



CORPORATE OVERVIEW

October 2026



Disclosures



The information contained in this presentation has been prepared by Spyre Therapeutics, Inc. and its affiliates (“Spyre” or the “Company”) and contains information pertaining to the business and operations of the Company. The information contained in this presentation: (a) is provided as at the date hereof, is subject to change without notice, and is based on publicly available information, internally developed data as well as third party information from other sources; (b) does not purport to contain all the information that may be necessary or desirable to fully and accurately evaluate an investment in the Company; (c) is not to be considered as a recommendation by the Company that any person make an investment in the Company; (d) is for information purposes only and shall not constitute an offer to buy, sell, issue or subscribe for, or the solicitation of an offer to buy, sell or issue, or subscribe for any securities of the Company in any jurisdiction in which such offer, solicitation or sale would be unlawful. Where any opinion or belief is expressed in this presentation, it is based on certain assumptions and limitations and is an expression of present opinion or belief only. This presentation should not be construed as legal, financial or tax advice to any individual, as each individual's circumstances are different. This document is for informational purposes only and should not be considered a solicitation or recommendation to purchase, sell or hold a security.

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 therapies for inflammatory bowel disease (IBD), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA) and hidradenitis suppurativa (HS) that are comparable-to-better or meaningfully improve efficacy, safety and dosing profile compared to today's standard of care and our ability to elevate the standard across inflammation and immunology (I&I); the potential for best-in-class monotherapies to provide a foundation for paradigm-changing combinations for IBD; our ability to develop three differentiated combinations and lead in IBD treatment; our ability to achieve the expected benefits or opportunities with respect to our product candidates and combinations thereof, including their target profiles and potential commercialization, and a multi-product category with multiple proof of concept (POC) wins in gastroenterology; 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 our combinations to deliver best-in-disease efficacy, deeper and sustained disease control, and simplified treatment experiences; the potential for each of SPY072 and SPY772 to become a best-in-indication therapy for HS; 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, and SPY772; expected competitors and competing products; our current and planned non-clinical and clinical development activities, including our plans for and timing of cohort initiation, data readouts and clinical enrollment for the ongoing SKYWAY Phase 2 basket trial, SKYLINE Phase 2 platform trial and SKYLIGHT Phase 2 surrogate POC study and planned monotherapy pivotal trial initiation of SPY072 for HS, the number of data readouts expected to be delivered in 2026-2028, development plans for our SPY007 and SPY772 programs and the potential combination and indication expansion of our programs; 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 potential efficacy, tolerability, convenience, commercial viability, dosing and safety profile, their expected benefits in comparison to expected competitor products and their potential best-in-indication product profiles; estimated market sizes and potential growth opportunities; 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. Forward-looking statements can often be identified by the use of words such as “may”, “will”, “could”, “would”, “anticipate”, “believe”, “expect”, “intend”, “potential”, “estimate”, “scheduled”, “plans”, “forecasts”, “goals” and similar expressions or the negatives thereof. Forward-looking statements are neither historical facts nor assurances of future performance. 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 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 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, the 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, and risk factors associated with companies that operate in the biopharma industry, including those associated with the uncertainties of drug development. All of the forward-looking statements made in this presentation are qualified by these cautionary statements and other cautionary statements or other factors contained herein. Although management believes that the expectations conveyed by forward-looking statements herein are reasonable based on information available on the date such forward-looking statements are made, there can be no assurance that forward looking statements will prove to be accurate, as actual results and future events could differ materially from those anticipated in such statements. The Company undertakes no obligation to update forward-looking statements if circumstances or management's estimates or opinions should change except as required by applicable securities laws. The forward-looking statements contained herein are presented for the purposes of assisting readers in understanding the Company's plan, objectives and goals and may not be appropriate for other purposes. The reader is cautioned not to place undue reliance on forward-looking statements.

Industry Information

This presentation also contains or references certain industry data that is based upon information from independent industry publications, market research, and surveys and other publicly available sources. Although the Company believes these sources to be generally reliable, such information is subject to interpretation and cannot be verified with complete certainty due to limits on the availability and reliability of data, the voluntary nature of the data gathering process and other inherent limitations and uncertainties. The Company has not independently verified any of the data from third party sources referred to in this presentation and accordingly, the Company makes no representation or warranty as to the origin, validity, accuracy, completeness, currency or reliability of the information in this presentation.

Building a diversified I&I portfolio across three large markets with high unmet need



Gastroenterology

\$40B+

2030 Global market
for UC and CD



Three potential
first- and best-in-class
combinations in IBD

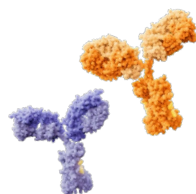


Potential
Multi-product category
with multiple POC wins

Dermatology

\$10B+

2035 Global market
for HS



Potential
first- and/or best-in-class
mono & combo in HS

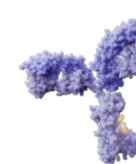


Potential
Indication expansion
following anti-TL1A POC

Rheumatology

\$10B+

2030 Global market
for PsA & axSpA



Potential
first- and best-in-class
anti-TL1A in rheumatology



Potential
Combination expansion
following anti-TL1A POC

Advancing a robust pipeline with exceptional financial strength

Therapeutic area	Indication	Program	Target	Phase 1	Phase 2	Phase 3	Anticipated Milestones
 Gastroenterology	UC	SPY120	α4β7 + TL1A				 2027: Ph2 POC
		SPY130	α4β7 + IL-23				
		SPY230	TL1A + IL-23				
		SPY001	α4β7				
		SPY002	TL1A				
		SPY003	IL-23				
 Dermatology	HS	SPY072	TL1A				2027: Pivotal trial initiation  Late '27/ Early '28: Ph2 POC²
		SPY772	TL1A + IL-17A/F				
 Rheumatology	PsA	SPY072	TL1A				 4Q 2026: Ph2 POC
	axSpA						

\$1.5 billion in proforma cash as of June 30, 2026¹, with expected runway into 2H 2029

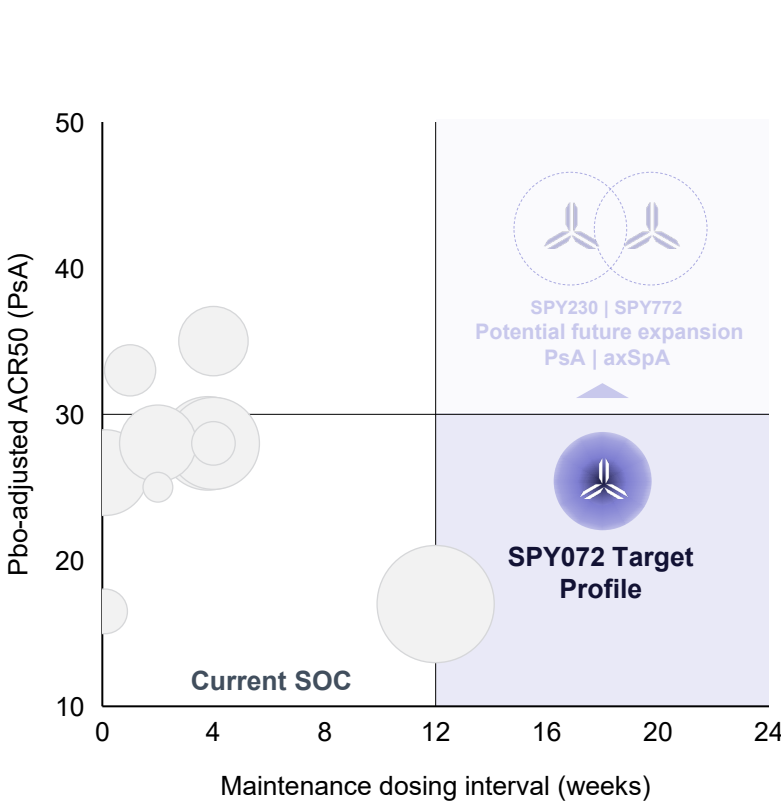
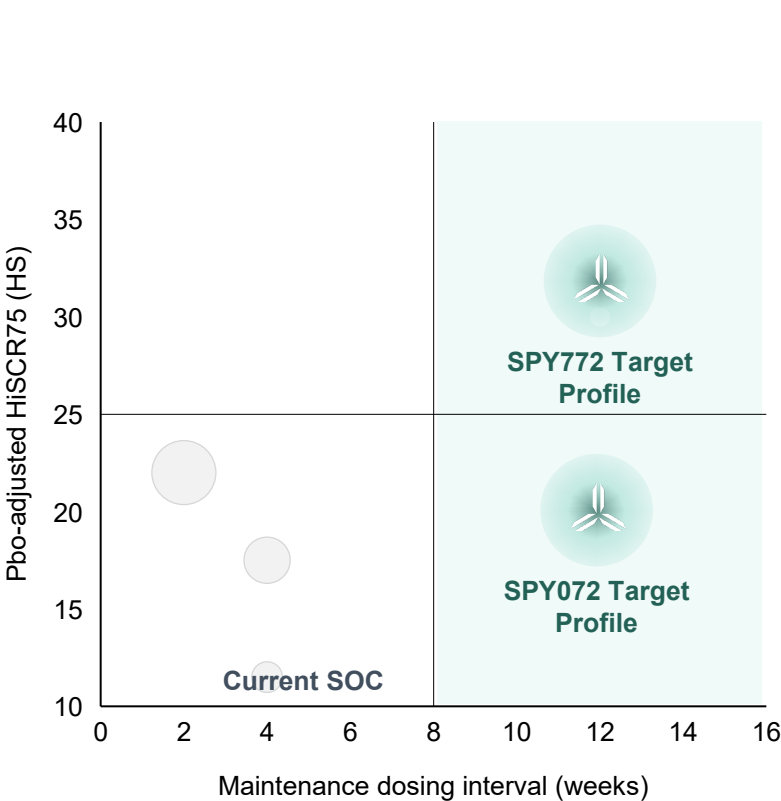
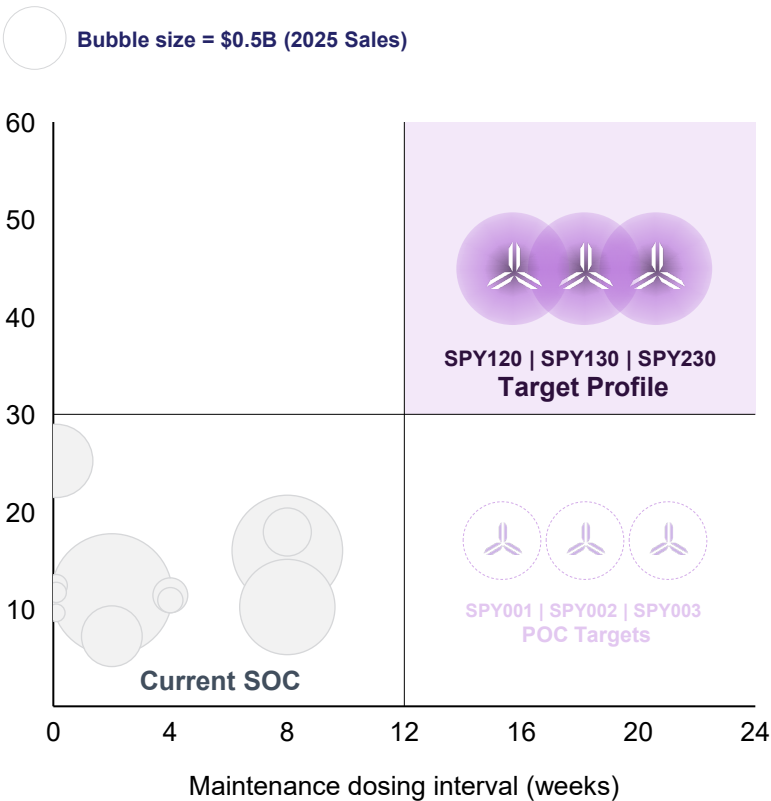
Spyre programs aim to elevate the standard on efficacy, safety, and dosing across I&I



Gastroenterology

Dermatology

Rheumatology



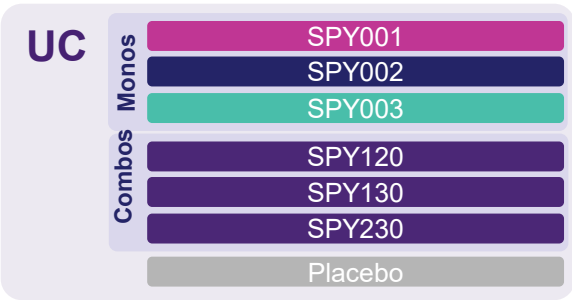
Multiple Ph2 POC readouts across GI, dermat, and rheum over the next ~18 months, plus an HS pivotal trial starting in 2027



Gastroenterology



Ph2 platform trial evaluating SPY001, SPY002, SPY003 and all pairwise combinations in UC



2027 (6 readouts)
Expected monotherapy and combination POC

Dermatology



Ph2 surrogate POC trial evaluating SPY072 + bimekizumab for the SPY772 combination program in HS



Late 2027 / Early 2028
Planned combination POC

PIVOTAL

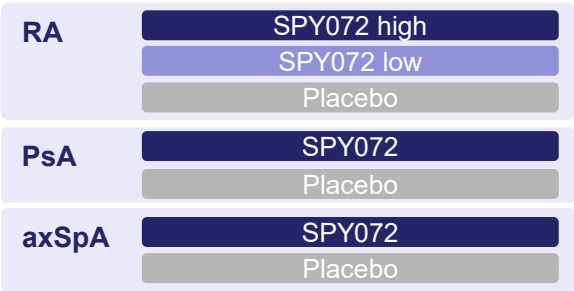
Pivotal trial evaluating SPY072 monotherapy in HS; design to be announced

2027
Planned monotherapy pivotal initiation

Rheumatology



Ph2 basket trial evaluating SPY072 in RA, PsA, and axSpA



RA POC did not meet bar to advance

4Q 2026 (PsA/axSpA)
Expected monotherapy POC



Gastroenterology

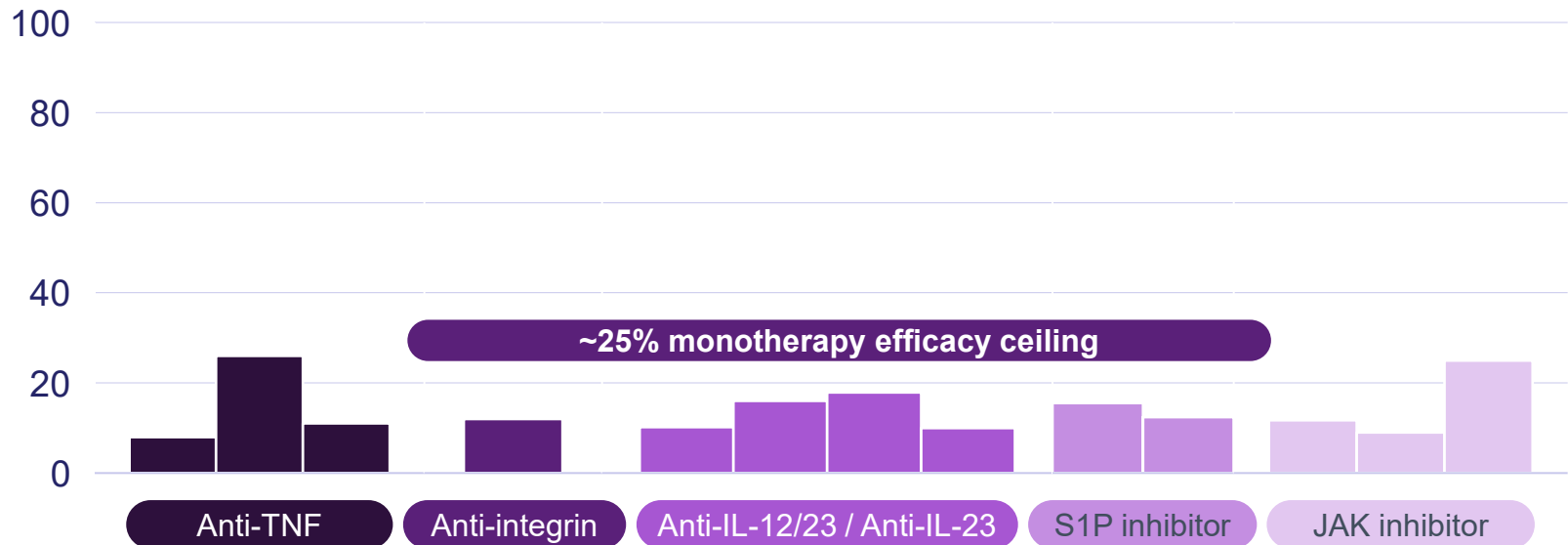
UC CD	 SPY120  SPY130  SPY230	 SKYLINE
Target markets	Key programs	Trials

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



- ~2.4M individuals in the U.S. have been diagnosed with IBD (~1.3M UC & ~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)

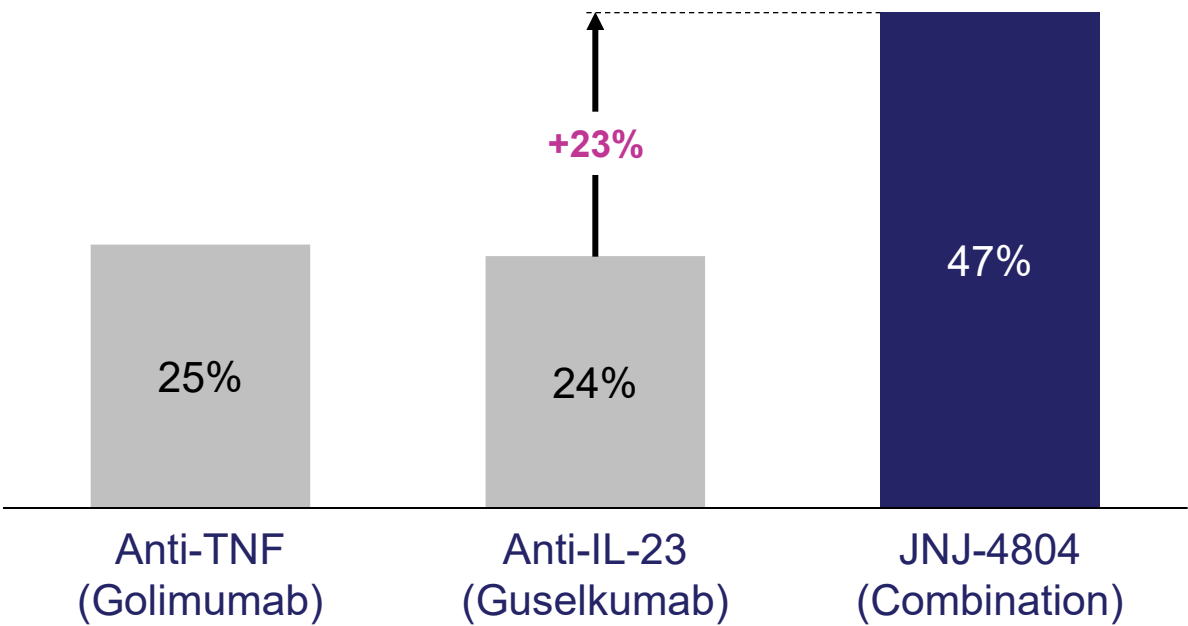


JNJ's VEGA and DUET studies demonstrated the ability for combinations to break the monotherapy efficacy ceiling



Naïve (1L) UC patients (VEGA)

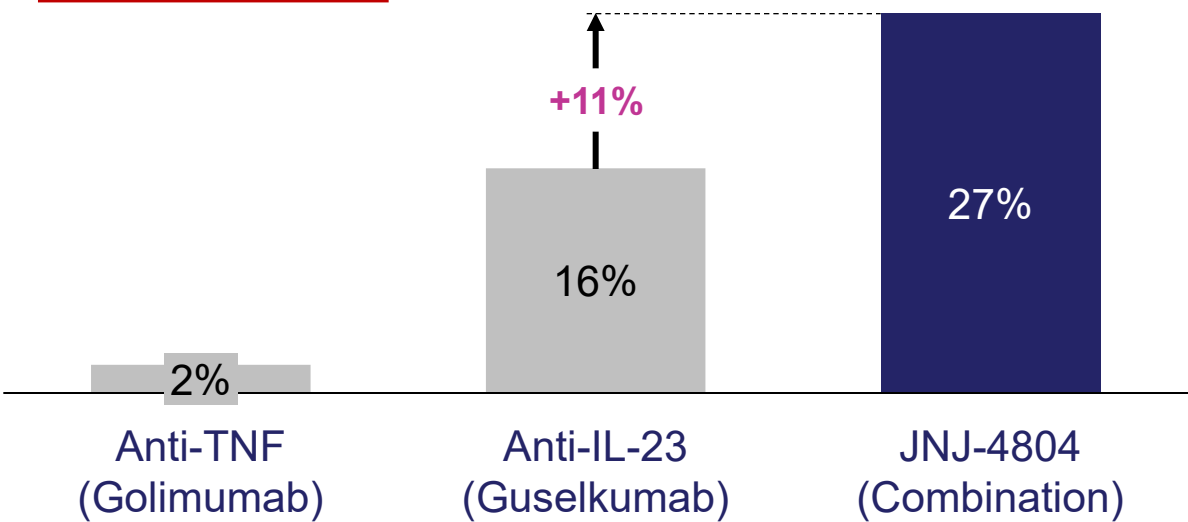
~Additive absolute W12 mMS clinical remission rate



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

Synergistic absolute W48 mMS clinical remission rate

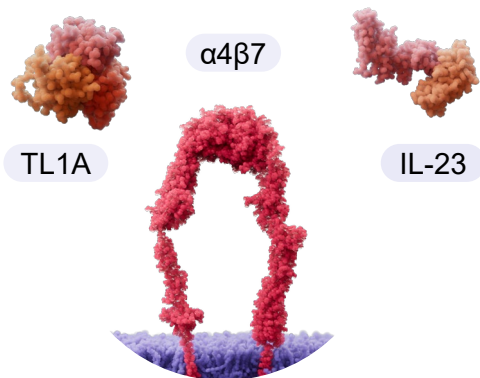
- 74% of patients were refractory to anti-TNF
- 1% were refractory to anti-IL-23



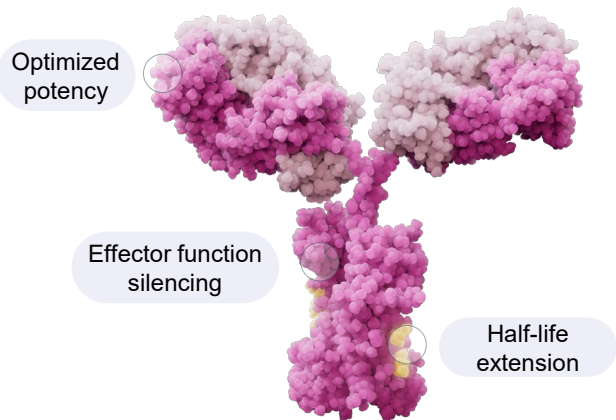
Spyre is unique in developing uncompromising combinations from first principles



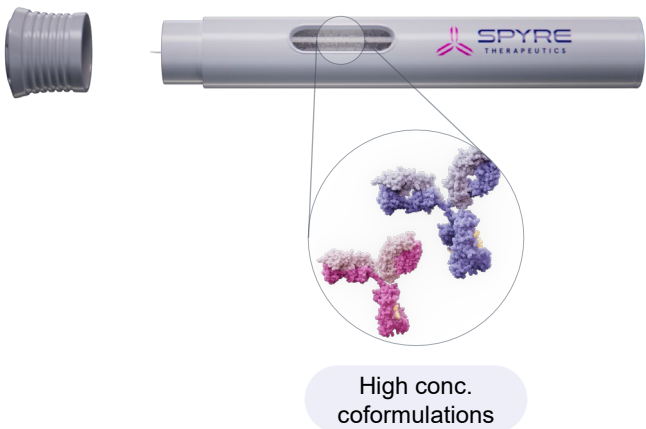
Orthogonal MOAs rationally chosen based on attractive risk-benefit profiles



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



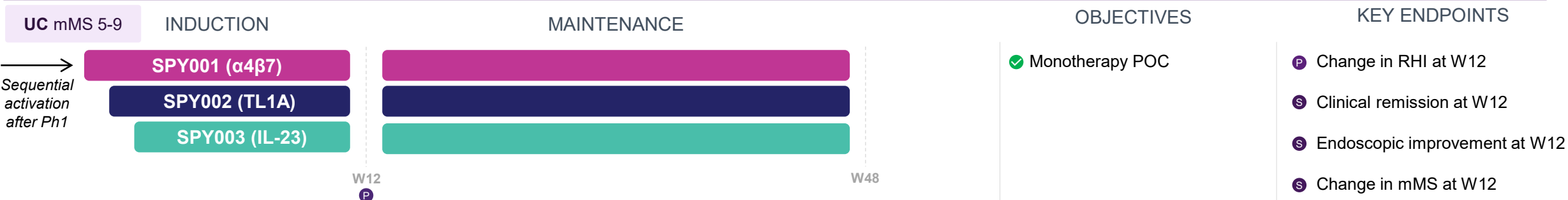
Developing coformulations optimized for infrequent, SC delivery



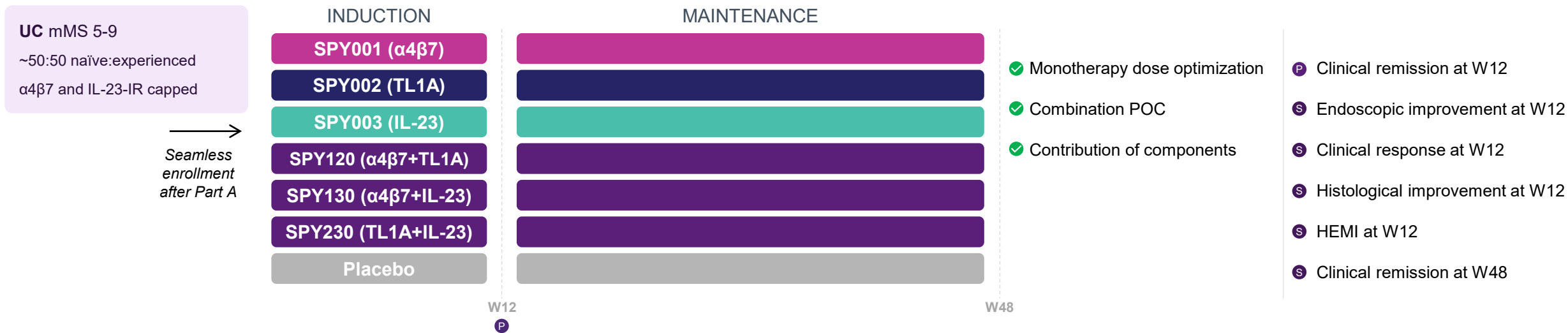
SKYLINE is a two-part study, with Part B combination evaluation now enrolling



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



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



Monotherapies met all objectives in SKYLINE Part A, progressing Spyre’s differentiated combination approach



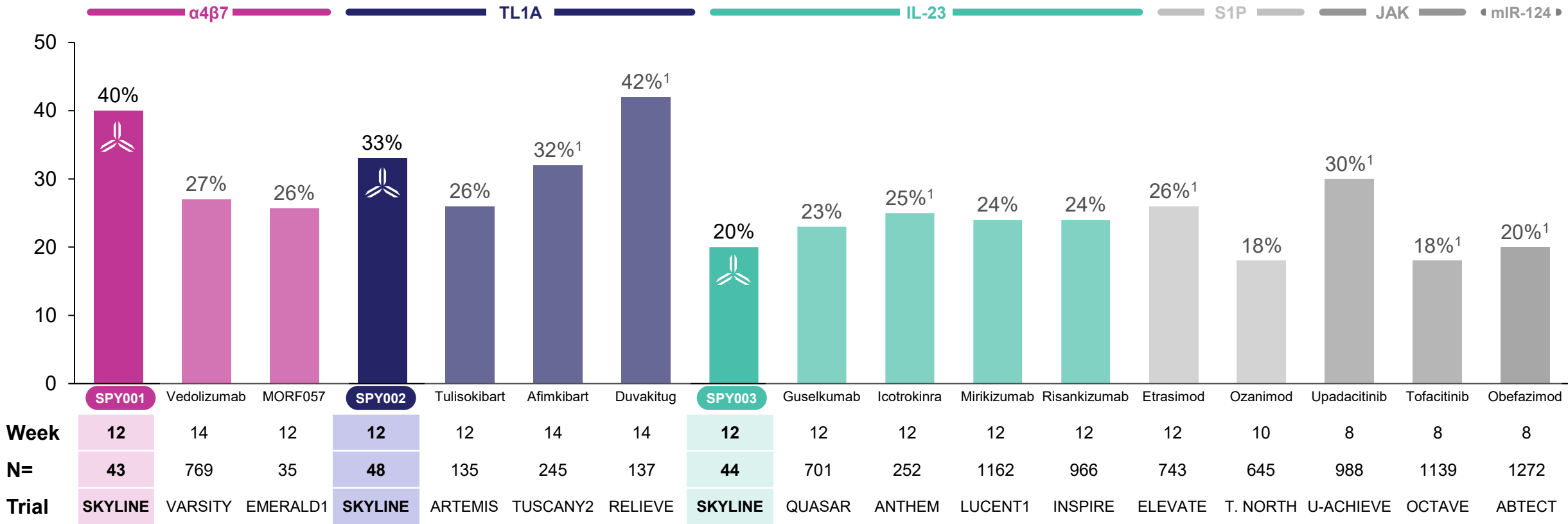
	SPY001	SPY002	SPY003	Combinations
PART A PRIMARY				
ΔRHI from baseline	-9.2	-10.7	-10.0	
PART A SECONDARY				
% Clinical remission	40%	33%	20%	2027
% Endoscopic improvement	51%	42%	30%	Objective: Deeper, sustained disease control & simplified treatment experience
ΔmMS from baseline	-3.7	-3.7	-3.5	
Safety	Consistent with class	Consistent with class	Consistent with class	
	✓	✓	✓	
Developing therapies to elevate the standard for inflammatory bowel disease				

SPY001, SPY002, and SPY003 demonstrated robust rates of clinical remission



Clinical remission

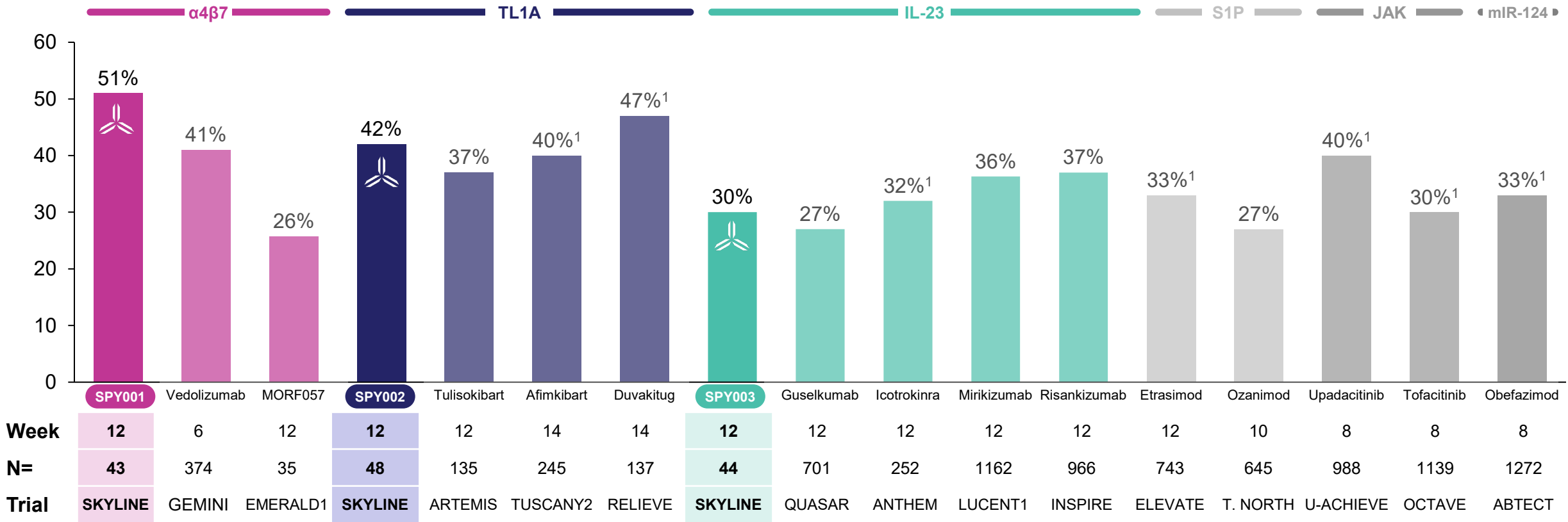
Percentage of subjects



SPY001, SPY002, and SPY003 endoscopic improvement rates are among the highest reported



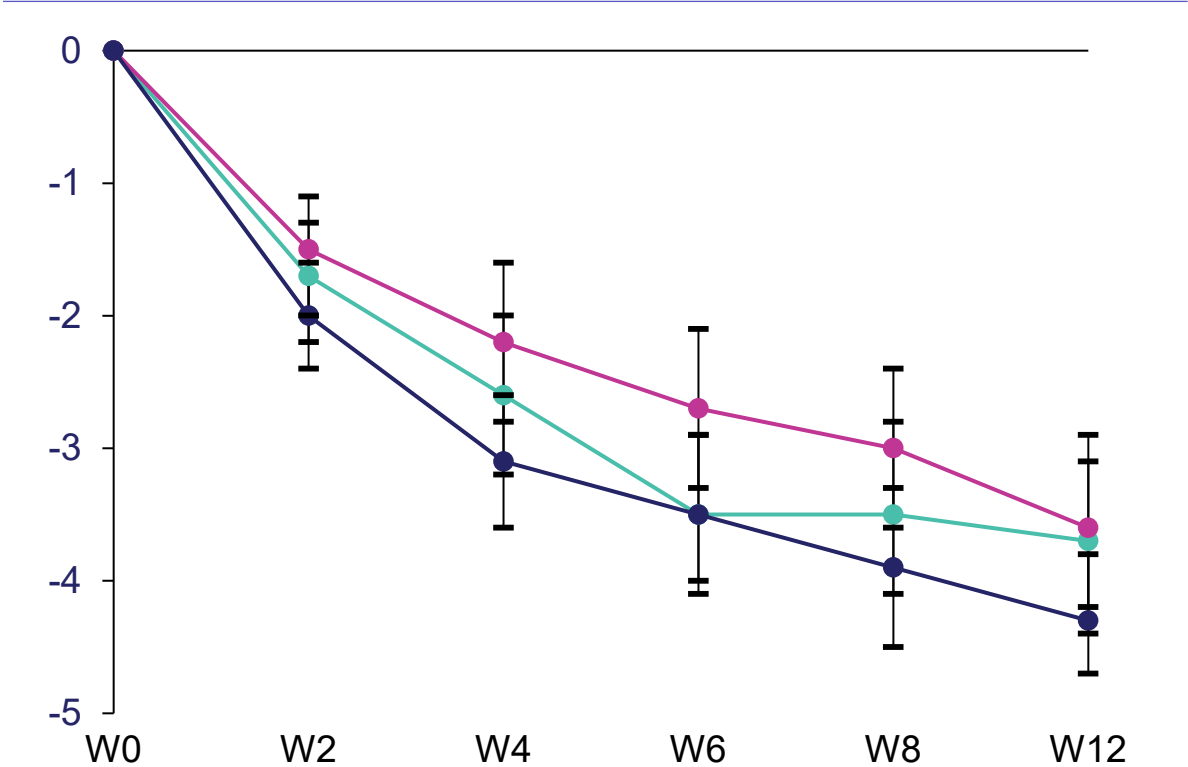
Endoscopic improvement Percentage of subjects



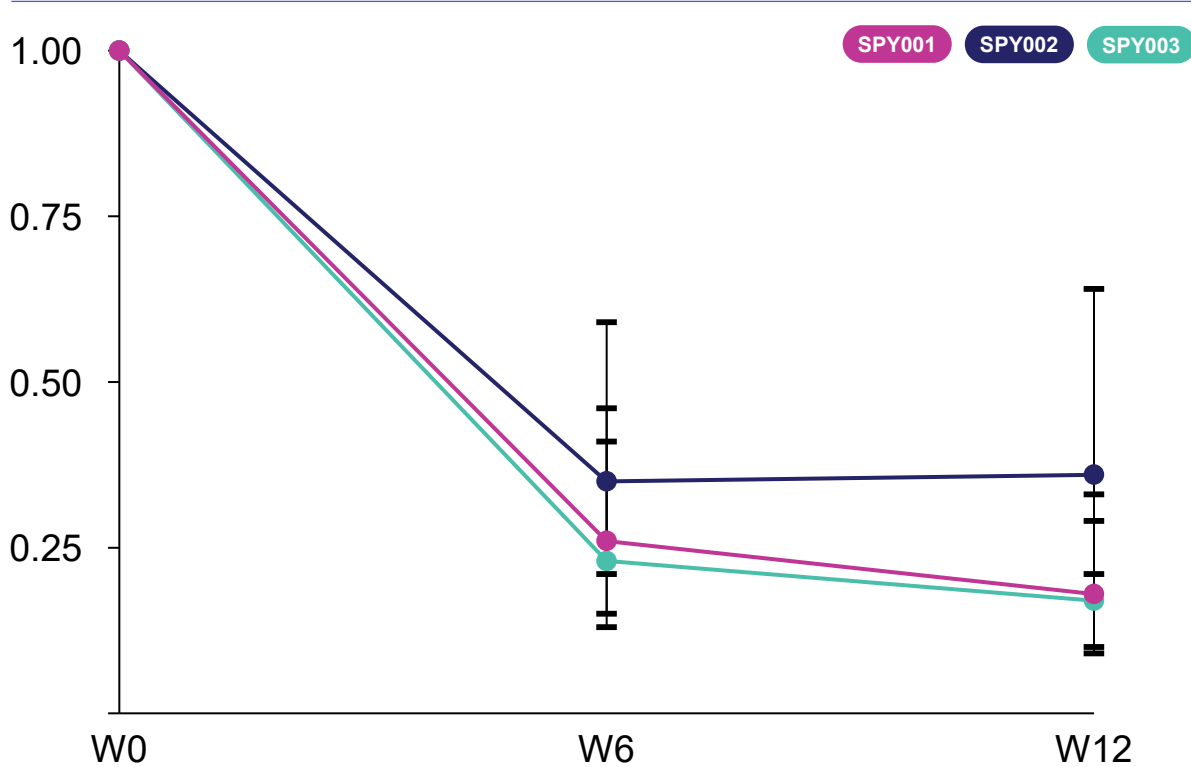
SPY001, SPY002, and SPY003 performed similarly on change in partial Mayo score and fecal calprotectin over time



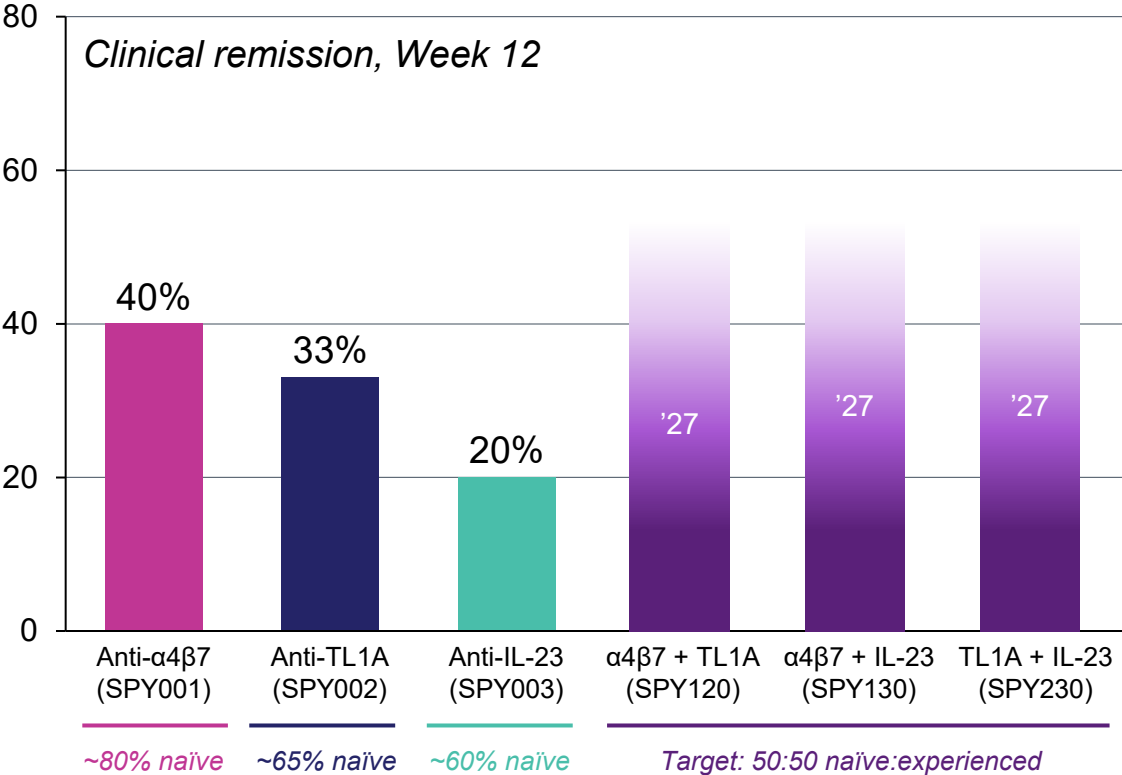
Partial Mayo score ($\Delta \pm 95\%$ CI)



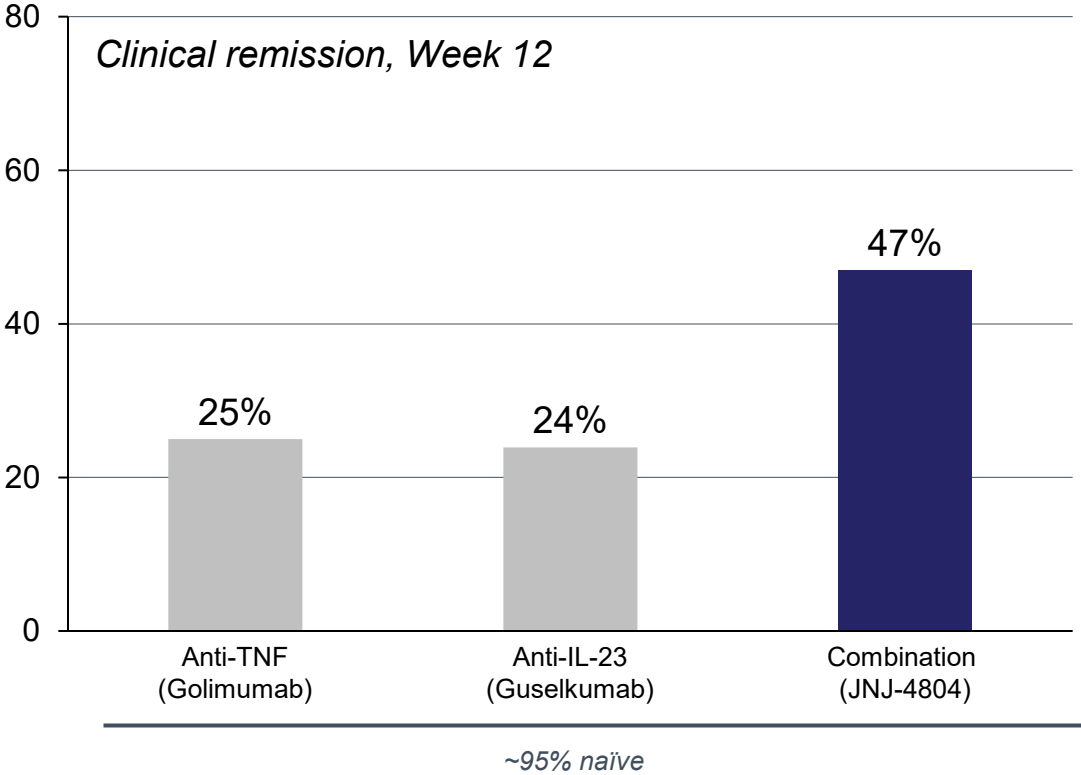
Fecal calprotectin (fold $\Delta \pm 95\%$ CI)



Monotherapy 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

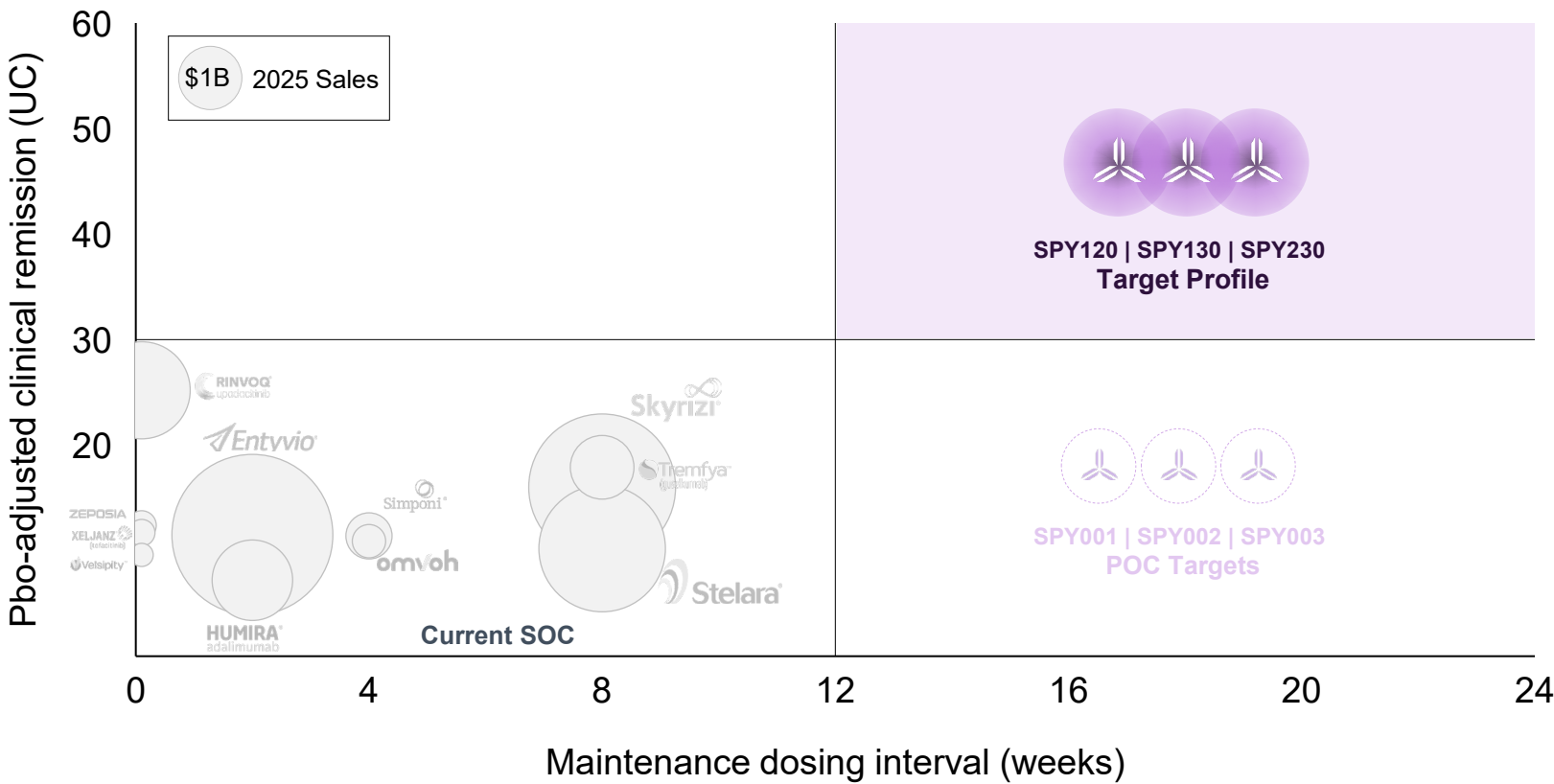


Sponsor	Program	MOAs	Target Profile	1-m	2	3	4	5	6	7	8	9	10	11	12
	SPY120	$\alpha 4\beta 7$ +TL1A	Q3M-Q6M AI												
	SPY130	$\alpha 4\beta 7$ +IL-23	Q3M-Q6M AI												
	SPY230	TL1A+IL-23	Q3M-Q6M AI												
	JNJ-4804	TNF+IL-23	Q4W AI												
	Skyrizi + ABBV382	$\alpha 4\beta 7$ +IL-23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



Dermatology

HS

Target markets



SPY072



SPY772

Key programs



SKYLIGHT

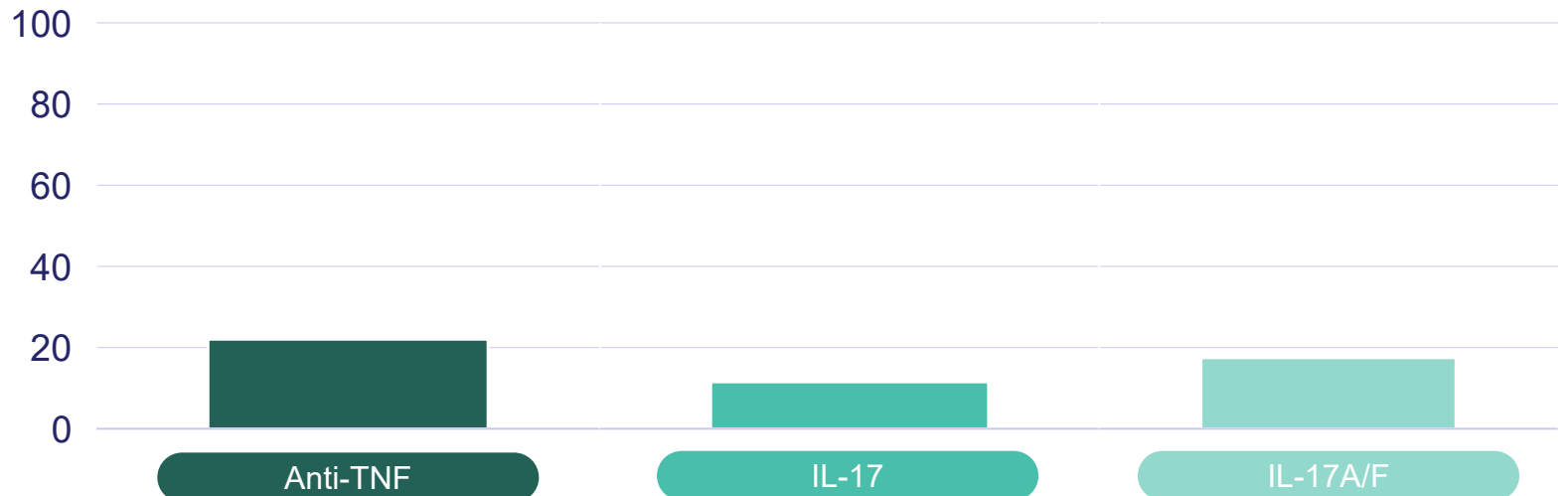
Trials

Hidradenitis suppurativa remains underdiagnosed and inadequately controlled, creating substantial lifelong burden



- HS is a chronic, recurrent inflammatory skin disease estimated to affect ~3M U.S. patients, though estimates vary widely and diagnosis is often delayed by 7-10 years
- Substantial unmet need remains due to:
 - Persistent pain, flares, draining tunnels, and irreversible scarring, even among treated patients
 - Limited ability to achieve durable control across the full spectrum of disease
 - Complex treatment journeys involving antibiotics, biologics, procedures, and surgery
 - Profound effects on quality of life, mental health, relationships, and work productivity

HS placebo-adjusted HiSCR75 by MOA (W12-16)

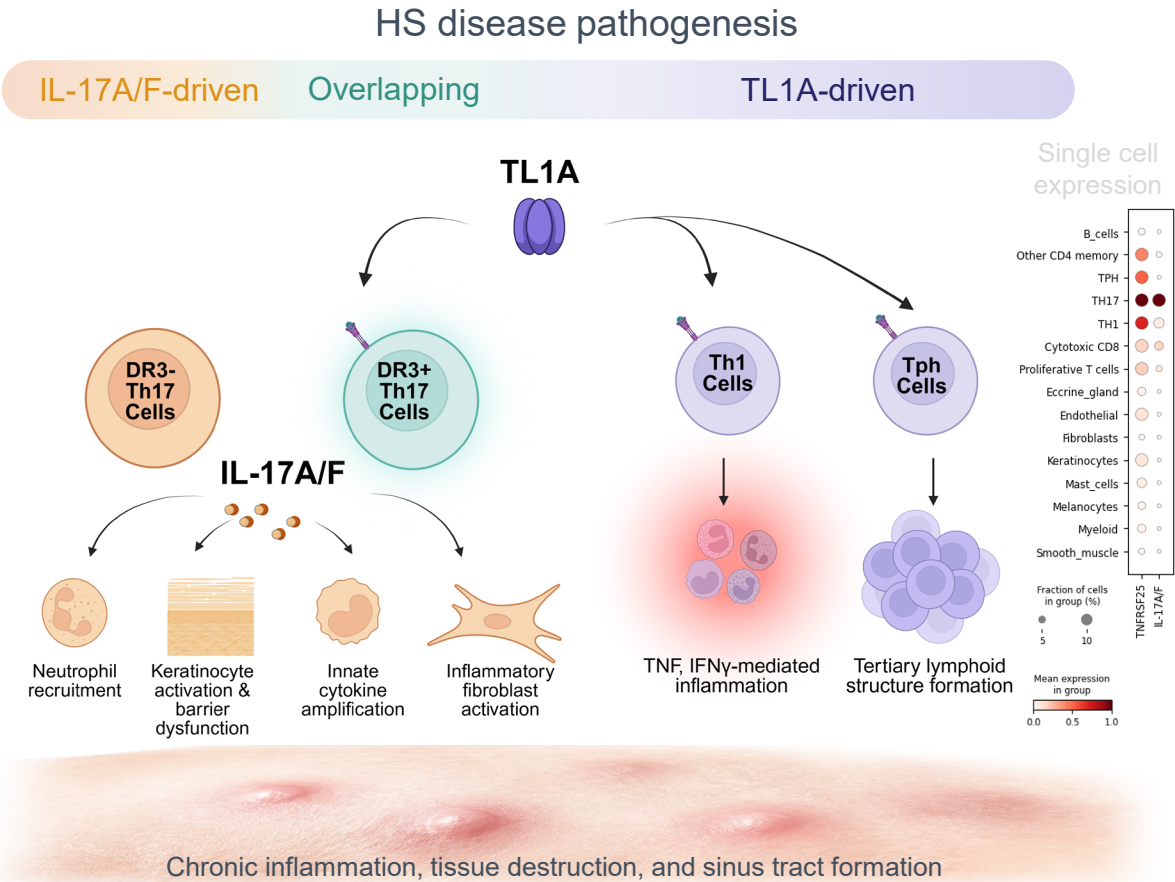
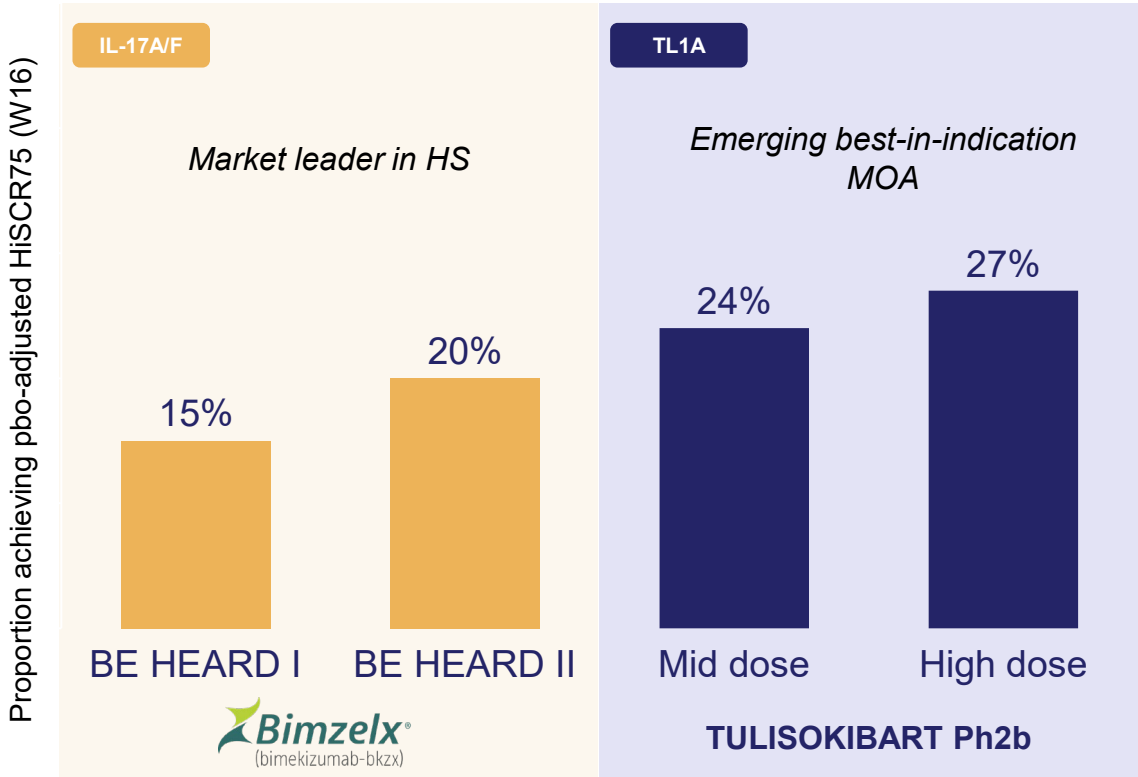


Our approach: Dual targeting of clinically validated TL1A & IL-17A/F pathways to address complementary drivers of HS



TL1A and IL-17A/F are clinically validated targets in HS

Biological & translational rationale for TL1A + IL-17A/F in HS

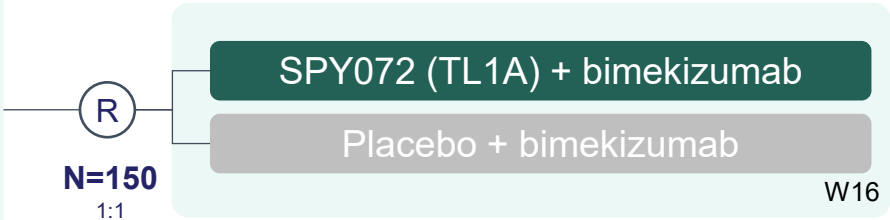


SKYLIGHT is a Phase 2 study evaluating dual inhibition of TL1A and IL-17A/F



SKYLIGHT

- Participants with moderate to severe HS**
- 18-75 years of age
 - HS lesions in ≥ 2 anatomical areas, with ≥ 1 area meeting Hurley Stage II or III criteria
 - AN count ≥ 5
 - ≤ 20 draining tunnels
 - Planning to initiate advanced SOC treatment (bimekizumab)



STUDY OBJECTIVE

- ✓ Combination efficacy and safety versus bimekizumab monotherapy

PRIMARY ENDPOINT

HiSCR75 at Week 16

KEY SECONDARY

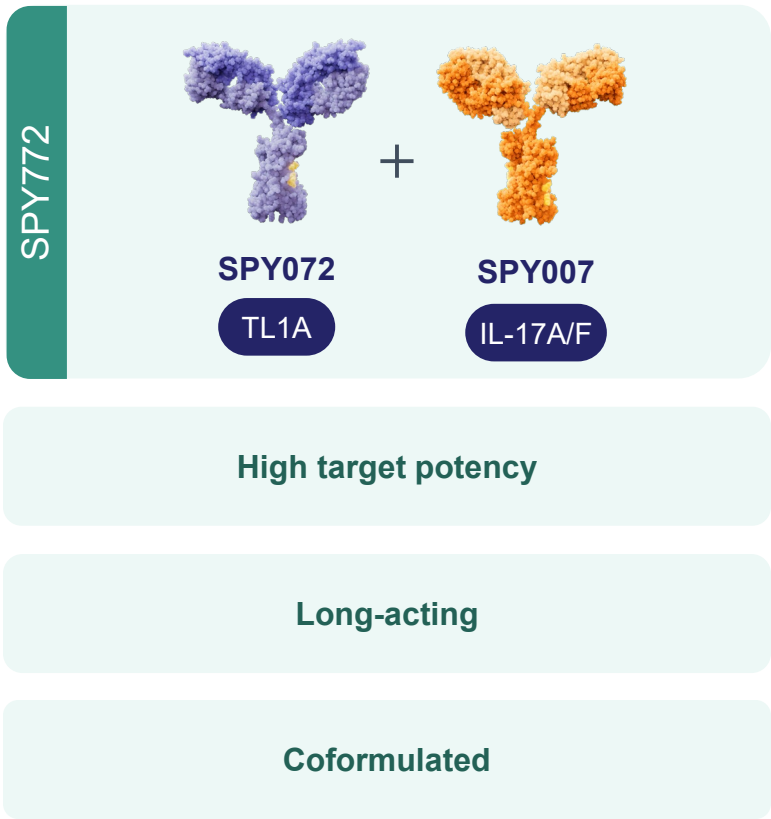
HiSCR50 at W16

SKYLIGHT aims to provide early POC for dual TL1A + IL-17A/F inhibition, POC results expected in late '27 / early '28

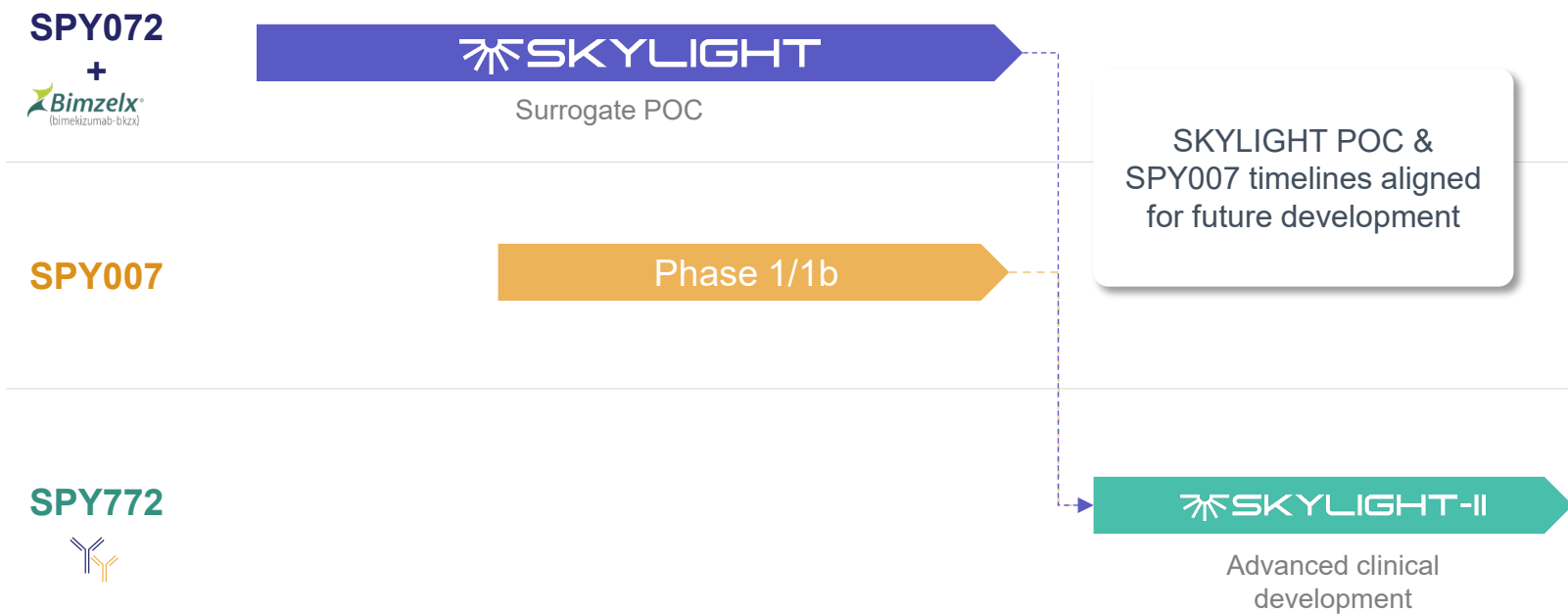
SPY772 combines our novel anti-TL1A and anti-IL-17A/F antibodies



SPY772 design principles



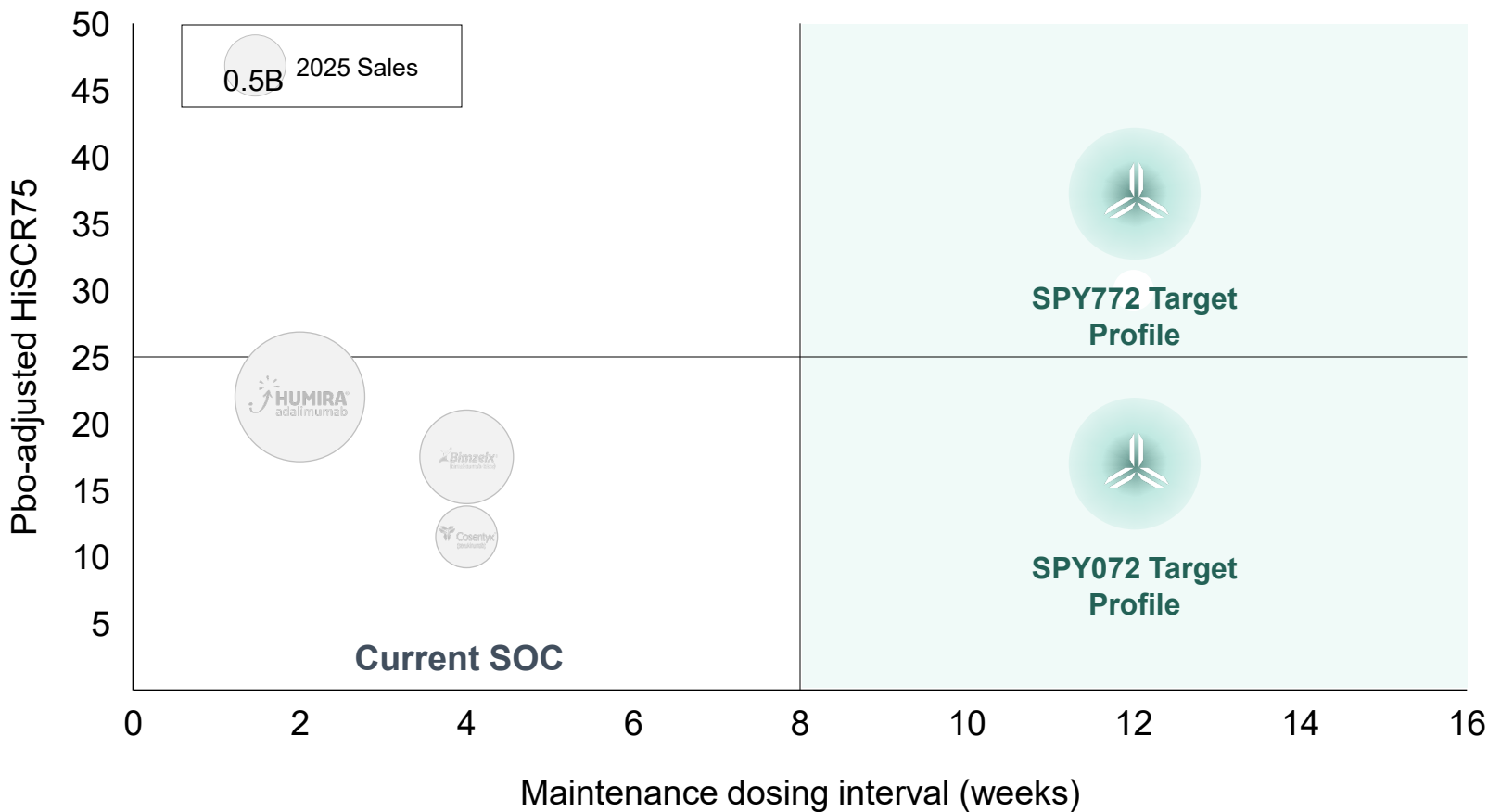
SPY772 development strategy



SPY772 has the potential to become a best-in-indication therapy for HS



Potential for best-in-indication positioning



SPY772 target product profile

Meaningfully improved efficacy vs. standard of care

Favorable safety profile
No black box warning

Q3M maintenance dosing



Rheumatology

PsA

axSpA

Target markets



SPY072



SPY772



SPY230

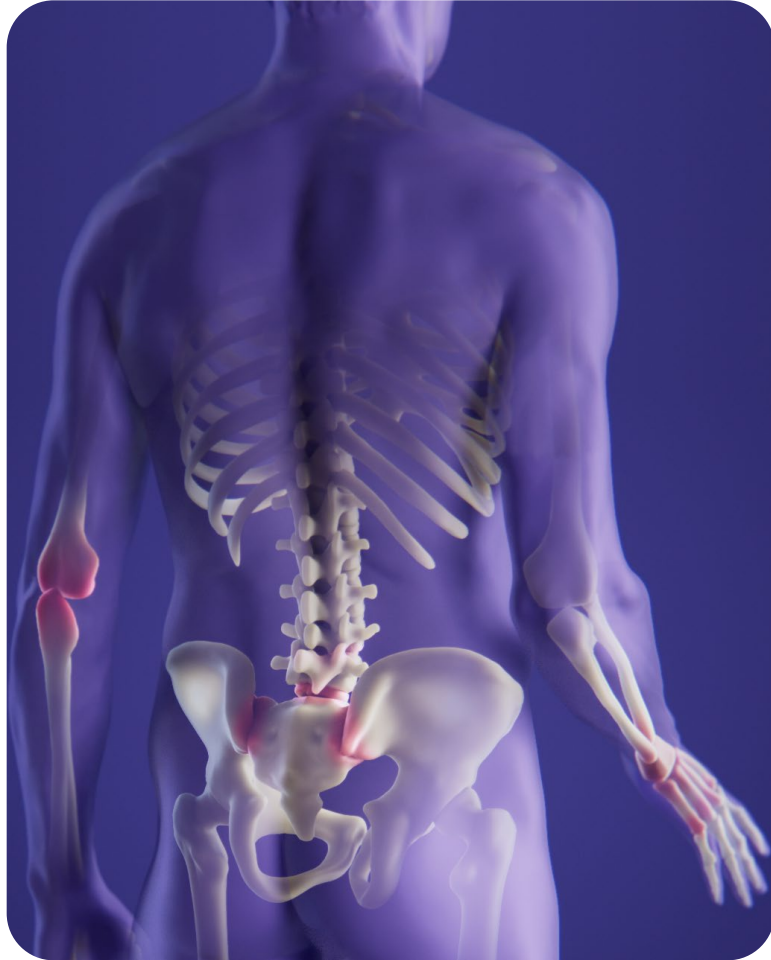
Key programs



SKYWAY

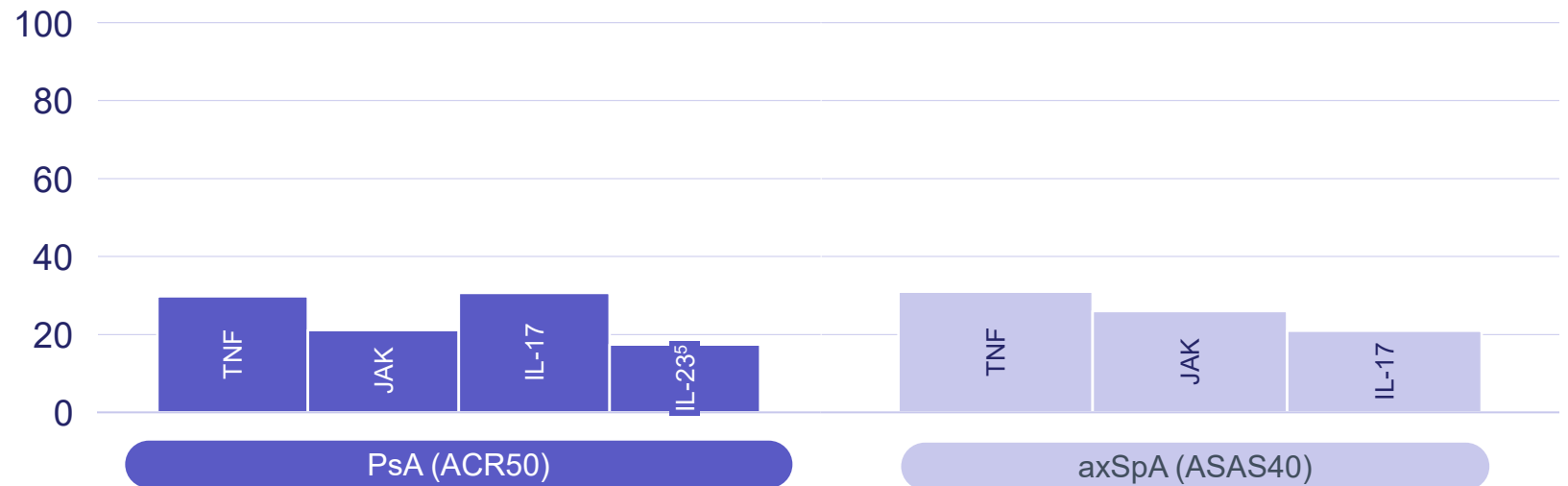
Trials

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



- ~2M individuals in the U.S. have been diagnosed with PsA (~1M¹), 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

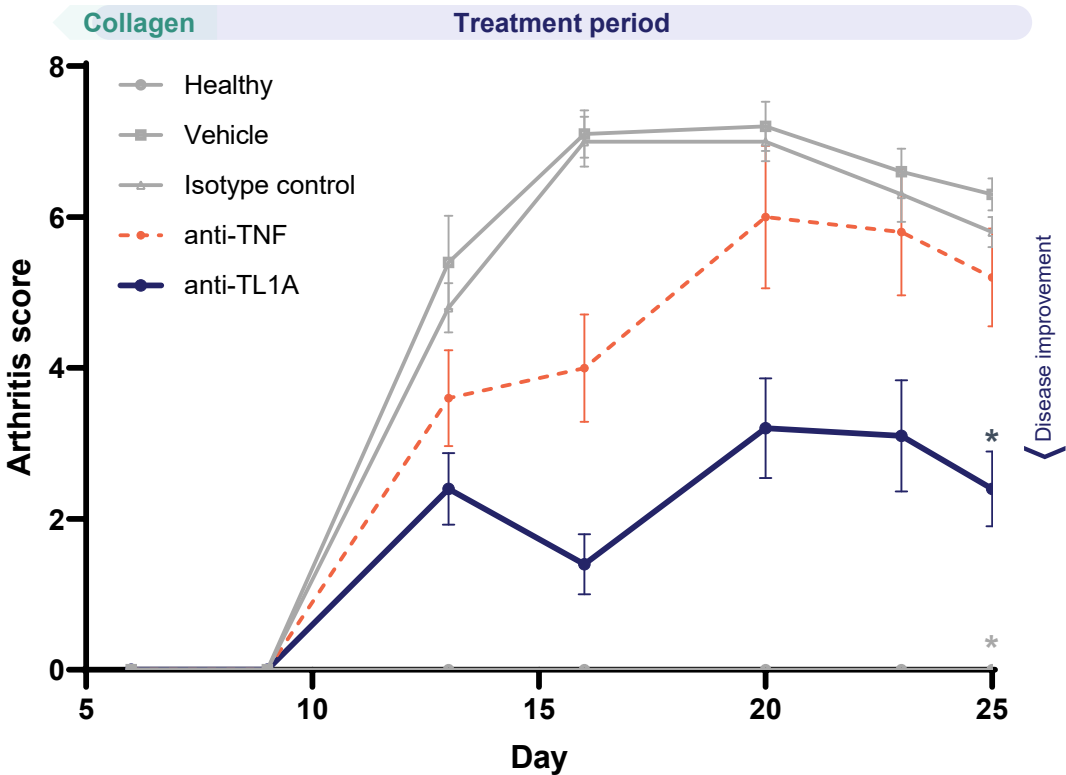
Placebo-adjusted efficacy rates by MOA (W24⁴)



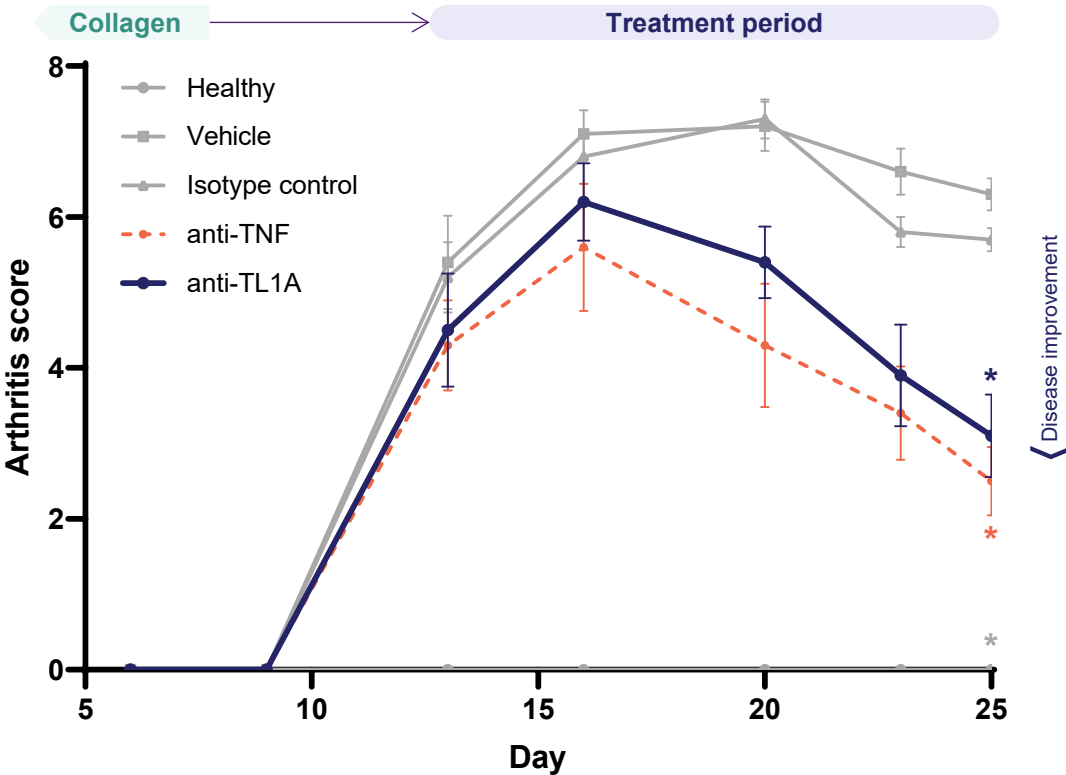
Spyre anti-TL1A antibody meets or exceeds the efficacy of etanercept (anti-TNF) in rat models of arthritis



Superior efficacy in semi-preventative model



Comparable efficacy in therapeutic model

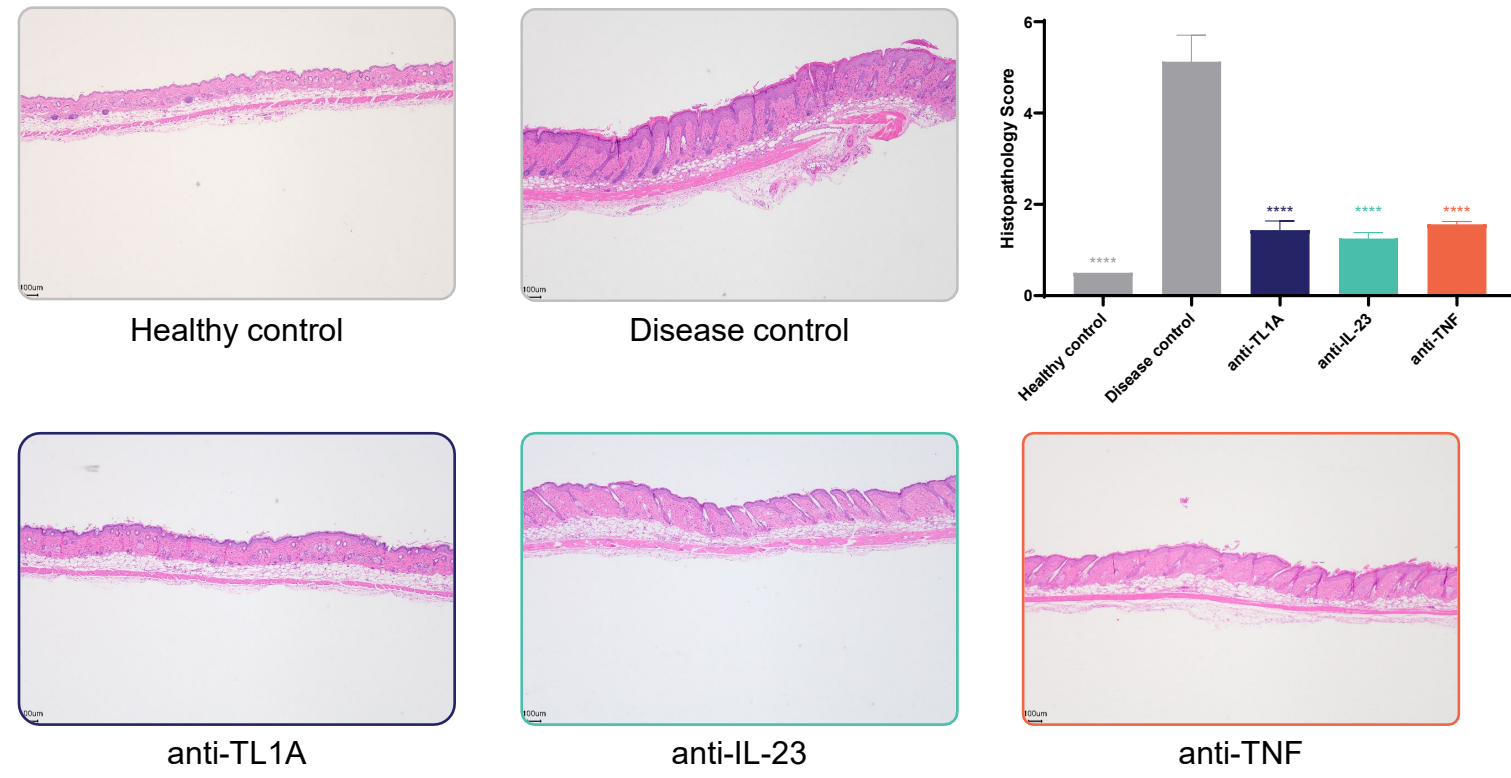
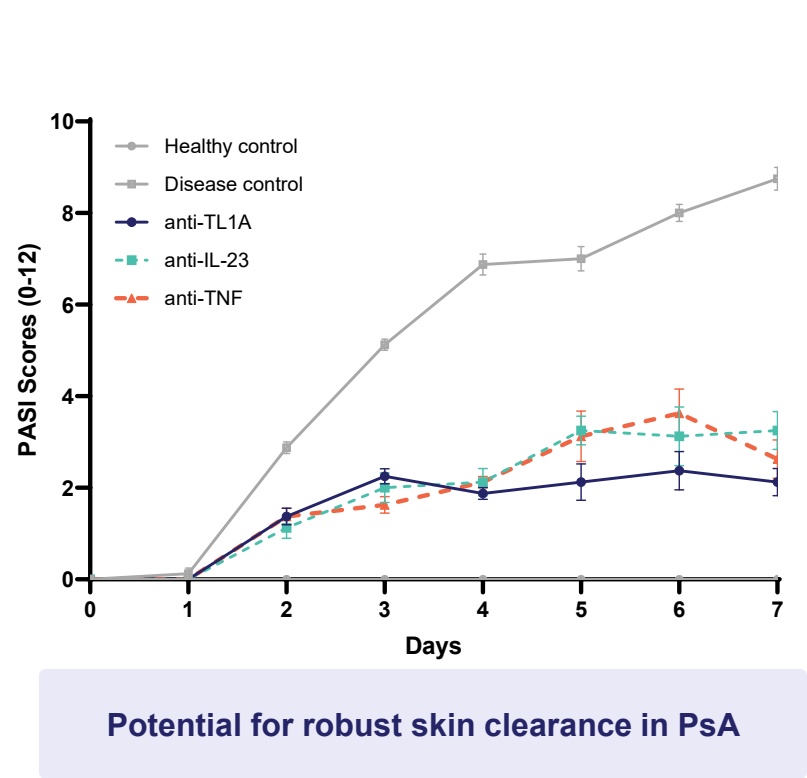


Additionally, anti-TL1A treatment led to comparable improvements in psoriatic skin lesions in mouse IMQ model



Anti-TL1A reduces skin lesions

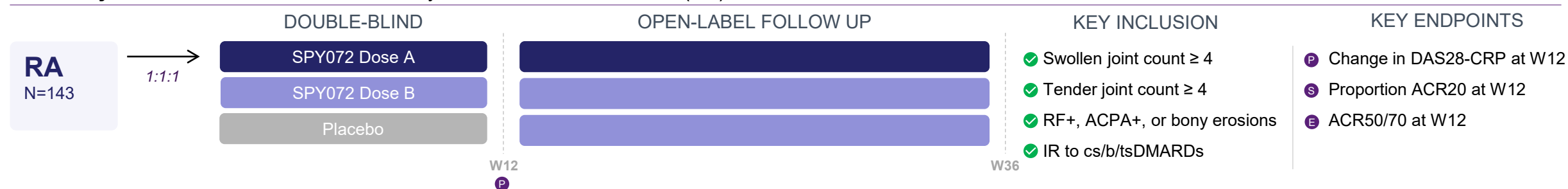
Comparable efficacy to anti-IL-23 and anti-TNF



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



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



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



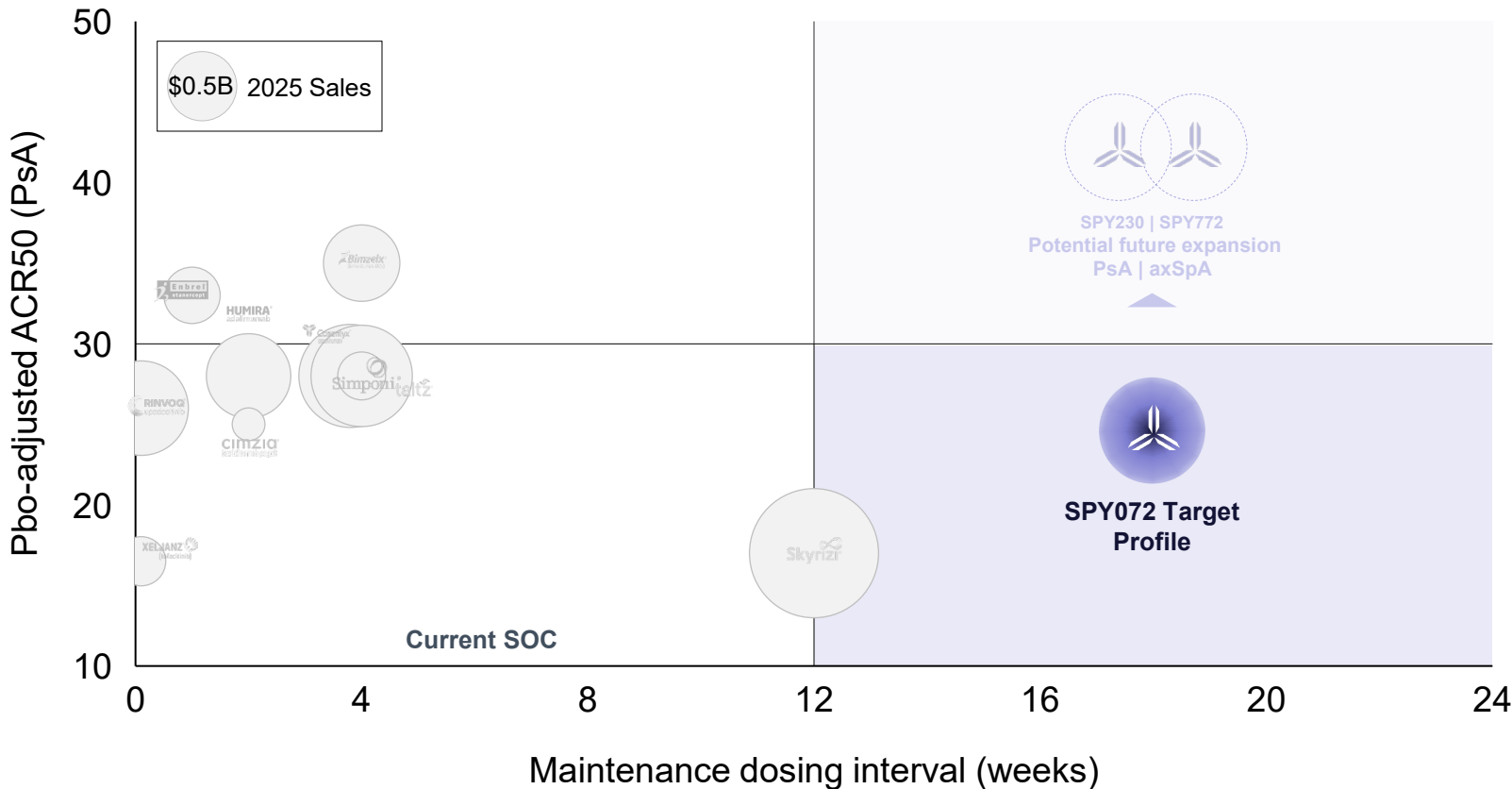
Sub-study C: SPY072 in moderate-to-severely active axial spondyloarthritis (axSpA)



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



Potential for best-in-indication positioning



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



Therapeutic area	2026	2027
 Gastroenterology SKYLINE Part A	✓ SPY001 α4β7 Ph2 UC induction POC ✓ SPY002 TL1A Ph2 UC induction POC ✓ SPY003 IL-23 Ph2 UC induction POC (Sept. 2026)	□ SPY001 α4β7 Ph2 UC maintenance data □ SPY002 TL1A Ph2 UC maintenance data □ SPY003 IL-23 Ph2 UC maintenance data
 Gastroenterology SKYLINE Part B	✓ Initiate SKYLINE Part B enrollment	□ SPY120 α4β7 + TL1A Ph2 UC induction POC □ SPY130 α4β7 + IL-23 Ph2 UC induction POC □ SPY230 TL1A + IL-23 Ph2 UC induction POC □ SPY001 SPY002 SPY003 monotherapy comparators
 Dermatology	✓ Initiate SKYLIGHT enrollment	□ SPY772 TL1A + IL-17 Ph2 surrogate POC (late '27 / early '28) □ SPY072 TL1A pivotal trial initiation NEW
 Rheumatology	✓ SPY072 TL1A Ph2 W12 POC in RA □ SPY072 TL1A Ph2 W16 POC in PsA (4Q 2026) □ SPY072 TL1A Ph2 W16 POC in axSpA (4Q 2026)	□ SPY072 TL1A Ph2 maintenance data in PsA □ SPY072 TL1A Ph2 maintenance data axSpA

\$1.5 billion proforma cash as of June 30, 2026¹, with expected runway into 2H 2029

Cash and shares outstanding



\$1.5B proforma cash as of June 30, 2026¹
Expected runway into 2H 2029

Number of shares (M)

Common stock ²	Shares outstanding	94.3
Common stock equivalents ³	Series A preferred stock	13.8
Common stock and common stock equivalents ^{2,3}	Total outstanding	108.1

¹Reflects cash, cash equivalents, & marketable securities as of 6/30/26 of \$1,145.3 million plus \$328.7 million in estimated net proceeds from the recently closed October 2026 underwritten public offering of common stock, and \$47.5 million in estimated net proceeds from share issuance under the ATM sales agreement; ²Shares outstanding as of 10/7/26; ³Common stock equivalents as of 10/7/26 (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.

ELEVATE THE STANDARD IN IMMUNOLOGY

Scientific illustrations by Visual Sciences



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



Appendix

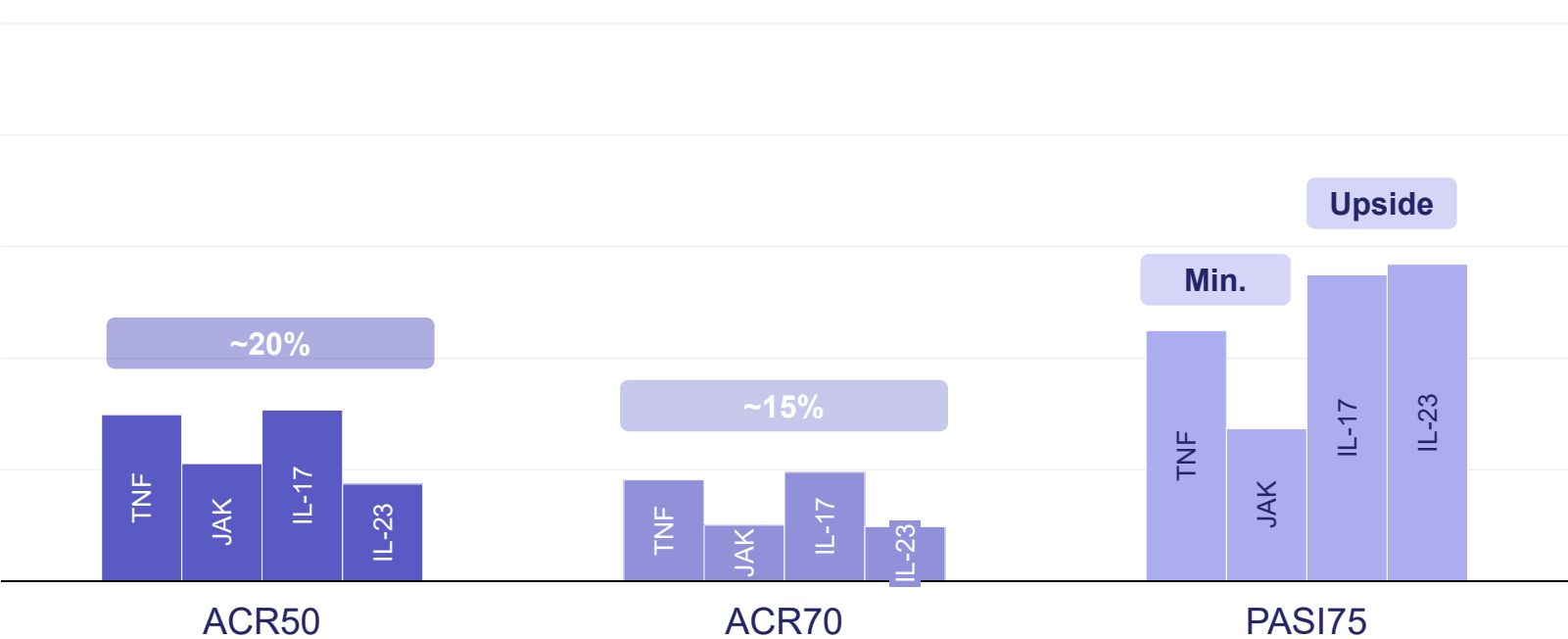
Primary endpoint

Placebo-adjusted % (W12-24)



Secondary & exploratory endpoints

Placebo-adjusted % (W12-24)

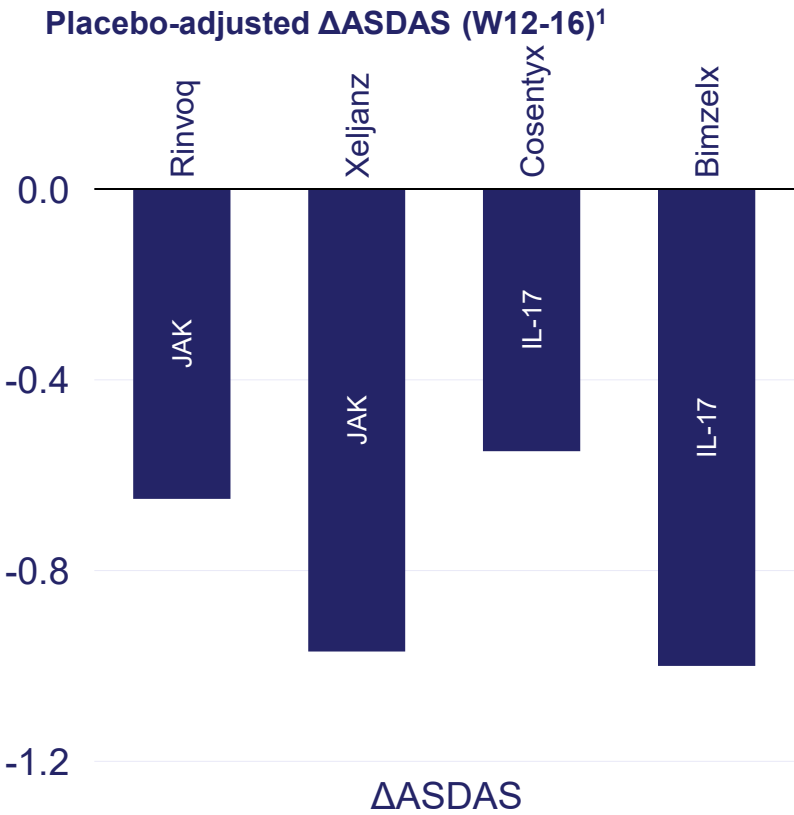


2026 axSpA readout: Aiming for Δ ASDAS and ASAS comparable-to-better than SOC analogs



Appendix

Primary endpoint



Secondary & exploratory endpoints

