SPYRE THERAPEUTICS

CORPORATE OVERVIEW

JUNE 23, 2026

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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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Forward-looking statements are based on a number of factors and assumptions made by management and considered reasonable at the time such information is provided, and forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause the actual results, performance or achievements to be materially different from those expressed or implied by the forward-looking statements, including uncertainties and risks arising from regulatory feedback, including potential disagreement by regulatory authorities with our interpretation of data; our ongoing or planned clinical trials for our product candidates, including our plans for and timing of cohort initiation for combination therapy arms for the ongoing SKYLINE Phase 2 platform trial across different jurisdictions; the unpredictable relationship between preclinical study results and clinical study results; the potential for interim data not being delivered within expected time frames or final clinical data not being consistent with or different than the previously disclosed data for our programs; the expected or potential impact of macroeconomic conditions, including inflationary pressures, rising interest rates, general economic slowdown or a recession, changes in tariff/trade and monetary policy, volatile market conditions, financial institution instability, as well as geopolitical instability, including the ongoing military conflicts between Ukraine and Russia, United States and Iran, conflicts in the Middle East, and geopolitical tensions between the United States and other countries, including China and Venezuela, on our operations; the implementation of changes in law, tariffs, sanctions, export or import controls, and other government measures that could impact our business operations, including restricting international trade by the United States, China or other countries and the BIOSECURE Act; the impacts of adverse events or disappointing results in clinical trials of third parties, including our competitors developing product candidates that target similar mechanisms of action and/or indications as our product candidates; and those uncertainties and factors described under the heading "Risk Factors," "Risk Factor Summary" and "Note about Forward-Looking Statements" in the Company's most recent Annual Report on Form 10-K, as supplemented and updated by subsequent Quarterly Reports on Form 10-Q and Current Reports on Form 8-K that the Company has filed or will file with the SEC, as well as discussions of potential risks, uncertainties, and other filings by the Company from time to time, as well as risk factors associated with companies that operate in the biopharma industry, including those associated with the uncertainties of drug development. 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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
SKYLINE	SPY001 α4β7 Ph2 POC in UC	Q2 ✓
	SPY002 TL1A Ph2 POC in UC	Q2 ✓
	SPY003 IL-23 Ph2 POC in UC	Q3
SKYWAY	SPY072 TL1A Ph2 POC in RA	Q3
	SPY072 TL1A Ph2 POC in PsA	Q4
	SPY072 TL1A Ph2 POC in axSpA	Q4

POC=proof of concept; UC=ulcerative colitis; RA=rheumatoid arthritis; PsA=psoriatic arthritis; axSpA=axial spondyloarthritis

Advancing a robust I&I pipeline with exceptional financial strength

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

$1.2 billion pro forma cash as of March 31, 2026[1], with expected runway into 2H 2029

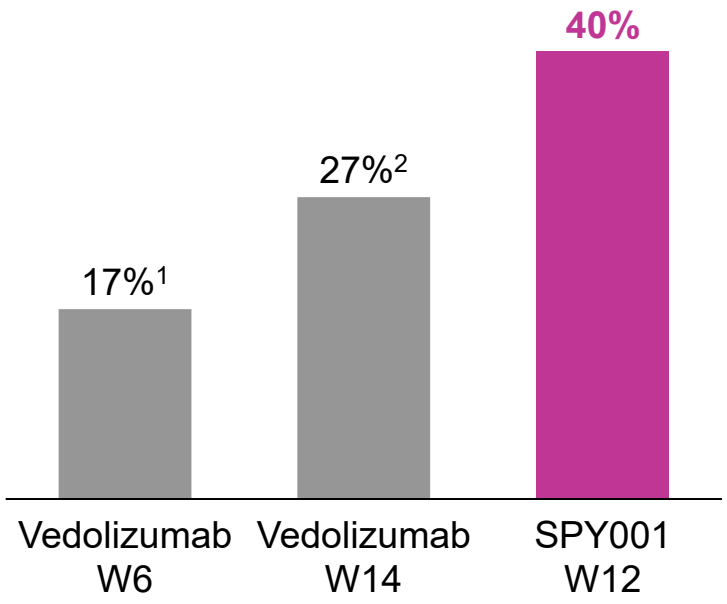
SPYRE

Milestones expected as of the date of this presentation. [1]Reflects preliminary and 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. Pipeline chart does not include preclinical research and development programs.

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

SPY001 (α4β7) efficacy

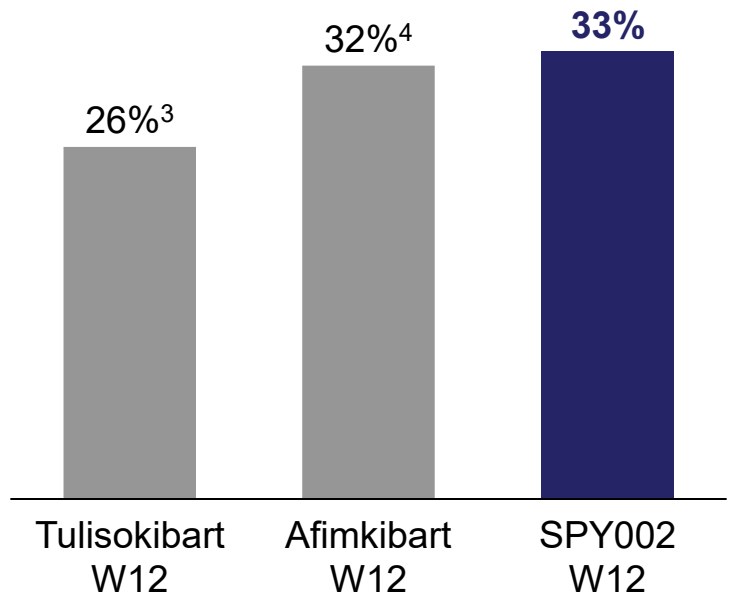
Clinical remission rate



SKYLINE Part A POC achieved
2Q 2026

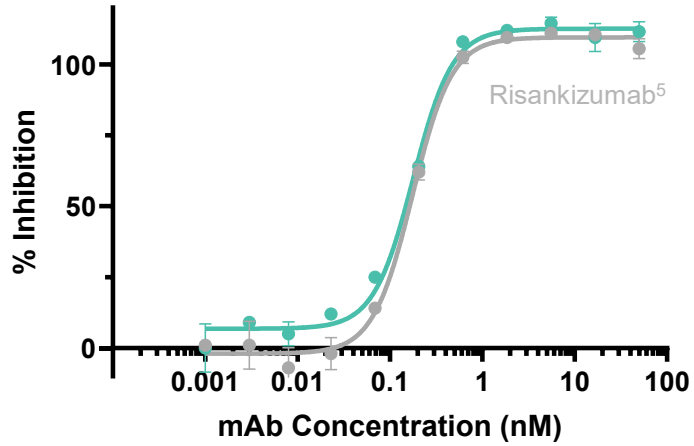
SPY002 (TL1A) efficacy

Clinical remission rate



SKYLINE Part A POC achieved
2Q 2026

SPY003 (IL-23) potency



SKYLINE Part A POC data
3Q 2026

Data on file. [1]GEMINI; [2]VARSITY [3]ARTEMIS-UC; [4]TUSCANY-2; [5]Risankizumab is a synthesized comparator antibody.
Trial designs differ and no head-to-head clinical trials have been conducted. Efficacy data pertain to Induction Treatment Period.

Engineered to be long-acting via YTE modification

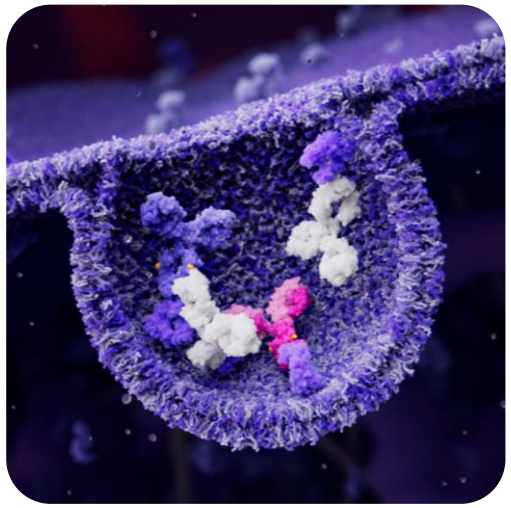
YTE modification

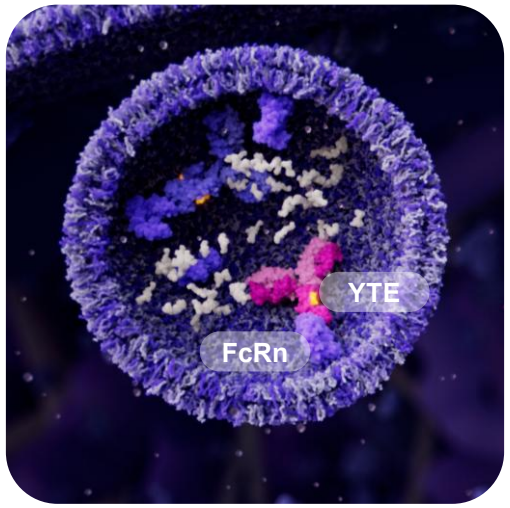
YTE-modified mAbs are returned to circulation for continued activity

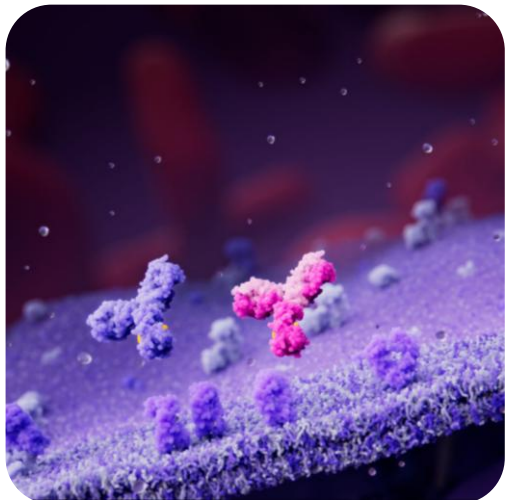
Antibodies are subject to degradation when internalized

YTE modification increases internal binding to FcRn, avoiding degradation

FcRn binding promotes recycling of mAbs to circulation



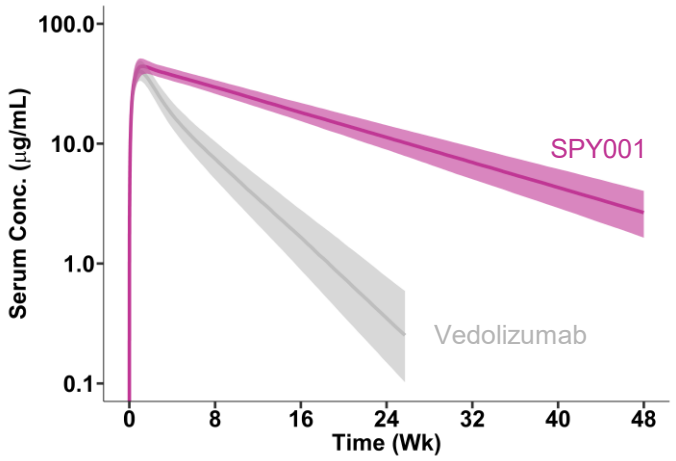




mAb=monoclonal antibody; FcRn=neonatal Fc receptor

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

SPY001 human PK simulation

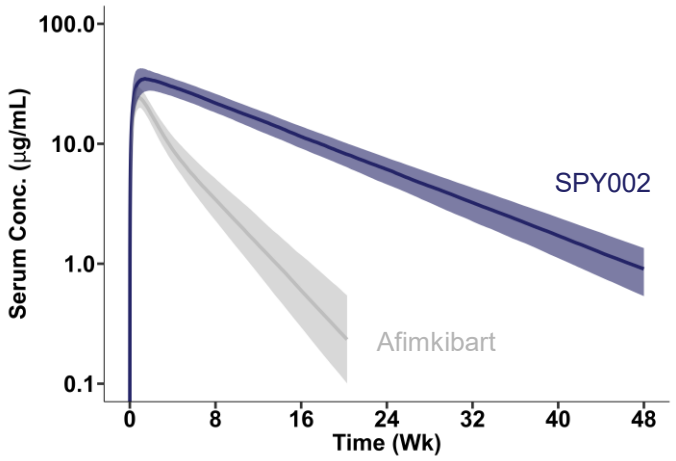


Target Profiles

Q3M-Q6M

Maintenance dosing

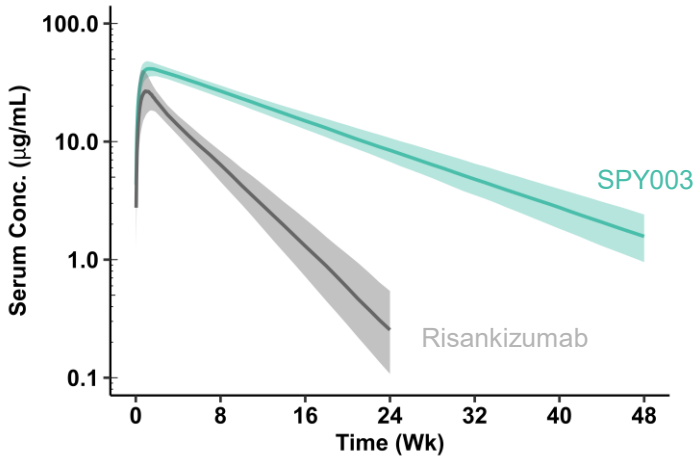
SPY002 human PK simulation



Q3M-Q6M

Maintenance dosing

SPY003 human PK simulation



Q3M-Q6M

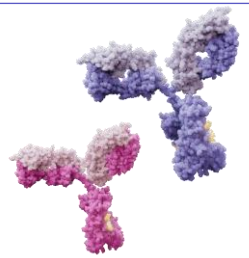
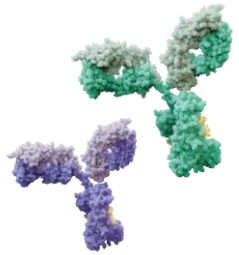
Maintenance dosing

SPY001 PK simulation based on PK data as of 03/19/2025 cutoff; SPY002 PK simulation based on PK data from 5/31/2025 cutoff; SPY003 PK simulation based on PK data from 9/15/2025 cutoff. Vedolizumab, Afimkibart, and Risankizumab simulations based on published data (Rosario, M, et. al. (2015); Danese, Silvio, et al. (2024) Thakre, Neha et. al. (2024)*; no head-to-head clinical trials have been conducted. Concept image of drug delivery device shown for illustrative purposes only.*

Potential paradigm-changing combination therapies in IBD

Inflammatory bowel disease

Rational combinations targeting diverse disease drivers

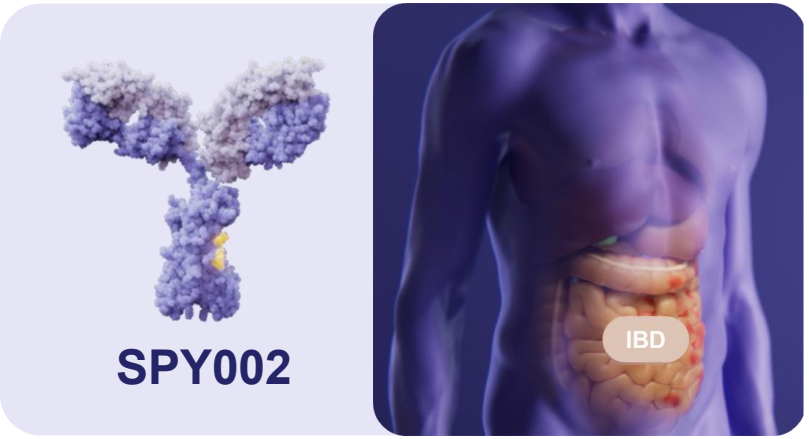
SPY120		TL1A + α4β7	❯	
SPY130		IL-23 + α4β7	❯	
SPY230		IL-23 + TL1A	❯	

Target Q3M-Q6M dosing

Potential Q3M-Q6M maintenance dosing interval based on PK modeling. Concept image of drug delivery device shown for illustrative purposes only.

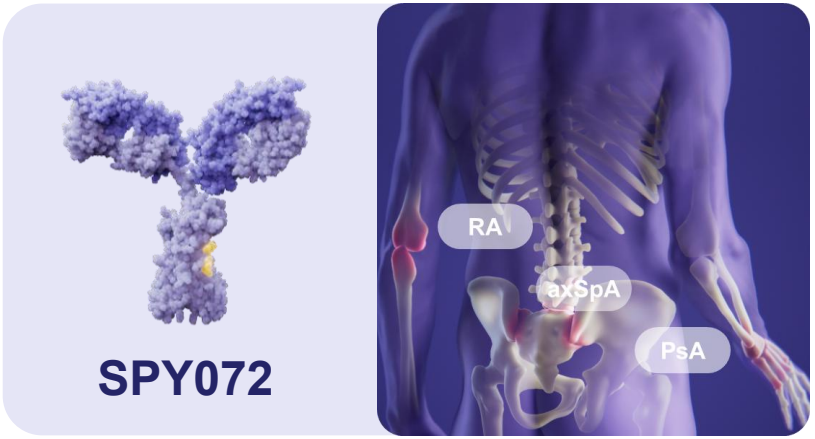
Spyre is developing two distinct, potentially best-in-class anti-TL1A antibodies for IBD and rheumatic disease

Inflammatory bowel disease



Potential best-in-class combination component

Rheumatic disease



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

- Distinct, novel epitopes
- High potency
- Target Q3M-Q6M dosing
- High-conc. SC formulation

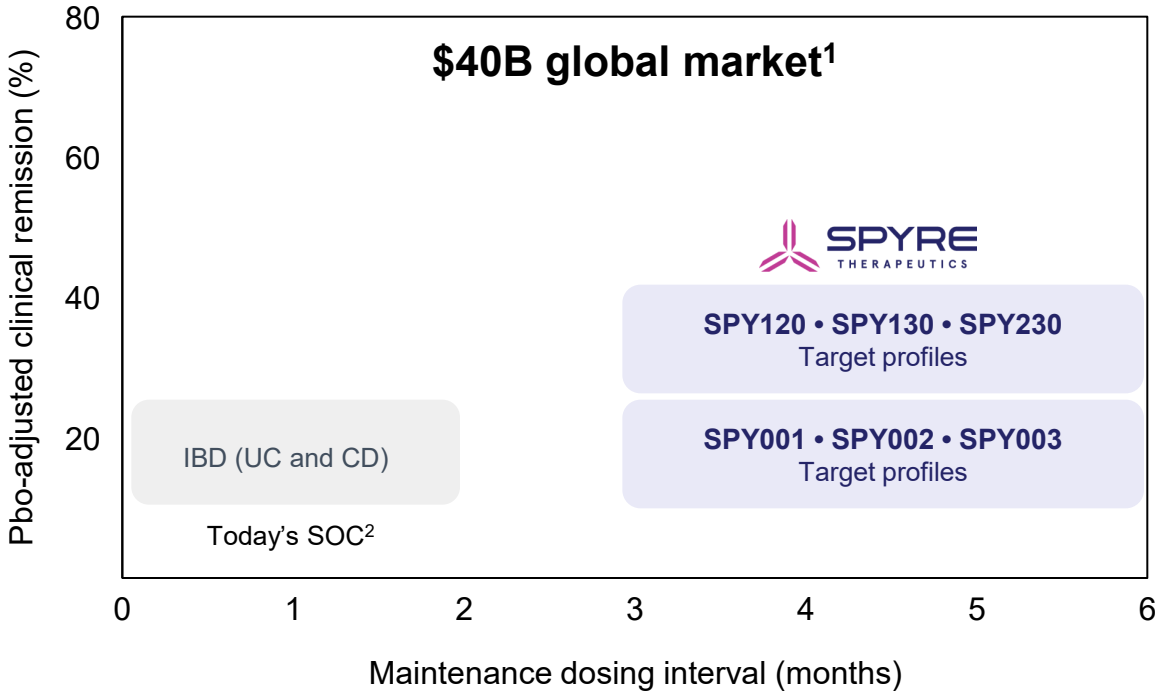
Advancing two distinct anti-TL1As provides strategic and commercial flexibility

Potential Q3M-Q6M maintenance dosing interval based on PK modeling.

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

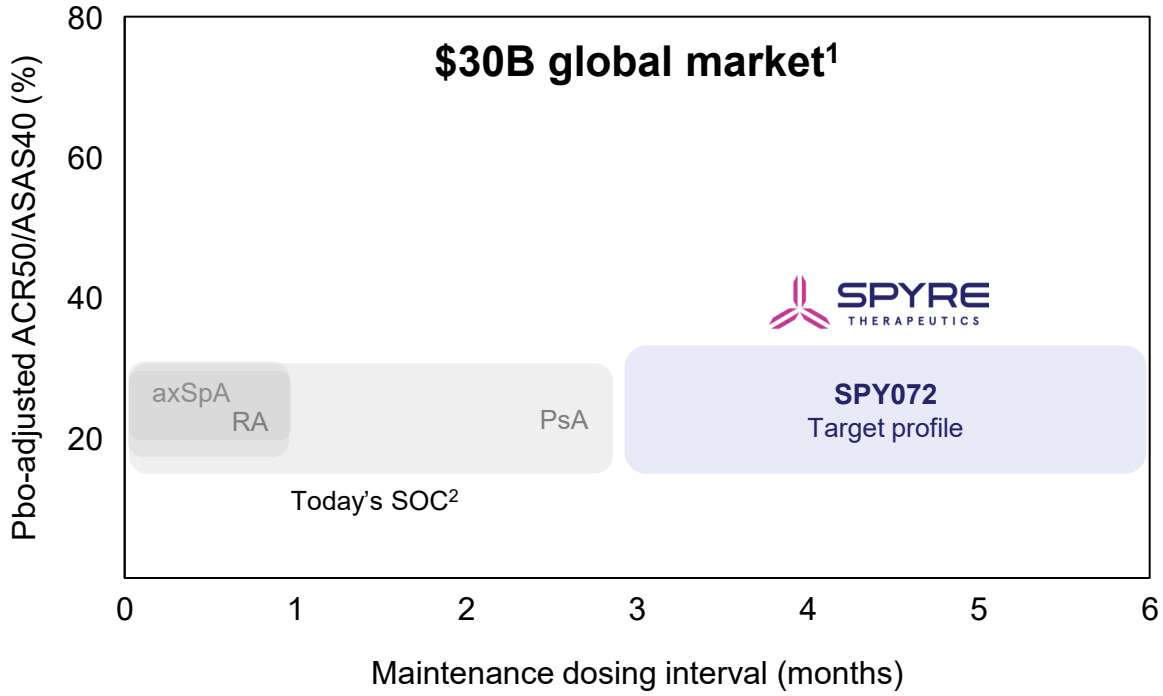
Inflammatory bowel disease

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



Rheumatic disease

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



Positioning of Spyre programs is illustrative and based on Phase 1 results and illustrates what we believe we can potentially achieve. Placebo-adjusted clinical remission data are derived from different clinical trials conducted at different times, with differences in trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted. [1]Evaluate Pharma 2030 Global Sales Forecast; Barclays Immunology Deep Dive (2023); [2]Oral and SC administered advanced therapies.

Ph2 trials ongoing in IBD and rheumatic diseases

SKYLINE

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

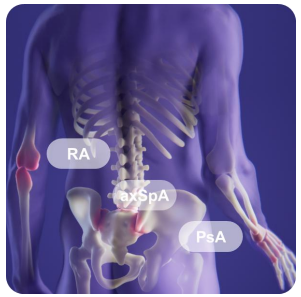
6 INTERVENTIONS

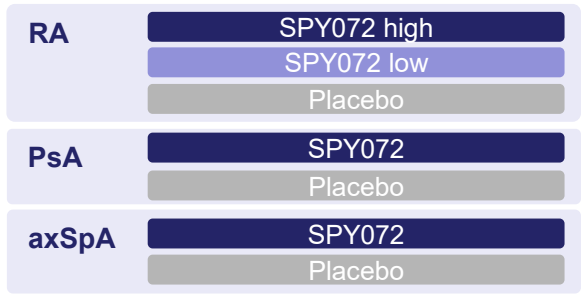
1 INDICATION

'26-'27 EXPECTED READOUTS*

SKYWAY

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



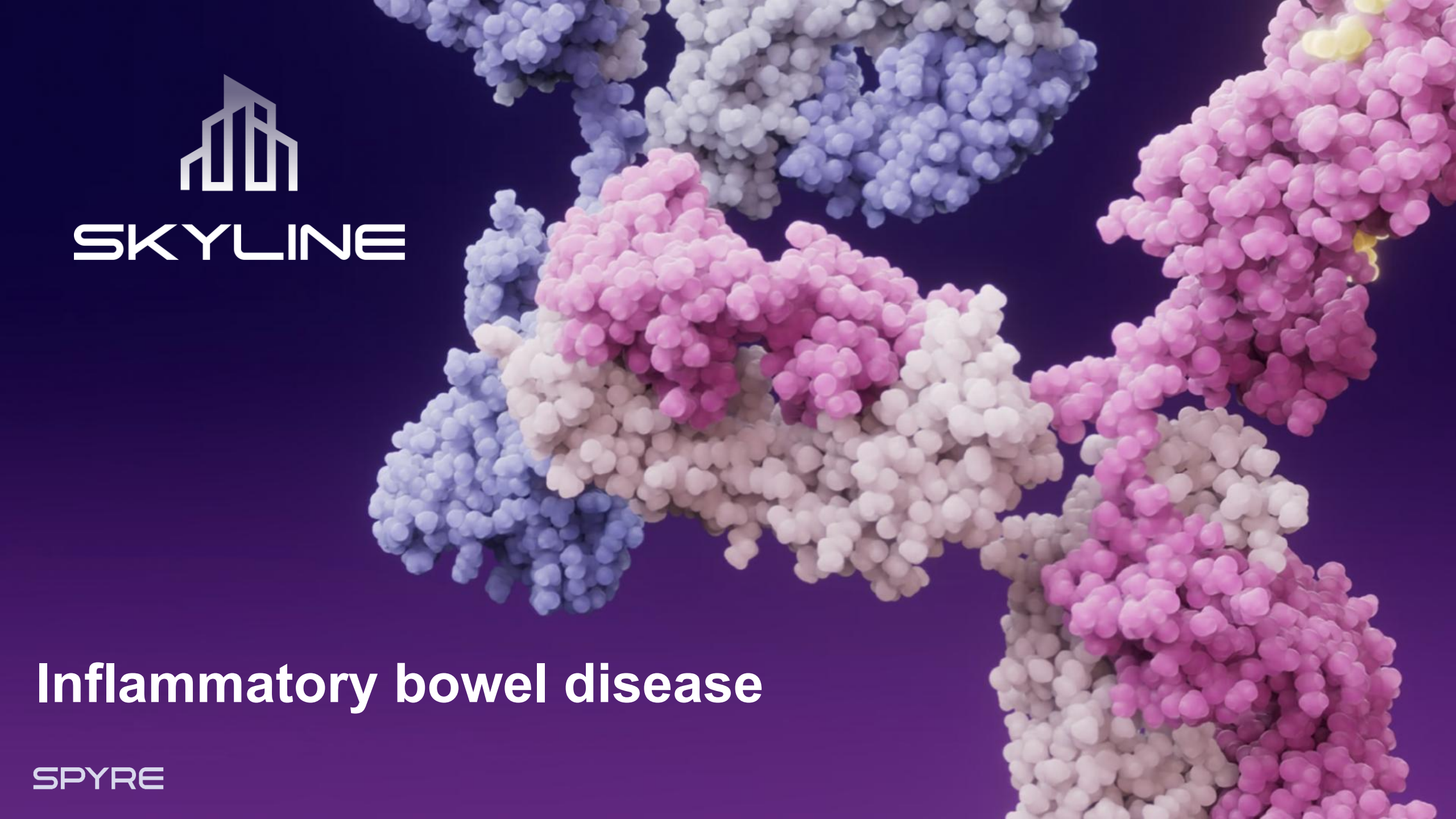


1 INTERVENTION

3 INDICATIONS

Q3-Q4'26 EXPECTED READOUTS

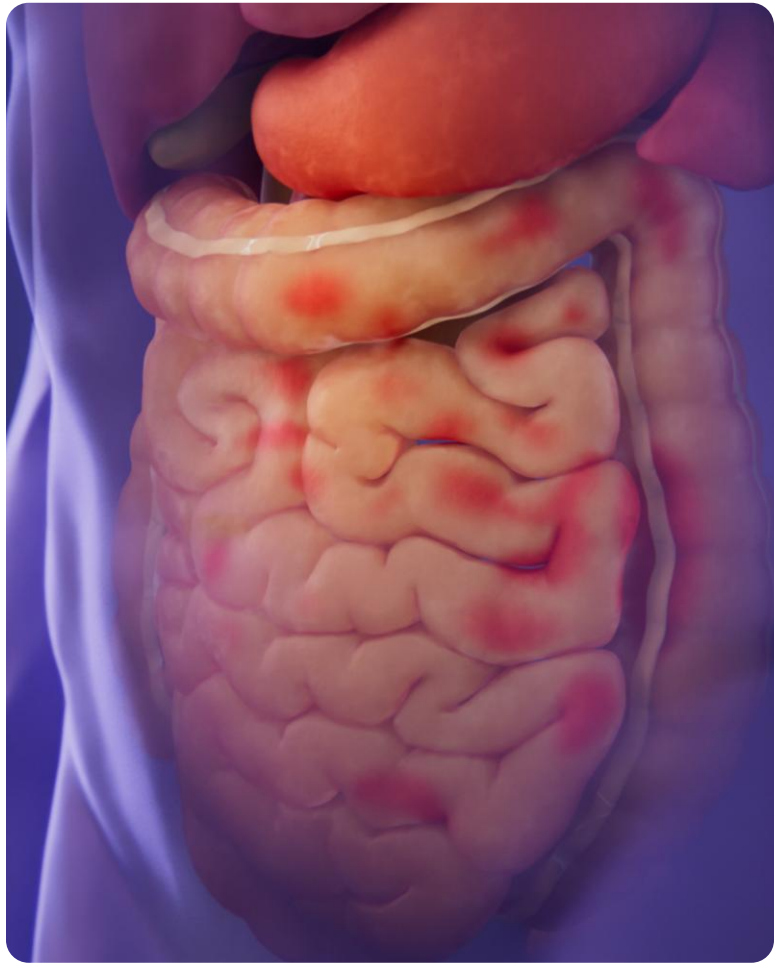
**Part A open-label monotherapy readouts: SPY001 (Q2 2026), SPY002 (mid-year 2026), SPY003 (Q3 2026); Part B (2027)*



Inflammatory bowel disease

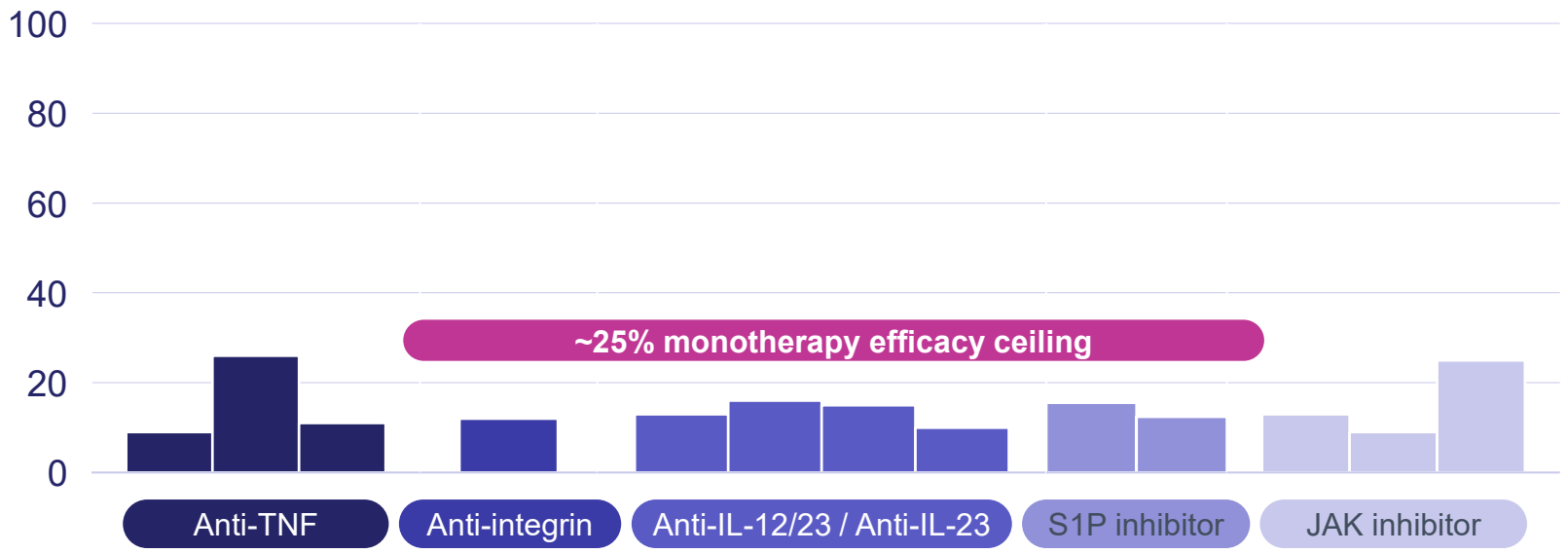
SPYRE

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)

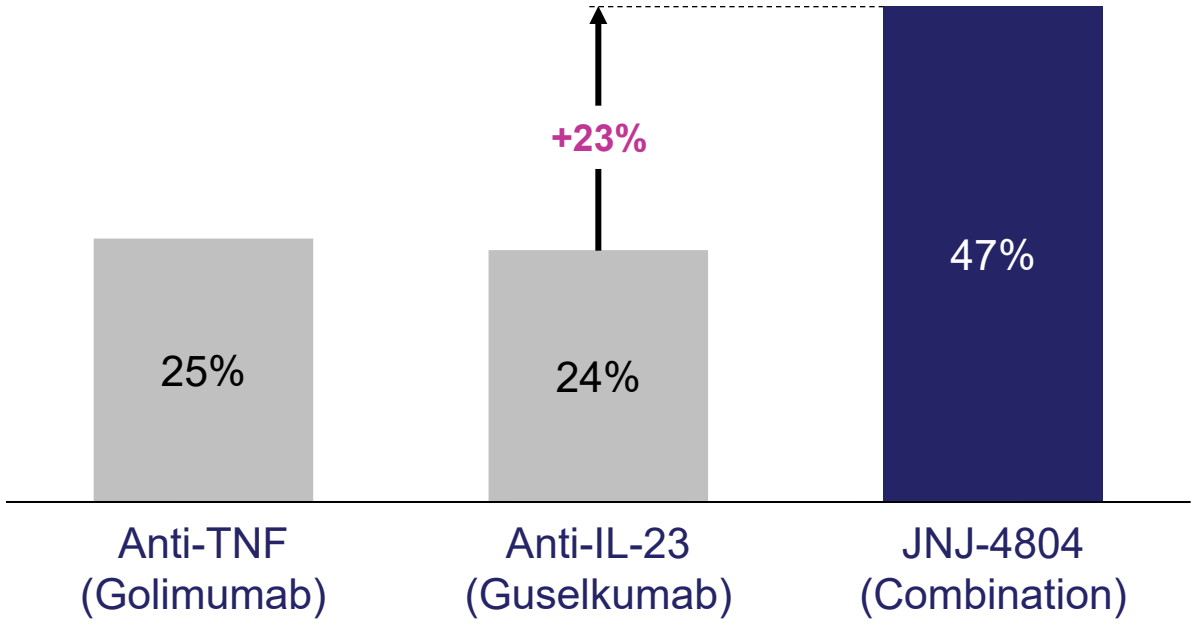


[1]*Lewis, James D., et al. Gastroenterology (2023). Estimate includes patients identified with indeterminate IBD. Clinical remission rates from product labels.*

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

Naïve (1L) UC patients (VEGA)

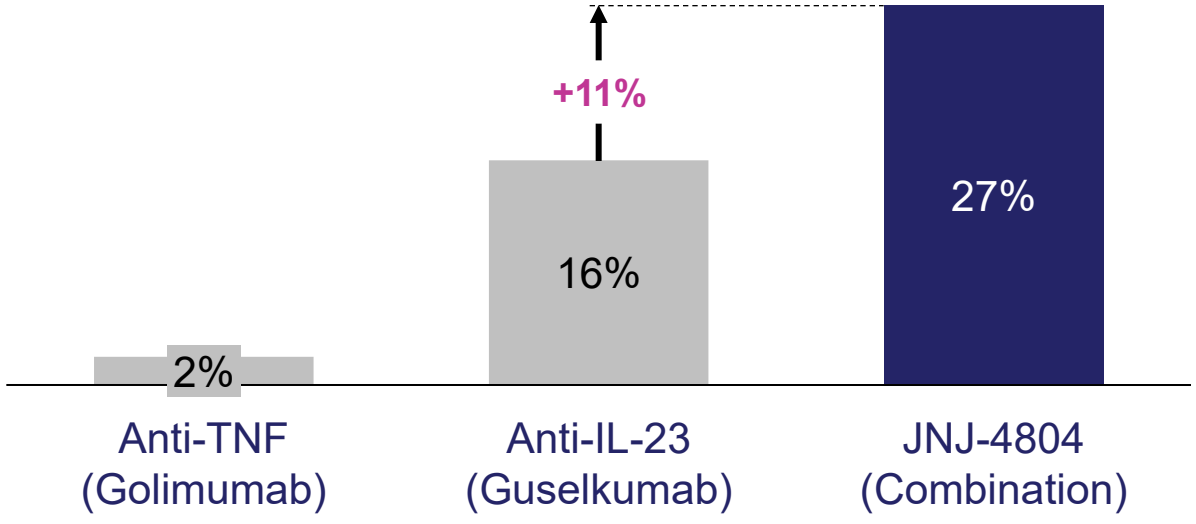
~Additive absolute W12 mMS clinical remission rate



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

Synergistic absolute W48 mMS clinical remission rate

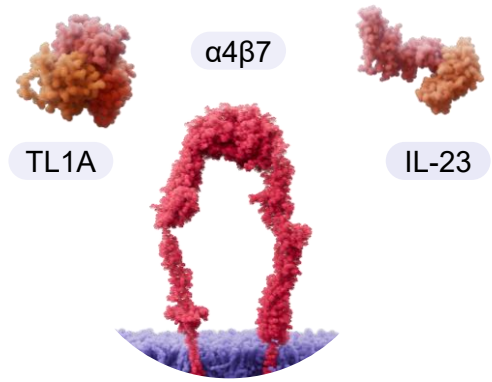
- 74% of patients were refractory to anti-TNF
- 1% were refractory to anti-IL-23



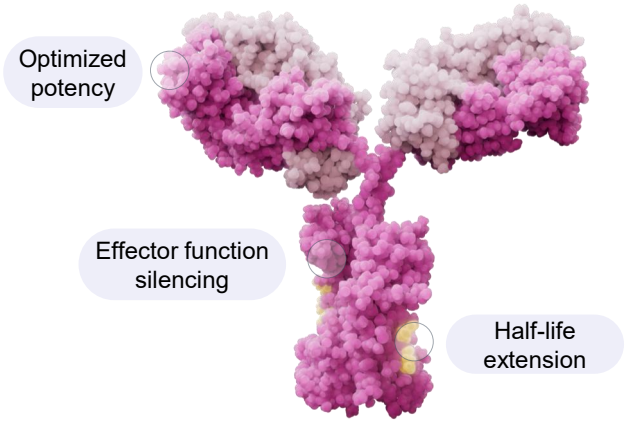
Feagan, B. G. et al. Lancet Gastroenterol. Hepatol. 8, 307–320 (2023); Abreu, Maria T., et al. Gastrointestinal Endoscopy 103.5 (2026): S-2857. mMS=modified mayo score

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]

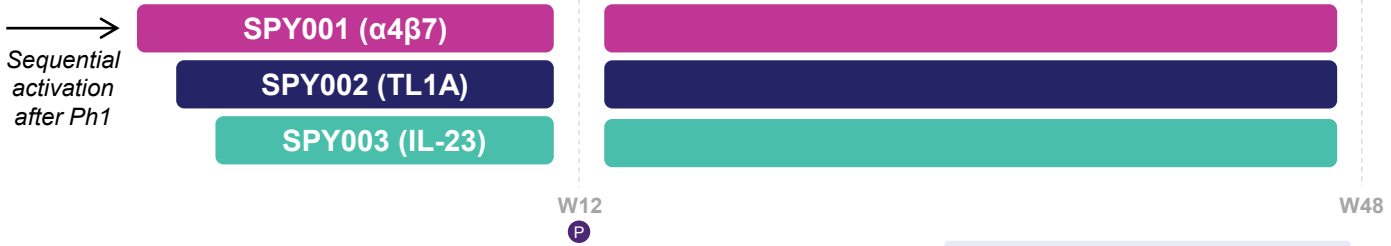
[1]After loading doses, concept image of drug delivery device shown for illustrative purposes only.

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

SKYLINE

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

UC mMS 5-9



OBJECTIVES

- Monotherapy POC

KEY ENDPOINTS

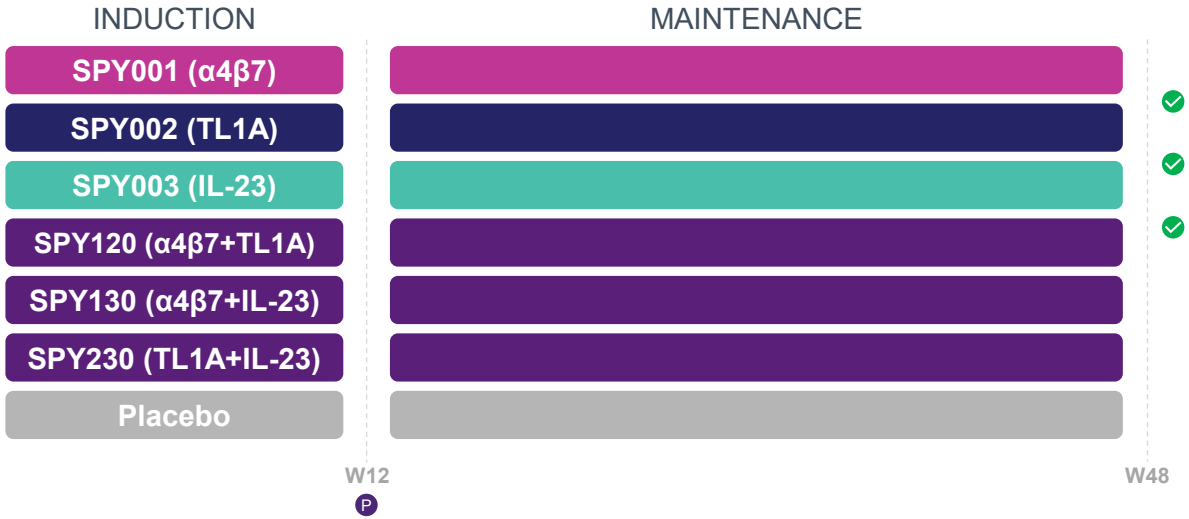
- P Change in RHI at W12
- S Clinical remission at W12
- S Endoscopic improvement at W12
- S Change in mMS at W12

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

UC mMS 5-9

~50:50 naïve:experienced

α4β7 and IL-23-IR capped



- Monotherapy dose optimization
- Combination POC
- Contribution of components

- P Clinical remission at W12
- S Endoscopic improvement at W12
- S Clinical response at W12
- S Histological improvement at W12
- S HEMI at W12
- S Clinical remission at W48

SPYRE

mMS=modified mayo score; RHI=Robarts Histopathology Index; HEMI=Histo-Endoscopic Mucosal Improvement; P=primary endpoint; S=secondary endpoint
Initiation of each cohort subject to regulatory clearance.

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	Q3 2026	2027
PART A SECONDARY				
% Clinical remission	40%	33%		
% Endoscopic improvement	51%	42%		
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

SPYRE THERAPEUTICS

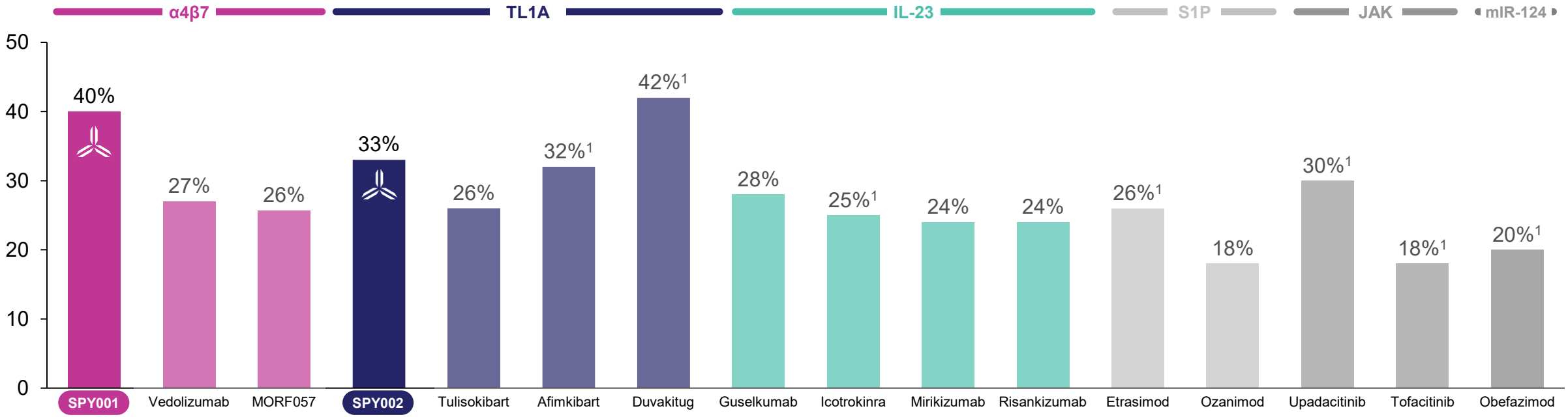
Developing therapies to elevate the standard for inflammatory bowel disease

Source: Data on file.

SPY001 and SPY002 demonstrated robust rates of clinical remission

Clinical remission

Percentage of subjects



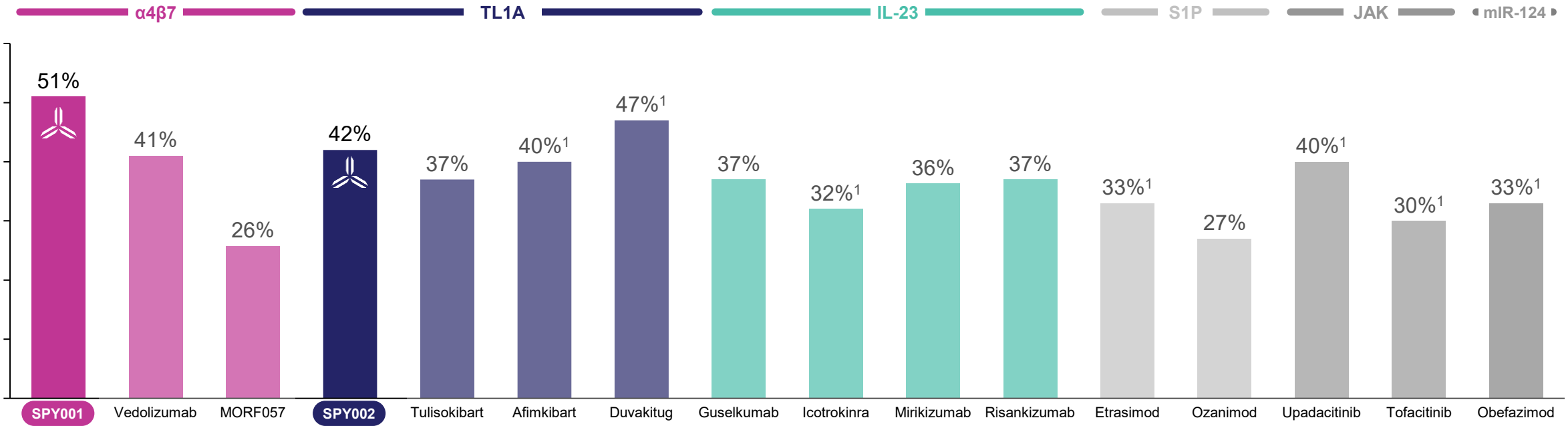
	SPY001	Vedolizumab	MORF057	SPY002	Tulisokibart	Afimkibart	Duvakitug	Guselkumab	Icotrokinra	Mirikizumab	Risankizumab	Etrasimod	Ozanimod	Upadacitinib	Tofacitinib	Obefazimod
Week	**12**	14	12	**12**	12	14	14	12	12	12	12	12	10	8	8	8
N=	**43**	769	35	**48**	120	245	137	701	252	1062	966	741	645	988	1139	955
Trial	**SKYLINE**	VARSITY	EMERALD-1	**SKYLINE**	ARTEMIS	TUSCANY-2	RELIEVE	ASTRO	ANTHEM	LUCENT-1	INSPIRE	ELEVATE	T. NORTH	U-ACHIEVE	OCTAVE	ABTECT

[1]Pooled doses and/or trials; trial designs differ and no head-to-head clinical trials have been conducted.

SPY001 and SPY002 endoscopic improvement rates are among the highest reported

Endoscopic improvement

Percentage of subjects



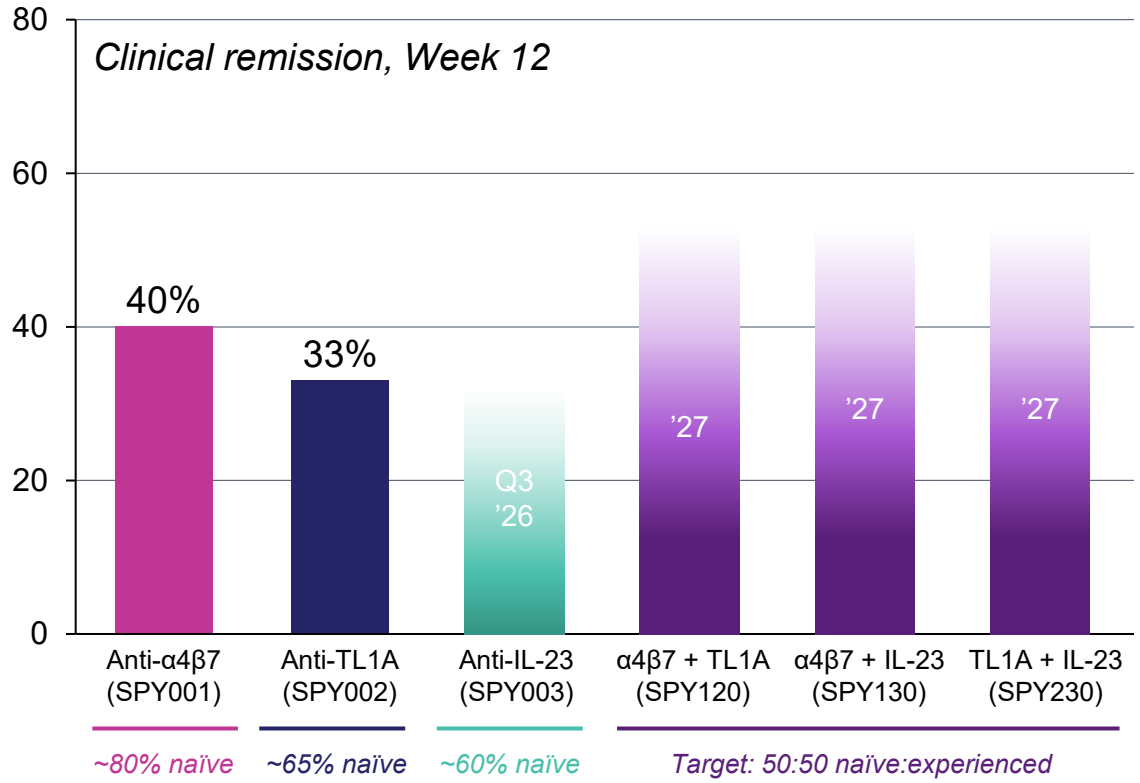
	SPY001	Vedolizumab	MORF057	SPY002	Tulisokibart	Afimkibart	Duvakitug	Guselkumab	Icotrokinra	Mirikizumab	Risankizumab	Etrasimod	Ozanimod	Upadacitinib	Tofacitinib	Obefazimod
Week	**12**	6	12	**12**	12	14	14	12	12	12	12	12	10	8	8	8
N=	**43**	374	35	**48**	120	245	137	701	252	1062	966	741	645	988	1139	955
Trial	**SKYLINE**	GEMINI	EMERALD-1	**SKYLINE**	ARTEMIS	TUSCANY-2	RELIEVE	ASTRO	ANTHEM	LUCENT-1	INSPIRE	ELEVATE	T. NORTH	U-ACHIEVE	OCTAVE	ABTECT

SPYRE

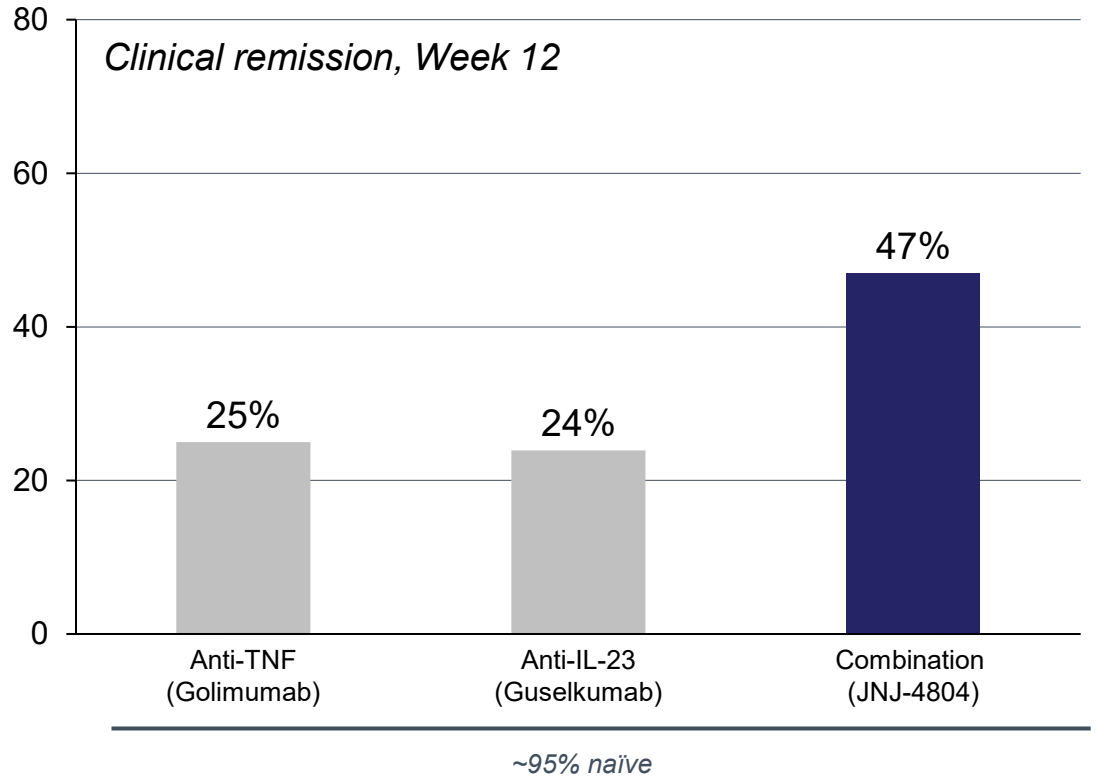
[1]*Pooled doses and/or trials; trial designs differ and no head-to-head clinical trials have been conducted.*

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

SKYLINE



JNJ VEGA study



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

SPYRE

Source: Feagan, B. G. et al. Lancet Gastroenterol. Hepatol. 8, 307–320 (2023).
Trial designs differ and no head-to-head clinical trials have been conducted.

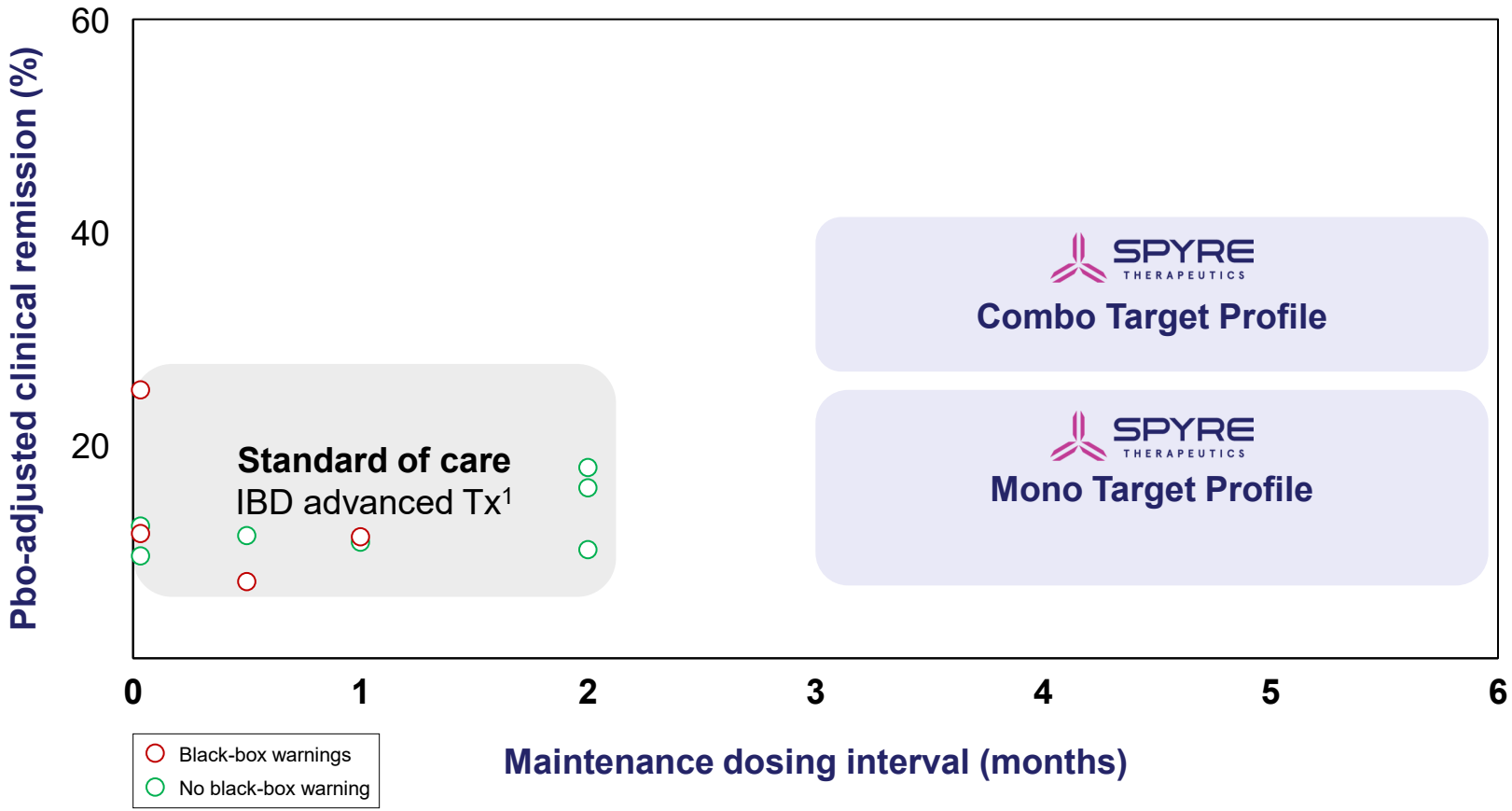
IBD treatment is moving to combination therapy and Spyre is positioned to lead with three differentiated combos

Sponsor	Program	MOAs	Target Profile	1-m	2	3	4	5	6	7	8	9	10	11	12
SPYRE THERAPEUTICS	SPY120	α4β7+TL1A	Q3M-Q6M AI		●			●			●			●	
	SPY130	α4β7+IL-23	Q3M-Q6M AI		●			●			●			●	
	SPY230	TL1A+IL-23	Q3M-Q6M AI		●			●			●			●	
J&J	JNJ-4804	TNF+IL-23	Q4W AI	●	●	●	●	●	●	●	●	●	●	●	●
abbvie	Skyrizi + ABBV382	α4β7+IL-23	Q4W OBI	●	●	●	●	●	●	●	●	●	●	●	●
Lilly	Omvoh + MORF057	α4β7+IL-23	Q4W AI + daily oral	●	●	●	●	●	●	●	●	●	●	●	●

Target profile refers to maintenance treatment period. Competitor target profiles based on publicly available clinical trial protocols, management guidance, or FDA labels for individual assets.

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

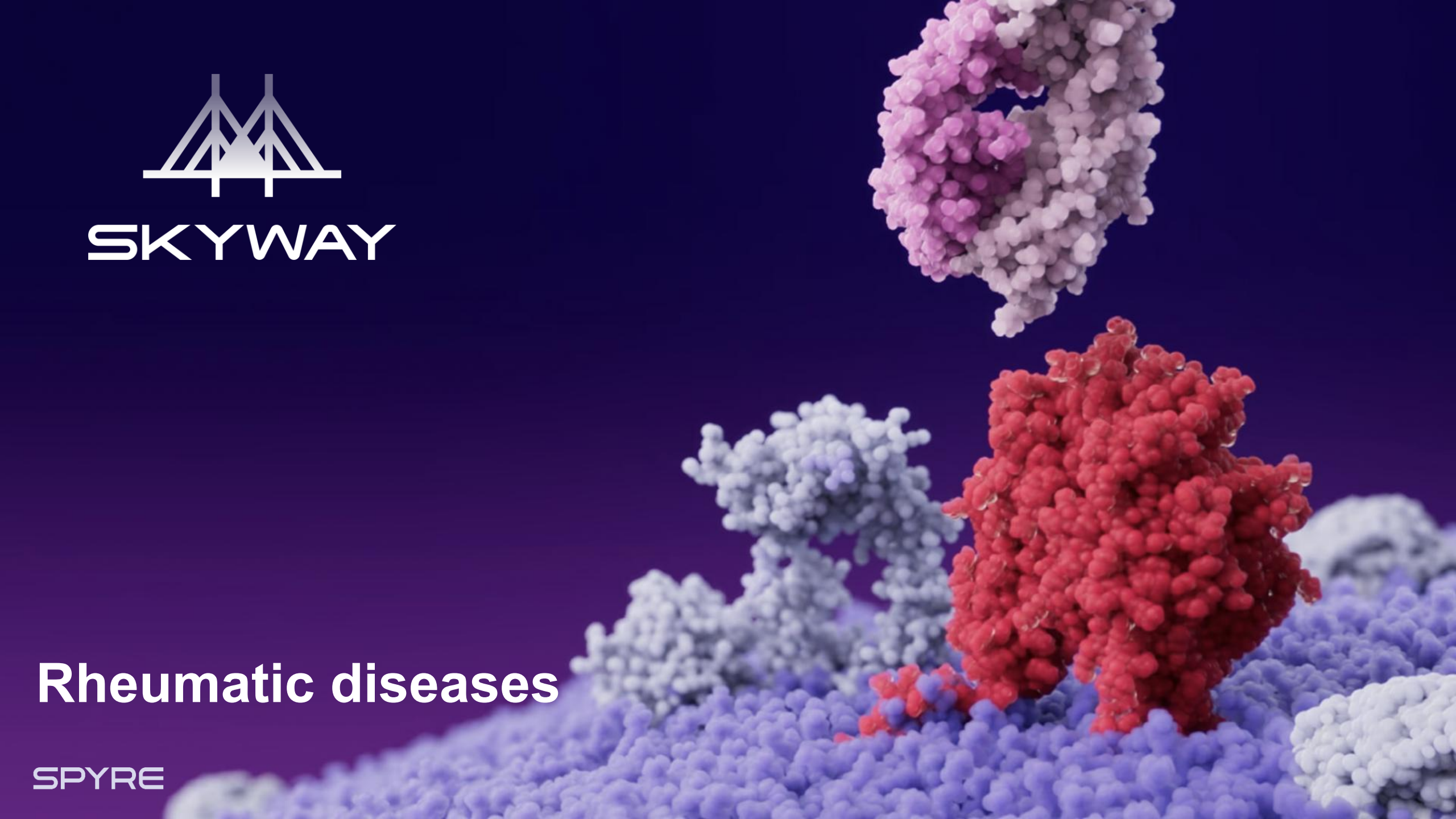
Favorable safety profile

No black box warning

Q3M-Q6M maintenance dosing

Positioning of Spyre programs is illustrative and based on Phase 1 results and illustrates what we believe we can potentially achieve. Placebo-adjusted clinical remission data are derived from different clinical trials conducted at different times, with differences in trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted. [1]Oral and SC administered products

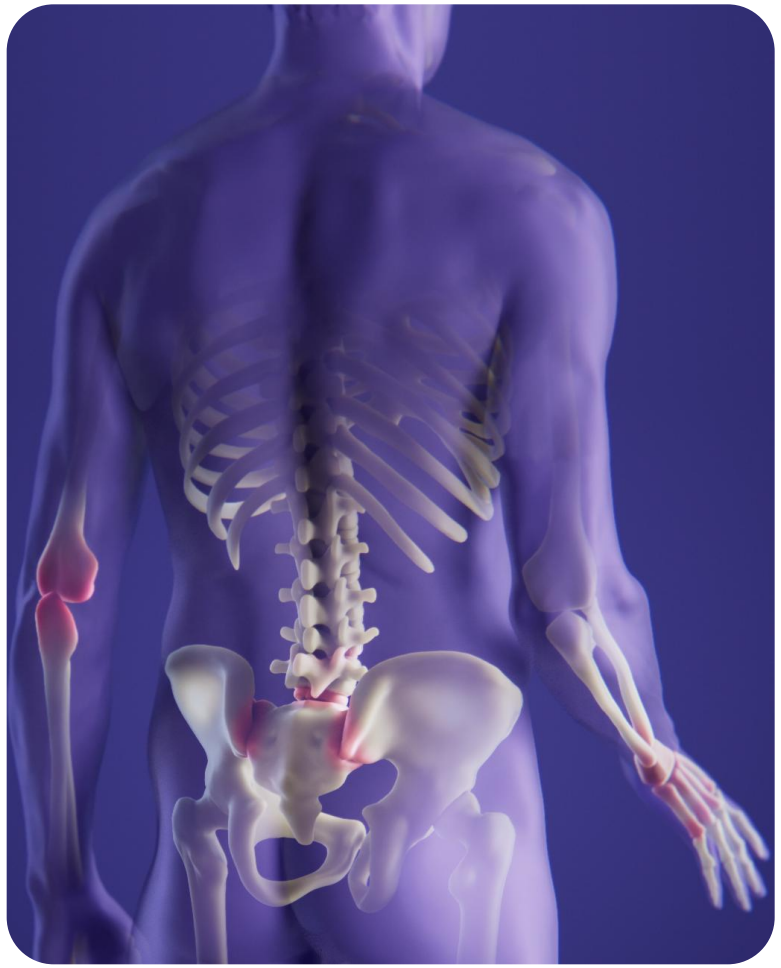
SKYWAY



Rheumatic diseases

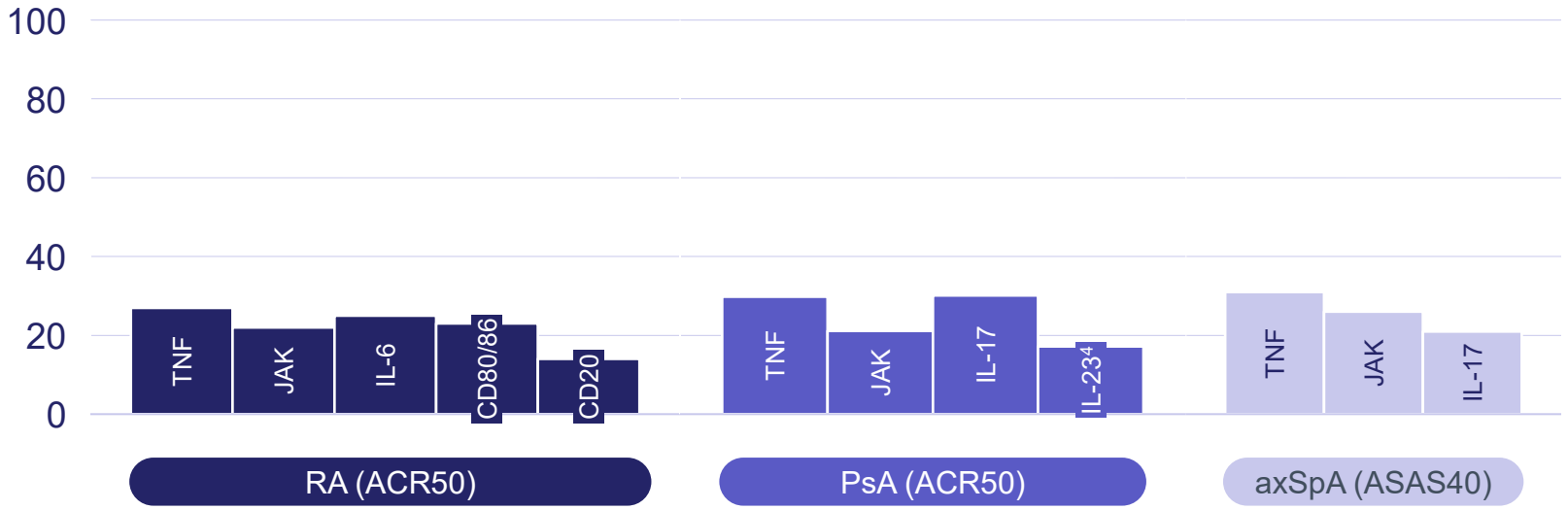
SPYRE

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



- >3M individuals in the U.S. diagnosed with RA (>1.5M[1]), PsA (~1M[2]), and axSpA (~1M[2])
- 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

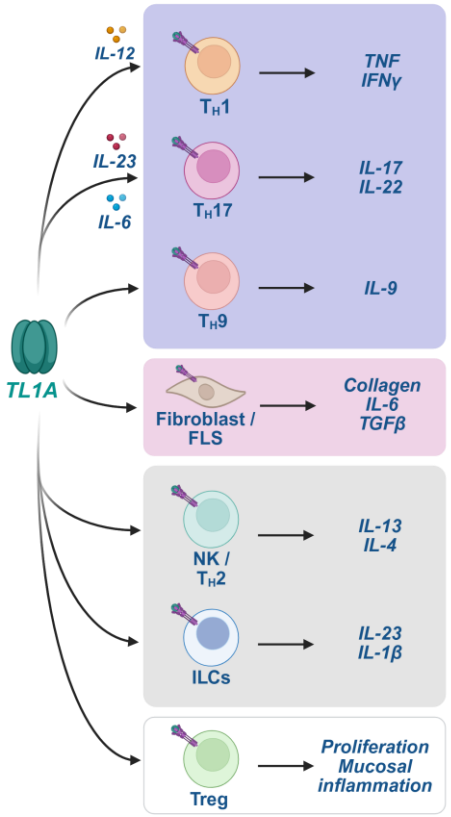
Placebo-adjusted efficacy rates by MOA (W24[3])



[1]*Hunter, Theresa M., et al. Rheumatol Int (2017);* [2]*Ogdie, Alexis, et al. Rheumatol Ther (2021);* Danve, Abhijeet, and Atul Deodhar. *Clinical rheumatology* 38.3 (2019). *Efficacy rates by MOA from product labels. Note:* [3]*Week 24 data when available, otherwise data is Week 12 or 16;* [4]*Includes IL-12/23 and IL-23*

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

	POC studies[1]	T_H1 | T_H17 | T_H9	Fibroblasts FLS | osteoclasts	NK | T_H2 | ILCs
Ulcerative colitis (UC)	✓	●		
Crohn's disease (CD)	✓	●	●	
Rheumatoid arthritis (RA)	Roche	●	●	
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)	Roche		●	
Atopic dermatitis (AD)	Roche			●
Asthma	✘			●

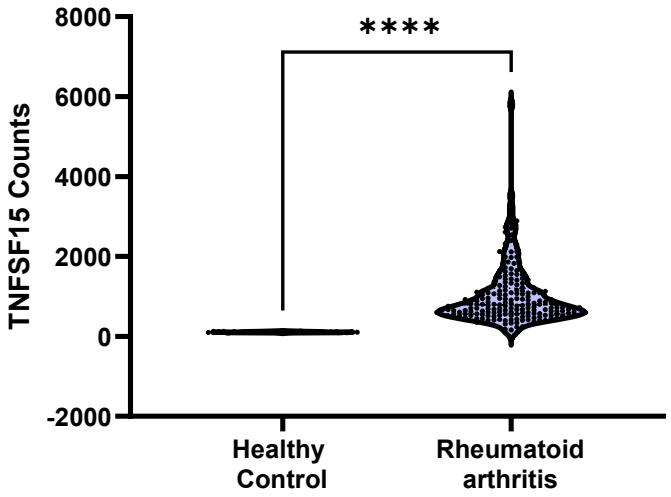
Figure created with BioRender.com. [1] Logos indicate active clinical POC studies.

Hisamoto, T. et al. Int. J. Mol. Sci. 24, 1813 (2023); Herro, R. et al. J. Immunol. 205(9), 2414-2422 (2020); Ma, C. et al. Int. Immunopharm. 137, 112360 (2024); Richard, A. et al. JLB 3(98), 333-345 (2015); Song, Y. et al. Arthritis Research & Therapy 22, 106 (2020); Xu, W. et al. Frontiers in Immunology 13, 891328 (2022).

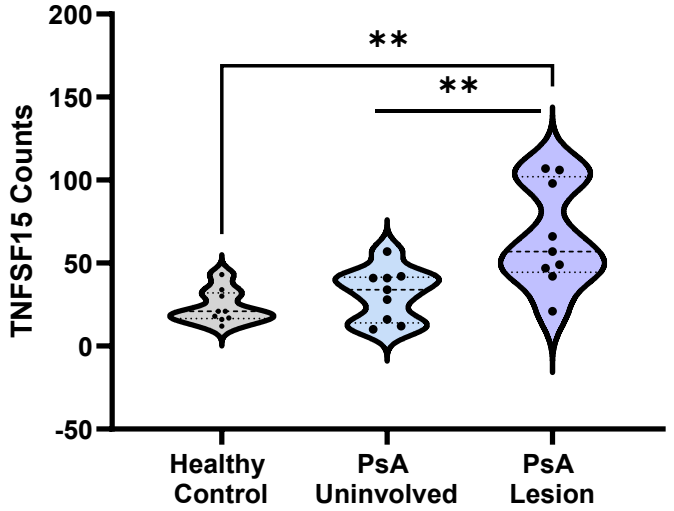
SPYRE

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

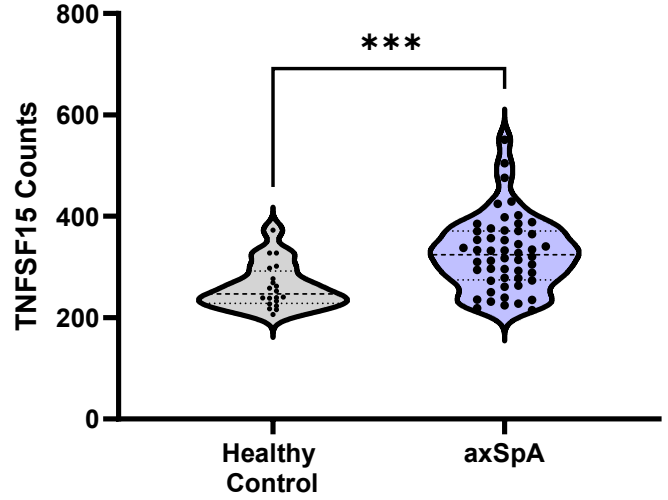
Rheumatoid arthritis



Psoriatic arthritis



Axial spondyloarthritis

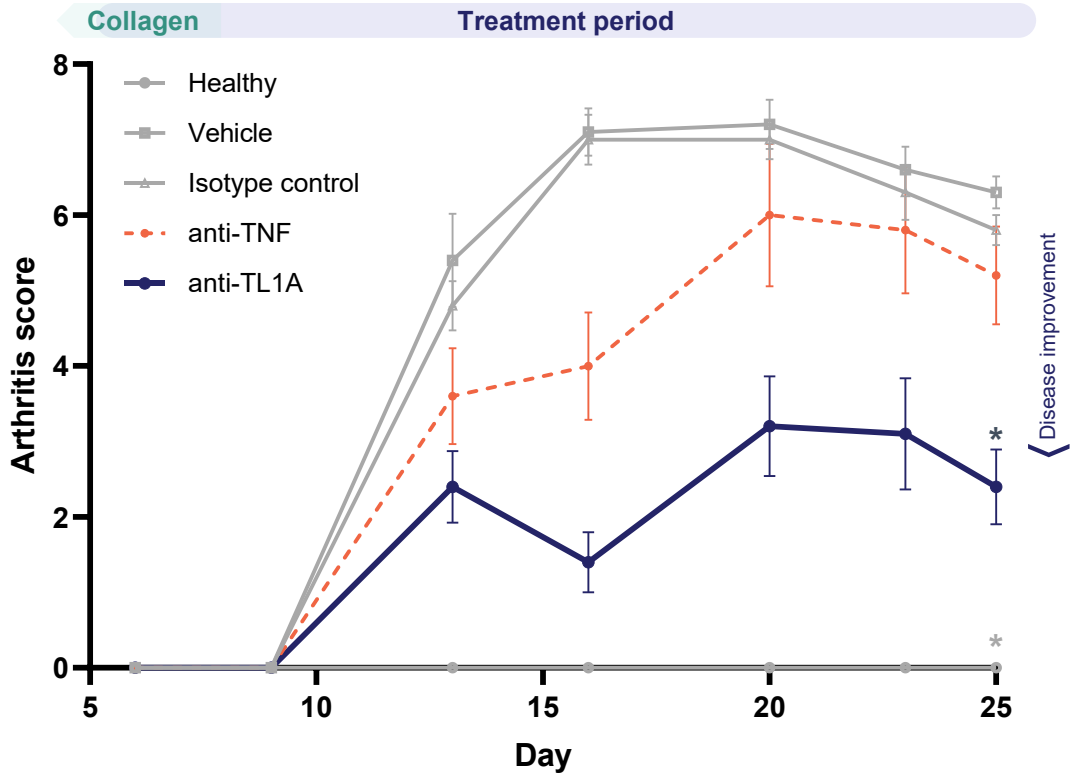


Source	Whole blood	Skin biopsy	Whole blood
Sequencing	Microarray	Bulk RNA seq	Microarray
Sample size	N=192 RA, 30 HC	N=9 per cohort	N=52 axSpA, 20 HC

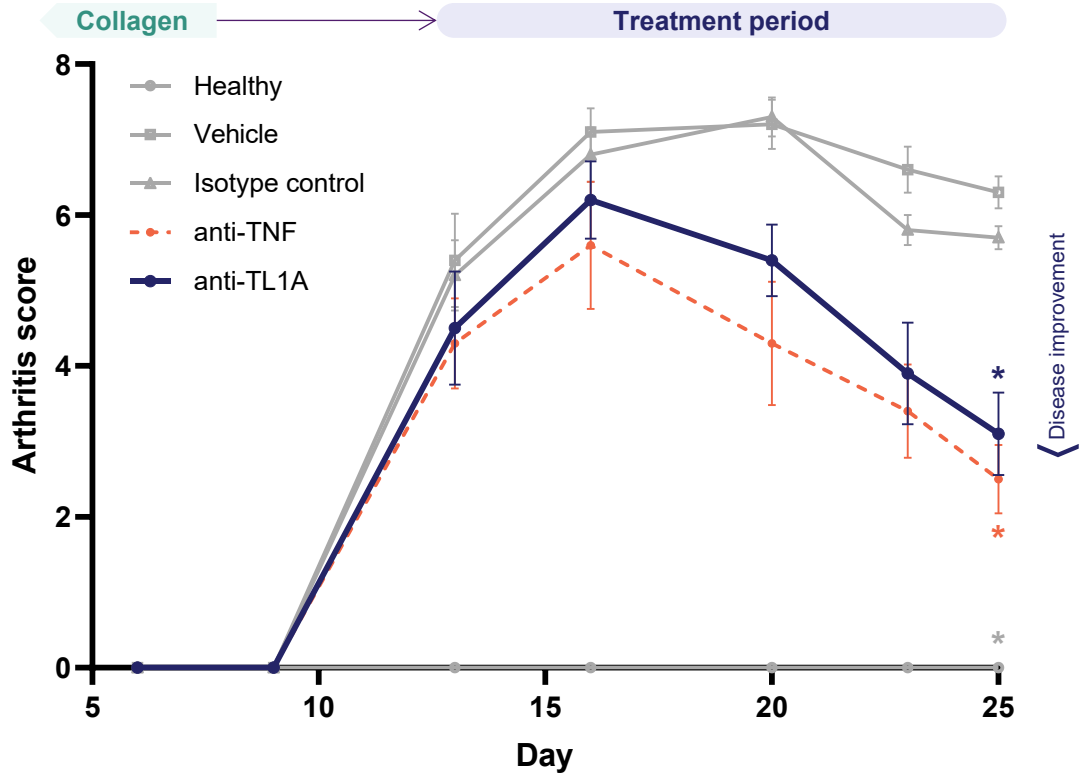
Spyre analysis of RA-MAP, Li, Sifang, et al. BMC Musculoskeletal Disorders 25.1 (2024), and Johnsson, Hanna, et al. Arthritis Research & Therapy.
*** P≤0.01, *** P ≤0.001, **** P ≤0.0001. Unpaired tailed t-test used for RA and axSpA analysis, One-way ANOVA used in PsA.*
RA=rheumatoid arthritis; PsA=psoriatic arthritis; axSpA=axial spondyloarthritis; HC=healthy controls.

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

Superior efficacy in semi-preventative model



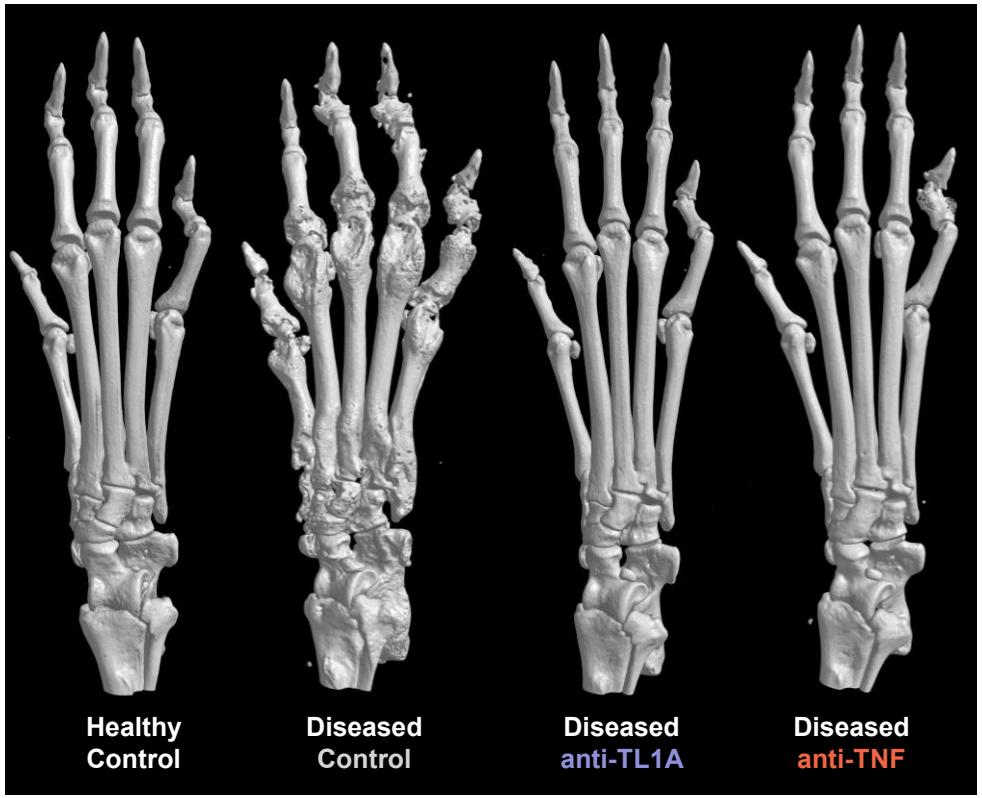
Comparable efficacy in therapeutic model



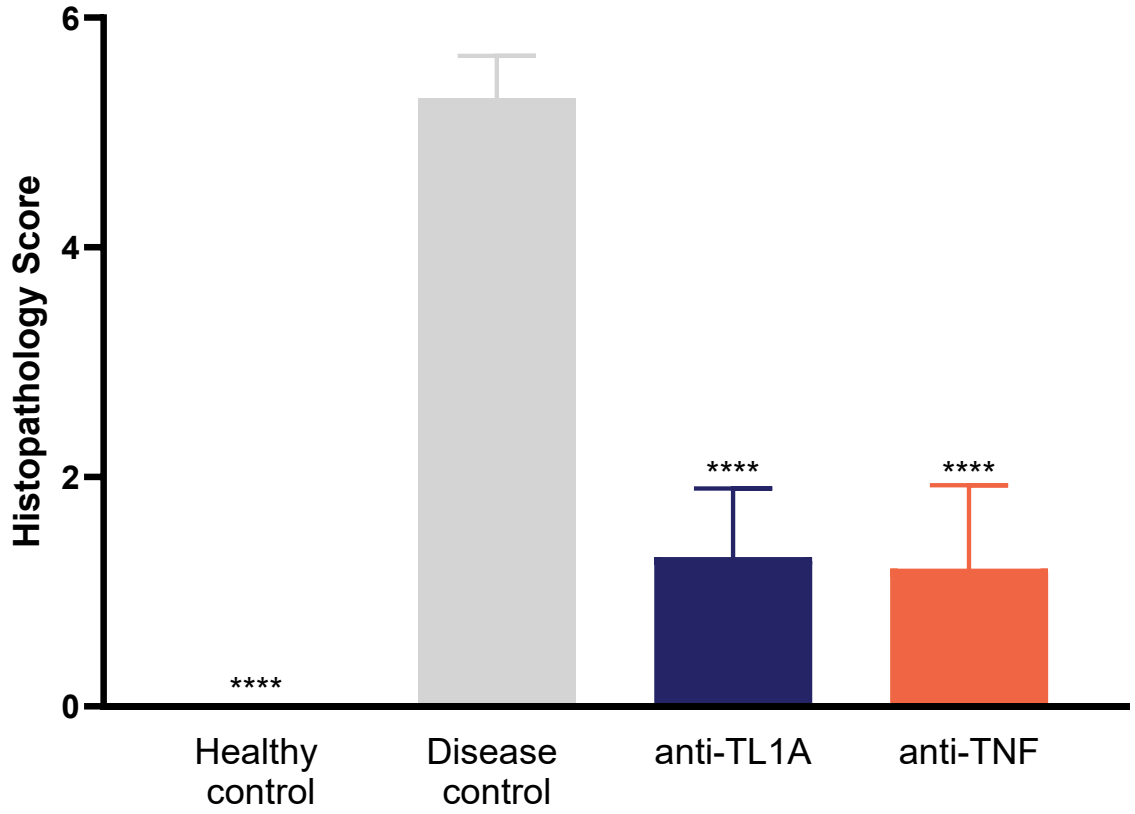
** P< 0.0001 vs. isotype control; 2-way ANOVA using Dunnett's correction for multiple comparisons. Data on file.*

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

Anti-TL1A prevents disease and bone erosion



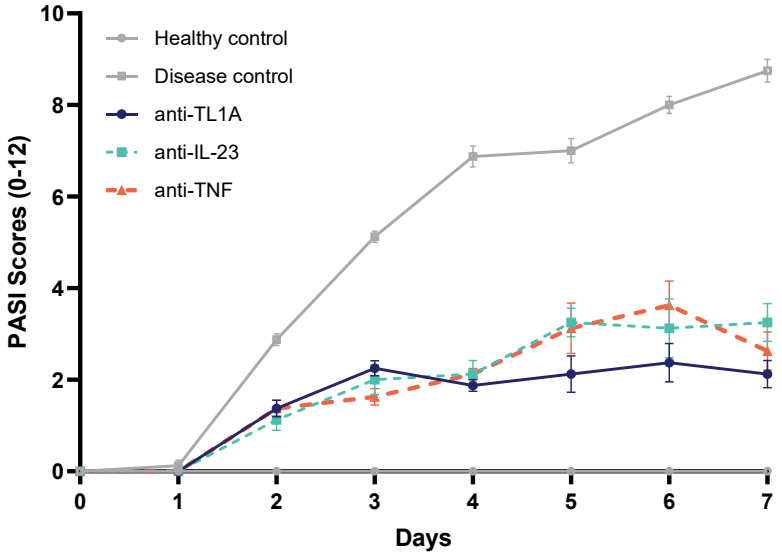
Comparable efficacy to anti-TNF



*Data on file. **** P ≤0.0001*

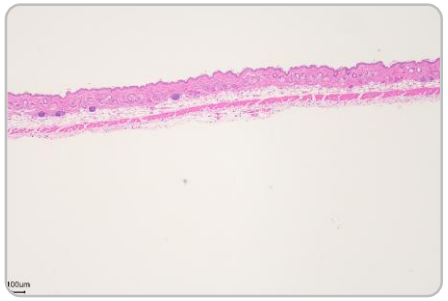
Additionally, anti-TL1A treatment led to comparable improvements in psoriatic skin lesions in mouse IMQ model

Anti-TL1A reduces skin lesions

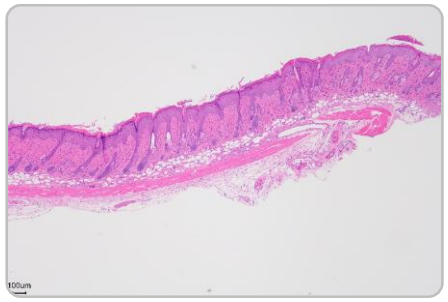


Potential for robust skin clearance in PsA

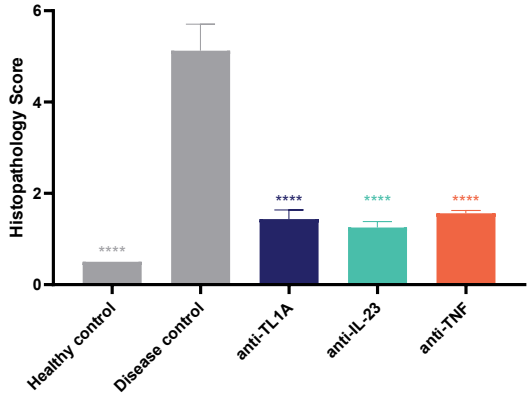
Comparable efficacy to anti-IL-23 and anti-TNF

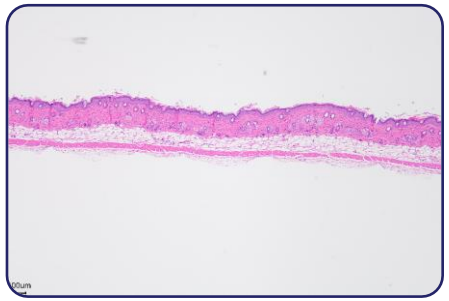


Healthy control

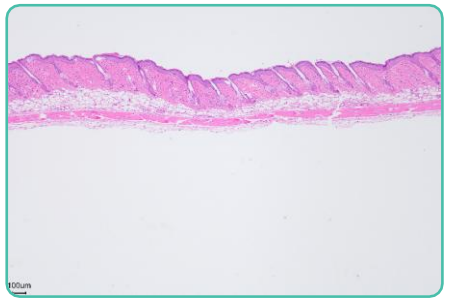


Disease control

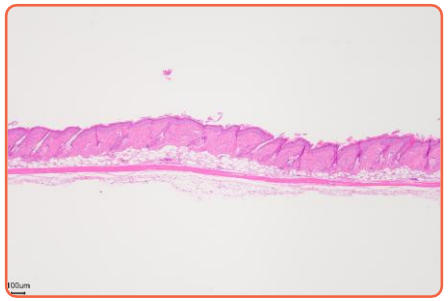




anti-TL1A



anti-IL-23



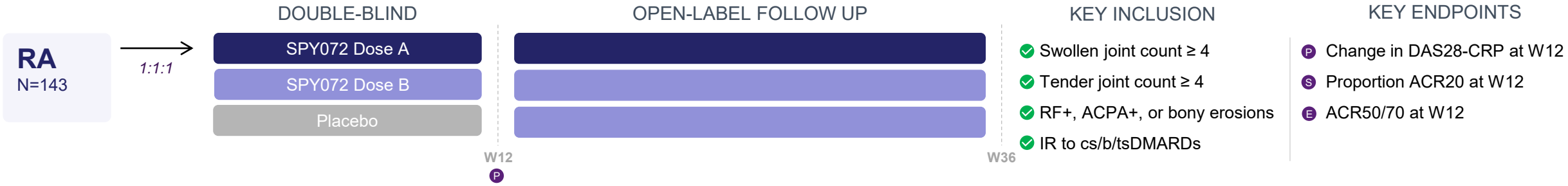
anti-TNF

*Data on file. **** P ≤0.0001*

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

SKYWAY

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



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

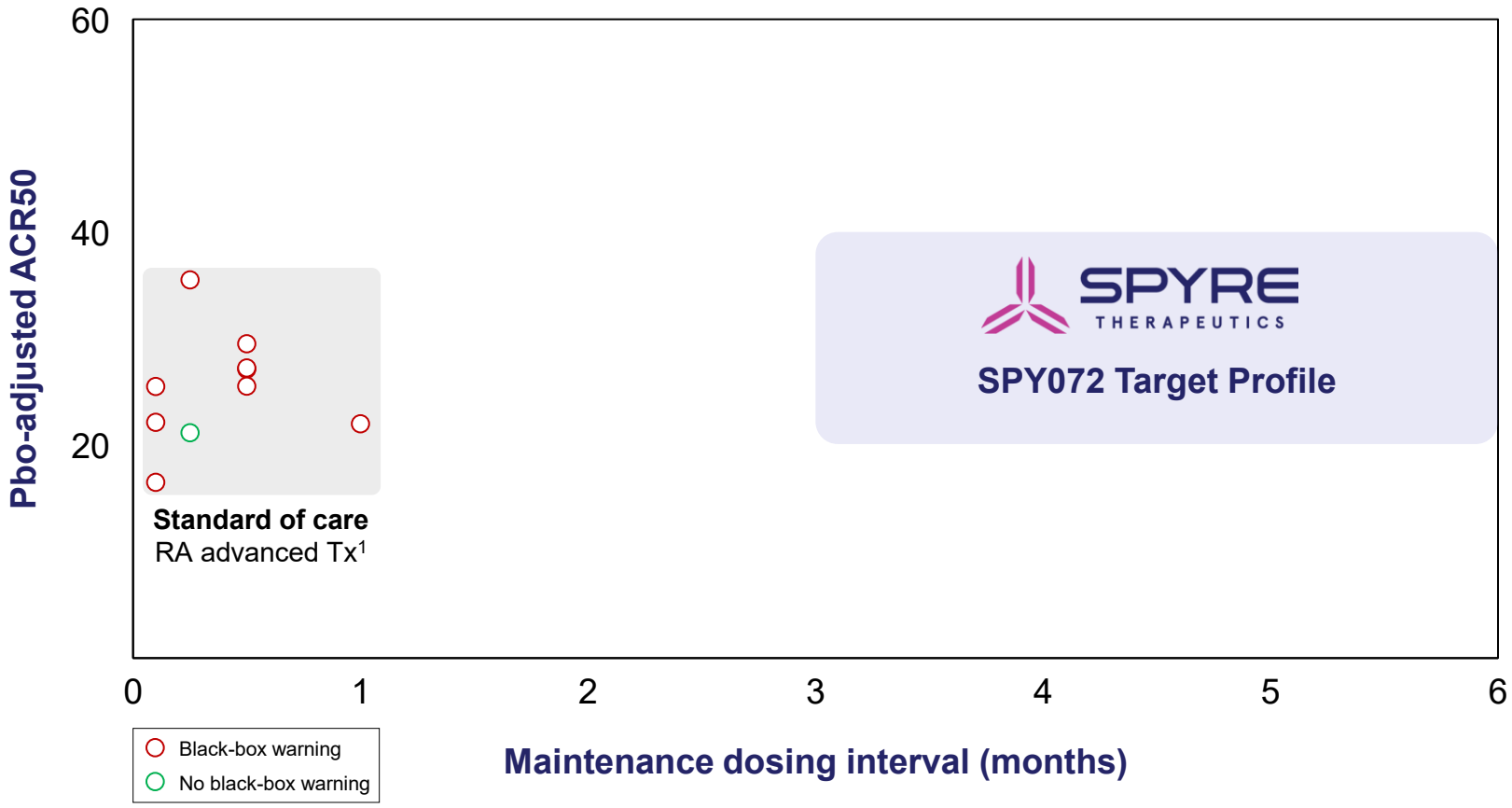
Sub-study C: SPY072 in moderate-to-severely active axial spondyloarthritis (axSpA)

SPYRE

RF=rheumatoid factor; ACPA= Anti-citrullinated protein antibodies; cs/b/tsDMARD=conventional synthetic, biologic, or targeted synthetic disease modifying antirheumatic drugs; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; P=primary endpoint; S=secondary endpoint; E=exploratory endpoint. IR=inadequate response

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

Positioning of Spyre programs is illustrative and based on Phase 1 interim results. Placebo-adjusted clinical data are derived from different clinical trials conducted at different times, with differences in trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted. [1]Oral and SC administered products.

Catalysts & capitalization

SPYRE

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

Trial	2026	2027
SKYLINE Part A (Open-label)	☑ SPY001 α4β7 Ph2 UC induction POC ☑ SPY002 TL1A Ph2 UC induction POC ❑ SPY003 IL-23 Ph2 UC induction POC (3Q 2026)	❑ SPY001 α4β7 Ph2 UC maintenance data ❑ SPY002 TL1A Ph2 UC maintenance data ❑ SPY003 IL-23 Ph2 UC maintenance data
SKYLINE Part B (Pbo-controlled)	☑ Initiate enrollment of Part B cohorts	❑ SPY120 α4β7 + TL1A Ph2 UC induction POC ❑ SPY130 α4β7 + IL-23 Ph2 UC induction POC ❑ SPY230 TL1A + IL-23 Ph2 UC induction POC ❑ SPY001 α4β7 Ph2 UC induction POC ❑ SPY002 TL1A Ph2 UC induction POC ❑ SPY003 IL-23 Ph2 UC induction POC
SKYWAY	❑ SPY072 TL1A Ph2 W12 POC in RA (3Q 2026) ❑ SPY072 TL1A Ph2 W16 POC in PsA (4Q 2026) ❑ SPY072 TL1A Ph2 W16 POC in axSpA (4Q 2026)	❑ SPY072 TL1A Ph2 maintenance data in RA ❑ SPY072 TL1A Ph2 maintenance data in PsA ❑ SPY072 TL1A Ph2 maintenance data axSpA

$1.2 billion pro forma cash as of March 31, 2026[1], with expected runway into 2H 2029

SPYRE

Milestones expected as of the date of this presentation. [1]Reflects pro forma unaudited cash, cash equivalents, & marketable securities as of 3/31/26 of $741.5 million plus $435.3 million in net proceeds from the recently closed April 2026 underwritten public offering of common stock

Cash and shares outstanding

$1.2B pro forma cash as of March 31, 2026[1]

Expected runway into 2H 2029

		Number of shares (M)
Common stock[2]	Shares outstanding	87.8
Common stock equivalents[3]	Series A preferred stock	13.8
Common stock and common stock equivalents[2,3]	**Total outstanding**	**101.7**

[1]Reflects pro forma 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; [2]Pro forma shares outstanding as of 6/22/26, inclusive of subsequent conversion of Series B preferred stock to common stock; [3] Common stock equivalents as of 6/23/26 (i) giving effect to the full conversion of the Company's preferred stock owned by Fairmount per SEC filings, and (ii) disregarding beneficial ownership limitations that may limit the ability of certain holders of preferred stock to convert into common stock.

SPYRE

ELEVATE THE STANDARD
IN IMMUNOLOGY

Scientific illustrations by Visual Sciences

Appendix

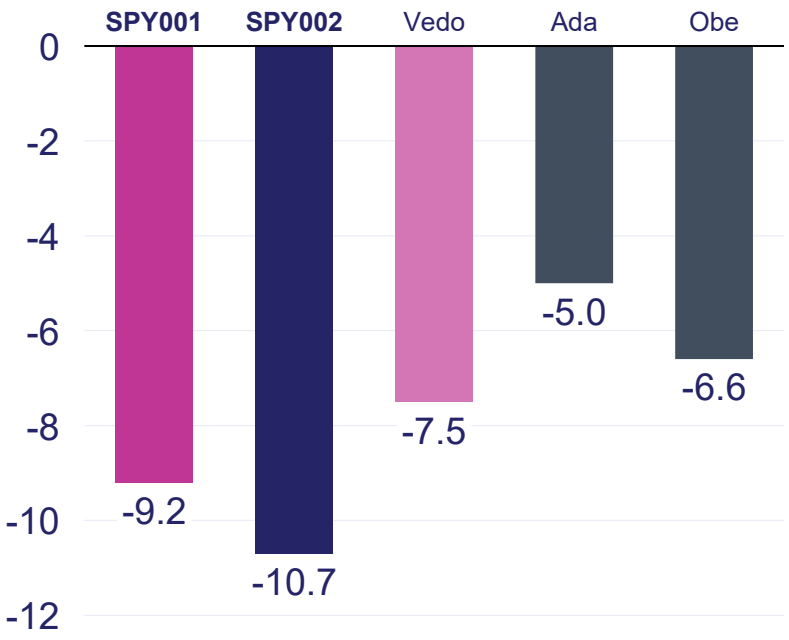
2026 Milestone Aims

SKYLINE Part A: SPY002

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

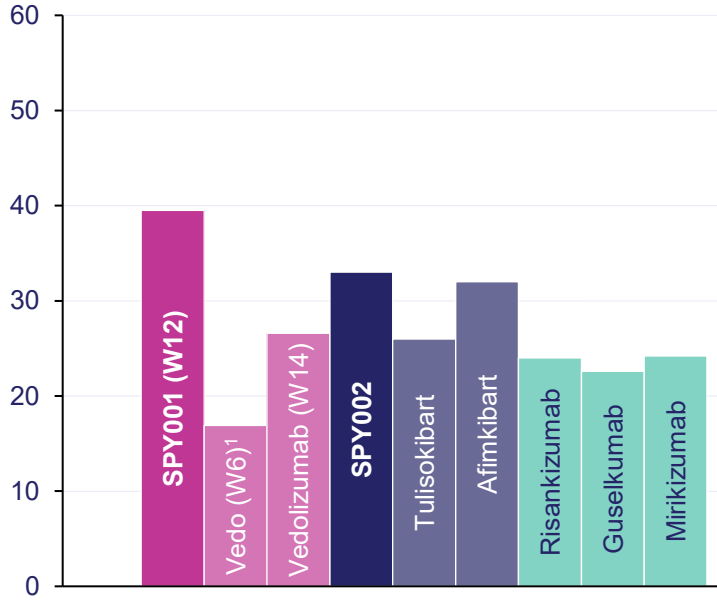
Primary endpoint

ΔRHI from baseline (W8-14)

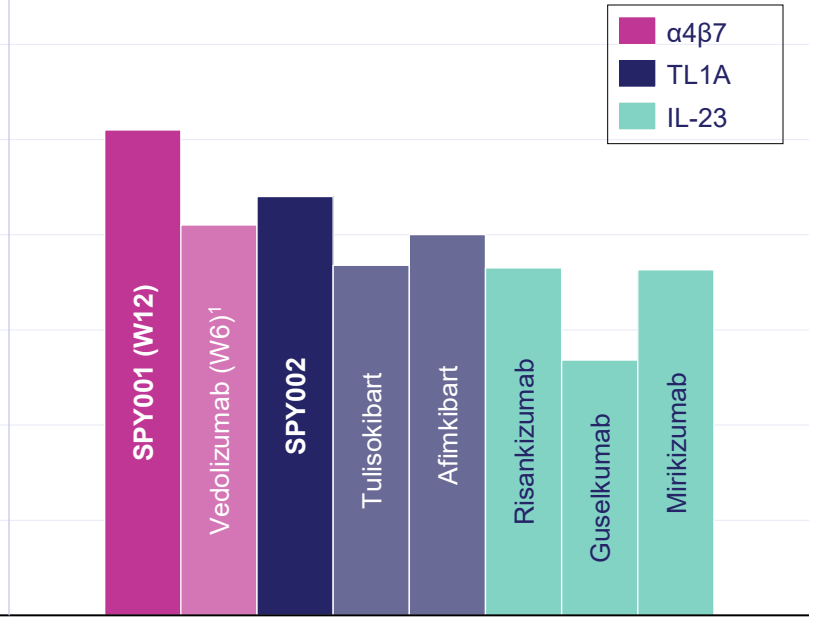


Secondary endpoints

Absolute % clinical remission (W6-14)



Absolute % endoscopic improvement (W6-14)

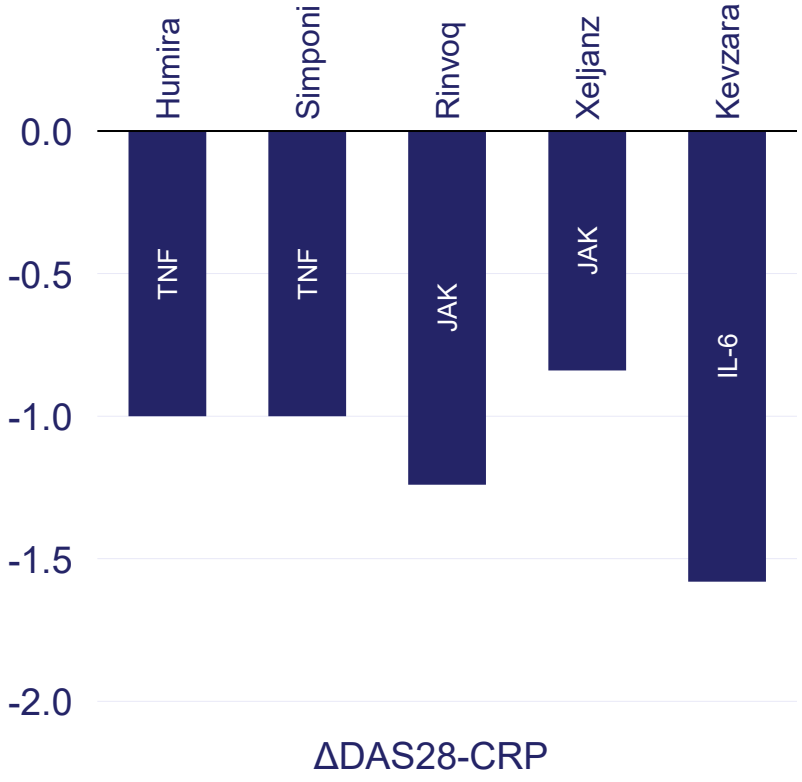


Source: Vedolizumab (VARSITY, GEMINI I), adalimumab (VARSITY), obefazimod (Ph2b – 25 mg and 50 mg pooled), tulisokibart (ARTEMIS-UC), afimkibart (TUSCANY-2), risankizumab (INSPIRE), guselkumab (QUASAR), mirikizumab (LUCENT 1); Duvakitug not shown given outlier placebo response rate. Trial designs differ and no head-to-head clinical trials have been conducted. [1]GEMINI endoscopies not centrally read

2026 RA readout: Aiming for ΔDAS28-CRP and ACRs comparable-to-better than SOC analogs

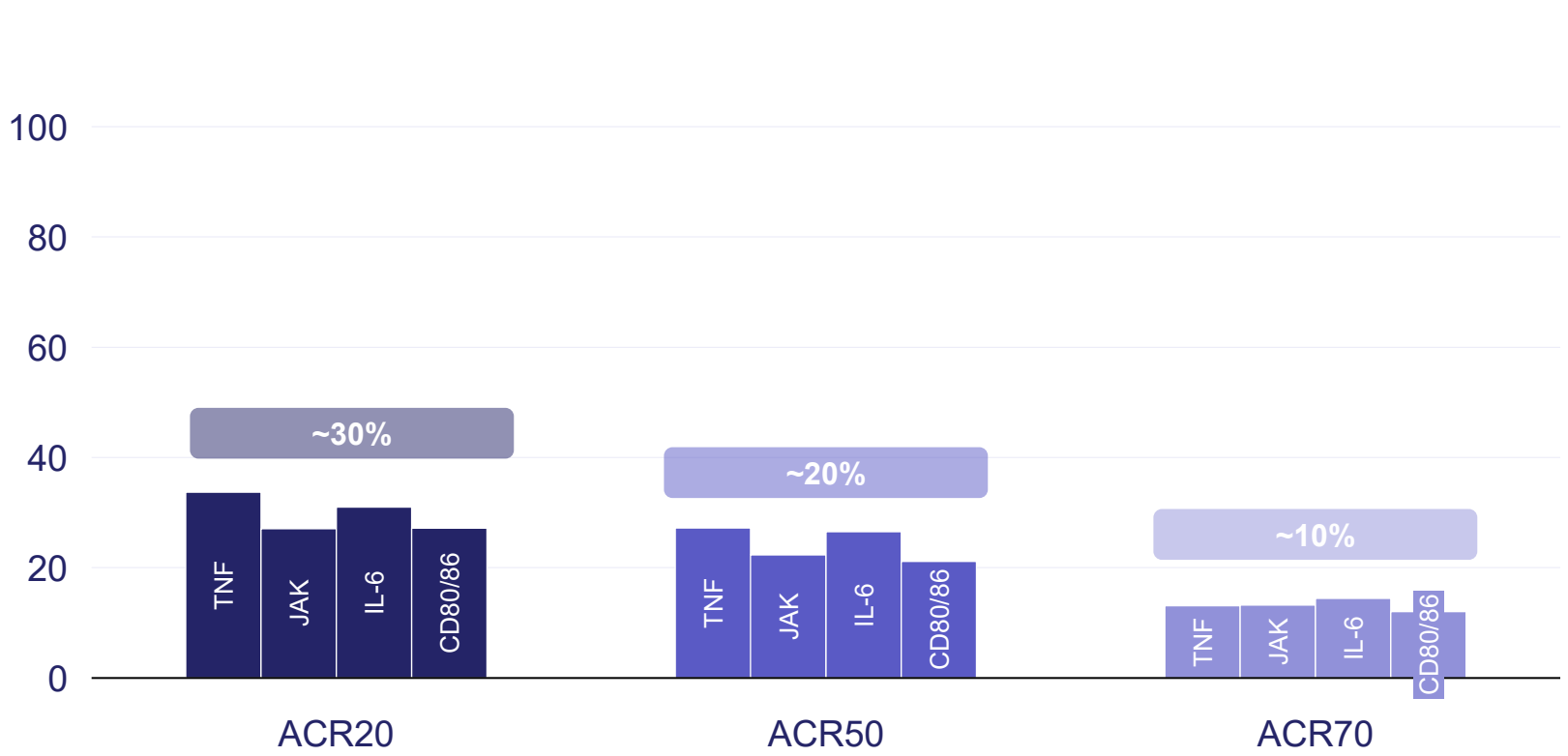
Primary endpoint

Placebo-adjusted ΔDAS28-CRP (W12-26)[1]



Secondary & exploratory endpoints

Placebo-adjusted % (W12-26)[2]

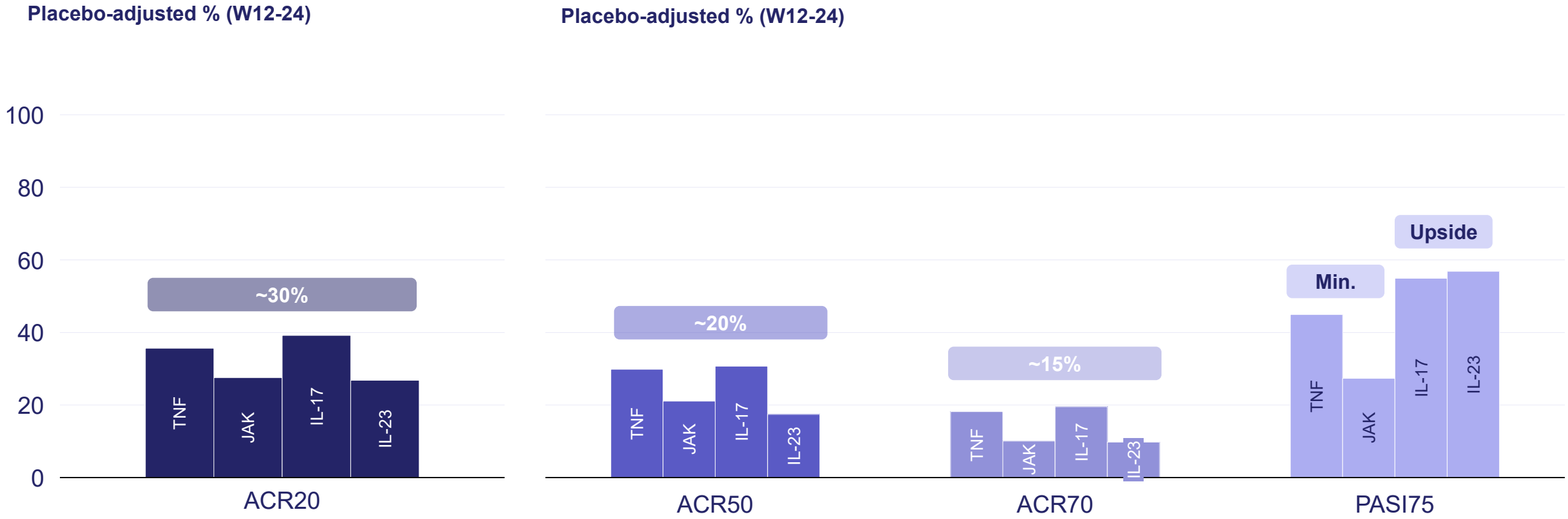


Notes: [1]Results from studies in mixed populations or weighted average of naïve and inadequate response (IR) trial results. [2]Average ACR values from pivotal studies of approved products within each class. Data on file.

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

Primary endpoint

Secondary & exploratory endpoints

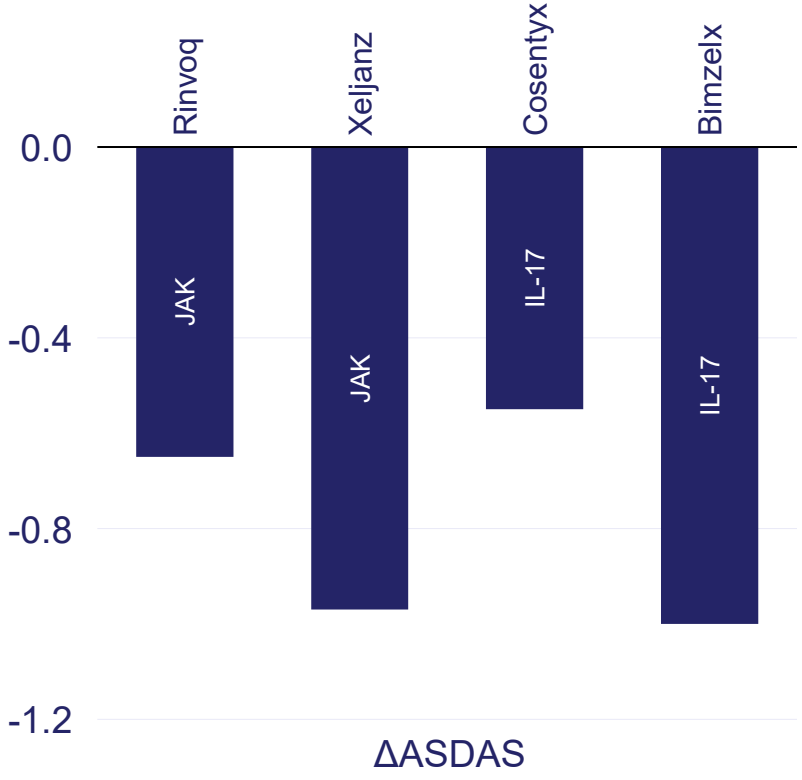


Average ACR and PASI values from pivotal studies of approved products within each class. IL-23 includes IL-12/23. Data on file.

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

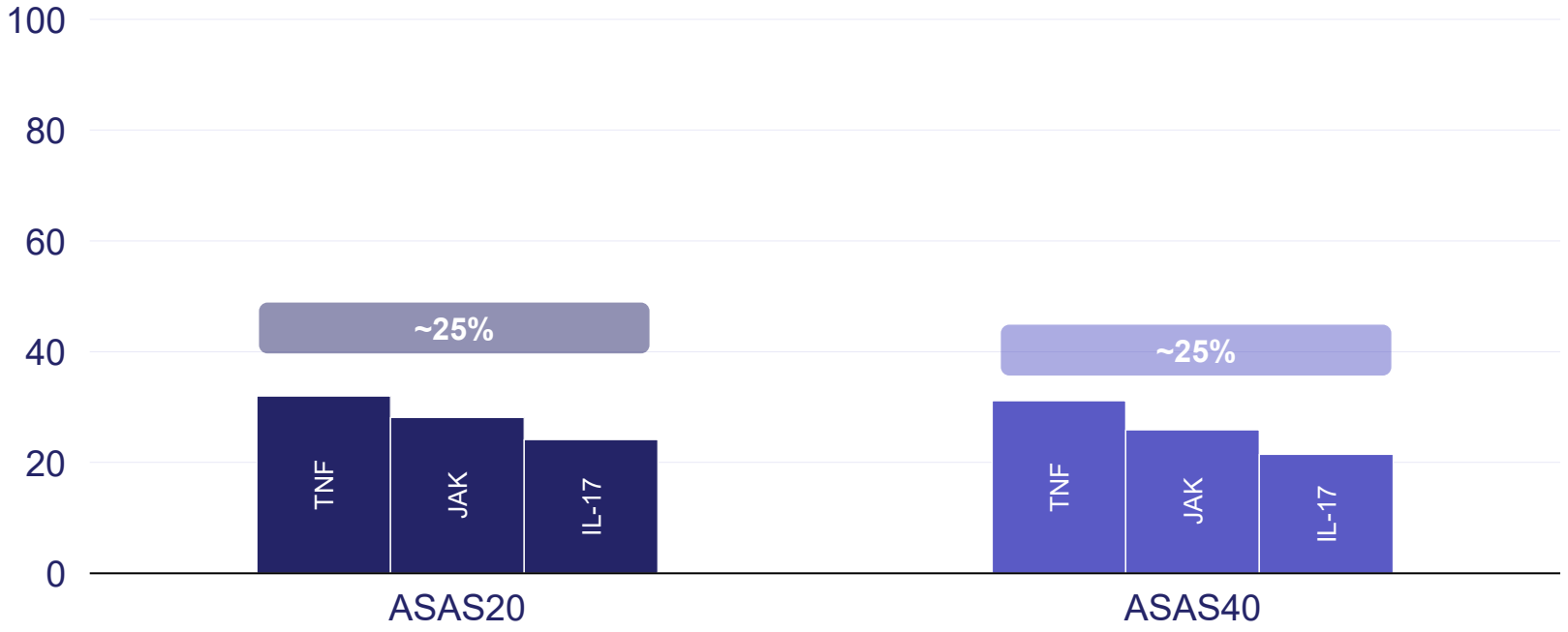
Primary endpoint

Placebo-adjusted ΔASDAS (W12-16)[1]



Secondary & exploratory endpoints

Placebo-adjusted % (W12-16)[2]



[1]Results from studies in mixed populations [2]Average ASAS values from pivotal studies of approved products within each class. Data on file.

Appendix

2026 Milestone Aims

SKYLINE Part A: SPY002

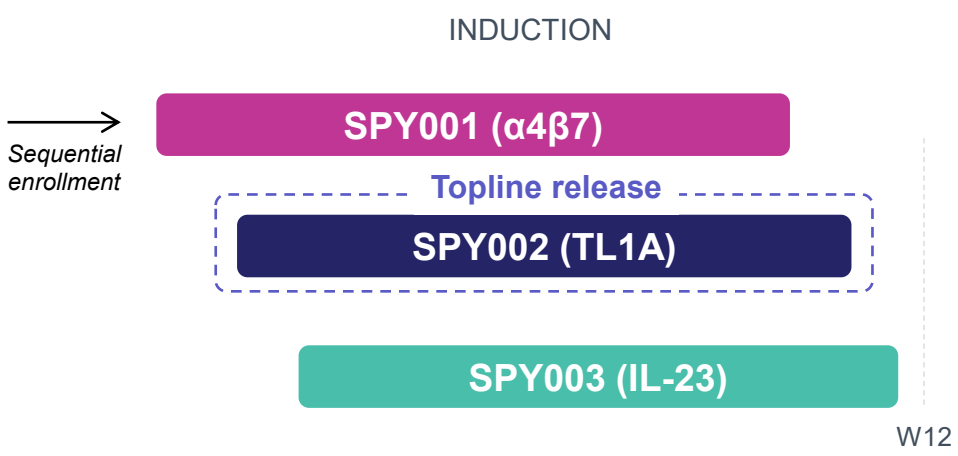
Most recent topline release: SPY002 Part A induction results

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

ΔRHI from baseline

SECONDARY

% Clinical remission

% Endoscopic improvement

Incidence of treatment-emergent adverse events

SPYRE

mMS=modified Mayo Score; RHI=Robarts Histopathology Index. Data pertain to SPY002 Induction Treatment Period. Primary endpoint of ΔRHI was analyzed using per protocol analysis set, and t-test was applied to test against the null hypothesis of ΔRHI =0; Secondary endpoints including Clinical Remission and Endoscopic Improvement rates were analyzed using full analysis set.

Baseline characteristics were consistent with expectations

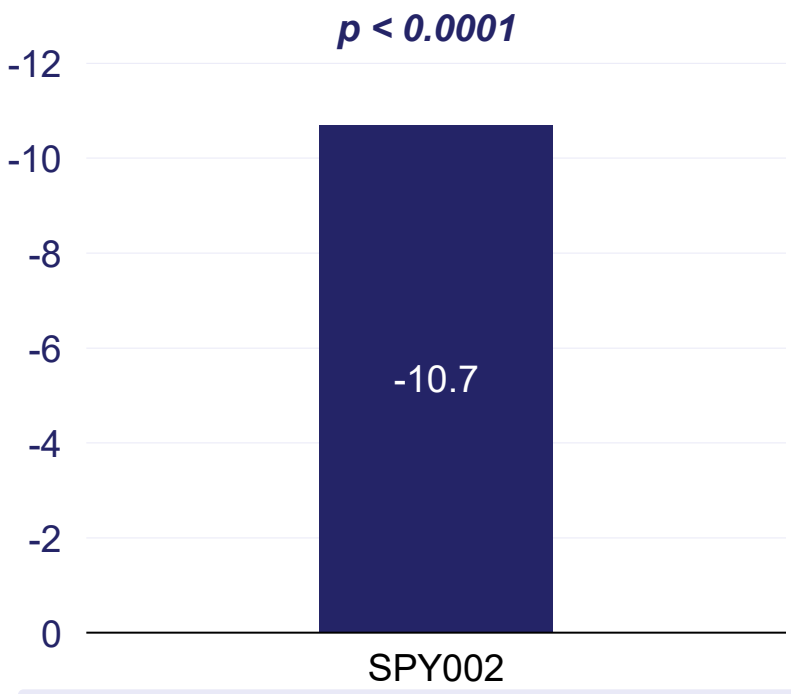
	SPY002 (TL1A), N = 48
Age (years, mean)	45
Sex (% female)	42
Weight (kg, mean)	74
Geographic region Europe North America APAC	 71% 23% 6%
Duration of UC (years, mean)	7.0
RHI (mean ± SD)	16.9 ± 8.5
Baseline mMS (mean ± SD)	6.9 ± 1.0
Mayo Endoscopy Score (MES) (n, %) 2 3	 21 (44%) 27 (56%)
Concomitant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

Source: Data on file. Percentages may not sum to 100% due to rounding.

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

Primary endpoint

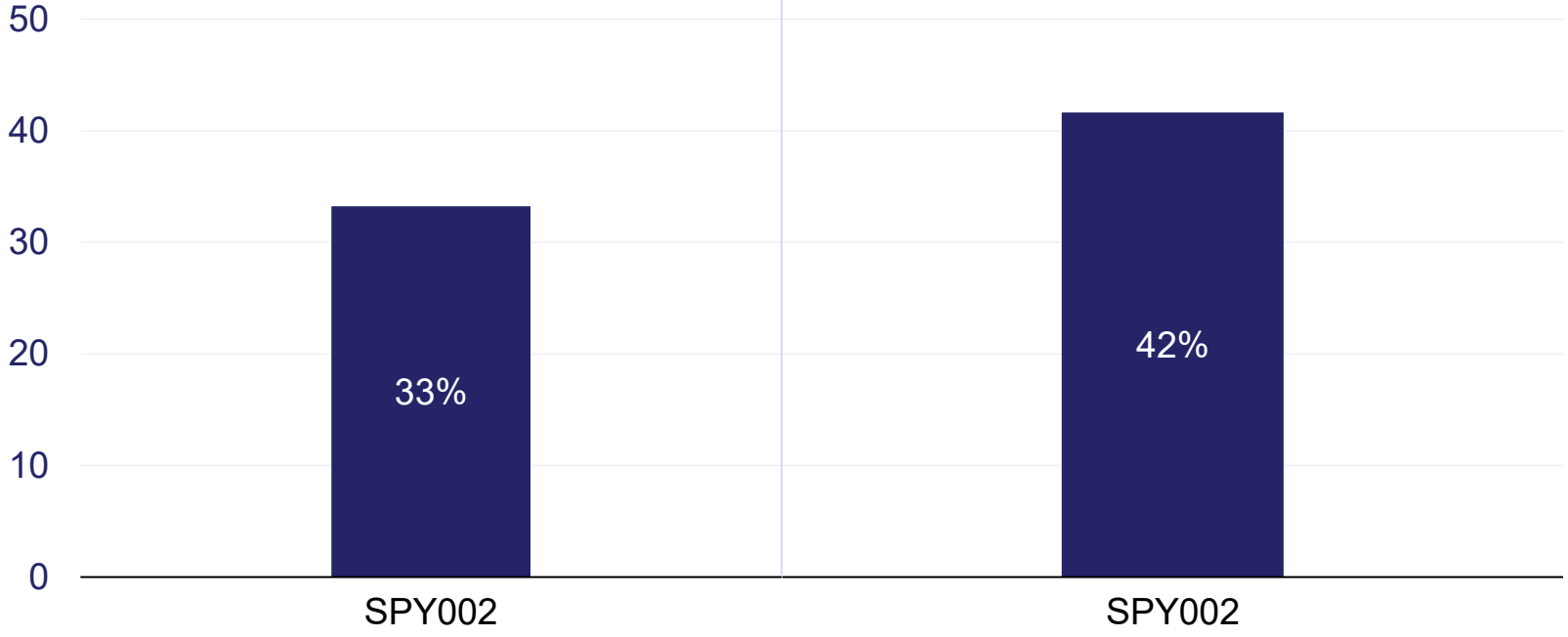
Mean ΔRHI at W12 from baseline



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

Key secondary endpoints

Proportion with clinical remission at W12



Proportion with endoscopic improvement at W12

Source: Data on file. Primary endpoint of ΔRHI was analyzed using per protocol analysis set and t-test was applied to test against the null hypothesis of ΔRHI=0 (N=45); Secondary endpoints including Clinical Remission and Endoscopic Improvement rates were analyzed using full analysis set (N=48).

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)

[1]Hospitalization for exacerbation of UC in one subject, not drug-related
[2]Hospitalization 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
[3]One case each of nausea, hypertension, arthralgia
[4]Exacerbation of UC, not drug-related.
Data pertain to SPY002 Induction Treatment Period.

SPYRE