL-1a/1b	II		-
ABBV-668	ABBV	small molecule	oral	RIPK1	II		-
Eclitasertib	SAN FP / DNLI	small molecule	Oral	RIPK1	II		-
OSE-127	OSE	biologic	SQ	IL-7R	II		-
ADS-051	Adiso Therapeutics	small molecule	oral	MRP2 / FPR1	II		-
ALTB-268	AltruBio	biologic	SC	PSGL1	II		-
BBT-401	Bridge Biotherapeutics	small molecule	oral	Pellino-1	II		-
Eltrekibart	LLY	biologic	IV/SC	CXCR1/2	II		-
Orismilast	UNION Therapeutics	small molecule	Oral	PDE4	II		-
PL8177	PTN	biologic	SQ	MCR1	II		-
Rosnilimab	ANAB	biologic	IV/SC	PD-1	II		-
VE202	Vedanta Biosciences	-	Oral	microbiota	II		-
Vixarelimab	RHHBY	biologic	IV/SC	IL-31	II		-
VTX002	VTYX	small molecule	Oral	S1P1R	II		-
Tilpisertib foscemecarbil	GILD	small molecule	Oral	TPL2	II		-
CU104	Curacle Co	small molecule	Oral	IL-6	II		-
IBI112	Innovent	biologic	SC	IL-23	II		-
Dupilumab	SAN FP / REGN	biologic	SC	IL-4R $\alpha$	II		-
SPH3127	Shanghai Pharma Biotherapeutics	small molecule	Oral	renin	II*		-
Efavaleukin alfa (AMG 592)	AMGN	biologic	SC	IL-2	II		-
AZD7798	AZN	biologic	IV	CCR9	-		II
SAR441566	SAN FP	small molecule	Oral	TNFR	-		II
AGMB-129	AgomAb	small molecule	Oral	ALK5	-		II

Source: Leerink Partners Research; Company Disclosures; Biomedtracker; Clinicaltrials.gov. \*Select programs based on screening of listed sources that are in Ph 2 development or later

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# Emerging target catalysts in 2025

**The ABTECT Ph 3 induction data in 3Q25 represents a binary catalyst for ABVX and the most consequential IBD readout of the year**

Company	Drug	Mechanism	Event	Expected Timing
AMGN	Efavaleukin alfa (AMG 592)	IL-2 mutein fusion protein	Topline Ph 2 data	1H25
ABVX	Obefazimod	miRNA inducer	Topline induction data from Ph 3 ABTECT program in UC	3Q25
ABBV	ABBV-113	Oral NLRX1 agonist	Ph 2 UC data	2025
ABBV	ABBV-8736	Oral TREM-1 agonist	Ph 2 CD initiation	2025
Vedanta Biosciences	VE202	Bacterial consortium	Ph 2b data	2025

# Obefazimod (ABVX)

## Obefazimod uses a novel MOA and has generated encouraging data to date

### Obefazimod program background

- Obefazimod is a **first-in-class oral small molecule** that reduces inflammation by upregulating a specific anti-inflammatory micro-RNA (miR-124)
- Clinical studies have implicated miR-124 as a negative regulator of pro-inflammatory cytokines (e.g., IL-6, IL-17, IL-23), and evidence suggests upregulation of miR-124 in IBD patients could drive **deep and sustainable clinical benefit**
- In a Phase 2b UC study, obe demonstrated highly encouraging clinical data with robust remission rates, strong durability of effect, and clean safety – we believe obe is well positioned ahead of the Phase 3 ABTECT readout in 3Q25
- ABVX is also developing obe for CD, which we view as a natural indication expansion opportunity with a multi-billion-dollar potential – we see strong mechanistic rationale here as well

### Data highlights

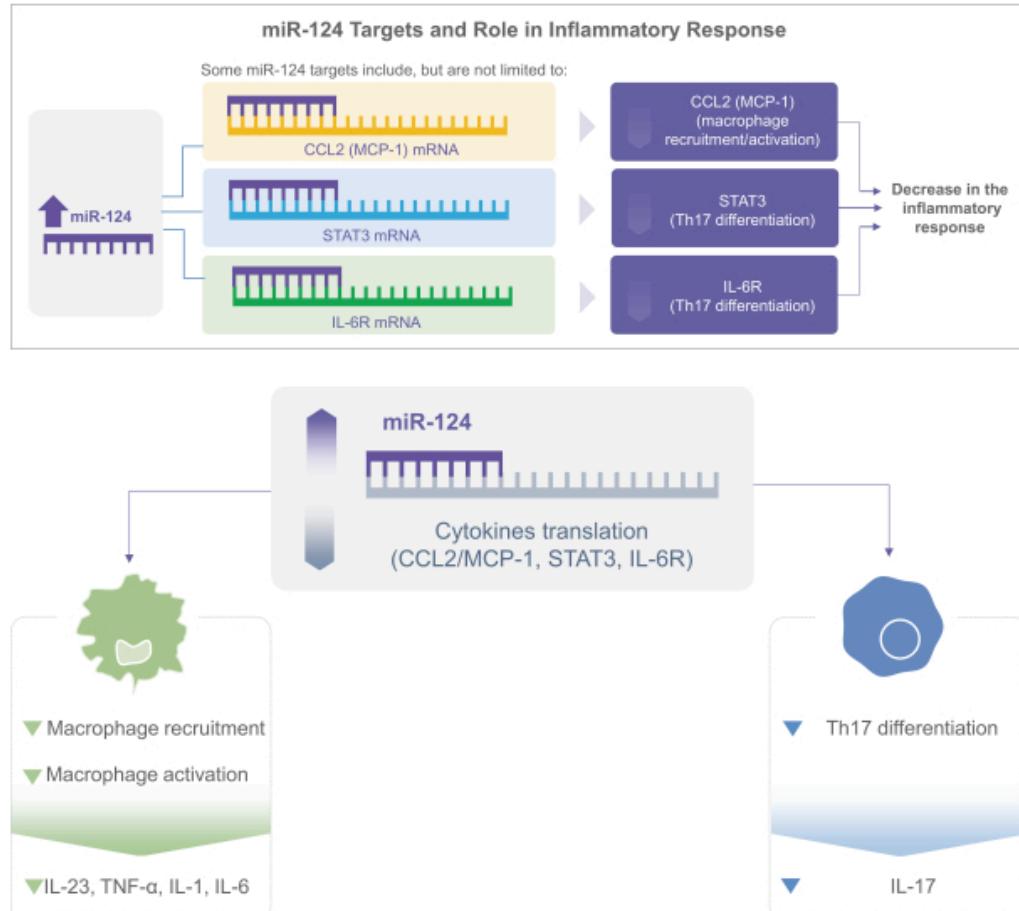
- Obe has demonstrated one of the most robust and comprehensive Phase 2 induction/maintenance datasets in UC, with high rates of clinical and symptomatic remission
- Obe has also demonstrated **impressive durability and clean safety**
- We see the totality of obe's clinical profile as potentially differentiating vs competing oral programs (e.g., JAKi, S1P, IL-23, etc.)

### Next up?

- Topline induction data from Phase 3 ABTECT trial in UC in 3Q25
- ABTECT 52wk maintenance data topline readout in 2Q26
- Topline induction data from Phase 2b ENHANCE-CD study in 2H26

# Obefazimod (ABVX): mechanism of action

## Obefazimod induces microRNA expression to modulate cytokine translation

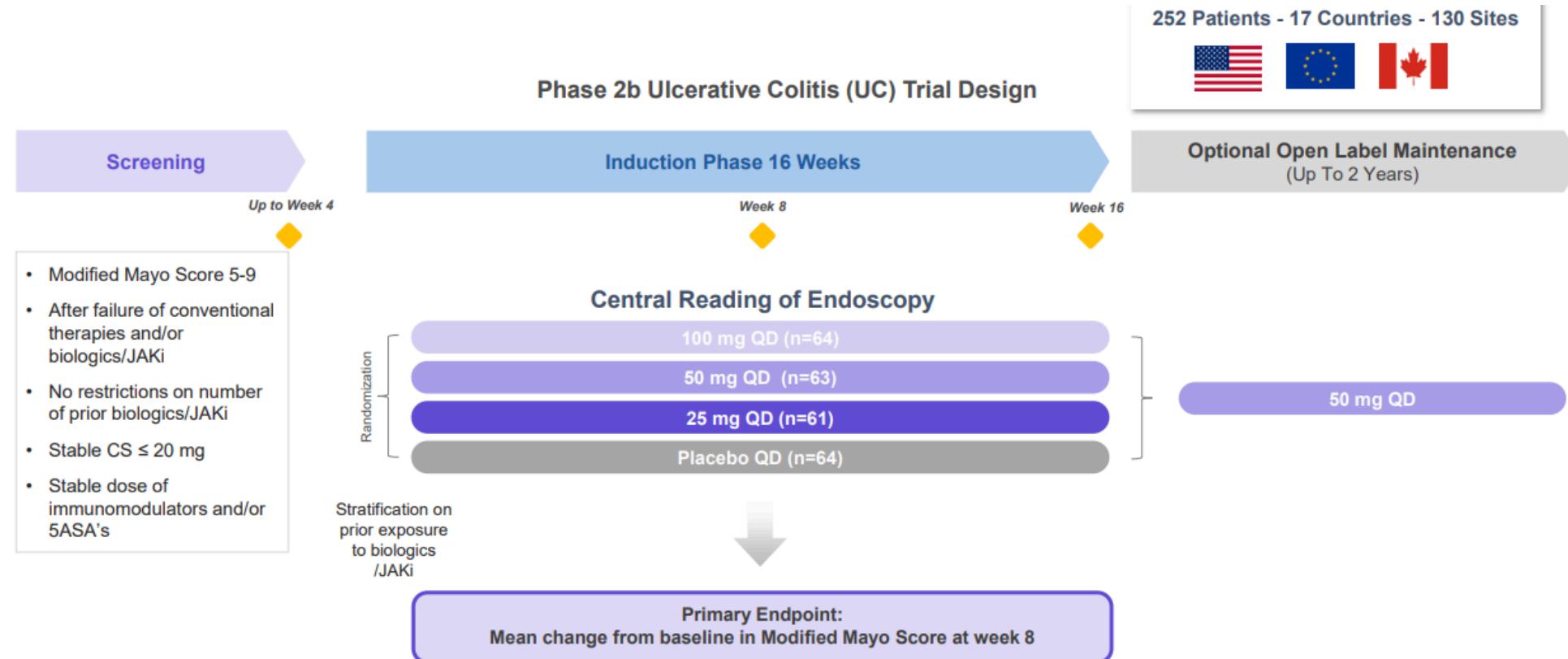


- Obefazimod enhances the expression of microRNA-124 (miR-124), with minimal impact on other microRNAs
- Obefazimod accomplishes this through binding to the cap binding complex (CBC) within the nucleus (as demonstrated by cryo-electron microscopy)
- This interaction results in a reduction in the translation of inflammatory mediators such as MCP-1/CCL2, STAT3, and IL-6R
- The effect of this is the stabilization of a dysregulated inflammatory response present in conditions like UC. Downstream effects include reduction in inflammatory cytokines, including IL-23 and IL-17, and stabilization of Th17 differentiation

# Obefazimod (ABVX): Ph 2b study design

UC

The obefazimod Ph 2b UC study used a reduction in MMS as a primary endpoint, but overall employed a standard design



# Obefazimod (ABVX): Ph 2b baseline characteristics

## The Ph 2b recruited a population with relatively active disease

- Baseline characteristics were balanced across arms
- 49% of patients were refractory to an advanced therapy, with many failing multiple
- 71% of patients had severe disease (MMS of 7–9)
- 66–75% of patients had the highest Mayo endoscopic score (Grade 3), indicating significant mucosal damage

	ABX464 100 mg (n=64)	ABX464 50 mg (n=63)	ABX464 25 mg (n=61)	Placebo (n=64)
Age, years	42.2 (12.3)	40.2 (13.9)	41.5 (14.2)	41.1 (14.4)
Sex				
Male	41 (64%)	27 (43%)	40 (66%)	40 (63%)
Female	23 (36%)	36 (57%)	21 (34%)	24 (37%)
Body-mass index at baseline, kg/m <sup>2</sup>	25.1 (3.9)	24.7 (5.1)	25.2 (5.5)	24.5 (4.8)
Previous therapy	32 (50%)	30 (48%)	30 (49%)	31 (48%)
TNF inhibitor	31 (48%)	25 (40%)	25 (41%)	27 (42%)
TNF inhibitor only	1 (2%)	0	3 (5%)	1 (2%)
Vedolizumab	20 (31%)	20 (32%)	19 (31%)	22 (34%)
Vedolizumab only	0	1 (2%)	0	1 (2%)
JAK inhibitor	13 (20%)	12 (19%)	10 (16%)	12 (19%)
JAK inhibitor only	0	0	0	1 (2%)
Concomitant ulcerative colitis medication				
Corticosteroids	37 (58%)	33 (52%)	32 (52%)	29 (45%)
5-aminoacicylic acids	47 (73%)	48 (76%)	46 (75%)	52 (81%)
Immunosuppressants	6 (9%)	9 (14%)	10 (16%)	10 (16%)
Duration of disease since diagnosis, years	7.8 (7.3)	8.2 (7.8)	7.4 (6.8)	8.8 (6.8)
Disease extent				
Proctitis	0	8 (13%)	7 (11%)	6 (9%)
Left sided	35 (55%)	33 (52%)	30 (49%)	26 (41%)
Extensive	29 (45%)	22 (35%)	24 (39%)	32 (50%)
Baseline modified Mayo Score				
4	0	0	0	1 (2%)
5-6	17 (27%)	16 (25%)	17 (28%)	21 (33%)
7-9	47 (73%)	47 (75%)	44 (72%)	42 (66%)
Baseline Mayo endoscopic score				
2	22 (34%)	16 (25%)	20 (33%)	16 (25%)
3	42 (66%)	47 (75%)	41 (67%)	48 (75%)
Patients without rectal bleeding	0	2 (3%)	4 (7%)	7 (11%)
Faecal calprotectin, µg/g	3778 (6205)	3441 (5017)	3022 (3818)	2452 (2281)

Data are mean (SD) or n (%).

Table 1: Patient demographics and baseline characteristics in full analysis set (received study treatment and had baseline data for at least 1 efficacy variable)

# Obefazimod (ABVX): Phase 2b safety profile

UC

## Obefazimod demonstrated a differentiated, and relatively benign, safety profile in Ph 2b

- Obefazimod has demonstrated a relatively benign safety profile to date
- Headache has been the most prominent AE, is typically transient, and has not led to many discontinuations
- High expression of miR-124 in the CNS and elevated rates of headache as an AE of special interest remain in focus for the larger Phase 3 ABTECT dataset as the full safety profile of obe continues to crystallize

	Placebo (N=64)	Obefazimod 25 mg (N=62)	Obefazimod 50 mg (N=63)	Obefazimod 100 mg (N=64)
<b><u>AEs Reported in ≥ 5% of patients in any treatment group</u></b>				
<b>Headache</b>	5 (7.8%)	13 (21.0%)	19 (30.2%)	27 (42.2%)
<b>Discontinuation Due to Headache</b>	0 (0%)	1 (1.6%)	3 (4.8%)	4 (6.3%)
<b>Nausea</b>	4 (6.3%)	5 (8.1%)	4 (6.3%)	9 (14.1%)
<b>Infections</b>	6 (9.4%)	3 (4.8%)	8 (12.7%)	5 (7.8%)
<b>Colitis Ulcerative</b>	4 (6.3%)	0	4 (6.3%)	1 (1.6%)
<b>Arthralgia</b>	3 (4.7%)	1 (1.6%)	1 (1.6%)	5 (7.8%)
<b>Vomiting</b>	1 (1.6%)	1 (1.6%)	2 (3.2%)	5 (7.8%)
<b>Abdominal Pain Upper</b>	0	3 (4.8%)	3 (4.8%)	4 (6.3%)
<b>Myalgia</b>	0	0	0	5 (7.8%)

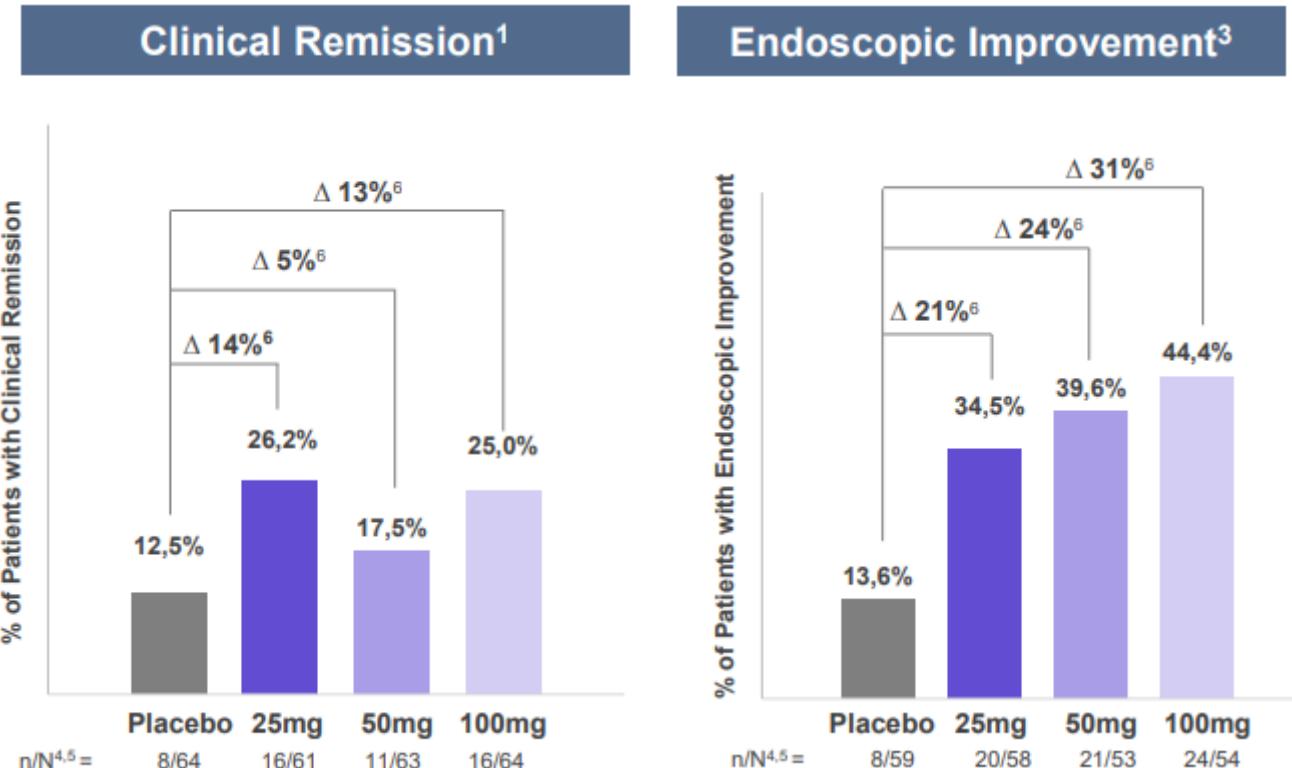
Only 100 mg  
AEs ≥5%  
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# Obefazimod (ABVX): Phase 2b efficacy

UC

## Obefazimod demonstrated efficacy at induction, which has been reaffirmed in OLE

- Obefazimod has generated Phase 2 data that we believe positions it competitively against other oral agents, including a 14% placebo-adjusted clinical remission rate generated during the induction portion of their Phase 2b dose-ranging study, though no clear dose-response relationship was observed on the clinical remission endpoint
- For endoscopic improvement, each dose cohort demonstrated higher rates than placebo and a dose-response was observed
- Obefazimod has also shown compelling efficacy in biologic/JAKi-experienced patients
- Data from the OLE continue to affirm obe's impressive durability, showing that patients on obe maintained very high rates of clinical and symptomatic remission at 96 weeks

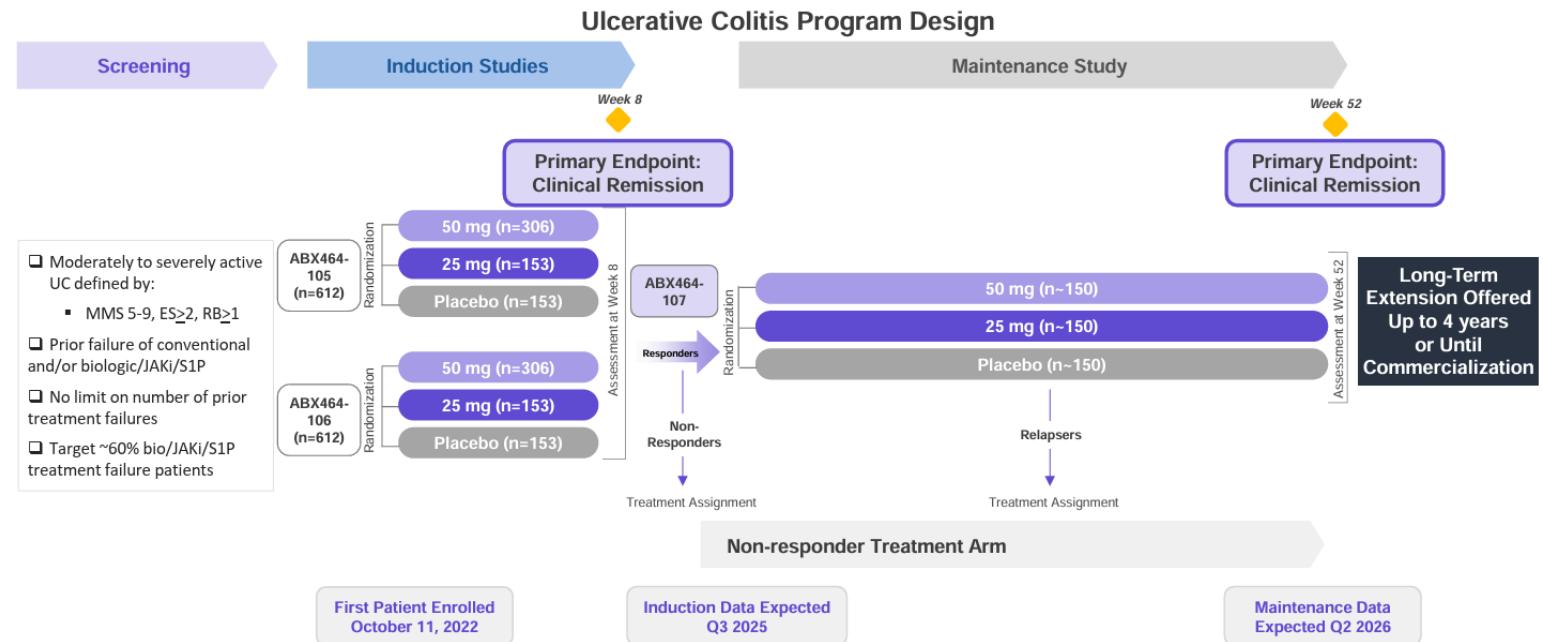


# Obefazimod (ABVX): ABTECT Ph 3 design

UC

## The ABTECT Ph 3 program uses a maintenance withdrawal design

- The Phase 3 ABTECT program consists of 2 identical induction trials and 1 maintenance trial
- The primary induction endpoint of ABTECT will evaluate clinical remission at week 8
- After 8wks, responders will be rerandomized for the maintenance portion – clinical remission will be assessed again at 52wks
- In January 2025, ABVX noted that 82% of the target population has been recruited (1,003 / 1,224 patients), with 600 sites activated



# Thoughts on obefazimod (ABVX) ahead of the ABTECT induction topline

## We have a favorable view on expectations for the ABTECT induction readout in 3Q25

Expectations	Positioning
<ul style="list-style-type: none"><li>Mgmt. comments during our fireside chat at GHC in March suggest Phase 3 ABTECT has enrolled a similar population and clinical experience to the Phase 2b study, including<ul style="list-style-type: none"><li>Treatment-naïve and treatment-experienced UC patients, with the current split of ~48%/~52% (compared to ~49%/~51% in the Phase 2b trial)</li><li>~51% patients achieved a clinical response during the 8-week induction portion and are advancing into the maintenance period (compared to ~53% in the Phase 2b study)</li><li>The current discontinuation rate is ~10% in ABTECT vs. 12.5% in the Phase 2b trial</li></ul></li><li><b><i>Mgmt. views ≥10% placebo-adjusted clinical remission at 8-week induction as a winning outcome (up to 14% placebo-adjusted clinical remission was reported in the Phase 2b trial)</i></b></li></ul>	<ul style="list-style-type: none"><li>In our view, obefazimod's clinical profile, which includes high rates of clinical remission and a generally clean safety profile in a convenient oral form, is highly compelling</li><li>We believe obe represents an attractive treatment option suitable for both first-line and biologic-experienced patients</li><li>We continue to see the ABTECT induction readouts as one of the most important in the IBD space this year and a potentially value-inflecting catalyst for ABVX shares.</li><li>Successful data would enable an NDA submission in 2H26</li><li>While we acknowledge enduring investor debate regarding the novel mechanism, AEs of interest, and dose response, <b><i>we have conviction in obe's mechanistic rationale in UC, and believe it is well positioned to succeed in ABTECT and de-risked by an encouraging clinical profile to date</i></b></li></ul>

# Obefazimod (ABVX) upcoming catalysts

**ABVX has an array of upcoming catalysts, although the ABTECT induction data will be the key focus**

Drug Candidate	Regimen	Indication	Research	Nonclinical Phase 1	Phase 2	Phase 3	Achieved & Anticipated Milestones
Obefazimod	Monotherapy	Moderately to Severely Active Ulcerative Colitis (UC)	Pivotal Phase 3 Program (ABTECT) Initiated First Patient Enrolled in the US on Oct. 11, 2022				<ul style="list-style-type: none"><li>Induction trial topline data readout in Q3 2025</li><li>Maintenance trial topline data readout in Q2 2026</li></ul>
	Monotherapy	Crohn's Disease (CD)	Phase 2b				<ul style="list-style-type: none"><li>IND filed Q4 2023</li><li>First patient enrolled Phase 2b trial in October in 2024</li><li>Phase 2b induction topline results expected in 2H 2026</li></ul>
	Combination Therapy	Moderately to Severely Active Ulcerative Colitis (UC)					<ul style="list-style-type: none"><li>Encouraging preclinical combination data generated</li><li>Decision on combination agent expected in 2025<sup>1</sup></li></ul>
miR-124 Follow On	Monotherapy	To be disclosed					<ul style="list-style-type: none"><li>Selection of follow-on compound in 2025</li></ul>

# Lusvertikimab (OSE): IL-7R

## Lusvertikimab is a first-in-class IL-7R antagonist with promising data in UC

### Lusvertikimab/OSE-127

- Lusvertikimab is a fully human mAb targeting the interleukin-7 receptor (IL-7R)
  - IL-7 signaling is a key driver of chronic inflammation in IBD, and sits upstream of IL-23 and TNF pathways, impacting T effector (Teff) and regulatory T cell (Treg) populations
- OSE is evaluating lusvertikimab in UC in the Ph 2 CoTikiS study, with data disclosed in late 2024 and additional detail presented at ECCO 2025 and a subsequent company webinar

### Data highlights

- Lusvertikimab met the primary endpoint, showing significant improvement in MMS at each dose level over 10 weeks in UC patients
- Enrollment of the lower dose cohort was stopped due to a prespecified futility analysis, although the arm later showed meaningful separation from placebo (although this does limit interpretation of the data by dose)
- Improvements on key secondary endpoints were also encouraging, demonstrating high rates of clinical and endoscopic remission
- Favorable safety and tolerability profile observed in induction

### Potential differentiation

- Positioned as a potential first-in-class IL-7R antagonist
- Addresses resistance to anti-TNF and anti-IL-12/23 therapies by targeting an upstream pathway
- Clean safety profile and preclinical data support potential combination with existing IBD therapies (e.g., IL-23)
- Personalized medicine approach possible given preliminary evidence of efficacy in patients with high FCP

### Next up?

- Data from the OLE component of CoTikiS study expected later this year given last patient visit in Jan 2025
- Strategic evaluation of development path, exploring potential partnerships and combinations
- Upcoming updates on further development and potential indication expansion in other Th1 and Th17 diseases

# Lusvertikimab/OSE-127: CoTikiS baseline characteristics

UC

Interpretation of the doses evaluated in CoTikiS is limited given the imbalance between cohorts

	Placebo (n=49)	Lusvertikimab 450 mg (n=35)	Lusvertikimab 850 mg (n=50)
Age: mean (SD)	42.7 (15.9)	38.8 (10.5)	42.5 (15.1)
Sex: Male, n (%)	28 (57.1%)	22 (62.9%)	27 (54.0%)
Never Smoker, n (%)	39 (79.6%)	25 (71.4%)	43 (86.0%)
UC Duration (Years) Mean (SD)	8.2 (7.5)	7.2 (6.5)	9.3 (8.6)
Modified Mayo Score (MMS) Mean (SD)	6.6 (1.2)	6.0 (1.4)	6.5 (1.0)
MMS, n (%)			
5-6	21 (42.9%)	17 (48.6%)	25 (50.0%)
7-9	26 (53.1%)	<b>13 (37.1%)</b>	<b>25 (50.0%)</b>
Mayo Endoscopic Subscore Mean (SD)	2.5 (0.5)	2.4 (0.5)	2.6 (0.5)
Mayo Endoscopic Subscore 3, n (%)	26 (53.1%)	<b>15 (42.9%)</b>	<b>32 (64.0%)</b>
UCEIS Mean (SD)	4.6 (1.3)	4.4 (1.3)	4.8 (1.2)
Nancy Histological Index 3 or 4, n (%)	31 (65.9%)	20 (58.8%)	34 (70.8%)
FCP (µg/g) Mean (SD)	1459.5 (1865.0)	1088.0 (1600.5)	1191.8 (1603.3)
C-Reactive Protein (mg/L) Mean (SD)	8.6 (13.6)	9.4 (16.7)	11.2 (18.1)
Previous Exposure to Biologics	19 (38.8%)	<b>5 (14.3%)</b>	<b>19 (38.0%)</b>
Previous Biologics >2 : n (%)	5 (10.2%)	0 (0%)	6 (12%)
Concomitant Use of Steroids, n (%)	23 (46.9%)	18 (51.4%)	25 (50.0%)

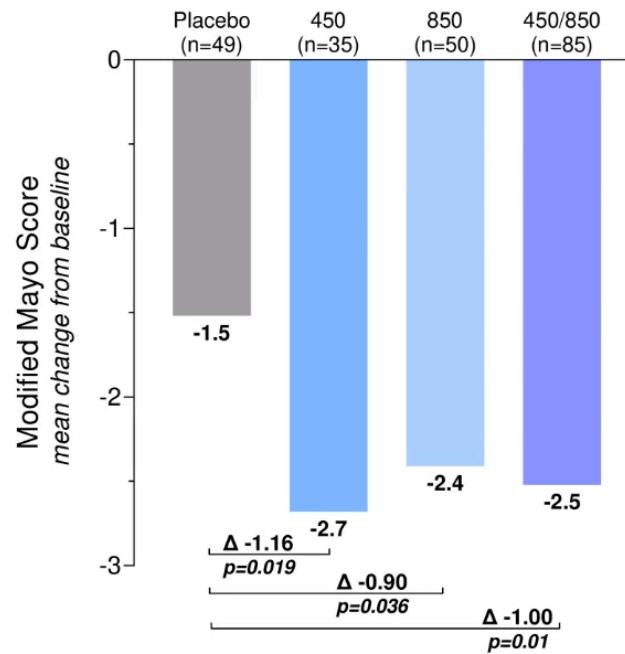
<sup>a</sup> Lusvertikimab 450mg was dropped at a prespecified futility analysis after 58 patients. It was later shown not to be futile

Baseline characteristics were not balanced across arms, and the 450 mg group appeared to enroll patients with less severe disease (e.g., MMS, endoscopic scores, and prior biologics), prior to enrollment in this cohort being stopped early for futility

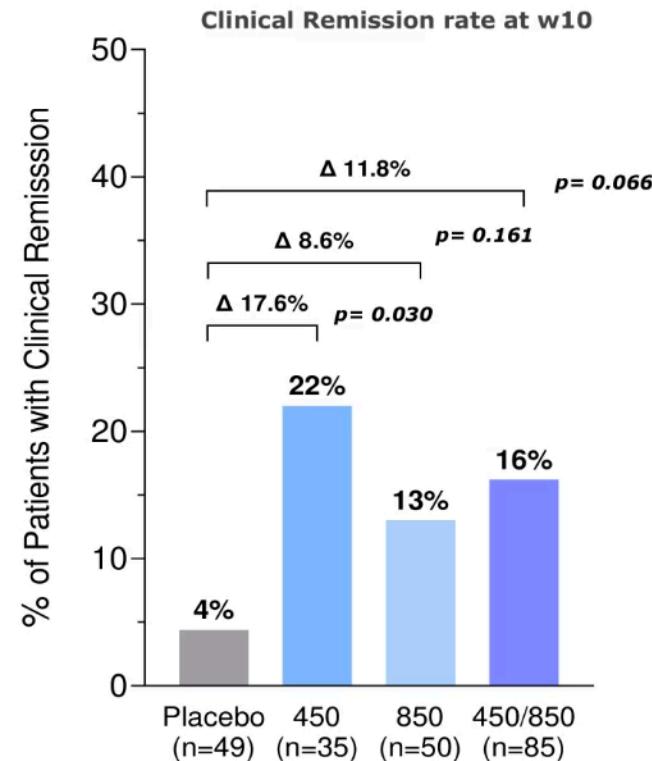
# Lusvertikimab/OSE-127: CoTikiS efficacy

UC

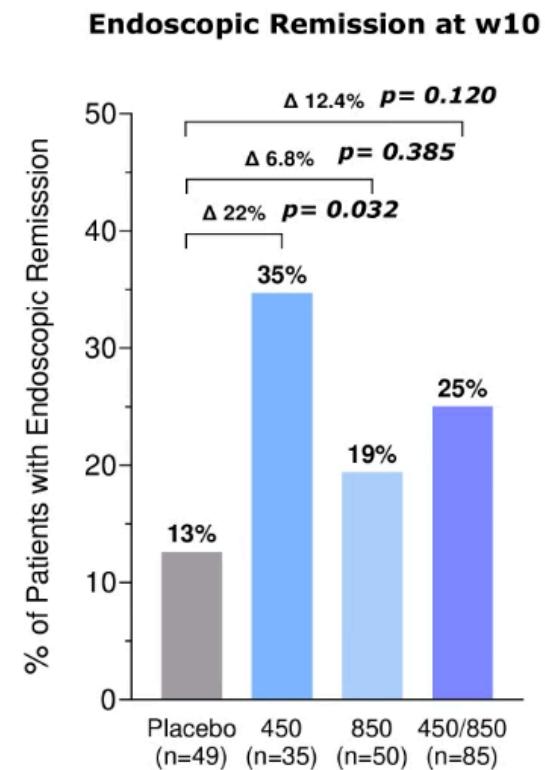
Despite these limitations, efficacy was encouraging, and the lack of a dose response can be explained by the potential imbalance in baseline



Despite enrollment being stopped at 450 mg, both arms showed statistically significant MMS reductions (primary endpoint). Note the relatively better performance by the 450 mg arm is likely due to the less severe nature of the patients enrolled (see prior slide)



Both arms showed numerical improvements on secondary (and more common from a regulatory standpoint) endpoints of clinical and endoscopic remission. It is important to flag these data are from week 10, which is 2-4 weeks earlier than many contemporary studies, indicating rapid onset of effect

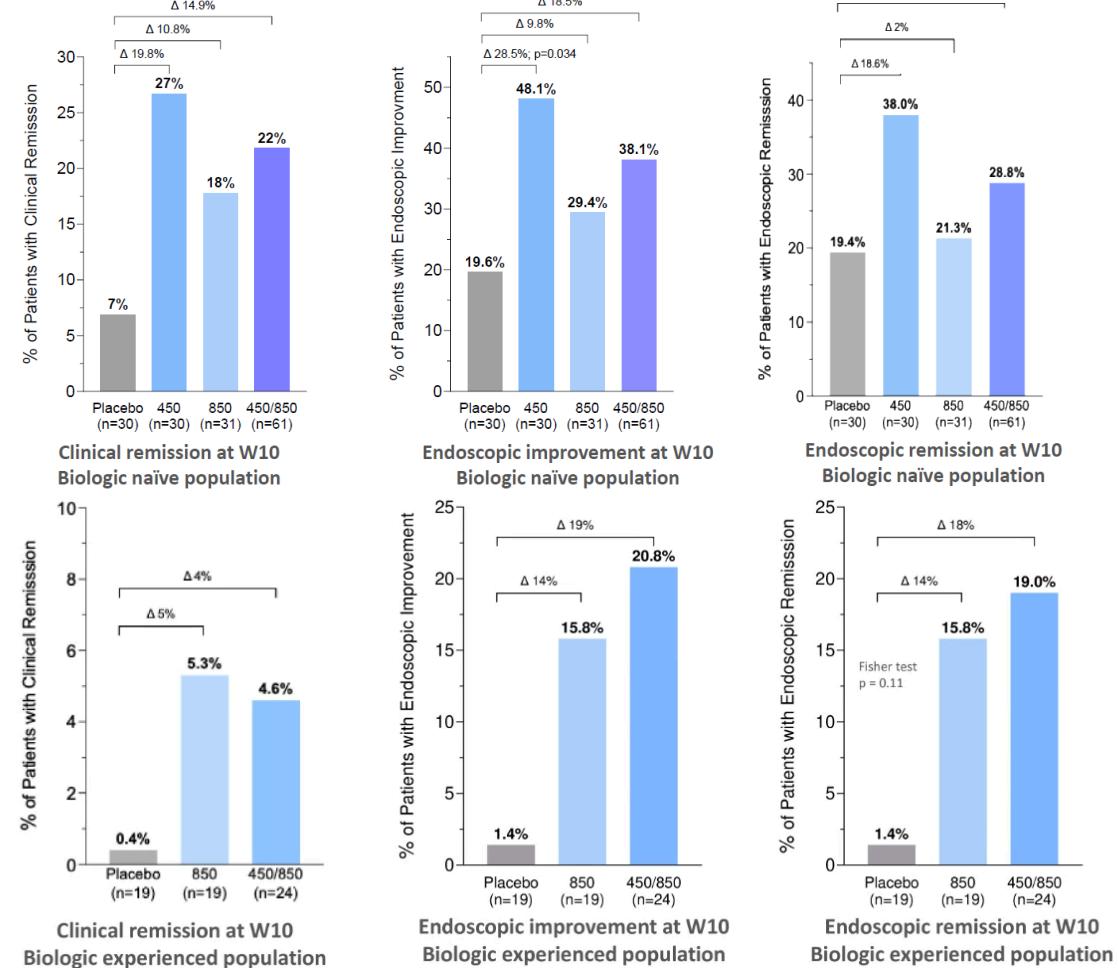


# Lusvertikimab/OSE-127: CoTikiS efficacy in biologic naïve and experienced

UC

## High doses of lusvertikimab were efficacious despite prior biologic experience

- Early efficacy signals in both biologic-naïve and experienced populations. Note relatively few patients in the 450 mg arm were biologic experienced
- Broadly, efficacy is in line with other therapies, and these data suggest potential as a first-line biologic or in patients who have failed prior therapies



# Lusvertikimab/OSE-127: safety

UC

**Lusvertikimab had a relatively clean safety profile at this early timepoint, although there was a slight increase in lymphopenia, this was noted to be transient and non-impactful**

- The safety profile was fairly benign with no treatment discontinuations
- Lymphopenia has been singled out, but was noted as transient and did not lead to higher rates of infection- although this will be important to follow in patients on treatment longer-term

	<b>L450 mg (N=36)</b> <b>N(%) [E]</b>	<b>L850 mg (N=51)</b> <b>N(%) [E]</b>	<b>Placebo (N=49)</b> <b>N(%) [E]</b>	<b>Total (N=136)</b> <b>N(%) [E]</b>
At least one TEAE	17 (47.2%) [33]	20 (39.2%) [42]	16 (32.7%) [29]	53 (39.0%) [104]
Lymphopenia	4 (11.1%) [5]	2 (3.9%) [2]	1 (2.0%) [1]	7 (5.1%) [8]
Anaemia	1 (2.8%) [1]	0	2 (4.1%) [2]	3 (2.2%) [3]
Ulcerative colitis	1 (2.8%) [2]	2 (3.9%) [2]	3 (6.1%) [4]	6 (4.4%) [8]
Pyrexia	2 (5.6%) [2]	0	1 (2.0%) [1]	3 (2.2%) [3]
Covid-19	1 (2.8%) [1]	0	2 (4.1%) [2]	3 (2.2%) [3]
Upper Respiratory Tract Infection	0	2 (3.9%) [2]	1 (2.0%) [1]	3 (2.2%) [3]
Hypertension	0	1 (2.0%) [1]	2 (4.1%) [2]	3 (2.2%) [3]

- Lymphopenia ( $<1 \times 10^9/L$ ): Lusvertikimab (6/87: 6.9%) than with placebo 1/49: 2%
- Lymphopenia  $<0.5 \times 10^9/L$ : Lusvertikimab 4.6% (4/87), transient, not associated with a higher rate of infection, no treatment discontinuation

# Other notable targets (1/3)

## A range of strategies are being employed with new targets

### LANCL2

#### Target background

- LANCL2 agonism is multi-modal, and believed to generate suppressive regulatory CD4+ T cells (T regs) that restore and maintain immune tolerance in the GI tract

#### Notable program

- Omilancor (NIimmune), an oral LANCL2 agonist, generated encouraging Ph 2 data in mild to moderate UC

#### Next up?

- NIimmune are planning to initiate a Ph 3 study in UC

### NLRX1

#### Target background

- NLRX1 is a regulatory protein that helps maintain gut homeostasis by modulating mucosal immunity, metabolism, and gut microbiome composition

#### Notable program

- ABBV acquired ABBV-113 (NX-13) from its \$163M acquisition of Landos in March 2024. ABBV-113 is an orally active, gut-selective NLRX1 agonist that has shown promise in a Ph 1b study in UC, and is currently being evaluated in a Ph 2 studies in UC and CD

#### Next up?

- Ph 2 UC data for ABBV-113 are expected in 2025

### IL-1 $\alpha$ /1 $\beta$

#### Target background

- IL-1 $\alpha$  and IL-1 $\beta$  are considered key pro-inflammatory cytokines that play a significant role in driving the inflammatory response within the colon

#### Notable program

- Lutikizumab (ABBV) is dual-variable-domain antagonist against both targets, with positive results demonstrated in HS. The company has an ongoing monotherapy Ph 2 and earmarked the program for combination in UC with risankizumab (Skyrizi)

#### Next up?

- ABBV plan to initiate combination studies with risankizumab (Skyrizi)

# Other notable targets (2/3)

## A range of strategies are being employed with new targets

### TYK2

#### Target background

- TYK2, a member of the JAK family, selectively modulates cytokine (e.g., IL-12, IL-23, IFN1) signaling

#### Notable programs

- Several failures for the mechanism (e.g., Ventyx's VTX958 and BMY's deucravacitinib) have tempered investor enthusiasm
- TAK's zasocitinib is in ongoing Phase 2b CD\* and UC\*\* trials
  - Topline data expected in 2Q/3Q26 and 4Q26/1Q27, respectively
- Robust Phase 2 data from JNJ's oral IL-23 icotrokinra in UC provides validation for drugging this pathway orally in IBD, and positive readthrough for the potential to leverage TYK2 inhibition in UC

### TREM-1

#### Target background

- TREM-1 amplifies innate immune activation in IBD by enhancing monocyte and neutrophil-driven inflammation, with preclinical data suggesting that TREM-1 inhibition can reduce pro-inflammatory cytokines and gut barrier dysfunction

#### Notable program

- ABBV acquired a TREM1 program (CEL383) in its \$250M acquisition of Celsius in June 2024

#### Next up?

- ABBV plans to initiate combinations with risankizumab (Skyrizi)

### RIPK1

#### Target background

- RIPK1 plays a key role in regulating intestinal epithelial cell death and inflammation in IBD, with inhibition aimed at reducing necroptosis and TNF-driven pathology to preserve gut barrier integrity

#### Notable programs

- GSK's program, GSK2982772, failed to show evidence of an effect on disease activity in a randomized, placebo-controlled UC trial
- SAN FP / DNLI are collaborating on eclitasertib, which continues to be developed in UC despite muted efficacy in SLE
- ABBV's ABBV-668 is in Ph 2 in UC, although no longer appears on the company's pipeline

\* NCT06233461, estimated primary completion 9/18/2026

\*\* NCT06254950, estimated primary completion 9/30/2026

Source: Weisel et al. BMJ Open Gasterol 2021 ([LINK](#))

# Other notable targets (3/3)

## A range of strategies are being employed with new targets

### PSGL1

#### Target background

- PSGL1 facilitates binding of leukocytes to blood vessels – targeting PSGL1 is thought to regulate T cell homeostasis by preferentially down-regulating late-stage, chronically activated T cells while sparing resting and early-activated T cells

#### Notable program

- AltruBio developing ALTB-268, an antibody targeting PSGL1, with a Phase 2a study in UC ongoing

#### Next Up?

- Topline Phase 2a biomarker study in biologic refractory UC expected 2H25
- Phase IIb study of ALTB-268 in UC to initiate in 1H25, open to both advanced therapy experienced and naïve patients
  - Topline data are expected to read out in 2H26.

### ALK5

#### Target background

- ALK5 (TGF $\beta$ R1) is a master regulator of fibrosis – clinical data suggests that targeting ALK5 is effective in fibrotic indications

#### Notable program

- Agomab developing AGMB-129 in fibrostenosing Crohn's disease (FSCD), Phase 2a STENOVA trial ongoing

#### Next up?

- Detailed interim STENOVA results to be presented at a future scientific conference, full results expected in 4Q25

### FPR

#### Target background

- FPR1 regulates neutrophil recruitment and activation, driving inflammation and tissue damage - inhibiting FPR1 may reduce neutrophil migration to the gut, alleviating inflammation while preserving systemic immune function

#### Notable program

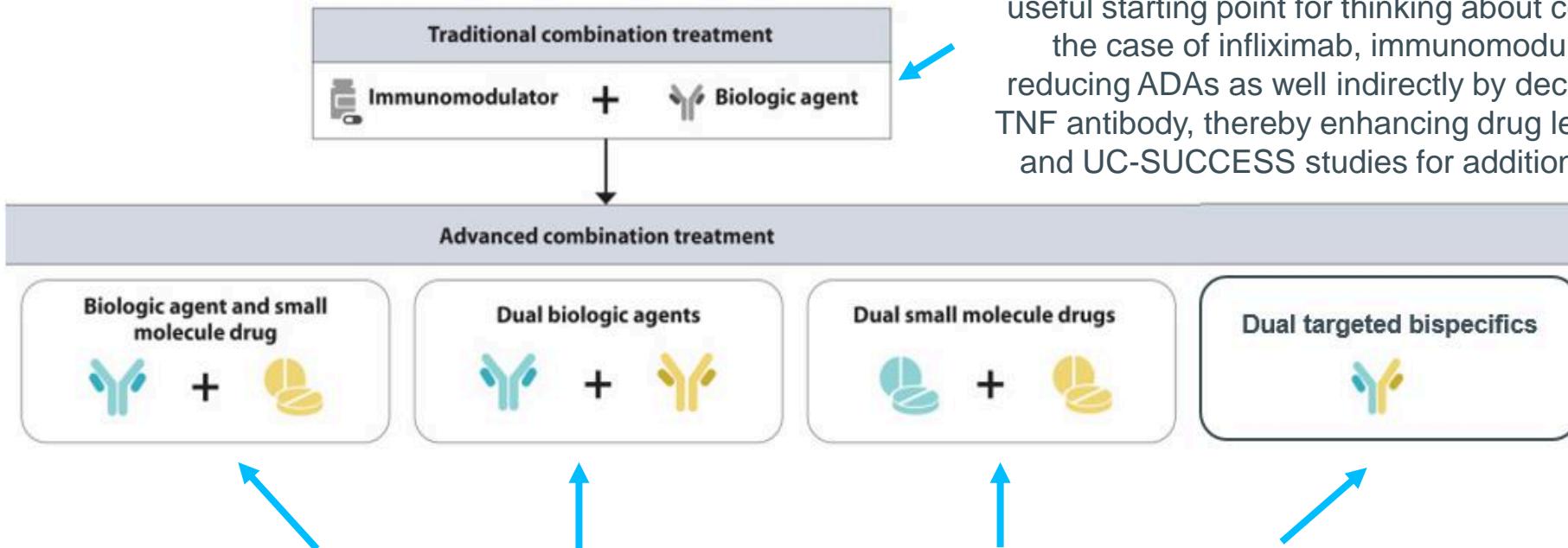
- Adiso's ADS051 is a novel, oral, gut-restricted small molecule that modulates neutrophil trafficking and activation by inhibiting MRP2 and FPR1, targeting neutrophil-driven tissue damage in a way that differentiates it from existing treatments.

## Combination therapy and bispecifics

- **Breaking the efficacy ceiling:** combining multiple mechanisms aims to enhance response rates and durability in IBD treatment, leveraging proof of concept provided by JNJ's VEGA study in UC and TAK's EXPLORER study in CD
- **JNJ's DUET study leads the way:** The Ph 2b study of a coformulation of guselkumab (Tremfya, IL-23p19/CD64) + golimumab (Simponi, TNF) has a primary completion date in May 2025, and we could see initial data for the program this year
- **SYRE's multi-target strategy:** SYRE is developing combinations of TL1A,  $\alpha$ 4 $\beta$ 7, and IL-23p19 to maximize efficacy, with early-stage readouts that will inform the TL1A and IL-23p19 program profiles expected this year
- **Bispecific antibodies offer a one-drug solution:** these therapies aim to provide multi-pathway modulation in a single molecule, although most are in early-stage development

# IBD combination therapy approaches

Emerging efforts are focused on combining “advanced” therapies



Using an immunomodulator such as azathioprine or methotrexate in combination with a TNF $\alpha$  is commonplace in practice and represents a useful starting point for thinking about combination therapy in IBD. In the case of infliximab, immunomodulators enhance efficacy by reducing ADAs as well indirectly by decreasing clearance of the anti-TNF antibody, thereby enhancing drug levels (trough). See the SONIC and UC-SUCCESS studies for additional background ([LINK](#), [LINK](#))

Currently, advanced combination therapy (ACT) is infrequently used in IBD. However, it has become a key theme in the next wave of development, with companies keen to explore how combining existing (or novel) therapeutics might help break some of the existing limitations of the current monotherapy options in moderate to severe disease. JNJ's VEGA study provided initial proof of concept that has helped spurred this broader interest

# Framework for thinking about how and why combination therapy is useful

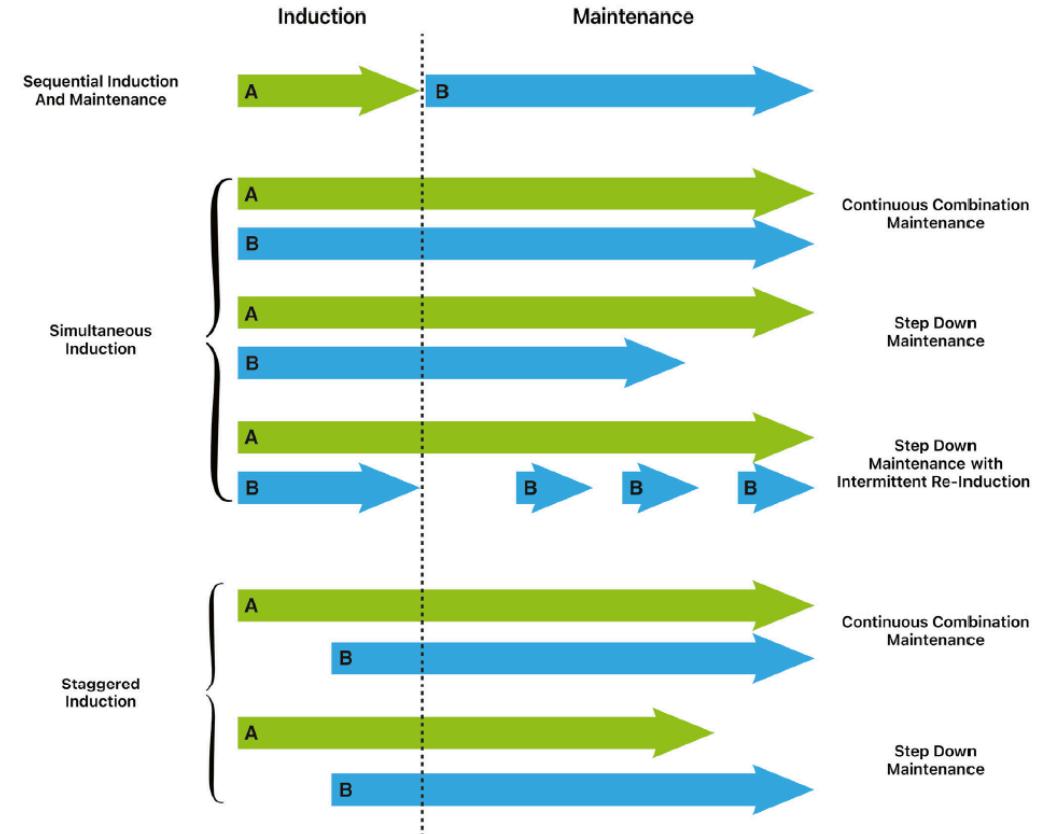
There are a couple reasons “why” and several ways “how” combination therapy can be used

## Pharmacologic

- **Pharmacokinetic synergy:** enhancing drug levels or delivery (e.g., oral and rectal mesalamine combination, or the prior example with infliximab)
- **Pharmacodynamic synergy:** combining drugs with different mechanisms of action for additive or synergistic effects

## Temporal

- Timing and sequencing becomes a consideration when using two agents (rather than in the case of a bispecific)
  - **Simultaneous induction:** starting two new therapies together at the beginning of treatment
  - **Staggered induction:** adding a second agent after partial response to the first during induction
  - **Sequential induction and maintenance:** using one agent for induction followed by a different agent for maintenance
  - **Continuous combination maintenance:** long-term use of two agents together
  - **Step-down therapy:** Withdrawing one agent after achieving remission with combination therapy
  - **Intermittent reinduction:** short-term use of a second agent to regain control during flares

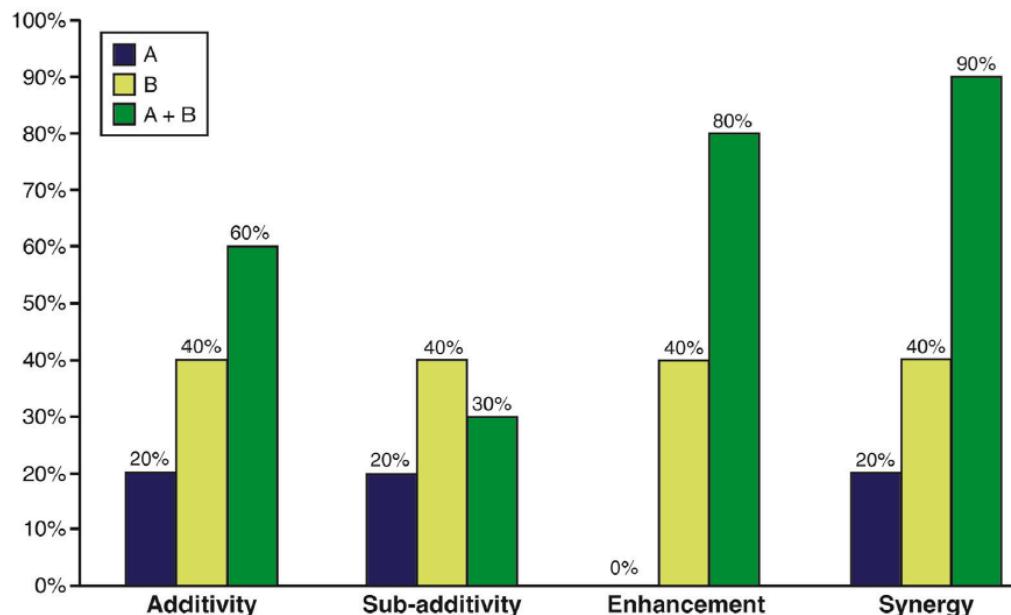


# Broad considerations for combination therapy

Improving efficacy, while limiting additive safety concerns, is the key goal

## Efficacy

- Effects can be subadditive, additive, or synergistic when combining therapies/targets
- Emerging combination (and bispecific) approaches are **seeking to break through efficacy plateaus seen with monotherapies**



## Safety

- Increased efficacy must be balanced against the potential for increased adverse events
- As such, one approach being used (with approved drugs) is to combine agents with favorable safety profiles (e.g., IL-23 or  $\alpha 4\beta 7$ ) with those with increased risk (e.g., JAKi or TNF $\alpha$ ) in order to maintain an acceptable overall safety profile
- Generally, based on known side-effects and the mechanism of actions of the classes of drugs involved, the main concerns are for increased risk for serious infections or malignancy

# Current use of ACT in IBD

ACT is used in very niche circumstances currently

## Recommendations for ACT in current practice

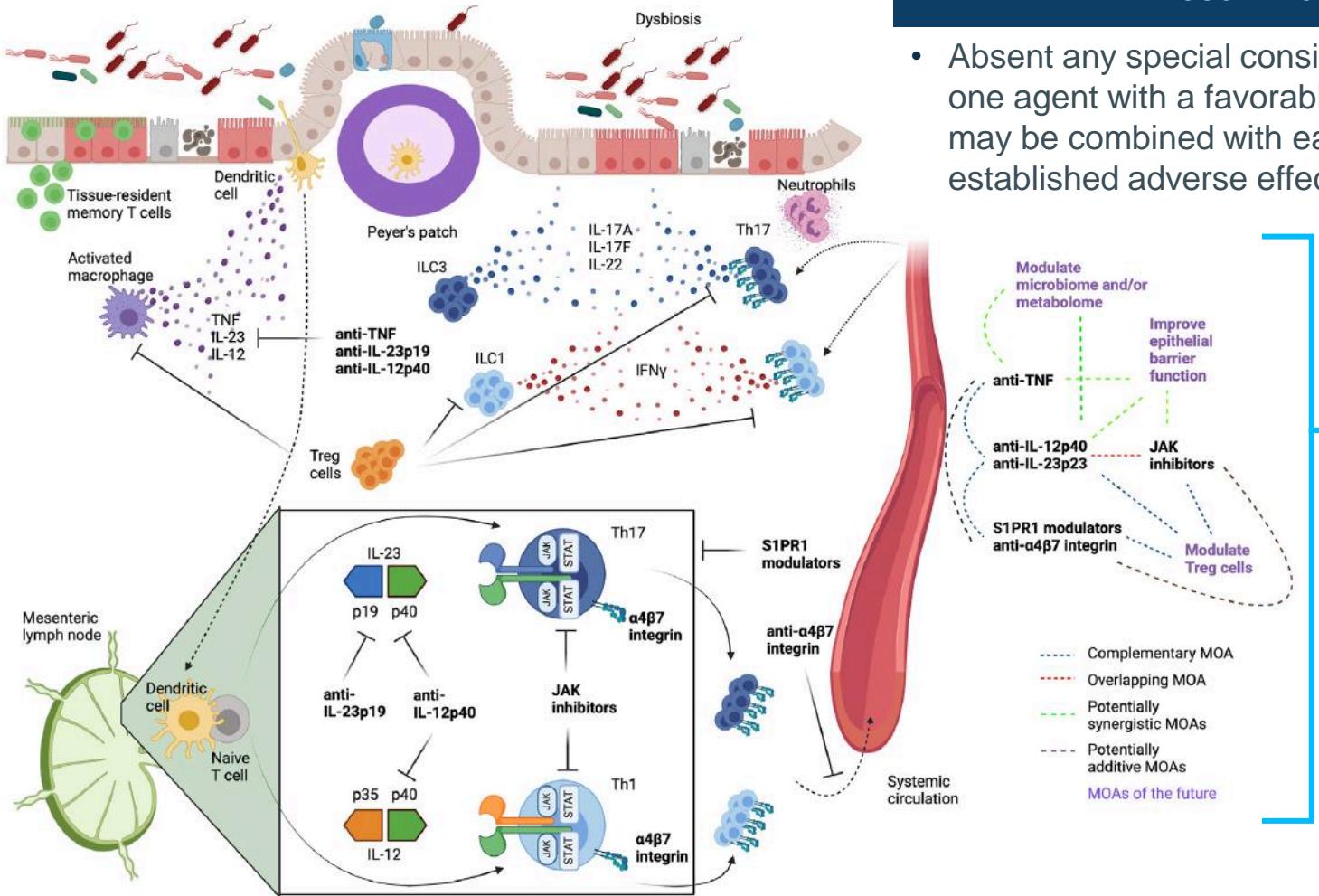
### Key Recommendations for the Use of ACT in Clinical Practice

<b>Who</b>	Patients with IBD refractory to multiple medical therapies Patients with very high-risk phenotypes Patients with a concomitant EIM/IMID
<b>When</b>	The risk of doing nothing (eg, uncontrolled disease) is higher than the risk of adding a combination molecule
<b>Where</b>	Centers with clinical expertise and multidisciplinary teams
<b>Why</b>	Differential and combination mechanisms of action with dual targeted treatments Lack of available options for inducing and maintaining remission and response
<b>How</b>	<ul style="list-style-type: none"><li>• Recycling strategy (using at least 1 agent already administered)</li><li>• Simultaneous induction (starting with 2 new agents)</li><li>• Add-on strategy (adding a new compound later on)</li></ul> Preference for agents with the most favorable safety profiles (eg, vedolizumab, ustekinumab), especially in frail or elderly patients Preference for an anti-TNF agent in CD, especially in ileal CD or with bowel damage Preference for vedolizumab in UC patients Preference for an anti-TNF agent or ustekinumab (or anti-IL-23 blocker when approved) or a JAK inhibitor in patients with concomitant EIM or IMID
<b>Unknown areas</b>	Most appropriate combinations to administer Treatment duration Cost-effectiveness of combination regimens

- There are no approved combination regimens, nor consensus on when ACT should be used in IBD. Currently ACT is used in relatively niche situations (see figure)
- Our academic-based MEDACorp KOL noted they most commonly used ACT when patients are being treated for two autoimmune disorders, although they added it wasn't necessarily easy to get this approved by insurance
- Our private-practice MEDACorp KOL noted that they will sometimes give patients a free sample of Rinvoq as a bridge before starting them on another slower acting biologic such as Stelara

# Rational combinations have been proposed

Combining orthogonal pathways that limit toxicity has been proposed, and is being explored



## Recommendations for ACT in current practice

- Absent any special considerations, among approved options combination of one agent with a favorable safety profile (e.g., vedolizumab or ustekinumab) may be combined with each other or a second advanced therapy with established adverse effects (i.e., TNFα or JAK inhibitors)

- Cytokine Neutralization + Lymphocyte Trafficking Inhibition**
  - TNFα or IL-23 or JAK+  $\alpha 4\beta 7$
  - Rationale: targets mucosal inflammation while reducing gut-specific lymphocyte migration
- Dual Cytokine Blockade**
  - TNFα + IL-23: maintenance
  - Rationale: addresses mucosal inflammation and IL-23-mediated T-cell activation synergistically
- Sequential induction-maintenance**
  - Example: TNFα or JAK for induction → vedolizumab/ustekinumab for maintenance
  - Rationale: reduces long-term immunosuppression risks

# Combination therapy quick hits

## Overview

- JNJ is out front with its Ph 2b DUET studies, evaluating its coformulation of guselkumab and golimumab (JNJ-4804), which was evaluated as a combination induction regimen in the VEGA study
- ABBV has signaled its broad intentions to combine novel MOAs with its blockbuster risankizumab (Skyrizi)
- TAK has several ongoing combination studies, but these are evaluating vedolizumab (Entyvio) with external assets, and are unlikely to be registrational
- SYRE is developing its own in-house HLE versions of successful IBD drugs ( $\alpha 4\beta 7$ , IL-23, and TL1A), and plans to explore them in various combinations as part of a platform Ph 2 study, set to initiate in mid-2025

## +/- considerations

- Combination therapy is already used (although in niche circumstances) in IBD
- VEGA and EXPLORER studies have partially derisked combination approaches in IBD
- Combination of near-expiry biologics (anti-IL23) into a novel formulation, can reset patent timelines potentially oversetting biosimilar erosion
- Which target combinations and how to sequence therapies remains an unanswered question
- Higher upfront costs of combination will be weighed against efficacy and safety considerations (potential reductions in hospitalization/surgery needs)

# IBD combination therapy development landscape

**JNJ and ABBV are both pushing ahead with combinations of internally-owned assets, while SYRE is aiming to develop rational, conveniently dosed combinations**

Branded drugs involved?	Drug	Company	Molecule	ROA	Target	UC	Status
							CD
Entyvio + Humira or Ustekinumab	vedolizumab + adalimumab or ustekinumab	TAK	biologic	IV / SC	$\alpha 4\beta 7$ + TNF $\alpha$ or IL-23	-	IV (EXPLORER 2.0)*
Entyvio + Xeljanz	vedolizumab + tofacitinib	TAK	biologic + small molecule	IV / oral	$\alpha 4\beta 7$ + JAKi	IV	-
Entyvio + Rinvoq	vedolizumab + upadacitinib	TAK	biologic + small molecule	IV / oral	$\alpha 4\beta 7$ + JAK1	-	III (VICTRIVA)
Coformulation of Simponi + Tremfya	JNJ-4804	JNJ	biologic	SC	TNF $\alpha$ + IL-23p19	II (DUET-UC)	II (DUET-CD)
Skyrizi	risankizumab + lutikizumab	ABBV	biologic	IV / SC	IL-23 + IL-1a/1b	-	II
Skyrizi	risankizumab + ABBV-382	ABBV	biologic	IV / SC	$\alpha 4\beta 7$ + IL-23	-	II
-	SPY120	SYRE	biologic	SC	$\alpha 4\beta 7$ + TL1A	-	-
-	SPY130	SYRE	biologic	SC	$\alpha 4\beta 7$ + IL-23	-	-
-	SPY230	SYRE	biologic	SC	IL-23 + TL1A	-	-

Source: Leerink Partners Research; Company Disclosures; Biomedtracker. Note: In 2024, GILD removed the combination component of its SWIFT study of its oral  $\alpha 4\beta 7$  ([LINK](#)) and BI terminated its kinase inhibitor, BI 706321, combination studies ([LINK](#))

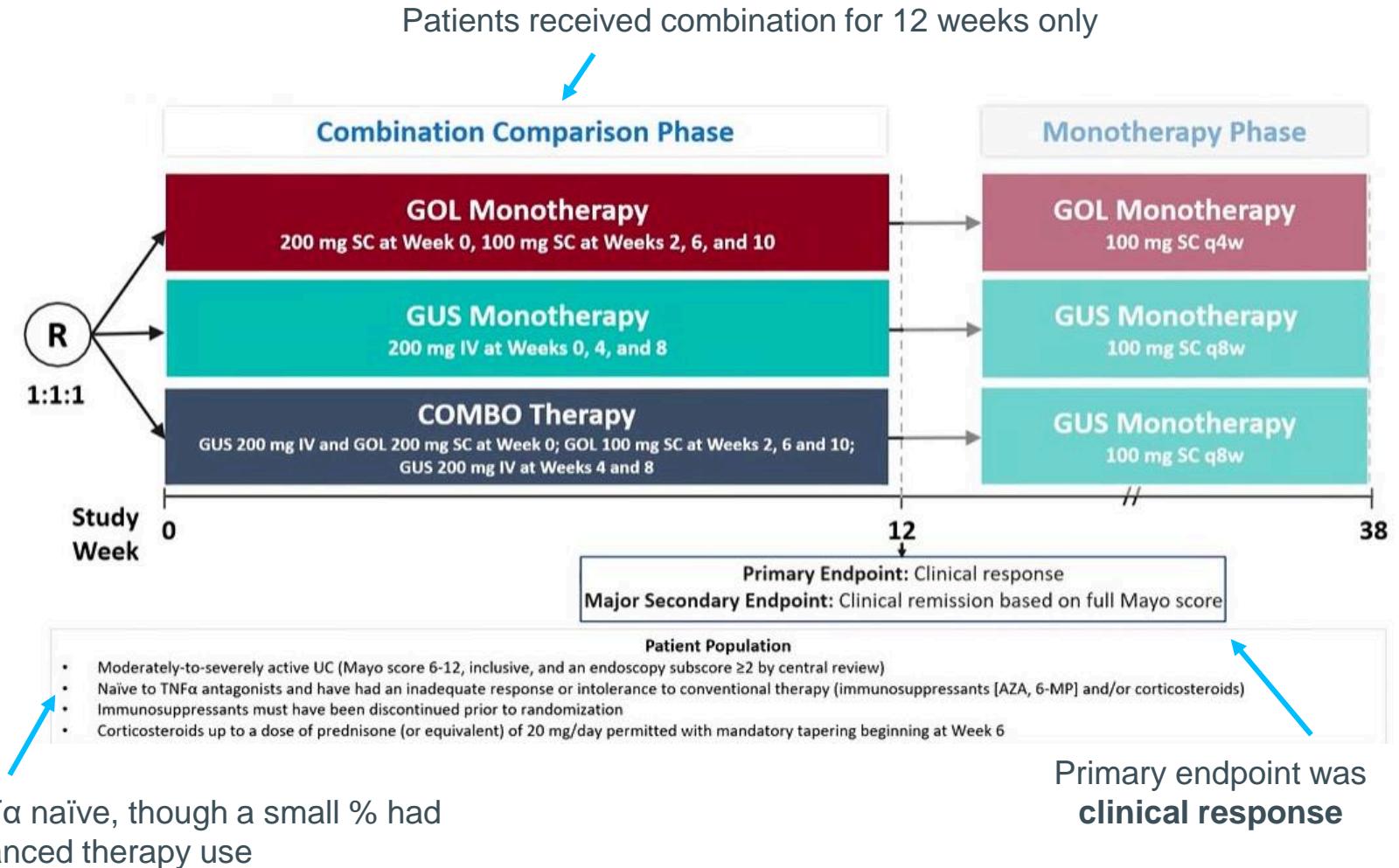
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# VEGA (JNJ): study design

UC

## JNJ initiated the VEGA study to evaluate combination induction

- VEGA was a randomized, active-comparator-controlled Ph 2a proof-of-concept study (run by JNJ) that evaluated the safety and efficacy of guselkumab (IL-23p19) and golimumab (TNF $\alpha$ ) combination induction followed by guselkumab maintenance compared to each drug alone in patients with moderate to severe UC
- The study was designed to confirm preclinical and IST findings that combination of two advanced therapies had potential to improve outcomes



# VEGA (JNJ): study design

## JNJ initiated the VEGA study to evaluate combination induction

	Combination therapy induction until week 12			Therapy until week 50		
	Combination therapy (n=71)	Golimumab monotherapy (n=72)	Guselkumab monotherapy (n=71)	Combination therapy (n=71)	Golimumab monotherapy (n=72)	Guselkumab monotherapy (n=71)
Duration of follow-up, weeks	12·4 (0·84)	12·0 (0·92)	12·1 (1·74)	48·8 (9·70)	45·8 (12·91)	48·6 (9·00)
Any adverse event	29 (41%)	38 (53%)	31 (44%)	45 (63%)	55 (76%)	46 (65%)
Common adverse events*						
Ulcerative colitis	4 (6%)	9 (13%)	1 (1%)	10 (14%)	17 (24%)	4 (6%)
Upper respiratory tract infection	1 (1%)	4 (6%)	5 (7%)	6 (8%)	5 (7%)	6 (8%)
Headache	4 (6%)	2 (3%)	3 (4%)	5 (7%)	4 (6%)	6 (8%)
Anaemia	4 (6%)	5 (7%)	6 (8%)	4 (6%)	7 (10%)	10 (14%)
Nasopharyngitis	2 (3%)	3 (4%)	2 (3%)	4 (6%)	5 (7%)	3 (4%)
Neutropenia	2 (3%)	2 (3%)	4 (6%)	3 (4%)	3 (4%)	5 (7%)
Pyrexia	1 (1%)	2 (3%)	0	2 (3%)	5 (7%)	1 (1%)
Infections†	10 (14%)	16 (22%)	10 (14%)	22 (31%)	23 (32%)	17 (24%)
Opportunistic infections	0	0	0	2 (3%)	0	0
Serious adverse events	1 (1%)	1 (1%)	2 (3%)	4 (6%)	4 (6%)	4 (6%)
Serious infections†	1 (1%)	0	0	2 (3%)	2 (3%)	2 (3%)
Adverse events leading to discontinuation of study treatment	2 (3%)	3 (4%)	1 (1%)	7 (10%)	4 (6%)	1 (1%)
Malignancies	0	0	0	0	0	1 (1%)
Deaths	0	0	0	1 (1%)	0	1 (1%)
Adverse events associated with an injection site reaction	1 (1%)	0	1 (1%)	1 (1%)	0	1 (1%)
Adverse events temporally associated with an infusion	1 (1%)	2 (3%)	2 (3%)	1 (1%)	2 (3%)	2 (3%)
Adverse events associated with COVID-19 infection	1 (1%)	0	0	2 (3%)	2 (3%)	3 (4%)

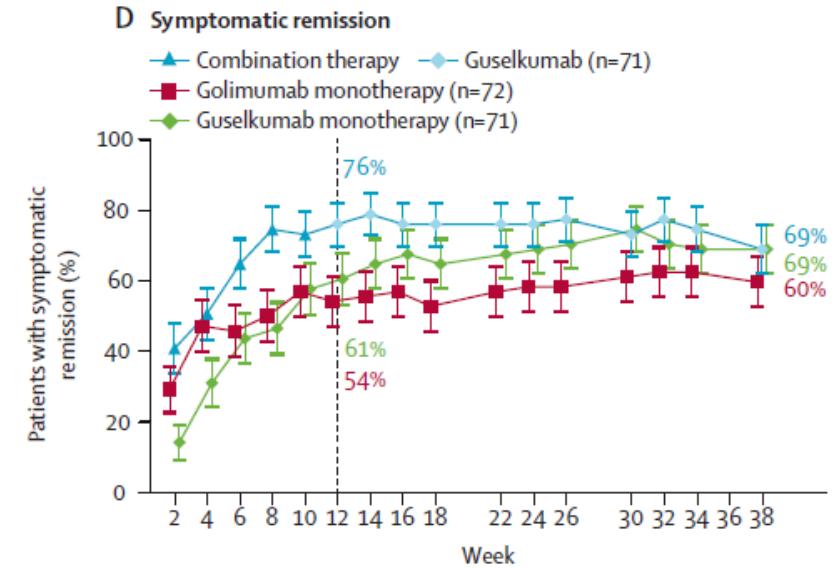
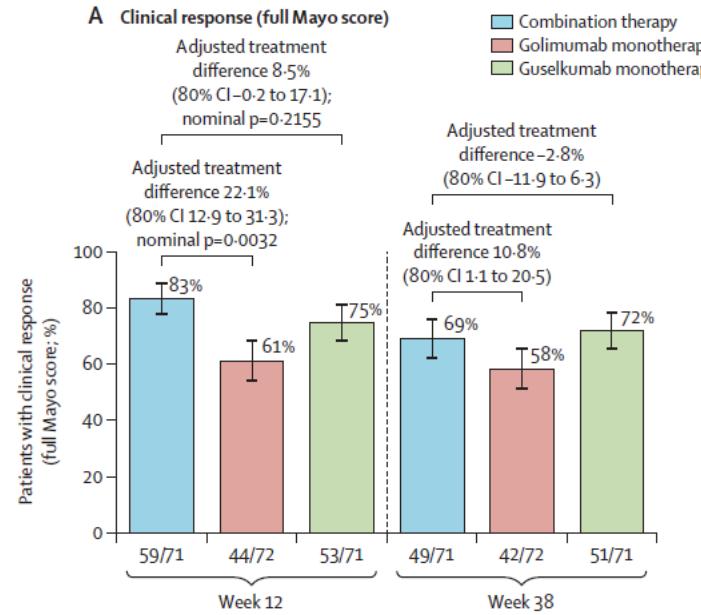
Data are mean (SD) or n (%). \*Reported by at least 5% of patients in any group. †As assessed by the investigator.

Table 3: Adverse events

- The safety profile of combination therapy in VEGA was generally comparable to monotherapies through 50 weeks of follow-up
- Rates of AEs were similar across groups, with infections being the most common
- Larger studies are needed to fully assess long-term safety, although these initial results are encouraging for the potential use of combination biologics in UC, where safety concerns have historically limited such approaches.

# VEGA (JNJ): primary endpoint efficacy

**VEGA showed a numerical, but not a stat. sig. benefit on the less important (but primary endpoint) of clinical response by TMS**

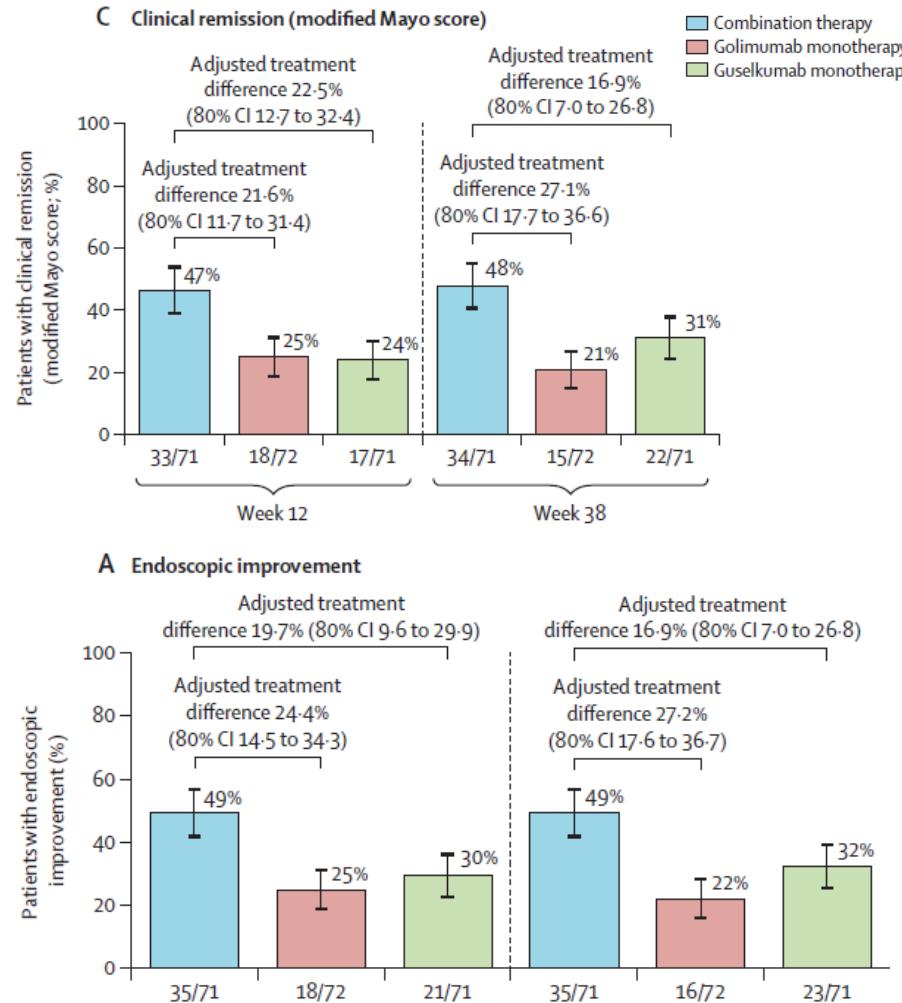


- On the primary endpoint of clinical response by TMS (which recall, includes the less objective subscore of physician's global assessment), the combination arm showed a numerical, but not statistically significant improvement compared to the monotherapy arms. During the monotherapy maintenance portion, the outcomes converged

- A similar trend was observed with one of the secondary endpoints, symptomatic remission, where the initial benefit observed with combination was followed by convergence during the maintenance portion

# VEGA (JNJ): efficacy on common trial endpoints

## VEGA demonstrated numerical improvements with combination on important regulatory endpoints



- On the more important endpoints (for regulators) of clinical remission and endoscopic improvement, there was a numerically greater effect with combination therapy for both at each time point, despite the withdrawal of the golimumab in the maintenance phase
- The authors noted that the magnitude of the differences observed were consistent with the hypothesis that the combination would yield additive efficacy from effects on overlapping and non-overlapping molecular pathways involved in IBD pathogenesis

# JNJ-4804 (JNJ)

## JNJ is evaluating a coformulation of the VEGA study combination in Ph 2b studies in UC and CD

### Program background

- JNJ initiated the Duet UC and Duet CD Ph 2b studies to evaluate a coformulation of guselkumab and golimumab (JNJ4804) tested in the VEGA study in both induction and maintenance portions in order to test this hypothesis further
- While VEGA included patients who were biologic naïve, both DUET studies will enroll patients who have failed at least one biologic

### Data highlights

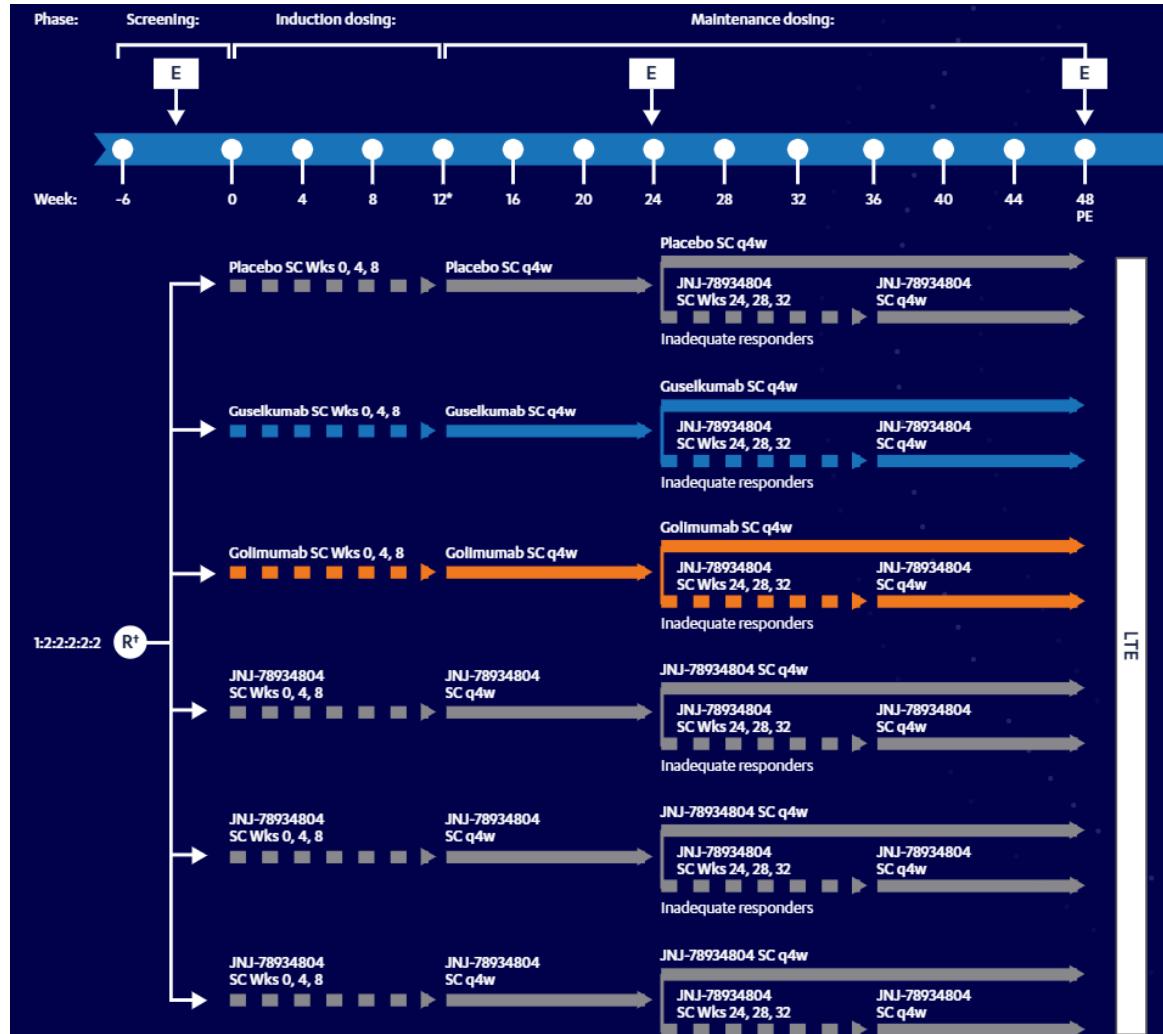
- VEGA demonstrate the potential for additive efficacy during induction without a diminished safety profile
- Notably, VEGA evaluated combination in the induction portion only, and the longitudinal effects of dosing of two agents is more of an unknown

### Next up?

- Both DUET-UC and DUET-CD could readout this year based on primary completion dates listed on CT.gov, with JNJ IR communicating that they will have the data in house around then

# JNJ-4804: DUET-UC study design

**DUET-UC is testing JNJ-4804 in biologic-experienced patients and evaluated combination in maintenance (in contrast to VEGA)**



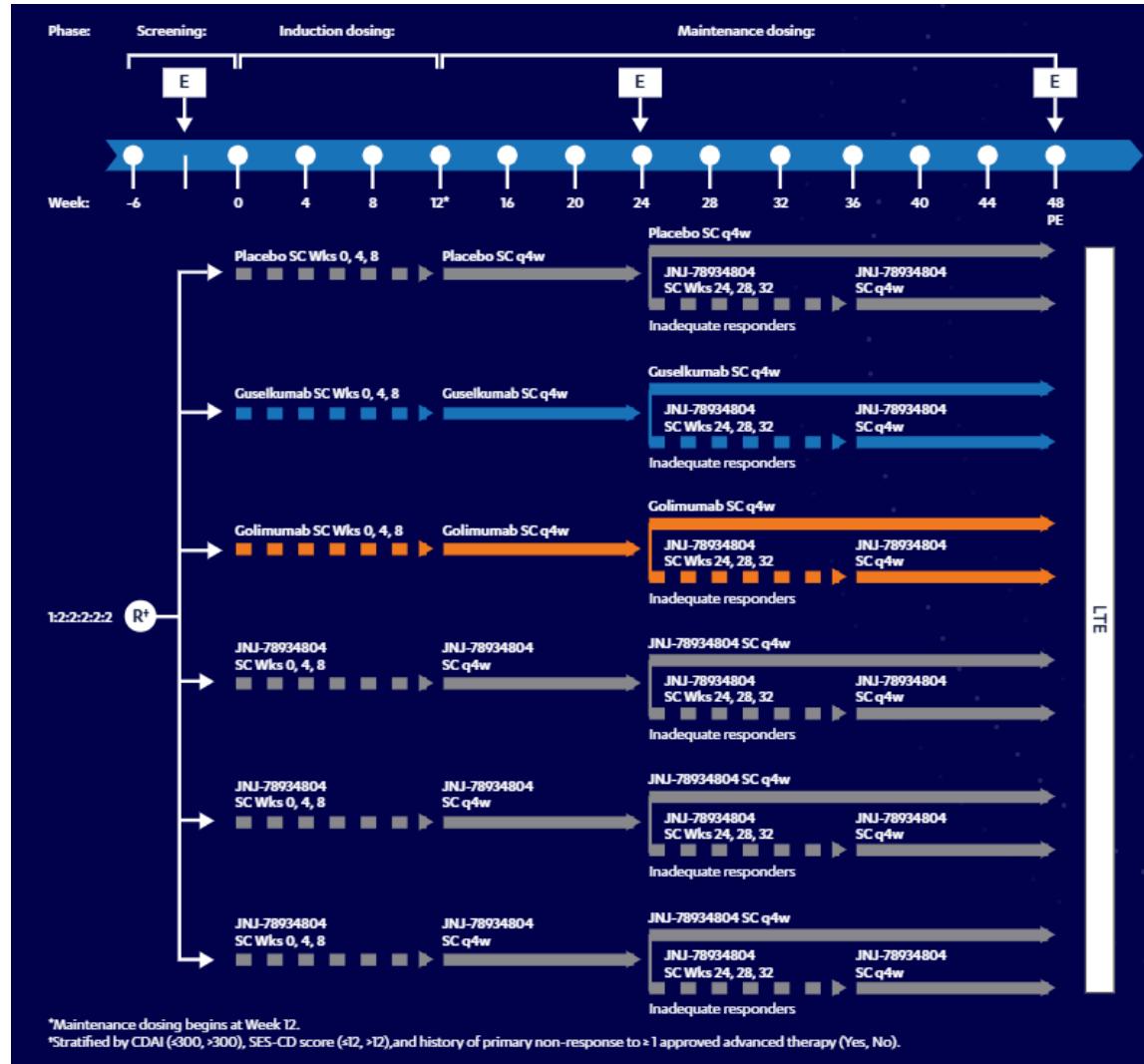
- DUET-UC is testing placebo vs. each monotherapy component vs. 3 doses of JNJ-4804
- Note the study is enrolling patients with demonstrated inadequate response, loss of response, or intolerance to at least one biologic
- Per CT.gov, the study has a primary completion date of 5.2025

Source: JNJ DUET-UC ([LINK](#)); [NCT05242484](#)

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# JNJ-4804: DUET-CD study design

DUET-CD uses a similar design, enrolling biologic-experienced patients in CD



- DUET-CD is using a similar design and is testing placebo vs. each monotherapy component vs. 3 doses of JNJ-4804
- Note the study is enrolling patients with demonstrated inadequate response, loss of response, or intolerance to at least one biologic
- Per CT.gov, the study has a primary completion date of 5.2025

# Thoughts on JNJ-4804 (JNJ) ahead of the DUET readouts

**JNJ-4804 will need to thread the needle of efficacy and safety to warrant development**

## Initial DUET readouts

- Efficacy: combination therapy should outperform monotherapies in key endpoints, especially clinical remission and endoscopic improvement (our MEDACorp KOLs said “double”). Note that the DUET studies enroll patients who have experienced at least one biologic, meaning placebo should perform poorly (low single digits), while combination would likely need 40-50% on the above endpoints to be considered meaningful
- Durability of response: the long-term extension will be critical in determining if combination therapy sustains remission better than monotherapies
- Kinetics of response: compared to IL-23 inhibitors alone (e.g., risankizumab, mirikizumab), JNJ-4804 could offer faster onset of action by leveraging TNF inhibition
- Safety expectations: combination therapy should maintain a safety profile comparable to established IL-23 and TNF inhibitors without a significant increase in infections or serious adverse events. No unexpected safety signals should emerge from dual cytokine inhibition, though infection risk (e.g., opportunistic infections) will need close monitoring
- Discontinuation rates: should not exceed those observed in monotherapy arms, supporting tolerability

## Thoughts on positioning of JNJ-4804

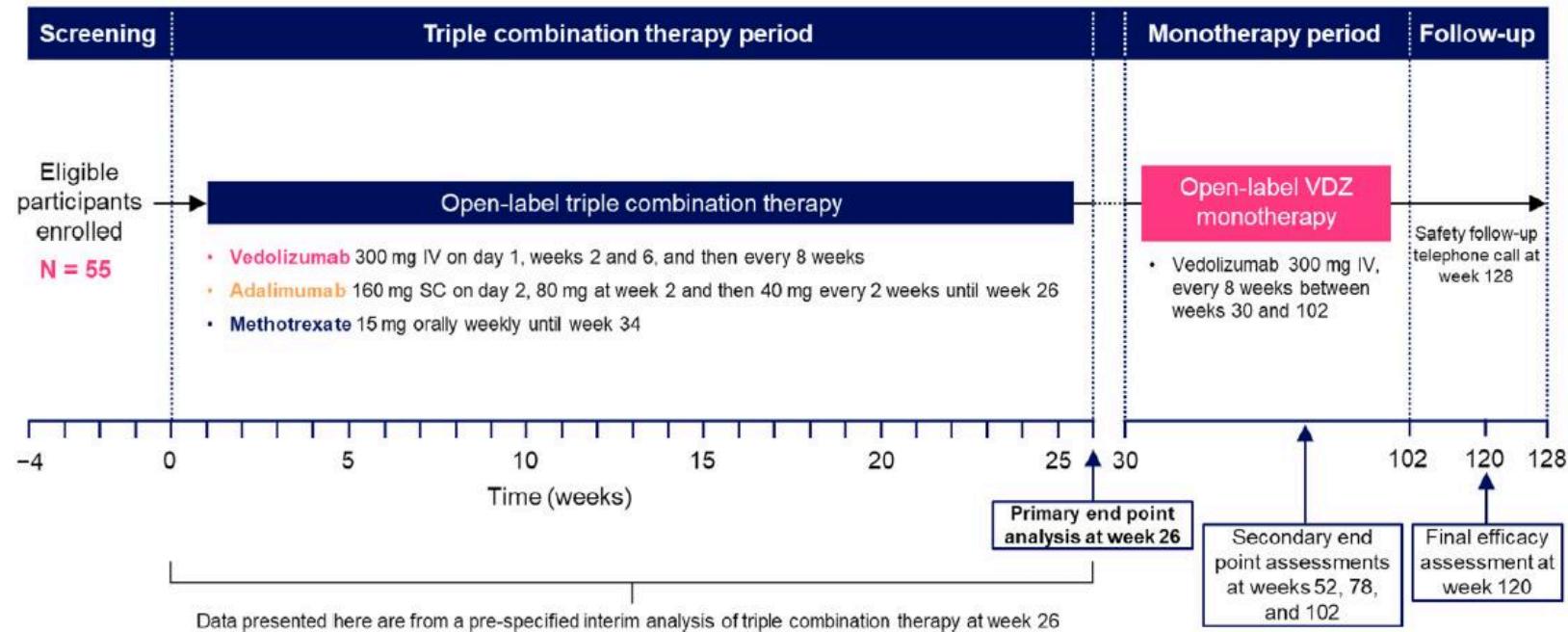
- If DUET demonstrates clear superiority of JNJ-4804 over monotherapies, it could support a Ph 3 pivotal program and eventual FDA approval as a first-in-class fixed-dose IL-23/TNF coformulation
- If successful, and depending on the design of the Ph 3, JNJ-4804 could be used in biologic-naïve patients or as a step-up therapy for those failing IL-23 or TNF monotherapy

# EXPLORER (TAK): study design

CD

**EXPLORER was a single-arm trial that exposed patients to combination for roughly half a year**

- EXPLORER was a single-arm Ph 4 proof-of-concept study run by TAK that evaluated the safety and efficacy of a triple regimen containing vedolizumab, adalimumab, and methotrexate in biologic naïve patients with moderate to severe CD
- The study was designed to confirm preclinical and IST findings that combination of two advanced therapies had potential to improve outcomes in CD

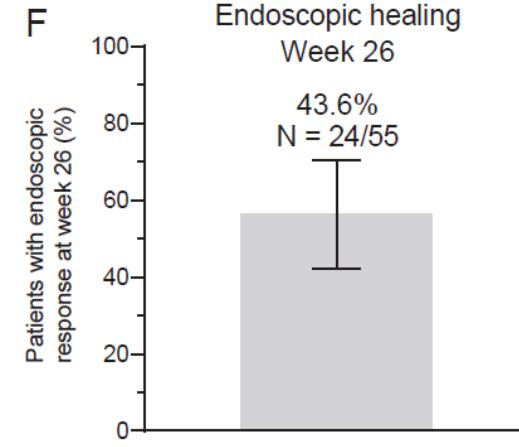
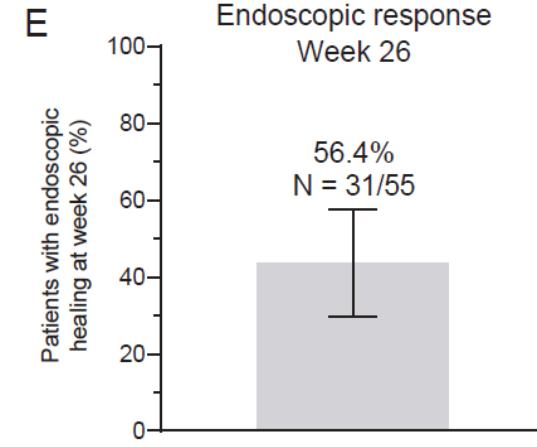
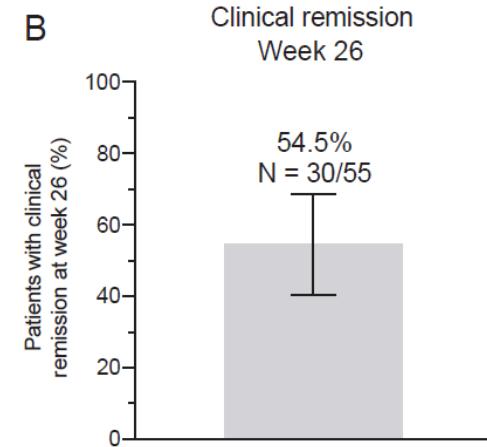
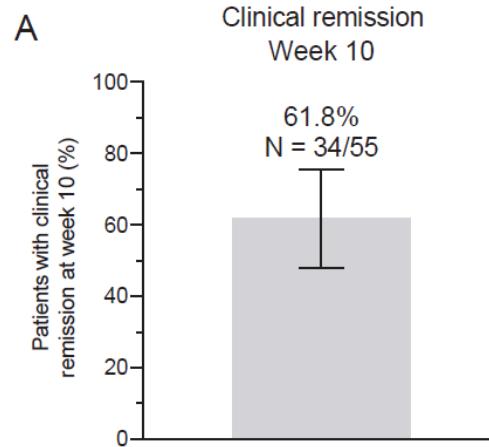


**Figure 1.** Study design. IV, intravenous; SC, subcutaneous; VDZ, vedolizumab.

# EXPLORER (TAK): efficacy

CD

EXPLORER demonstrated ACT efficacy in CD, but interpretation is limited by study size and lack of a placebo arm



Vedolizumab	15% at 6 weeks
Adalimumab	21-36% at 4 weeks

Vedolizumab	39-48% at 52 weeks
Adalimumab	36% at 56 weeks

Vedolizumab	Not Reported
Adalimumab	Not Reported

Vedolizumab	Not Reported
Adalimumab	Not Reported

- Although limited given it was a single arm study, EXPLORER demonstrated that adding adalimumab (Humira) and vedolizumab (Entyvio), can impart additive efficacy during induction (as opposed to comparing them in SEAVUE study). These rates compare well with historical benchmarks (with the caveat of cross-trial comparison and the different timepoints) - see above

# EXPLORER (TAK): safety profile

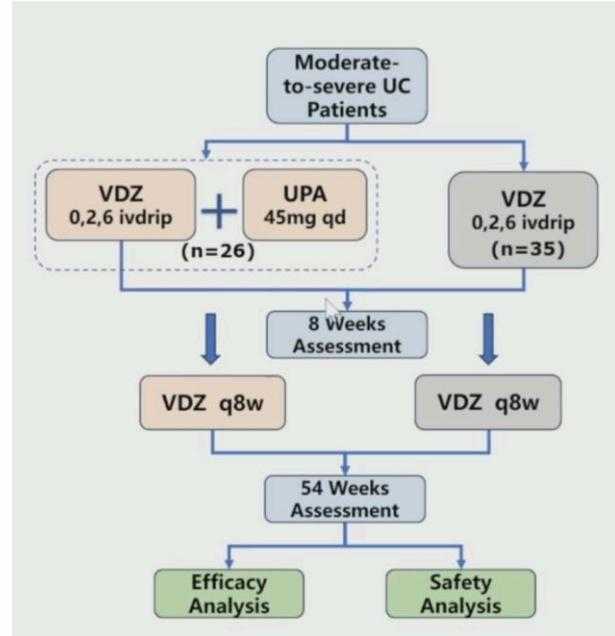
**EXPLORER provided initial evidence that using ACT was safe in CD**

- Although interpretation is limited by the small sample size and lack of a placebo arm, it was noted that no “unique safety signals” emerged with the triple regimen
- Furthermore, it was noted that the profiles of and rates of AEs and SAEs with the combination were similar to those already described in clinical trials and with real-world use of vedolizumab, adalimumab, and methotrexate monotherapy
- The combination appeared tolerable with low rates of SAEs and few patients discontinuing the study drugs due to AEs
- The EXPLORER results provide an additional piece of evidence to suggest the feasibility of combination regimens, helping to allay concerns about the safety of combining biologic therapies were a key consideration
- **TAK has several ongoing Ph 4 combination studies with its drug vedolizumab, each including external assets (as noted on the landscape slide), and none that would be registration-enabling**

AE <sup>a</sup>	Event, n	Patients with an event, n (%)
Most frequent (>5% of patients) nonserious AEs with triple combination therapy		
Arthralgia	10	9 (16.4)
Crohn's disease	9	9 (16.4)
Nasopharyngitis	6	6 (10.9)
Abdominal pain	6	5 (9.1)
Headache	5	5 (9.1)
Nausea	4	4 (7.3)
Fatigue	4	4 (7.3)
Abdominal pain upper	3	3 (5.5)
Gastroenteritis	3	3 (5.5)
Urinary tract infection	4	3 (5.5)
Blood creatinine phosphokinase level increased	3	3 (5.5)
Rash	5	3 (5.5)
SAE <sup>a,b</sup>	Patients with an event, n (%)	
SAEs with triple combination therapy		
Small-intestine obstruction	2	3 (3.6)
Crohn's disease	1	1 (1.8)
Lymphadenopathy	1	1 (1.8)
Pyrexia	1	1 (1.8)
Gastroenteritis	1	1 (1.8)
Perirectal abscess	1	1 (1.8)

# EC25-1140 data at ECCO 2025 also supports combination therapy in UC

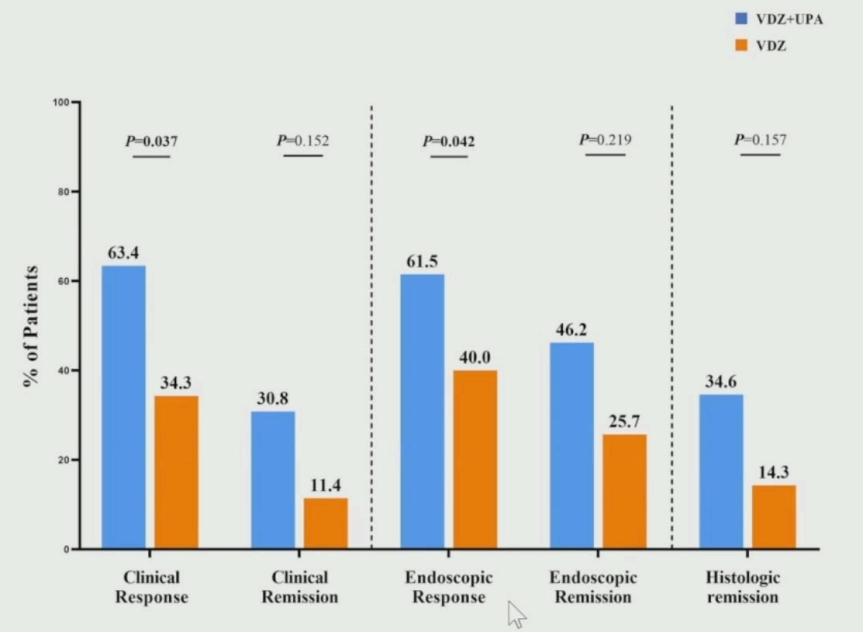
**EC25-1140 was a small RCT in China that demonstrated vedolizumab (Entyvio) + upadacitinib (Rinvoq) is superior to vedolizumab alone**



EC25-1140 was a small RCT that enrolled 51 UC patients in China to evaluate if adding upadacitinib (Rinvoq) to vedolizumab (Entyvio) could improve outcomes

## Results

- Clinical response:**  
63.4% vs 34.3% ( $P=0.037$ )
- Endoscopic response:**  
61.5% vs 40.0% ( $P=0.042$ )
- Clinical remission:**  
30.8% vs 11.4%
- Endoscopic remission:**  
46.2% vs 25.7%
- Histological remission:**  
34.6% vs 14.3%

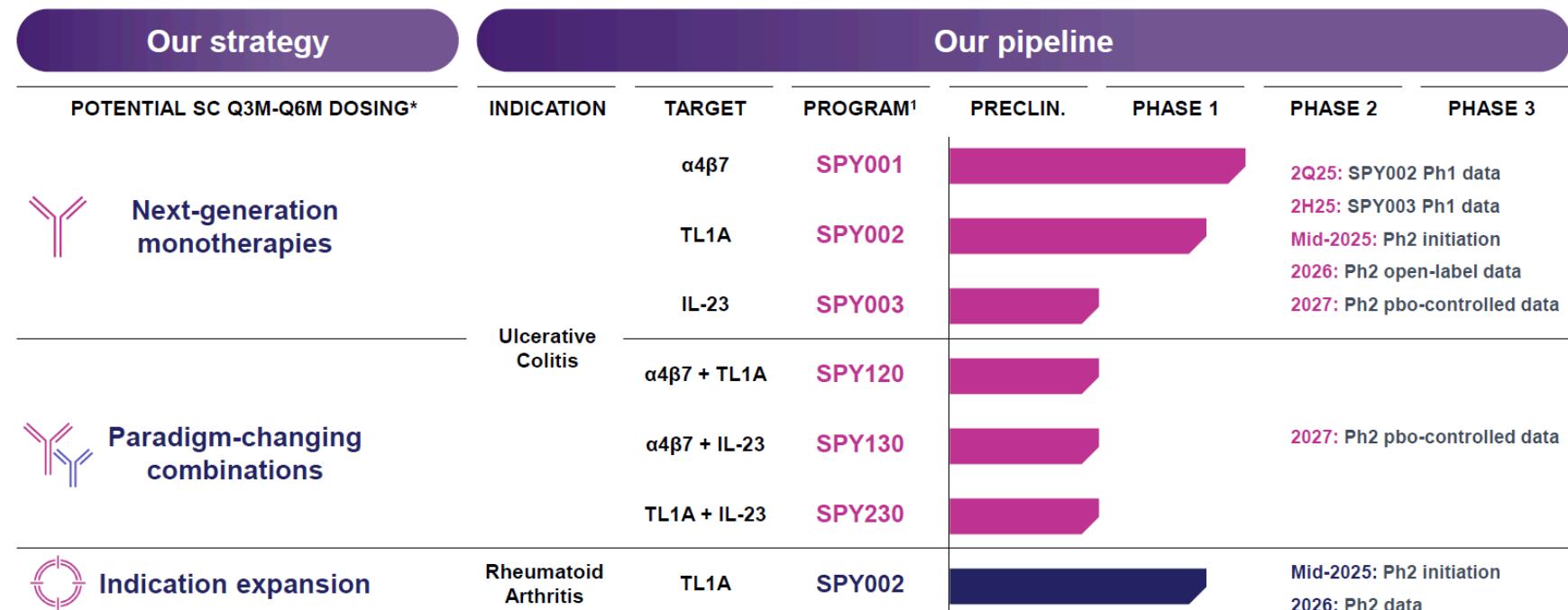


At week 8, all endpoints numerically favored the combination arm. Safety was noted to be similar between the two groups, although the combination arm had an increased incidence of acne. Overall, we view this small study as another piece of evidence that combination therapy can improve outcomes in IBD, and warrants further testing

# SPY002 (SYRE)

**SYRE is a combination-centric company, aiming to pair best-in-class molecules in convenient dosing schedules**

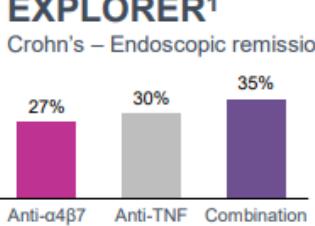
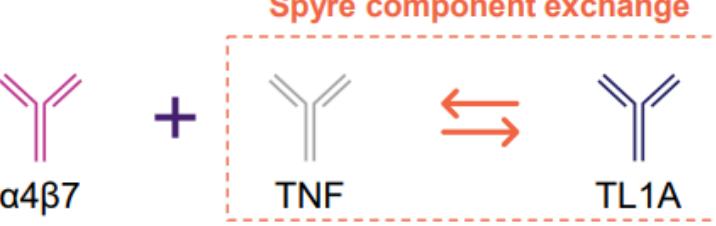
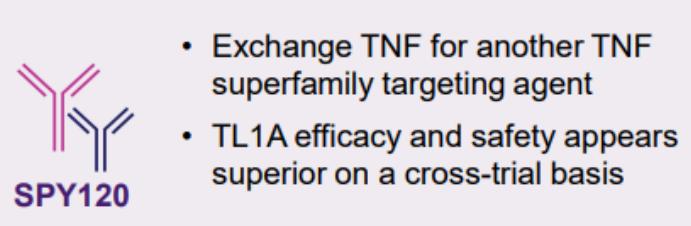
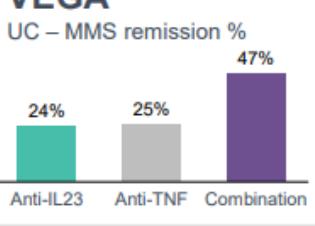
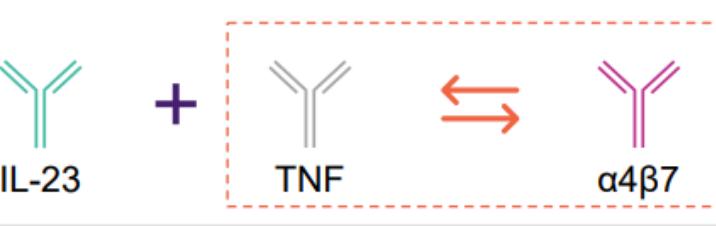
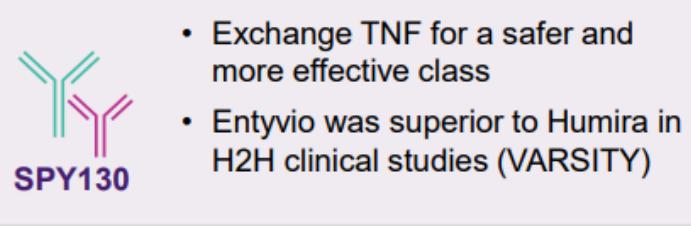
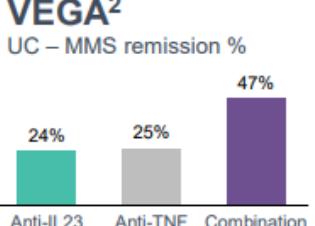
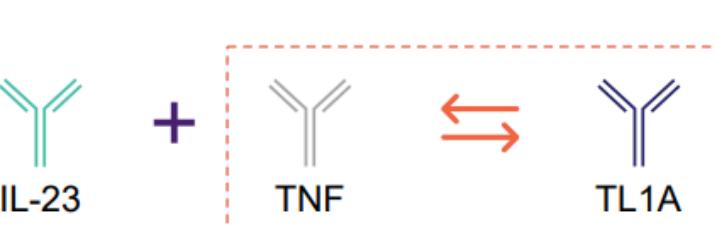
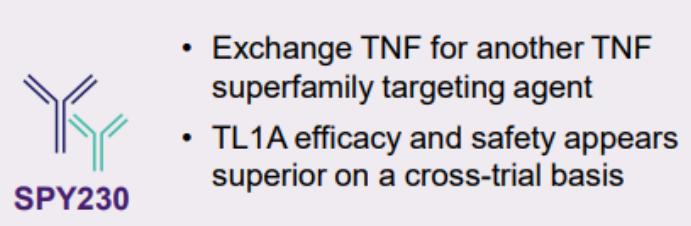
- SYRE's TL1A programs that we discussed earlier are part of the company's larger ambition to develop rational combinations (see next slide) that can be conveniently dosed
- The company reported encouraging PK/PD data from the SPY001 last year, and 2025 will be a busy year with FIH data for SPY002/003 and the launch of its Ph 2 program in UC



<sup>1</sup>Sytre holds exclusive worldwide licensed rights for SPY001, SPY002, and SPY003 from Paragon Therapeutics, Inc. SPY003 license is restricted to IBD, all other program licenses are unrestricted as to indication. \*SC=subcutaneous, Q3M-Q6M dosing profiles are expected maintenance profiles based on human PK simulations. All of the milestones for data including timing are as anticipated or expected as of the date of this presentation and subject to regulatory feedback.

# SYRE's approach entails combining safer components with HLE

SYRE plans to use HLE and swap out TNF component of combination therapy, with the goal of convenient, safe options

Clinical trial	Precedent combination	Spyre combinations & rationale								
<b>EXPLORER<sup>1</sup></b> Crohn's – Endoscopic remission %  <table border="1"><thead><tr><th>Treatment</th><th>Remission %</th></tr></thead><tbody><tr><td>Anti-a4β7</td><td>27%</td></tr><tr><td>Anti-TNF</td><td>30%</td></tr><tr><td>Combination</td><td>35%</td></tr></tbody></table>	Treatment	Remission %	Anti-a4β7	27%	Anti-TNF	30%	Combination	35%		 <ul style="list-style-type: none"><li>• Exchange TNF for another TNF superfamily targeting agent</li><li>• TL1A efficacy and safety appears superior on a cross-trial basis</li></ul>
Treatment	Remission %									
Anti-a4β7	27%									
Anti-TNF	30%									
Combination	35%									
<b>VEGA<sup>2</sup></b> UC – MMS remission %  <table border="1"><thead><tr><th>Treatment</th><th>Remission %</th></tr></thead><tbody><tr><td>Anti-IL23</td><td>24%</td></tr><tr><td>Anti-TNF</td><td>25%</td></tr><tr><td>Combination</td><td>47%</td></tr></tbody></table>	Treatment	Remission %	Anti-IL23	24%	Anti-TNF	25%	Combination	47%		 <ul style="list-style-type: none"><li>• Exchange TNF for a safer and more effective class</li><li>• Entyvio was superior to Humira in H2H clinical studies (VARSITY)</li></ul>
Treatment	Remission %									
Anti-IL23	24%									
Anti-TNF	25%									
Combination	47%									
<b>VEGA<sup>2</sup></b> UC – MMS remission %  <table border="1"><thead><tr><th>Treatment</th><th>Remission %</th></tr></thead><tbody><tr><td>Anti-IL23</td><td>24%</td></tr><tr><td>Anti-TNF</td><td>25%</td></tr><tr><td>Combination</td><td>47%</td></tr></tbody></table>	Treatment	Remission %	Anti-IL23	24%	Anti-TNF	25%	Combination	47%		 <ul style="list-style-type: none"><li>• Exchange TNF for another TNF superfamily targeting agent</li><li>• TL1A efficacy and safety appears superior on a cross-trial basis</li></ul>
Treatment	Remission %									
Anti-IL23	24%									
Anti-TNF	25%									
Combination	47%									

Note: <sup>1</sup>EXPLORER meta-analysis assumes a 27% remission rate for vedolizumab and 30% remission rate for adalimumab; EXPLORER included methotrexate treatment

Source: <sup>1</sup>Colombel, Jean-Frederic, et al. Clinical Gastroenterology and Hepatology 22.7 (2024): 1487-1496. <sup>2</sup>Feagan, Brian G., et al. The Lancet Gastroenterology & Hepatology 8.4 (2023): 307-320;

# Bispecific quick hits

## Overview

- Bispecific antibodies (BsAbs) are engineered biologics capable of targeting two distinct antigens or pathways simultaneously, offering unique therapeutic advantages
- Several companies are developing BsAbs as a different way to address the complexity and heterogeneity of IBD and break through the existing therapeutic ceiling
- BsAbs are now being explored across a number of autoimmune and inflammatory diseases, including IBD, with several candidates in preclinical and clinical trials. We cover this in further detail in our recent, landscape on the topic: [LINK](#)

## Development considerations

- Bispecifics have shown proven efficacy in a number of disease areas
- Combination targeting has been partially derisked in IBD
- Reduces complexity of administering multi-targeting therapeutics
- Although the field is in its infancy, there have already been some notable failures, with some BsAbs showing limited efficacy or high immunogenicity in IBD (e.g., AMGN and PFE)
- Fixed stoichiometry presents an engineering challenge
- Larger datasets are needed to better understand the safety profile of targeting multiple pathways in IBD, particularly those including newer targets such as TL1A
- Manufacturing complexity is potentially higher than coformulation approaches
- Commercialization and marketing of BsAb may be difficult if one or more of the targets is addressed by a biosimilar, and in general within the crowded IBD landscape

# IBD bispecific development landscape

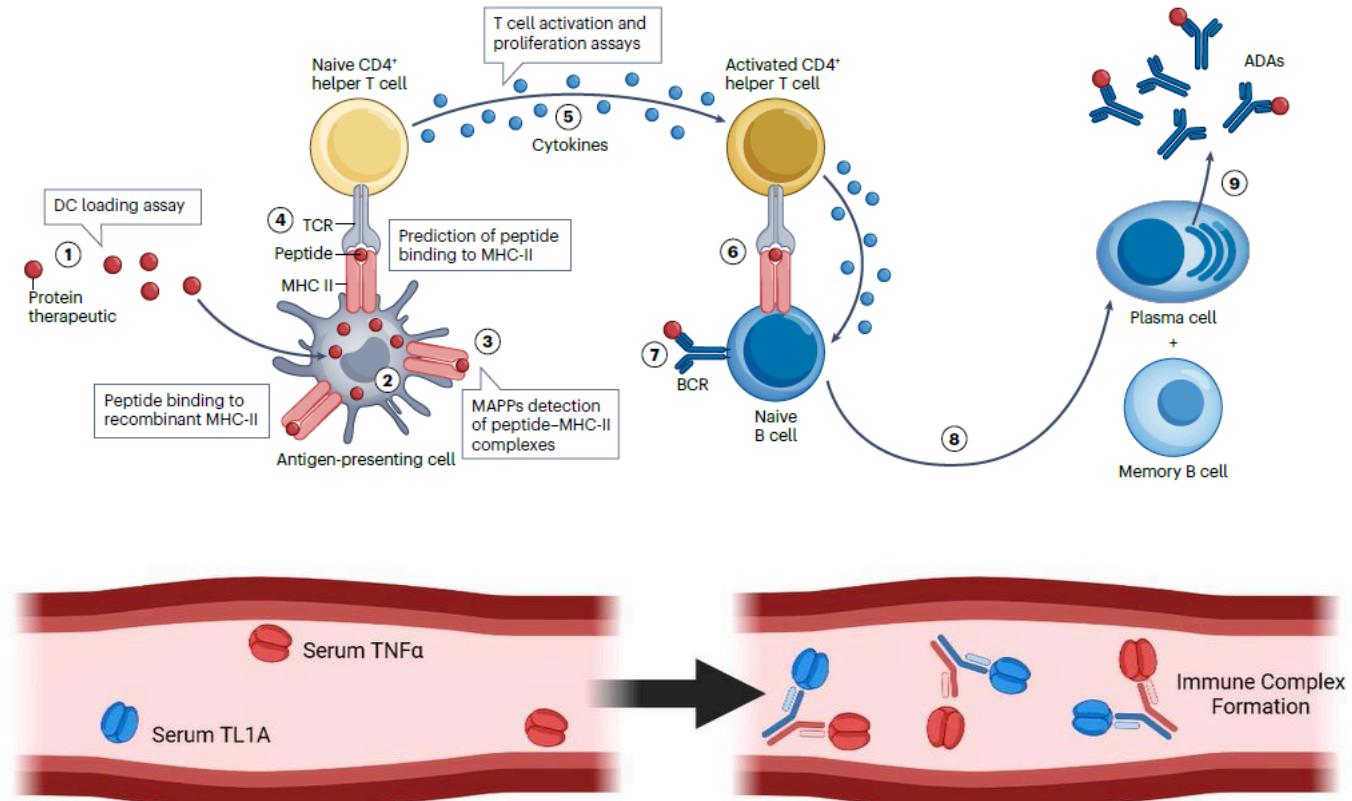
**Bispecific development in IBD is early-stage and largely centered on a few, well-understood targets**

Drug	Company	Molecule	ROA	Target	Status	
					UC	CD
PF-07261271	PFE / RHHBY	biologic	-	TL1A / p40	II planned	II planned
GSK4528287	GSK	biologic	-	IL-23 / IL-18	I	I
SOR102	Sorriso Pharma (private)	biologic	Oral	TNF $\alpha$ / IL-23	I	-
LQ080	Novamab Biopharma (private)	biologic	SC	TL1A / IL-23p19	-	-
HXN-1002	Helixon Therapeutics (private)	biologic	-	TL1A / $\alpha 4\beta 7$	-	-
HXN-1003	Helixon Therapeutics (private)	biologic	-	TL1A / IL-23p19	-	-
-	XNCR	biologic	-	TL1A / IL-23p19	-	-
MTX-201	Mozart Therapeutics (private)	biologic	-	KIR / ICOS	-	-
-	STTK	biologic	-	DR3 / ???	-	-
ATTO-004	Attovia Therapeutics (private)	biologic	-	Undisclosed	-	-
BBT003	Bambusa Therapeutics (private)	biologic	-	Undisclosed	-	-
ND081	Numab Therapeutics (private)	biologic	-	Undisclosed	-	-

# Immunogenicity could be a problem for certain BsAbs in IBD

## BsAbs that bind soluble targets could form highly immunogenic complexes, leading to ADAs

- All protein therapeutics are at risk of generating anti-drug antibodies (ADAs), see top diagram
- Infliximab, the first biologic approved in IBD, is known for its propensity to generate ADAs (given its chimeric design) and coadministration with an immunomodulator is recommended
  - Adalimumab also generates ADAs, but less so given it uses a humanized format
- Companies developing BsAbs in IBD will need to consider which targets they choose to best control immunogenicity given ADAs could impact long-term efficacy and safety (important for differentiation, etc. in the crowded IBD landscape)
- AMGN discontinued its TL1A x TNF $\alpha$  BsAb, AMG966, following high rate of ADA formation. The choice of targets, both which have soluble forms, led to the formation of large, immunogenic complexes (recall, TL1A targeting programs also have a high rate of ADAs)
- One solution to help reduce this could be having one or both binding domains target a surface-bound receptor



# SOR-102 (Sorriso Pharma)

**SOR-102 is an orally delivered bispecific that is cleaved in the tissue to deliver independent anti TNF and IL-23p19 suppression**

## SOR-102 Program background

- SOR-102 is a bispecific comprising of two glycine-linked VH<sub>H</sub> single domain antibodies with picomolar affinity to TNF $\alpha$  and IL-23p19- see [HERE](#) for additional detail
- SOR-102 is orally delivered. The bispecific molecules are contained within a capsule that dissolves in the stomach. Following this step, SOR-102 molecules are cleaved by trypsin in the upper GI tract, resulting in individual monomers capable of penetrating intestinal tissue and binding each target simultaneously
- Sorriso Pharma presented SAD/MAD from a small Ph 1b data evaluating patients with mild to severe UC at UEG 2024 and preliminary efficacy data at ECCO 2025
- Currently the pill burden for the drug is high, with patients in the Ph 1b taking 12 pills a day at the high dose, although this is expected to be 6 a day in the upcoming Ph 2

## Data highlights

- Recent Ph 1b data at ECCO 2025 were highlighted by a relatively clean safety profile
- Preliminary efficacy exhibited a dose response, although interpretation is limited by few biologic experienced patients and small numbers
- There was an initial signal of ADAs (although this was not associated with clinical response)

## Next up?

- Sorriso plans to initiate a Ph 2 trial in UC in 2025
- Additional steps are being taken to improve manufacturing and reduce pill burden

# Select bispecific program overview (1/2)

**Bispecific development is an emerging area in IBD with an array of targets being explored**

## RHHBY / PFE

### Program details

- RHHBY and PFE are collaborating on a TL1A / IL-23p40 (PF-07261271), which completed a Ph 1 study last year per clinicaltrials.gov
- This program is a result of RHHBY gaining an option to collaborate with PFE on this asset through the acquisition of Televant from ROIV

### Next up?

- Ph 2 initiations planned for 1H25 per RHHBY

## GSK

### Program details

- GSK announced plans with 4Q24 earnings it would develop GSK4528287 - an IL-18 / IL-23 bispecific in IBD
- The addition of an IL-18 targeting arm is designed to address the cytokines theorized proinflammatory effects on T helper cells

### Next up?

- Ph 2 initiations planned in both UC and CD

## Select bispecific program overview (2/2)

### Bispecific development is an emerging area in IBD with an array of targets being explored

#### XNCR

##### Program details

- XNCR announced it will follow development of its own HLE TL1A program, XmAb942, with a TL1A x IL-23p19 bispecific

##### Next up?

- Lead selection in 2025 and FIH expected during 2026

#### STTK

##### Program details

- Similarly, STTK plans to tail its DR3-targeting SL-325 program with a DR3 bispecific (other domain undisclosed)
- Additional thoughts on the program and strategy can be found in our accompanying initiation LINK

##### Next up?

- Lead selection in 2025 and FIH expected during 2026

## Oral formulations

- **Oral therapies aim to improve convenience:** small molecules offer an alternative to injectable biologics, with data suggesting a preference for oral options in the case of equivalent safety and efficacy
- **Oral IL-23 and  $\alpha 4\beta 7$  inhibitors emerging:** JNJ / PTGX recently reported encouraging Ph 2b data for icotrokinra (oral IL-23R inhibitor) in UC, with advanced studies in both UC and CD planned. LLY acquired MORF-057 (oral  $\alpha 4\beta 7$  inhibitor) from its \$3.2B buyout of MORF, with the program currently being evaluated in the EMERALD-2 Ph 2b study in UC
- **Pipeline expansion continues:** in addition to the ABVX's obefazimod, other new oral agents targeting novel targets, such as NLRX1, LANCL2, and RIPK1, are in development
- **Upcoming trial readouts in 2025:** as previously noted, Ph 3 topline data for ABVX's oral drug, obefazimod are expected in 3Q25, while data from LLY's EMERALD-2 study are expected in 1H25

# Oral formulations quick hits

Overview	+/- considerations
<ul style="list-style-type: none"><li>Several companies are developing or have acquired rights to programs that aim to provide orally available formulations against targets already addressed by approved IV/SC drugs (e.g., JNJ/PTGX with icotrokinra and LLY with MORF-057)</li><li>Others are developing orally available small molecules against novel targets, we cover several of these in the prior section on novel targets (e.g., ABVX with obefazimod)</li></ul>	<ul style="list-style-type: none"><li>Oral options rank highly amongst patients and may improve patient adherence and quality of life,</li><li>The targeting pathways are derisked by approved therapies</li><li>Oral therapies may enable earlier treatment in the disease course, potentially preventing irreversible tissue damage</li><li>IL-23 and <math>\alpha 4\beta 7</math> inhibitors generally demonstrate favorable safety, with minimal systemic side effects compared to broader immunosuppressants</li><li>Oral delivery may face bioavailability and pharmacokinetic challenges, potentially reducing efficacy compared to IV/SC options</li><li>Oral formulations require robust preclinical and clinical testing to ensure adequate drug stability, absorption, and targeted delivery to inflamed gut tissues</li><li>Oral formulations of a biologic that has approved biosimilars may have access headwinds (i.e., MORF's <math>\alpha 4\beta 7</math> vs a biosimilar vedolizumab [Entyvio])</li></ul>

Several companies are developing oral formulations of approved therapies, with two notable data readouts expected in 2025

**Several companies are developing oral formulations and there are two important data readouts expected this year for the field**

Drug	Company	Molecule	ROA	Target	Status	
					UC	CD
Etrasimod	PFE	small molecule	Oral	S1PR	Approved	III (CULTIVATE)
Obefazimod	ABVX	small molecule	Oral	miR-124	III	II
Omilancor	Nimmune	small molecule	Oral	LANCL2	III	II
MORF-057	MORF	small molecule	Oral	α4β7	II	II
Ritlecitinib	PFE	small molecule	Oral	JAK3	II	II
ABBV-113	ABBV	small molecule	Oral	NLRX1	II	II
JNJ-2113 (PN-234)	JNJ / PTGX	small molecule	Oral	IL-23R	II	--
GS-1427	GILD	small molecule	Oral	α4β7	II	-
ABBV-668	ABBV	small molecule	Oral	RIPK1	II	-
Eclitasertib	SAN FP / DNLI	small molecule	Oral	RIPK1	II	-
ADS-051	Adiso Therapeutics	small molecule	Oral	MRP2 / FPR1	II	-
BBT-401	Bridge Biotherapeutics	small molecule	Oral	Pellino-1	II	-
Orismilast	UNION Therapeutics	small molecule	Oral	PDE4	II	-
VE202	Vedanta Biosciences	-	Oral	microbiota	II	-
VTX002	VTYX	small molecule	Oral	S1P1R	II	-
Tilpisertib foscemecarbil	GILD	small molecule	Oral	TPL2	II	-
CU104	Curacle Co	small molecule	Oral	IL-6	II	-
SPH3127	Shanghai Pharma Biotherapeutics	small molecule	Oral	renin	II*	-
SAR441566	SAN FP	small molecule	Oral	TNFR	-	II
AGMB-129	AgomAb	small molecule	Oral	ALK5	--	II
Company	Drug	Mechanism	Event		Expected Timing	
JNJ / PTGX	Icotrokinra (JNJ-2113)	Oral anti-IL-23R	Detailed data from the Ph 2b ANTHEM study		2025	
Ensho Therapeutics	NSHO-101	Oral anti-α4β7	Ph 2 initiation in UC		1H25	
LLY	MORF-057	Oral anti-α4β7	Topline data from Ph 2b EMERALD-2 study in UC		1H25	
ABVX	Obefazimod	miR-124 inducer	Topline data from Ph 3 ABTECT program in UC		3Q25	

# Icotrokinra (JNJ / PTGX)

Preliminary data from the ANTHEM study will help to better understand the path forward for JNJ's oral IL-23 targeting program

## Program background

- Icotrokinra (JNJ-2113) is an investigational targeted oral peptide that selectively blocks the IL-23 receptor, a key player in the inflammatory pathways of plaque psoriasis and other IL-23-mediated diseases
- JNJ and PTGX entered a collaboration in 2017, additional detail on the terms, [HERE](#)

## Data highlights

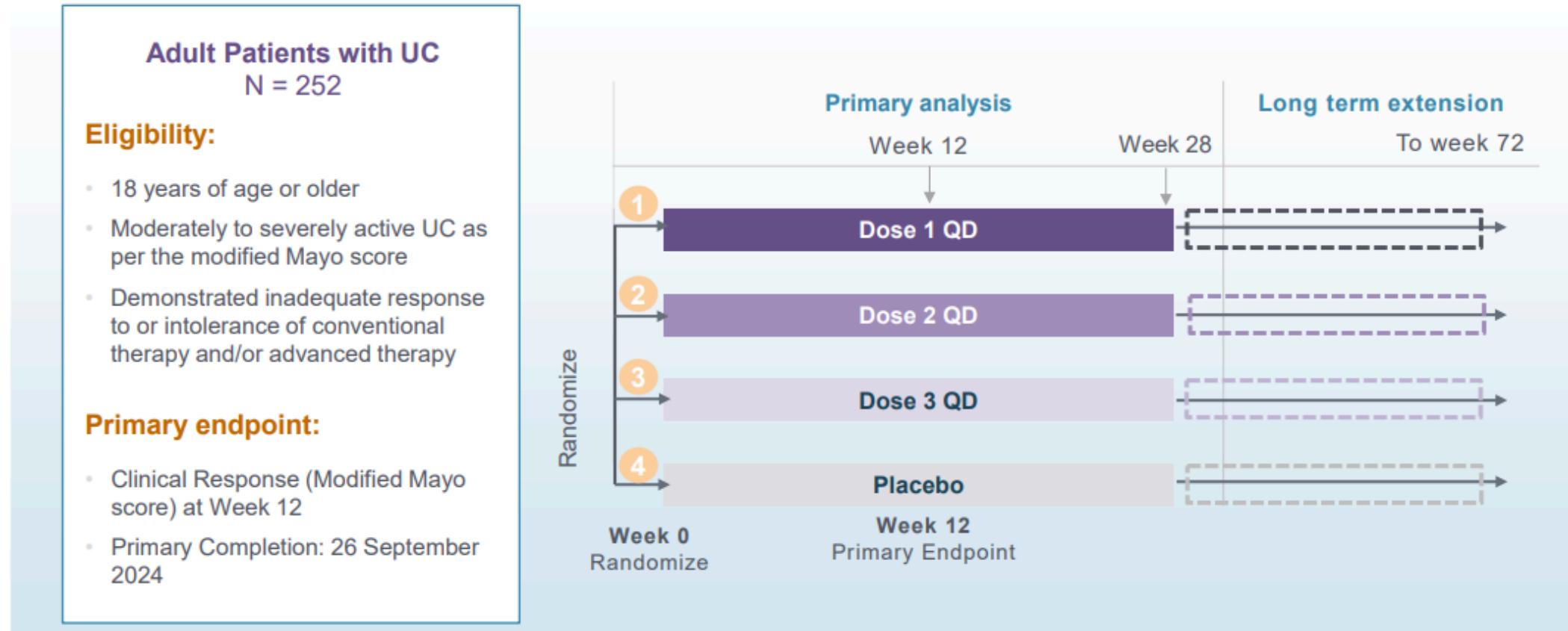
- Potent inhibition of IL-23 signaling in preclinical models and in a Ph 1 study of healthy volunteers
- Following topline results last year, improved and encouraging data were recently reported from a Ph 3 ICONIC-LEAD study results in plaque psoriasis (PsO) at AAD. See our colleague's notes: [LINK](#), [LINK](#)
- In UC, Ph 2b data from ANTHEM were published in March, and showed icotrokinra to have competitive efficacy and good safety/tolerability—although more is needed to fully contextualize these results, our colleague's note on the data ([LINK](#)), and highlights on the next slides

## Next up?

- PTGX plan to file an NDA in 4Q25 in PsO
- In UC and CD, more advanced studies are being planned

# Icotrokinra (JNJ / PTGX): Ph 2b ANTHEM study design

ANTHEM used a typical design with an LTE component



Note: icotrokinra must be taken on an empty stomach (no food/drink\* 30 minutes prior)

# Icotrokinra (JNJ / PTGX): Ph 2b ANTHEM study results

**ANTHEM supports additional studies of icotrokinra, but additional detail will be needed to fully understand the drug's profile**

- Topline results from ANTHEM-UC study showed all 3 doses of once-daily icotrokinra met the primary endpoint of clinical response at week 12
- Clinical remission and response rates continued to improve through week 28
- Regarding safety, it was noted that icotrokinra was well tolerated, with similar proportions of participants reporting  $\geq 1$  AEs between the icotrokinra dose groups and the placebo groups
- Importantly, baseline characteristics were not reported it is unclear to what extent the study enrolled biologic-experienced vs. naïve patients (and which therapies these were), which will be important to contextualize the efficacy signals
- Positive outcome showing potential to transform UC treatment paradigm
- At week 12, the highest dose achieved
  - 1° endpoint: **Clinical response = 63.5% versus 27% for placebo**
  - 2° endpoint: **Clinical remission = 30.2% versus 11.1% for placebo**
  - Clinical remission and response rates continued to improve through week 28
- All 3 doses met the primary endpoint of clinical response at week 12, with a favorable safety profile
- Clinically meaningful differences versus placebo in key secondary endpoints of clinical remission, symptomatic remission, and endoscopic improvement at week 12
- **Next steps:** More advanced clinical studies in ulcerative colitis and Crohn's disease

# MORF-057 (LLY)

**LLY is evaluating an oral  $\alpha$ 4 $\beta$ 7, with topline data from EMERALD-2 expected this year**

## Program background

- MORF-057 is an oral, selective  $\alpha$ 4 $\beta$ 7 inhibitor designed to modulate lymphocyte trafficking, aiming to reduce GI inflammation in IBD, effectively an “oral vedolizumab”
- LLY received MORF-057 when it acquired MORF in 2024 for \$3.2B, the asset had been derisked by Ph 2a clinical data in UC

## Data highlights

- Ph 2a EMERALD-1 study in UC demonstrated encouraging clinical remission data, although endoscopic improvement was a point of contention (though this was attributed to small sample size and high disease burden)
- Safety was acceptable and reported AEs were mild and did not lead to discontinuation

## Next up?

- Topline data from Ph 2b EMERALD-2 study in UC are expected in 1H25
- The Ph 2 GARNET study evaluating MORF-057 in CD has an estimated primary completion of May 2026

## Appendix

# Appendix: Harvey-Bradshaw Index (HBI)

- HBI is considered more “user-friendly” than the CDAI though is not used during clinical trials
- However, the HBI has been shown to correlate with the CDAI
  - A drop in the CDAI of 100 points corresponds to a 3-point drop in the HBI. A CDAI of <150 (i.e., clinical remission) corresponds to an HBI of <4

**Table 4.** Harvey-Bradshaw Index (HBI)

- **General well being**  
(0=very well; 1=slightly below average; 2=poor; 3=very poor; 4=terrible)
- **Abdominal pain**  
(0=none; 1=mild; 2=moderate; 3=severe)
- **Number of liquid stools per day**  
(0=0–1 stools; 1=2–3 stools; 2=4–5 stools; 3=6–7 stools; 4=8–9 stools; 5=10+ stools)
- **Abdominal mass**  
(0=none; 1=dubious; 2=definite; 3=tender)
- **Complications**  
Arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissures, new fistulas, abscesses (1 point for each)
- **Total score**

Remission: HBI score <3 points.  
Relapse: HBI score >7 points.

# Appendix: Crohn's disease endoscopic index of severity (CDEIS)

	Rectum	Sigmoid & Left Colon	Transverse Colon	Right Colon	Ileum	TOTAL
Deep ulceration If present, score 12 If absent, score 0	—	—	—	—	—	—
Superficial ulceration If present, score 6 If absent, score 0	—	—	—	—	—	—
Surface involved by the disease (measured in cm*)	—	—	—	—	—	—
Ulcerated surface (measured in cm*)	—	—	—	—	—	—
TOTAL		—		<b>A</b>		
Number ( <i>n</i> ) of segments totally or partially explored (1-5)		—		<b>n</b>		
Total A divided by <i>n</i>		—		<b>B</b>		
Ulcerated Stenosis If present anywhere, score 3 If absent, score 0		—		<b>C</b>		
Non-Ulcerated Stenosis If present anywhere, score 3 If absent, score 0		—		<b>D</b>		
TOTAL B+C+D		—		<b></b>		

\* For partially explored segments and for the ileum, the 10 cm linear scale represents the surface effectively explored.

Table 1. Features of the Crohn's disease endoscopic index of severity (CDEIS) [14,15].

Features described in the system	Scoring	Division of the ileocolon	Definitions of disease severity
1. Superficial ulcers	Total: 0-44 (all segments added together)	5 segments: terminal ileum; ascending colon;	Not clearly defined: Healed: ≤3
2. Deep ulcers		transverse colon; descending and	Mild: <5 Moderate: 5-
3. Surface involved in disease	Each feature has a different point value	sigmoid colon; rectum	15 Severe: >15 Response to therapy: not defined
4. Ulcerated surface			
5. Ulcerated stenosis			
6. Non-ulcerated stenosis			

# Appendix: baseline characteristics and endpoints in UC Ph 3 trials (1/3)

**Table 1 | Baseline characteristics of participants randomized to recent phase III trials in ulcerative colitis**

Trial	Trial design	Treatment assignment	Disease duration (years)	Extensive pancolitis (n (%))	Modified Mayo score	Endoscopy subscore=3 (n (%))	Baseline corticosteroid use (n (%))	Prior biologic treatment (n (%))	Prior TNF antagonist use (n (%))	Primary end point
OCTAVE Induction 1 (Sandborn et al.) <sup>39</sup>	8-week randomized induction trials x2, responders re-randomized to OCTAVE Sustain maintenance trial	Tofacitinib 10mg (n=476)	Median 6.5 (range 0.3-42.5)	252 (53)	NR	NR	214 (45)	243 (51)	243 (51)	Clinical remission (total Mayo score ≤2 with no subscore >1 and rectal bleeding subscore 0)
		Placebo (n=122)	Median 6.0 (range 0.5-36.2)	66 (54)	NR	NR	58 (48)	64 (53)	64 (53)	
	OCTAVE Induction 2 (Sandborn et al.) <sup>39</sup>	Tofacitinib 10mg (n=429)	Median 6.0 (range 0.4-39.4)	211 (49)	NR	NR	198 (46)	222 (52)	222 (52)	
		Placebo (n=112)	Median 6.2 (range 0.4-27.9)	56 (51)	NR	NR	55 (49)	60 (54)	60 (54)	
UNIFI (Sands et al.) <sup>37</sup>	8-week randomized induction trial, 44-week responder re-randomization maintenance trial	Ustekinumab 130mg (n=320)	Mean 8.1 (s.d. 7.2)	NR	NR	NR	173 (54)	164 (51)	107 (33)	Clinical remission (total Mayo score ≤2 and no subscore >1)
		Ustekinumab 6mg/kg (n=322)	Mean 8.2 (s.d. 7.8)	NR	NR	NR	168 (53)	166 (52)	160 (33)	
		Placebo (n=319)	Mean 8.0 (s.d. 7.2)	NR	NR	NR	157 (49)	161 (51)	112 (35)	
VARSITY (Sands et al.) <sup>16</sup>	Treat-through 52-week head-to-head active comparator trial	Vedolizumab (n=385)	Mean 7.3 (s.d. 7.2)	NR	NR	NR	139 (36)	80 (21)	80 (21)	Clinical remission (total Mayo score ≤2 and no subscore >1)
		Adalimumab (n=386)	Mean 6.4 (s.d. 6.0)	NR	NR	NR	140 (36)	81 (21)	81 (21)	
TRUE NORTH (Sandborn et al.) <sup>14</sup>	10-week randomized induction trial+open-label induction cohort, responders re-randomized to maintenance trial	Ozanimod cohort 1 (n=429)	Mean 6.8 (s.d. 7.0)	161 (38)	Mean 6.6 (s.d. 1.2)	NR	119 (28)	130 (30)	130 (30)	Clinical remission (rectal bleeding subscore 0, stool frequency subscore ≤1 or decreased ≥1 from baseline, endoscopy subscore 0 or 1)
		Ozanimod cohort 2 (n=367)	Mean 7.9 (s.d. 7.4)	130 (35)	Mean 6.8 (s.d. 1.3)	NR	124 (34)	159 (43)	159 (43)	
		Placebo (n=216)	Mean 6.9 (s.d. 6.6)	82 (38)	Mean 6.6 (s.d. 1.2)	NR	70 (32)	65 (30)	65 (30)	

# Appendix: baseline characteristics and endpoints in UC Ph 3 trials (2/3)

SELECTION Study A (Feagan et al.) <sup>34</sup>	Phase IIb/III, 10-week random- ized induc- tion trials $\times 2$ , responders re-randomized to 58-week maintenance trial	Filgotinib 100 mg (n=277)	Mean 6.7 (s.d. 7.4)	NR	NR	159 (57)	67 (24)	2 (1)	2 (1)	Clinical remission (rectal bleeding subscore 0, stool frequency subscore $\leq 1$ and decrease $\geq 1$ from baseline, endoscopy subscore 0 or 1)
		Filgotinib 200 mg (n=245)	Mean 7.2 (s.d. 6.9)	NR	NR	133 (54)	54 (22)	0 (0)	0 (0)	
		Placebo (n=137)	Mean 6.4 (s.d. 7.4)	NR	NR	76 (56)	34 (25)	0 (0)	0 (0)	
SELECTION Study B (Feagan et al.) <sup>34</sup>		Filgotinib 100 mg (n=285)	Mean 9.7 (s.d. 7.2)	NR	NR	222 (78)	103 (36)	283 (99)	266 (93)	
		Filgotinib 200 mg (n=262)	Mean 9.8 (s.d. 7.6)	NR	NR	203 (78)	94 (36)	259 (99)	242 (92)	
		Placebo (n=142)	Mean 10.2 (s.d. 8.2)	NR	NR	111 (78)	51 (36)	139 (98)	130 (92)	
U-ACHIEVE (Danese et al.) <sup>11</sup>	8-week random- ized induction trials $\times 2$ , responders re-randomized to 52-week mainte- nance trial	Upadacitinib 45 mg (n=319)	Median 6.6 (IQR 9.6)	161 (50)	Mean 7.0 (s.d. 1.2)	223 (70)	124 (39)	174 (55)	163 (51)	Clinical remission by modified Mayo score (stool frequency subscore $\leq 1$ and not greater than baseline, rectal bleeding subscore 0, endoscopy subscore 0 or 1)
		Placebo (n=154)	Median 6.0 (IQR 10.0)	80 (52)	Mean 7.0 (s.d. 1.2)	104 (68)	61 (40)	82 (53)	73 (47)	
U-ACCOMP- LISH (Danese et al.) <sup>11</sup>		Upadacitinib 45 mg (n=341)	Median 5.6 (IQR 7.5)	176 (52)	Mean 7.0 (s.d. 1.2)	233 (68)	120 (35)	173 (51)	163 (48)	
		Placebo (n=174)	Median 4.9 (IQR 7.4)	86 (49)	Mean 7.0 (s.d. 1.2)	121 (70)	72 (41)	93 (53)	82 (47)	
LUCENT (D'Haens et al.) <sup>47</sup>	12-week randomized induction trials $\times 2$ , responders re-randomized to 52 week maintenance trial	Mirikizumab 300 mg (n=868)	Mean 7.2 (s.d. 6.7)	324 (37)	Score $\geq 7$ (53%)	574 (66)	351 (40)	360 (42)	325 (37)	Clinical remission by modified Mayo score (stool frequency subscore 0 or 1 with $\geq 1$ point decrease from baseline, rectal bleed- ing subscore 0, endo- scopy subscore 0 or 1)
		Placebo (n=294)	Mean 6.9 (s.d. 7.0)	105 (36)	Score $\geq 7$ (53%)	200 (68)	113 (39)	117 (40)	97 (33)	

# Appendix: baseline characteristics and endpoints in UC Ph 3 trials (3/3)

**Table 1 (continued) | Baseline characteristics of participants randomized to recent phase III trials in ulcerative colitis**

Trial	Trial design	Treatment assignment	Disease duration (years)	Extensive pancolitis (n (%))	Modified Mayo score	Endoscopy subscore=3 (n (%))	Baseline corticosteroid use (n (%))	Prior biologic treatment (n (%))	Prior TNF antagonist use (n (%))	Primary end point
ELEVATE UC 52 (Sandborn et al.) <sup>15</sup>	12-week and 52-week randomized treat-through trials	Etrasimod 2mg (n=289)	Mean 7.5 (s.d. 8.0)	93 (32)	Mean 6.7 (s.d. 1.2)	163 (56)	96 (33)	108 (37)	60 (21)	Co-primary end points: clinical remission at week 12 and week 52 by modified Mayo score (stool frequency subscore 0 or 1 with ≥1 point decrease from baseline, rectal bleeding subscore 0, endoscopy subscore 0 or 1)
		Placebo (n=144)	Mean 5.9 (s.d. 5.5)	47 (33)	Mean 6.7 (s.d. 1.2)	88 (61)	46 (32)	55 (38)	31 (22)	
ELEVATE UC 12 (Sandborn et al.) <sup>15</sup>		Etrasimod 2mg (n=238)	Mean 7.3 (s.d. 6.6)	77 (32)	Mean 6.6 (s.d. 1.2)	129 (54)	78 (33)	89 (37)	57 (24)	
		Placebo (n=116)	Mean 7.7 (s.d. 7.3)	41 (35)	Mean 6.6 (s.d. 1.2)	60 (52)	38 (33)	43 (37)	29 (25)	

IQR, interquartile range; NR, not reported; TNF, tumour necrosis factor.

# Appendix: baseline characteristics and endpoints in CD Ph 3 trials (1/2)

**Table 2 | Baseline characteristics of participants randomized to recent phase III trials in Crohn's disease**

Trial	Trial design	Treatment assignment	Disease duration (years)	Isolated ileal disease (n (%))	Baseline CDAI	Baseline SES-CD	Baseline corticosteroid use (n (%))	Prior biologic treatment (n (%))	Prior TNF antagonist use (n (%))	Primary end point
UNITI-1 (Feagan et al.) <sup>36</sup>	Randomized 8 week induction trials ×2, responders re-randomized to maintenance trial (IM-UNITI)	Ustekinumab 130 mg (n=245)	Mean 11.8 (s.d. 8.3)	38 (16)	Mean 321.0 (s.d. 64.7)	Mean 14.2 <sup>a</sup>	121 (49)	243 (99)	243 (99)	Week 6 clinical response (decrease from baseline in CDAI ≥100 points or total CDAI <150)
		Ustekinumab 6 mg/kg (n=249)	Mean 12.7 (s.d. 9.2)	37 (15)	Mean 327.6 (s.d. 62.0)	Mean 14.2 <sup>a</sup>	108 (43)	246 (99)	246 (99)	
		Placebo (n=247)	Mean 12.1 (s.d. 8.4)	28 (11)	Mean 319.0 (s.d. 59.7)	Mean 12.3 <sup>a</sup>	111 (45)	246 (99)	246 (99)	
UNITI-2 (Feagan et al.) <sup>36</sup>		Ustekinumab 130 mg (n=209)	Mean 8.7 (s.d. 8.5)	53 (26)	Mean 304.1 (s.d. 57.0)	Mean 14.2 <sup>a</sup>	80 (38)	57 (27)	57 (27)	
		Ustekinumab 6 mg/kg (n=209)	Mean 8.7 (s.d. 8.4)	49 (23)	Mean 302.2 (s.d. 58.9)	Mean 14.2 <sup>a</sup>	92 (44)	65 (31)	65 (31)	
		Placebo (n=210)	Mean 10.4 (s.d. 9.8)	44 (21)	Mean 302.2 (s.d. 61.7)	Mean 12.3 <sup>a</sup>	75 (36)	79 (38)	79 (38)	
SEAVUE (Sands et al.) <sup>21</sup>	Treat-through 52-week head-to-head active comparator trial	Ustekinumab (n=191)	Median 2.6 (IQR 0.7–5.8)	60 (32)	Mean 301.6 (s.d. 61.6)	Median 7.0 (IQR 5.0–14.0)	70 (37)	0 (0)	0 (0)	Clinical remission (CDAI <150)
		Adalimumab (n=195)	Median 2.6 (IQR 0.9–8.6)	55 (28)	Mean 300.0 (s.d. 56.0)	Median 8.0 (IQR 5.0–13.0)	75 (39)	0 (0)	0 (0)	
ADVANCE (D'Haens et al.) <sup>10</sup>	Randomized 12-week induction trials ×2, responders re-randomized to maintenance trial	Risankizumab 600 mg (n=336)	Mean 9.0 (s.d. 8.8)	52 (15)	Mean 311.2 (s.d. 62.4)	Mean 14.7 (s.d. 7.7)	102 (30)	195 (58)	183 (55)	Co-primary end points clinical remission (defined by CDAI or PRO2 by average daily stool frequency and abdominal pain subscores) + endoscopic response (50% reduction in SES-CD)
		Risankizumab 1,200 mg (n=339)	Mean 8.9 (s.d. 8.4)	54 (16)	Mean 311.5 (s.d. 68.4)	Mean 13.4 (s.d. 6.5)	101 (30)	199 (59)	187 (55)	
		Placebo (n=175)	Mean 8.2 (s.d. 7.1)	19 (11)	Mean 319.2 (s.d. 59.4)	Mean 13.8 (s.d. 6.8)	50 (29)	97 (55)	97 (55)	
MOTIVATE (D'Haens et al. 2022) <sup>10</sup>		Risankizumab 600 mg (n=191)	Mean 10.9 (s.d. 7.7)	33 (17)	Mean 310.7 (s.d. 63.6)	Mean 14.4 (s.d. 7.6)	65 (34)	191 (100)	177 (93)	
		Risankizumab 1,200 mg (n=191)	Mean 11.9 (s.d. 9.1)	21 (11)	Mean 312.5 (s.d. 61.2)	Mean 15.1 (s.d. 7.6)	62 (32)	191 (100)	181 (95)	
		Placebo (n=187)	Mean 12.5 (s.d. 9.7)	26 (14)	Mean 319.6 (s.d. 69.8)	Mean 15.0 (s.d. 8.1)	68 (36)	187 (100)	181 (97)	

## Appendix: baseline characteristics and endpoints in CD Ph 3 trials (2/2)

U-EXCEL (Loftus et al.) <sup>13</sup>	Randomized 12-week induction trials ×2, responders re-randomized to maintenance trial	Upadacitinib 45 mg (n=350)	Median 6.7 (range 0.1–52.1)	58 (17)	Mean 292.4 (s.d. 81.3)	Mean 13.7 (s.d. 7.3)	126 (36)	161 (46)	NR	Co-primary end points clinical remission + endoscopic response (50% reduction in SES-CD)
		Placebo (n=176)	Median 5.7 (range 0.3–46.3)	27 (15)	Mean 293.9 (s.d. 85.4)	Mean 13.6 (s.d. 7.0)	64 (36)	78 (44)	NR	
U-EXCEED (Loftus et al.) <sup>13</sup>		Upadacitinib 45 mg (n=324)	Median 9.3 (range 0.5–55.2)	48 (15)	Mean 306.6 (s.d. 89.4)	Mean 15.2 (s.d. 7.8)	108 (33)	324 (100)	NR	
		Placebo (n=171)	Median 9.8 (range 0.6–46.1)	23 (14)	Mean 308.1 (s.d. 84.3)	Mean 14.9 (s.d. 7.8)	60 (35)	171 (100)	NR	
SEQUENCE (Peyrin-Biroulet et al.) <sup>20</sup>	Randomized treat-through 48-week head-to-head active comparator trial	Risankizumab (n=255)	Mean 9.4 (s.d. 7.8)	42 (17)	Mean 309.4 (s.d. 61.7)	Mean 13.5 (s.d. 7.1)	58 (23)	255 (100)	255 (100)	Non-inferiority clinical remission at week 24 (50% of trial population) + endoscopic remission at week 48 (superiority)
		Ustekinumab (n=265)	Mean 9.4 (s.d. 8.7)	45 (17)	Mean 310.1 (s.d. 62.6)	Mean 14.1 (s.d. 7.4)	71 (27)	265 (100)	265 (100)	
VIVID-1 (Ferrante et al.) (abstract) <sup>61</sup>	Randomized treat-through 52-week head-to-head placebo and active comparator (UST) comparator trial	Mirikizumab (n=579)	Mean 7.4 (s.d. 8.2)	65 (11.2)	Mean 323.1 (s.d. 85.8)	Mean 13.5 (s.d. 6.6)	177 (31)	281 (49)	NR	Superiority vs placebo, composite PRO clinical response at week 12 + endoscopic response at week 52; composite PRO clinical response at week 12 + clinical remission at week 52
		Ustekinumab (n=287)	Mean 7.2 (s.d. 7.7)	29 (10.1)	Mean 318.5 (s.d. 93.2)	Mean 13.9 (s.d. 6.6)	90 (31)	139 (48)	NR	
		Placebo (n=199)	Mean 7.8 (s.d. 7.4)	19 (9.5)	Mean 318.9 (s.d. 86.2)	Mean 13.1 (s.d. 6.0)	58 (29)	97 (49)	NR	

CDAI, Crohn's Disease Activity Index; IQR, interquartile range; NR, not reported; PRO, patient-reported outcome; PRO2, two-component PRO; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumour necrosis factor; UST, ustekinumab. <sup>a</sup>Pooled data between the UNITI-1 and UNITI-2 studies and based on substudy population (n=97 placebo; n=155 ustekinumab pooled dosing).

# Appendix: ROA for TNF $\alpha$ inhibitors

	ROA	Induction	Maintenance
<b>Infliximab (e.g., Remicade)</b>	Given IV in a clinical setting (SC formulation has been introduced in some regions for maintenance). Each IV infusion typically takes 2 hours and requires medical supervision	Weight-based dosing of 5 mg/kg IV at weeks 0, 2, and 6. This three-dose loading phase is the standard protocol to induce remission in CD and UC. Patients not responding by week 14 are usually deemed non-responders	5 mg/kg IV every Q8W. Patients who respond to induction stay on Q8W infusions long-term. Dose or frequency can be escalated (e.g. 10 mg/kg or Q4W) if loss of response occurs. Ongoing IV infusions are required. Patients who have been induced with IV infliximab to switch to 120 mg SC injections (Zymfentra) Q2W for maintenance. This SC option – administered via a prefilled syringe or injector
<b>Adalimumab (e.g., Humira)</b>	Administered SC, typically by patients themselves at home. It comes in prefilled syringes and autoinjector pens for SC injection into the thigh or abdomen. No IV infusion is needed for adalimumab. This option offers a more convenient at-home dosing schedule compared to IV therapies	160 mg SC at week 0, followed by 80 mg SC at week 2. In practice, the 160 mg starting dose is given as four 40 mg injections in one day (or split over two consecutive days). This loading phase is standard for inducing response in CD and UC	40 mg SC every other week (starting at week 4). If needed (e.g. for loss of response), some patients escalate to 40 mg QW, but the label maintenance is 40 mg Q2W. Maintenance is long-term, administered continuously as SC injections
<b>Certolizumab pegol (e.g., Cimzia)</b>	Delivered SC, with no IV formulation. It comes as prefilled syringes (and an optional autoinjector pen in some markets) for self-injection. Like adalimumab, it's a fully at-home therapy. Notably, certolizumab is a pegylated Fab' fragment of an anti-TNF antibody (lacking an Fc region), but this does not change the ROA or patient experience	400 mg SC at weeks 0, 2, and 4. Each 400 mg dose is given as two injections of 200 mg (since each syringe/pen contains 200 mg). This three-dose induction schedule is used to induce remission in Crohn's disease.	400 mg SC Q4W. After the induction phase, patients continue with a 400 mg dose once Q4W for maintenance of response (In rheumatoid arthritis, an alternate maintenance of 200 mg every 2 weeks is used, but for CD the approved maintenance is one 400 mg dose Q4W). Patients or caregivers administer certolizumab via SC injection, typically into the abdomen or thigh. Prefilled syringes are provided and must be kept refrigerated. UCB also offers a novel autoinjector pen (branded "AutoClicks" in some regions) for certolizumab 200 mg, which many patients find convenient. After proper training, most patients can self-inject at home. Because certolizumab lacks an IgG Fc portion, it does not actively cross the placenta, but this does not affect its injection method (it remains SC only)
<b>Golimumab (Simponi)</b>	Given SC, as in UC, it is available as an SC injection only (Simponi). There is an IV form (Simponi Aria) approved for arthritis indications. The medication comes in a single-use prefilled syringe or a disposable autoinjector pen (the SmartJect device).	200 mg SC at week 0, then 100 mg SC at week 2. Induction involves two injections (each 100 mg) on day 0 (total 200 mg) and one 100 mg injection at week 2. This loading schedule was derived from clinical trials to optimize drug levels for induction of UC remission	100 mg SC Q4W. The first maintenance dose is given at week 6 (4 weeks after the week 2 dose) and then Q4W ongoing. All patients use the 100 mg dose for maintenance in UC (unlike in Europe where weight-based 50 mg vs 100 mg was studied, the US standard is 100 mg for all). Golimumab was designed for patient self-injection. The SmartJect autoinjector is an easy-to-grip pen that delivers the 100 mg dose with a push of a button. Patients can also use prefilled 100 mg glass syringes if preferred. After a healthcare provider approves and trains the patient, golimumab can be injected at home in the abdomen or thigh. The autoinjector has visual and audible cues to ensure proper use. Overall, Simponi's SC route (just one injection a month for maintenance) is convenient and improves adherence for many UC patients

Source: USPI; UpToDate

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# Appendix: ROA for integrin inhibitors

	ROA	Induction	Maintenance
Vedolizumab (Entyvio)	<p>Administered either by IV infusion or by SC injection, depending on the phase of therapy and formulation. Traditionally, vedolizumab was IV-only for both induction and maintenance, but a SC form is now approved for maintenance</p> <p>300 mg IV infusions at weeks 0, 2, and 6. Induction requires three vedolizumab infusions over the first 6 weeks (each given over ~30 minutes). This IV loading schedule is used for both UC and CD. Patients are assessed around week 14; if no benefit, therapy is usually discontinued. (There is currently no purely SC induction; even when using SC maintenance, the first doses are given IV.)</p>		<p>300 mg IV Q8W or 108 mg SC Q2W. Patients have two maintenance options: the original IV infusion Q8W (staying on IV long-term), or switching to the SC which is typically started after at least two IV loading doses. In the US, the label allows giving vedolizumab IV at week 0 and 2, then starting 108 mg SC injections Q2W from week 6 onward. For example, a UC patient could receive IV vedolizumab at 0 and 2 weeks, then take over with self-injected 108 mg SC Q2W thereafter as maintenance. In trials, SC dosing Q2W provided comparable drug exposure to 300 mg IV Q8W. Both IV and SC maintenance are effective; the choice can be based on patient preference and logistics. The new SC form of Entyvio is supplied as either a prefilled syringe or a single-dose Entyvio Pen autoinjector. Patients or caregivers can self-administer the SC injection after proper training. TAK designed the autoinjector pen to be user-friendly, allowing patients to avoid regular infusions. Switching from IV to SC vedolizumab does not require re-induction; the first SC dose replaces the next scheduled IV dose. Some patients who were stable on IV choose SC for the comfort of home administration, while others remain on IV due to insurance coverage or infusion center support. Regardless of route, vedolizumab dosing is fixed (not weight-based), simplifying the regimen</p>
Natalizumab (Tysabri)	<p>Given by IV infusion only. It's mainly used in CD patients who have failed other therapies. Due to the risk of PML (a serious infection), its use is fairly restricted, and it is not recommended for routine use. Should be used in patients who are JC virus antibody negative and agree to regular screening for the virus</p> <p>300 mg IV Q4W. Dosing does not differentiate between induction and maintenance, with the same dose given monthly from the start. Typically, clinicians assess response after about 12 weeks (i.e., after 3 infusions); if a patient hasn't responded by then, natalizumab is typically discontinued. For those who respond, the monthly infusions continue as maintenance to sustain remission. Each infusion is about 1 hour long and must be done at an authorized infusion center under the TOUCH REMS monitoring program (because of PML risk). There are no home injections or pills for natalizumab. Patients on concomitant immunosuppressants must stop them when starting natalizumab due to infection risk. If a patient starts natalizumab while on steroids, guidelines recommend attempting to taper off steroids by 6 months of therapy</p>		

# Appendix: ROA for JAK inhibitors

	ROA	Induction	Maintenance
<b>Tofacitinib (Xeljanz)</b>	<p>Taken orally as a pill (immediate-release or extended-release). No injections or infusions are needed, providing a convenient alternative to biologic injections for some patients. As an oral drug, tofacitinib offers maximum convenience, patients just swallow pills at home, with or without food. There are no device or injection training requirements. It also means drug levels are maintained by daily dosing rather than periodic high doses.</p> <p>Patients should be aware of the need for regular blood test monitoring (lipids, liver enzymes, blood counts) due to the JAK inhibitor safety profile.</p> <p>The option of Xeljanz XR (QD) can improve adherence for those who prefer a single daily dose. Overall, tofacitinib provides a flexible administration (oral, home-based) which is an attractive feature for those who are candidates</p>	<p>Immediate-release 10 mg tablet BID or extended-release 22 mg tablet QD for at least 8 weeks.</p> <p>Induction therapy in moderate-to-severe UC typically lasts 8 weeks. If a patient is not in remission by this time point, high dose can be continued for up to 16 weeks total. If still no adequate response by 16 weeks, tofacitinib should be discontinued</p>	<p>Responders are usually transitioned to 5 mg immediate-release tablets BID or an 11 mg extended-release tablet QD for maintenance. This lower dose is used long-term to maintain remission. In patients who lose response on maintenance, a return to the induction dosing can be considered, but due to safety risks higher doses are limited to the shortest duration necessary</p>
<b>Upadacitinib (Rinvoq)</b>	<p>Taken orally QD as an extended-release tablet, similarly with or without food. Patients should avoid concomitant strong CYP3A4 inducers (which can reduce drug levels) or adjust dose if on CYP3A4 inhibitors (the label recommends 30 mg induction instead of 45 mg in certain inhibitor situations, etc.). As with tofacitinib, regular lab monitoring is required, but the ability to simply take a pill at home gives patients a high degree of autonomy in their treatment.</p>	<p>Extended-release 45 mg tablet QD. In UC this regimen is given for 8 weeks, and if a patient has not achieved adequate response by 8 weeks, an extension up to 12–16 weeks of 45 mg QD may be used in clinical practice (the label specifies 8 weeks, with some evidence supporting up to 16 weeks in partial responders). For Crohn's disease, the FDA-approved induction is 45 mg QD for 12 weeks (a longer induction)</p>	<p>Extended release 15 mg tablet QD. After induction, patients transition to 15 mg QD for maintenance of remission. This is the lowest effective dose and is recommended for long-term use. If a patient has refractory or severe disease and begins to lose response on 15 mg, the dose can be increased to 30 mg QD for maintenance. However, using 30 mg ongoing comes with higher risk, so guidelines say to use the lowest dose that maintains response and discontinue 30 mg if no benefit. CD, the maintenance dosing is similarly 15 mg QD (with 30 mg for refractory cases) after the 12-week induction</p>

Source: USPI; UpToDate

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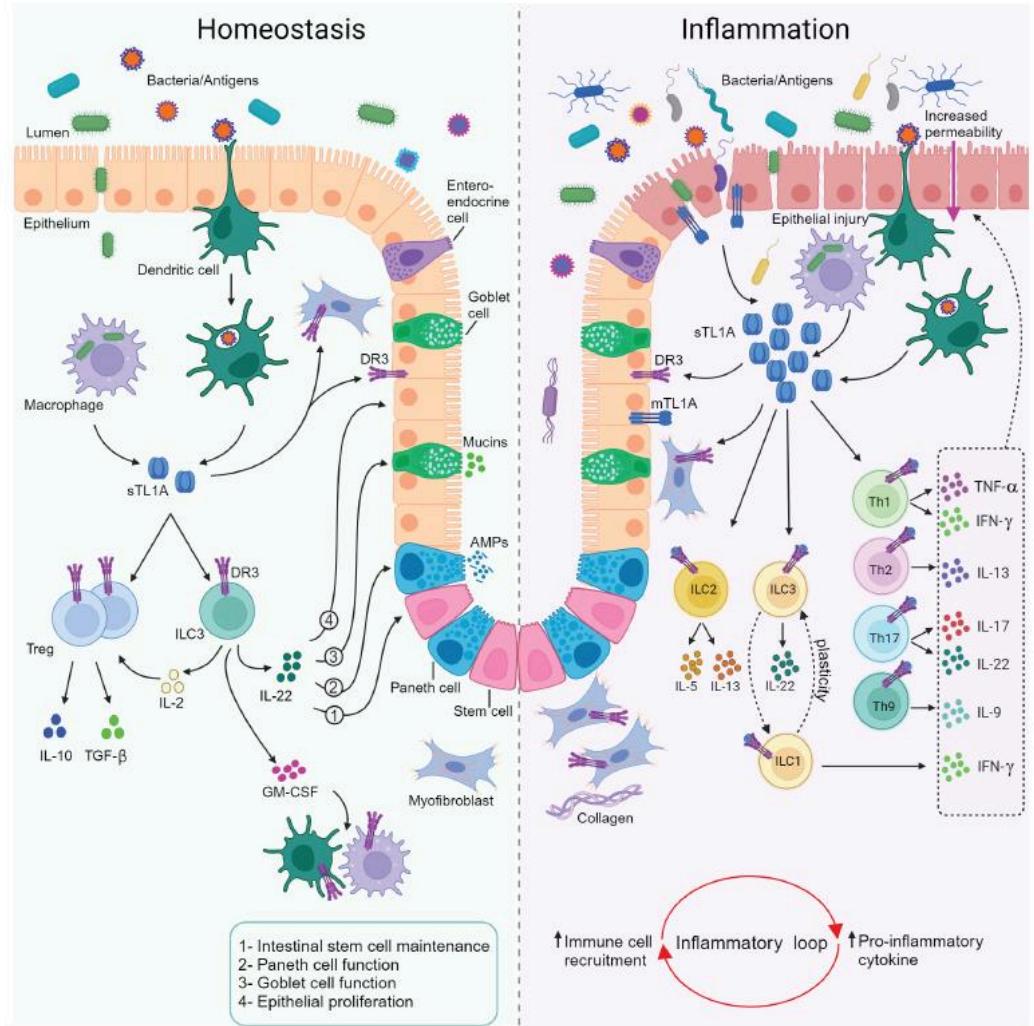
# Appendix: ROA for S1PR modulators

	ROA	Induction	Maintenance
Ozanimod (Zeposia)	<p>Taken orally QD as a capsule with or without food. Has a built-in titration period at the start, but otherwise induction and maintenance dosing are the same continuous daily oral dose. Patients starting ozanimod must undergo a few baseline checks (e.g., ECG, liver enzymes, varicella immunity) and following the 7-day titration starter pack. Baseline and routine eye exams are also recommended. After that, administration is as simple as taking one capsule each morning. There are no injections or infusions, making it very patient-friendly. If the drug is interrupted, a re-titration may be needed after a week off</p>	<p>The first 7 days of therapy involve a titration pack to gradually increase the dose: Days 1–4 at 0.23 mg daily, then days 5–7 at 0.46 mg daily, reaching the full 0.92 mg dose on day 8. This induction titration is done to mitigate first-dose heart rate effects of S1P modulators. After day 8, the maintenance dose is 0.92 mg daily ongoing, with no breaks. In clinical trials (True North), patients took ozanimod 0.92 mg daily during the induction period (after titration) and continued the same dose in maintenance.</p>	<p>0.92 mg (equivalent to 1 mg) capsule QD for maintenance. In practical terms, there is no separate high-dose induction phase for ozanimod aside from the initial up-titration. Once the patient reaches 0.92 mg on day 8, that dose is continued every day during both induction (typically assessed at week 10) and maintenance beyond. If a patient responds, they simply stay on daily ozanimod; if no response by week 10–12, therapy may be stopped. Thus, the “induction” is just the first 10 weeks of daily therapy (with the first week being lower doses)</p>
Etrasimod (Velsipity)	<p>Taken orally QD as a tablet with or without food. Does not require titration, although baseline checks and monitoring requirements are similar to ozanimod</p>		<p>2 mg QD tablet</p>

# Appendix: ROA for integrin inhibitors

	ROA	Induction	Maintenance
Ustekinumab (Stelara)	<p>Utilizes a two-phase route: IV infusion for induction followed by SC injections for maintenance. Induction is delivered via a one-time weight-based IV dose at an infusion center over ~1 hour, then continued with periodic SC doses. Maintenance injections can be done at home. Ustekinumab is supplied as a prefilled syringe for SC use, and recently as a one-click "Stelara OnePress" prefilled pen for easier self-injection. Patients are usually taught to self-inject into the thigh, abdomen, or upper arm (if someone else administers it). Because Stelara's maintenance is infrequent (only once every 2 months) and can be done by the patient, it offers a high degree of flexibility compared to drugs requiring regular infusions. Screening for vaccination is recommended prior to therapy, and regular CBC and LFTs and monitoring for infection are recommended during</p>	<p>Single IV infusion dose at week 0, dosed by body weight (~6 mg/kg). The infusion is weight-tiered: patients ≤55 kg get 260 mg, 55–85 kg get 390 mg, and &gt;85 kg get 520 mg IV. No additional IV doses are given in induction; maintenance starts subsequently</p>	<p>90 mg SC injections Q8W. Some clinicians use 90 mg Q4–6W in patients who lose response, but the standard label recommendation is Q8W). Maintenance dosing typically continues indefinitely to maintain remission</p>
Risankizumab (Skyrizi)	<p>Uses an IV infusion for induction followed by SC injections for maintenance, mirroring Stelara's two-phase approach. SC maintenance uses a prefilled cartridge that is administered via the On-Body Injector (OBI) system. There is reduced infection risk compared with ustekinumab, but monitoring requirements are similar</p>	<p>600 mg IV infusions at weeks 0, 4, and 8. Patients receive three loading doses via IV infusion (each over at least an hour). After the third infusion at week 8, the patient transitions to SC maintenance starting at week 12</p>	<p>180-360 mg SC Q8W 8 weeks, starting at week 12. The first SC dose is given 4 weeks after the last induction infusion. Maintenance injections are then every 8 weeks (6 doses per year). Risankizumab's SC maintenance is unique in that the dose is higher-volume, so it is delivered via the OBI system. The Skyrizi OBI is a wearable injector that comes preloaded with the medication. The patient attaches it to the abdomen or thigh, and with one button it delivers the full dose subcutaneously, hands-free. Each cartridge contains either 180 mg/1.2 mL or 360 mg/2.4 mL, and the OBI ensures the injection is given over the proper time. Patients receive training on how to use the on-body device, but after that they can self-administer at home. The OBIs have lights and sounds to indicate when the dose is fully delivered. This technology spares patients from having to manually inject two separate syringes for a 360 mg dose</p>
Mirikizumab (Omvohe)	<p>Similarly, uses IV infusion for induction, with maintenance delivered SC via self-injection. Prefilled autoinjector pens and prefilled syringes are available for SC dosing. Each device delivers either 100 mg or 200 mg of mirikizumab, used in combination to achieve the needed dose. Patients or caregivers can self-inject at home once trained in proper technique. Monitoring requirements are similar to risankizumab</p>	<p>Induction Dosing differs between UC and CD. In UC, a 300 mg IV infusion is given at Weeks 0, 4, and 8, while in CD, a higher dose, 900 mg, is given by IV infusion at Weeks 0, 4, and 8. (Each infusion is given over at least 30 minutes for 300 mg, and ~90 minutes for the 900 mg dose) These three loading infusions constitute the induction phase. No additional IV doses are needed after week 8 if adequate response is achieved by week 12</p>	<p>Starting at Week 12, patients switch to SC injections Q4W for maintenance . For UC, the maintenance dose is 200 mg SC. For CD, the maintenance dose is 300 mg SC. Because the SC injections come in 100 mg and 200 mg units, the UC maintenance is given as two 100 mg injections and the CD maintenance is given as two injections (one 200 mg + one 100 mg) to total 300 mg. Routine dose adjustment isn't required; if patients lose response later, re-induction with IV infusions can be considered as per guidelines</p>
Guselkumab (Tremfya)	<p>For UC, currently induction is given as IV infusions, and maintenance is given SC (while an sBLA has been filed for CD). JNJ filed for approval of an all-SC regimen (both induction and maintenance) based on the positive ASTRO study in UC in 2024, which could improve convenience. A similar regimen is being evaluated in the GALAXI study in CD, with results expected in 2025. As it stands, SC maintenance can be given via pre-filled syringes and autoinjector pens ("One-Press" injector), available in 100 mg and 200 mg doses. For example, a 100 mg dose is given with a 1 mL prefilled syringe (or pen), and a 200 mg dose is given with a 2 mL prefilled syringe or pen. Patients can self-inject SC doses at home after appropriate training, using either the prefilled syringe or the one-press auto-injector device. Monitoring requirements are similar to risankizumab</p>	<p>Induction dosing in UC consists of 200 mg IV at Weeks 0, 4, and 8 (each infusion over at least 1 hour). This 3-dose IV induction is followed by a transition to SC maintenance dosing at week 12 or 16. In CD (not yet FDA-approved) trials have evaluated 400 mg given SC at Weeks 0, 4, and 8 as an induction regimen for CD. This high-dose SC induction showed robust early remission rates in studies, suggesting an alternative to IV induction if approved</p>	<p>In UC SC injection is given either Q4W or Q8W based on what is needed to maintain response. The standard option is 100 mg SC Q8W (after a first SC dose at Week 16). High-intensity maintenance can be used and consists of 200 mg SC Q4W (with the first 200 mg injection at Week 12) . Patients who respond to induction can start on the Q8W regimen; the 4-week regimen is an option for those needing additional efficacy. The label recommends using the lowest effective dosing frequency. No routine dose adjustments are required beyond choosing one of these intervals</p>

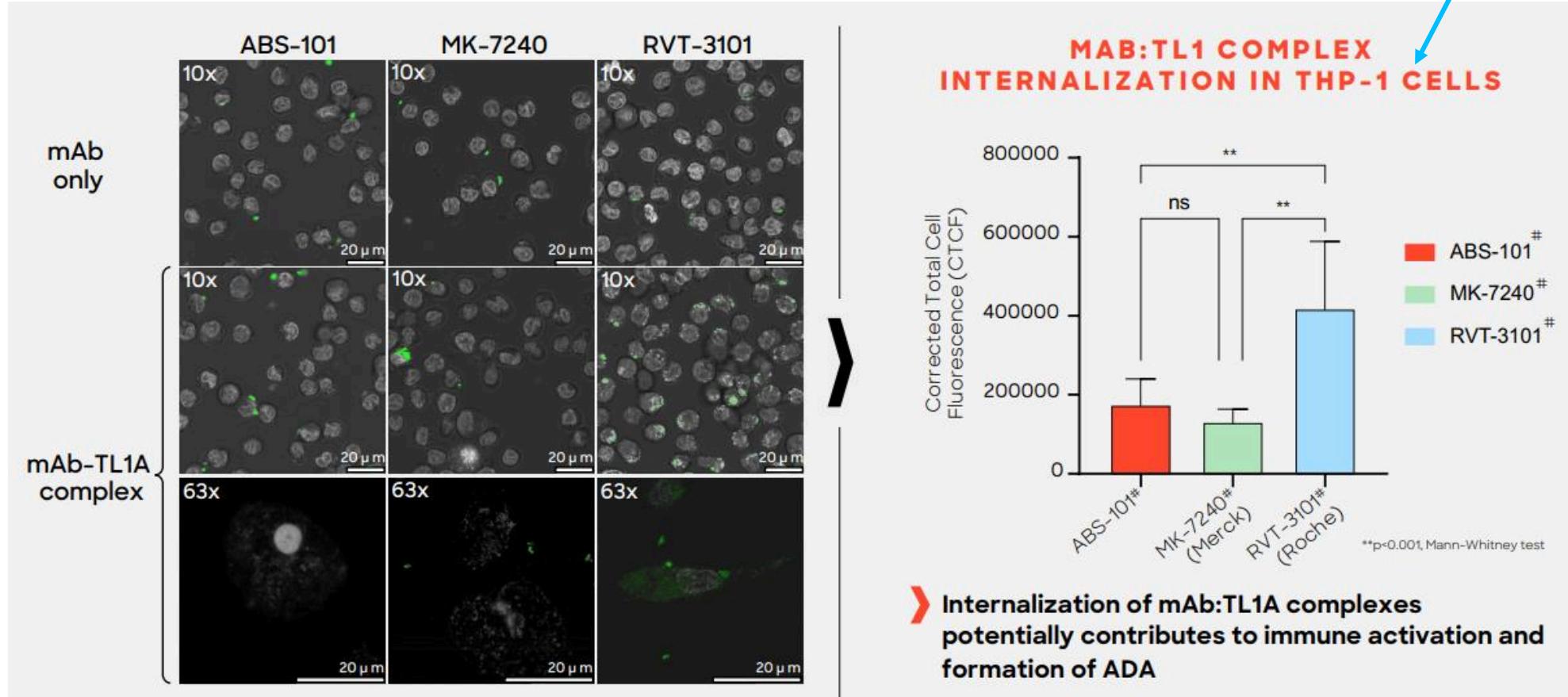
# Appendix: TL1A and DR3 axis



**Figure 3** TL1A:DR3 as master regulators of homoeostatic and inflammatory mucosal pathways. TL1A:DR3 signalling appears to be necessary for the uneventful recovery from an acute insult to the intestinal wall via several different mechanisms. On such triggers, TL1A-expressing cells, such as DCs and CX3CR1 $^{+}$  mononuclear phagocytes, interact with DR3-expressing homoeostatic cell populations to reinstate a healthy mucosal status. Those TL1A-mediated responses include enhancement of proliferation of Tregs with increased regulatory cytokine secretion and maintenance of suppressor function, secretion of the epithelial barrier-protecting cytokine, IL-22, by gut-resident ROR $\gamma$ t $^{+}$  group 3 ILCs and direct effects on the epithelial compartment itself. Such effects are highly influenced by microbiota-derived signals, which are shown to regulate the expression of TL1A on monocytes and DCs. In addition, TL1A:DR3 engagement in monocytes is necessary for optimal bacterial uptake and intracellular bacterial clearance, indicating the existence of locally organised and tightly regulated homoeostatic responses. The establishment of intestinal inflammation is associated with high mucosal upregulation of both TL1A and DR3, which act as powerful amplifiers of inflammatory pathways. Activated lymphocytes express DR3 and respond to APC-derived TL1A, with the net result of a universal costimulatory stimulation of effector adaptive immunity pathways. Teff and their corresponding cytokines act as pivotal pathogenetic modules, which perpetuate mucosal inflammation in IBD. Pathogenic ILCs are equally affected and contribute to the generation of a proinflammatory mucosal milieu, enriched with IL-13/IL-5 secreted by ILC2s and IFN $\gamma$  by ILC1s. Inflammatory chemotactic factors are also elevated and may facilitate the trafficking of inflammatory cells towards the intestinal mucosa, thus creating a self-amplifying loop between cell recruitment and inflammatory mediator production. Overall, current evidence supports the concept that TL1A:DR3 act on complex cellular and molecular networks, the net effect of which dictates the balance between homoeostasis and inflammation in the intestinal mucosa. Created with Biorender.com. APC, antigen presenting cell; DCs, dendritic cells; IBD, inflammatory bowel disease; ILCs, innate lymphoid cells.

# Appendix: ABSI comparative TL1A complex internalization data

THP-1 cells are a human cell line resembling macrophages and monocytes used to study immune responses

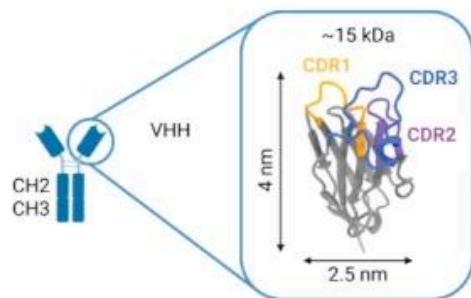


# Appendix: duvakitug (SAN FP/TEVA) terms

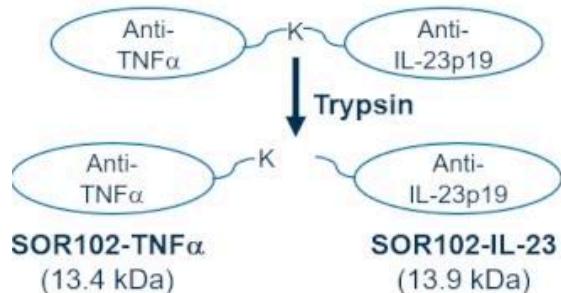
Teva / Sanofi Alliance Key Terms	
<b>Upfront signing</b>	➢ \$500 million in Q4 2023
<b>Milestones</b>	➢ Phase 3 initiations: up to \$600 million, including additional indications ➢ Launches: up to \$400 million
<b>Development and commercial costs</b>	➢ 50% Teva / 50% Sanofi
<b>Co-commercialization</b>	➢ Each partner records in-market revenues in its territory
<b>Profit share</b>	➢ 50% Teva / 50% Sanofi in major markets paid via COGS; Royalty-based in other regions

# Appendix: SOR-102 mechanism

## Heavy Chain Only VHH Single Domain Antibody<sup>1</sup>



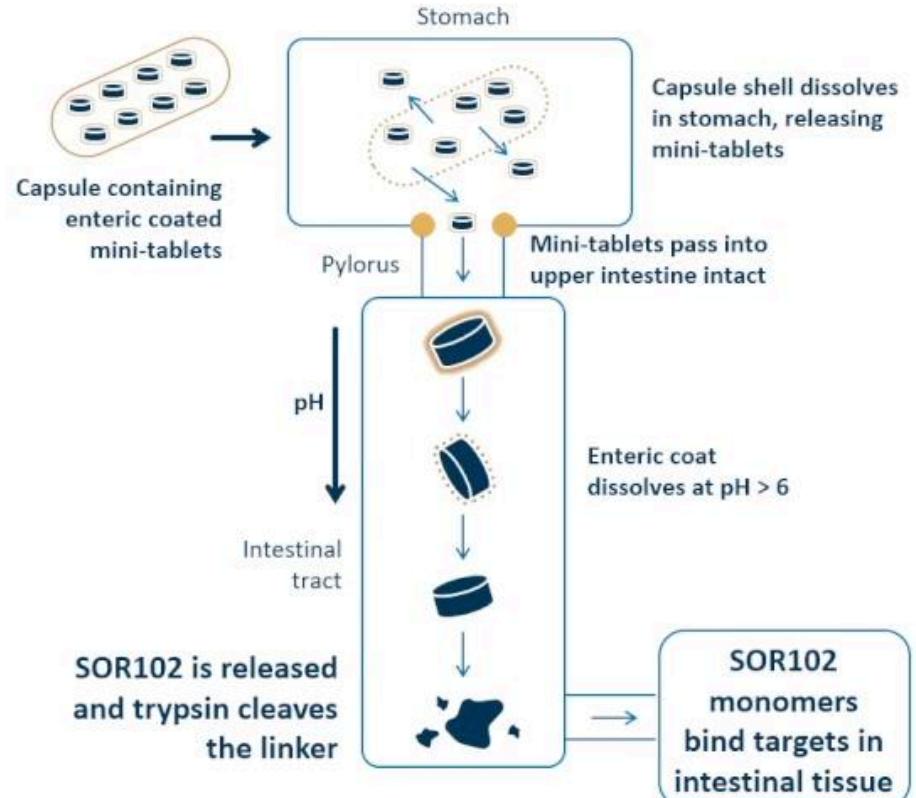
## SOR102<sup>2</sup>



## SOR102 Mechanism of Action

- Picomolar affinity to TNF $\alpha$  and IL-23p19
- Humanized and GI stable (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<sup>3</sup>



# Appendix: baseline characteristics and endpoints in UC Ph 3 trials (1/3)

## JNJ Partnership overview

- 2017 to present: Icotrokinra
  - Protagonist completed pre-clinical and first Ph1 study
  - JNJ responsible for further development and commercialization
- **Successful outcome in Phase 3 psoriasis studies**
- Potential peak sales: **\$5B+**<sup>1,2</sup>
  - Psoriasis, psoriatic arthritis, ulcerative colitis, Crohn's disease



**\*\$165 million milestone earned in Q4 '24:**

- \$115M for Ph3 1° end point achievement
- \$35 million accelerated payment (previously due on NDA acceptance)
- \$15 million accelerated payment (previously due on phase 3 2nd indication initiation)

## Disclosures Appendix

Completion: March 17, 2025 6:00 A.M. EDT.

Distribution: March 17, 2025 6:00 A.M. EDT.

Revised Completion: March 18, 2025 12:54 P.M. EDT.

Revised Distribution: March 18, 2025 12:54 P.M. EDT.

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I, Thomas J. Smith, certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

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	Count	Percent	Count	Percent
BUY [OP]	220	74.1	107	48.6
HOLD [MP]	76	25.6	14	18.4
SELL [UP]	1	0.3	0	0

### Explanation of Ratings

Outperform (Buy): We expect this stock to outperform its benchmark over the next 12 months.

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The degree of outperformance or underperformance required to warrant an Outperform or an Underperform rating should be commensurate with the risk profile of the company.

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