UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): January 12, 2026

SPYRE THERAPEUTICS, INC.
(Exact name of Registrant as Specified in Its Charter)

Delaware	**001-37722**	**46-4312787**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

221 Crescent Street **Building 23** **Suite 105** **Waltham, MA**	**02453**
(Address of Principal Executive Offices)	**(Zip Code)**

Registrant's Telephone Number, Including Area Code: 617 651-5940

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 Par Value Per Share	SYRE	The Nasdaq Stock Market LLC (Nasdaq Global Select Market)

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On January 12, 2026, Spyre Therapeutics, Inc. (the "Company") issued a press release (the "Press Release") and posted an updated corporate presentation (the "Corporate Presentation") on its website. The Press Release and the Corporate Presentation include, without limitation, updates on the Company's ongoing clinical trials and the appointment of Kate Tansey Chevlen as Chief Commercial Officer. Copies of the Press Release and Corporate Presentation are attached as Exhibit 99.1 and Exhibit 99.2, respectively, to this Current Report on Form 8-K and are incorporated herein by reference.

The information in this Item 7.01 of this Current Report on Form 8-K, including Exhibits 99.1 and 99.2 attached hereto, is intended to be furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or under the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit Number	Description
99.1	Press Release of the Company, dated January 12, 2026
99.2	Corporate Presentation (January 2026)
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

SPYRE THERAPEUTICS, INC.

Date: January 12, 2026

By: /s/ Cameron Turtle
Cameron Turtle
Chief Executive Officer

Spyre Therapeutics Poised for Transformational 2026 With Six Expected Proof-of-Concept Readouts Beginning in Q2

"6 in '26" expected proof-of-concept (POC) readouts across SKYLINE and SKYWAY trials

SKYLINE platform trial in ulcerative colitis (UC) recruiting faster than expected with SPY001 enrollment complete ahead of schedule; Part A readouts accelerated, now expected to start in Q2

SKYWAY basket trial enrollment on track across rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA); All readouts expected in 4Q 2026

Kate Tansey Chevlen appointed Chief Commercial Officer (CCO)

Strong balance sheet with pro forma cash, cash equivalents, and marketable securities balance of $783M as of September 30, 2025, anticipated to provide cash runway into the second half of 2028*

WALTHAM, Mass., January 12, 2026 (GLOBE NEWSWIRE) – Spyre Therapeutics, Inc. (NASDAQ: SYRE), a clinical-stage biotechnology company pioneering long-acting antibodies and antibody combinations to redefine the standard of care for inflammatory bowel disease ("IBD") and rheumatic diseases, today highlighted its 2026 priorities including six expected POC readouts (three from the SKYLINE platform trial in UC and three from the SKYWAY basket trial in RA, PsA, and axSpA). The Company also expanded its leadership team with the appointment of Kate Tansey Chevlen as CCO. Ms. Tansey Chevlen is a seasoned biopharma commercial leader with nearly two decades of experience driving strategy, execution, and growth across U.S. and global markets at Amgen.

"Our six expected readouts this year have the potential to identify products, delivered as monotherapies or as combinations, that meaningfully improve upon the standard-of-care for patients suffering from IBD and rheumatic diseases," said Cameron Turtle, DPhil, CEO of Spyre. "As we plan to initiate late-stage development in 2027, we are excited to welcome Kate as our new CCO. Kate's experience securing access and driving product uptake will be invaluable as we shape our Phase 3 strategy to unlock the full value of our pipeline."

Updated topline guidance for SKYLINE and SKYWAY trials

SKYLINE (NCT07012395) is a Phase 2 platform trial of SPY001 (anti-α4ß7), SPY002 (anti-TL1A), SPY003 (anti-IL-23), and pairwise combinations thereof (six investigational long-acting agents in total) in patients with moderately to severely active ulcerative colitis. The trial consists of two parts: Part A is an open-label assessment of the safety and preliminary efficacy of monotherapies and Part B is a randomized and placebo-controlled assessment of the safety and efficacy of monotherapies and combinations. Enrollment in Part A has exceeded expectations with SPY001 enrollment completed ahead of schedule. Readouts for Part A are now expected to begin in Q2.

SKYWAY (NCT07148414) is a Phase 2 basket trial of SPY072 (anti-TL1A) in patients with moderate to severely active RA, PsA, or axSpA. Enrollment is on track, and all indications are expected to readout in 4Q 2026.

Trial	Arm	Status	Anticipated milestones
SKYLINE	SPY001 UC Part A	Enrollment complete	Readouts beginning **Q2**
Platform study	SPY002 UC Part A	Enrolling	
	SPY003 UC Part A	Enrolling	
SKYWAY	SPY072 RA	Enrolling	All readouts **4Q 2026**
Basket study	SPY072 PsA	Enrolling	
	SPY072 axSpA	Enrolling	

Appointment of Chief Commercial Officer

Ms. Tansey Chevlen joins Spyre from Amgen where she most recently held the position of VP, Global Marketing Head for Immunology and Inflammation. During her time at Amgen, she has held senior leadership roles across marketing, sales, and market access, and has played a pivotal role in multiple successful product launches. Ms. Tansey Chevlen has been instrumental in shaping as well as implementing go-to-market

and patient access strategies, and partnering closely with cross-functional teams to translate scientific innovation into meaningful commercial impact. Ms. Tansey Chevlen holds a BA in Politics from Brandeis University and an MBA from the Johnson Graduate School of Management at Cornell University.

“Spyre has one of the most compelling portfolios and development strategies in the autoimmune market, with multiple opportunities to deliver breakthrough medicines for patients in markets currently totaling more than $60B of annual revenue,” said Ms. Tansey Chevlen. “I am thrilled to join Spyre at this critical juncture as we deliver proof-of-concept data and prepare to execute pivotal trials and commercialize highly differentiated products.”

** Pro forma cash includes cash, cash equivalents, and marketable securities as of September 30, 2025 of $486.2 million plus $296.5 million in net proceeds from the October 2025 underwritten public offering of common stock.*

About Spyre Therapeutics

Spyre Therapeutics is a clinical-stage biotechnology company pioneering long-acting antibodies and antibody combinations to redefine the standard of care for inflammatory bowel disease (“IBD”) and rheumatic diseases. Spyre’s pipeline includes investigational extended half-life antibodies targeting α4ß7, TL1A, and IL-23.

For more information, please visit http://spyre.com.

Forward-Looking Statements

Certain statements in this press release, other than purely historical information, may constitute “forward-looking statements” within the meaning of the federal securities laws, including for purposes of the safe harbor provisions under the United States Private Securities Litigation Reform Act of 1995. These statements include, but are not limited to, statements regarding: Spyre’s ability to achieve the expected benefits or opportunities with respect to its product candidates, including their potential commercialization; Spyre’s ongoing and future clinical development activities, including the expected timing and results of the ongoing SKYWAY Phase 2 basket trial and SKYLINE Phase 2 platform trial, including timing and number of data readouts expected to be delivered; the potential therapeutic benefits of Spyre’s product candidates as monotherapies or in combinations and their extended half-life; estimated market sizes

and potential growth opportunities; expectations of cash runway extending into the second half of 2028; and Spyre's business plans, milestones, strategy and goals. The words "opportunity," "potential," "milestones," "pipeline," "strategy," "anticipate," "believe," "could," "estimate," "expect," "may," "might," "plan," "possible," "predict," "should," "will," "would," and similar expressions (including the negatives of these terms) may identify forward-looking statements, but the absence of these words does not mean that a statement is not forward-looking. These forward-looking statements are based on current expectations and beliefs and involve a number of risks and uncertainties, many of which are beyond Spyre's control, and other assumptions that may cause actual results or performance to be materially different from those expressed or implied by these forward-looking statements. These risks and uncertainties include, but are not limited, uncertainties and risks arising from regulatory feedback, including potential disagreement by regulatory authorities with the Company's interpretation of data and the Company's clinical trials for its product candidates; the potential for interim data not being delivered within expected time frames or final data not being consistent with or different than the interim data reported for our programs; the potential impact of Trump Administration policies and changes in law on our business; and those uncertainties and factors described in Spyre's most recent Annual Report on Form 10-K, as supplemented and updated by subsequent Quarterly Reports on Form 10-Q and any other filings that Spyre has made or may make with the SEC from time to time. You should not place undue reliance on forward-looking statements in this press release, which speak only as of the date they are made and are qualified in their entirety by reference to the cautionary statements herein. Spyre does not undertake or accept any duty to make any updates or revisions to any forward-looking statements.

For Investors:

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Exhibit 99.2

SPYRE THERAPEUTICS

CORPORATE OVERVIEW

January 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 therapeutics for inflammatory bowel disease (IBD), rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA) and other immune-mediated diseases that 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 final data readouts with previously disclosed data for our programs; the efficacy, safety profile, dosing regime, convenience, commercial viability and tolerability of SPY001, SPY002, SPY072 and SPY003, including combinations thereof; Spyre's ongoing and future clinical development activities, including the 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 and 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 SPY001 and our other product candidates and combinations thereof, including the potential for a Q3M-Q6M dosing profile; the potential therapeutic benefits of our product candidates as monotherapies or in combinations and their extended half-life, including the expected duration of half-life in comparison to competitor products; potential alignment with regulatory authorities and anticipated regulatory submissions; expected timing for regulatory feedback; estimated market sizes and potential growth opportunities; the length of time that the Company believes its existing cash resources will fund its operations, including expectations of cash runway extending into the second half of 2028; 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 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 clinical trial design, interpretation of data and our ongoing or 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, 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. 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.

Spyre is pioneering long-acting antibodies and combinations to redefine standard of care in IBD and rheumatic diseases

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 2-4 doses per year

After loading doses

Rheumatic disease

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

SPY072 — TL1A → RA, PsA, axSpA

Target 2-4 doses per year

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 SPY002 TL1A Ph2 POC in UC SPY003 IL-23 Ph2 POC in UC	Readouts beginning **Q2**
SKYWAY	SPY072 TL1A Ph2 POC in RA SPY072 TL1A Ph2 POC in PsA 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

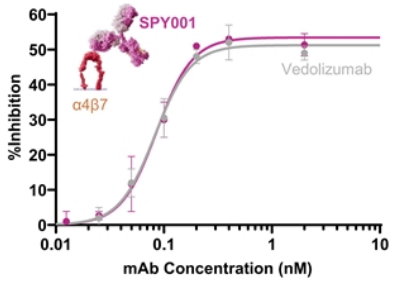
Trial	Indication	Program	Target	Phase 1	Phase 2	Phase 3	Anticipated Milestones
SKYLINE	UC	SPY001	α4β7				2026: Ph2 open-label POC Beginning in Q2
		SPY002	TL1A				2027: Ph2 pbo-controlled data
		SPY003	IL-23				
		SPY120	α4β7 + TL1A				2027: Ph2 pbo-controlled data
		SPY130	α4β7 + IL-23				
		SPY230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

$783 million pro forma cash as of September 30, 2025[1], with expected runway into 2H 2028

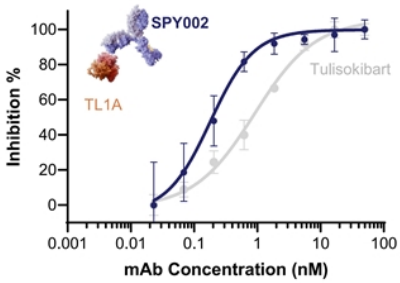
Milestones expected as of the date of this presentation. [1]Reflects cash, cash equivalents, & marketable securities as of 9/30/25 of $486.2 million plus $296.5 million in net proceeds from the October 2025 underwritten public offering of common stock; UC=ulcerative colitis; RA=rheumatoid arthritis; PsA=psoriatic arthritis; axSpA=axial spondyloarthritis; POC=proof of concept

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

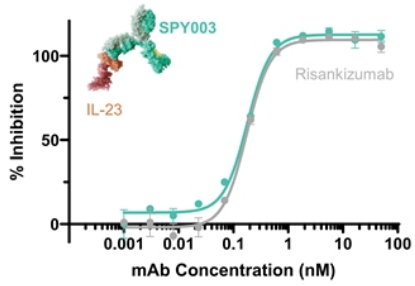
SPY001 (α4β7) potency



SPY002 (TL1A) potency



SPY003 (IL-23) potency

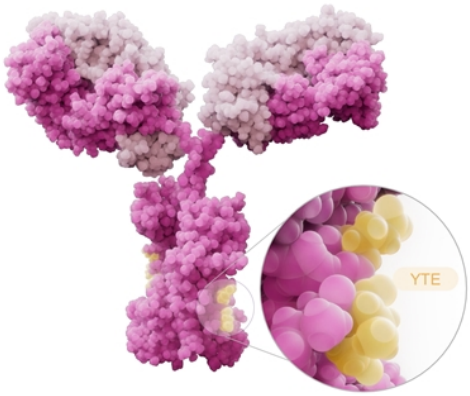


Potential for comparable efficacy at similar or lower doses

Data on file. Potency refers to in vitro potency: SPY001 assay reports inhibition of cells expressing a4b7 binding to MAdCAM-1. SPY002 assay reports inhibition of TL1A-induced apoptosis in TF-1 cells. SPY003 assay reports inhibition of cellular STAT3 signaling. Vedolizumab, tulisokibart, and risankizumab are synthesized comparator antibodies.

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

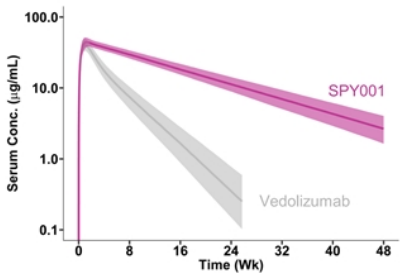
YTE modification increases internal binding to FcRn, avoiding degradation

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

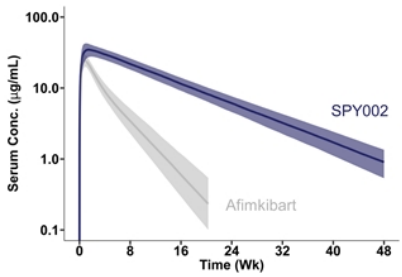


Target Profiles

After loading doses

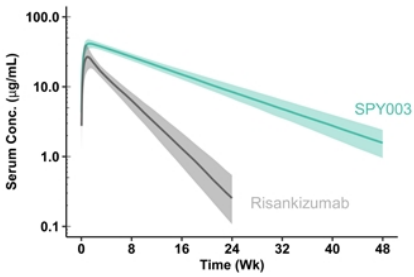
2-4
Doses per year

SPY002 human PK simulation



2-4
Doses per year

SPY003 human PK simulation



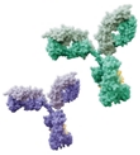
2-4
Doses per year

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

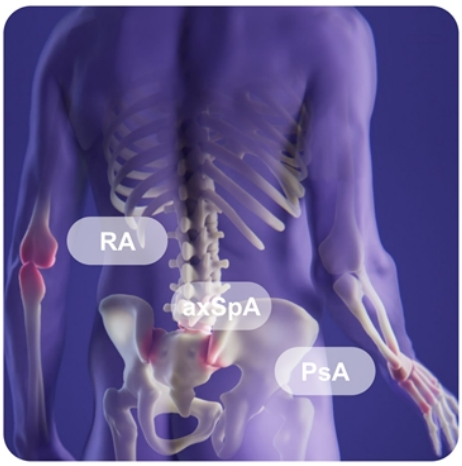
SPY120		TL1A + α4β7
SPY130		IL-23 + α4β7
SPY230		IL-23 + TL1A

Target 2-4 doses per year

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

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

Rheumatic diseases



Distinct anti-TL1A targeting quarterly or twice-annual dosing

SPY072

- Rheumatoid arthritis
- Psoriatic arthritis
- Axial spondyloarthritis

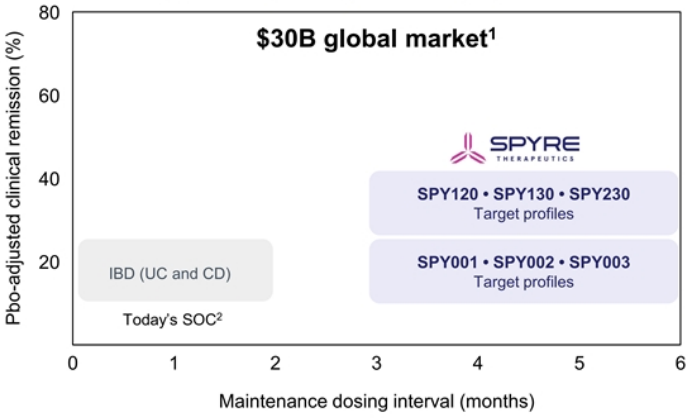
Target 2-4 doses per year

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

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

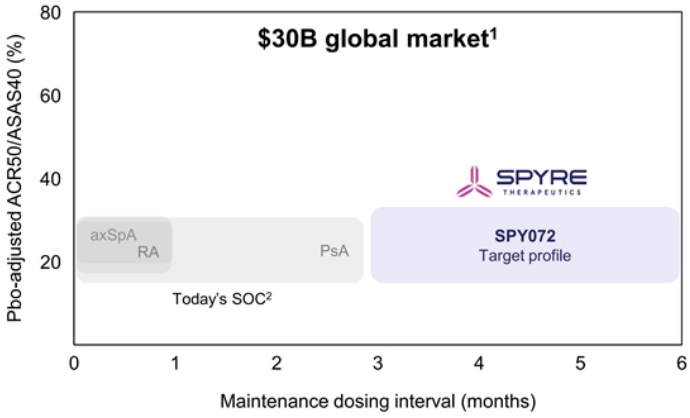
Inflammatory bowel disease

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 2028 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

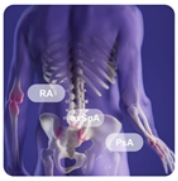
6 INTERVENTIONS

1 INDICATION

Q2'26 READOUTS BEGINNING*

SKYWAY

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

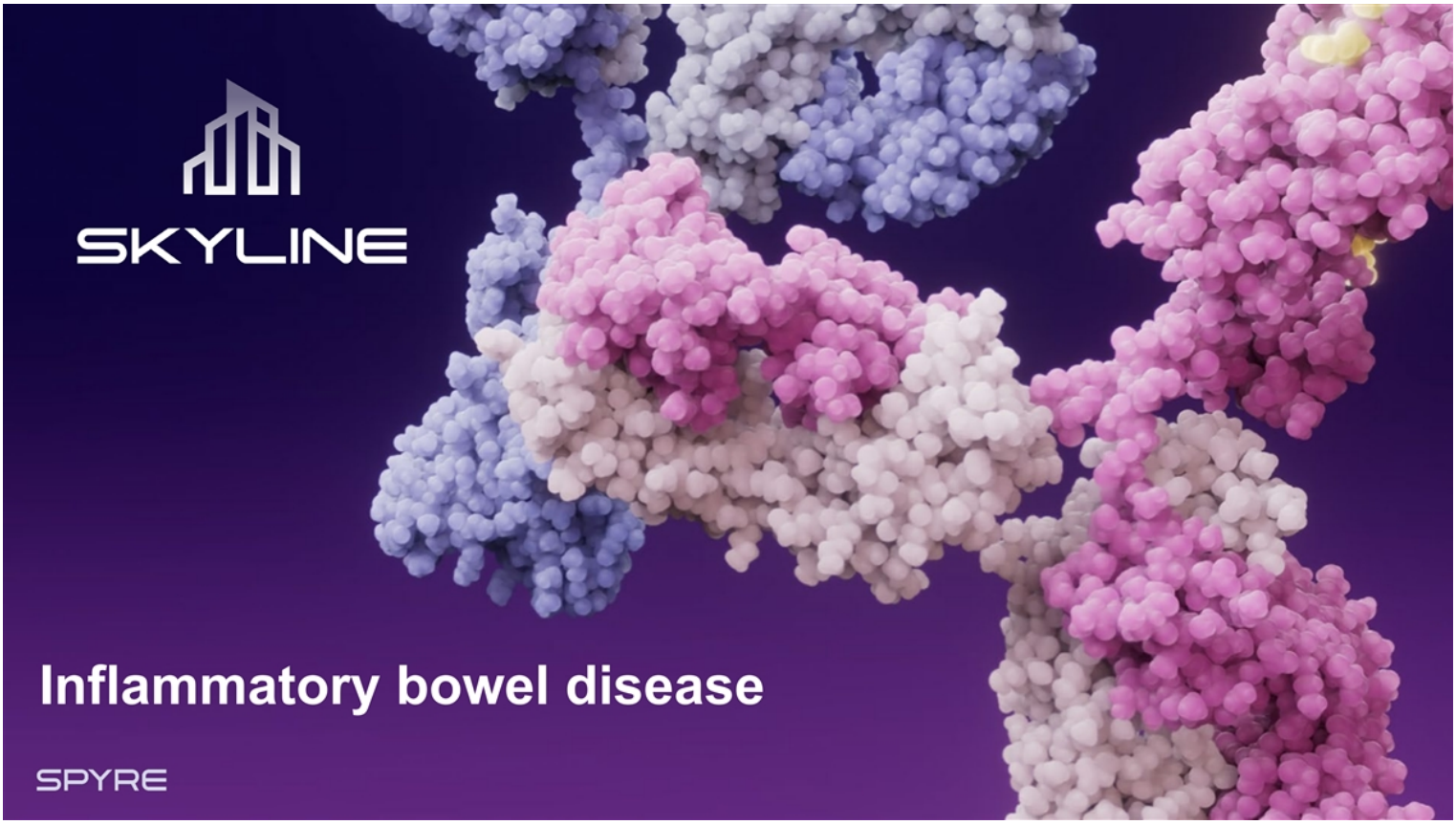


1 INTERVENTION

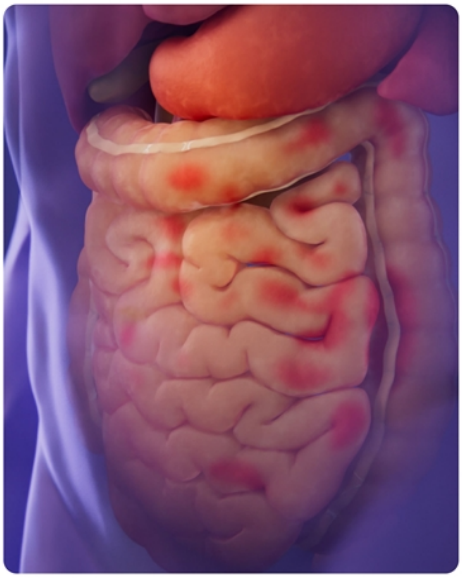
3 INDICATIONS

4Q'26 EXPECTED READOUTS

*Part A open-label monotherapy readouts beginning in Q2 2026.

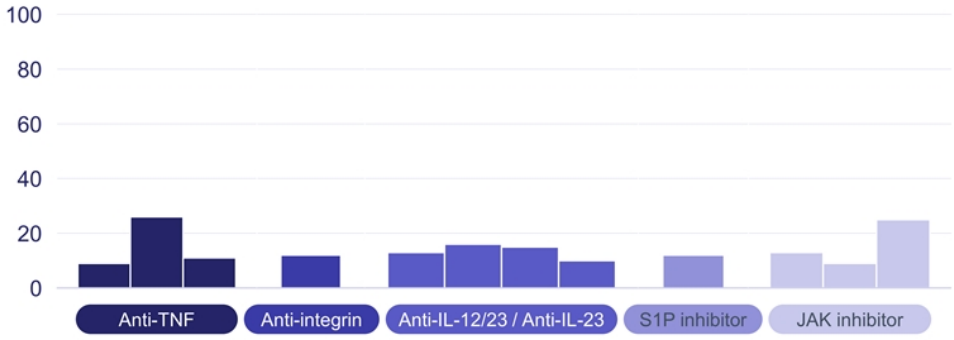

SKYLINE
Inflammatory bowel disease
SPYRE

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

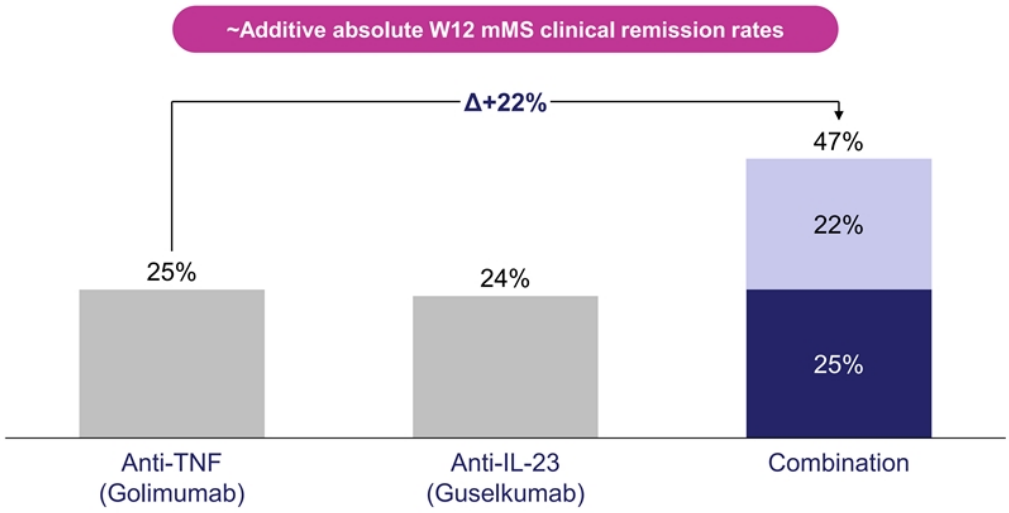
UC placebo-adjusted clinical remission rates by MOA (Induction)



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

JNJ's VEGA study demonstrated the power of combination therapy to break the efficacy ceiling in IBD

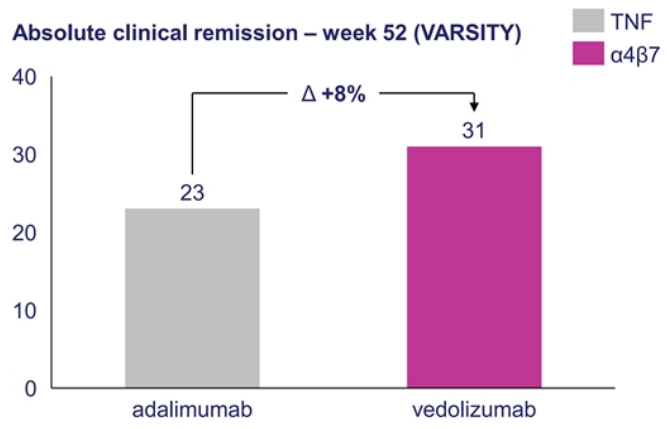
VEGA combination study • Ulcerative colitis



Feagan, B. G. et al. Lancet Gastroenterol. Hepatol. 8, 307–320 (2023). mMS=modified mayo score

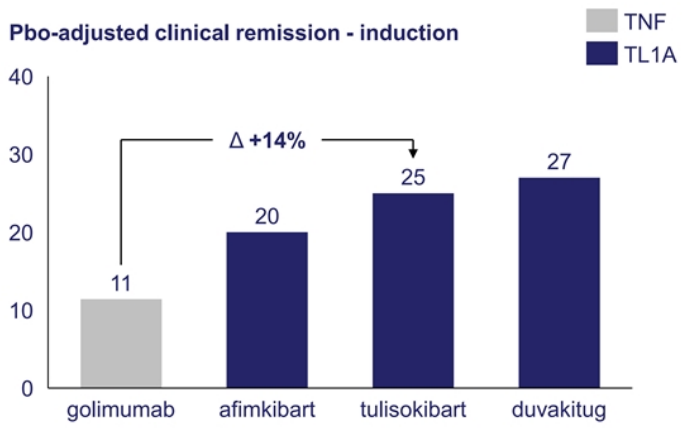
Replacing anti-TNF with anti-α4β7 or anti-TL1A may yield combinations with improved safety and efficacy

anti-α4β7 was superior to anti-TNF in H2H UC study



Established α4β7 long-term safety profile and gut-restrictive MOA

anti-TL1A exceeds anti-TNF on cross-trial comparison

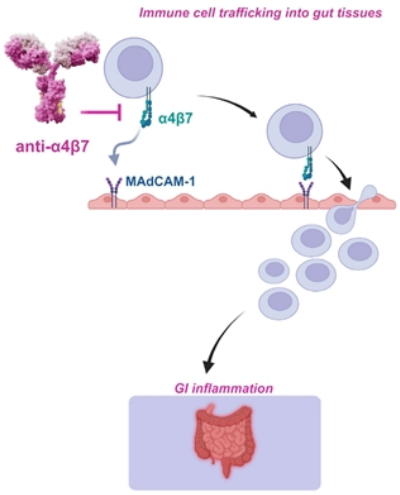


TL1A safety is encouraging to date

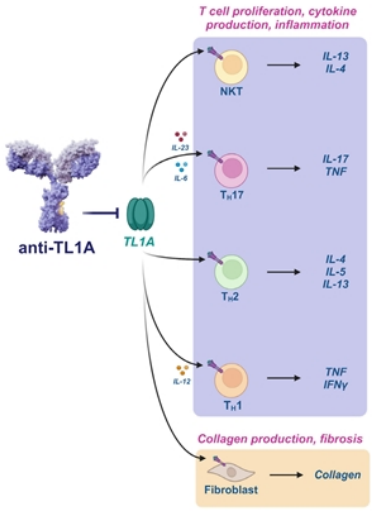
Product labels, Sands BE. et al. N Engl J Med. 2019; Roivant corporate presentation January 2023; Sands, Bruce E., et al. New England Journal of Medicine 391.12 (2024); Teva corporate presentation February 2025.

Spyre MOAs address the diverse pathophysiology of IBD by targeting distinct pathways

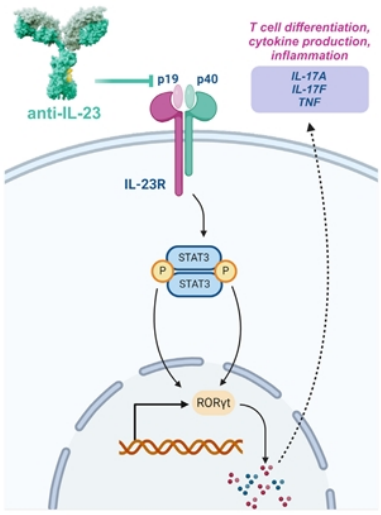
Blockade of α4β7 prevents circulating immune cells from entering inflamed gut tissues



Neutralization of TL1A suppresses inflammation and reduces fibrosis by inhibiting fibroblast activation



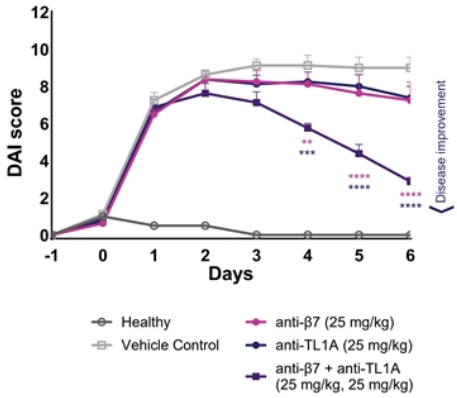
Neutralization of IL-23 inhibits cascade of various proinflammatory cytokines



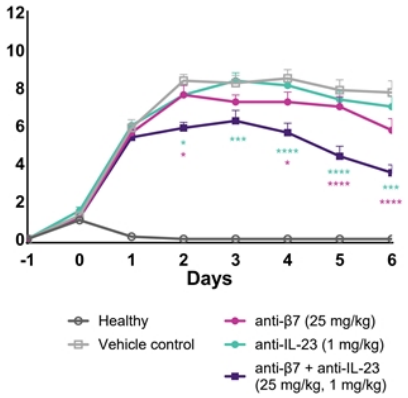
Created with BioRender.com; Neurath, Markus F. Nature Reviews Gastroenterology & Hepatology 14.5 (2017): 269-278; Solitano, Virginia, et al. Med (2024).

Combination therapy results in additive-to-superior efficacy in mouse TNBS colitis model

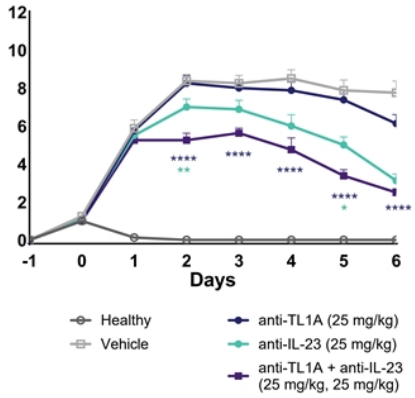
α4β7 + TL1A



α4β7 + IL-23



TL1A + IL-23



*Data on file. Preclinical models utilized surrogate antibodies. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001 vs. vehicle (2-way ANOVA with Dunnett's correction). N=8 per group. TNBS=trinitrobenzene sulfonic acid.*

SKYLINE: Phase 2 *platform* study evaluating three monotherapies and three combinations in UC

SKYLINE

Part A: Open-label monotherapy evaluation (N=~100)

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)

- 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.

Comparison to other trials highlights advantage of designing a portfolio from the ground up w/ unified dosing

SKYLINE

ARM	INDUCTION	MAINTENANCE (THROUGH W24)
SPY001		
SPY002		
SPY003		
SPY120		
SPY130		
SPY230		
PBO		

- ✓ Unified dosing intervals and formats enables blinded trial
- ✓ Two IV induction doses, Q3M-Q6M SC chronic dosing
- ✓ Clear approach to advance coformulation for Ph3

TARGET-CD[1]

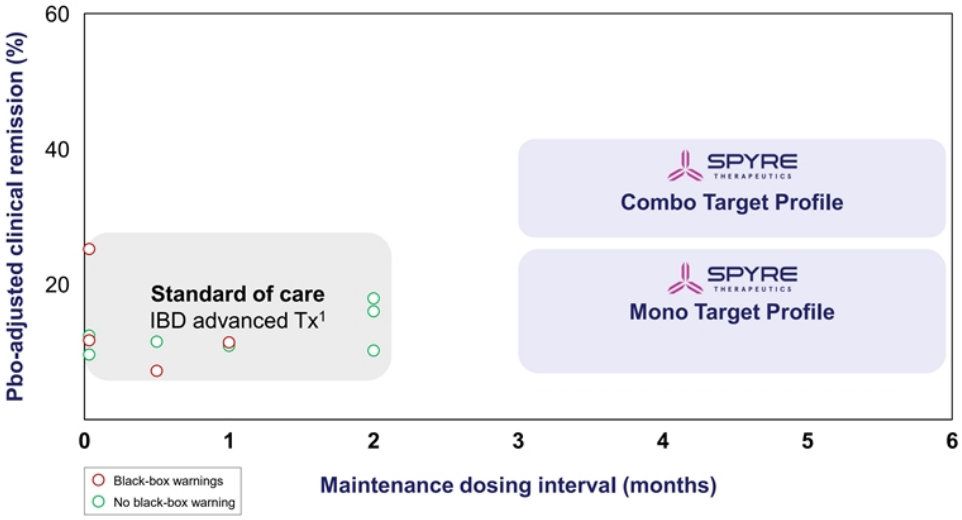
ARM	INDUCTION	MAINTENANCE (THROUGH W24)
Mono 1		
Mono 2		
Mono 3		
Combo 1		
Combo 2		

- × Mix of IV, SC, and OBI routes of administration; open label trial
- × Combos default to highest dosing frequency (Q2W or Q4W)
- × Unclear strategy to single product combination for Ph3

Pending regulator feedback; [1]Inferred dosing regimen based on Clinicaltrials.gov posting and dosing regimens of individual agents in commercial or prior monotherapy clinical trial settings. OBI=on body injector

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

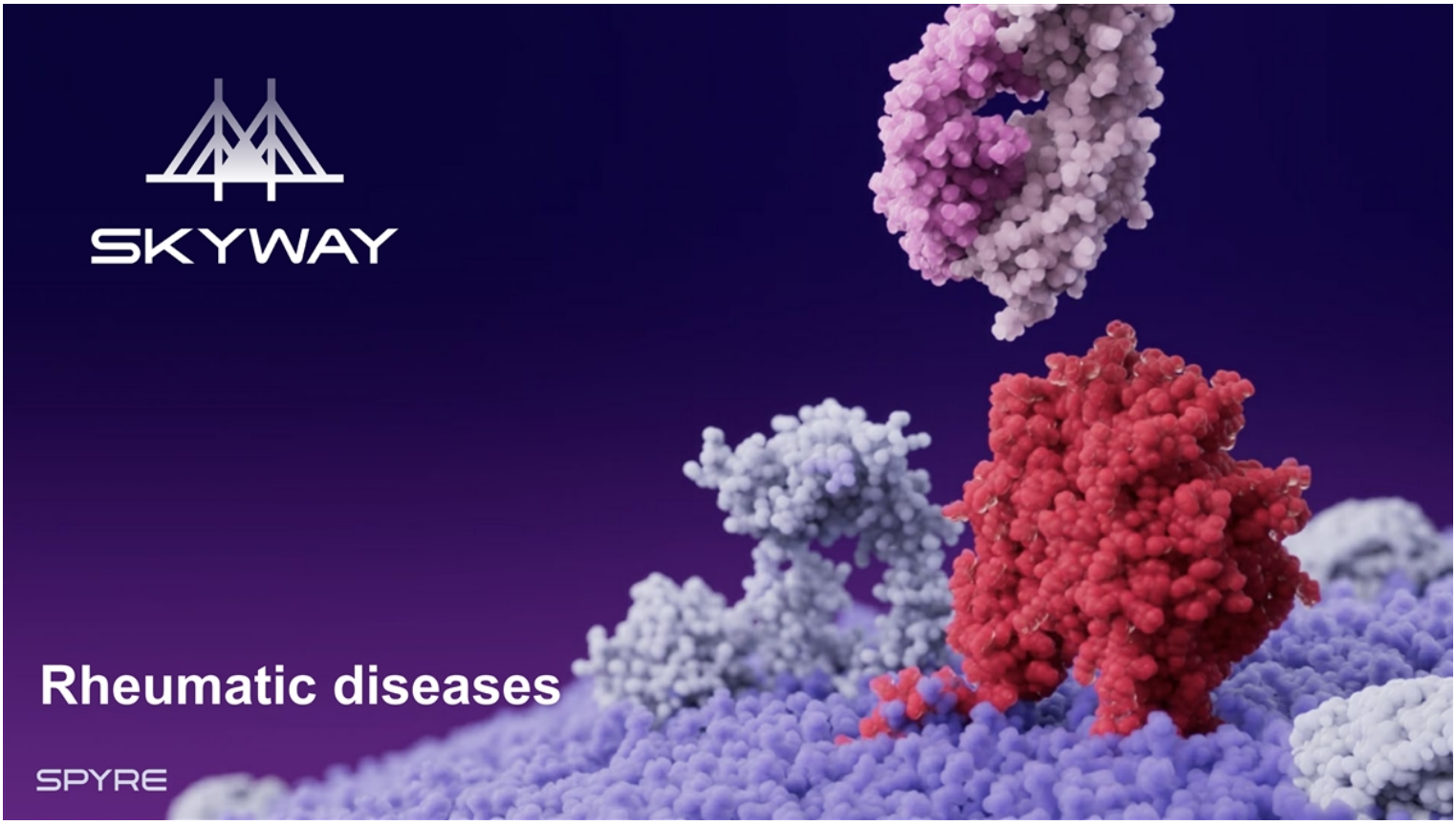
Combos: Meaningfully improved efficacy vs. standard of care

Favorable safety profile

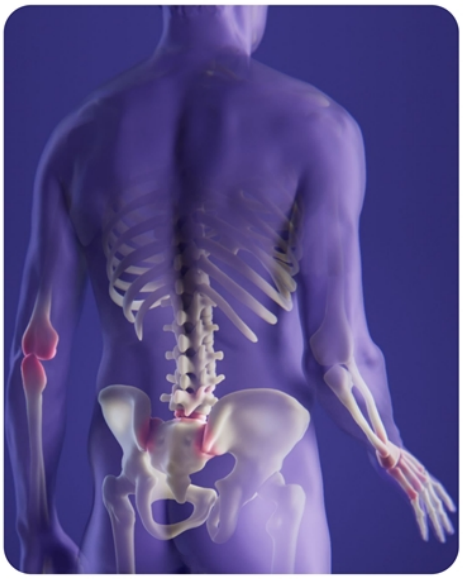
No black box warning

2-4 doses per year

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



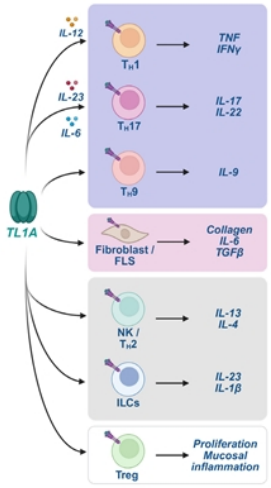
- >3M individuals in the U.S. diagnosed with RA (>1.5M[1]), PsA (~1M[2]), and axSpA (~1M[2])
- Substantial unmet need remains due to:
  - Minority remission rates, inability to control multiple aspects of disease, and lack of durability with existing therapies
  - Limited MOAs to cycle through following 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

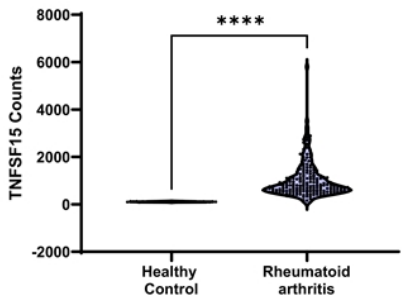
	POC studies[1]	T_H1 | T_H17 | T_H9	Fibroblasts FLS | osteoclasts	NK | T_H2 | ILCs
Ulcerative colitis (UC)	✓	●		
Crohn's disease (CD)	✓	●	●	
Rheumatoid arthritis (RA)	Roche	●	●	
Psoriatic arthritis (PsA)		●		
Axial spondyloarthritis (axSpA)		●		
Psoriasis (PsO)		●		
Hidradenitis suppurativa (HS)		●	●	
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.

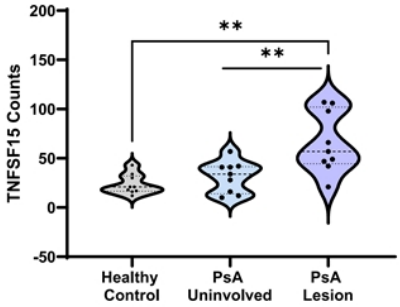
Hisamoto, T. et al. Int. J. Mol. Sci. 24, 1813 (2023); Herro, R. et al. J. Immunol. 205(9), 2414-2422 (2020); Ma, C. et al. Int. Immunopharm. 137, 112360 (2024); Richard, A. et al. JLB 3(98), 333-345 (2015); Song, Y. et al. Arthritis Research & Therapy 22, 106 (2020); Xu, W. et al. Frontiers in Immunology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

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

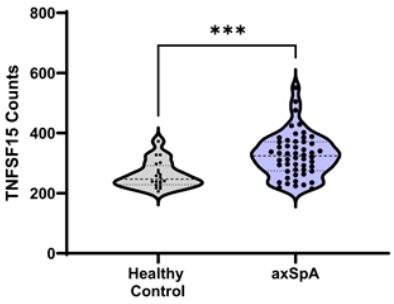
Rheumatoid arthritis



Psoriatic arthritis



Axial spondyloarthritis



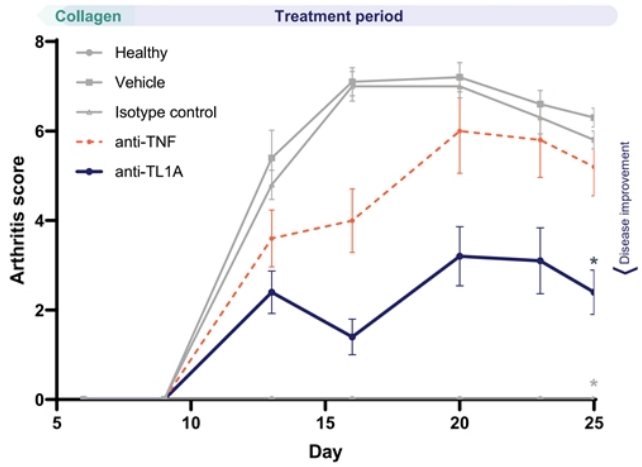
Source	Whole blood	Skin biopsy	Whole blood
Sequencing	Microarray	Bulk RNA seq	Microarray
Sample size	N=192 RA, 30 HC	N=9 per cohort	N=52 axSpA, 20 HC

SPYRE

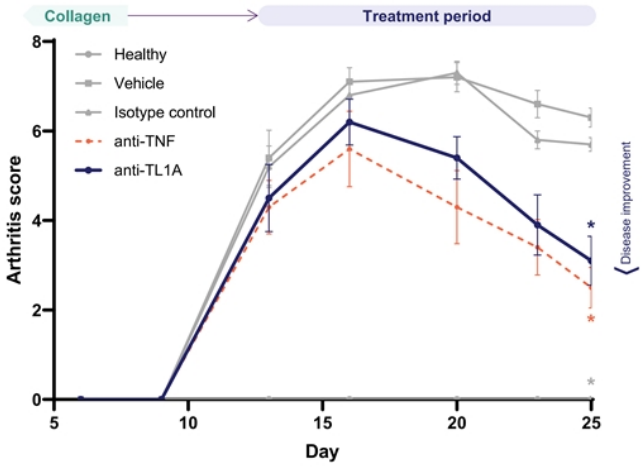
Spyre analysis of RA-MAP, Li, Sifang, et al. BMC Musculoskeletal Disorders 25.1 (2024), and Johnsson, Hanna, et al. Arthritis Research & Therapy.
*** P≤0.01, *** P ≤0.001, **** P ≤0.0001. Unpaired tailed t-test used for RA and axSpA analysis, One-way ANOVA used in PsA.*
RA=rheumatoid arthritis; PsA=psoriatic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



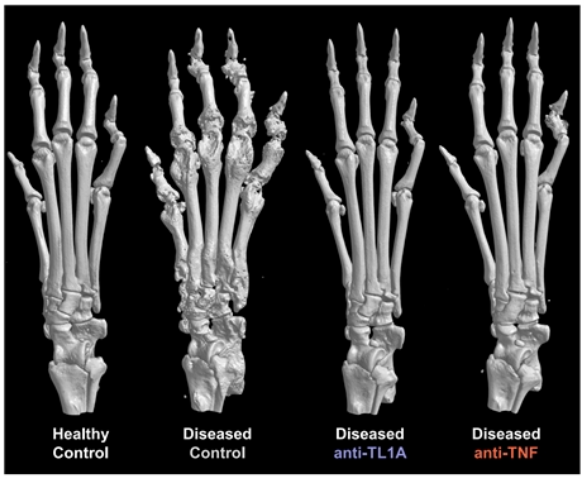
Comparable efficacy in therapeutic model



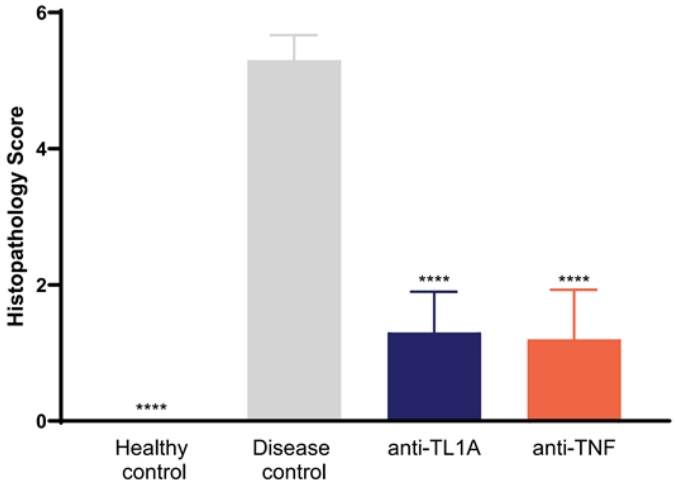
** P< 0.0001 vs. isotype control; 2-way ANOVA using Dunnett's correction for multiple comparisons. Data on file.*

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

Anti-TL1A prevents disease and bone erosion



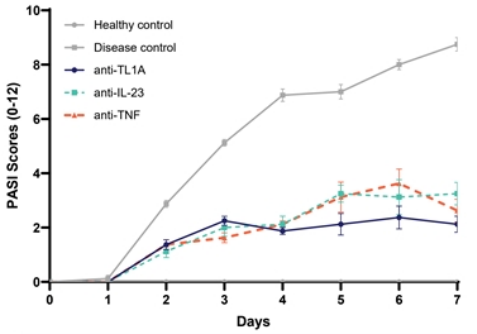
Comparable efficacy to anti-TNF



*Data on file. **** P ≤0.0001*

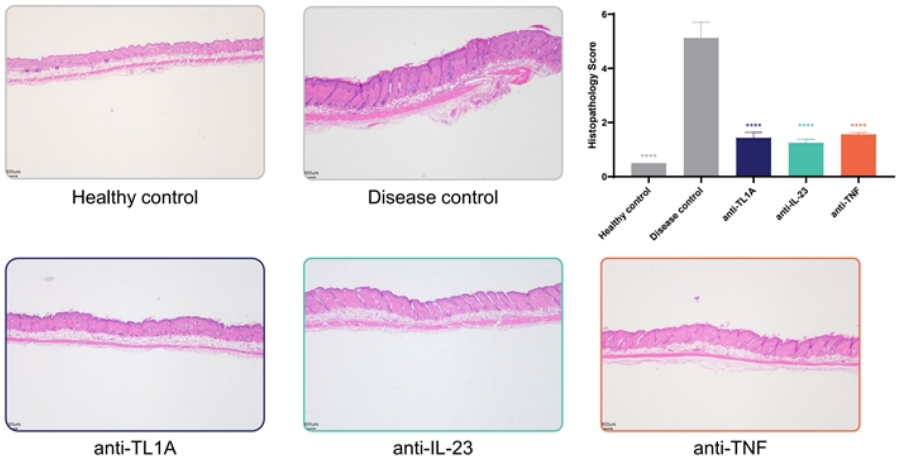
Additionally, anti-TL1A treatment led to comparable improvements in psoriatic skin lesions in mouse IMQ model

Anti-TL1A reduces skin lesions



Potential for robust skin clearance in PsA

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

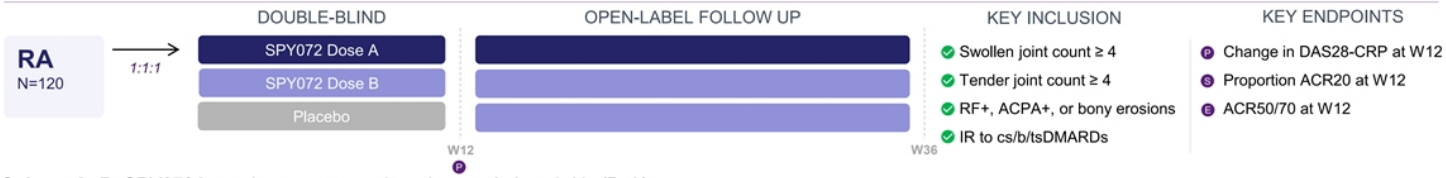


*Data on file. **** P ≤0.0001*

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

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)

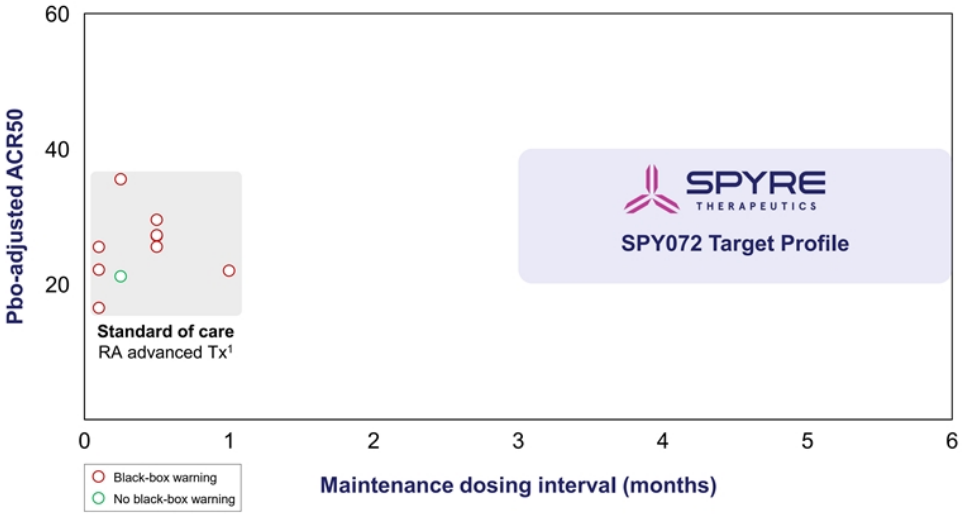
Sub-study C: SPY072 in moderate-to-severely active axial spondyloarthritis (axSpA)

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 with quarterly or twice-annual dosing

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



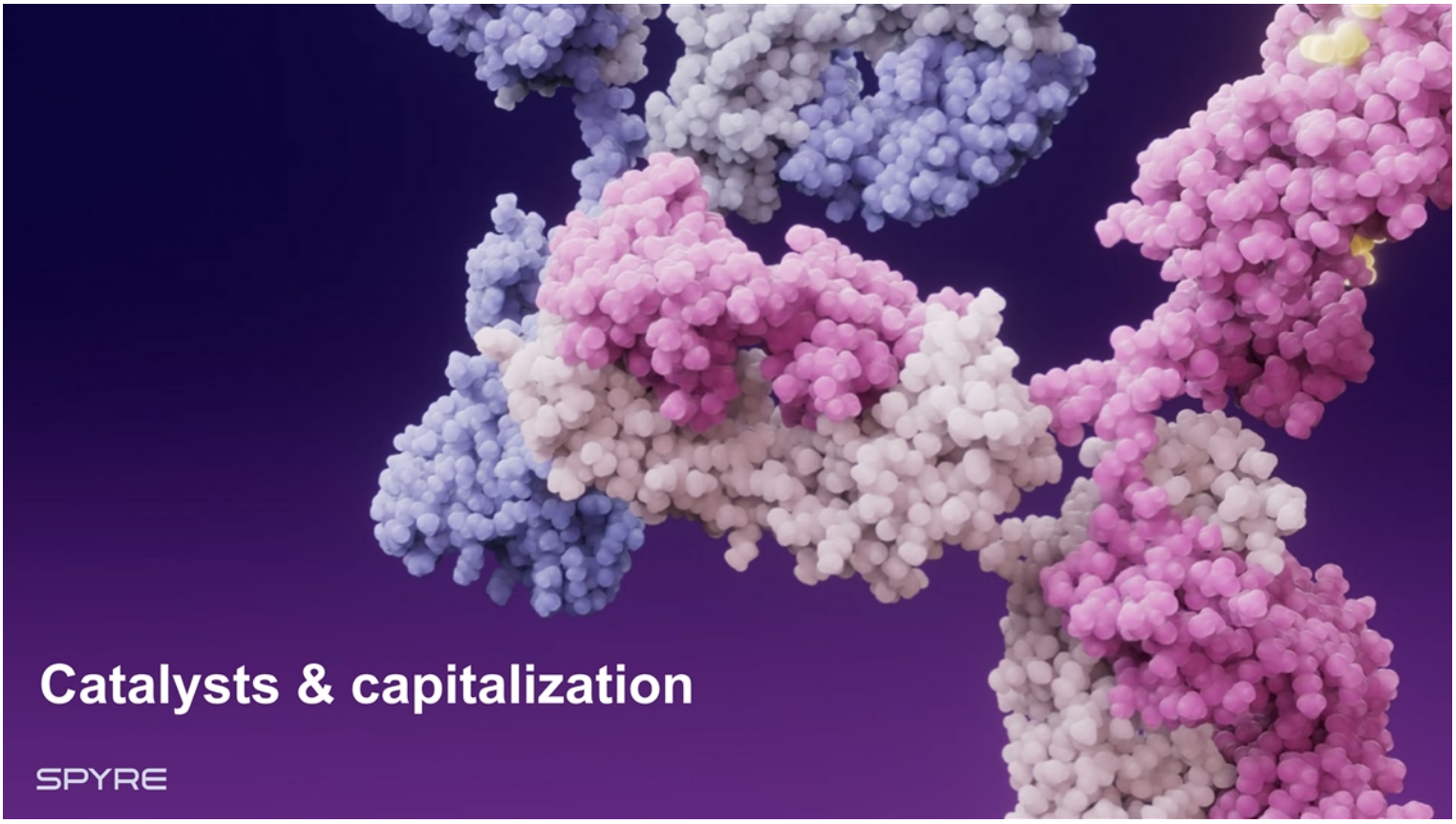
SPY072 target product profile

- First-in-class anti-TL1A
- Comparable-to-better efficacy

- Favorable safety profile
- No black box warning

- 2-4 doses per year

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	Readouts beginning Q2	❑ 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 ❑ SPY072 TL1A Ph2 W16 POC in PsA ❑ SPY072 TL1A Ph2 W16 POC in axSpA	All readouts expected Q4	❑ SPY072 TL1A Ph2 maintenance data in RA ❑ SPY072 TL1A Ph2 maintenance data in PsA ❑ SPY072 TL1A Ph2 maintenance data axSpA

$783 million pro forma cash as of September 30, 2025[1], with expected runway into 2H 2028

Milestones expected as of the date of this presentation. [1]Reflects cash, cash equivalents, & marketable securities as of 9/30/25 of $486.2 million plus $296.5 million in net proceeds from the October 2025 underwritten public offering of common stock

Cash and shares outstanding

$783M pro forma cash as of September 30, 2025[1]
Expected runway into 2H 2028

		Number of shares (M)
Common stock	Shares outstanding	77.6
Common stock equivalents	• Series A preferred stock	13.8
	• Series B preferred stock	0.7
Common stock and common stock equivalents[2]	**Total outstanding**	**92.1**

[1]Reflects cash, cash equivalents, & marketable securities as of 9/30/25 of $486.2 million plus $296.5 million in net proceeds from the October 2025 underwritten public offering of common stock; [2]Shares outstanding on a pro forma and as-converted basis as of 9/30/25, inclusive of the October 2025 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.

THANK YOU

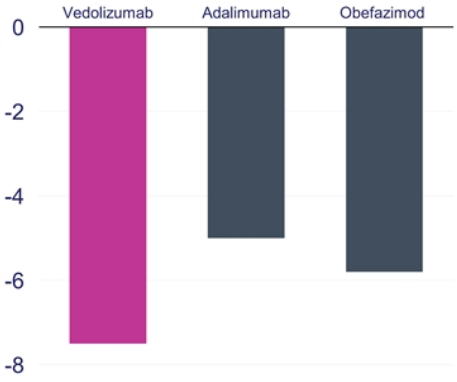
Engineering for new heights in the treatment of IBD and beyond

Scientific illustrations by Visual Sciences

2026 Part A readout: Comparable safety and efficacy as in-class comparators

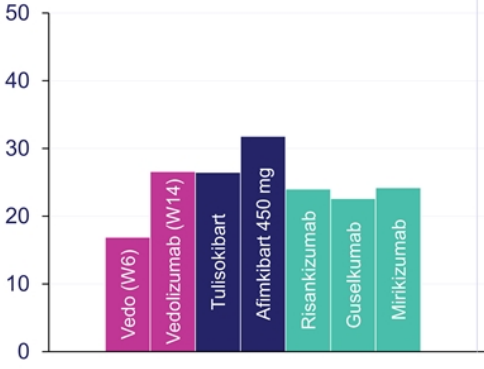
Primary endpoint

ΔRHI from baseline (W14-16)

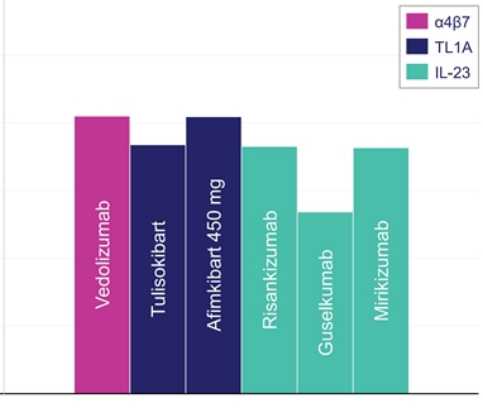


Secondary endpoints

Absolute % clinical remission (W6-14)



Absolute % endoscopic improvement (W6-14)



Source: Vedolizumab (VARSITY, GEMINI I), adalimumab (VARSITY), obefazimod (Ph2b – 50 mg), tulisokibart (ARTEMIS-UC), afimkibart (TUSCANY-2), risankizumab (INSPIRE), guselkumab (QUASAR), mirikizumab (LUCENT 1); Duvakitug not shown given outlier placebo response rate.

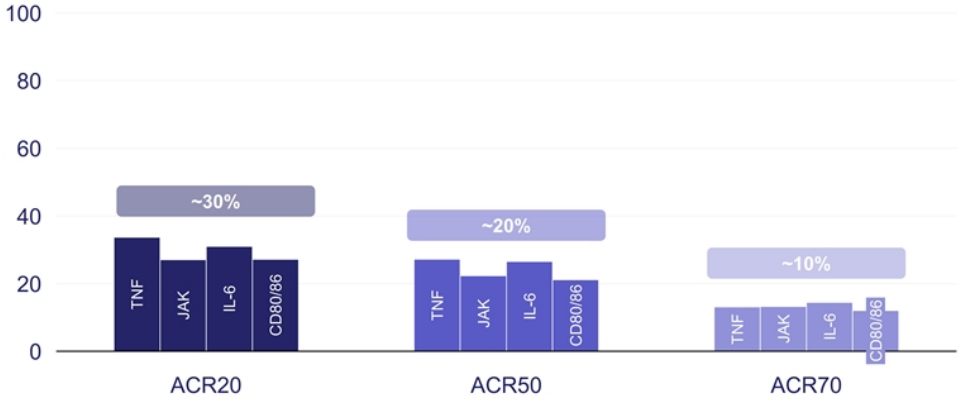
2026 RA readout: Aiming for ΔDAS28-CRP and ACRs comparable-to-better than SOC analogs

Primary endpoint

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

Secondary & exploratory endpoints

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

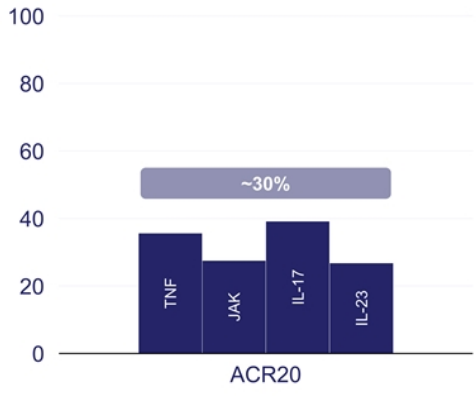


Notes: [1]Results from studies in mixed populations or weighted average of naïve and inadequate response (IR) trial results. [2]Average ACR values from pivotal studies of approved products within each class. Data on file.

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

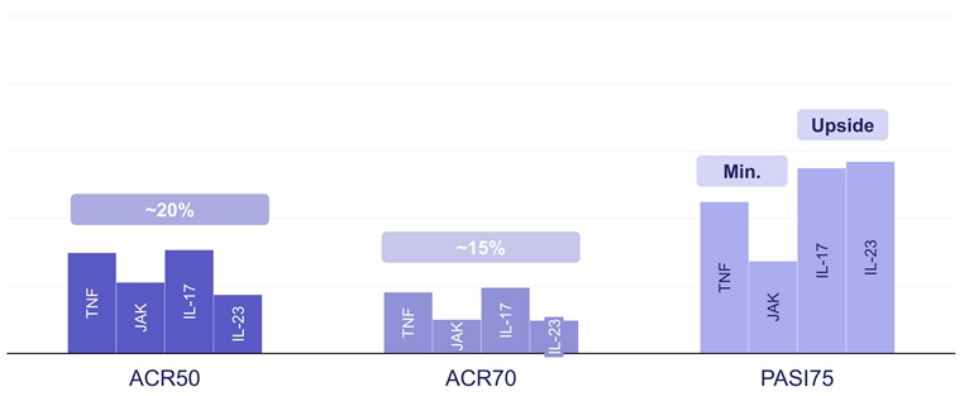
Primary endpoint

Placebo-adjusted % (W12-24)



Secondary & exploratory endpoints

Placebo-adjusted % (W12-24)

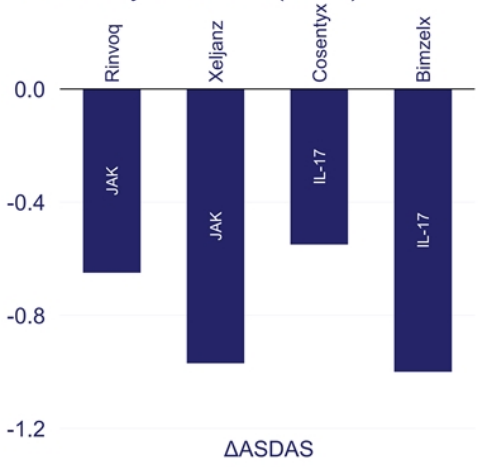


Average ACR and PASI values from pivotal studies of approved products within each class. IL-23 includes IL-12/23. Data on file.

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

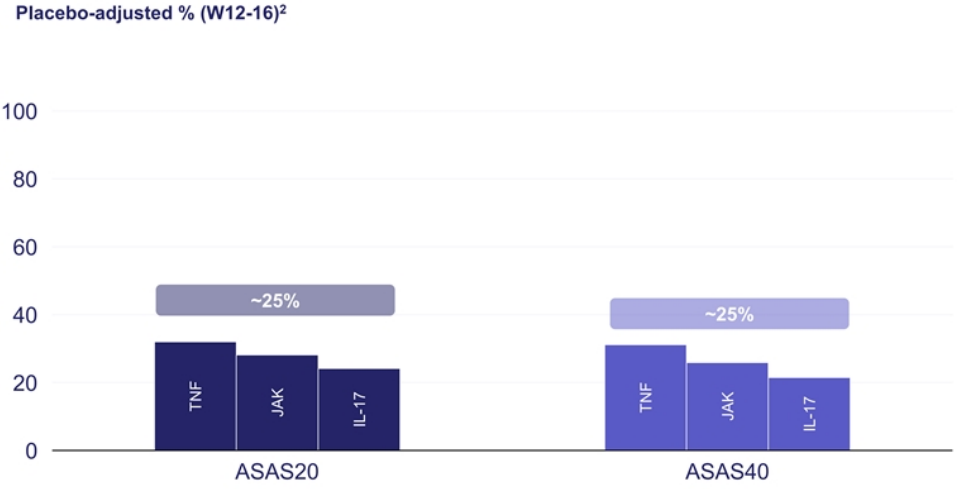
Primary endpoint

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.