



SPYRE
THERAPEUTICS

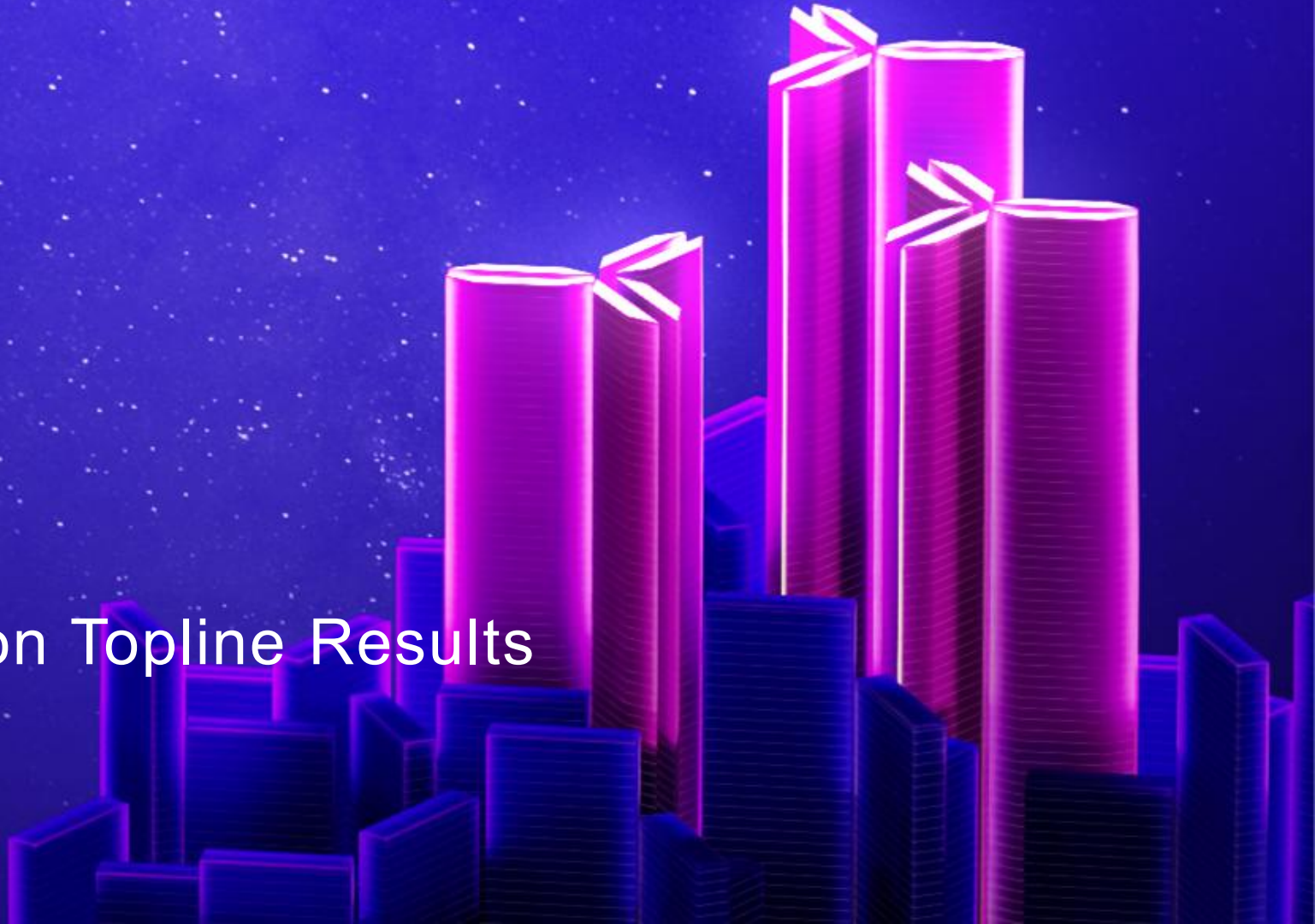


SKYLINE

SPY001

Part A Induction Topline Results

April 13, 2026



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Agenda



Introduction



Cameron Turtle, DPhil
Chief Executive Officer



SPY001 Part A Induction Topline Results



Deanna Nguyen, MD
SVP, Clinical Development

Summary Remarks



Cameron Turtle, DPhil
Chief Executive Officer

Analyst Q&A



Cameron Turtle, CEO
Sheldon Sloan, CMO
Deanna Nguyen, SVP
Scott Burrows, CFO
Kate Tansey Chevlen, CCO

Introduction

Cameron Turtle, DPhil, CEO

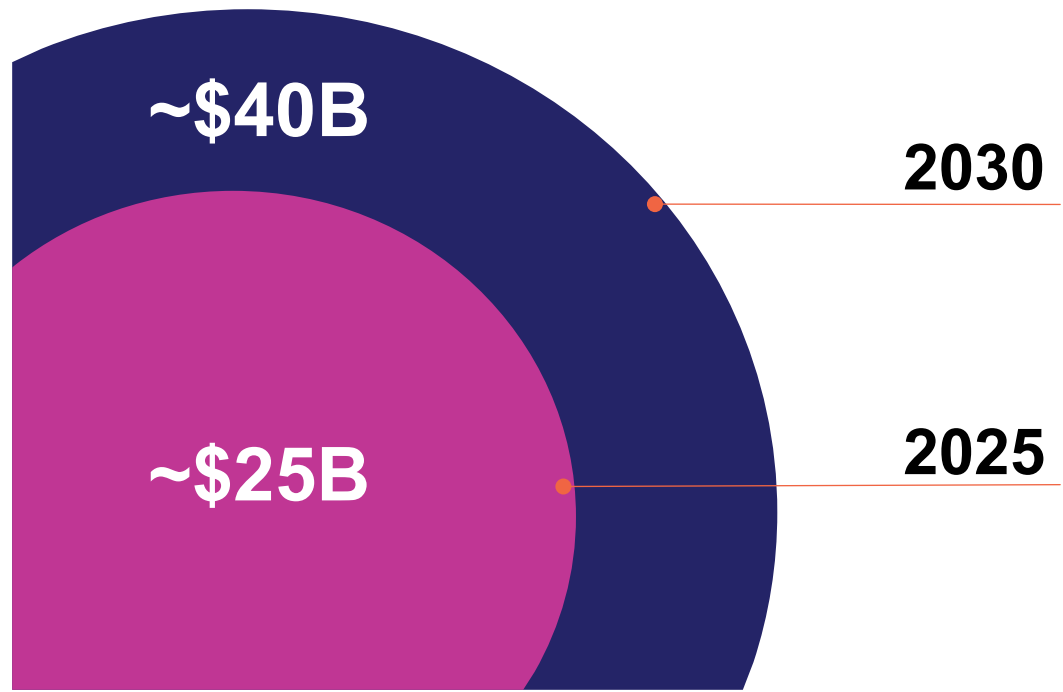


IBD is a large & growing market that demands better therapies



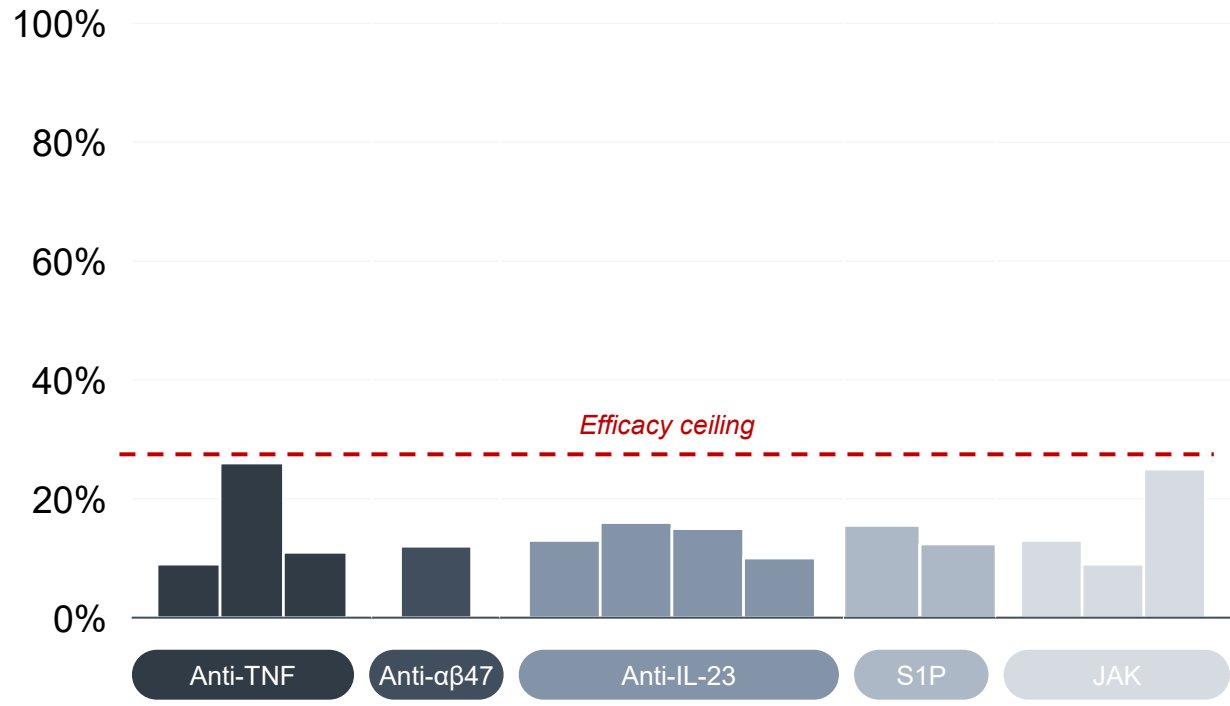
Expanding inflammatory bowel disease (IBD) market

Global IBD Market



Persistent therapeutic ceiling

Placebo-adjusted clinical remission rates in ulcerative colitis (UC) Induction

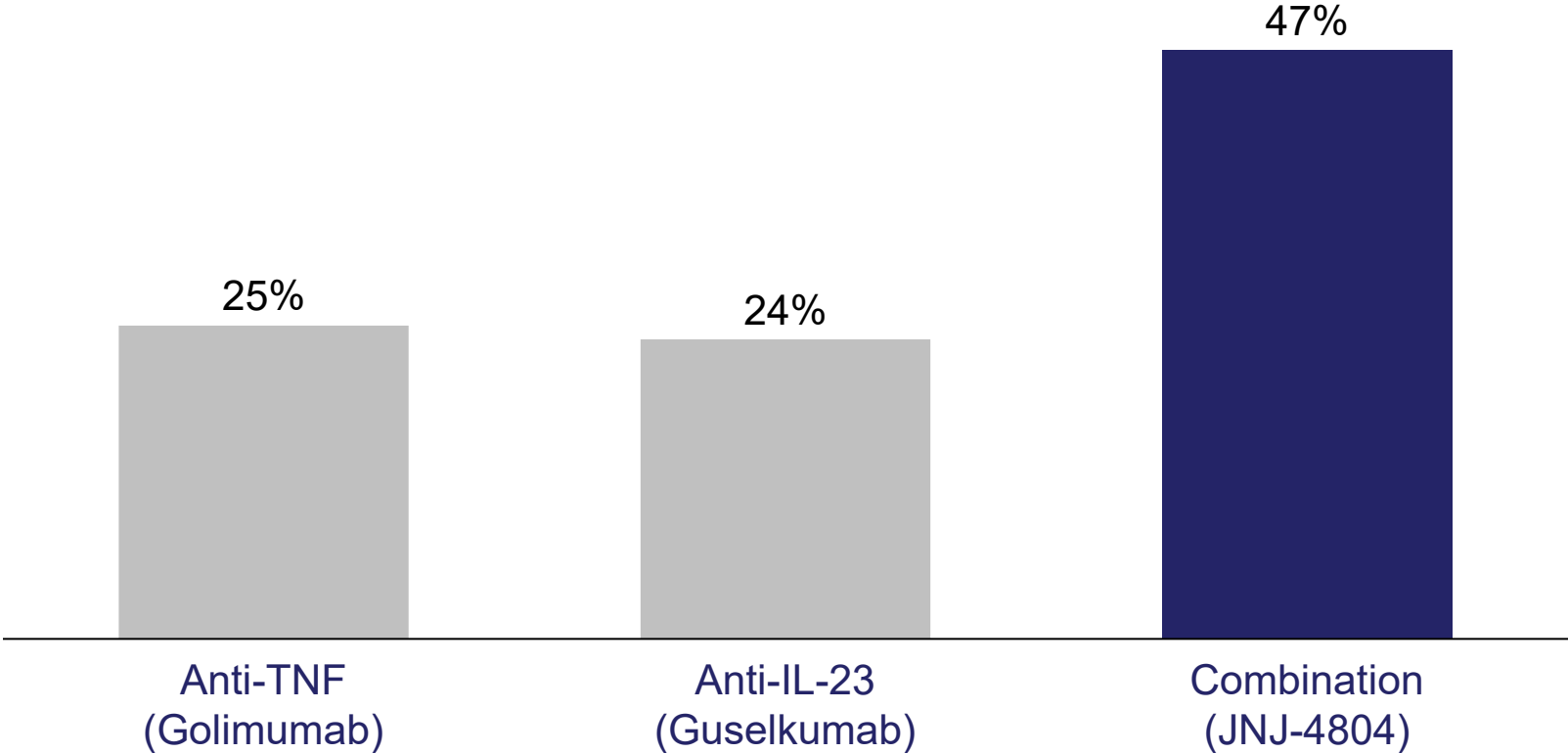


Advanced combination therapy has demonstrated potential to break the therapeutic ceiling in IBD



JNJ's VEGA demonstrated near-additive remission with advanced combination

Clinical remission, Week 12



Field is converging on combos

- ✓ Increasing case reports
- ✓ Confirmatory academic trials
- ✓ Focus of strategic investment

- AbbVie
- Boehringer Ingelheim
- Johnson & Johnson
- Lilly
- Roche
- Sanofi
- Takeda

Spyre is investigating a fundamentally differentiated portfolio of advanced combination therapies



Uncompromising combinations from first principles:

- ✓ Validated mechanisms of action with leading safety and efficacy
- ✓ Next-generation molecules engineered for best-in-class potential
- ✓ Co-formulations optimized for convenient, subcutaneous delivery (Q3-6M)¹

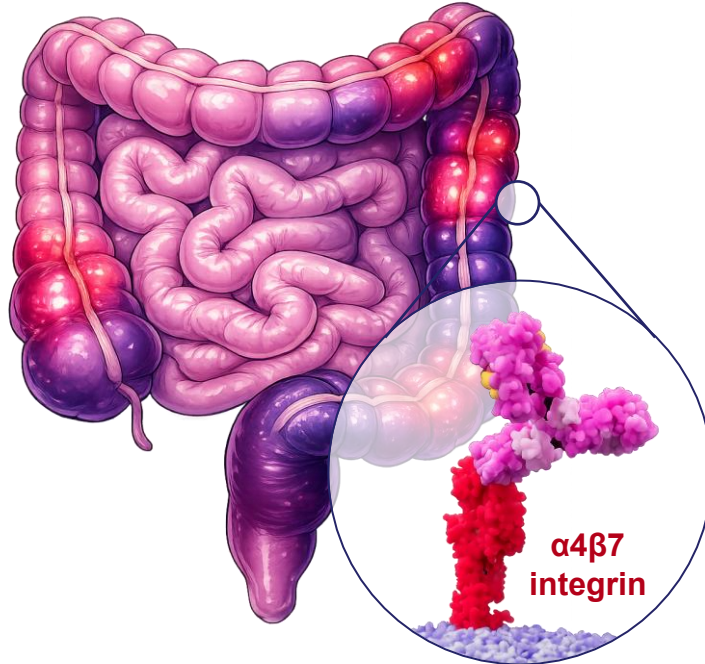
Spyre combinations aim to reach new heights in IBD across efficacy, safety, and convenience


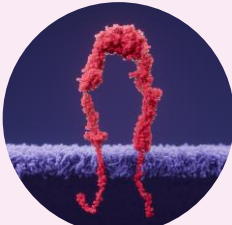

$\alpha 4\beta 7$ inhibition may be an optimal backbone for advanced combination therapy in IBD



The only approved gut-selective mechanism in IBD¹

Mechanistically orthogonal to anti-cytokine therapies



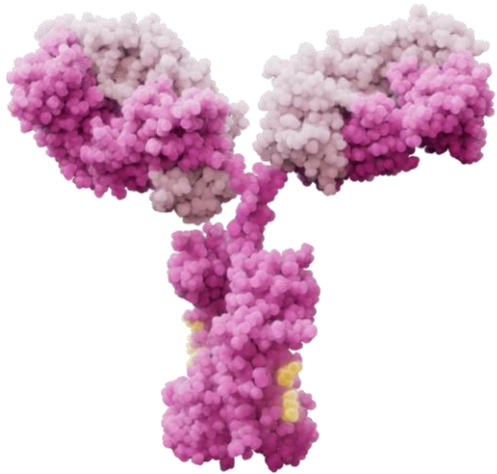
Anti-cytokine	Gut-selective anti-integrin	Anti-cytokine
		
TL1A	$\alpha 4\beta 7$	IL-23
T-cell activation & fibrosis	Immune cell trafficking	T-cell proliferation

Combinations including $\alpha 4\beta 7$ aim to provide dual immune suppression in the affected gastrointestinal tissue with lower systemic immunosuppressive risk

SPY001 is a potential best-in-class anti- $\alpha 4\beta 7$ with dosing designed to test efficacy at higher exposures



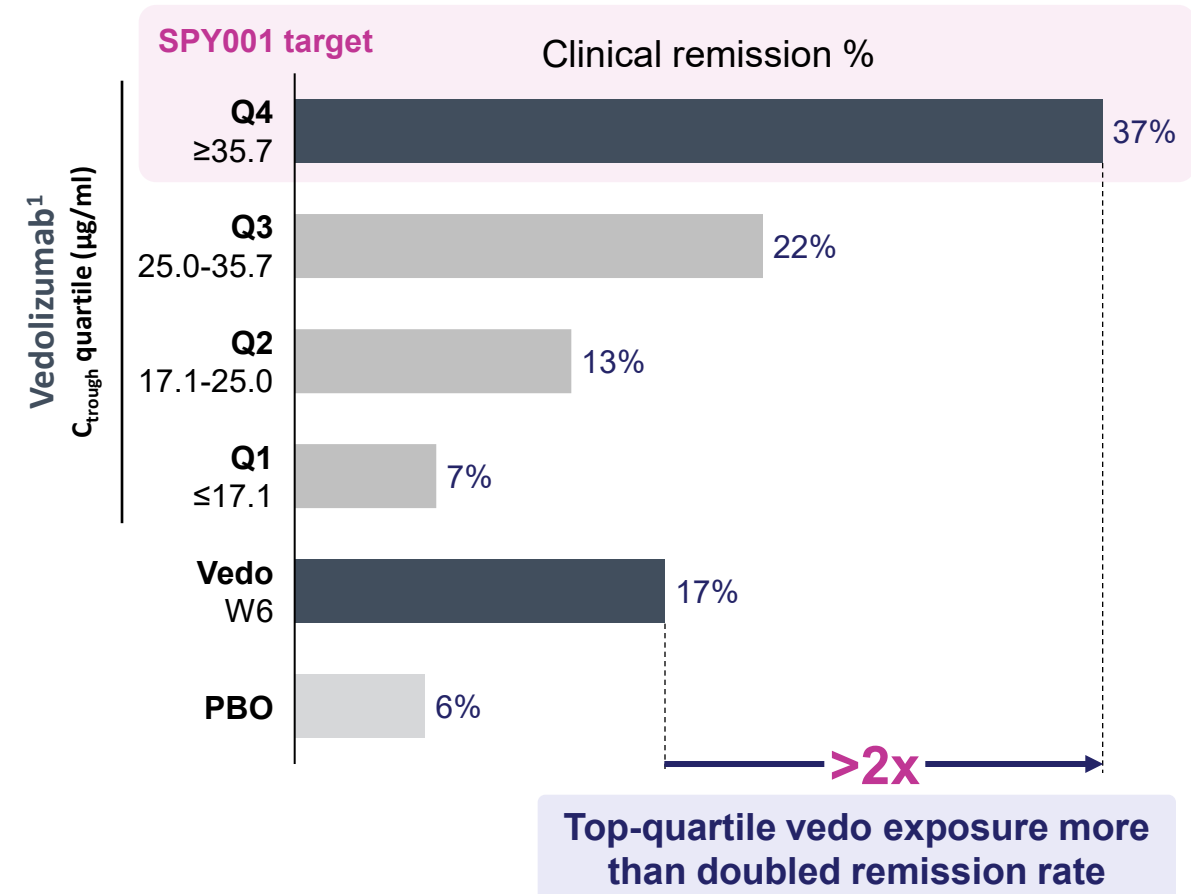
SPY001 improves upon proven vedolizumab mechanism



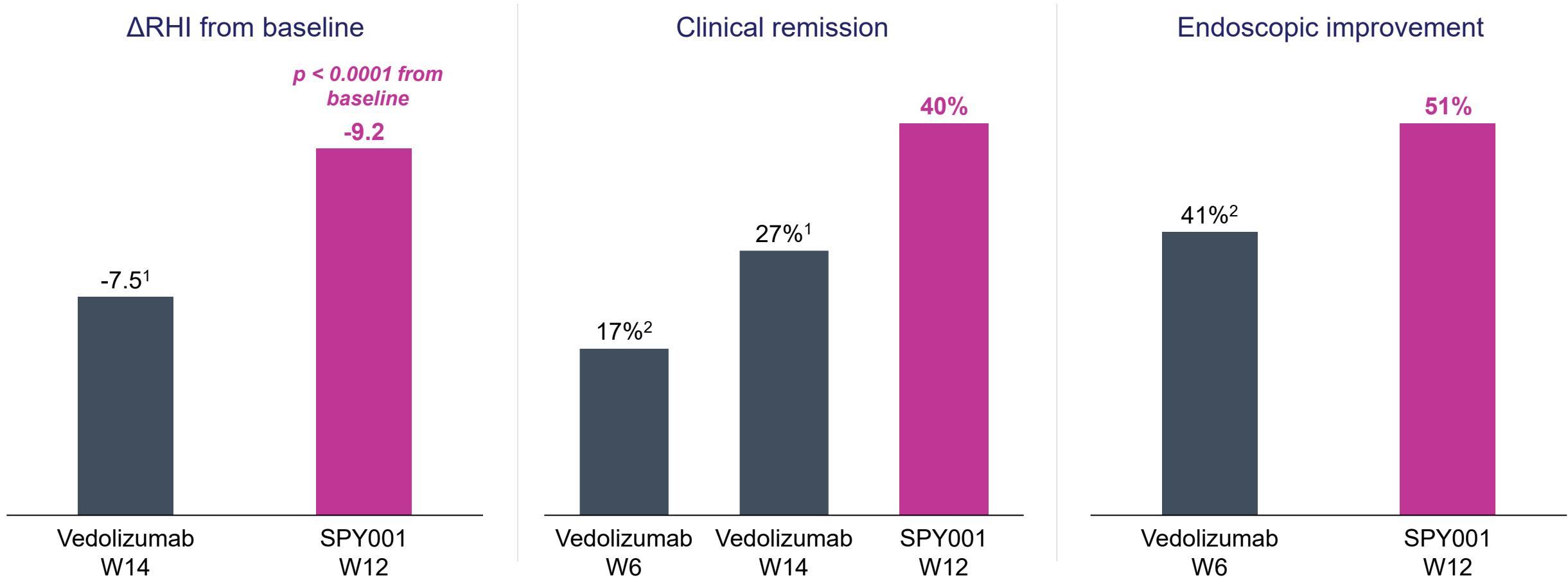
SPY001

- ✓ Same validated epitope
- ✓ Equivalent target potency
- ✓ Effector function silenced
- + Extended half-life
- + High conc. SC format²

SPY001 dosing targets top quartile exposure



SPY001 consistently outperformed objectives in Part A, supporting a potential best-in-class profile



SPY001 was well-tolerated, consistent with the α4β7 class

SPY001 Topline Induction Results

Deanna Nguyen, MD, SVP Clinical Development



SKYLINE is a two-part study, with Part B now enrolling

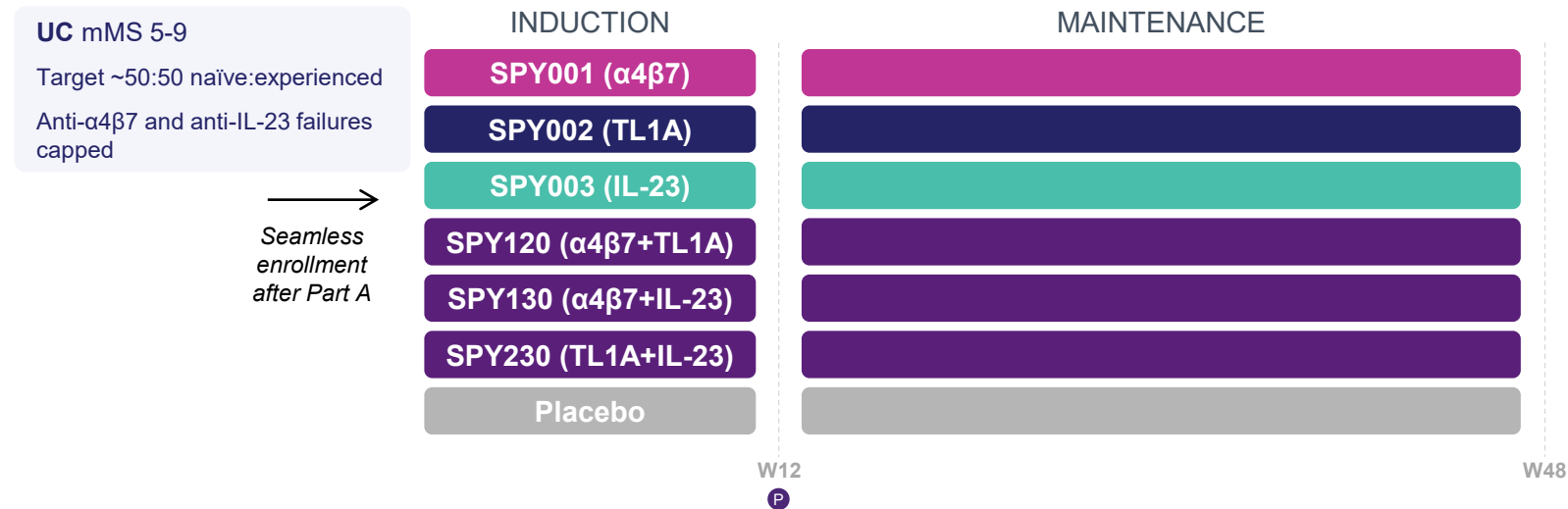


Part A: Open-label monotherapy evaluation (N = ~130)



Recruitment closed
Trial enrollment exceeded target

Part B: PBO-controlled factorial combination evaluation (N = ~550)



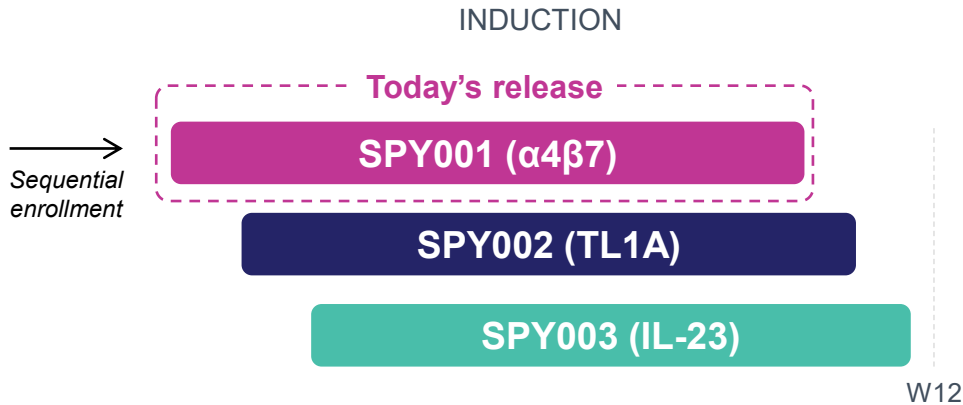
Now enrolling

Today's release describes SPY001 Part A induction results



SKYLINE Part A: Open label monotherapy evaluation

- Patient characteristics**
- Adults with moderately to severely active UC (mMS 5-9)
 - Rectal bleeding subscore ≥ 1
 - Mayo endoscopic subscore ≥ 2



Key topline endpoints

PRIMARY

Δ RHI from baseline

SECONDARY

% Clinical remission

% Endoscopic improvement

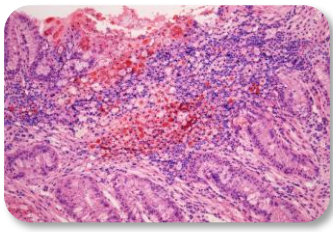
Incidence of treatment-emergent adverse events

Endpoints focus on objective measures of disease activity

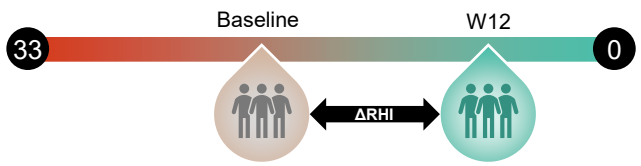


Robarts Histopathology Index (RHI)

Direct measure of tissue inflammation

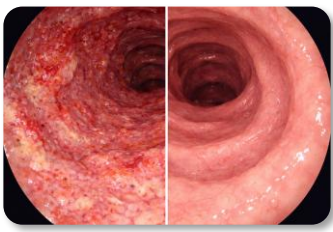


Change in RHI

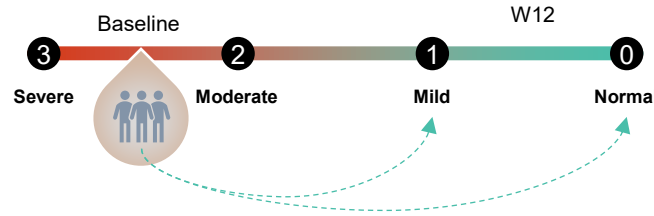


Endoscopic Improvement

Direct visualization of mucosal healing

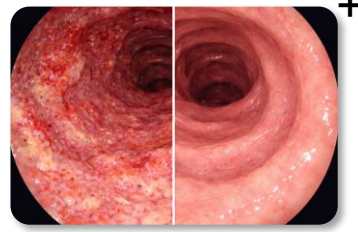


Endoscopy Subscore

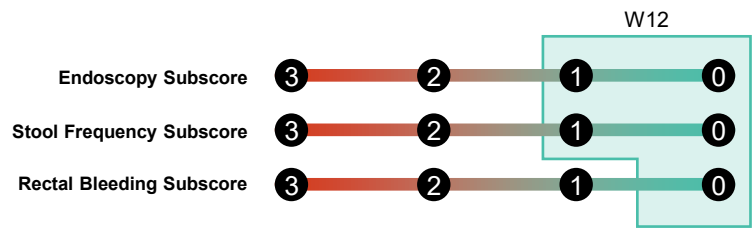


Clinical Remission

Composite endpoint aligned with regulatory guidance



Modified Mayo Score

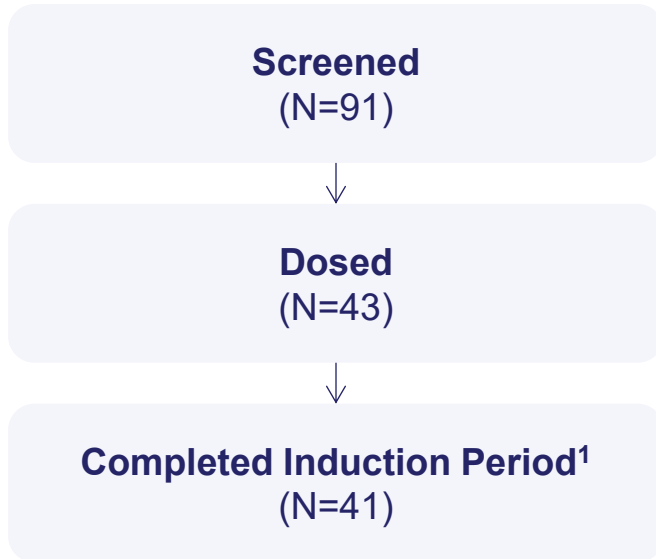


Endpoints are anchored in objective, centrally assessed¹ measures

Baseline characteristics were consistent with expectations

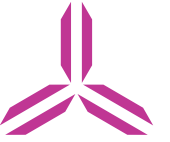


Patient disposition



	SPY001 (α4β7), N = 43
Age (years, mean)	44
Sex (% female)	28
Weight (kg, mean)	76
Geographic region	
Europe	88%
North America	12%
Duration of UC (years, mean)	4.5
RHI (mean ± SD)	15.6 ± 8.6
RHI ≥ 10 (n, %)	34 (79%)
Baseline mMS (mean ± SD)	6.8 ± 1.1
Mayo Endoscopy Score (MES) (n, %)	
2	19 (44%)
3	24 (56%)
Concomitant immunomodulator use (n, %)	0
Concomitant corticosteroid use (n, %)	18 (42%)
Number of prior advanced therapies (n, %)	
Naïve	35 (81%)
1	7 (16%)
≥2	1 (2%)

SPY001 was well tolerated with a favorable safety profile



	SPY001 ($\alpha 4\beta 7$), N=43
Subjects with any Adverse Event (n, %)	6 (14%)
Severe (Grade ≥ 3) AE	1 (2%)*
Drug-Related AE	0
AE Leading to Drug Discontinuation	0
Serious Adverse Event (SAE)	1 (2%)*
Drug-Related SAE	0
AEs of Special Interest	0
Death	0

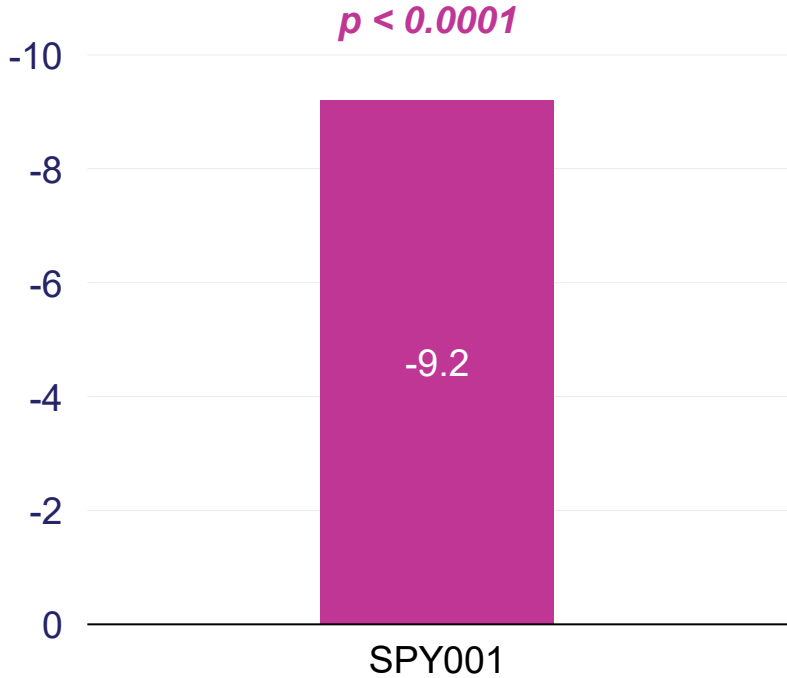
Most common AE (≥ 2 patients) was back pain (n=2)

SPY001 met its primary endpoint and outperformed our expectations on key secondary endpoints



Primary endpoint

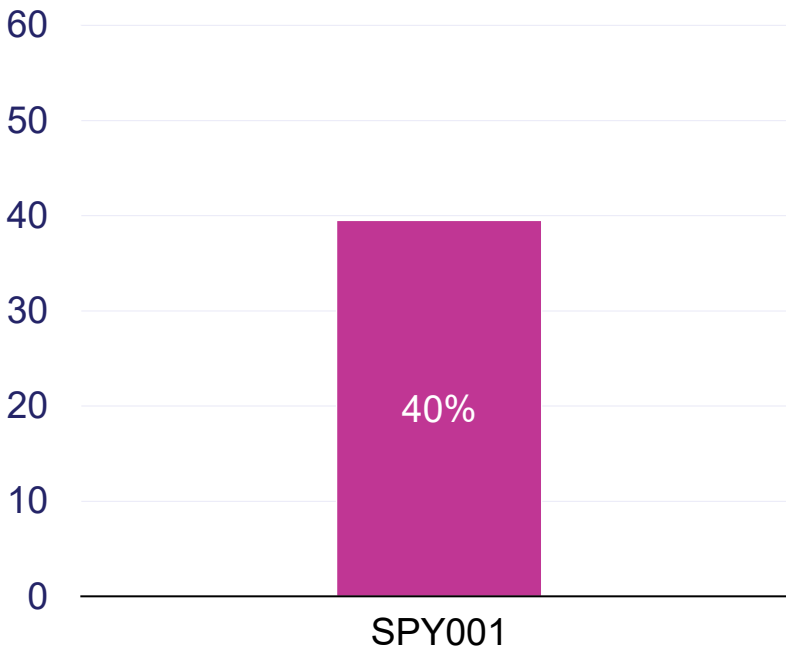
Mean Δ RHI at W12 from baseline



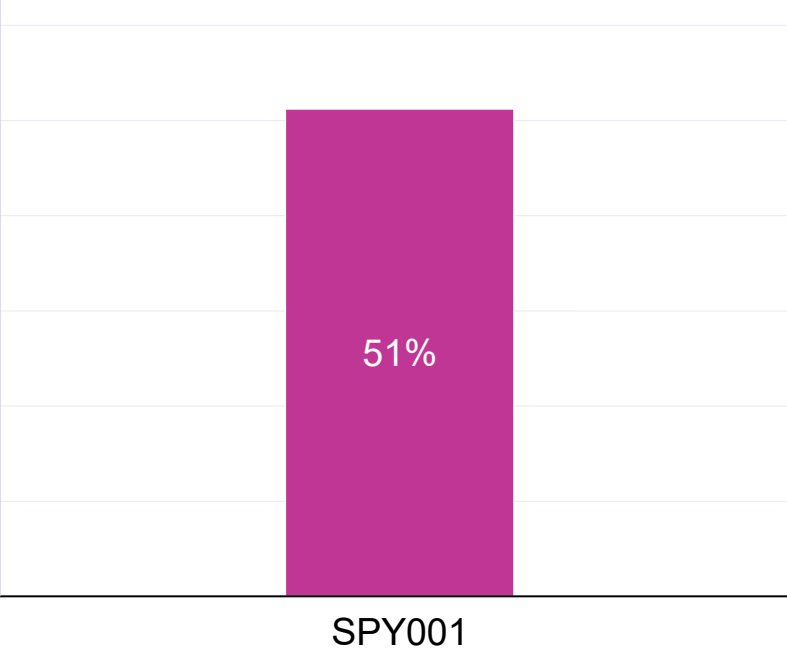
Pre-specified sensitivity analysis:
-10.6 for participants with a baseline RHI ≥ 10

Key secondary endpoints

Proportion with clinical remission at W12



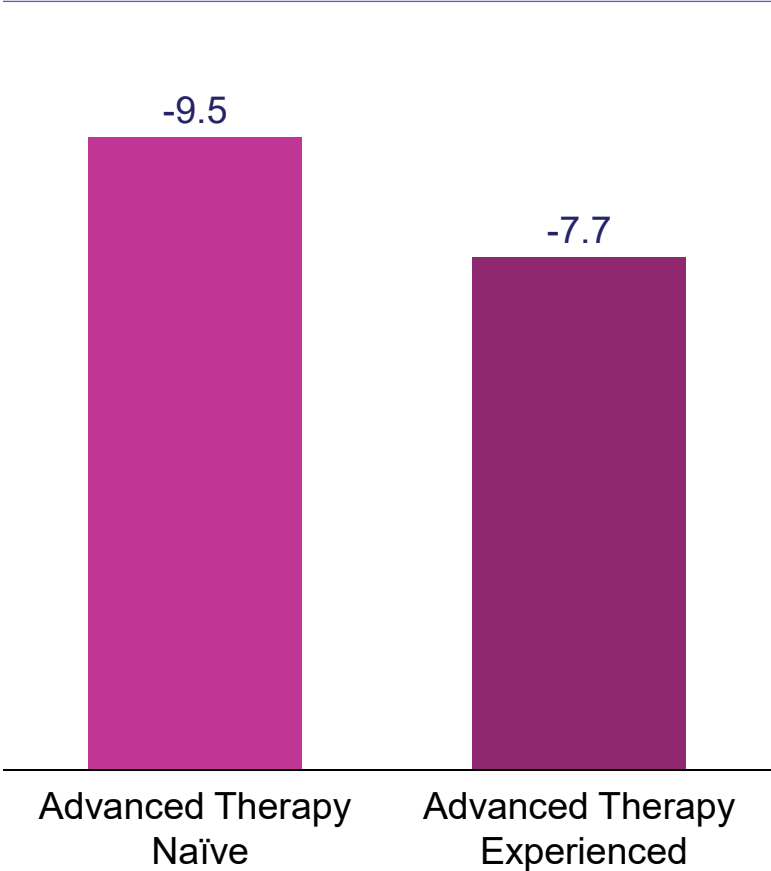
Proportion with endoscopic improvement at W12



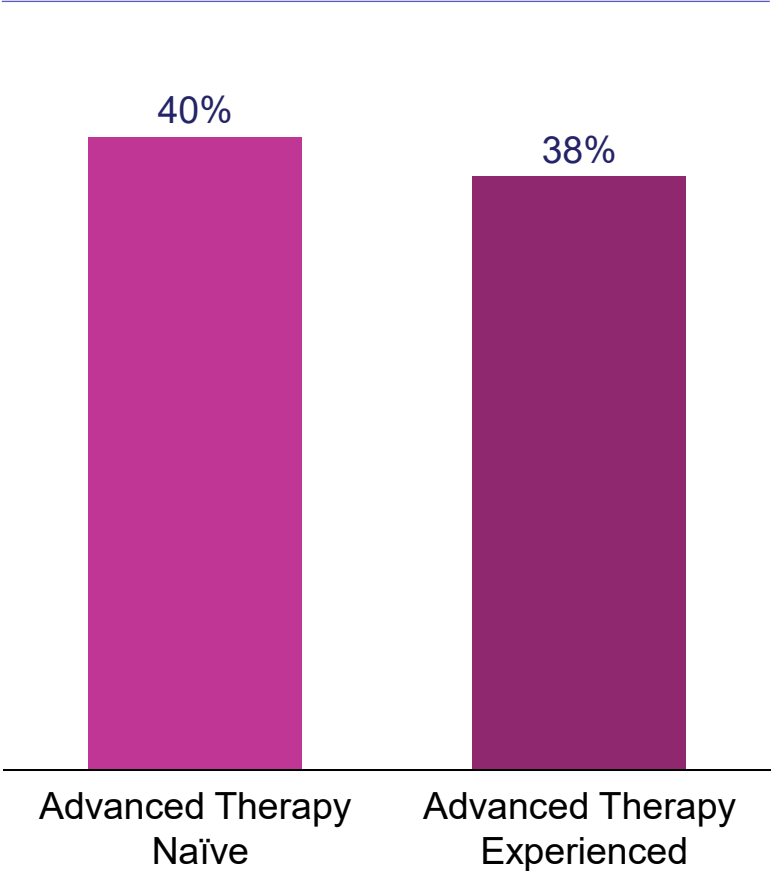
SPY001 response rates were consistent between naïve and experienced UC patients



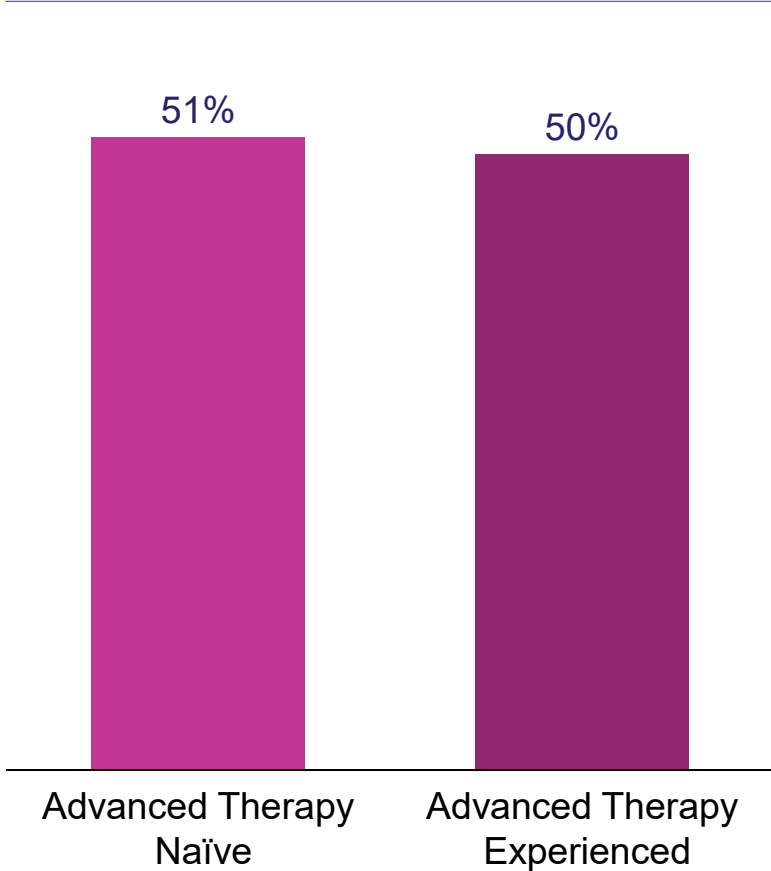
ΔRHI from baseline at W12



Clinical remission at W12



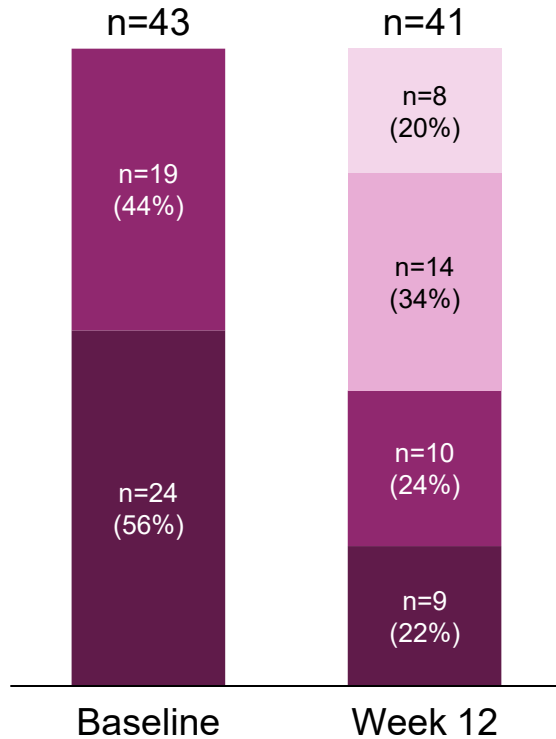
Endoscopic improvement at W12



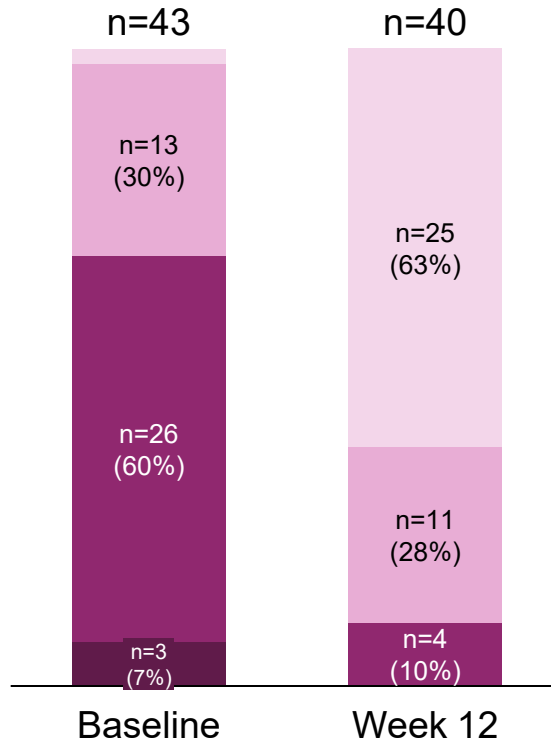
SPY001 demonstrated robust, consistent improvements across endoscopic and symptom measures



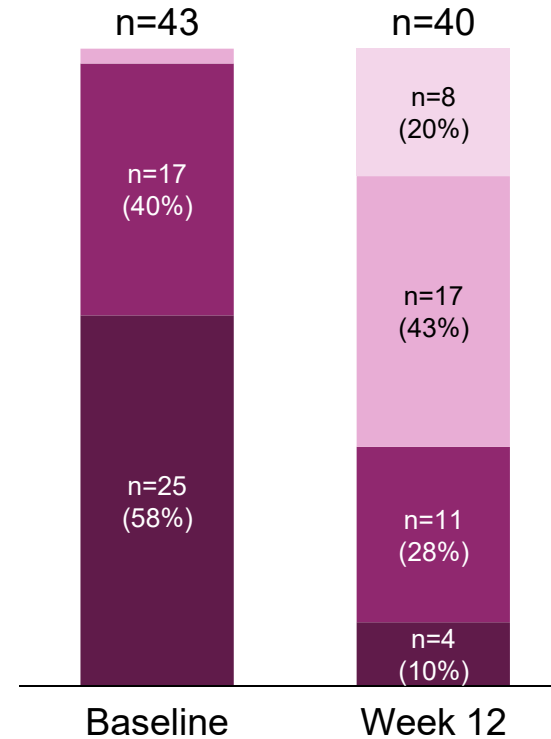
Mayo endoscopic score



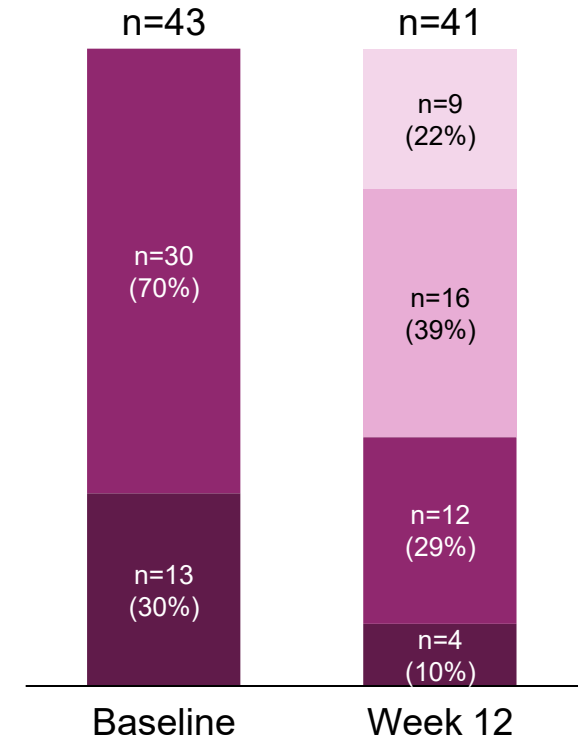
Rectal bleeding



Stool frequency



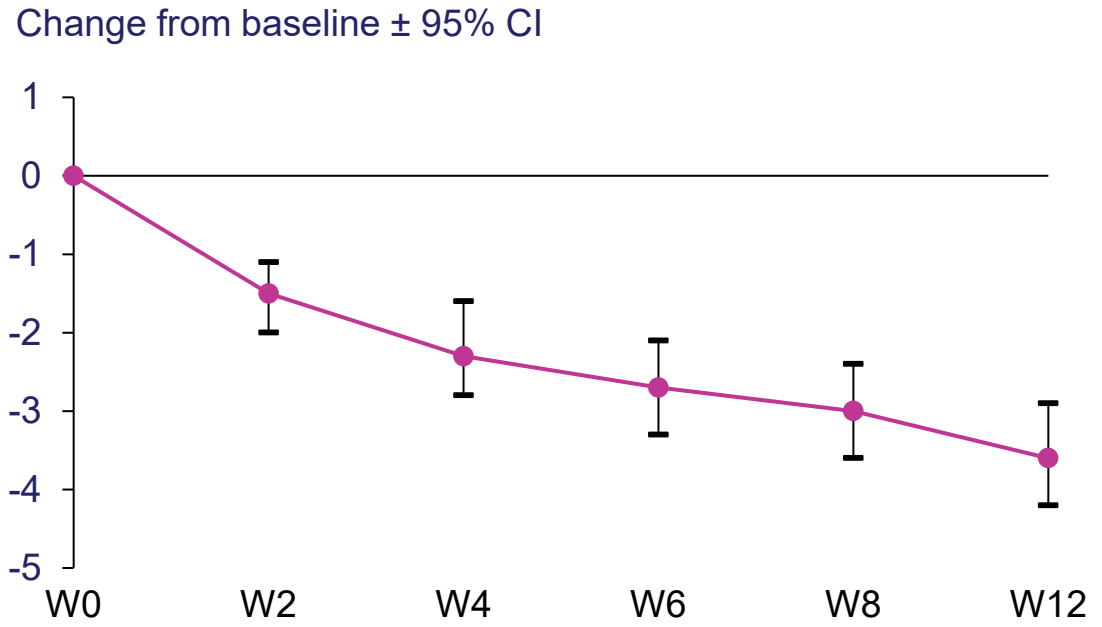
PGA score



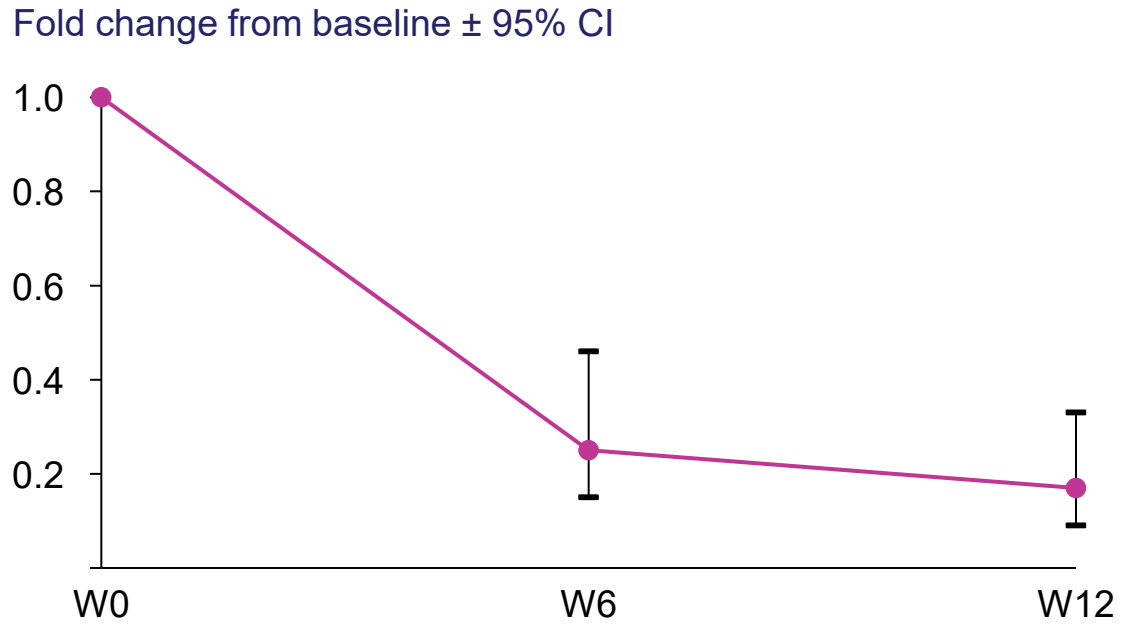
SPY001 demonstrated rapid improvements in reported symptoms and biomarkers of intestinal inflammation



Partial Mayo score



Fecal calprotectin



Patients treated with SPY001 experienced rapid and meaningful symptom and biomarker improvement

Summary Remarks

Cameron Turtle, DPhil, CEO



SPYRE
THERAPEUTICS

SKYLINE Part A enrolled with leading execution



Sponsor	Drugs	Trial	N=	Enrollment months																					
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
SPYRE THERAPEUTICS	SPY001, SPY002, SPY003	SKYLINE Part A cohorts	~130	~10 months										<i>Includes three novel investigational agents</i>											
Morphic	MORF-057	EMERALD-1	35	~9 months																					
Morphic	MORF-057	EMERALD-2	280	~21 months																					
Prometheus	Tulisokibart	ARTEMIS	120	~12 months																					
Roivant	Afimkibart	TUSCANY-2	246	~21 months																					
Teva	Duvakitug	RELIEVE-UCCD	290	~21 months																					
Anaptys	Rosnilimab	ROSETTA	136	~22 months																					
Ventyx	Tamuzimod	Phase 2	213	~17 months																					

The SPY001 Part A cohort enrolled a moderately-to-severely active population comparable to prior anti- α 4 β 7 trials



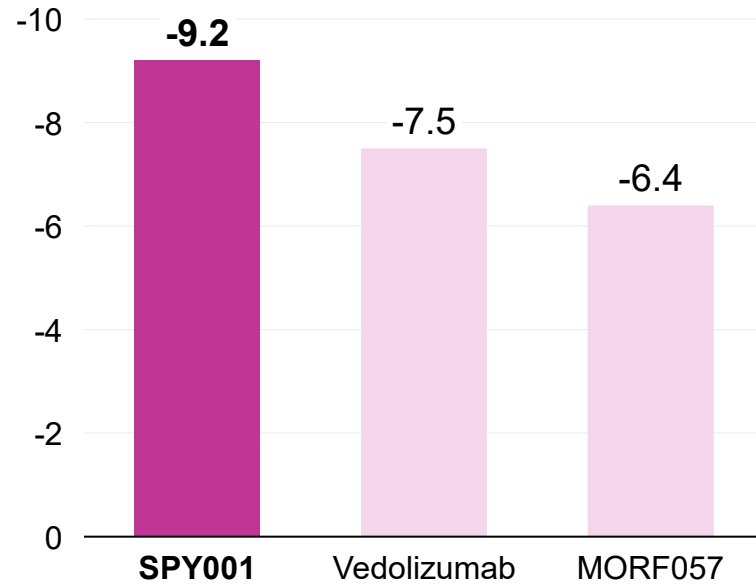
	SPY001	Vedolizumab	Vedolizumab	MORF057
Trial	SKYLINE Part A	VARSITY	GEMINI	EMERALD-1
N =	43	769	374	35
Baseline RHI Mean \pm SD	15.6 \pm 8.6	19.5 \pm 8.7	N/A	22.7 \pm 7.3
Baseline mMS Mean \pm SD	6.8 \pm 1.1	6.1 \pm 1.5*	6.0 \pm 1.6*	6.7 \pm 1.1
MES 3 %	56%	N.R.	N.R.	49%
Steroid use %	42%	36%	56%	26%
Advanced Tx naïve %	81%	79%	58%	63%

SPY001 results across multiple endpoints supports a potential best-in-class product



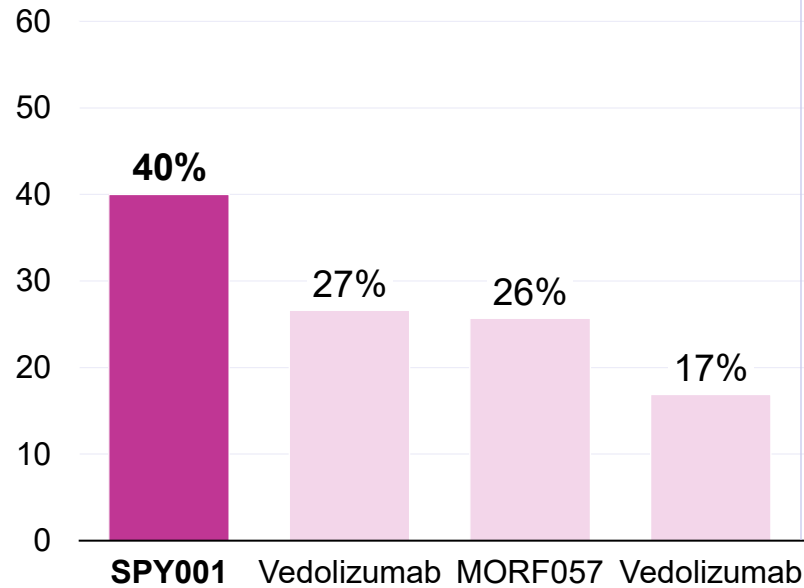
Primary endpoint

ΔRHI from baseline

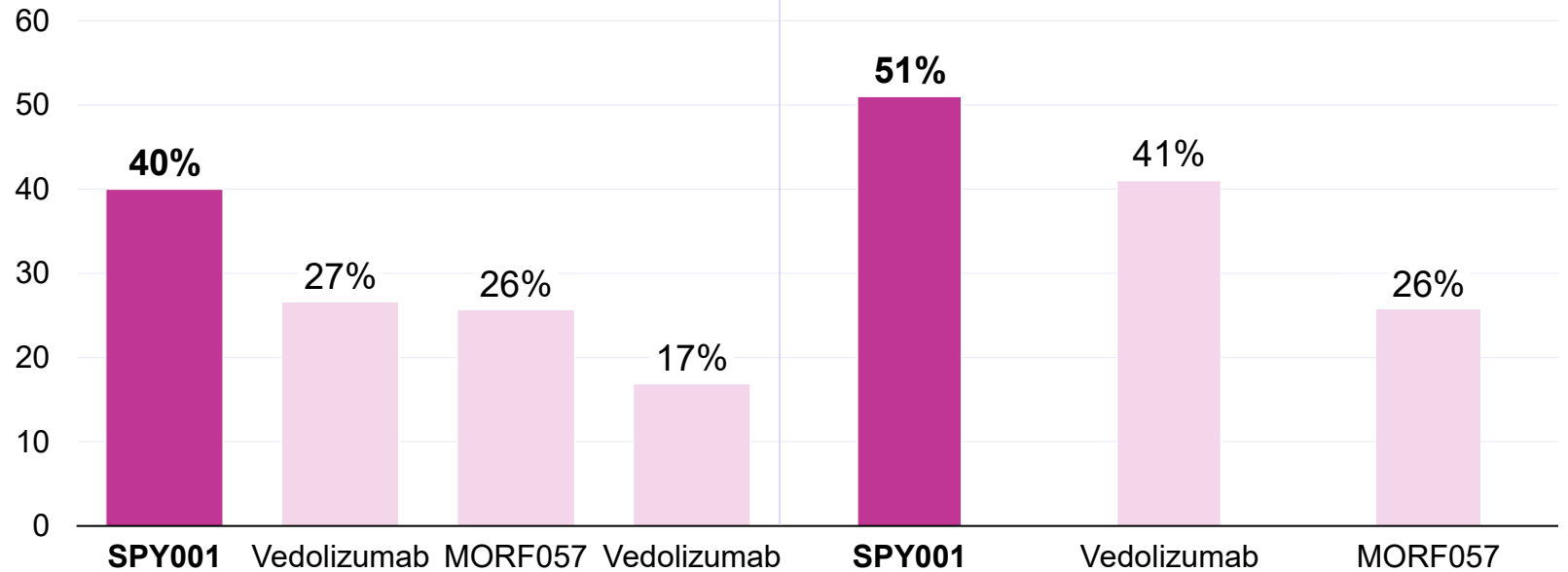


Key secondary endpoints

Proportion with clinical remission



Proportion with endoscopic improvement



Central reading



Week

12

14

12

12

14

12

6

12

6

12

Trial

SKYLINE

VARSITY

EMERALD

SKYLINE

VARSITY

EMERALD

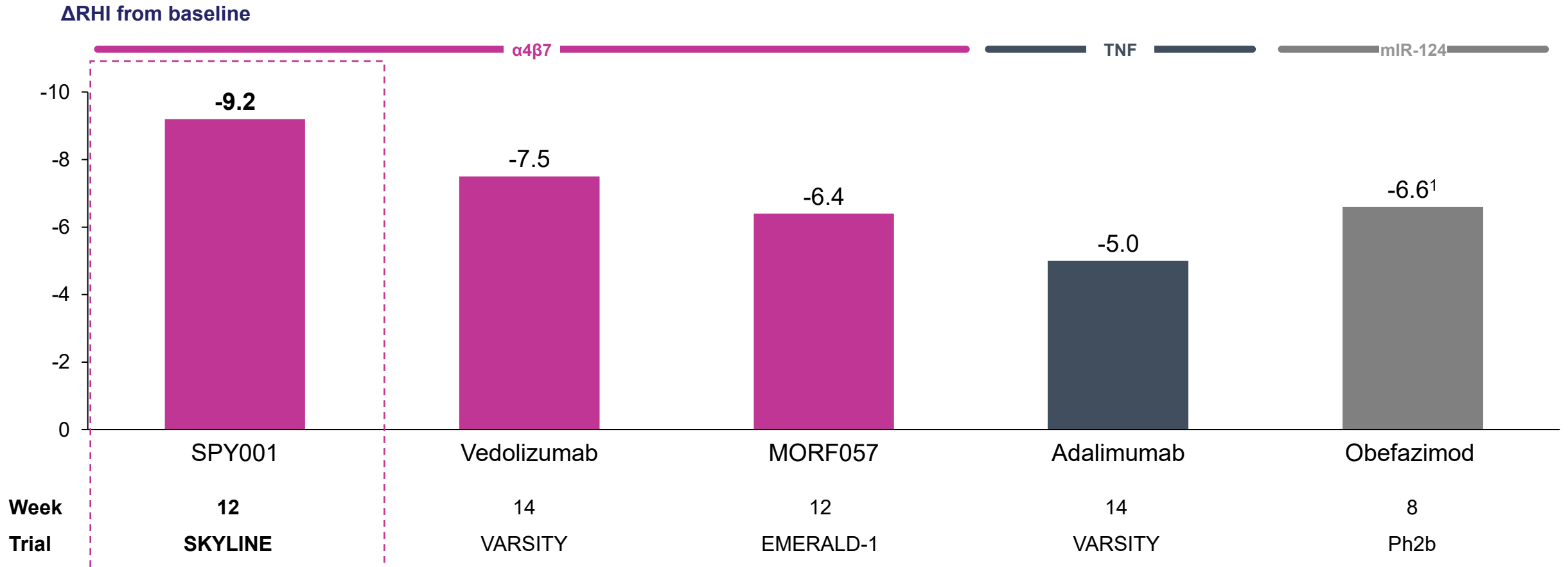
GEMINI

SKYLINE

GEMINI

EMERALD

SPY001 change in RHI outperformed previously reported results in UC trials

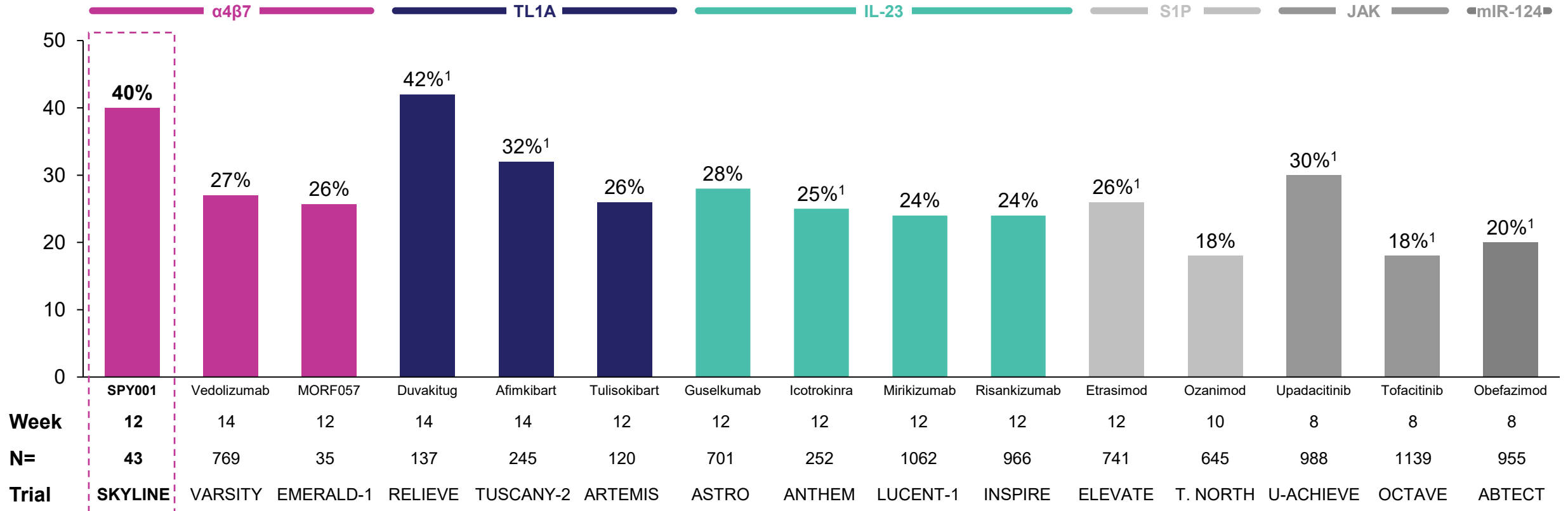


Pre-specified sensitivity analysis:
 -10.6 for participants with a baseline RHI ≥ 10

SPY001's 40% clinical remission among the highest reported in UC trials



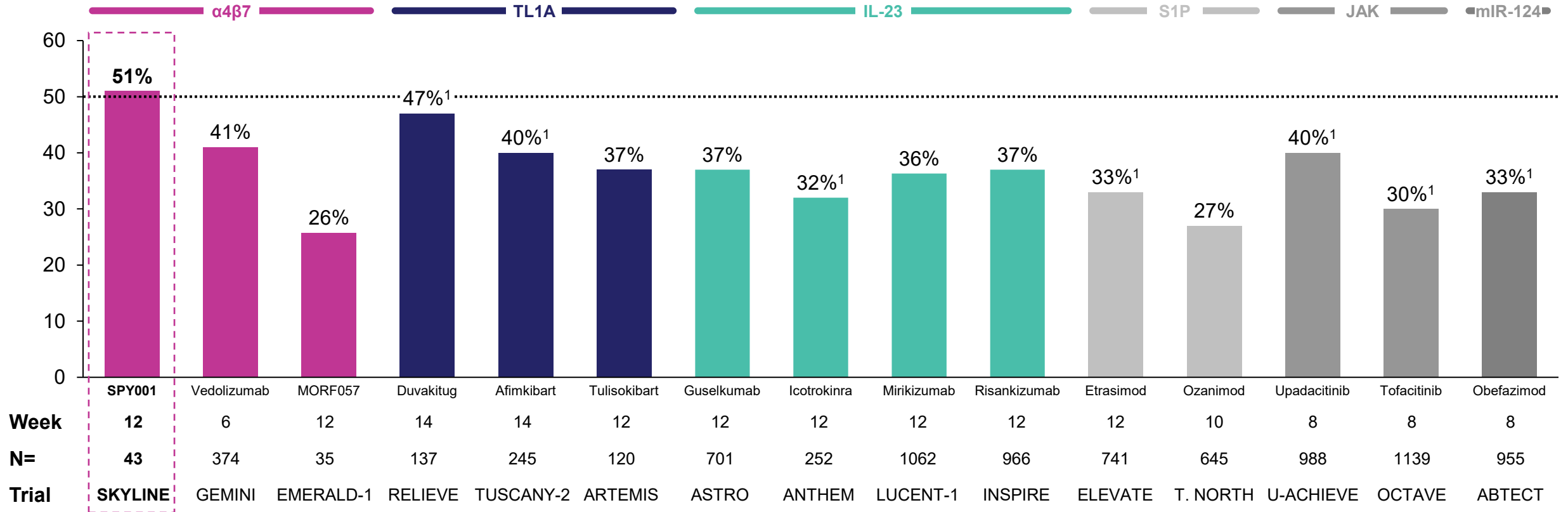
Proportion of participants with clinical remission



SPY001's 51% endoscopic improvement outperformed previously reported results in UC trials

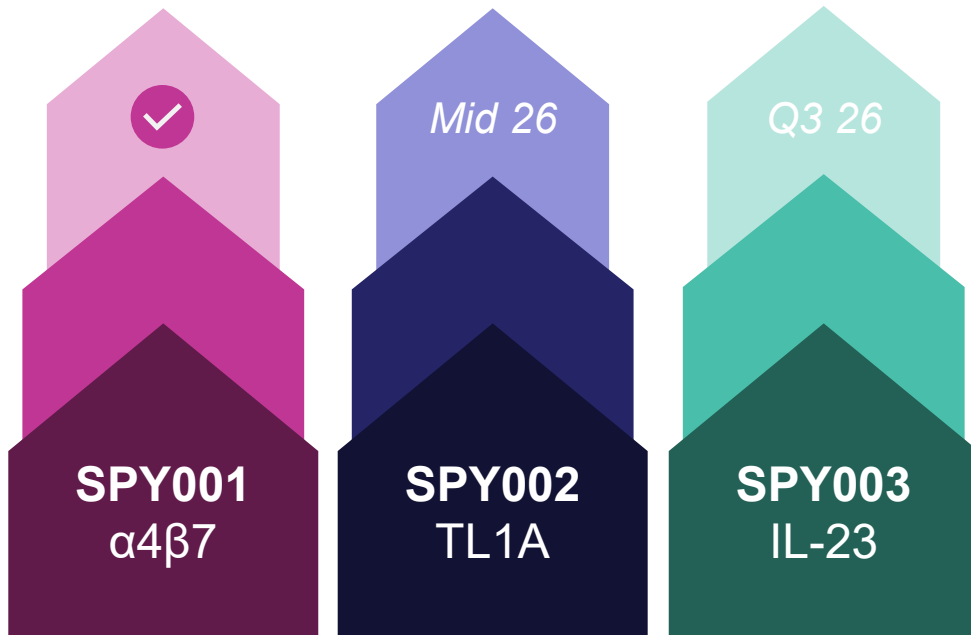


Proportion of participants with endoscopic improvement



Endoscopic improvement results support potential for best-in-indication mucosal healing

SPY001 Part A data supports its potential as one of the most promising single agents in IBD



SPY001 Part A data supports upside target product profile:



Favorable safety profile consistent with class



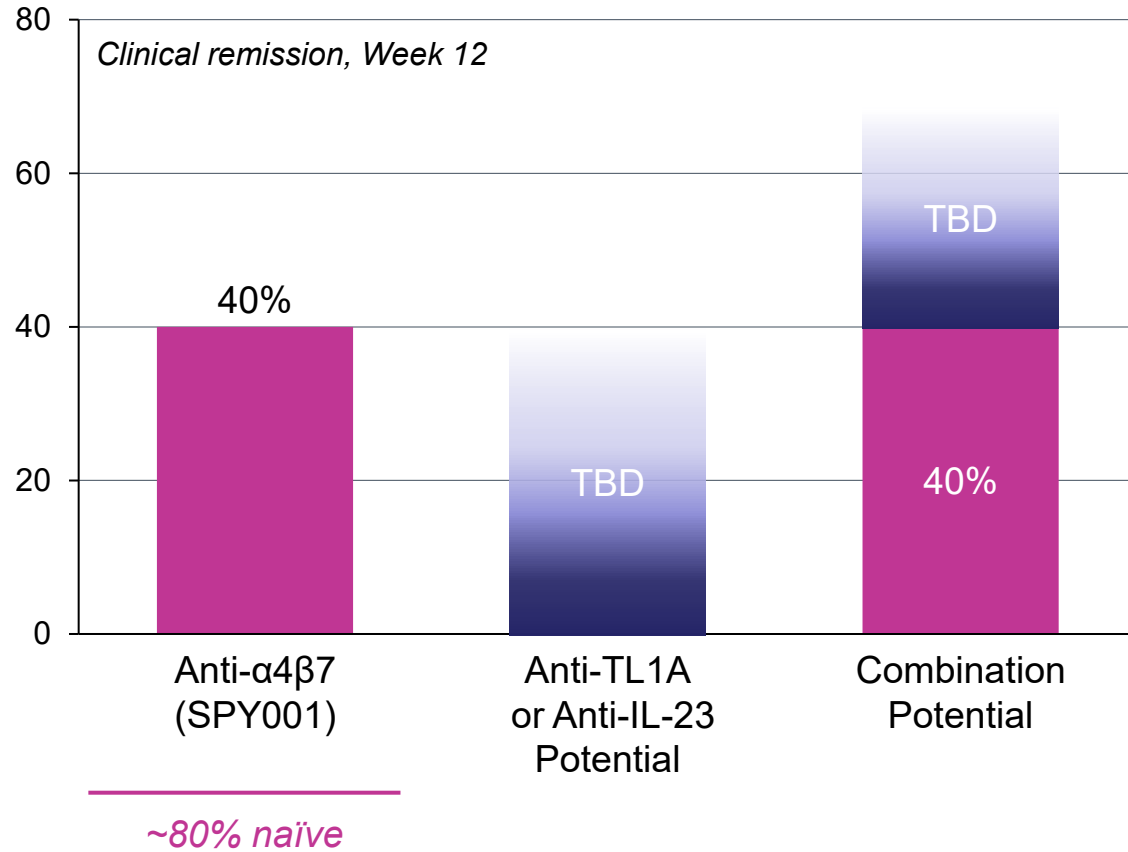
Potential best-in-class efficacy



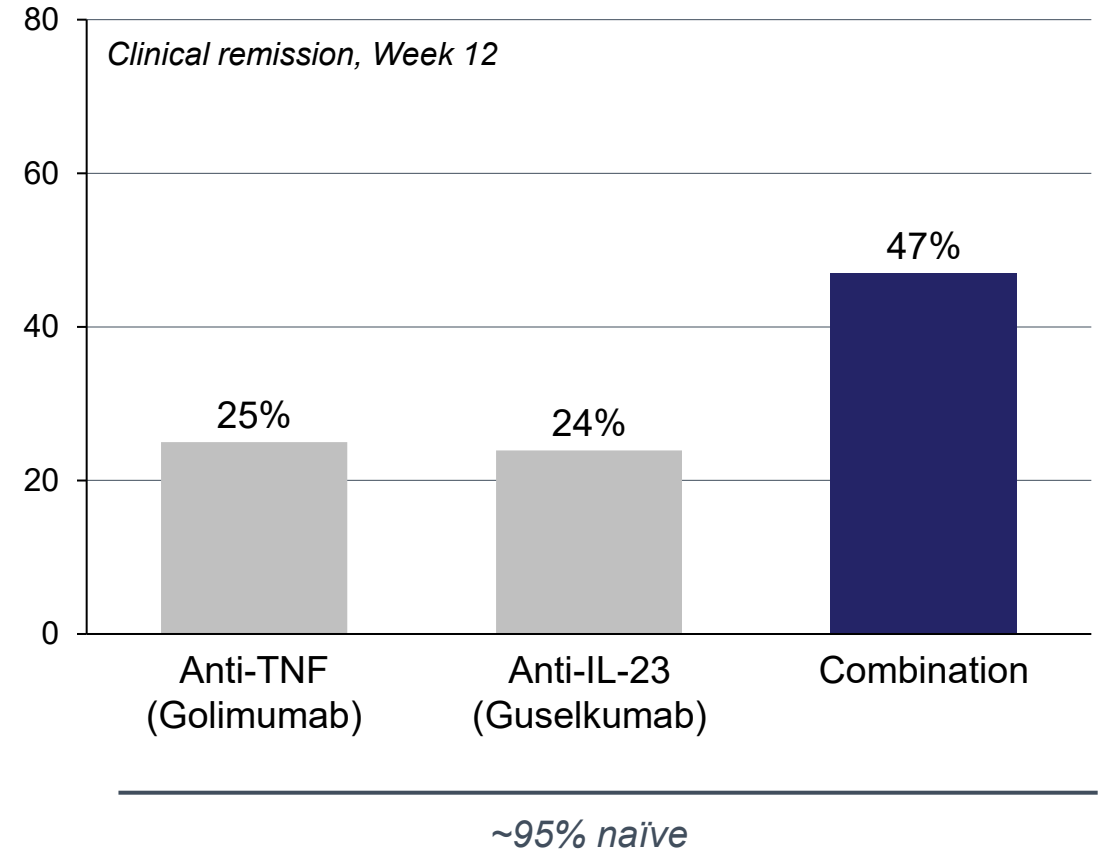
Formulated for potential best-in-indication convenience (Q3-6M)¹

Now enrolling: Multi-dose, placebo controlled SPY001 cohorts + combos with SPY002 and SPY003

SPY001 data support improved combination potential






JNJ VEGA study



Catalyst rich 2026 with multiple accelerated readouts expected



Trial	Milestone	Expected timing
 Part A (Open-label)	SPY001 α4β7 Ph2 UC induction POC SPY002 TL1A Ph2 UC induction POC SPY003 IL-23 Ph2 UC induction POC	<div style="background-color: #e0e0e0; padding: 10px; text-align: center; margin-bottom: 10px;">Recruitment closed</div> <input checked="" type="checkbox"/> 2Q 2026 <input type="checkbox"/> Mid-year 2026 <input type="checkbox"/> 3Q 2026
 Part B (Pbo-controlled)	Initiate enrollment of Part B cohorts	<input checked="" type="checkbox"/> 2Q 2026
	SPY072 TL1A Ph2 W12 POC in RA SPY072 TL1A Ph2 W16 POC in PsA SPY072 TL1A Ph2 W16 POC in axSpA	<div style="background-color: #e0e0e0; padding: 10px; text-align: center; margin-bottom: 10px;">Enrollment complete</div> <input type="checkbox"/> 3Q 2026 <input type="checkbox"/> 4Q 2026 <input type="checkbox"/> 4Q 2026

Q&A

