SPYRE THERAPEUTICS

Corporate overview

February 2025

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 therapeutics for inflammatory bowel disease (IBD) or rheumatoid arthritis (RA) that meaningfully improve both efficacy and convenience compared to today's standard of care; our ability to develop first-in-class therapeutics for RA; our plans to expand the development of our product candidates, including SPY002, to indications beyond IBD and RA; the expected timing of Phase 1 trial for SPY003, including timing of trial initiation and data readouts; the SPY001 phase 1 trial final data readouts not being consistent with or being different than the interim Phase 1 results; the efficacy, safety, tolerability, convenience and commercial viability of SPY001 and our other product candidates; the planned induction and maintenance dosing regimen for SPY001 and our other product candidates; the potential for increased or accelerated efficacy; the therapeutic benefits of our product candidates as monotherapies or in combinations and their extended half-life; the expected design, patient population and timing of the platform Phase 2 trial, including timing of each cohort and data readouts; our plans to provide Phase 2 platform study proof-of-concept readouts in 2027, including quantity of such readouts and our ability to provide such readouts ahead of any disclosed bispecific approaches against our targets; potential cost savings from the Phase 2 trial design; potential alignment with regulatory authorities and anticipated regulatory submissions; expected timing for regulatory feedback; estimated market sizes and potential market opportunities; expectations regarding patient, investigator and physician preferences; the potential for a Q3M-Q6M dosing profile for each of our product candidates, including combinations thereof; expectations regarding our potential therapeutic combinations and the potential benefits thereof; estimated cash runway lasting into 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", "planned", "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 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.

Engineering for new heights in the treatment of IBD & beyond

Our strategy

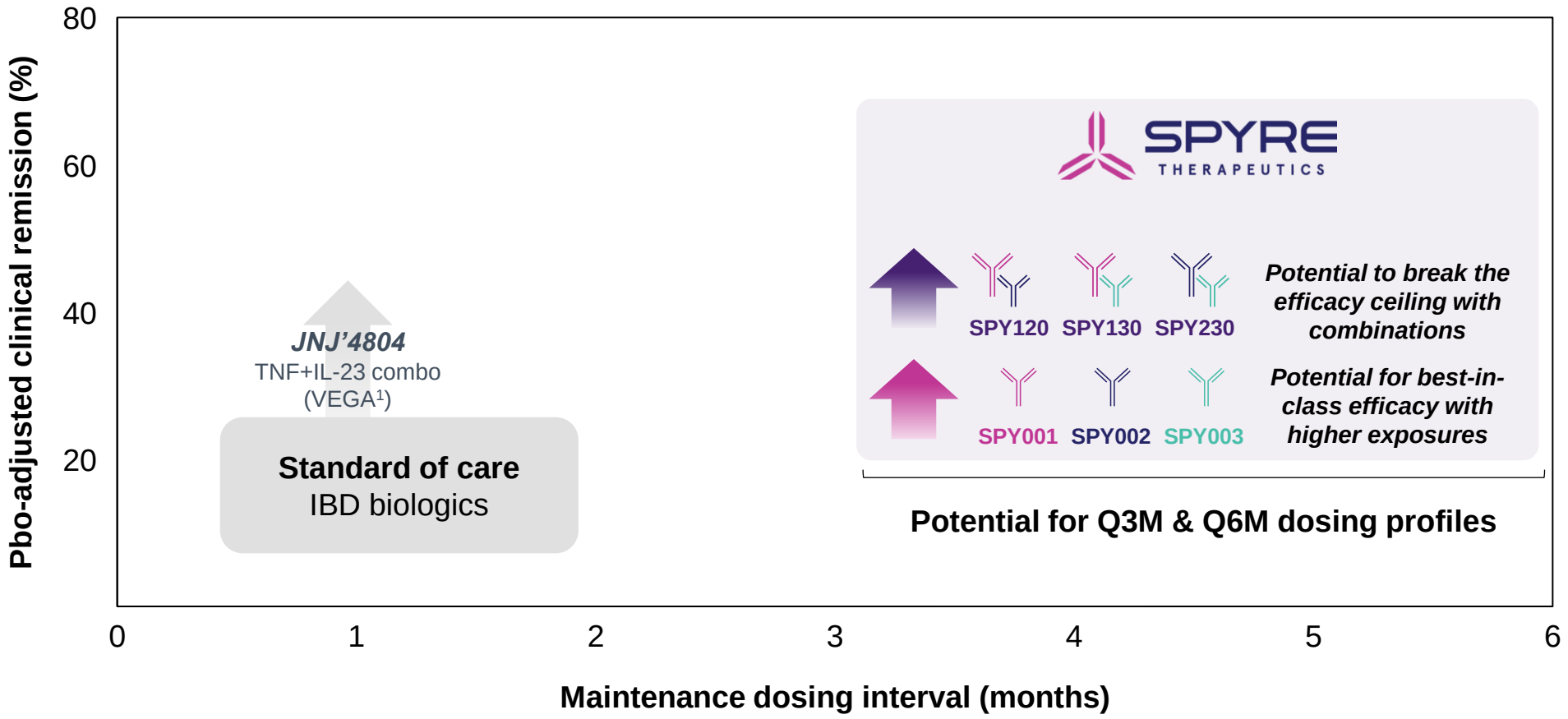
Our pipeline

POTENTIAL SC Q3M-Q6M DOSING*	INDICATION	TARGET	PROGRAM[1]	PRECLIN.	PHASE 1	PHASE 2	PHASE 3
Next-generation monotherapies	Ulcerative Colitis	α4β7	SPY001			2Q25: SPY002 Ph1 data 2H25: SPY003 Ph1 data Mid-2025: Ph2 initiation 2026: Ph2 open-label data 2027: Ph2 pbo-controlled data	
		TL1A	SPY002				
		IL-23	SPY003				
Paradigm-changing combinations		α4β7 + TL1A	SPY120			2027: Ph2 pbo-controlled data	
		α4β7 + IL-23	SPY130				
		TL1A + IL-23	SPY230				
Indication expansion	Rheumatoid Arthritis	TL1A	SPY002			Mid-2025: Ph2 initiation 2026: Ph2 data	

*[1]Spyre holds exclusive worldwide licensed rights for SPY001, SPY002, and SPY003 from Paragon Therapeutics, Inc. SPY003 license is restricted to IBD, all other program licenses are unrestricted as to indication. *SC=subcutaneous, Q3M-Q6M dosing profiles are expected maintenance profiles based on human PK simulations. All of the milestones for data including timing are as anticipated or expected as of the date of this presentation and subject to regulatory feedback.*

Spyre's portfolio uniquely enables product profiles with potential superior efficacy and convenience

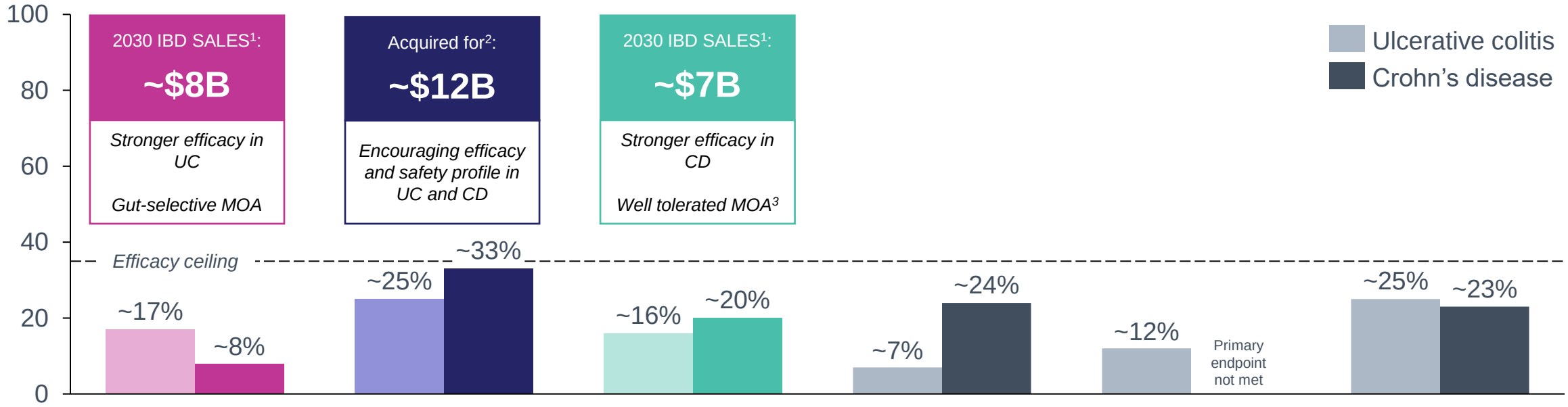
ILLUSTRATIVE



Note: [1]VEGA trial was not pbo-controlled.

Our MOAs were rationally chosen based on attractive risk-benefit profiles

Induction clinical remission rates (pbo-adjusted) by MOA

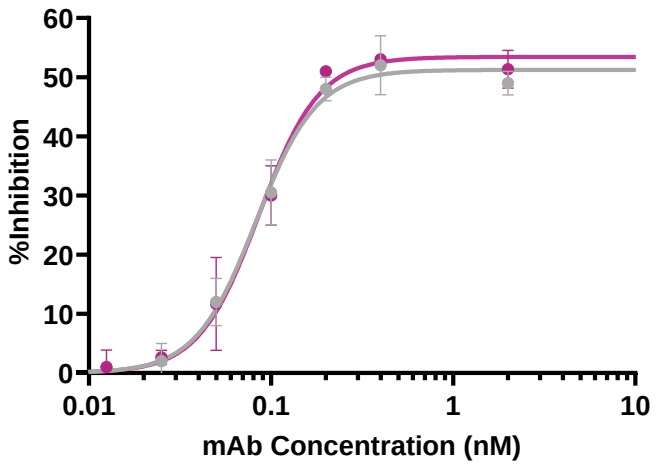


Week	W14 | W6	W12 | W12	W12 | W12	W8 | W4	W10 | W12	W8 | W12
Safety	No black box warning	Not approved	No black box warning	*Black box warning*	*Cardiac monitoring*	*Black box warning*
MOA	α4β7	TL1A	IL-23	TNF	S1P	JAK
Example	Entyvio vedolizumab	TULISOKIBART	Skyrizi risankizumab-rzaa	HUMIRA adalimumab	ZEPOSIA (ozanimod)	RINVOQ upadacitinib

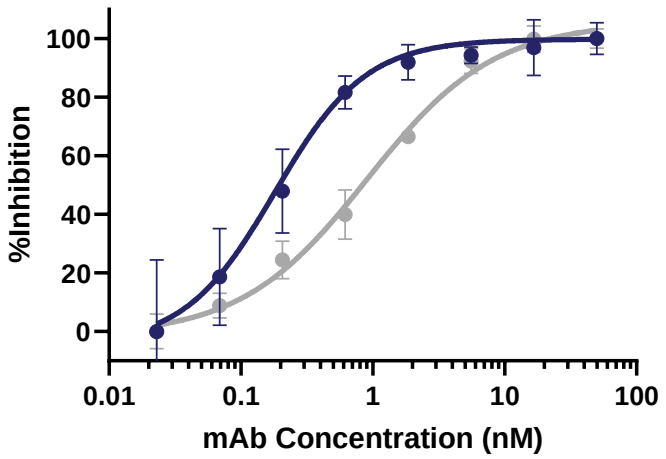
Source: Studies include Entyvio UC (VARSITY, assumes a 10% historical pbo control), CD (GEMINI II); tulisokibart UC (ATREMIS-UC), CD (APOLLO-CD, study was open label and adjusted using a historical pbo rate of 16%); Skyrizi UC (INSPIRE), CD (ADVANCE); Humira UC (ULTRA-II), Humira CD (CLASSIC-1, Bio-naïve patients); Zeposia UC (TRUE NORTH), CD (YELLOWSTONE), Rinvoq UC (U-ACCOMPLISH and U-ACHIEVE), CD (U-EXCEL); [1]EvaluatePharma 2030 Consensus Sales; [2]Merck press release; [3]Ferrante M, et. al. J Crohns Colitis. 2021 Dec 18;15(12):2001-2010. MOA=mechanism of action.

Our next-generation antibodies are engineered to match or exceed the potency of first-generation molecules …

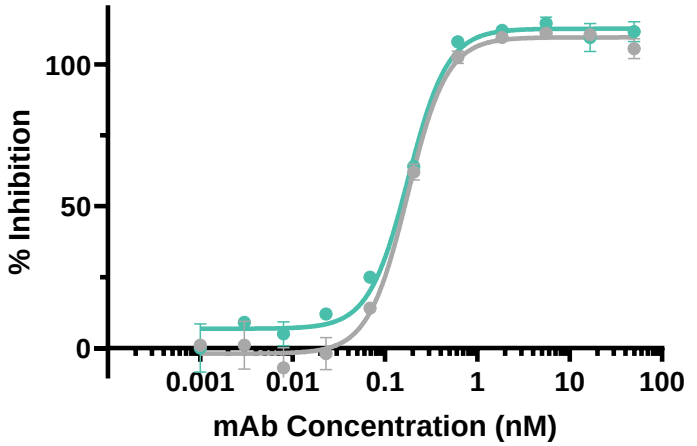
SPY001 (α4β7) *in vitro* potency



SPY002 (TL1A) *in vitro* potency



SPY003 (IL-23) *in vitro* potency



Potential for comparable efficacy at similar or lower doses

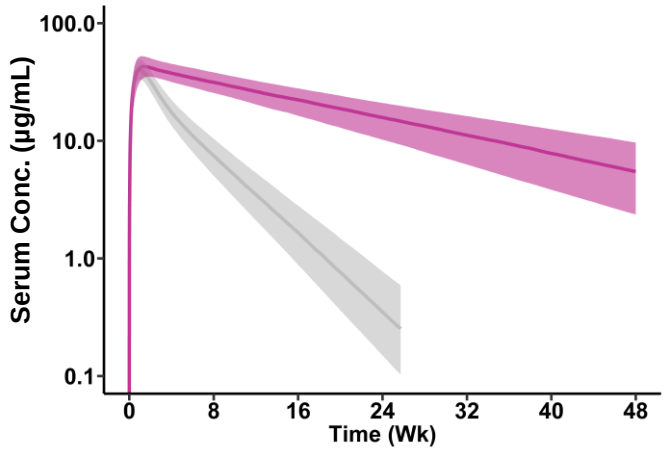
Potential upside: Improved efficacy with higher exposures

Note: Data on file. Details on number of replicates per study are included in later sections. SPY001 assay reports inhibition of cells expressing α4β7 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.

… and share a YTE backbone that significantly extends half-life …

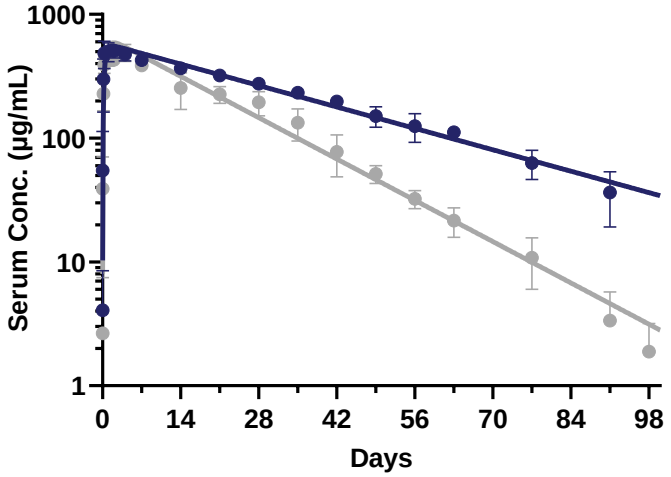
SPY001 (α4β7) Human PK

- SPY001 $t_{1/2}$ = >90 days
- Vedolizumab $t_{1/2}$ = ~25 days



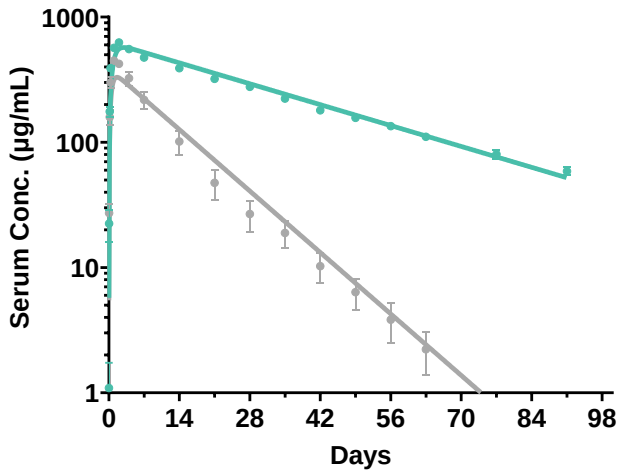
SPY002 (TL1A) NHP PK

- SPY002 $t_{1/2}$ = ~24 days
- Tulisokibart $t_{1/2}$ = ~12 days



SPY003 (IL-23) NHP PK

- SPY003 $t_{1/2}$ = ~30 days
- Risankizumab $t_{1/2}$ = ~9 days

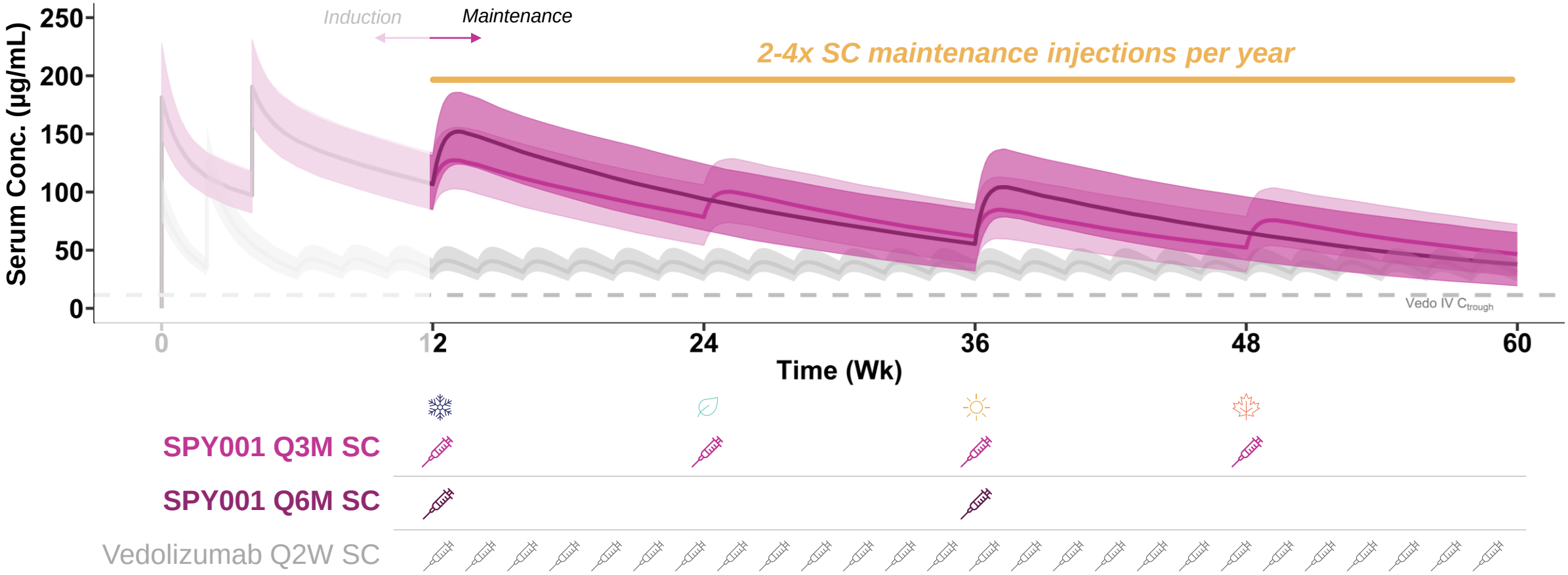


Greater than 2-3x half-life extension vs. competitor molecules across our portfolio

Note: Human PK data in this presentation are derived from different clinical trials at different points in time, with differences in trial design and patient populations. No head-to-head clinical trials have been conducted. Vedolizumab PopPK simulation based on published PK parameters of vedolizumab, Rosario, M, et. al. (2015). Data on file. Pharmacokinetic data shown for SPY002, SPY003, tulisokibart, and risankizumab are from NHP studies, details on number of animals per study are included in later sections. Tulisokibart, and risankizumab are synthesized comparator antibodies.

Population PK modeling for SPY001 supports potential for both Q3M and Q6M maintenance dosing regimens

Maintenance human PK simulations



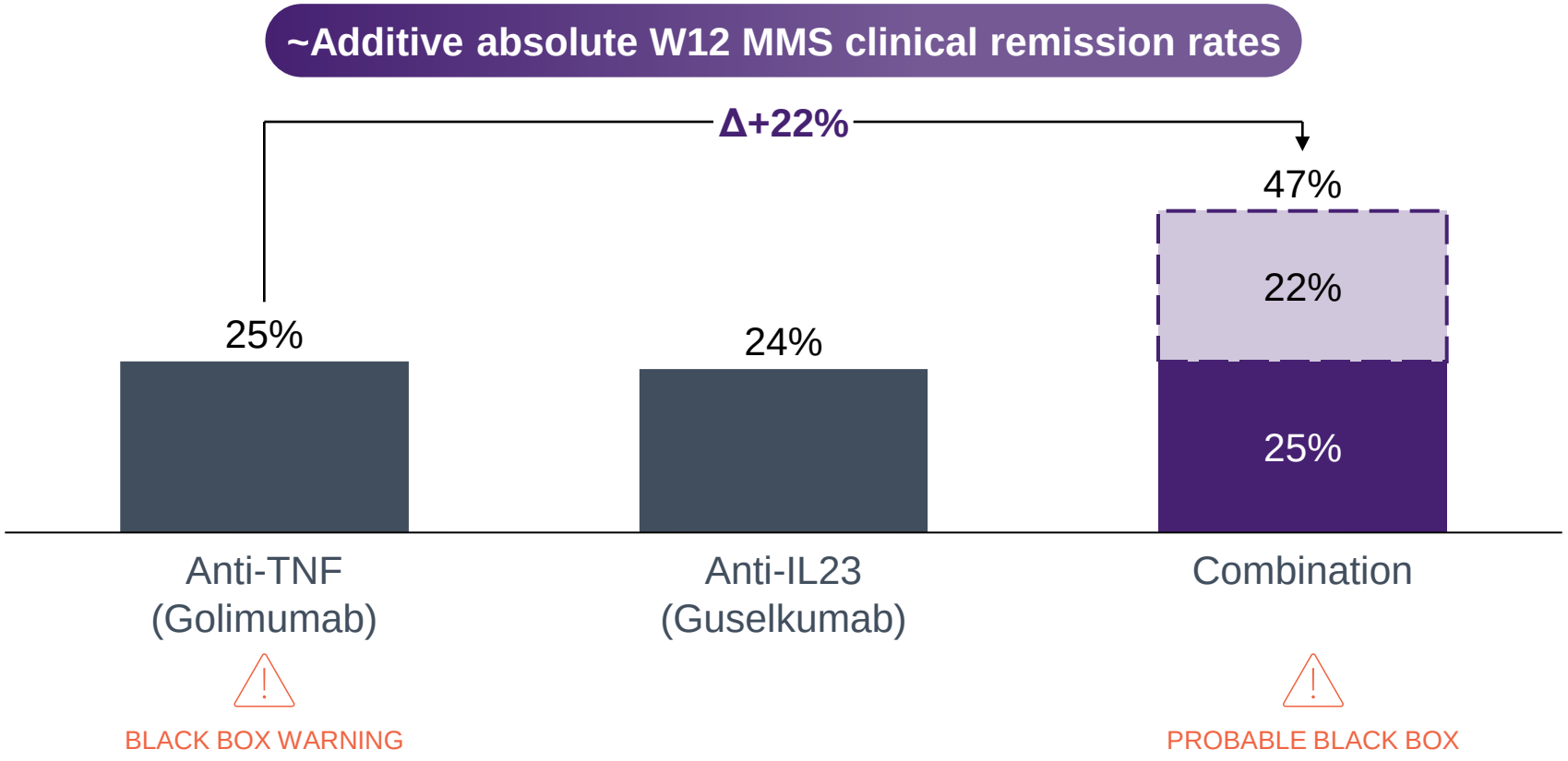
Data on file, simulations represent median +/- interquartile range.

SPY001 Phase 1 interim results summary (10/30/24 cutoff)

SPY001 was well tolerated	**Favorable safety profile across all dose levels**
Half-life of >90 days, far exceeding expectations	**Potential for as little as twice-yearly maintenance dosing in a single SC injection compared to 26 yearly SC injections for vedo**
Ph2 induction dosing to test higher exposures	**Potential for increased or accelerated induction efficacy by targeting all patients in the 4th quartile of vedo's reported E-R relationship**
PD markers demonstrated target engagement	**Single dose of SPY001 saturated α4β7 receptors through available 12 weeks of follow-up (inhibition still ongoing)**

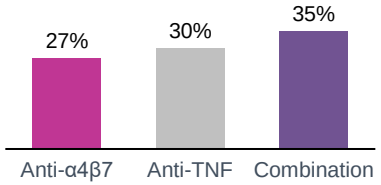
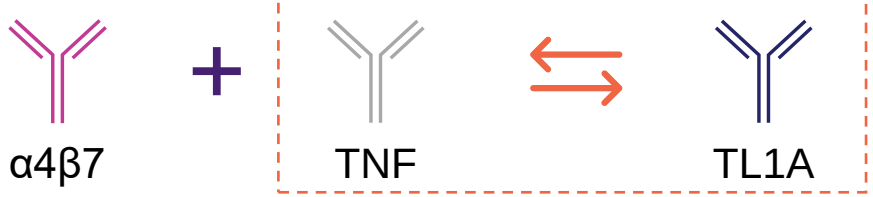
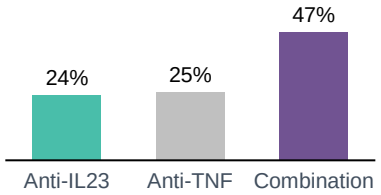
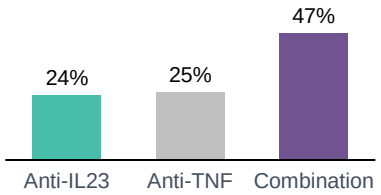
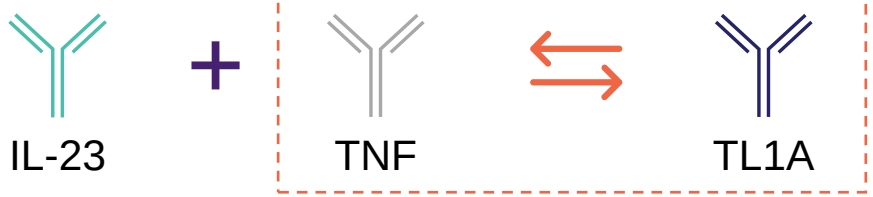
JNJ's VEGA study demonstrated the power of combination therapy in IBD

VEGA combination study (N=71/arm) – Ulcerative colitis



Sources: Feagan, B. G. et al. Lancet Gastroenterol. Hepatol. 8, 307–320 (2023).

Spyre combinations are rational alternatives to combos with clinical precedent

Clinical trial	Precedent combination	Spyre combinations & rationale
EXPLORER[1] Crohn's – Endoscopic remission % 	Spyre component exchange 	 **SPY120** • Exchange TNF for another TNF superfamily targeting agent • TL1A efficacy and safety appears superior on a cross-trial basis
VEGA[2] UC – MMS remission % 		 **SPY130** • Exchange TNF for a safer and more effective class • Entyvio was superior to Humira in H2H clinical studies (VARSITY)
VEGA[2] UC – MMS remission % 		 **SPY230** • Exchange TNF for another TNF superfamily targeting agent • TL1A efficacy and safety appears superior on a cross-trial basis

Note: [1]EXPLORER meta-analysis assumes a 27% remission rate for vedolizumab and 30% remission rate for adalimumab; EXPLORER included methotrexate treatment
Source: [1]Colombel, Jean-Frederic, et al. Clinical Gastroenterology and Hepatology 22.7 (2024): 1487-1496. [2]Feagan, Brian G., et al. The Lancet Gastroenterology & Hepatology 8.4 (2023): 307-320;

Spyre's planned platform trial enables multiple placebo-controlled readouts of monotherapies and combinations

Design elements

Design

- Master protocol platform trial
- Double blind, placebo-controlled

Population

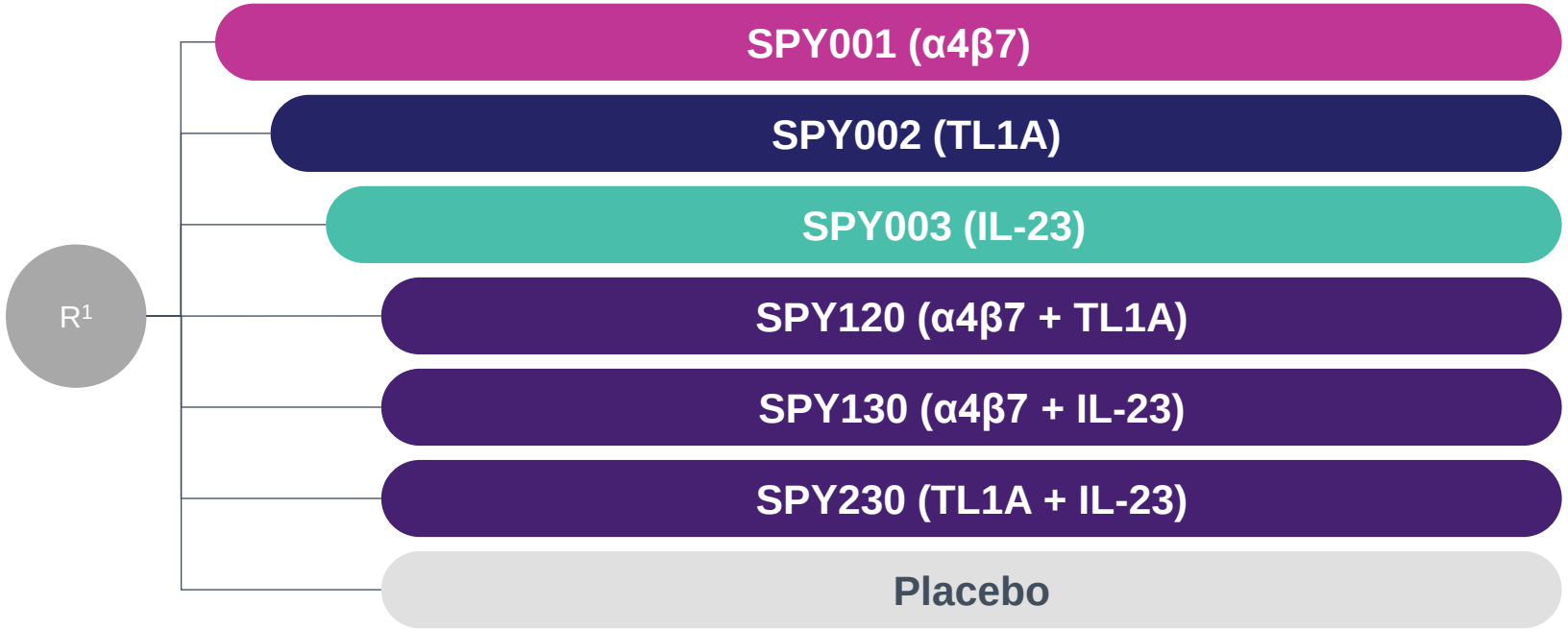
- Moderately-to-severely active ulcerative colitis
- N = ~600

Key endpoints

- Primary: Clinical remission (W12)
- Secondary: Endoscopic improvement (W12), Clinical response (W12), Histological improvement (W12), Histologic-endoscopic improvement (W12)

Illustrative schematic

Pending regulatory feedback



Platform design allows cohorts to be added over time. Anticipate initiating trial with monotherapies beginning in mid-2025 with open-label mono readouts beginning in mid-2026.

Notes: [1]Randomization among active arms; all arms may not start and finish simultaneously

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

SPYRE Planned platform trial[1]

Trial arm	Induction (12W)	Maintenance (through 26W)
Placebo		Q3M
SPY001		Q3M
SPY002		Q3M
SPY003		Q3M
SPY120		Q3M
SPY130		Q3M
SPY230		Q3M

- ✓ Unified dosing intervals and formats enables blinded trial
- ✓ Two IV induction doses, Q3M-Q6M SC chronic dosing
- ✓ Clear approach to advance coformulation for Ph3; >180mg/mL citrate-free formulations in development for all SPY product candidates

Example 3rd party platform trial[2]

Trial arm	Induction (12W)	Maintenance (through 24W)
Mono 1		Q4W
Mono 2		Q2W
Mono 3		Q8W
Combo 1		Q2W
Combo 2		Q4W

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

Note: [1]Pending regulator feedback; [2]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

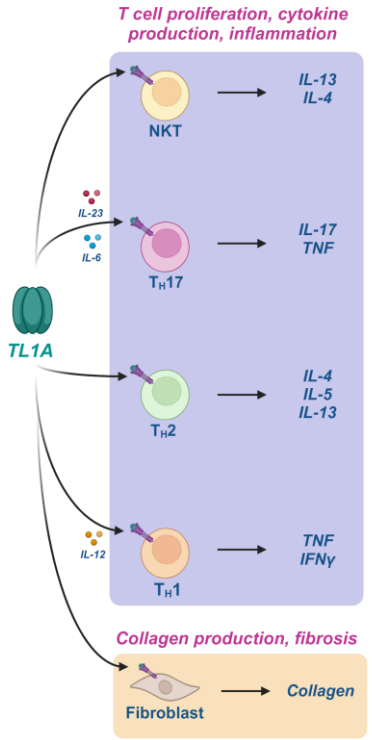
Optimized coformulations are the preferred approach for inhibiting multiple targets in IBD

Allows for dose optimization of each component	Coformulations allow opportunity for adjustment of antibody ratios to achieve desired concentration of each mAb, including for targets in distinct compartments (e.g., circulating α4β7 vs. cytokines in inflamed tissue)
Extended dosing intervals	Coformulations retain extension of monoclonal half-lives and support synchronized extended dosing intervals
Potentially improved immunogenicity profile	Coformulations have the potential to retain or improve immunogenicity profile of monotherapy antibody components

Spyre's planned Phase 2 platform study in UC is expected to provide three combination proof-of-concept readouts in 2027, ahead of any disclosed bispecific approaches against our targets

TL1A has scientific rationale across multiple diseases

TL1A exacerbates inflammation and fibrosis



TL1A has been implicated in a wide range of human diseases[1] based on genetic, proteomic, and/or preclinical data

Not exhaustive

Gastroenterology
- Ulcerative colitis (UC)
- Crohn's disease (CD)

Rheumatology
- Rheumatoid arthritis (RA)
- Systemic lupus erythematosus (SLE)
- Axial spondyloarthritis (axSpA)
- Psoriatic arthritis (PsA)

Pulmonology
- Systemic sclerosis-interstitial lung disease (SSc-ILD)
- Asthma
- Pulmonary sarcoidosis

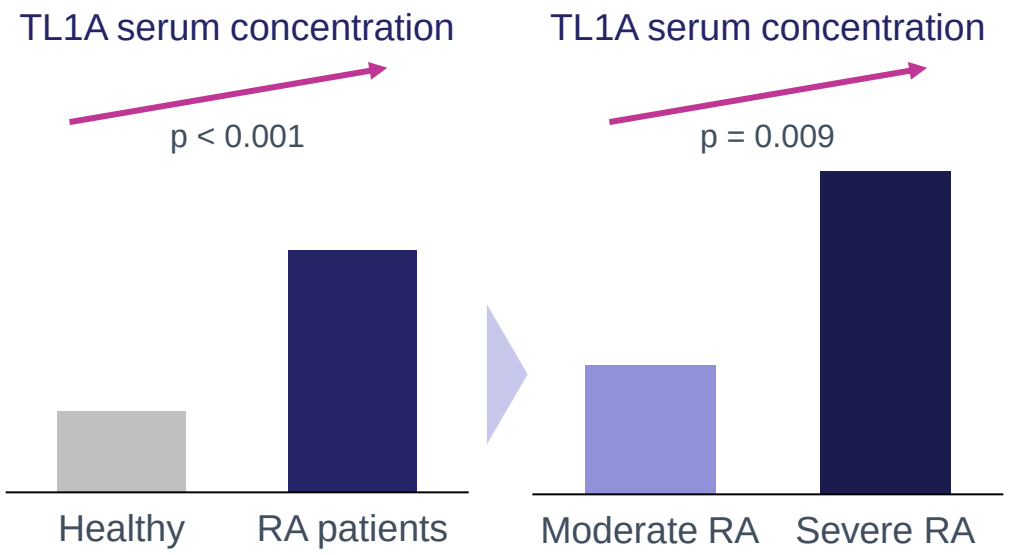
Dermatology
- Psoriasis (PsO)
- Hidradenitis suppurativa (HS)
- Atopic dermatitis (AD)

Note: Figure created with BioRender.com; [1]Non-exhaustive.

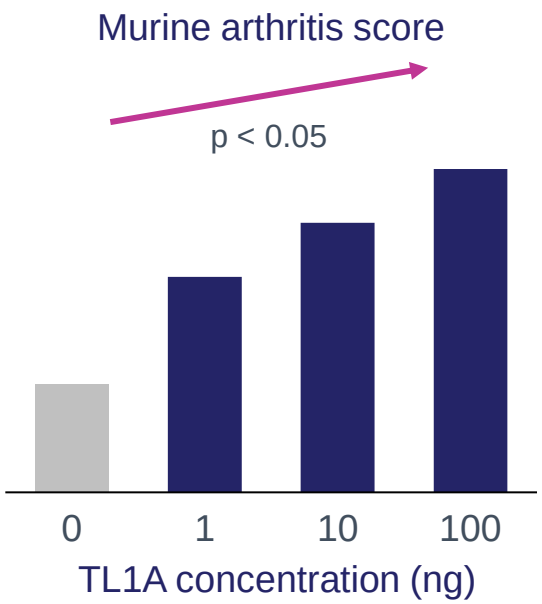
Source: Hisamoto, T. et al. Int. J. Mol. Sci. 24, 1813 (2023); Herro, R. et al. J. Immunol. 205(9), 2414-2422 (2020); Ma, C. et al. Int. Immunopharm. 137, 112360 (2024); Richard, A. et al. JLB 3(98), 333-345 (2015); Song, Y. et al. Arthritis Research & Therapy 22, 106 (2020); Xu, W. et al. Frontiers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

Multiple published studies support anti-TL1A as a potential treatment option in RA

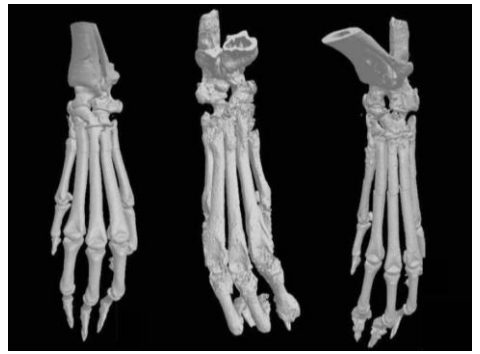
TL1A is elevated in RA patients relative to healthy controls & increases with disease severity[1, 2, 3]



TL1A administration exacerbates arthritis in murine models and administration of **anti-TL1A** reduces arthritis[2,4]



Anti-TL1A dramatically reduces erosions in hind paws of CIA mice

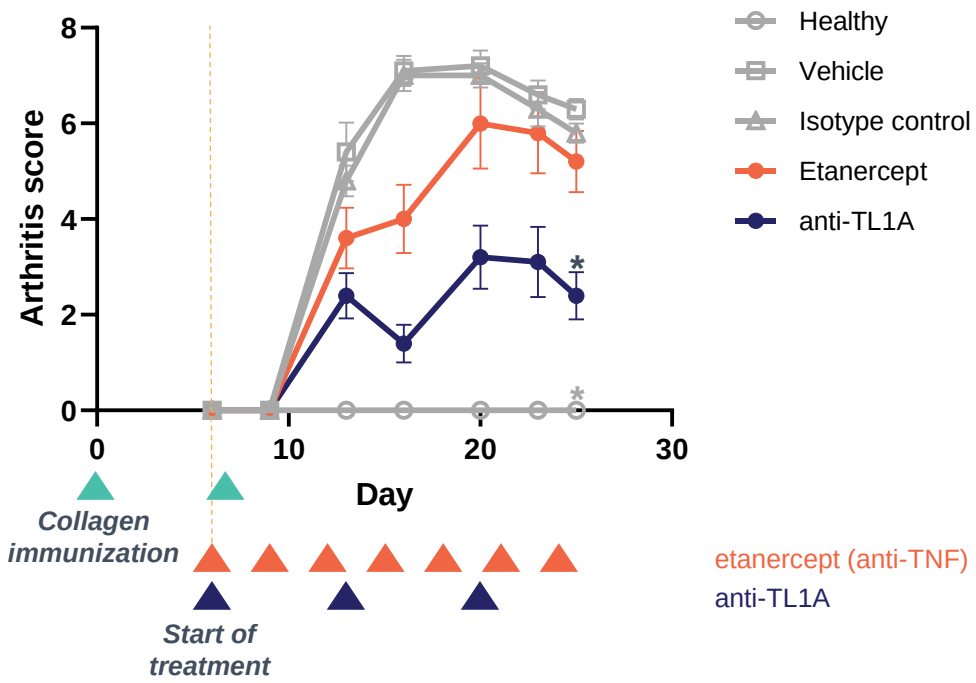


No CIA ***Ig control*** ***anti-TL1A***

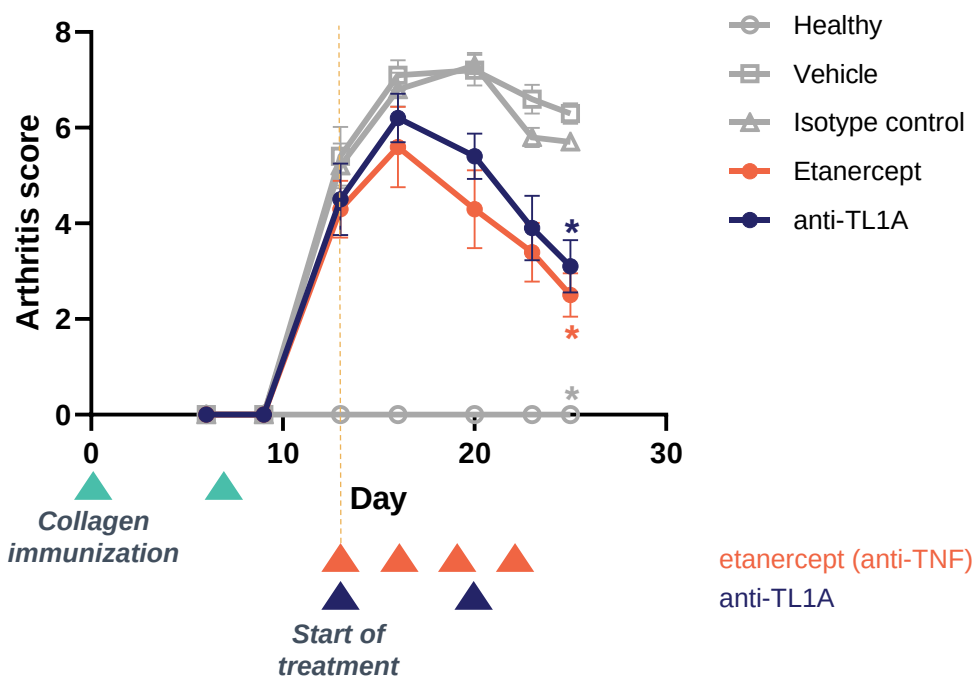
Source: [1]Sun, X. et al. Scand. J. Rheumatol. 42(2), 97-101 (2013); [2]Song, Y. et al. Arthritis Res. Ther., 22(1), 106 (2020); [3]Bamias, G., Clin. Immunol., 129(2), 249-255 (2008); [4]Bull, M., et al. J. Exp. Med. 205(11); Charts are illustrative representations of figures within data sources. CIA=collagen-induced arthritis

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

Superior efficacy vs. anti-TNF in semi-preventative model



Comparable efficacy vs. anti-TNF in therapeutic model



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

Catalyst rich 2025 planned with expected Ph1 readouts on TL1A and IL-23 programs and multiple Ph2 initiations

	2025		2026
SPY001 (α4β7)		❑ UC Platform Ph2 Initiation	❑ **UC Ph2 data**
SPY002 (TL1A)	❑ **Ph1 data (2Q)**	❑ RA Ph2 Initiation	❑ **UC Ph2 data** ❑ **RA Ph2 data**
SPY003 (IL-23)	❑ Ph1 Initiation (1Q)	❑ **Ph1 data**	❑ **UC Ph2 data**
External events		❑ **DUET-UC/CD Ph2b** *JNJ TNF + IL-23 combo*	

All of the milestones for data including timing are as anticipated or expected as of the date of this presentation and subject to regulatory feedback.


Thank you – Q&A