



# Anti-TL1A Phase 1 Results and Phase 2 Development Updates

June 2025

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Certain information set forth in this presentation contains “forward-looking statements” within the meaning of applicable United States securities legislation. Except for statements of historical fact, certain information contained herein constitutes forward-looking statements which include but are not limited to statements regarding: our business strategy, including our ability to develop best-in-class and first-in-class 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; the potential consistency of the SPY001, SPY002 and SPY072 Phase 1 trial final data readouts with interim Phase 1 results; the efficacy, safety profile, dosing regime, convenience, commercial viability and tolerability of SPY002, SPY072 and our other product candidates; our plans to advance both SPY002 and SPY072 programs into Phase 2 clinical trials; Spyre’s ongoing and future clinical development activities, including the expected design and timing of the planned platform SKYWAY-RD Phase 2 basket trial, including timing of data readouts, timing of data readout for the ongoing SPY003 Phase 1 trial, timing of each part, cohort and data readouts for the ongoing SKYLINE-UC 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 planned 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 cost savings from the trial designs of our Phase 2 platform trial and Phase 2 basket trial; potential alignment with regulatory authorities and anticipated regulatory submissions; expected timing for regulatory feedback; estimated market sizes, potential growth opportunities, potential value creation and sample transactions; 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; expectations regarding our potential therapeutic combinations, including dosing regime, and the potential benefits thereof; and management’s assessment of future plans and operations which are based on current internal expectations, estimates, projections, assumptions and beliefs, which may prove to be incorrect. 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# Agenda



## Introduction and Executive Summary



**Cameron Turtle, DPhil**  
Chief Executive Officer

## SPY002 & SPY072 Phase 1 Interim Results



**Joshua Friedman, MD, PhD**  
SVP, Clinical Development

## SKYLINE-UC Phase 2 Study



**Deanna Nguyen, MD**  
SVP, Clinical Development

## SKYWAY-RD Phase 2 Study



**Joshua Friedman, MD PhD**  
SVP, Clinical Development

## Closing and Analyst Q&A



**Cameron Turtle, CEO**  
**Joshua Friedman, SVP**  
**Sheldon Sloan, CMO**  
**Deanna Nguyen, SVP**  
**Scott Burrows, CFO**



## Today's Objectives



**Cameron Turtle**  
Chief Executive Officer

1

Report  
**Anti-TL1A data**  
Phase 1 results for **two potential best-in-class molecules**

2

Launch  
**SKYLINE-UC**  
A Phase 2 platform study in ulcerative colitis evaluating **three monotherapies & three combinations**

3

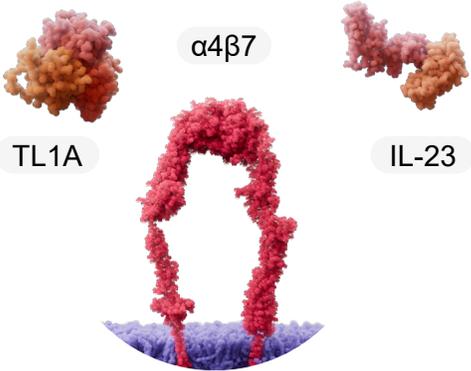
Unveil  
**SKYWAY-RD**  
A Phase 2 basket study evaluating anti-TL1A in **three rheumatologic conditions**

# Engineering for new heights in the treatment of IBD & beyond



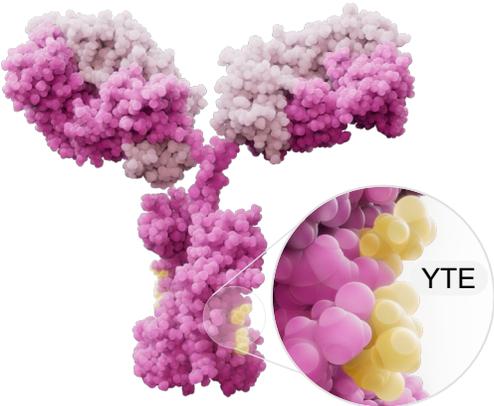
## Validated targets

MOAs rationally chosen based on attractive risk-benefit profiles



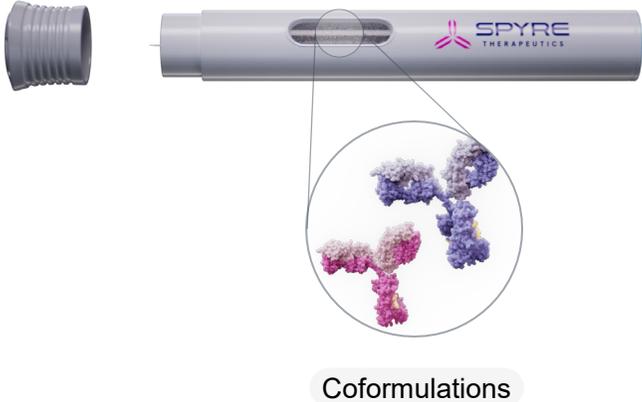
## Half-life extension

Engineered for prolonged activity to enable infrequent administration



## Fixed-dose combinations

Rationale combinations to address distinct disease drivers

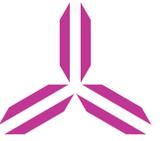


Potential best-in-class monotherapies & combinations in **IBD**



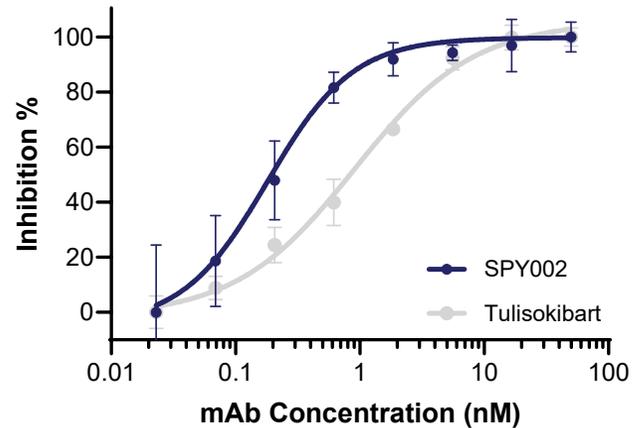
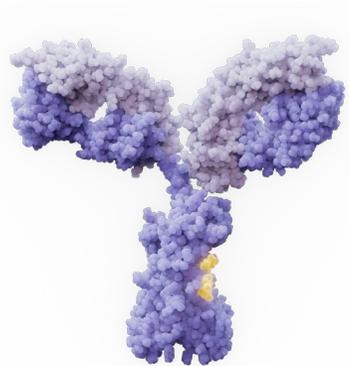
Potential first-in-class anti-TL1A in **rheumatologic conditions**

# Recall: We advanced two anti-TL1A antibodies into Ph1 with best-in-class preclinical properties



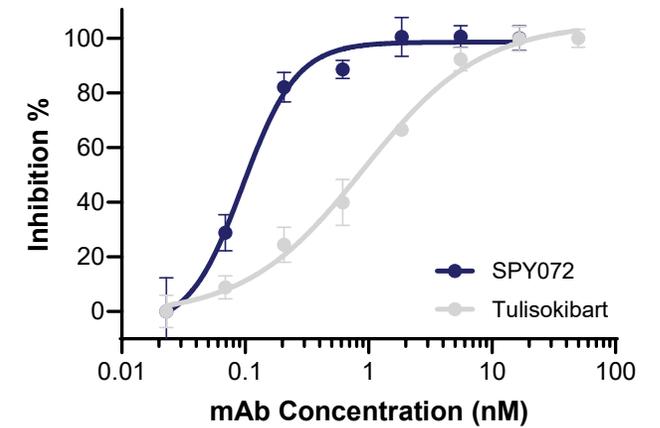
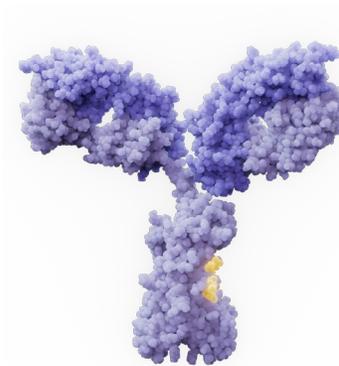
## SPY002 (formerly SPY002-091)

*In vitro* potency (TF-1 apoptosis)



## SPY072 (formerly SPY002-072)

*In vitro* potency (TF-1 apoptosis)



Distinct epitopes



Superior-to-comparable *in vitro* potency



NHP half-life >2-3x

*vs. first-generation anti-TL1As*

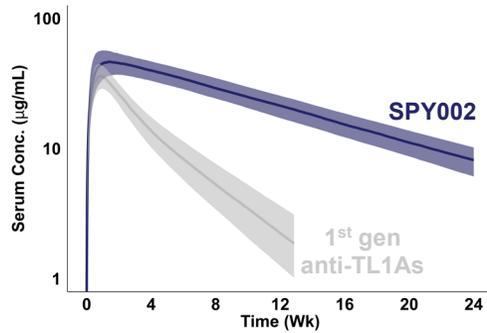
# SPY002 and SPY072 met Phase 1 objectives, and Spyre plans to advance both into Phase 2



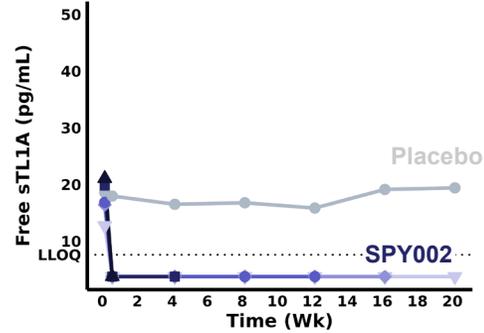
## SPY002

## SPY072

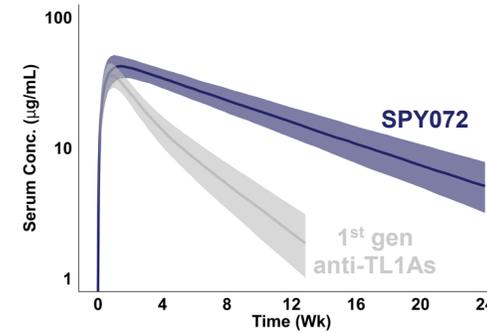
Simulated mean PK profiles



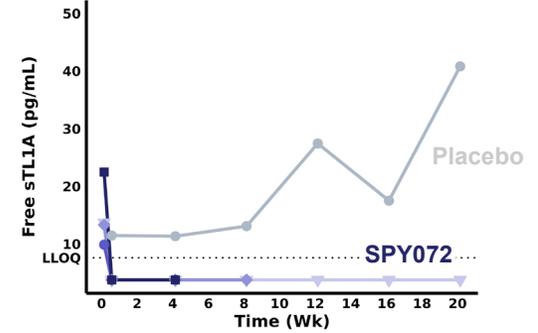
Median PD profiles



Simulated mean PK profiles



Median PD profiles



Well tolerated  
favorable safety profile



PK supports quarterly or  
less frequent dosing



Rapid & sustained  
target engagement



No apparent impact of  
ADAs on PK/PD

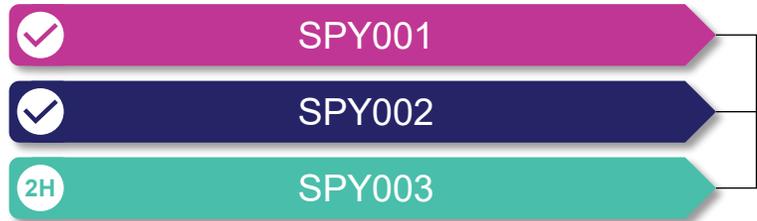
# Transitioning to a mid-stage development company...



PHASE 1

PHASE 2

PHASE 3



**Rationale for advancing two anti-TL1As:**  
**Strategic:** Partnering optionality  
**Commercial:** Pricing flexibility, separate IRA timing and revenue

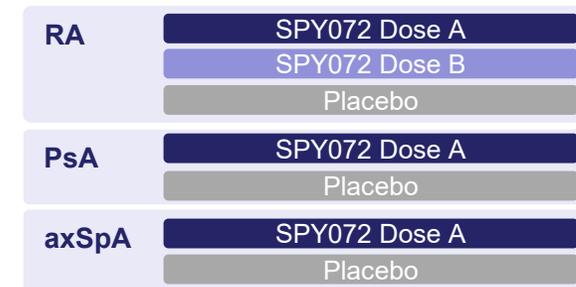
# ...with two innovative and capital-efficient Phase 2 trials



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



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



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AGENTS

1

INDICATION



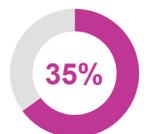
COST SAVINGS<sup>1</sup>

1

AGENT

3

INDICATIONS



COST SAVINGS<sup>1</sup>

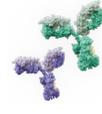
# Anticipated 9 proof-of-concept readouts in 2026-27 for the treatment of IBD & beyond



Trial	Indication	Program	Target	Phase 1	Phase 2	Phase 3	Anticipated Milestones	
	UC	SPY001	α4β7	[Phase 1, 2, 3 bars]			<b>2026: Ph2 open-label POC</b> <b>2027: Ph2 pbo-controlled data</b>	
		SPY002	TL1A	[Phase 1, 2 bars]				
		SPY003	IL-23	[Phase 1, 2 bars]				
			SPY120	α4β7 + TL1A	[Phase 1, 2 bars]			<b>2027: Ph2 POC</b>
			SPY130	α4β7 + IL-23	[Phase 1, 2 bars]			
			SPY230	TL1A + IL-23	[Phase 1, 2 bars]			
	RA	SPY072	TL1A	[Phase 1, 2, 3 bars]			<b>2026: Ph2 POC</b>	
	PsA			[Phase 1, 2, 3 bars]				
	axSpA			[Phase 1, 2, 3 bars]				

# Potential additive paths to significant value creation in 2026-27



	mid-2025	2026			2027							
<b>Trial</b>	Phase 1s	SKYLINE-UC			SKYWAY-RD			SKYLINE-UC				
<b>Programs</b>	 SPY001  SPY002  SPY072  SPY003	 SPY001  SPY002  SPY003	 SPY072	 SPY120  SPY130  SPY230								
<b>Readout</b>	Interim safety, PK, PD HVs	Monotherapy OL POC UC			Anti-TL1A POC RA, PsA, axSpA			Combination POC UC				
<b>Analog type</b>		Validated MOA, improved convenience			First-in-class MOA in \$30B+ market			Paradigm-changing combinations				
<b>Precedent<sup>1</sup></b>		 \$3B+ acquisition			+	 \$10B+ acquisition			+	 \$10B+ post-POC <sup>2</sup>		

# SPY002 and SPY072 Phase 1 interim results



## Today's Objectives



**Josh Friedman**

SVP, Clinical Development

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**Anti-TL1A data**  
Phase 1 results for **two potential best-in-class molecules**

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**SKYWAY-RD**  
A Phase 2 basket study evaluating anti-TL1A in **three rheumatologic conditions**

# Both molecules studied in similar Ph1 SAD studies, with interim data up to 20-weeks of follow up



## Trial design elements

### Design

- Double-blind, pbo-controlled, first-in-human trial
- Escalating SAD cohorts

### Population

- Healthy adult volunteers
- N=8/cohort (3:1 randomization)

### Endpoints

- Primary: Safety
- Secondary: Pharmacokinetics, anti-drug antibodies (ADAs)
- Exploratory: Pharmacodynamic markers

## SPY002 and SPY072 SAD PK and safety follow up



# SPY002 and SPY072 were well tolerated with a favorable safety profile (pooled, blinded data)



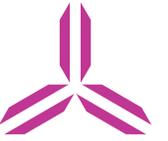
## SPY002 safety profile

N (%)	 100 mg	 300 mg	 300 mg	 1000 mg	 1500 mg	SAD Pooled
N=	8	8	8	8	8	40
At least one TEAE	3 (38%)	2 (25%)	3 (38%)	3 (38%)	0	11 (28%)
At least one TESAE	0	0	0	0	0	0
At least one Treatment-related AE	2 (25%) <sup>1</sup>	0	0	0	0	2 (5%)
At least one Grade 3/4 TEAE	0	0	0	0	0	0

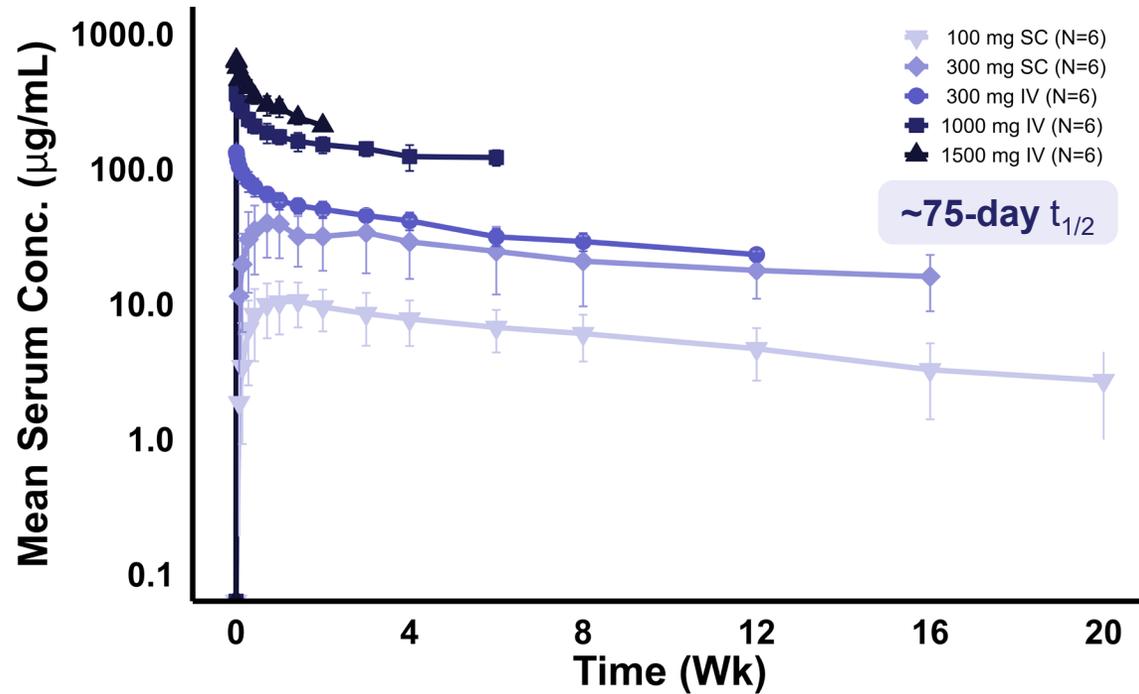
## SPY072 safety profile

N (%)	 100 mg	 300 mg	 300 mg	 1000 mg	 1500 mg	SAD Pooled
N=	8	8	8	8	8	40
At least one TEAE	2 (25%)	5 (63%)	5 (63%)	2 (25%)	1 (13%)	14 (35%)
At least one TESAE	0	0	0	0	0	0
At least one Treatment-related AE	0	2 (25%) <sup>2</sup>	0	1 (13%) <sup>3</sup>	0	3 (8%)
At least one Grade 3/4 TEAE	0	0	0	0	0	0

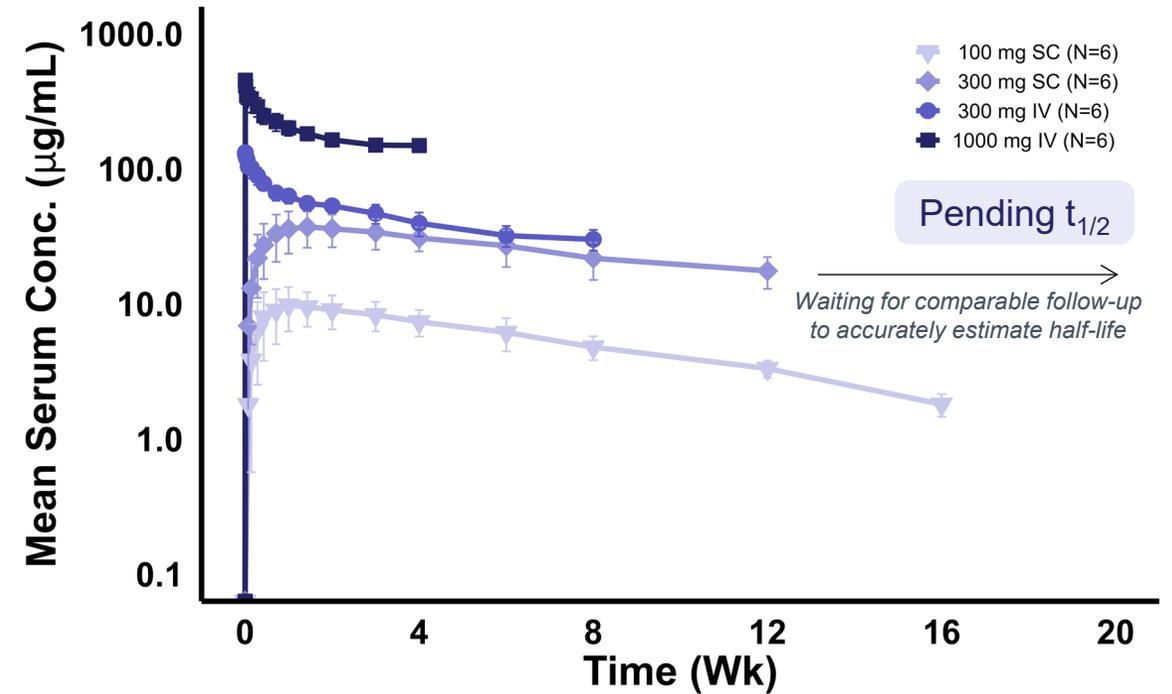
# SPY002 and SPY072 demonstrated prolonged and dose proportional PK



## SPY002 mean PK profiles



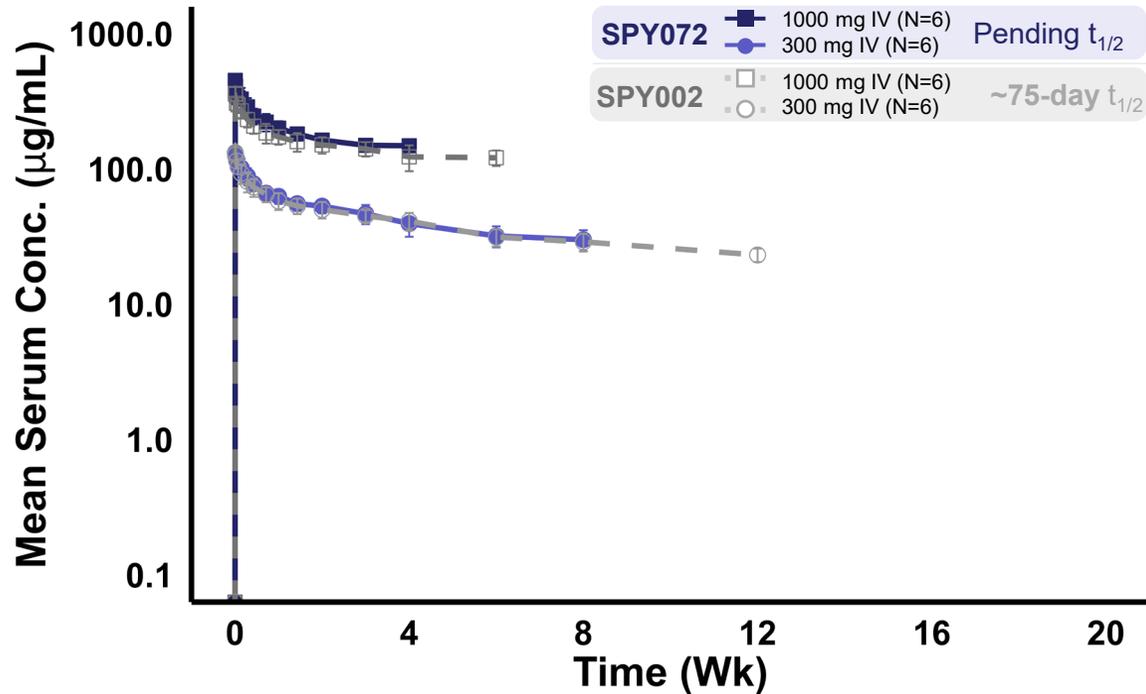
## SPY072 mean PK profiles



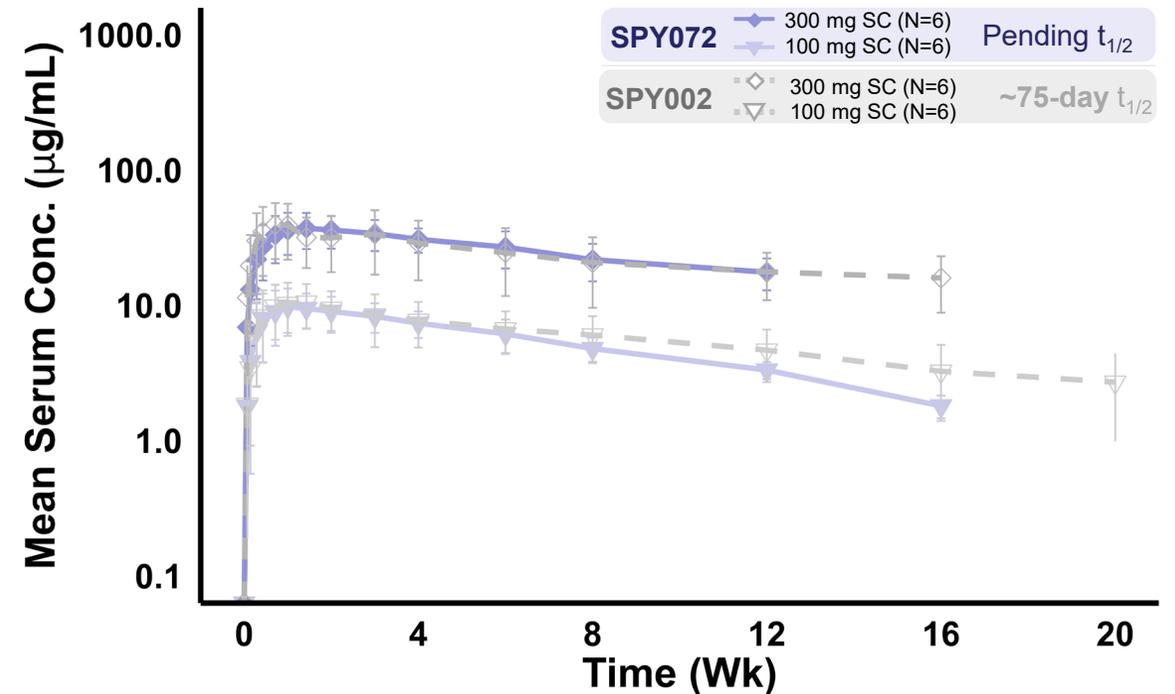
# SPY072 showed comparable PK to SPY002 at clinically relevant doses through available follow up



## SPY002 & SPY072 mean PK profiles (IV)



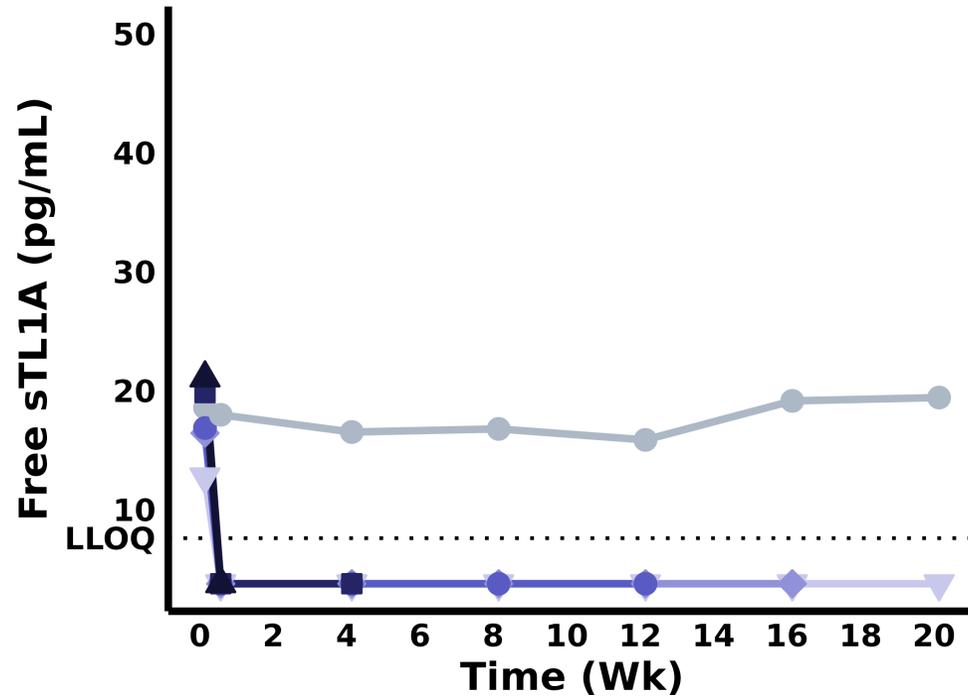
## SPY002 & SPY072 mean PK profiles (SC)



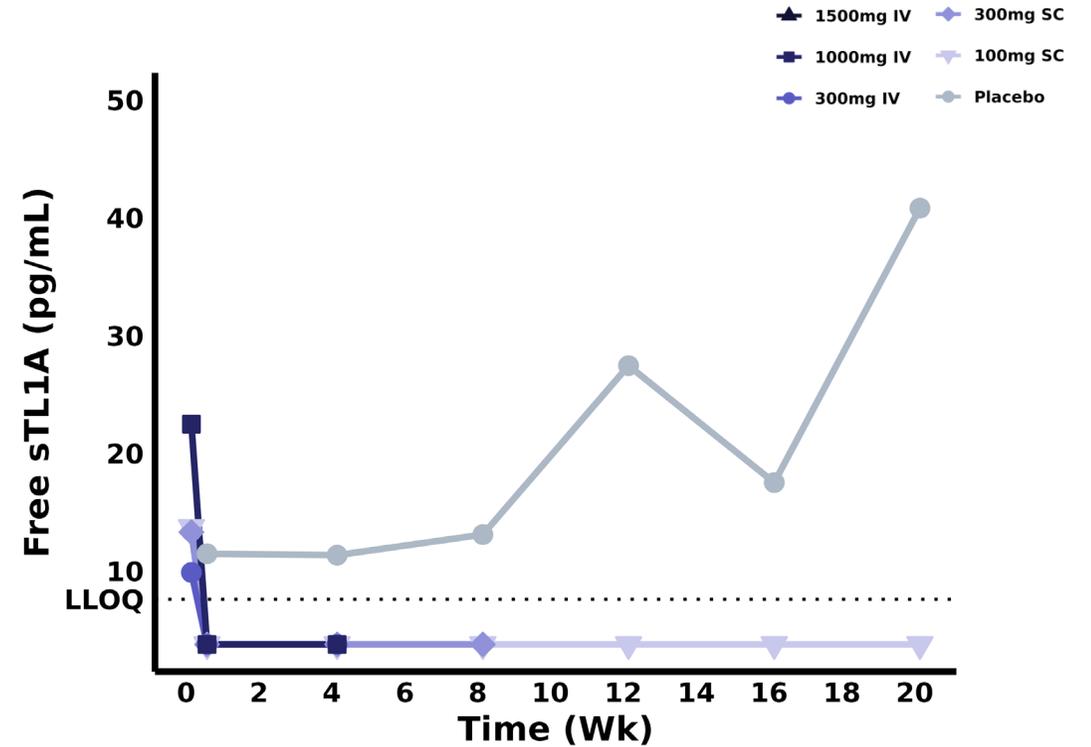
# SPY002 and SPY072 suppressed free TL1A through 20-weeks of follow-up at the lowest dose tested



## SPY002 median free sTL1A PD profiles



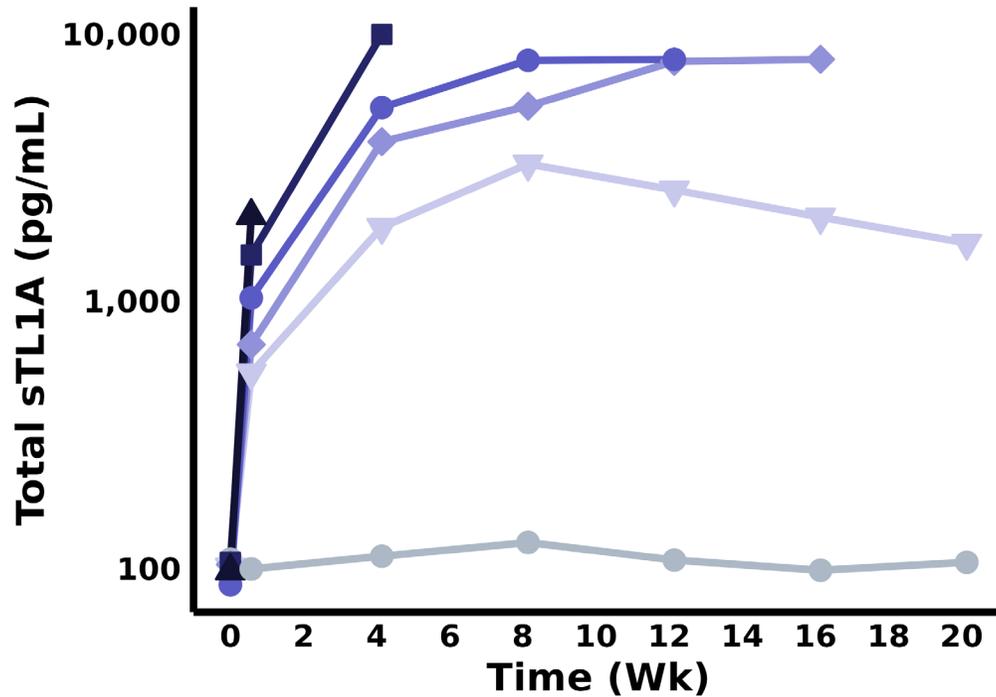
## SPY072 median free sTL1A PD profiles



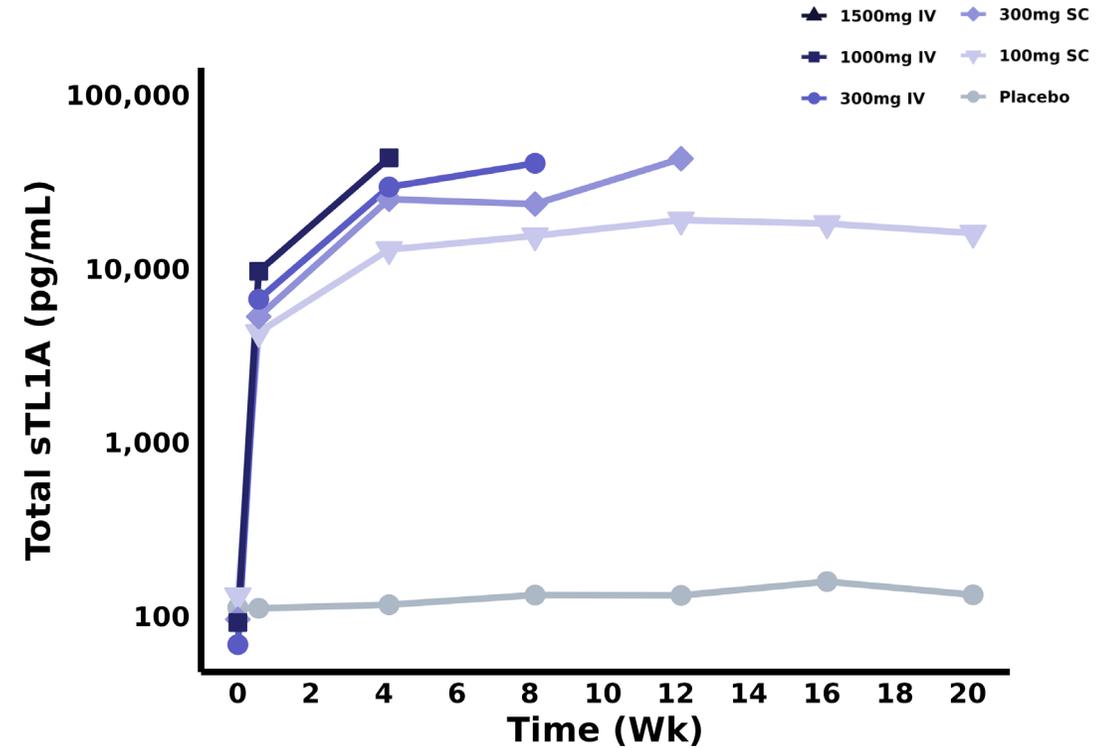
# SPY002 and SPY072 increased total TL1A in a durable and dose-dependent manner



### SPY002 mean total sTL1A PD profiles



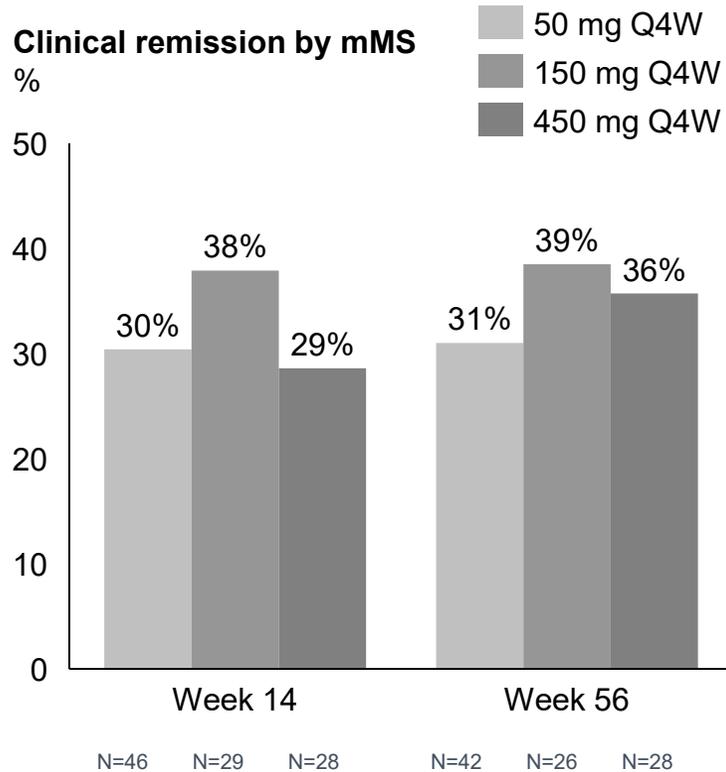
### SPY072 mean total sTL1A PD profiles



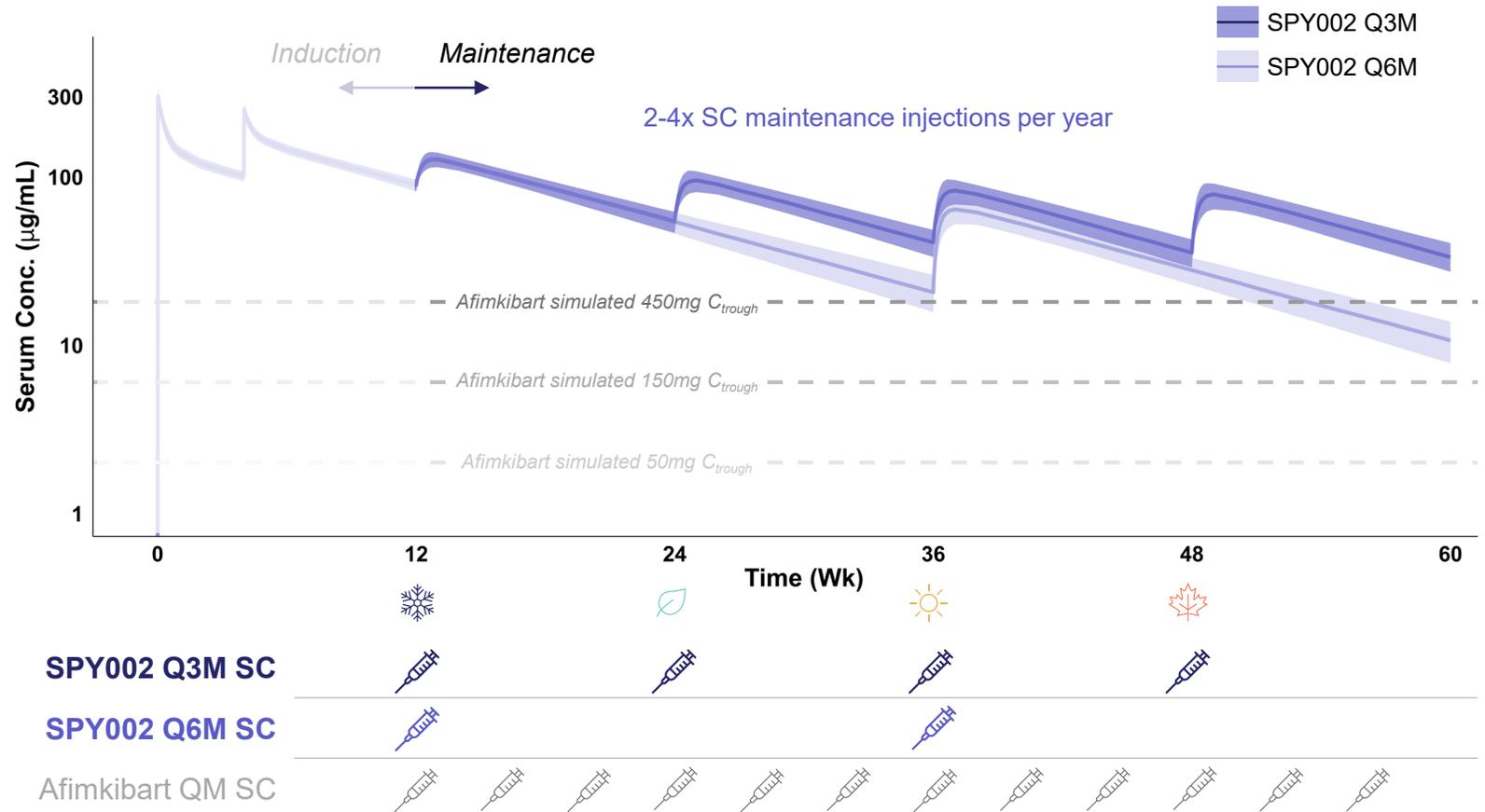
# Interim PK supports quarterly or twice annual dosing



## Afimkibart Ph2 UC results



## SPY002 simulated concentration-time profile



# SPY002 and SPY072 Phase 1 interim results summary



**Well-tolerated**

**Favorable safety profile across all dose levels**

**Prolonged PK exposure**

**Extended half-lives support potential for quarterly or twice annual dosing**

**Rapid & sustained target engagement**

**PD was durable through 20-weeks at the lowest dose tested**

**No apparent immunogenicity impact**

**No apparent impact of ADAs on PK or PD through available follow up**

**SPY002 expected to advance to the SKYLINE-UC study and SPY072 expected to advance to SKYWAY-RD study**

# SKYLINE-UC Phase 2 study



## Today's Objectives



**Deanna Nguyen**

SVP, Clinical Development

1

Report  
**Anti-TL1A data**  
Phase 1 results for **two potential best-in-class molecules**

2

Launch  
**SKYLINE-UC**  
A Phase 2 platform study in ulcerative colitis evaluating **three monotherapies & three combinations**

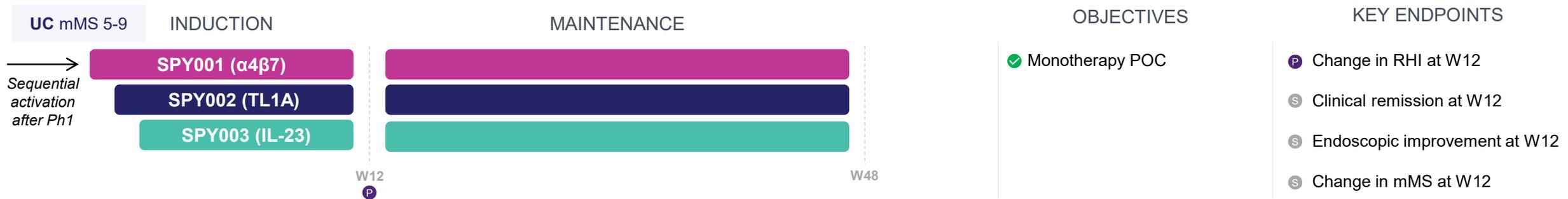
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Unveil  
**SKYWAY-RD**  
A Phase 2 basket study evaluating anti-TL1A in **three rheumatologic conditions**

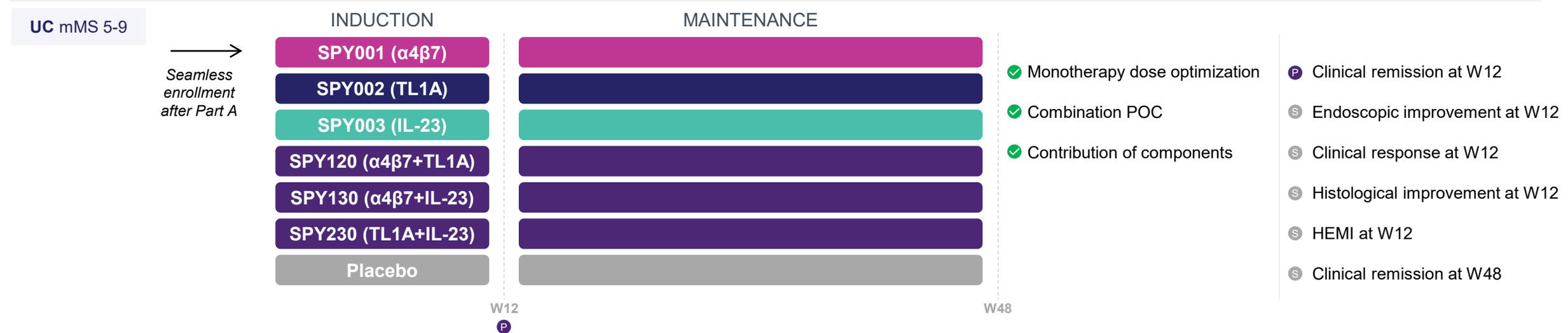
# SKYLINE-UC: Phase 2 *platform* study evaluating three monotherapies and three combinations in UC



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



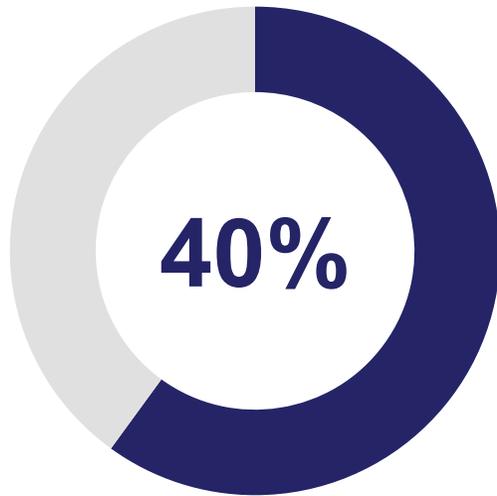
## Part B: PBO-controlled factorial combination evaluation (N=~550)



# Capital-efficient trial that is designed to be attractive to patients and investigators



CAPITAL EFFICIENT



Cost savings and reduced sample size compared to individual Ph2 studies for each program

PATIENT CENTRIC

PART A

Open-label

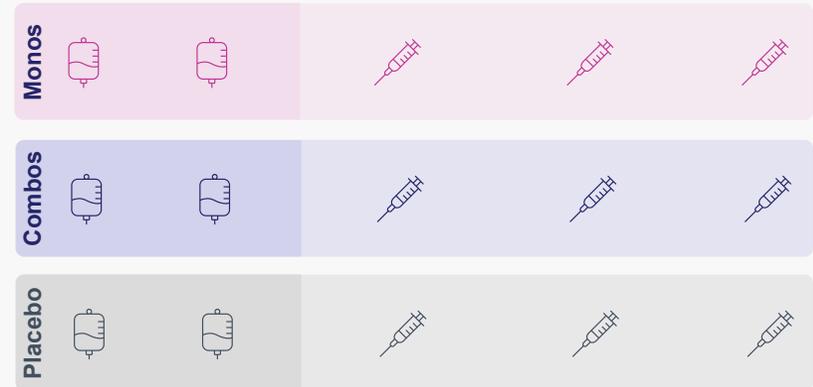
PART B

6 actives  
vs.  
1 placebo

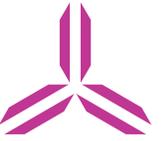
STREAMLINED UNIFIED DOSING

INDUCTION

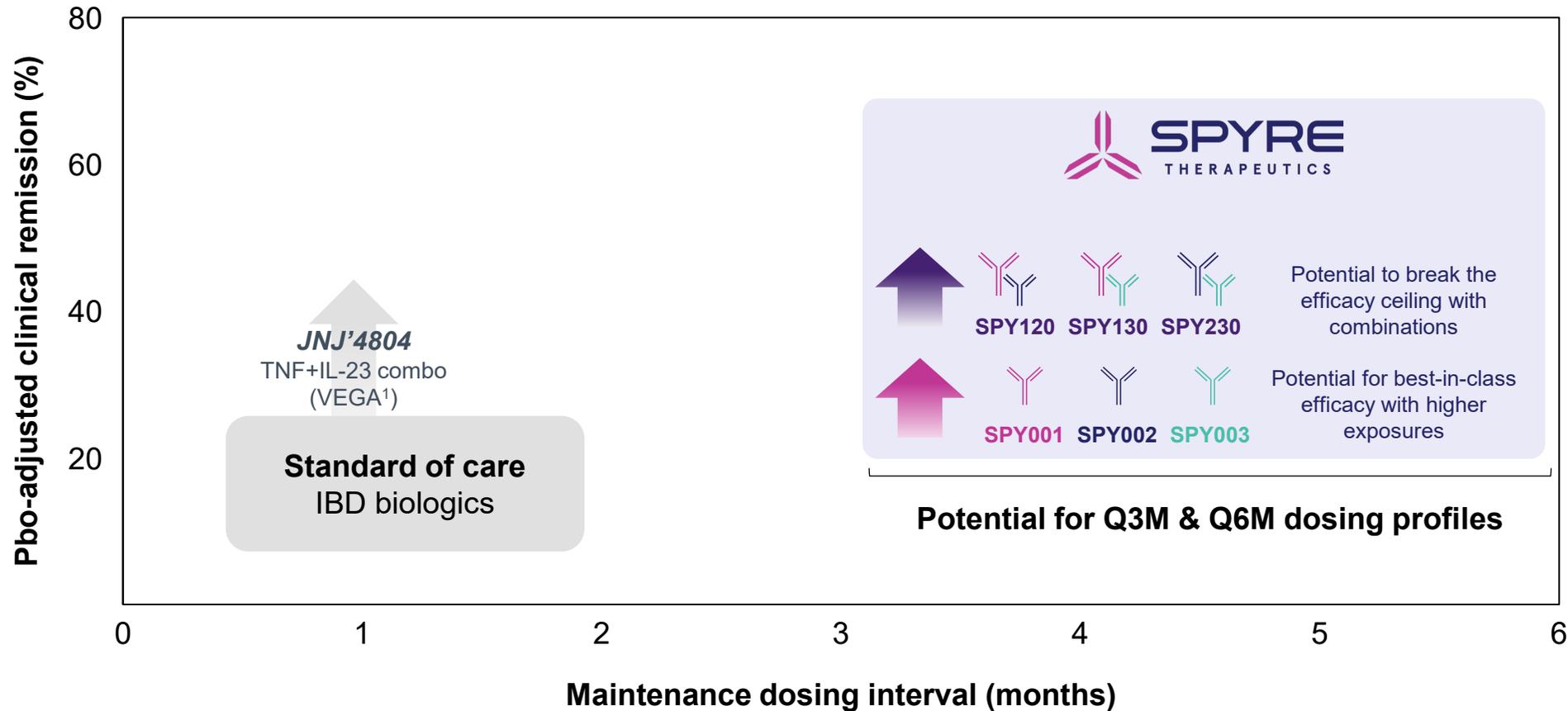
MAINTENANCE



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



ILLUSTRATIVE



# Co-administration of mAbs can reduce immunogenicity whereas bispecific formats can increase immunogenicity

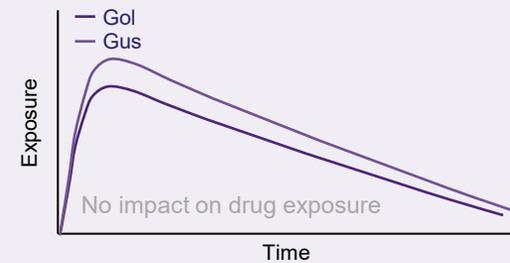


## ADA rates for TNF or TL1A bsAbs vs. coformulations

Asset	Target	Immunogenicity	Population	Structure
golimumab + guselkumab (JNJ-4804)	TNFα + IL-23	6% PHASE 2	UC	Separate human IgG1 mAbs
JNJ-3539	TNFα / IL-17	DISCONTINUED 93%	HVs	IgG-fynomer (2x2)
JNJ-8104	TNFα / IL-17	DISCONTINUED 100%	HVs	Duobody (1x1)
ABT-122	TNFα / IL-17	DISCONTINUED 99%	HVs	Dual variable domain (2x2)
AMG-966	TNFα / TL1A	DISCONTINUED 98%	HVs	Four unique heavy and light chain pairs (1x1)
MEDI-7352	TNFα / NGF	DISCONTINUED 72%	OA	IgG-scFv (2x2)
RO7837195 (PF-07261271)	TL1A / p40	PHASE 2 100%	HVs	CrossmAb (1x1)

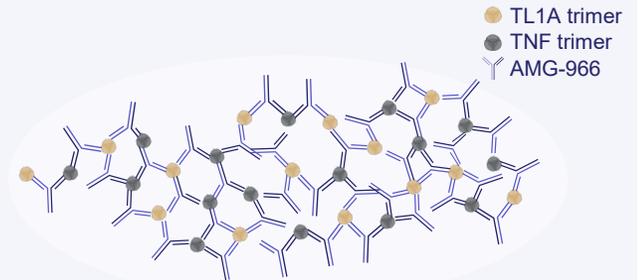
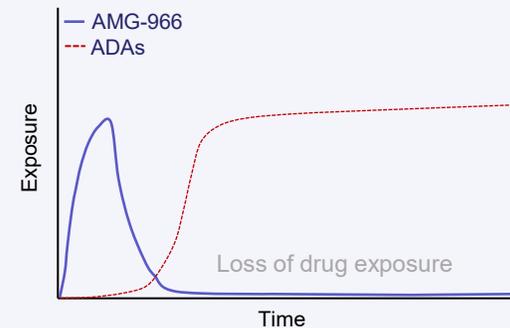
## Case studies

### JNJ-4804 coformulation



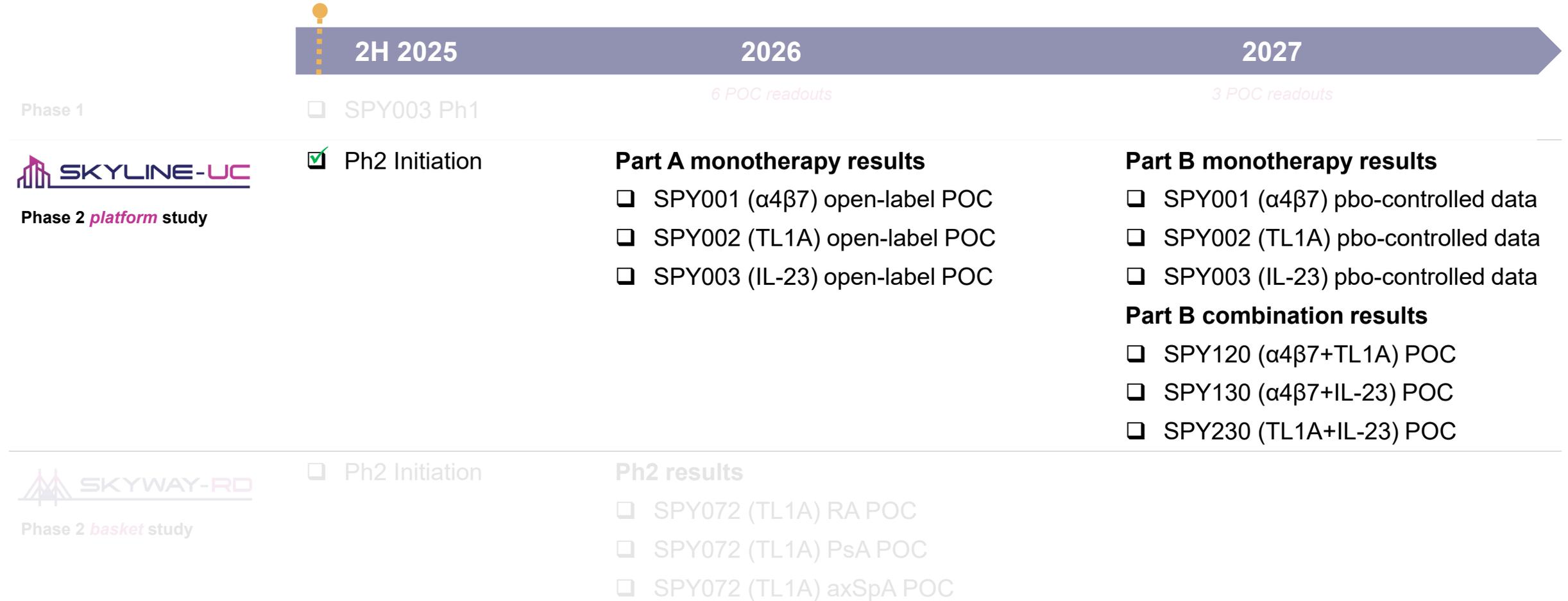
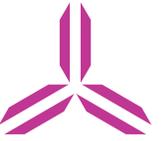
“... Combination therapy appeared to decrease the incidence of antibodies to golimumab ...”

### AMG-966 bispecific



“... We demonstrate here that AMG966 forms large immune complexes ... which drive an antibody response and resulted in loss of exposures ...”

# SKYLINE-UC: First patients in screening and on-track for expected 6 POC readouts through 2027



# SKYWAY-RD Phase 2 study



## Today's Objectives



**Josh Friedman**

SVP, Clinical Development

1

Report  
**Anti-TL1A data**  
Phase 1 results for **two potential best-in-class molecules**

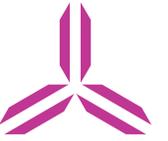
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Launch  
**SKYLINE-UC**  
A Phase 2 platform study in ulcerative colitis evaluating **three monotherapies & three combinations**

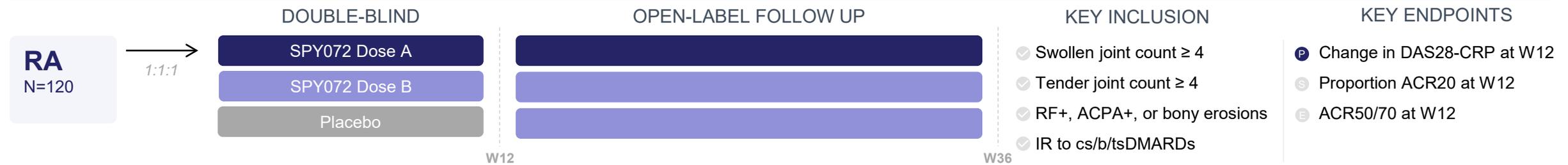
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Unveil  
**SKYWAY-RD**  
A Phase 2 basket study evaluating anti-TL1A in **three rheumatologic conditions**

# SKYWAY-RD: 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)



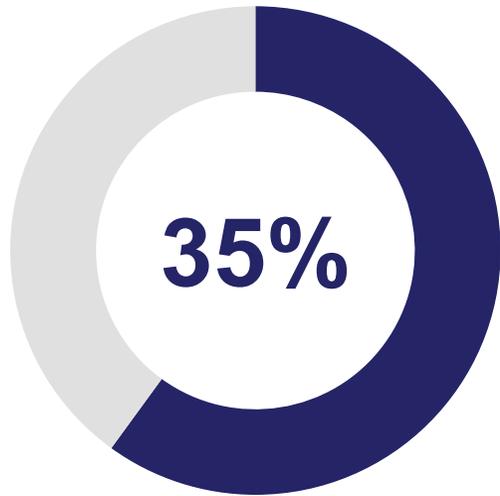
## Sub-study C: SPY072 in moderate-to-severely active axial spondyloarthritis (axSpA)



# Operationally-efficient design with shared sites and specialty

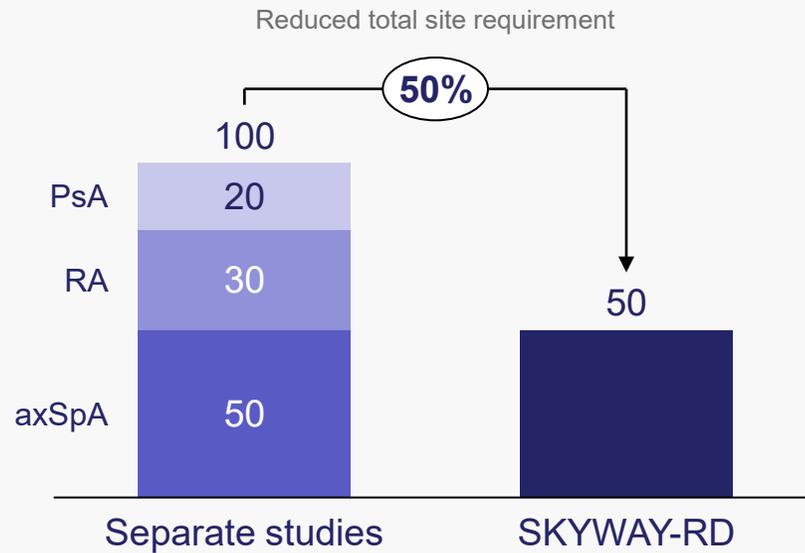


CAPITAL EFFICIENT

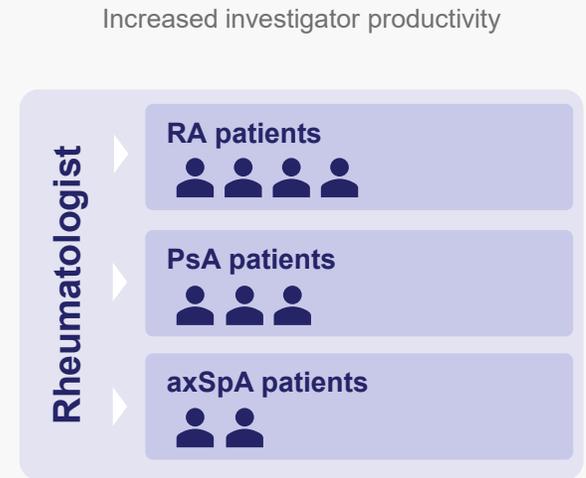


Cost savings compared to individual Ph2 studies for each indication<sup>1</sup>

SHARED SITES



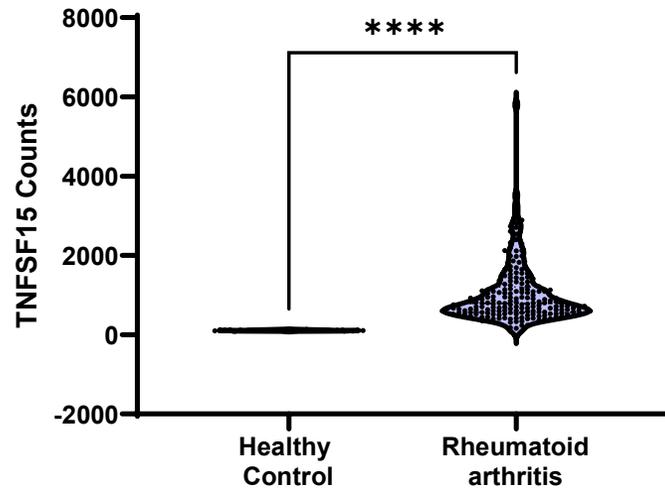
SHARED SPECIALTY



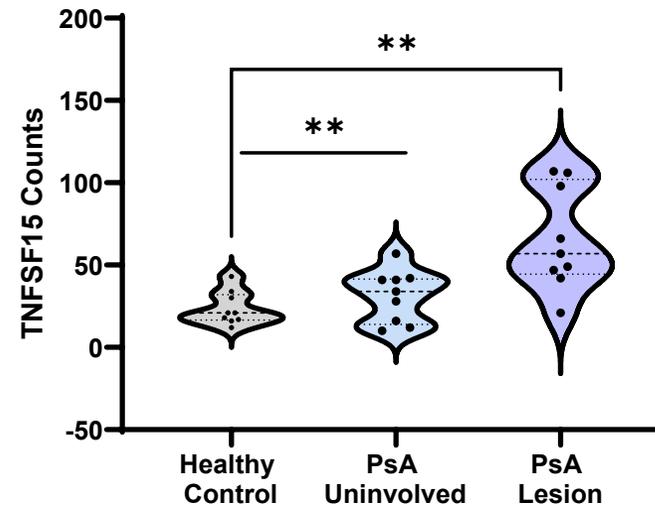
# TL1A is upregulated in RA, PsA, and axSpA relative to healthy controls



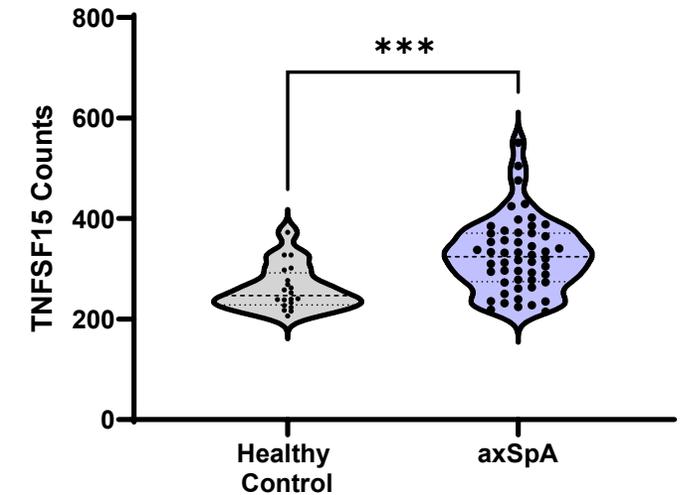
## Rheumatoid arthritis



## Psoriatic arthritis



## Axial spondyloarthritis

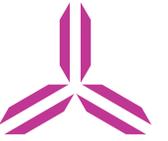


**Source** Whole blood  
**Sequencing** Microarray  
**Sample size** N=192 RA, 30 HC

**Source** Skin biopsy  
**Sequencing** Bulk RNA seq  
**Sample size** N=9 per cohort

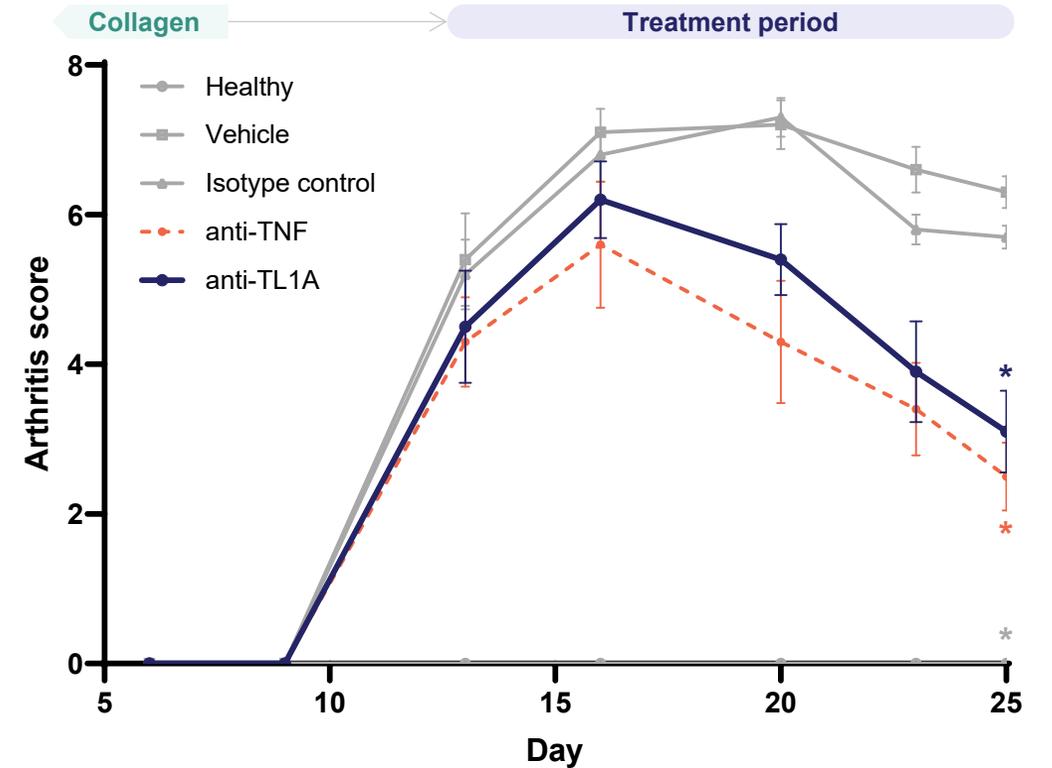
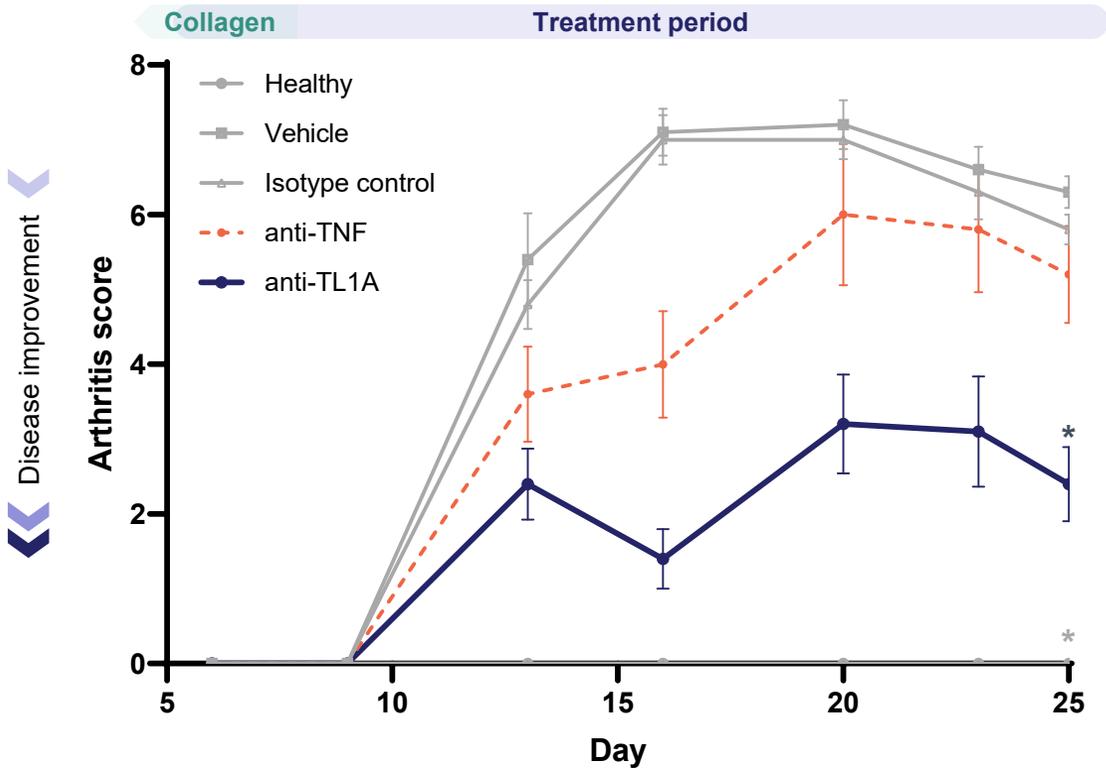
**Source** Whole blood  
**Sequencing** Microarray  
**Sample size** N=52 axSpa, 20 HC

# Spyre anti-TL1A antibody met or exceeded the efficacy of etanercept (anti-TNF) in rat models of arthritis



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

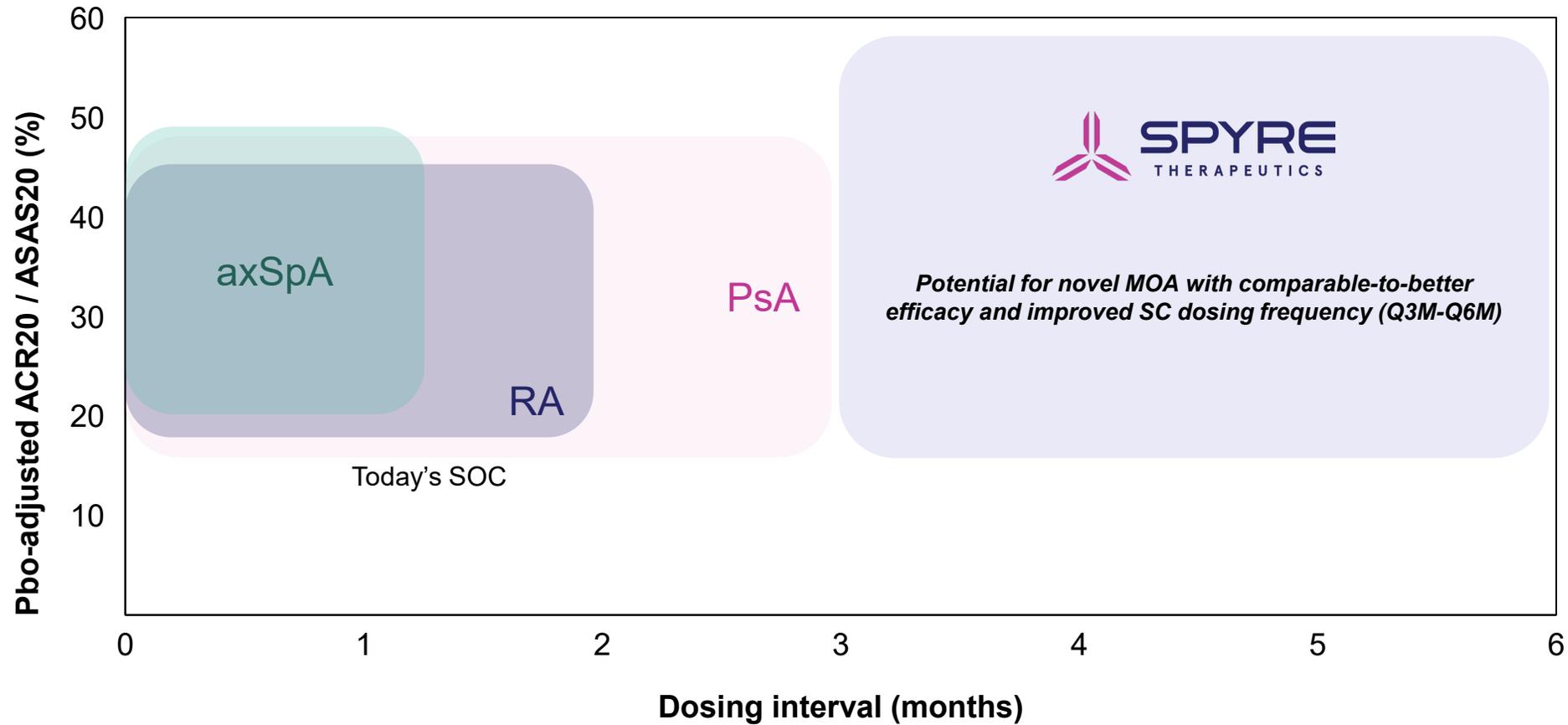
Comparable efficacy vs. anti-TNF in therapeutic model



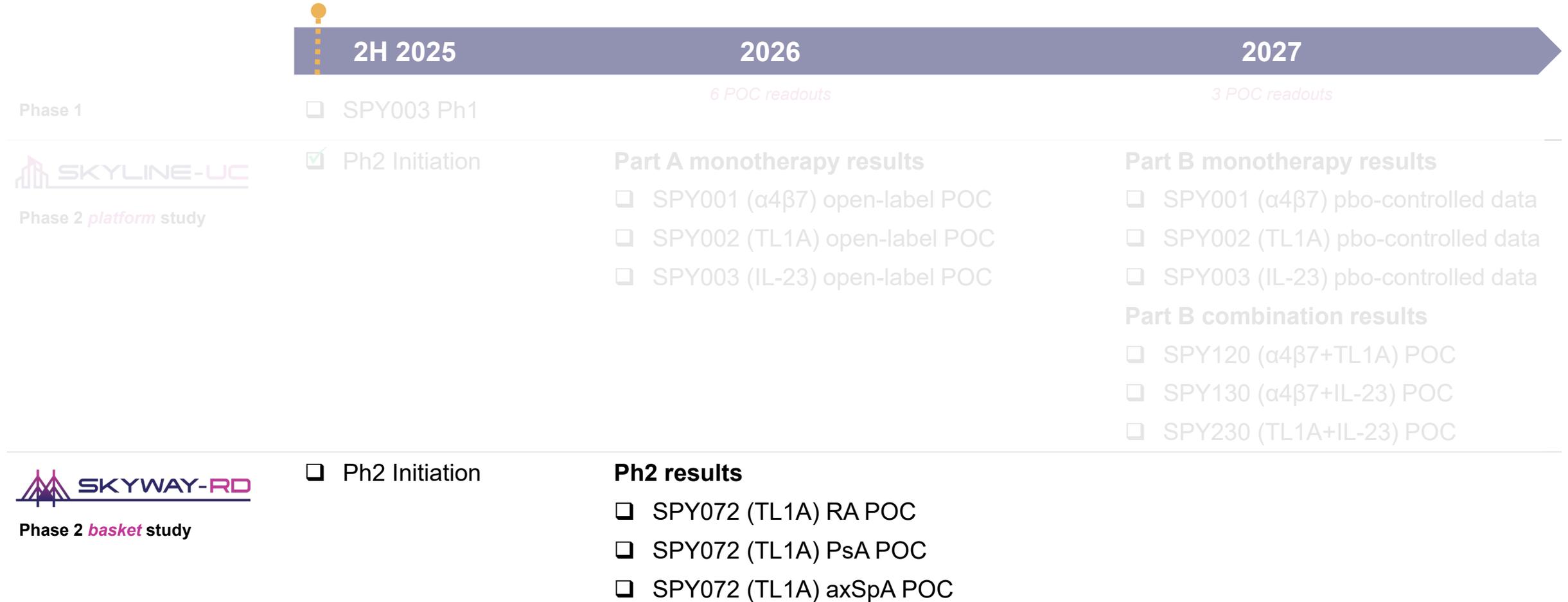
# SPY072 is a potential first-in-class therapy for rheumatologic conditions with anticipated Q3M-Q6M dosing



ILLUSTRATIVE



# SKYWAY-RD: 3 POC readouts expected through 2026



# Closing and Q&A



## Today's Spokespeople



**Cameron Turtle**  
Chief Executive Officer



**Josh Friedman**  
SVP, Clinical  
Development



**Deanna Nguyen**  
SVP, Clinical  
Development



**Sheldon Sloan**  
Chief Medical Officer



**Scott Burrows**  
Chief Financial Officer

# Anticipated 9 proof-of-concept readouts in 2026-27 for the treatment of IBD & beyond



**\$565M cash<sup>1</sup>**  
Runway into 2H 2028



Phase 1

- SPY003 Ph1

6 POC readouts

3 POC readouts



Phase 2 *platform* study

- Ph2 Initiation

### Part A monotherapy results

- SPY001 ( $\alpha 4\beta 7$ ) open-label POC
- SPY002 (TL1A) open-label POC
- SPY003 (IL-23) open-label POC

### Part B monotherapy results

- SPY001 ( $\alpha 4\beta 7$ ) pbo-controlled data
- SPY002 (TL1A) pbo-controlled data
- SPY003 (IL-23) pbo-controlled data

### Part B combination results

- SPY120 ( $\alpha 4\beta 7$ +TL1A) POC
- SPY130 ( $\alpha 4\beta 7$ +IL-23) POC
- SPY230 (TL1A+IL-23) POC



Phase 2 *basket* study

- Ph2 Initiation

### Ph2 results

- SPY072 (TL1A) RA POC
- SPY072 (TL1A) PsA POC
- SPY072 (TL1A) axSpA POC

# Thank you

Engineering for new heights in the treatment of IBD and beyond

