



SPYRE
THERAPEUTICS

CORPORATE OVERVIEW

JUNE 15, 2026



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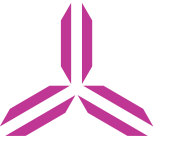
Forward-Looking Information

Certain information set forth in this presentation contains “forward-looking statements” within the meaning of applicable United States securities legislation. Except for statements of historical fact, certain information contained herein constitutes forward-looking statements which include but are not limited to statements regarding: our business strategy, including our ability to develop best-in-class and first-in-class next-generation therapies for inflammatory bowel disease (IBD), rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) that are designed to elevate the standard in immunology and are comparable-to-better or meaningfully improve both efficacy and convenience compared to today’s standard of care; our ability to achieve the expected benefits or opportunities with respect to our product candidates, including their potential commercialization; the potential consistency of the SPY001, SPY002, SPY072 and SPY003 Phase 1 trial and Phase 2 trial final data readouts with topline, interim and previously disclosed data for our programs; the potential for combination therapies to break the monotherapy efficacy ceiling with respect to IBD; the potential for combinations of our monotherapy product candidates to deliver best-in-disease efficacy, safety, and treatment experiences; the potential of anti-TL1A treatment for robust skin clearance in PsA; expectations regarding the drug delivery of our product candidates; the efficacy, safety profile, dosing regime, convenience, commercial viability and tolerability of SPY001, SPY002, SPY072 and SPY003, including combinations thereof; expected competitors and competing products; Spyre’s non-clinical and clinical development activities, including clinical trial designs, our plans for and timing of cohort initiation and data readouts for the ongoing SKYWAY Phase 2 basket trial and SKYLINE Phase 2 platform trial, enrollment of clinical trials, the inclusion of each rational combination in Part B of the SKYLINE Phase 2 platform trial and the number of data readouts expected to be delivered in 2026 and 2027; our ability to provide anticipated readouts ahead of any disclosed bispecific approaches against our targets; the induction and maintenance dosing regimen for our product candidates and combinations thereof, including the potential for a Q3M-Q6M dosing profile; the potential therapeutic benefits and economic value of our product candidates as monotherapies or in combinations and their extended half-life, including their expected benefits in comparison to expected competitor products and potential best-in-indication product profiles; estimated market sizes and potential growth opportunities; the length of time that the Company believes its existing cash resources will fund its operations; statements regarding the Company’s cash guidance; and management’s assessment of future plans and operations which are based on current internal expectations, estimates, projections, assumptions and beliefs, which may prove to be incorrect. 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Spyre is developing next-generation therapies designed to elevate the standard in immunology



Inflammatory bowel disease

Potential
best-in-class
monotherapies

SPY001 **α4β7**

SPY002 **TL1A**

SPY003 **IL-23**



Enable potential
paradigm changing
combinations

SPY120 **α4β7 + TL1A**

SPY130 **α4β7 + IL-23**

SPY230 **TL1A + IL-23**



Target Q3M-Q6M dosing

After loading doses

Rheumatic disease

Potential
first-in-class & best-in class
anti-TL1A

SPY072 **TL1A**



RA

PsA

axSpA





Target Q3M-Q6M dosing

After loading doses

Two innovative trials provide six expected Ph2 readouts in '26



6 expected POC readouts
in
'26

Trial	Readout	Anticipated Milestones
	SPY001 α4β7 Ph2 POC in UC SPY002 TL1A Ph2 POC in UC SPY003 IL-23 Ph2 POC in UC	Q2 ✓ Q2 ✓ Q3
	SPY072 TL1A Ph2 POC in RA SPY072 TL1A Ph2 POC in PsA SPY072 TL1A Ph2 POC in axSpA	Q3 Q4 Q4

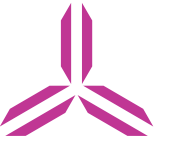
Advancing a robust I&I pipeline with exceptional financial strength



Trial	Indication	Program	Target	Phase 1	Phase 2	Phase 3	Anticipated Milestones
	UC	SPY001	α4β7	[Progress bar]			Q2 2026: Ph2 open label POC ✓
		SPY002	TL1A	[Progress bar]			Q2 2026: Ph2 open label POC ✓
		SPY003	IL-23	[Progress bar]			Q3 2026: Ph2 open label POC
		SPY120	α4β7 + TL1A	[Progress bar]			2027: Ph2 pbo-controlled POC
		SPY130	α4β7 + IL-23	[Progress bar]			
		SPY230	TL1A + IL-23	[Progress bar]			
	RA	SPY072	TL1A	[Progress bar]			Q3 2026: Ph2 POC
	PsA			[Progress bar]			Q4 2026: Ph2 POC
	axSpA			[Progress bar]			Q4 2026: Ph2 POC

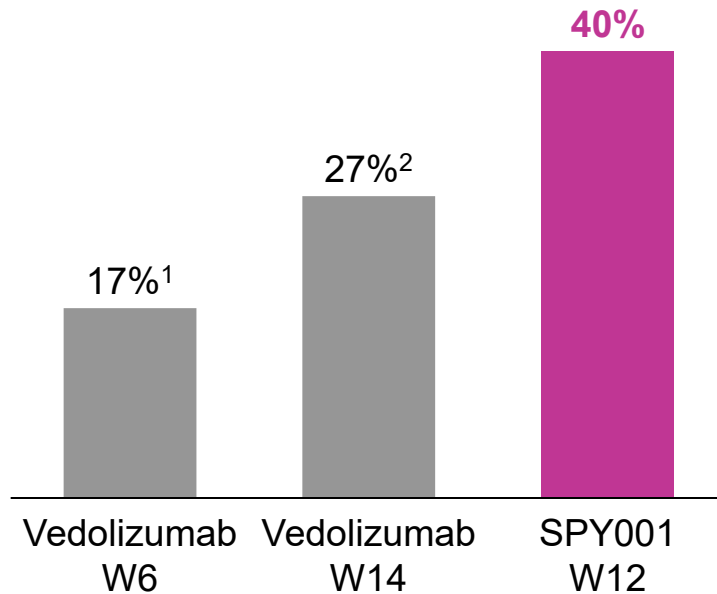
\$1.2 billion proforma cash as of March 31, 2026¹, with expected runway into 2H 2029

Next-generation antibodies designed to match or exceed the efficacy of first-generation molecules



SPY001 ($\alpha 4\beta 7$) efficacy

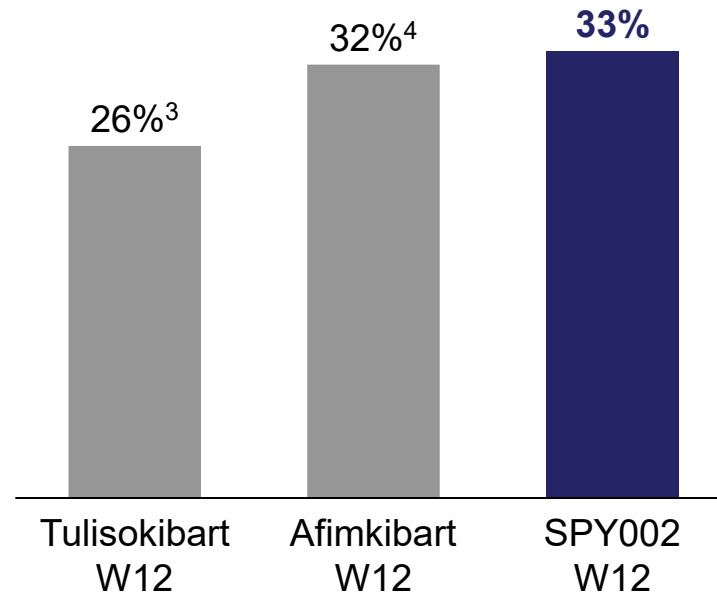
Clinical remission rate



✓ SKYLINE Part A POC achieved
2Q 2026

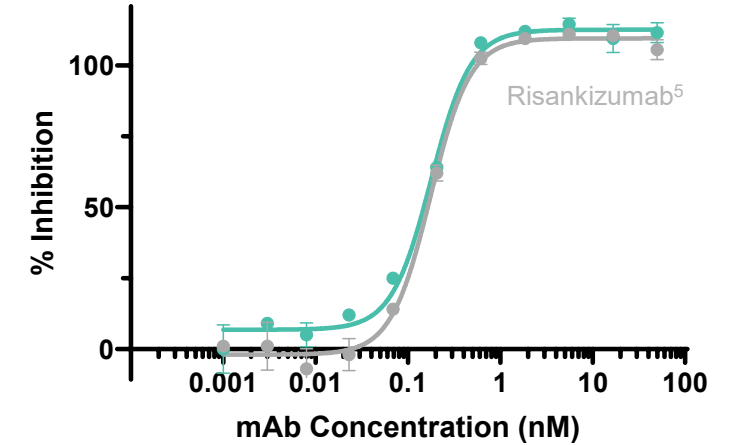
SPY002 (TL1A) efficacy

Clinical remission rate



✓ SKYLINE Part A POC achieved
2Q 2026

SPY003 (IL-23) potency

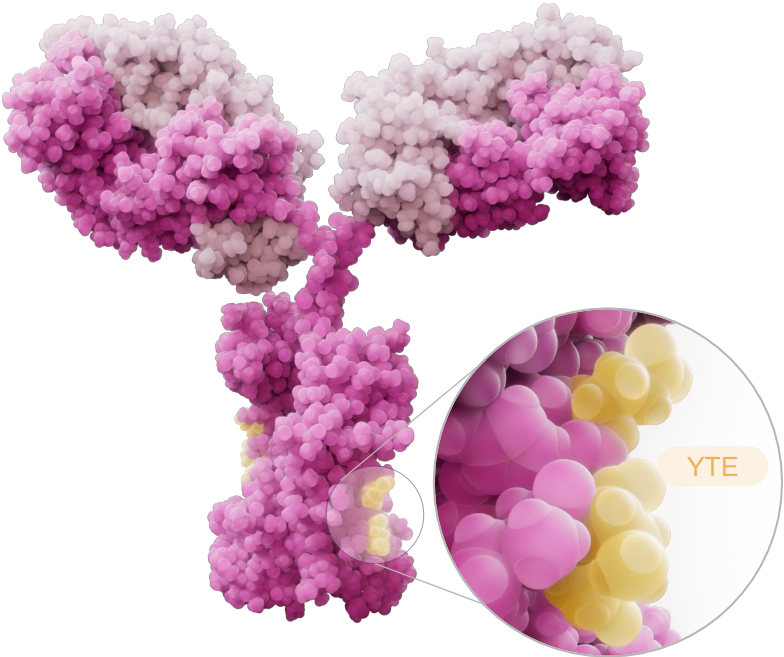


SKYLINE Part A POC data
3Q 2026

Engineered to be long-acting via YTE modification

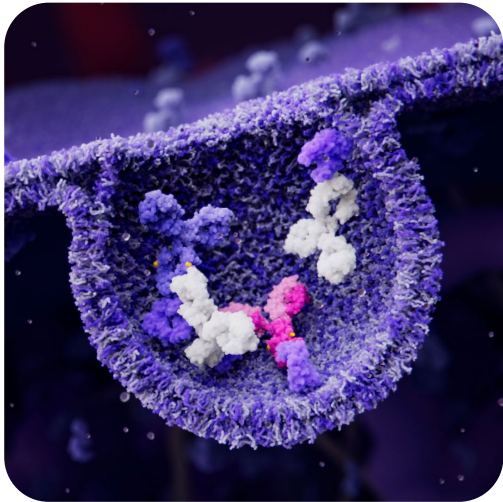


YTE modification

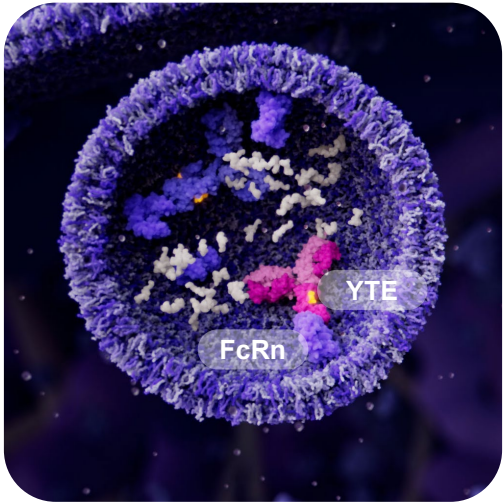


YTE-modified mAbs are returned to circulation for continued activity

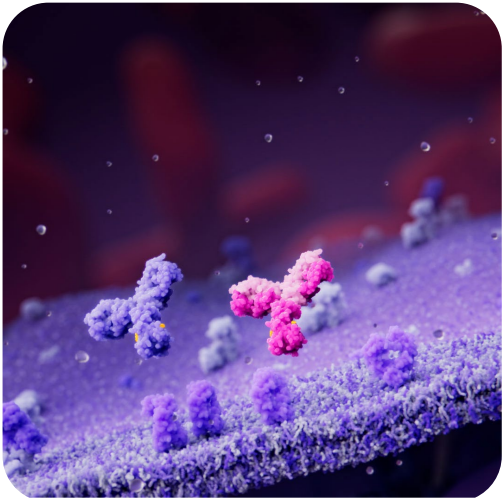
Antibodies are subject to degradation when internalized



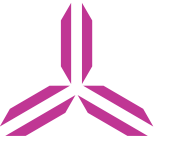
YTE modification increases internal binding to FcRn, avoiding degradation



FcRn binding promotes recycling of mAbs to circulation



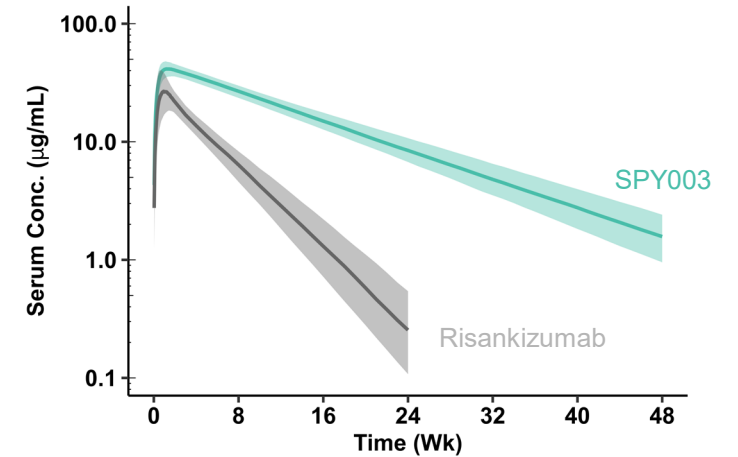
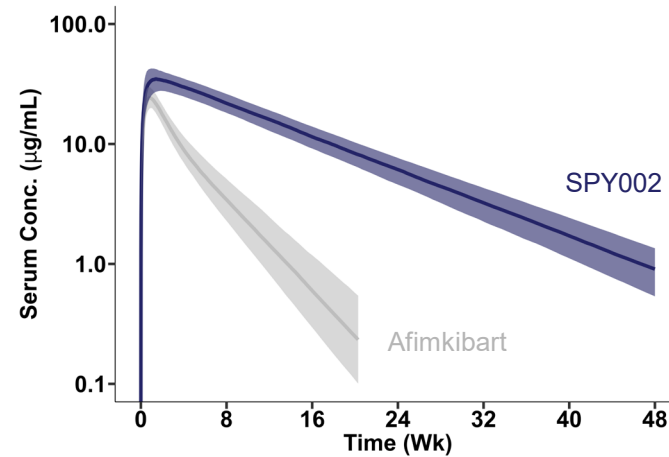
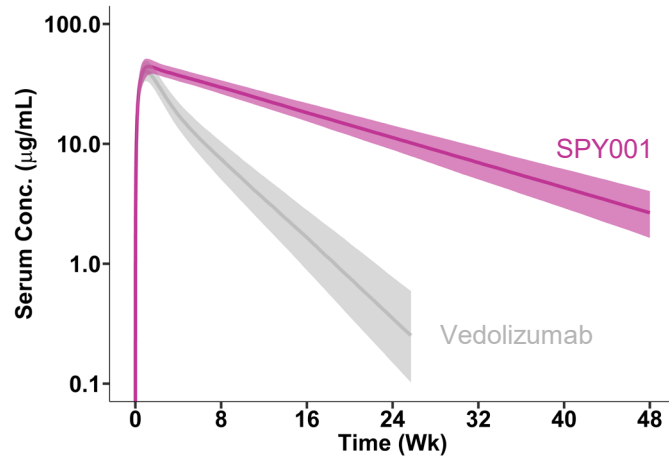
Demonstrated half-life extension for potential quarterly or twice-annual dosing



SPY001 human PK simulation

SPY002 human PK simulation

SPY003 human PK simulation



Target Profiles



Q3M-Q6M
Maintenance dosing



Q3M-Q6M
Maintenance dosing



Q3M-Q6M
Maintenance dosing

Potential paradigm-changing combination therapies in IBD



Inflammatory bowel disease



Rational combinations targeting diverse disease drivers

SPY120




TL1A
+
 $\alpha 4\beta 7$

>

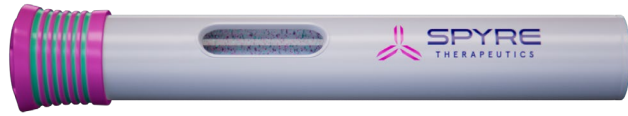


SPY130



IL-23
+
 $\alpha 4\beta 7$

>



SPY230



IL-23
+
TL1A

>



Target Q3M-Q6M dosing

Spyre is developing two distinct, potentially best-in-class anti-TL1A antibodies for IBD and rheumatic disease



Inflammatory bowel disease

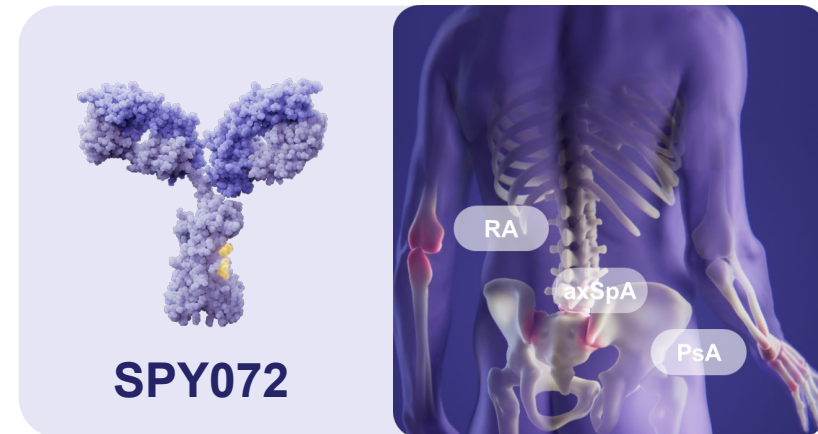


SPY002

IBD

Potential best-in-class combination component

Rheumatic disease



SPY072

RA

axSpA

PsA

Potential first-in-class, best-in-class agent



Distinct, novel epitopes



High potency



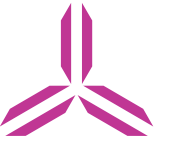
Target Q3M-Q6M dosing



High-conc. SC formulation

Advancing two distinct anti-TL1As provides strategic and commercial flexibility

Spyre is uniquely positioned to enable superior product profiles in IBD and rheumatic diseases

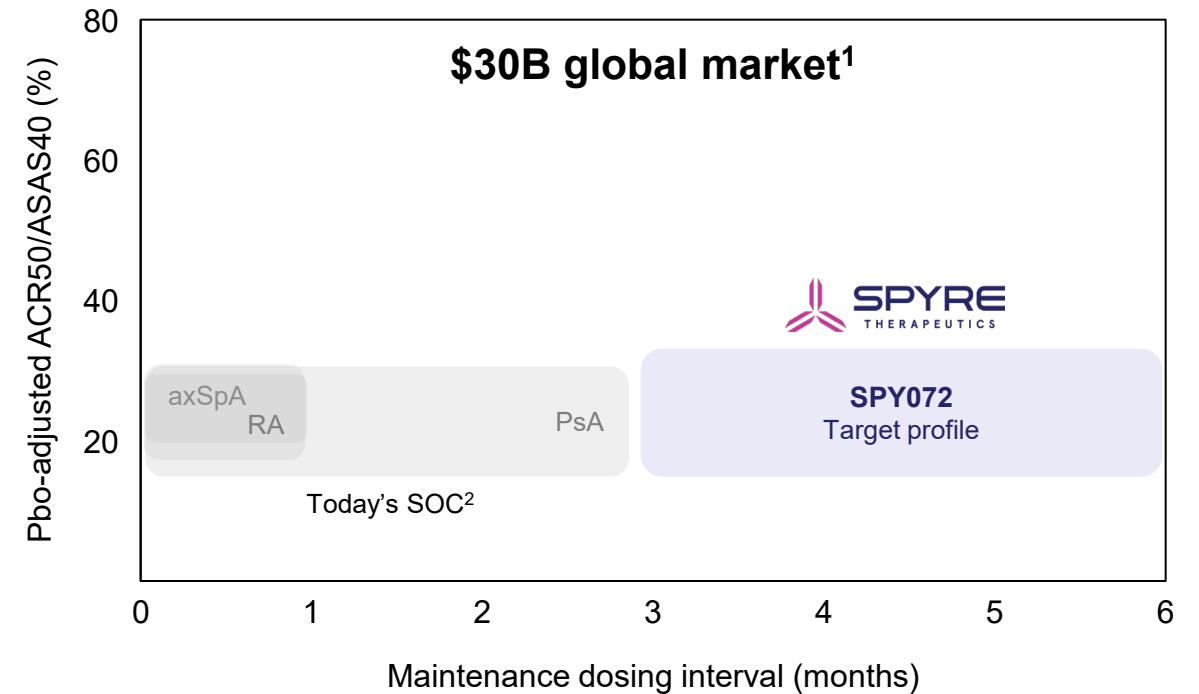
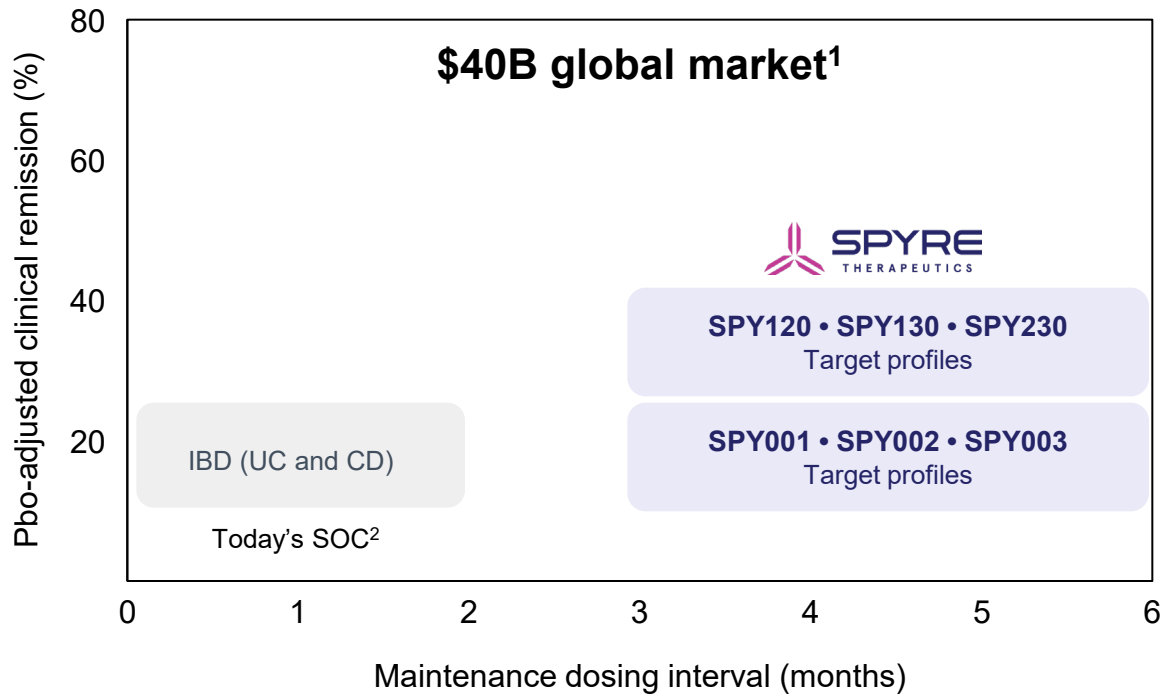


Inflammatory bowel disease

Rheumatic disease

Advancing potential **best-in-class** monotherapies
 Enabling potential **paradigm changing** combinations

Advancing potential **first-in-class & best-in-class** anti-TL1A



Ph2 trials ongoing in IBD and rheumatic diseases



Ph2 *platform* trial evaluating SPY001, SPY002, SPY003 and pairwise combinations in ulcerative colitis



UC	
Monos	SPY001
	SPY002
	SPY003
Combos	SPY120
	SPY130
	SPY230
	Placebo

6

INTERVENTIONS

1

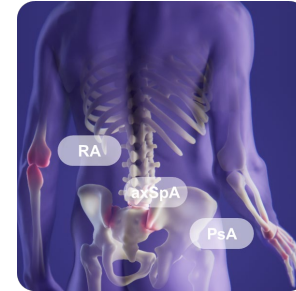
INDICATION

'26-'27

EXPECTED READOUTS*



Ph2 *basket* trial evaluating SPY072 in rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis



RA	SPY072 high
	SPY072 low
	Placebo
PsA	SPY072
	Placebo
axSpA	SPY072
	Placebo

1

INTERVENTION

3

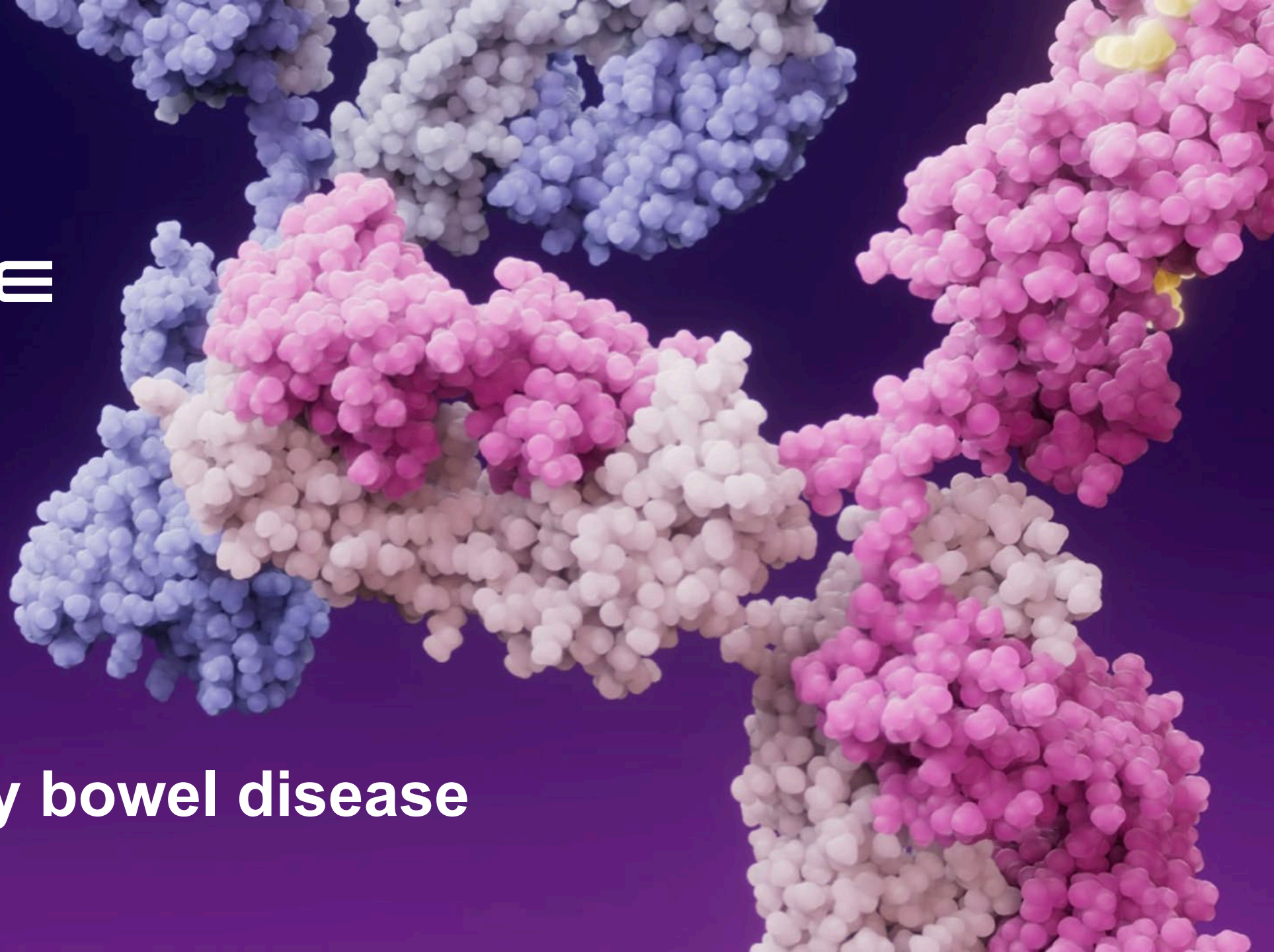
INDICATIONS

Q3-Q4'26

EXPECTED READOUTS



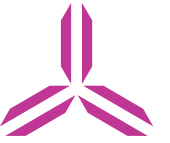
SKYLINE



Inflammatory bowel disease

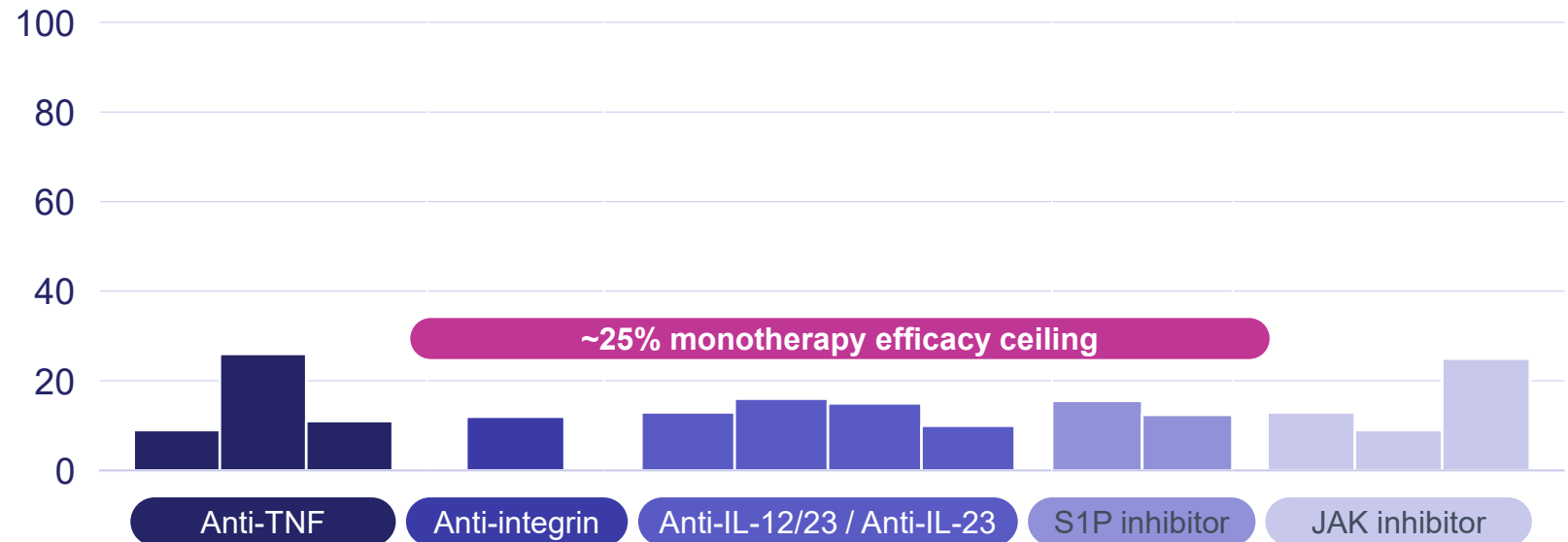
SPYRE

Substantial unmet need remains for the millions of individuals living with IBD



- ~2.4M individuals in the U.S. are diagnosed with IBD (~1.3M UC and ~1.0M CD)¹
- Substantial unmet need remains due to:
 - Minority remission rates and lack of durability with existing therapies
 - Side effects and safety concerns associated with certain treatments
 - Poor adherence to frequent and/or inconvenient dosing regimens

UC placebo-adjusted clinical remission rates by MOA (Induction)

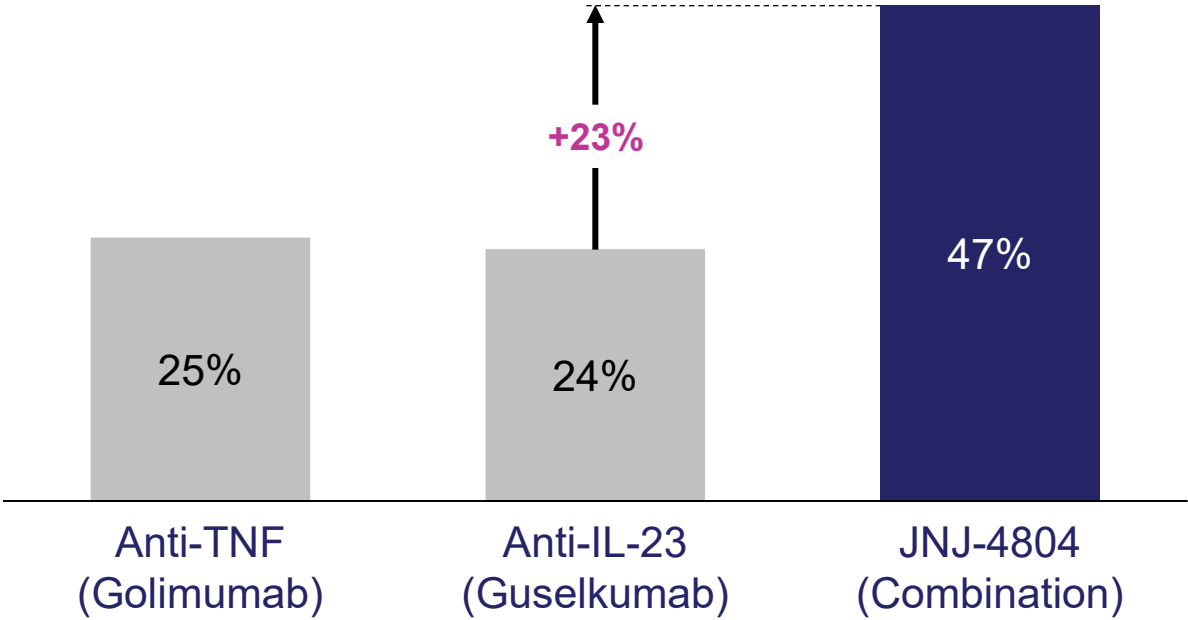


JNJ's VEGA and DUET studies demonstrated the ability for combinations to break the monotherapy efficacy ceiling



Naïve (1L) UC patients (VEGA)

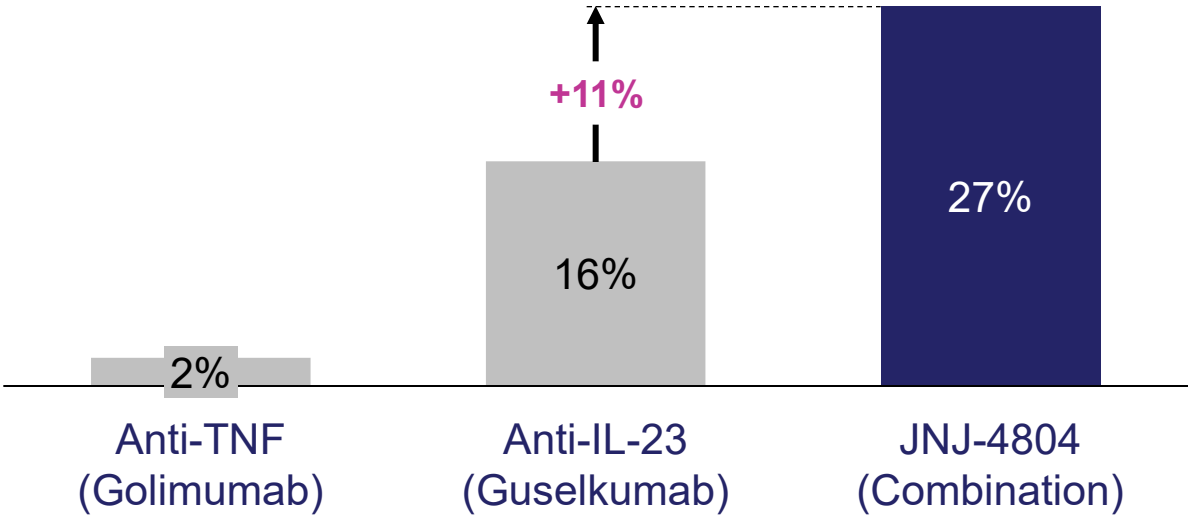
~Additive absolute W12 mMS clinical remission rate



Refractory (3L+) UC patients (DUET-UC)

Synergistic absolute W48 mMS clinical remission rate

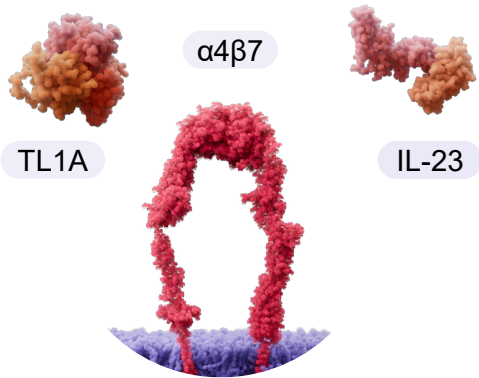
- 74% of patients were refractory to anti-TNF
- 1% were refractory to anti-IL-23



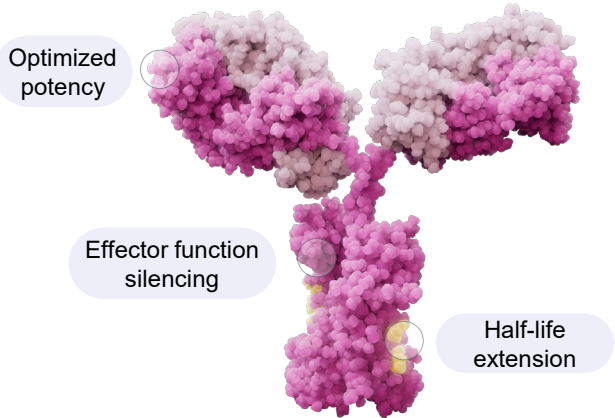
Spyre is unique in developing uncompromising combinations from first principles



Orthogonal MOAs rationally chosen based on attractive risk-benefit profiles



Next-generation molecules engineered for best-in-class potential



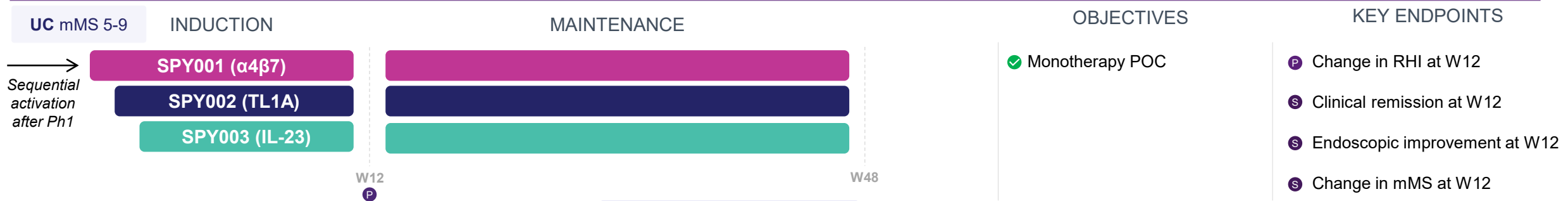
Coformulations optimized for convenient, SC delivery (Q3M-Q6M)¹



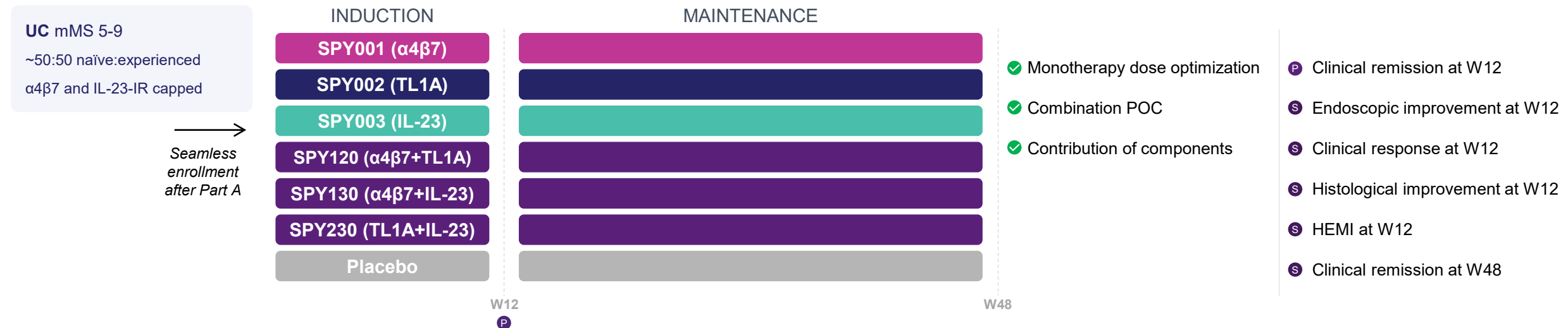
SKYLINE is a two-part study, with Part B combination evaluation now enrolling



Part A: Open-label monotherapy evaluation (N~130) **Enrollment complete**



Part B: PBO-controlled factorial combination evaluation (N~550) **Now enrolling**



SPY001 and SPY002 met all objectives in SKYLINE Part A, progressing Spyre's differentiated combination approach



	SPY001	SPY002	SPY003	Combinations
PART A PRIMARY				
ΔRHI from baseline	-9.2	-10.7		
PART A SECONDARY				
% Clinical remission	40%	33%		
% Endoscopic improvement	51%	42%	Q3 2026	2027
Safety	Consistent with class	Consistent with class		
Objective	Potential best-in-class efficacy and dosing ✓	Efficacy in-line, potential best-in-class dosing ✓	Efficacy in-line, potential best-in-class dosing	Deeper, sustained disease control & simplified treatment experience



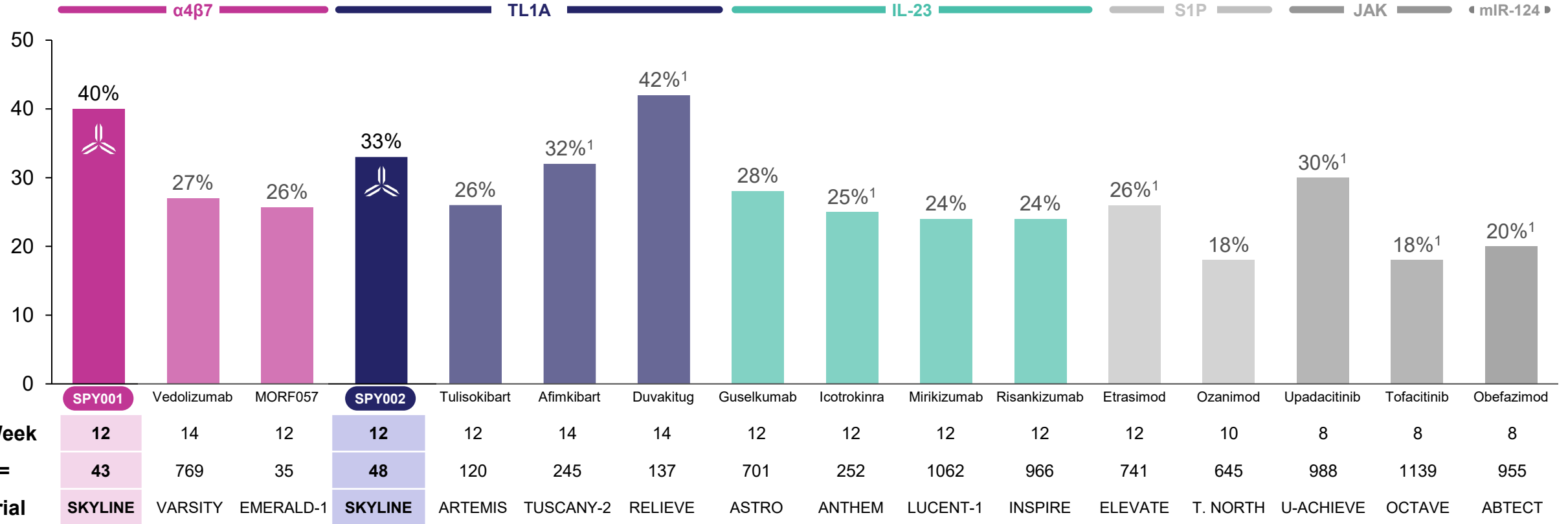
Developing therapies to elevate the standard for inflammatory bowel disease

SPY001 and SPY002 demonstrated robust rates of clinical remission



Clinical remission

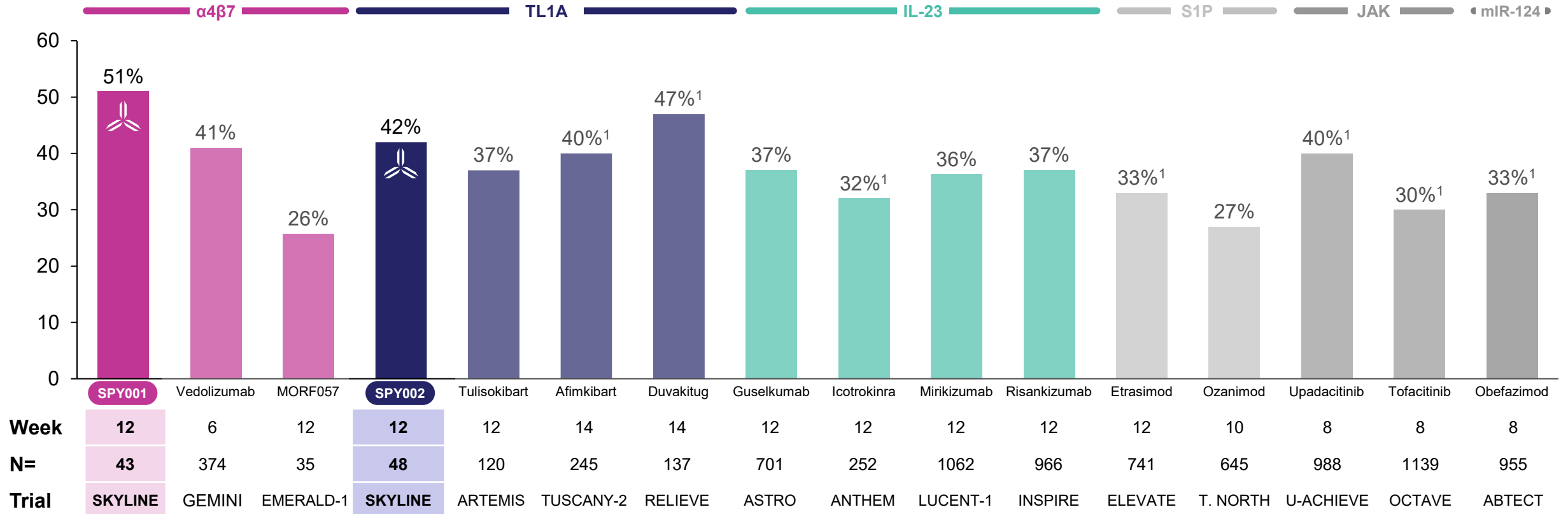
Percentage of subjects



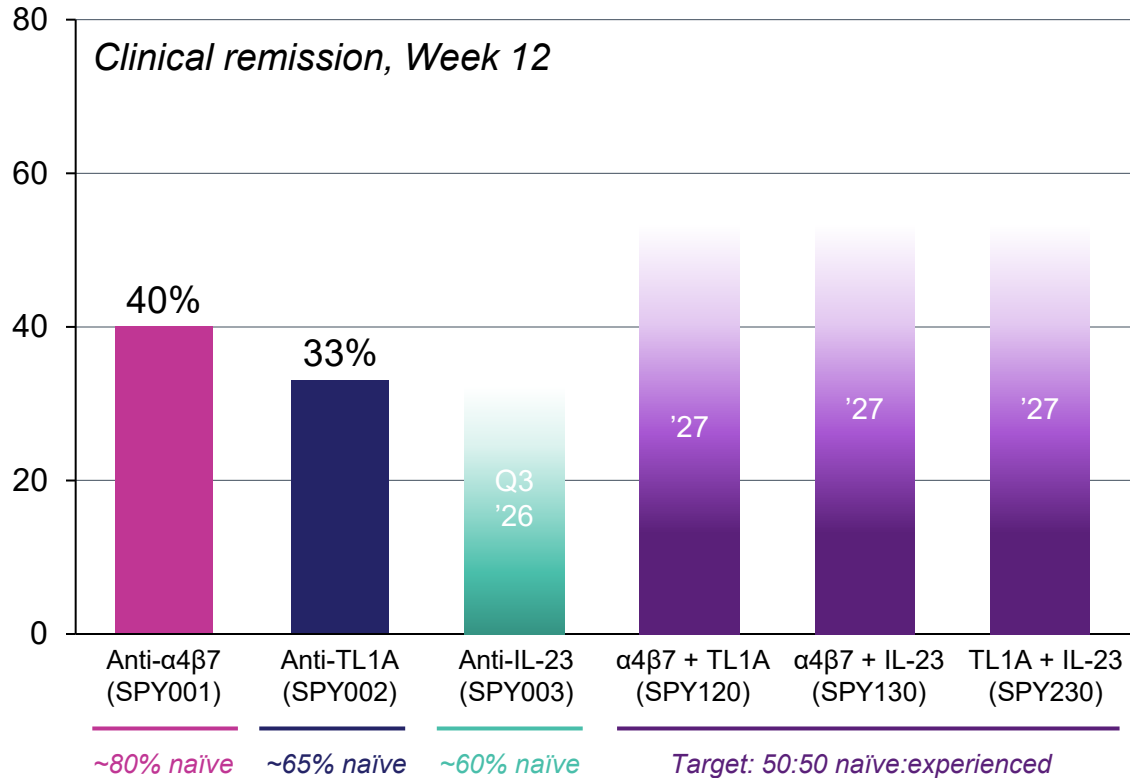
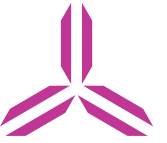
SPY001 and SPY002 endoscopic improvement rates are among the highest reported



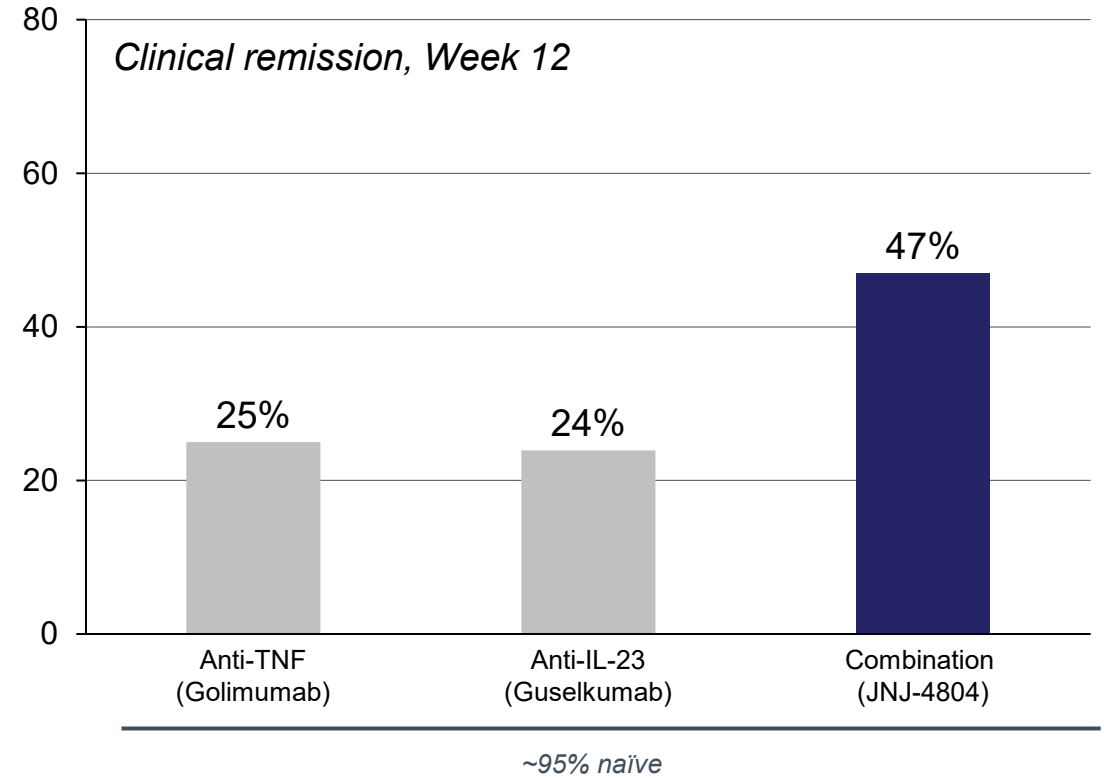
Endoscopic improvement Percentage of subjects



SPY001 and SPY002 results establish a strong foundation for best-in-disease combination potential

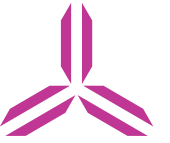


JNJ VEGA study



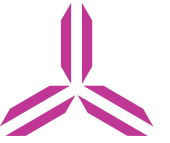
Spyre monotherapy components demonstrated favorable cross-trial efficacy despite enrolling a more refractory population

IBD treatment is moving to combination therapy and Spyre is positioned to lead with three differentiated combos

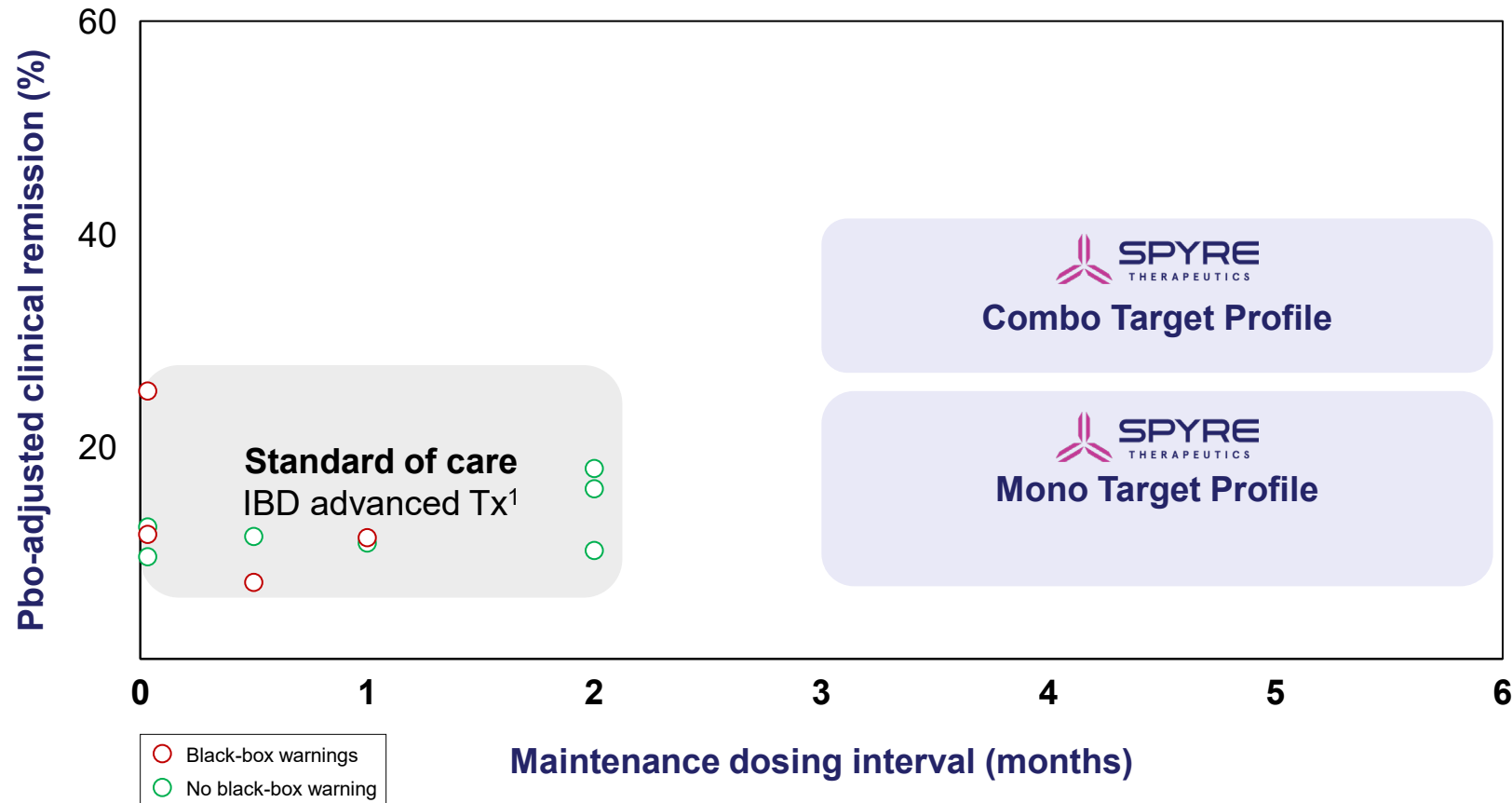


Sponsor	Program	MOAs	Target Profile	1-m	2	3	4	5	6	7	8	9	10	11	12
	SPY120	$\alpha 4\beta 7$ +TL1A	Q3M-Q6M AI												
	SPY130	$\alpha 4\beta 7$ +IL-23	Q3M-Q6M AI												
	SPY230	TL1A+IL-23	Q3M-Q6M AI												
	JNJ-4804	TNF+IL-23	Q4W AI												
	Skyrizi + ABBV382	$\alpha 4\beta 7$ +IL-23	Q4W OBI												
	Omvoh + MORF057	$\alpha 4\beta 7$ +IL-23	Q4W AI + daily oral												

Best-in-class monotherapies provide foundation for paradigm-changing combinations for IBD



Potential for best-in-indication positioning (UC example)



Target product profiles



Monos: Comparable-to-better efficacy vs. standard of care

Combos: Meaningfully improved efficacy vs. standard of care



Favorable safety profile

No black box warning



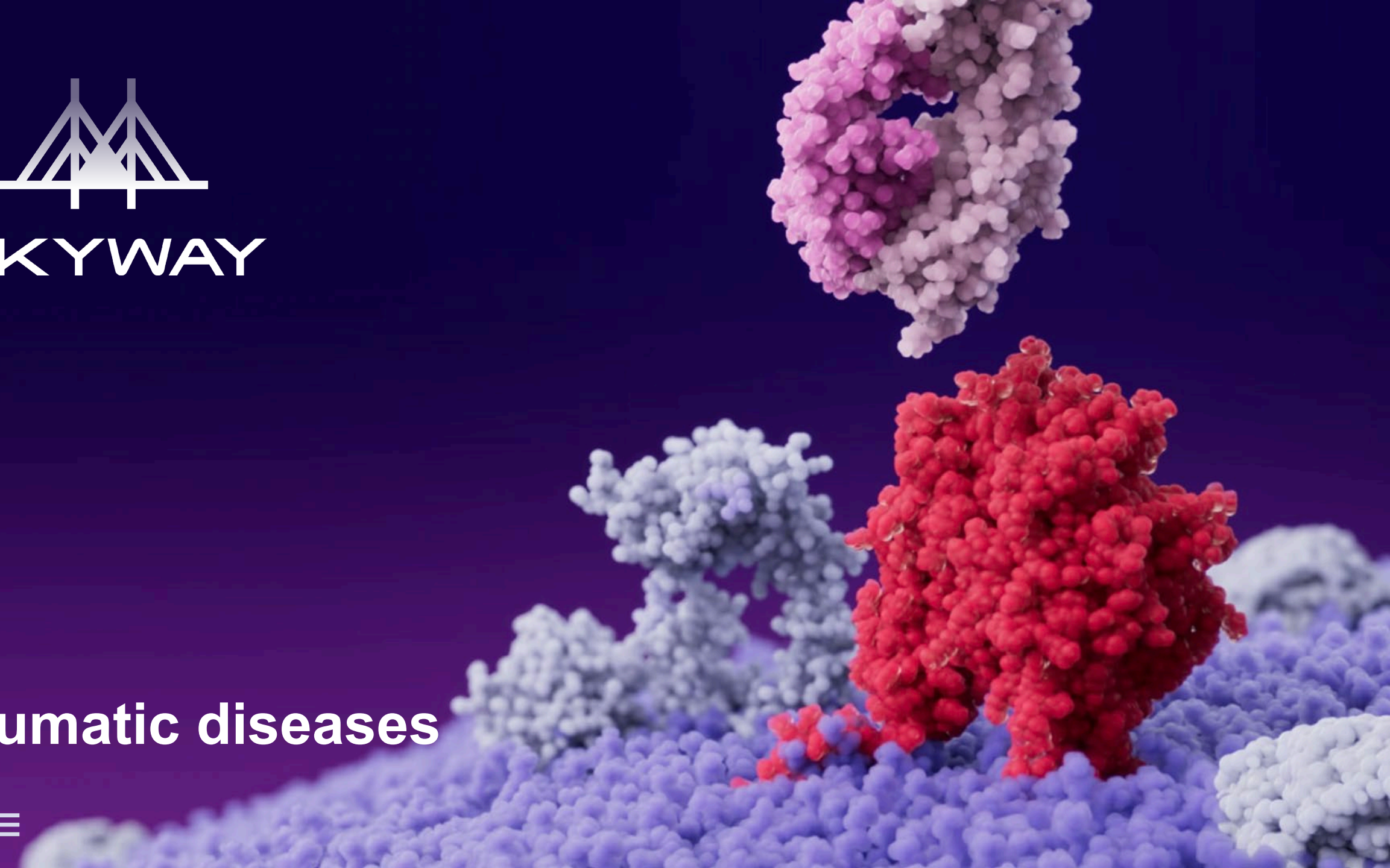
Q3M-Q6M maintenance dosing



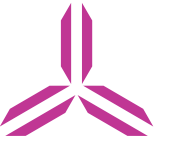
SKYWAY

Rheumatic diseases

SPYRE



Substantial unmet need remains for the millions of individuals living with RA, PsA, and axSpA



- >3M individuals in the U.S. diagnosed with RA (>1.5M¹), PsA (~1M²), and axSpA (~1M²)
- Substantial unmet need remains due to:
 - Minority remission rates, inability to control multiple aspects of disease, and lack of durability with existing therapies
 - Limited MOAs to cycle through following incomplete responses
 - Poor adherence to frequent and/or inconvenient dosing regimens

Placebo-adjusted efficacy rates by MOA (W24³)



TL1A has been implicated in several inflammatory and fibrotic diseases, with strong rationale in rheumatic diseases



TL1A exacerbates inflammation and fibrosis

Target rheumatic diseases share mechanistic pathways with IBD, where POC is established



Increasing overlap with clinically validated biology

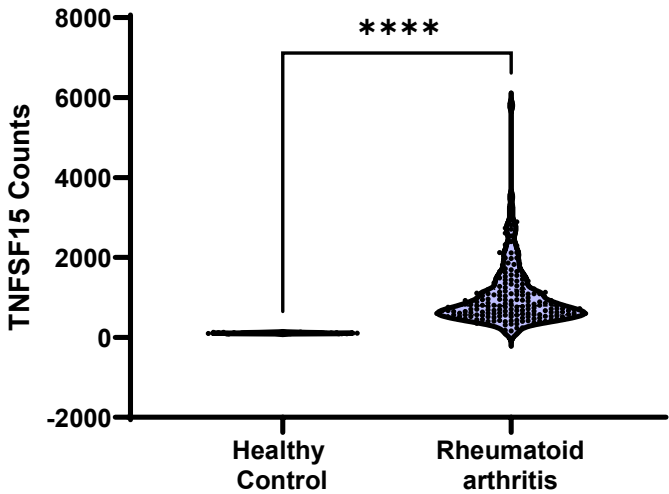
	Ulcerative colitis (UC)
	Crohn's disease (CD)
	Rheumatoid arthritis (RA)
	Psoriatic arthritis (PsA)
	Axial spondyloarthritis (axSpA)
	Psoriasis (PsO)
	Hidradenitis suppurativa (HS)
	Primary biliary cholangitis (PBC)
	Pulmonary sarcoidosis
	Interstitial lung disease (SSc-ILD)
	Metabolic steatohepatitis (MASH)
	Atopic dermatitis (AD)
	Asthma

POC studies ¹	T _H 1 T _H 17 T _H 9	Fibroblasts FLS osteoclasts	NK T _H 2 ILCs
✓	●		
✓	●	●	
	●	●	
	●		
	●		
	●		
	●	●	
	●	●	
		●	
		●	
			●
✗			●

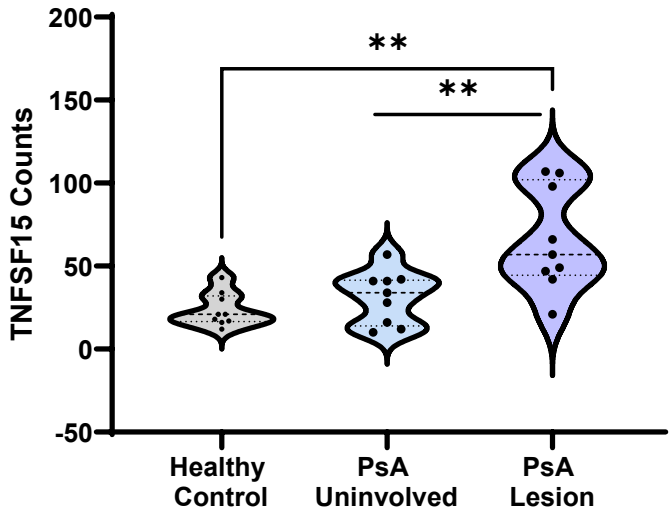
TL1A is upregulated in RA, PsA, and axSpA relative to healthy controls



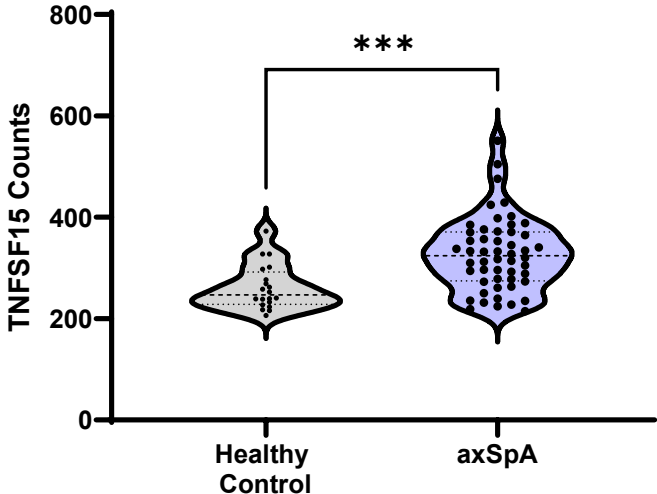
Rheumatoid arthritis



Psoriatic arthritis



Axial spondyloarthritis



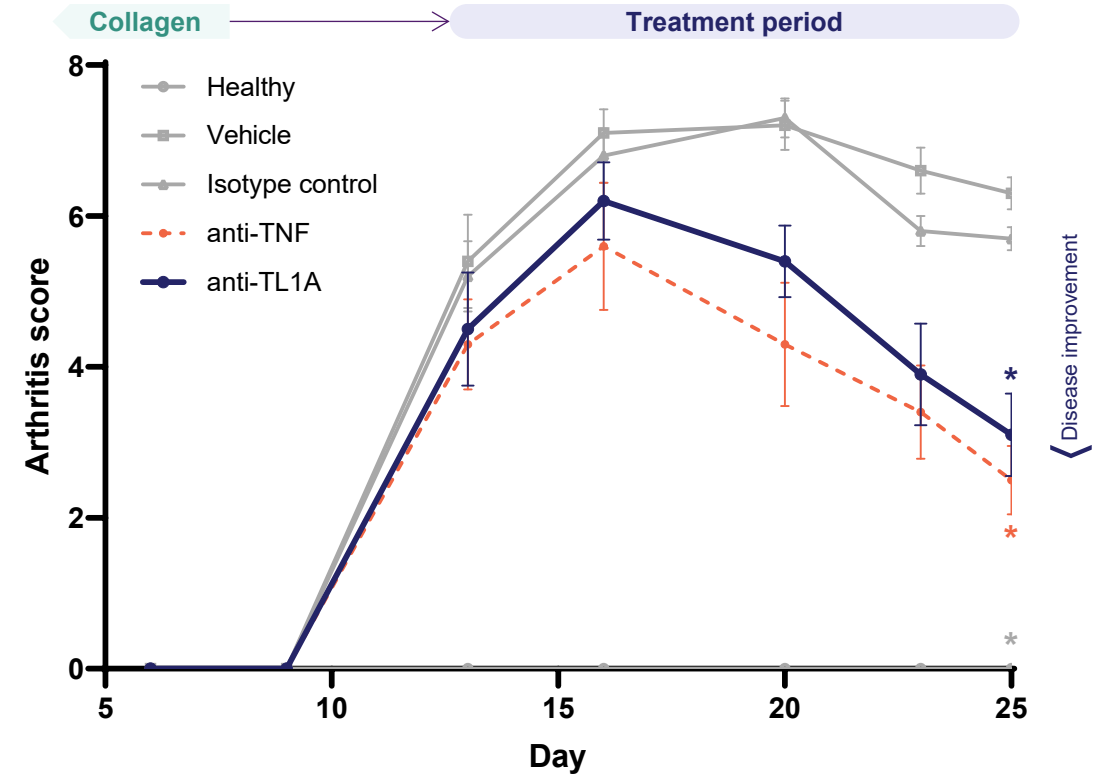
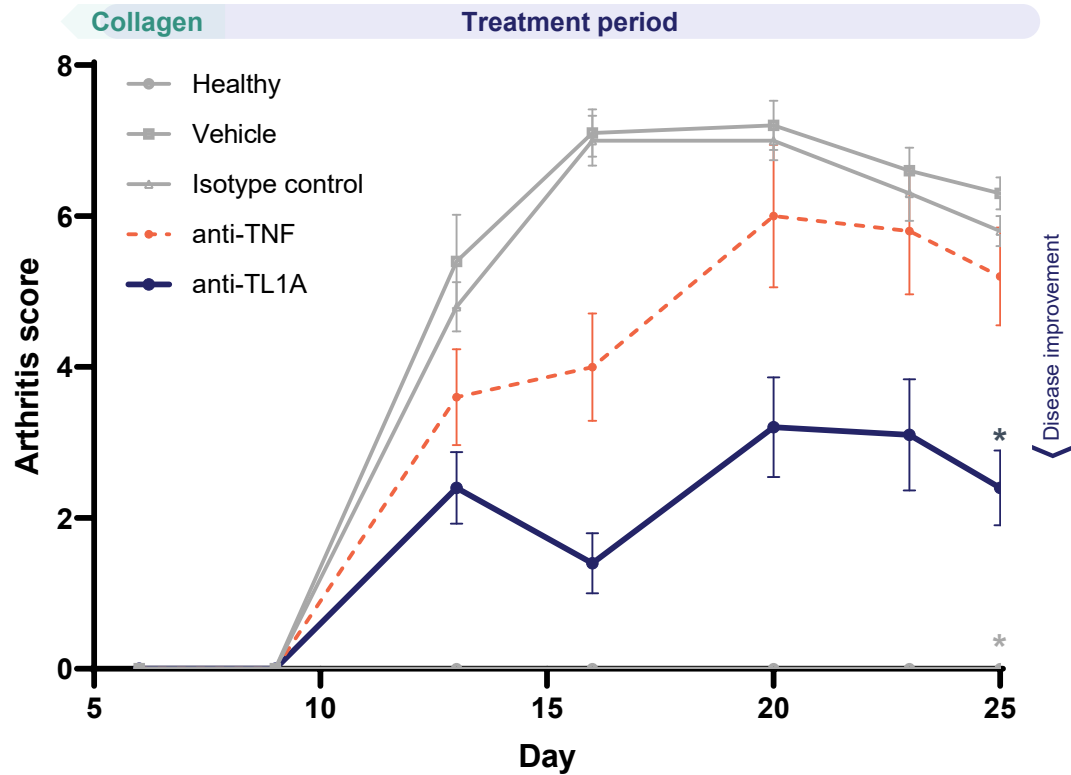
Source	Whole blood	Skin biopsy	Whole blood
Sequencing	Microarray	Bulk RNA seq	Microarray
Sample size	N=192 RA, 30 HC	N=9 per cohort	N=52 axSpA, 20 HC

Spyre anti-TL1A antibody meets or exceeds the efficacy of etanercept (anti-TNF) in rat models of arthritis



Superior efficacy in semi-preventative model

Comparable efficacy in therapeutic model

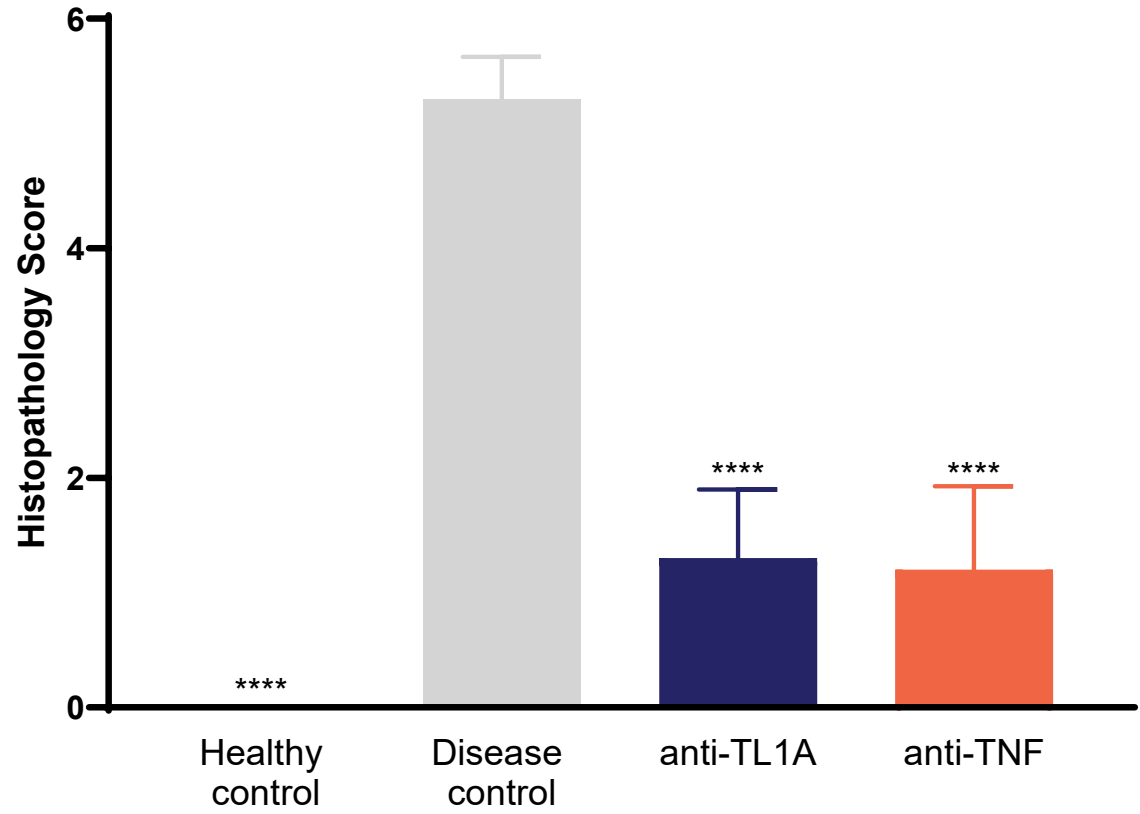
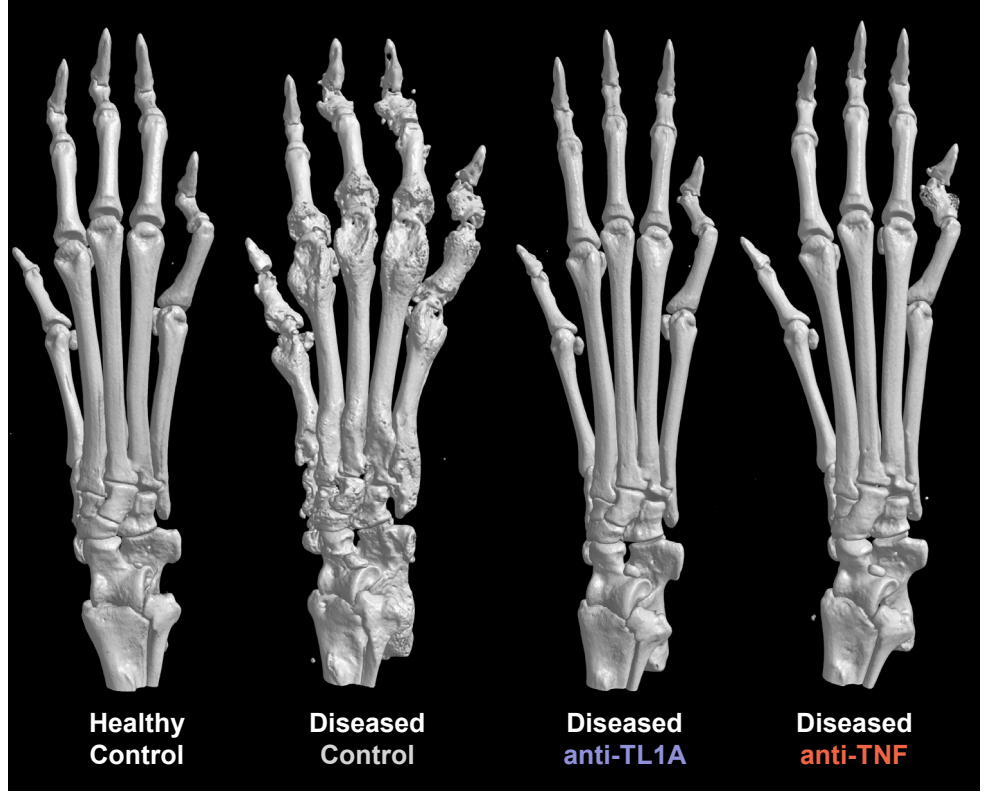


Robust anti-TL1A activity further replicated in mouse models of arthritis



Anti-TL1A prevents disease and bone erosion

Comparable efficacy to anti-TNF

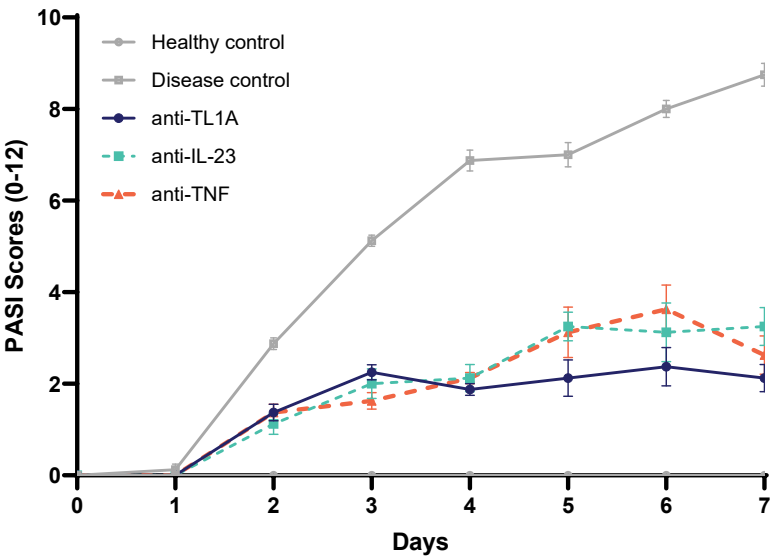


Additionally, anti-TL1A treatment led to comparable improvements in psoriatic skin lesions in mouse IMQ model

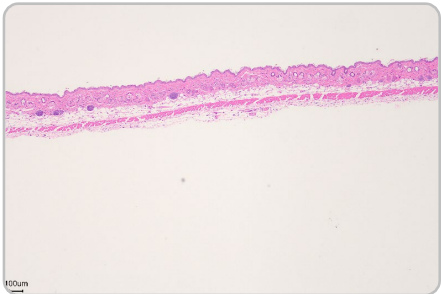


Anti-TL1A reduces skin lesions

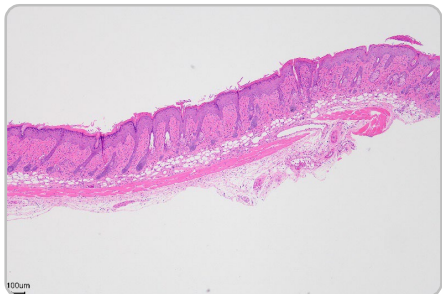
Comparable efficacy to anti-IL-23 and anti-TNF



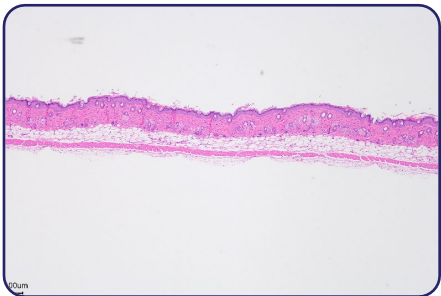
Potential for robust skin clearance in PsA



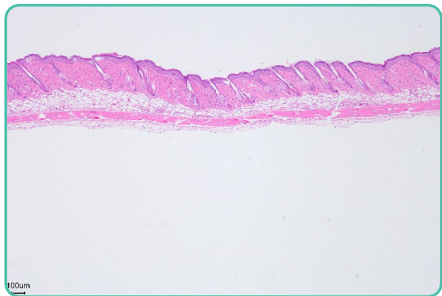
Healthy control



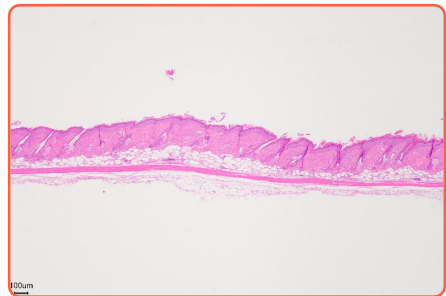
Disease control



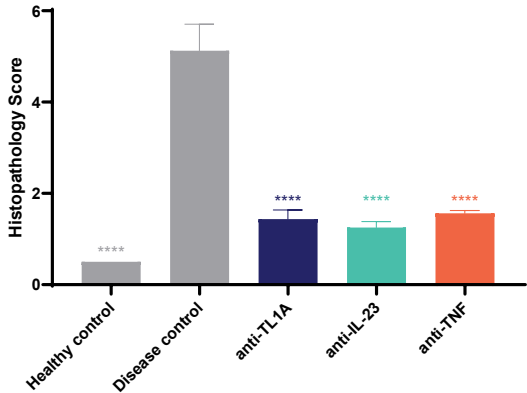
anti-TL1A



anti-IL-23



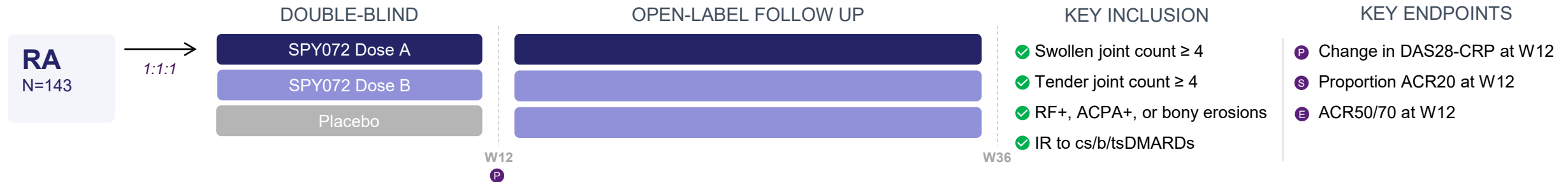
anti-TNF



SKYWAY Phase 2 *basket* study evaluating SPY072 (anti-TL1A) in RA, PsA, and axSpA – enrollment complete



Sub-study A: SPY072 in moderate-to-severely active rheumatoid arthritis (RA)



Sub-study B: SPY072 in moderate-to-severely active psoriatic arthritis (PsA)



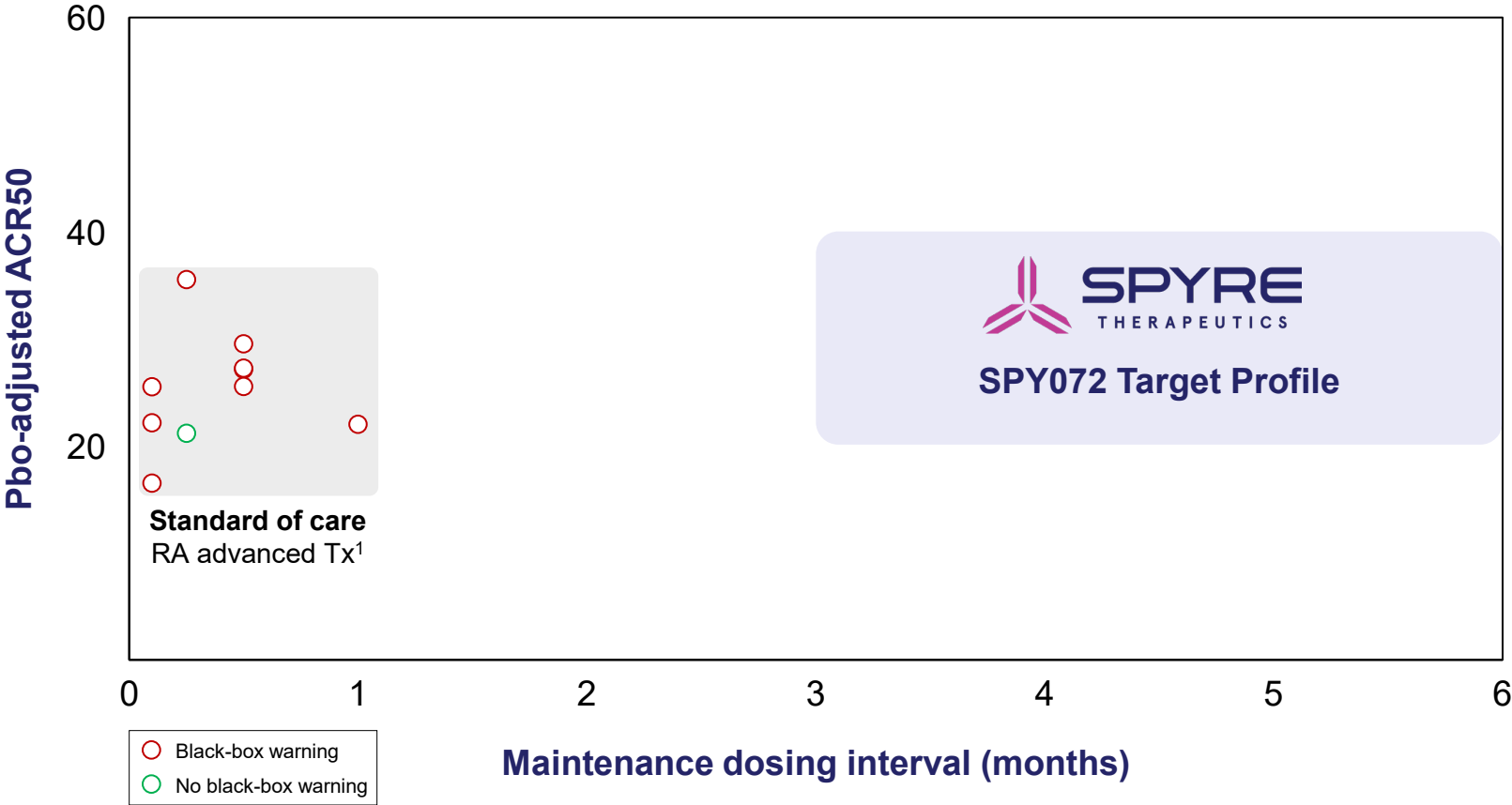
Sub-study C: SPY072 in moderate-to-severely active axial spondyloarthritis (axSpA)



SPY072 is a potential first-in-class & best-in-class therapy for rheumatic diseases



Potential for best-in-indication positioning (RA example)



SPY072 target product profile

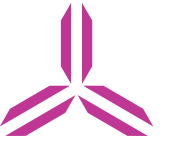
- First-in-class anti-TL1A
Comparable-to-better efficacy
- Favorable safety profile
No black box warning
- Q3M-Q6M maintenance dosing





Catalysts & capitalization

SPYRE

Capitalized to deliver one of the industry's most compelling catalyst maps



Trial	2026	2027
 <p>Part A (Open-label)</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> SPY001 α4β7 Ph2 UC induction POC <input checked="" type="checkbox"/> SPY002 TL1A Ph2 UC induction POC <input type="checkbox"/> SPY003 IL-23 Ph2 UC induction POC (3Q 2026) 	<ul style="list-style-type: none"> <input type="checkbox"/> SPY001 α4β7 Ph2 UC maintenance data <input type="checkbox"/> SPY002 TL1A Ph2 UC maintenance data <input type="checkbox"/> SPY003 IL-23 Ph2 UC maintenance data
 <p>Part B (Pbo-controlled)</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Initiate enrollment of Part B cohorts 	<ul style="list-style-type: none"> <input type="checkbox"/> SPY120 α4β7 + TL1A Ph2 UC induction POC <input type="checkbox"/> SPY130 α4β7 + IL-23 Ph2 UC induction POC <input type="checkbox"/> SPY230 TL1A + IL-23 Ph2 UC induction POC <input type="checkbox"/> SPY001 α4β7 Ph2 UC induction POC <input type="checkbox"/> SPY002 TL1A Ph2 UC induction POC <input type="checkbox"/> SPY003 IL-23 Ph2 UC induction POC
	<ul style="list-style-type: none"> <input type="checkbox"/> SPY072 TL1A Ph2 W12 POC in RA (3Q 2026) <input type="checkbox"/> SPY072 TL1A Ph2 W16 POC in PsA (4Q 2026) <input type="checkbox"/> SPY072 TL1A Ph2 W16 POC in axSpA (4Q 2026) 	<ul style="list-style-type: none"> <input type="checkbox"/> SPY072 TL1A Ph2 maintenance data in RA <input type="checkbox"/> SPY072 TL1A Ph2 maintenance data in PsA <input type="checkbox"/> SPY072 TL1A Ph2 maintenance data axSpA

\$1.2 billion proforma cash as of March 31, 2026¹, with expected runway into 2H 2029

Cash and shares outstanding



\$1.2B proforma cash as of March 31, 2026¹

Expected runway into 2H 2029

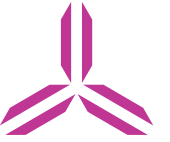
Number of shares (M)

Common stock	Shares outstanding	86.3
Common stock equivalents	• Series A preferred stock	13.8
	• Series B preferred stock	0.7
Common stock and common stock equivalents ²	Total outstanding	100.8

¹Reflects proforma unaudited cash, cash equivalents, & marketable securities as of 3/31/26 of \$741.5 million plus \$435.3 million in estimated net proceeds from the Company's April 2026 underwritten public offering of common stock; ²Shares outstanding on a pro forma and as-converted basis as of 3/31/26, inclusive of the April 2026 financing, which (i) gives effect to the full conversion of the Company's preferred stock, and (ii) disregards beneficial ownership limitations that may limit the ability of certain holders of preferred stock to convert into common stock

ELEVATE THE STANDARD IN IMMUNOLOGY





2026 Milestone Aims

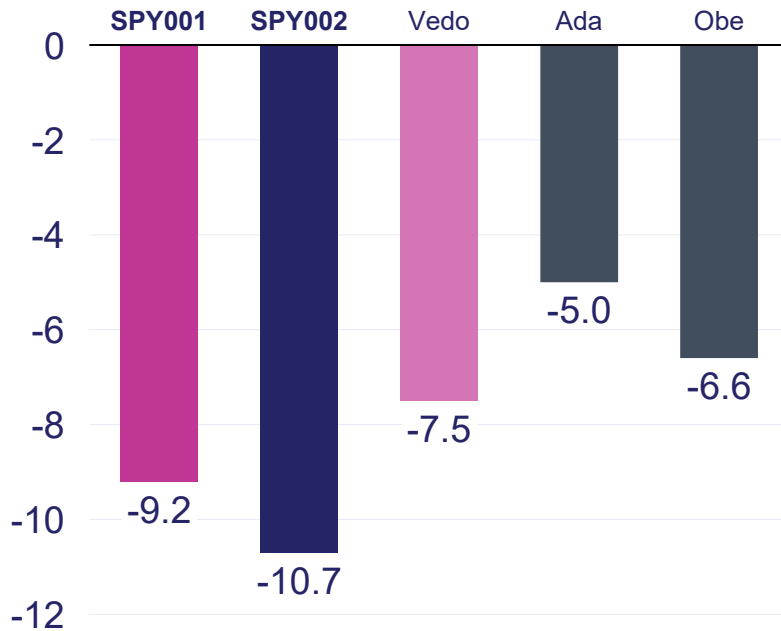
SKYLINE Part A: SPY002

2026 Part A readout: Aiming for comparable safety and efficacy as in-class comparators



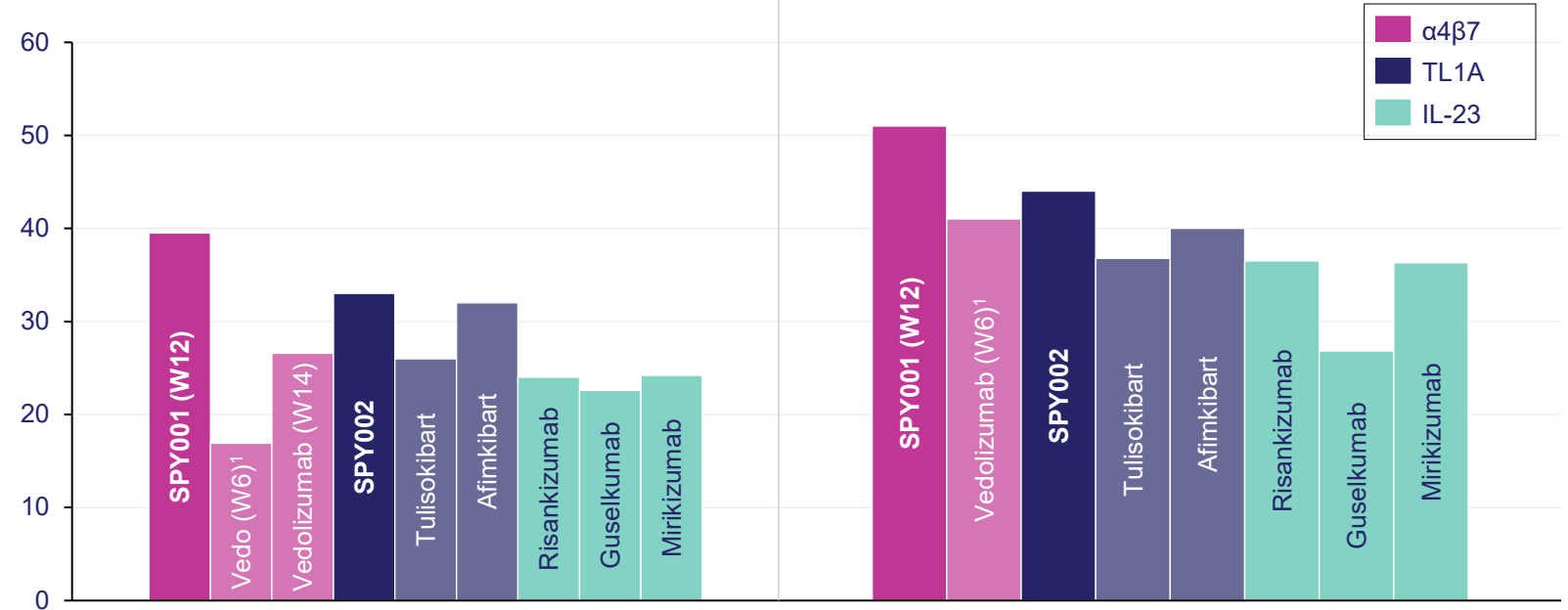
Primary endpoint

ΔRHI from baseline (W8-14)

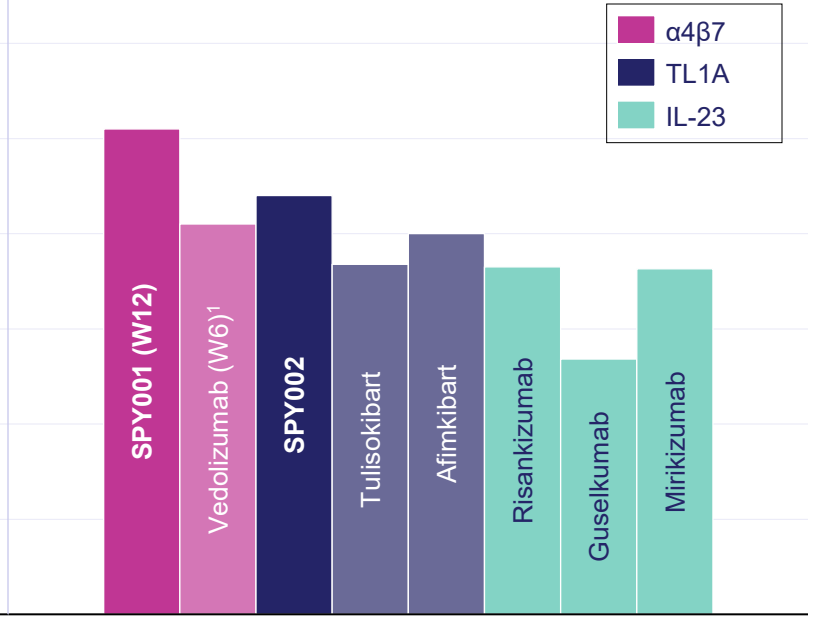


Secondary endpoints

Absolute % clinical remission (W6-14)



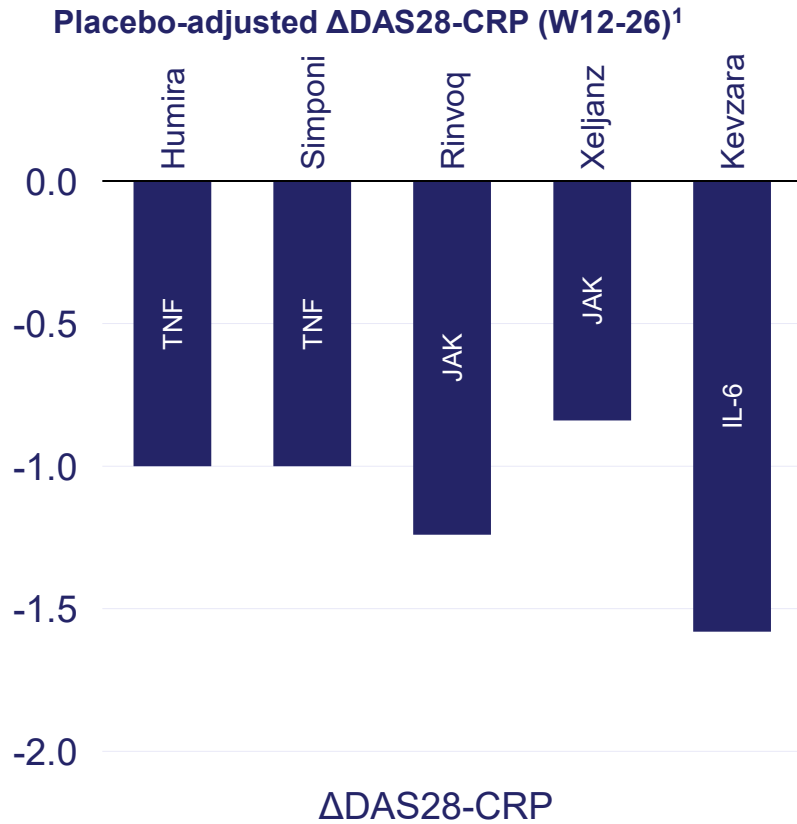
Absolute % endoscopic improvement (W6-14)



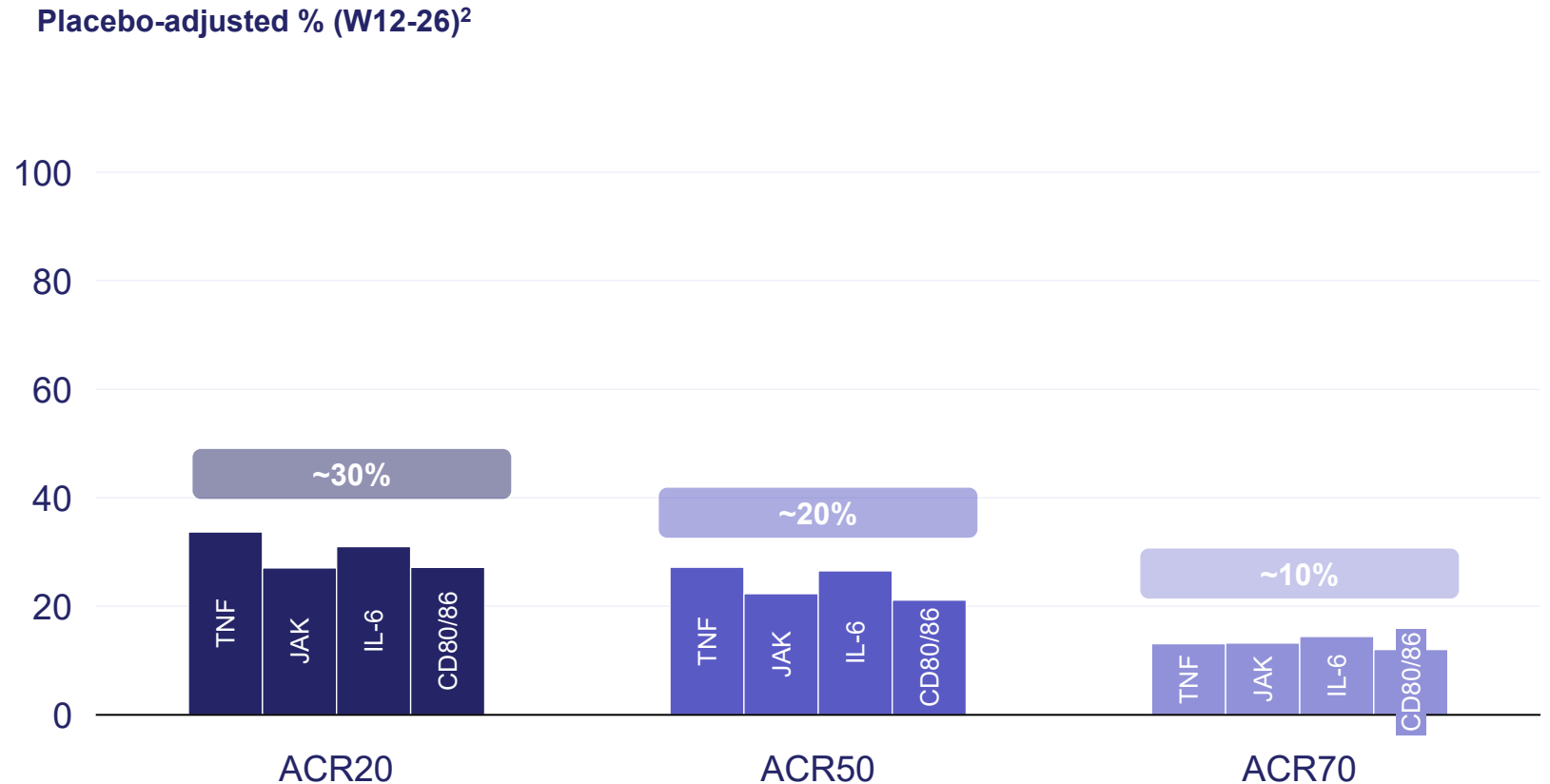
2026 RA readout: Aiming for Δ DAS28-CRP and ACRs comparable-to-better than SOC analogs



Primary endpoint



Secondary & exploratory endpoints



2026 PsA readout: Aiming for ACRs and PASI comparable-to-better than SOC analogs



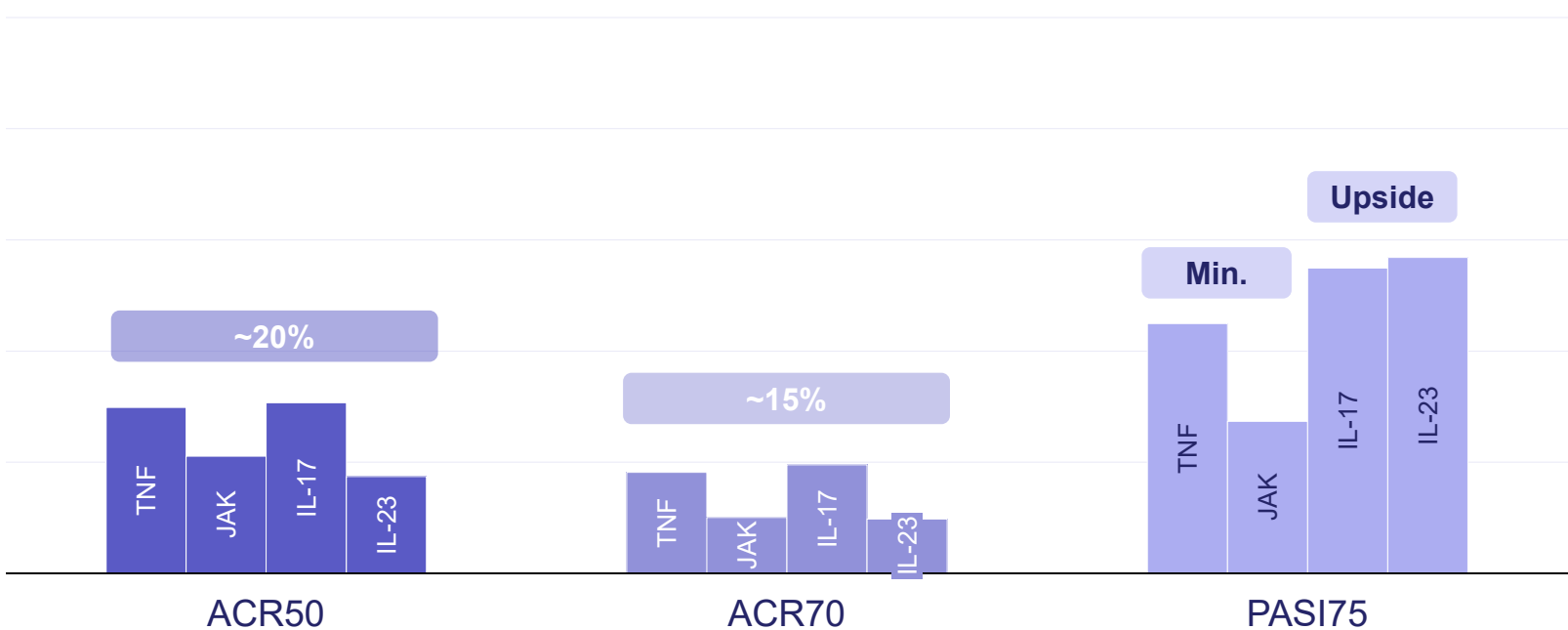
Primary endpoint

Secondary & exploratory endpoints

Placebo-adjusted % (W12-24)



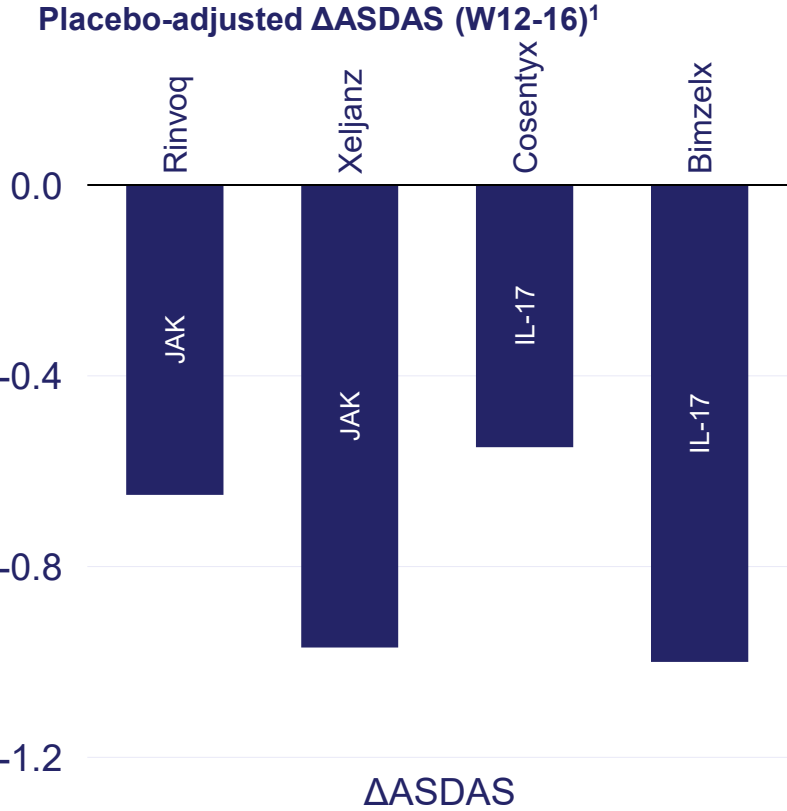
Placebo-adjusted % (W12-24)



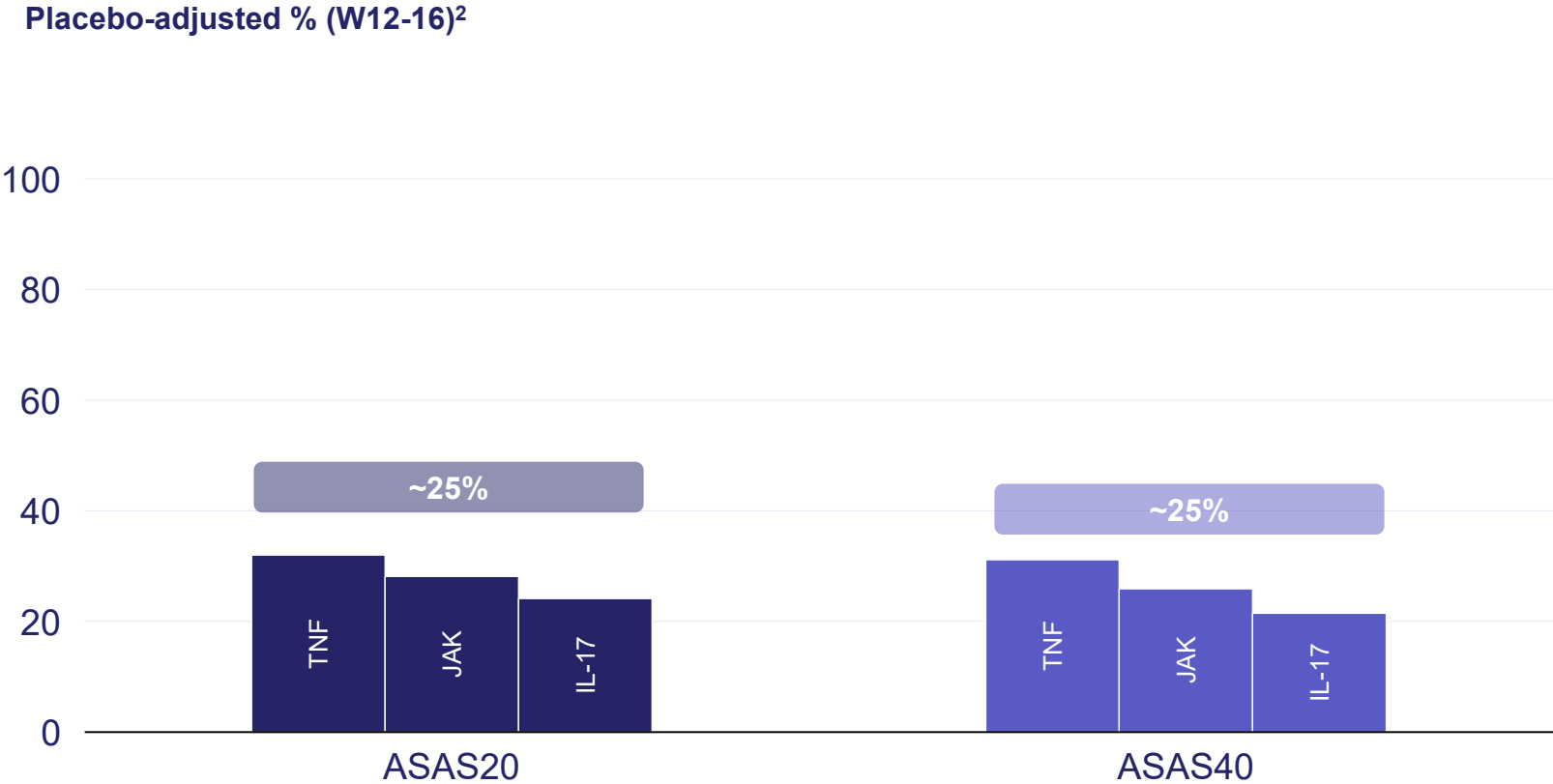
2026 axSpA readout: Aiming for Δ ASDAS and ASAS comparable-to-better than SOC analogs



Primary endpoint



Secondary & exploratory endpoints





2026 Milestone Aims

SKYLINE Part A: SPY002

Most recent topline release: SPY002 Part A induction results



Part A: Open label monotherapy evaluation

Key topline endpoints

INDUCTION

Patient characteristics

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

→
Sequential
enrollment

SPY001 ($\alpha 4\beta 7$)

Topline release

SPY002 (TL1A)

SPY003 (IL-23)

W12

PRIMARY

Δ RHI from baseline

SECONDARY

% Clinical remission

% Endoscopic improvement

Incidence of treatment-emergent
adverse events

Baseline characteristics were consistent with expectations

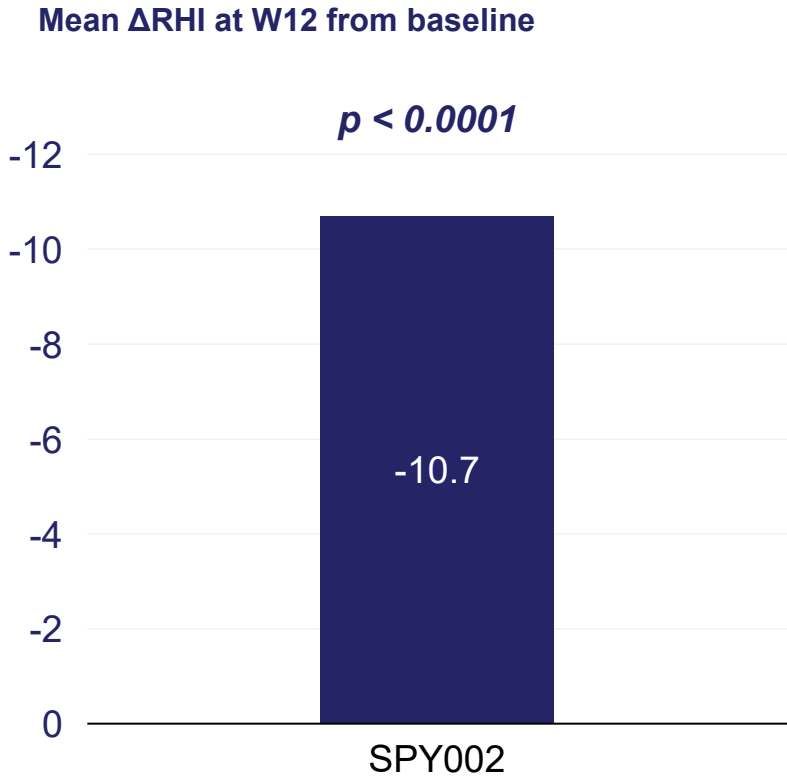


	SPY002 (TL1A), N = 48
Age (years, mean)	45
Sex (% female)	42
Weight (kg, mean)	74
Geographic region	
Europe	71%
North America	23%
APAC	6%
Duration of UC (years, mean)	7.0
RHI (mean ± SD)	16.9 ± 8.5
Baseline mMS (mean ± SD)	6.9 ± 1.0
Mayo Endoscopy Score (MES) (n, %)	
2	21 (44%)
3	27 (56%)
Concomitant immunomodulator use (n, %)	0
Concomitant corticosteroid use (n, %)	19 (40%)
Number of prior advanced therapies (n, %)	
Naïve	31 (65%)
1	12 (25%)
≥2	5 (10%)

SPY002 met its primary endpoint and key secondary endpoints were clinically meaningful

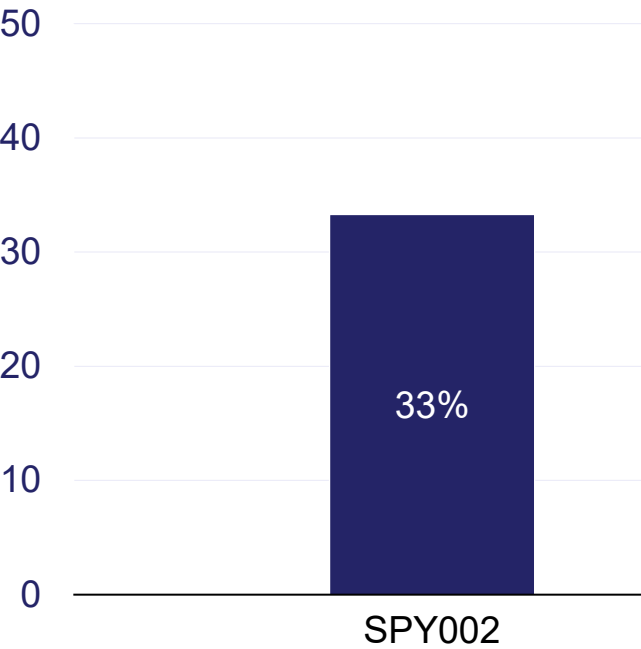


Primary endpoint

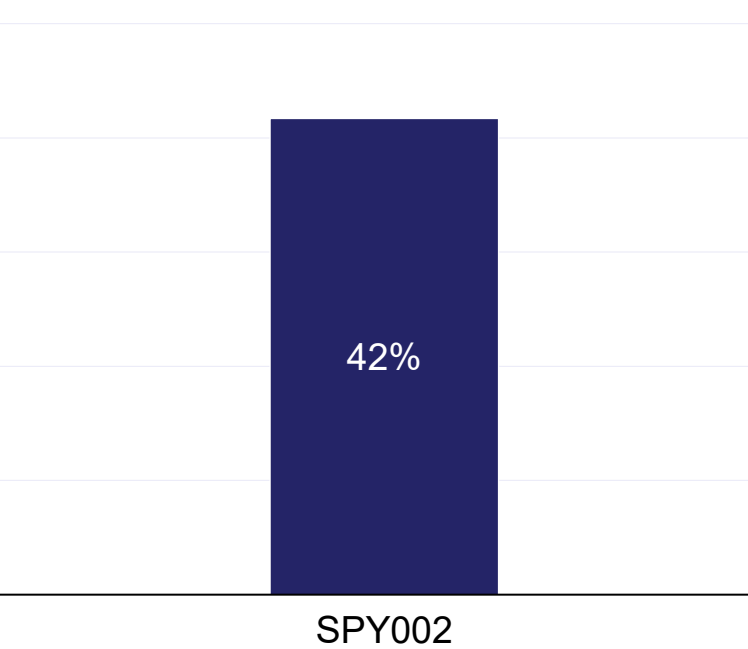


Key secondary endpoints

Proportion with clinical remission at W12



Proportion with endoscopic improvement at W12



Pre-specified sensitivity analysis:
-13.9 for participants with a baseline RHI ≥ 10

SPY002 was well tolerated with a safety profile consistent with the class



	SPY002 (TL1A), N = 48
Subjects with any Adverse Event (n, %)	20 (41.7%)
Severe (Grade ≥ 3) AE	2 (4.2%) ^{1,2}
Drug-Related AE	3 (6.3%) ³
AE Leading to Drug Discontinuation	2 (4.2%) ^{2,4}
Serious Adverse Event (SAE)	2 (4.2%) ^{1,2}
Drug-Related SAE	0
AEs of Special Interest	0
Death	0

Most common TEAEs (≥2 patients) were arthralgia (n=2), hypertension (n=3), nausea (n=2), ulcerative colitis (n=2), and viral respiratory tract infection (n=2)

¹Hospitalization for exacerbation of UC in one subject, not drug-related

²Hospitalization for worsening heart failure in one subject with history of heart failure & atrial fibrillation who was later diagnosed with worsening aortic stenosis, not drug related

³One case each of nausea, hypertension, arthralgia

⁴Exacerbation of UC, not drug-related.

Data pertain to SPY002 Induction Treatment Period.