SPYRE THERAPEUTICS

aeglea™

CORPORATE OVERVIEW

24 October 2023

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Targeting new heights in the treatment of IBD

SPYRE THERAPEUTICS

THREE-PILLAR STRATEGY

OPPORTUNITY FOR BEST-IN-CLASS LONG-ACTING ANTIBODIES
SUBCUTANEOUS (SC) Q8-12W DOSING

RATIONAL THERAPEUTIC COMBINATIONS

PRECISION IMMUNOLOGY

PARALLEL LEAD PROGRAMS AGAINST HIGH VALUE TARGETS

TARGET	PROGRAM	DISCOVERY	IND-ENABLING	CLINICAL
α4β7	SPY001			Phase 1 interim data expected YE24
TL1A	SPY002			Phase 1 interim data expected 1H25
IL-23	SPY003			
Novel MOA	SPY004			
α4β7 + IL-23	SPY130			
α4β7 + TL1A	SPY120			
TL1A + IL-23	SPY230			

Potential best-in-class lead programs

DESIGN ATTRIBUTES

SPY001 (α4β7)

- ✓ IDENTICAL EPITOPE TARGETING AS VEDOLIZUMAB
- ✓ COMPARABLE POTENCY AND SELECTIVITY AS VEDOLIZUMAB
- ✓ SC EXTENDED HALF-LIFE mAb TO ENABLE Q8-12W REGIMEN

INTERIM HV PK DATA EXPECTED YE 2024

SPY002 (TL1A)

- ✓ DUAL MONOMER AND TRIMER BINDER
- ✓ PICOMOLAR POTENCY AGAINST MONOMERS AND TRIMERS
- ✓ SC EXTENDED HALF-LIFE mAb TO ENABLE Q8-12W REGIMEN

INTERIM HV PK DATA EXPECTED 1H 2025

COMBINATIONS

- ✓ ONLY KNOWN PORTFOLIO WITH α4β7, TL1A, AND IL-23
- ✓ POTENTIAL TO ADDRESS ORTHOGONAL BIOLOGY
- ✓ TARGETING UNIFIED SC Q8-12W DOSING

INITIATION EXPECTED AFTER PH1 DATA

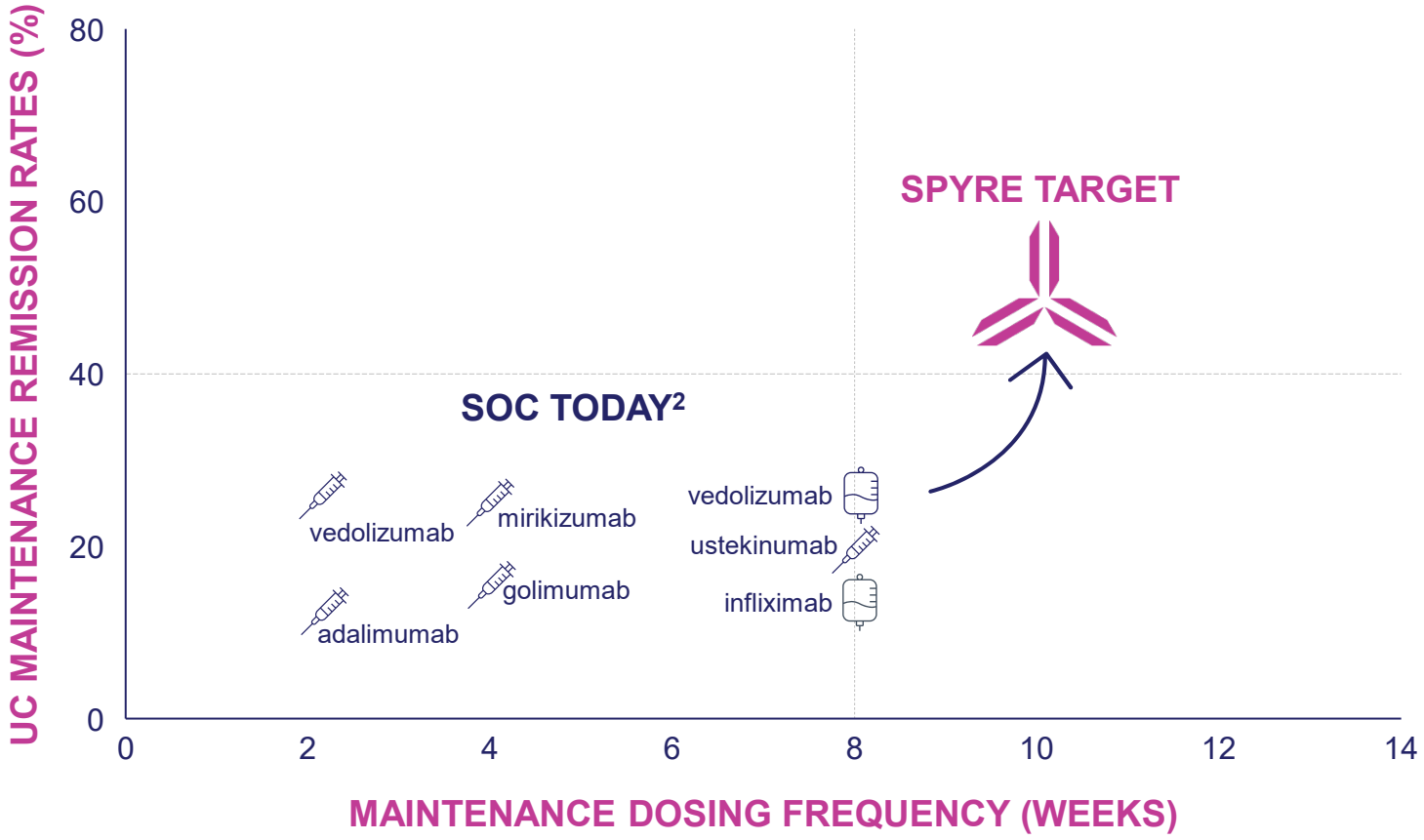
Despite advances, new approaches are needed to break the efficacy ceiling and improve convenience of biologics

UNMET NEED

~1.7 million individuals are currently diagnosed with IBD in the U.S.[1]

There remain substantial unmet needs in IBD management, including:

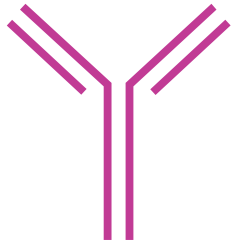
- Inadequate response or loss of response to existing therapies
- Side effects and safety concerns associated with long-term medication use
- Adherence to frequent and/or inconvenient dosing regimens



Source: [1]Crohn's and Colitis Foundation. [2]Summary data for select agents that randomize patients post response to induction; data from labels, company reports.
TL1A maintenance data not available. Orals not shown (pbo-adj maintenance remission rates): Jaks - tofacitinib (27%), upadacitinib (30% 15mg, 40% 30mg); S1Ps: ozanimod (19%); etrasimod (25% - P3 treat-through design).

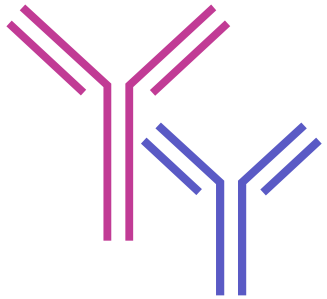
Our strategy is built on three validated approaches to address unmet needs in IBD

BEST-IN-CLASS ANTIBODY ENGINEERING



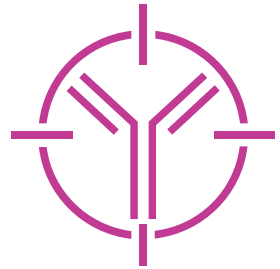
HALF-LIFE EXTENSION TECHNOLOGIES TO IMPROVE CONVENIENCE[1]

RATIONAL THERAPEUTIC COMBINATIONS



COMBINATION TARGETING TO ENHANCE REMISSION RATES[2]

PRECISION IMMUNOLOGY APPROACHES

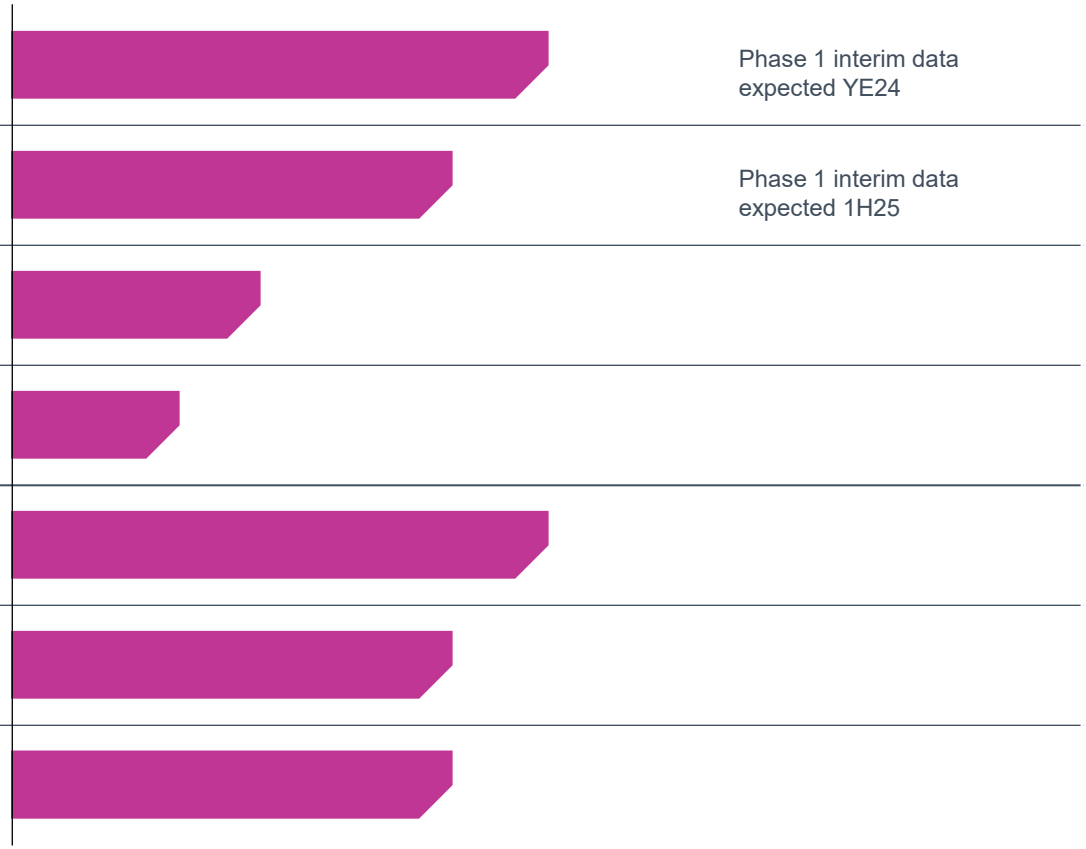


GENETIC AND BIOMARKER SELECTION TO IDENTIFY MOST LIKELY RESPONDERS[3]

Sources: [1] Several half-life extended antibodies are in clinical development, with at least two commercially approved (Evusheld, Beyfortus), Rosario, M, et. al. (2017); [2]JNJ VEGA Phase 2 study demonstrated approximately additive efficacy with a TNFα and IL-23 combination (~47% clinical remission at week 12) versus monotherapies (25% and 24% remission rates, respectively, Feagan, B. G. et al. Lancet Gastroenterol. Hepatol. 8, 307–320 (2023); [3]Prometheus Biosciences demonstrated a ~13% increase in clinical remission rates in CDx+ patients versus all-comers, Prometheus corporate materials

Spyre is building a potentially best-in-class IBD pipeline with next-generation mAbs and rational combinations

STRATEGY	TARGET	PROGRAM[1]	DISCOVERY	IND-ENABLING	CLINICAL
Potentially best-in-class mAbs	α4β7	SPY001			Phase 1 interim data expected YE24
	TL1A	SPY002			Phase 1 interim data expected 1H25
	IL-23	SPY003			
	Novel MOA	SPY004			
Rational combinations	α4β7 + IL-23	SPY130			
	α4β7 + TL1A	SPY120			
	TL1A + IL-23	SPY230			



[1]Spyre exercised its option to license worldwide rights from Paragon Therapeutics, Inc. for SPY001. Spyre continues to hold an option to license similar rights from Paragon for all other programs. SPY003 license will be restricted to IBD, all other program licenses will be indication agnostic.

SPY001

LONG-ACTING A4B7 ANTIBODY

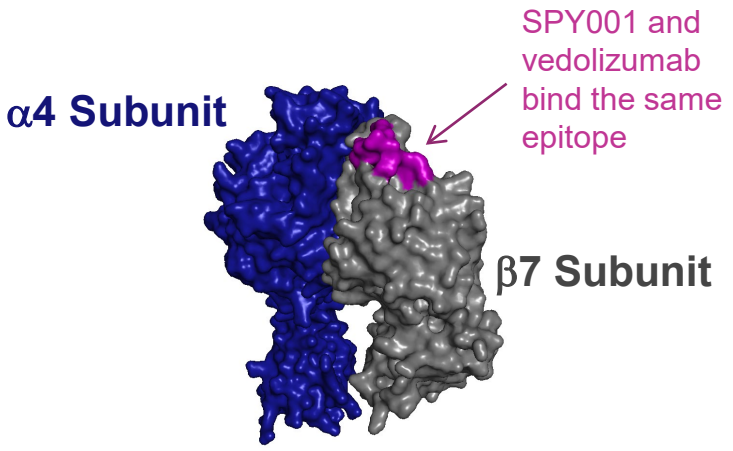


SPY001 is designed to be a long-acting anti-α4β7

- ✓ IDENTICAL EPITOPE TARGET AS VEDOLIZUMAB
- ✓ COMPARABLE POTENCY AND SELECTIVITY AS VEDOLIZUMAB
- ✓ SUB-CUTANEOUS, EXTENDED HALF-LIFE mAb PREDICTED TO ENABLE Q8-12W DOSING

SPY001 potency & selectivity matches vedolizumab

SPY001 & VEDOLIZUMAB EPITOPE



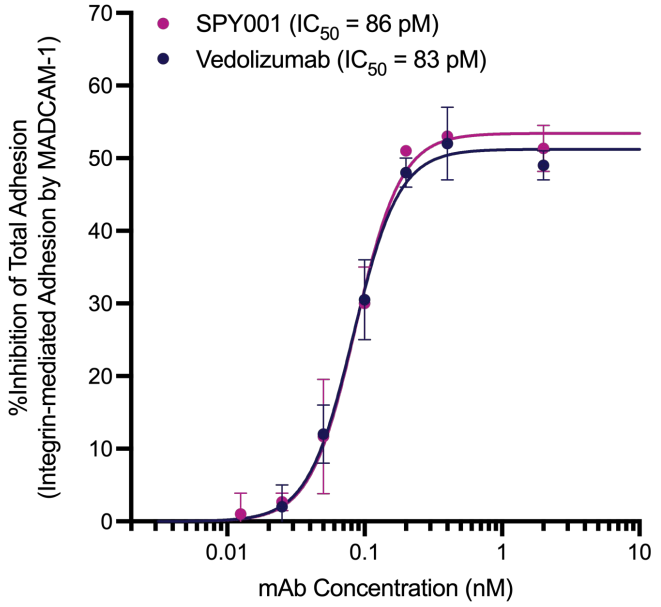
POTENT & SELECTIVE BINDING TO α4β7

Antibody	α4β7[1]	α4β1	αEβ7
SPY001	K_D <1 nM	NB[2]	NB[2]
Vedolizumab	K_D <1 nM	NB[2]	NB[2]

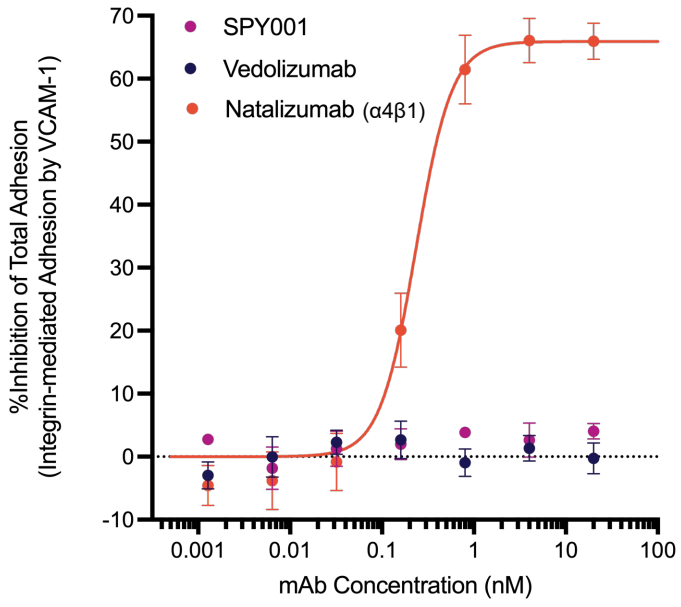
[1]*Dissociation constant (K_D) measured by surface plasmon resonance (SPR)*
[2]*NB = no binding by a particular antibody to a test molecule*

POTENT AND SELECTIVE INHIBITION OF CELLULAR ADHESION

SPY001 and vedolizumab potently inhibit MAdCAM-1-mediated (gut) cellular adhesion



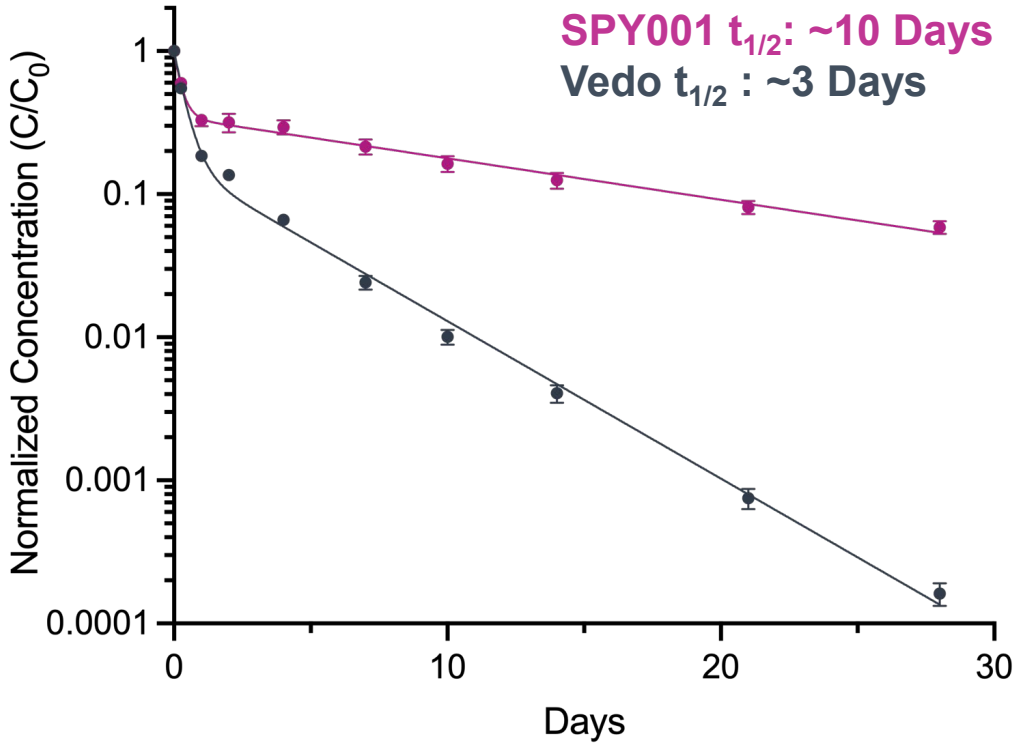
No inhibition of unwanted VCAM-1-mediated (CNS) cellular adhesion



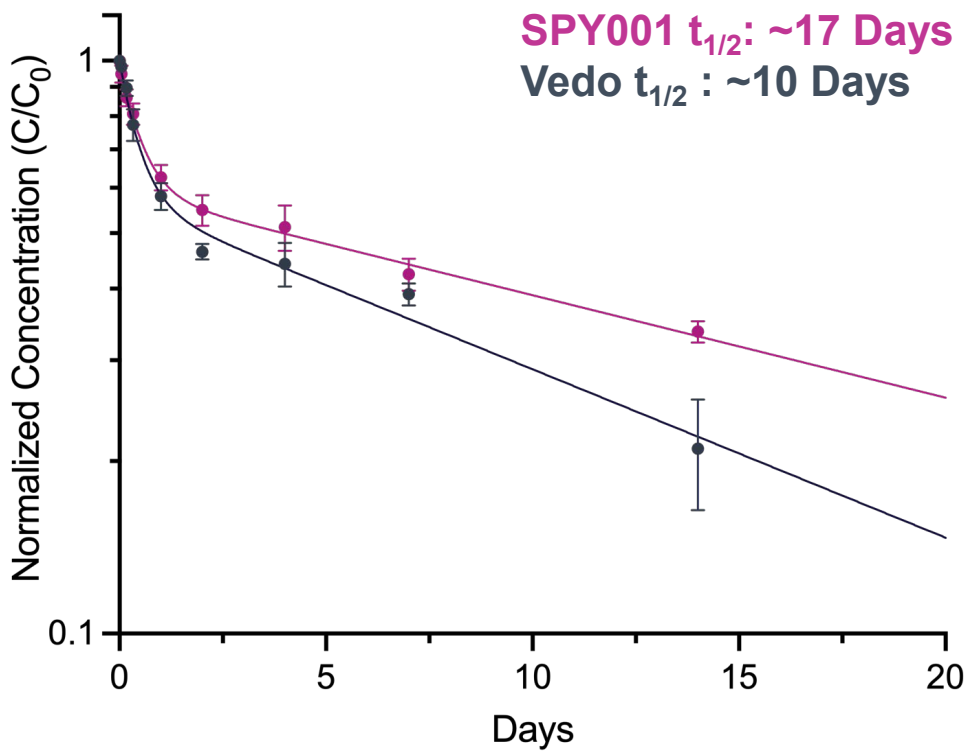
Source: Data on file.

SPY001 has exhibited ~2x the half-life of vedolizumab in NHPs

DEMONSTRATED EXTENDED HALF-LIFE IN Tg276 MICE



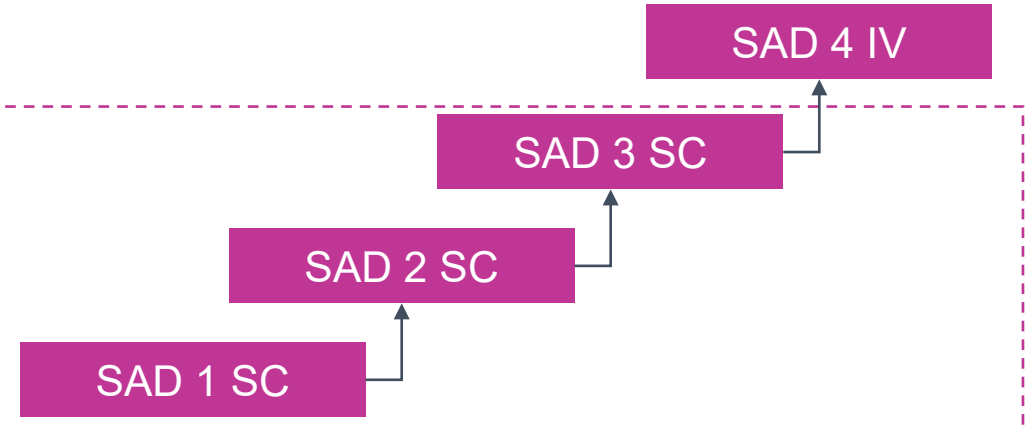
DEMONSTRATED EXTENDED HALF-LIFE IN NHPs



Source: Data on file.

SPY001 Phase 1 clinical trial design

SINGLE-ASCENDING DOSE



Expected interim YE2024 readout *to include 2-3 SAD cohorts and is sufficient to answer key objectives with PK modeling*

Single-ascending dose cohorts

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

MULTIPLE-ASCENDING DOSE



Multiple-ascending dose cohorts

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

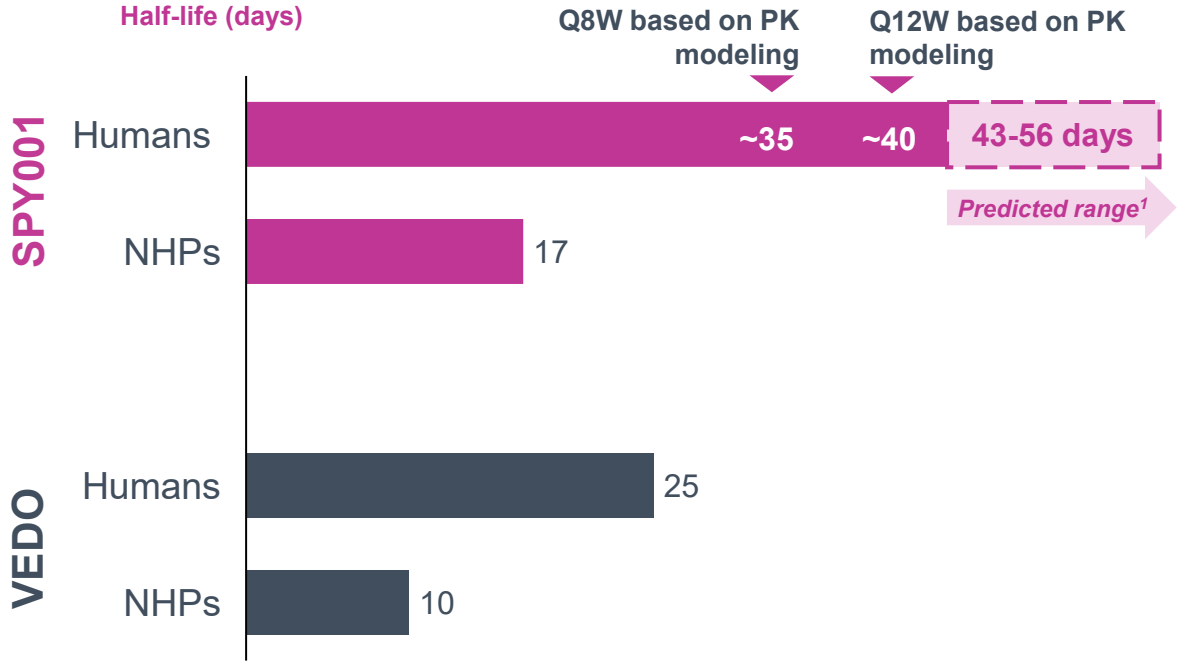
We aim to demonstrate the following for SPY001 in the expected interim Phase 1 readout

1	HALF-LIFE ENABLES Q8-12W SC MAINTENANCE DOSING BASED ON PK MODELING
2	POTENTIAL TO ADDRESS VEDO'S SLOW ONSET OF ACTION WITH HIGHER INDUCTION EXPOSURES
3	ESTABLISH SPY-001 HAS FAVORABLE SAFETY PROFILE AND IS WELL-TOLERATED
4	MINIMAL TO NO IMPACT ON ADA RATES VS VEDOLIZUMAB

Phase 1 interim PK will serve as confirmation of Q8-12W SPY001 dosing, as predicted by NHP allometric scaling

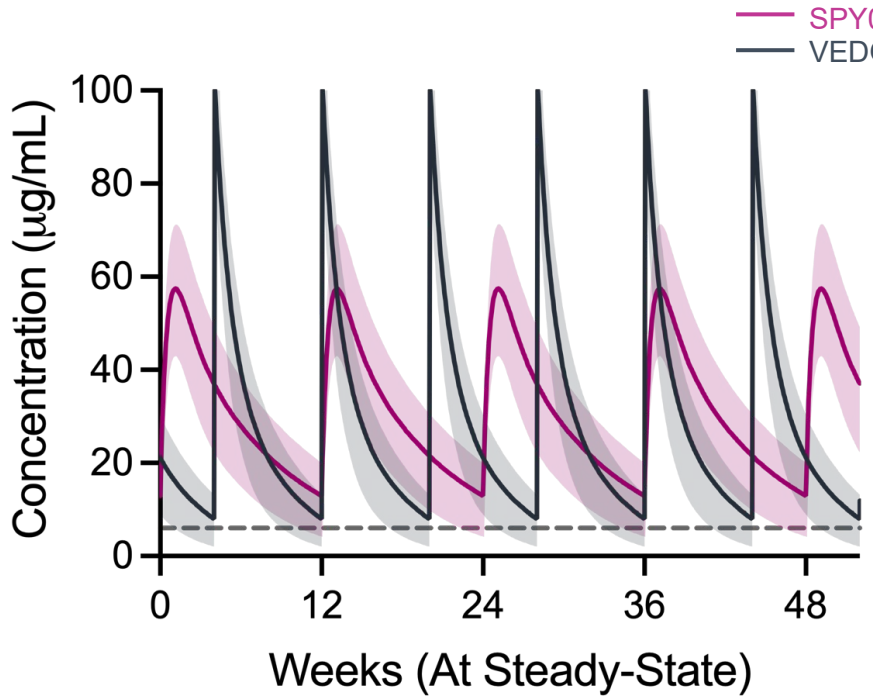
SPY001 HUMAN HALF-LIFE PREDICTIONS

1



MAINTENANCE PK SIMULATIONS

Q12W SPY001 dosing simulation based on 50d half-life



SPY001 C_{trough} exceeds vedo by ~1.5x

6 ug/mL
C_{trough} associated with maximal efficacy[2]

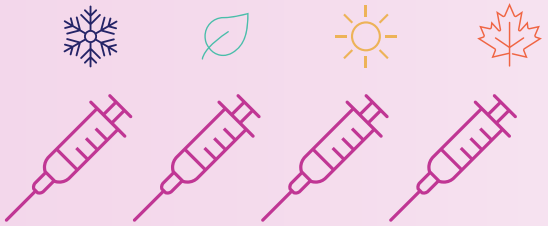
Source: [1]Human YTE mAb half-life is on average 3.1x of NHP half-life; Rosario, M, et. al. (2017); [2]*Feagan, et. al. (2013)*

A half-life of 43-56 days in a 300mg SC format is expected to offer a superior product profile

MAINTENANCE DOSING PROFILE

SPY001 SC
300 MG
CITRATE FREE

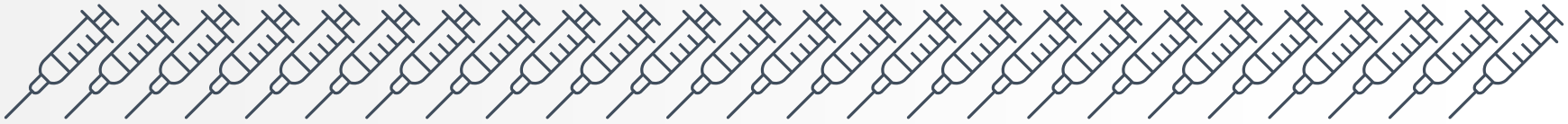
4-6
INJECTIONS
PER YEAR



POTENTIAL FOR SEASONAL DOSING

VEDOLIZUMAB SC
108 MG
20 MM CITRATE

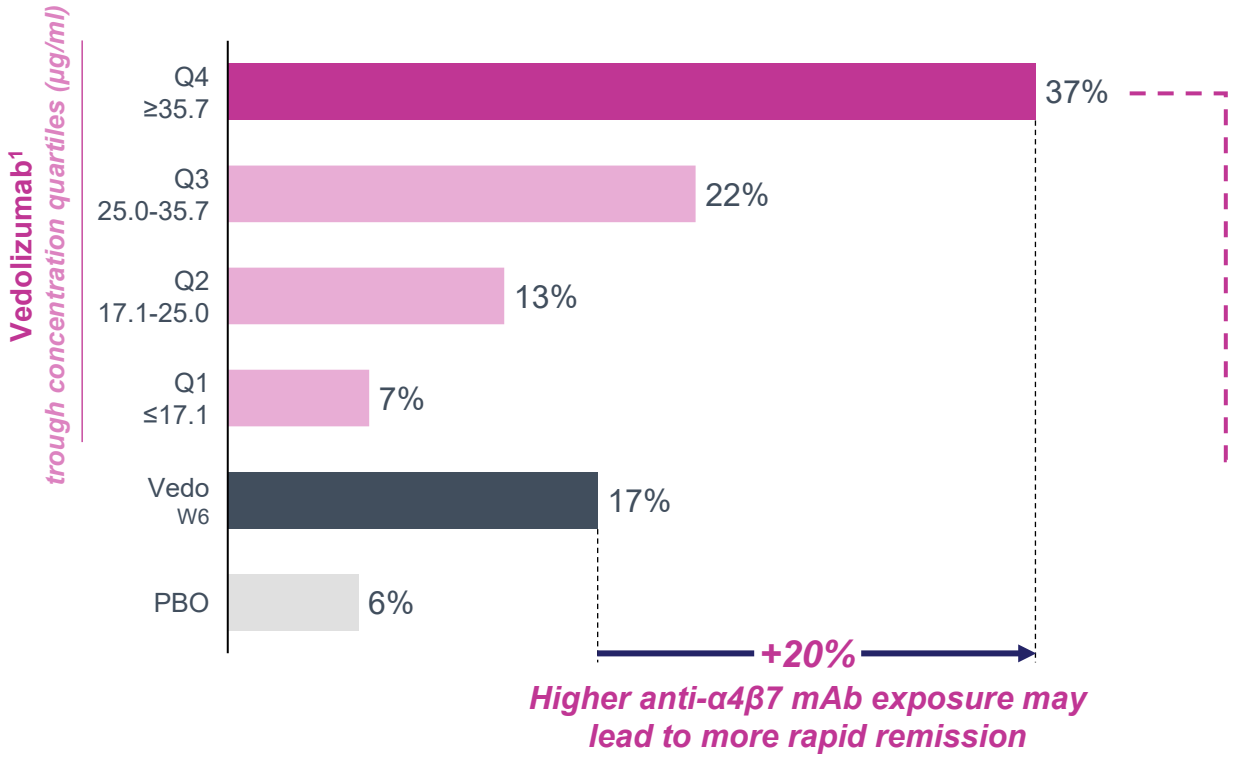
26
INJECTIONS
PER YEAR



Expected interim PK data will also inform our ability to test induction exposure-response relationship in Phase 2

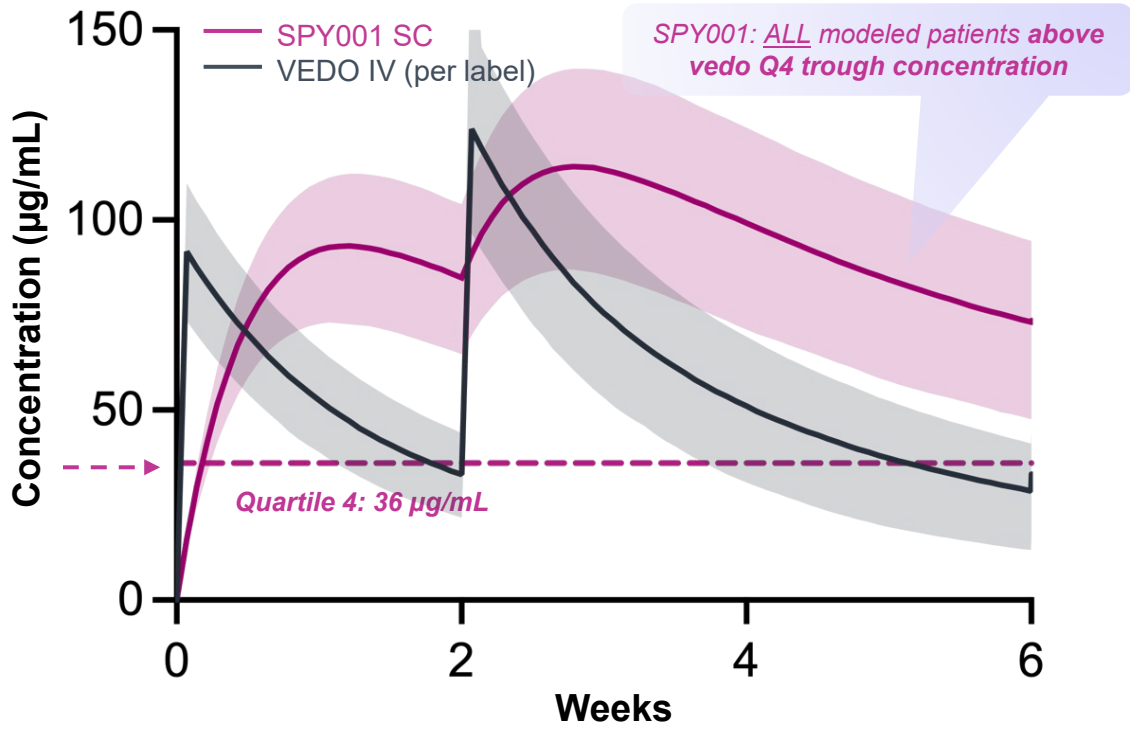
UPSIDE: GREATER REMISSION VIA HIGHER EXPOSURE

2 GEMINI I: WEEK 6 CLINICAL REMISSION RATES IN UC (%)



INDUCTION PK SIMULATIONS

SPY001 INDUCTION SIMULATION BASED ON 50-DAY HALF-LIFE



Source: [1]Vedolizumab exposure-response data from Rosario, M., et. al. (2017); Vedolizumab FDA Clinical Pharmacology Review

SPY001 is designed for fully SC induction dosing with upside efficacy potential

INDUCTION DOSING PROFILE

SPY001

SC
INDUCTION DOSING



PATIENT-ADMINISTERED

UPSIDE POTENTIAL FOR ENHANCED EFFICACY

VEDOLIZUMAB

IV
INDUCTION DOSING



REQUIRES PHYSICIAN ADMINISTRATION / OFFICE VISIT

POTENTIALLY UNDER-DOSED

SPY001 is designed to match vedolizumab's favorable safety profile and low rate of ADAs

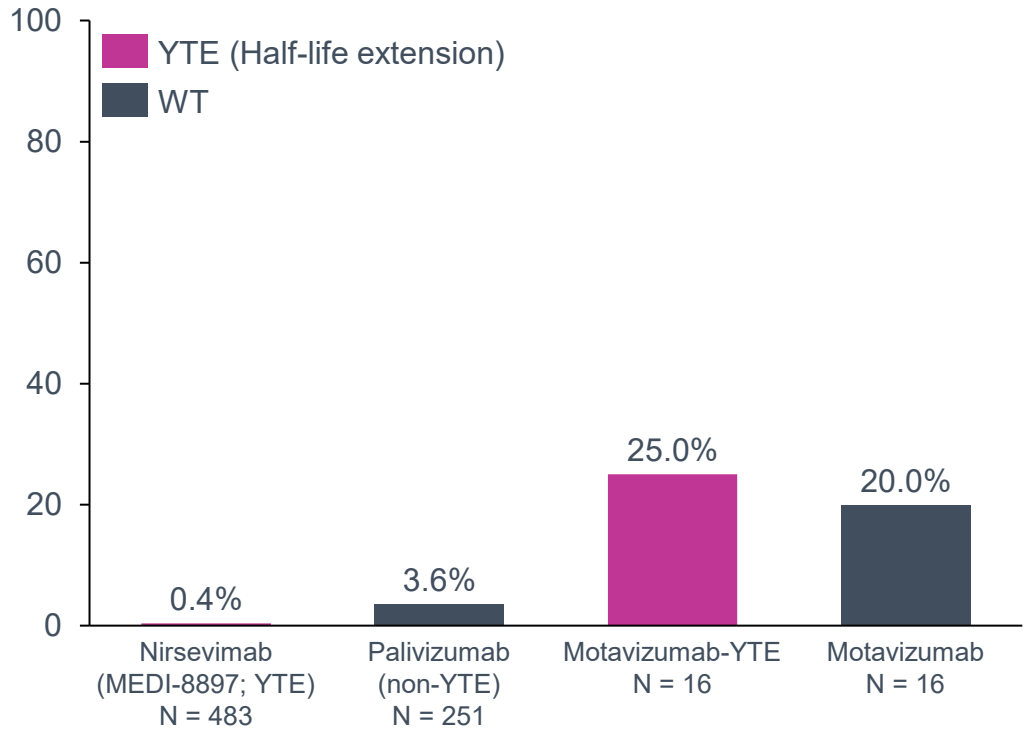
VEDO IS WELL TOLERATED WITH LOW IMMUNOGENICITY[1]

3

	Vedolizumab	Placebo
Infection rates	**0.85** per patient-year	**0.70** per patient-year
Serious infection rates	**0.07** per patient-year	**0.06** per patient-year
Adverse reaction rates	**52%** (N=1434)	**45%** (N=297)
Malignancy rates	**0.4%** (N=1434)	**0.3%** (N=297)
Infusion reactions	**4%** (N=1434)	**3%** (N=297)
Immunogenicity rates	**6%** (N=1434)	**N/A**

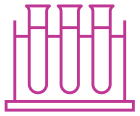
ADA RATES ARE SIMILAR FOR YTE AND WT ANTIBODIES[2,3]

4



Source: [1]Entyvio prescribing information; [2]Rocca, A, et al. Int J of Mol Sci, 2021; [3]Domachowske NEJM 2022

SPY001 summary



COMPARABLE IN VITRO PERFORMANCE TO VEDOLIZUMAB



PK MODELLING SUPPORTS Q8-12W SC DOSING; UPSIDE POTENTIAL FOR GREATER INDUCTION EFFICACY



DEVELOPING PATIENT SELECTION APPROACHES TO IDENTIFY RESPONDERS



INTERIM PHASE 1 PK DATA EXPECTED YE2024

SPY002

POTENTIAL BEST-IN-CLASS TL1A ANTIBODY

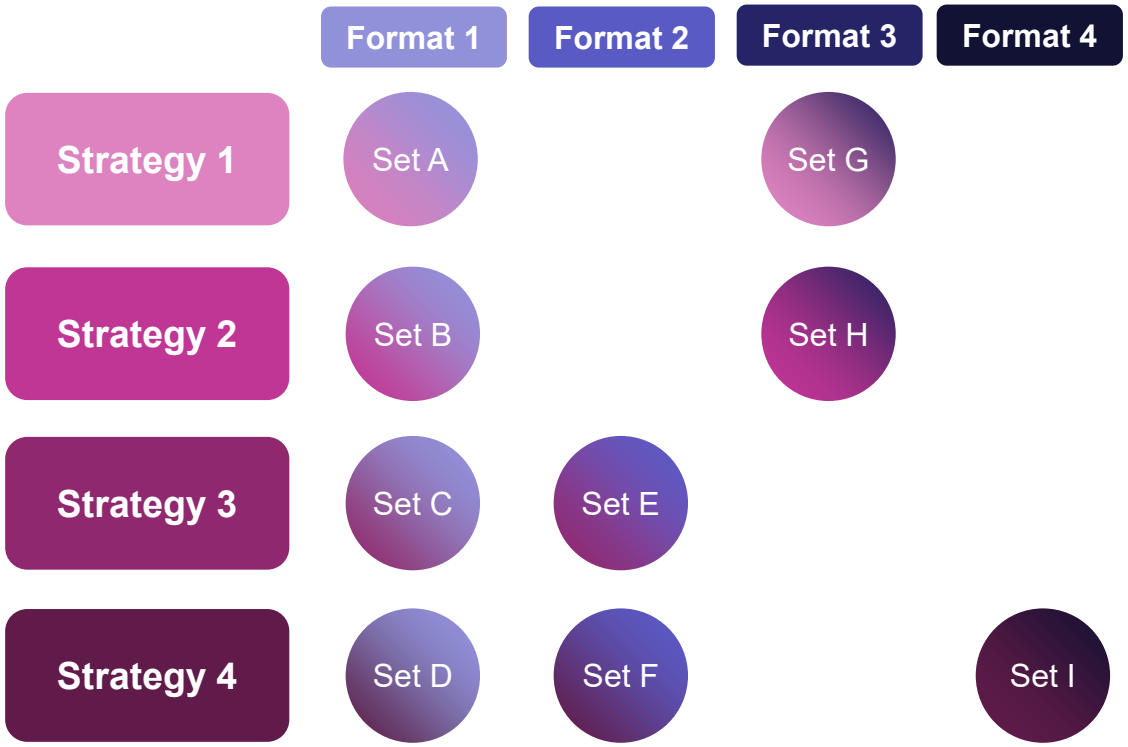


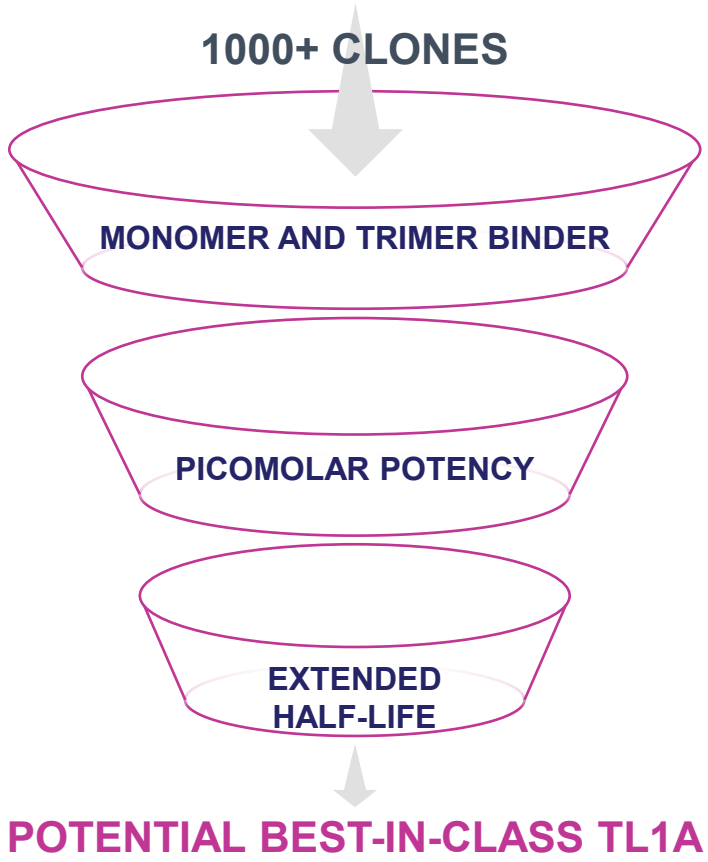
SPY002 is designed to achieve an optimal anti-TL1A product profile

- ✓ DUAL MONOMER AND TRIMER BINDING
- ✓ PICOMOLAR POTENCY AGAINST MONOMERS & TRIMERS
- ✓ FULLY SC, EXTENDED HALF-LIFE mAb PREDICTED TO ENABLE Q8-12W DOSING

Extensive discovery campaign pursued to identify an uncompromising TL1A antibody

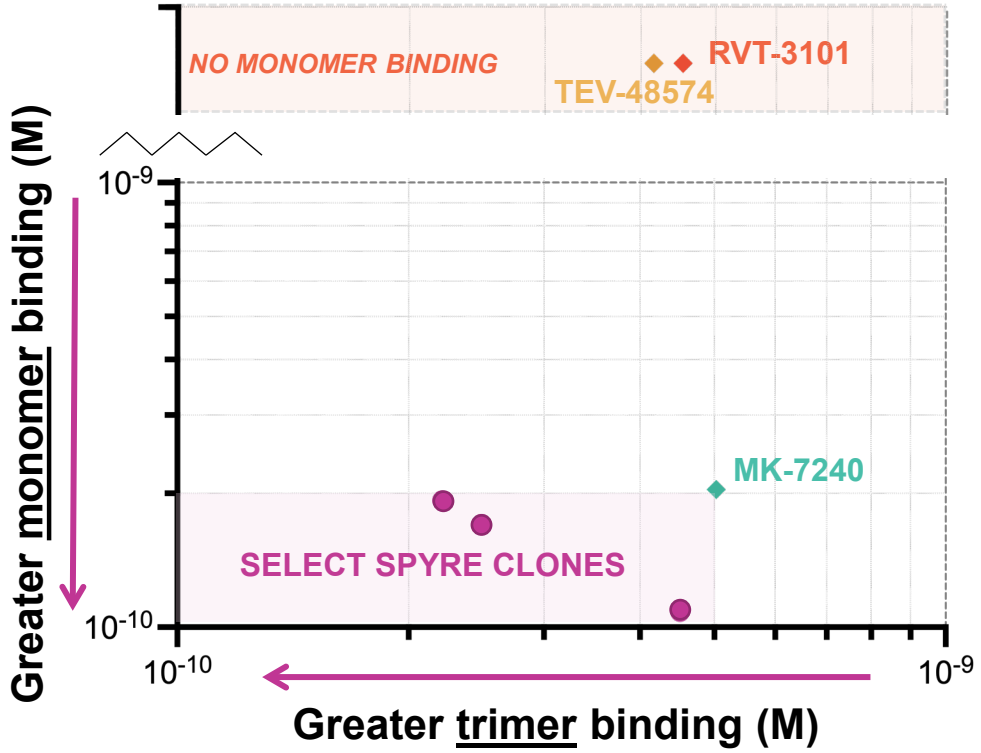
Heavily resourced campaign employing multiple strategies and formats enabled discovery of desirable TL1A clones



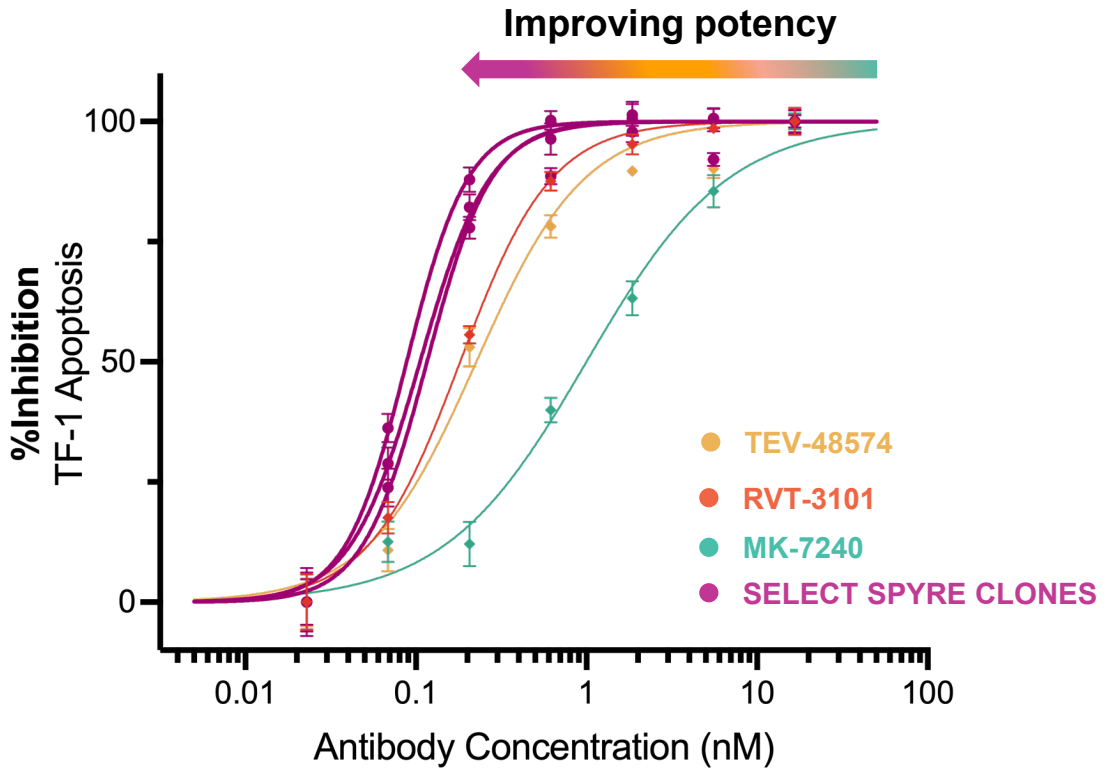


SPY002 clones are unique in binding both monomers and trimers with picomolar potency

SUPERIOR MONOMER AND TRIMER BINDING[1]



SUPERIOR TF-1 APOPTOSIS INHIBITION[1]



Source: Nonclinical data on file. [1]Compared to TEV-48574, RVT-3101, MK-7240 using surface plasmon resonance

SPY002 is a potential best-in-class TL1A mAb

	SPY002	MK-7240	RVT-3101	TEV-48574
Complete TL1A blockade Monomer and trimer	✓	✓		
Picomolar trimer potency	✓		✓	✓
Half-life extension Q8-12W dosing	✓			

Source: Company materials

SPY002 is potentially the most advanced unencumbered TL1A in development



Source: Company press releases

SPY002 summary



LEAD CLONES ARE MONOMER AND TRIMER BINDERS WITH POTENCY DESIGNED TO BE SUPERIOR TO SELECT ANTIBODIES



ONLY KNOWN EXTENDED HALF-LIFE TL1A ANTIBODY IN DEVELOPMENT



DEVELOPING PATIENT SELECTION APPROACHES TO IDENTIFY RESPONDERS



INTERIM PHASE 1 PK DATA EXPECTED 1H2025

THERAPEUTIC COMBINATIONS



Spyre is unique in its portfolio approach evaluating multiple combination regimens

- ONLY KNOWN PORTFOLIO WITH α4β7, TL1A, AND IL-23
- POTENTIAL TO ADDRESS ORTHOGONAL BIOLOGY
- FAVORABLE TARGET PRODUCT PROFILE WITH UNIFIED Q8-12W SC DOSING ACROSS TARGETS

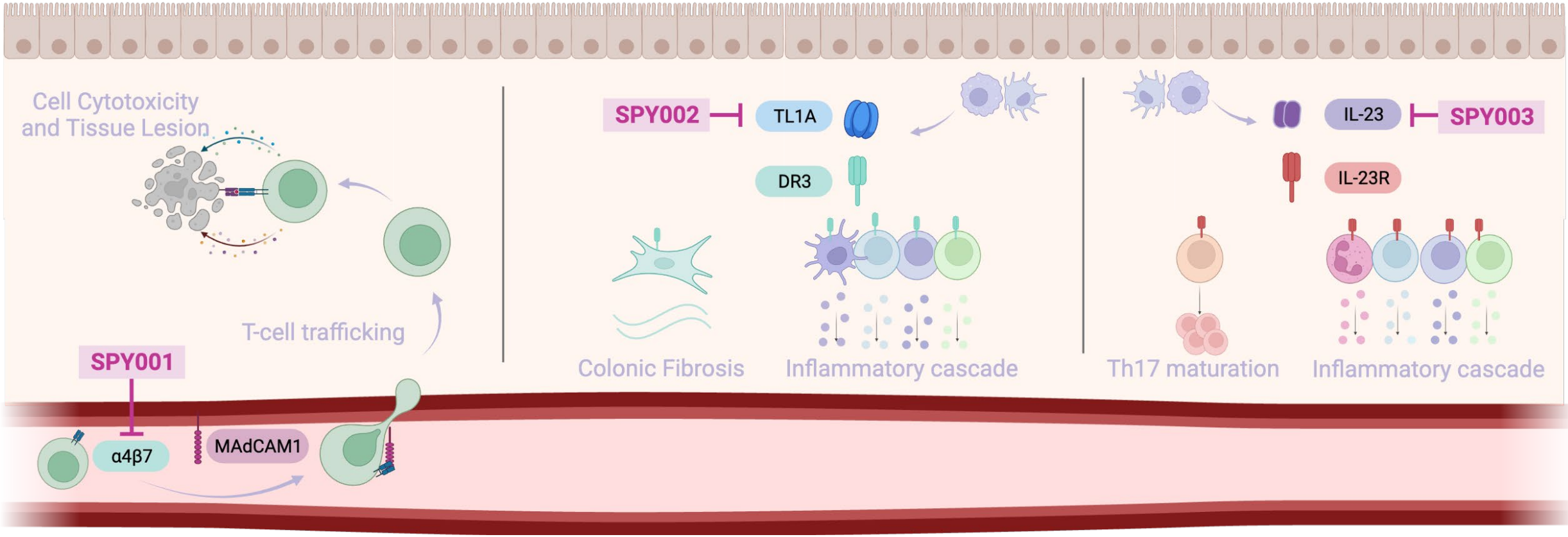
Spyre portfolio addresses the diverse pathophysiology of IBD

MOA

Blockade of α4β7 prevents circulating T cells from entering inflammatory gut tissues

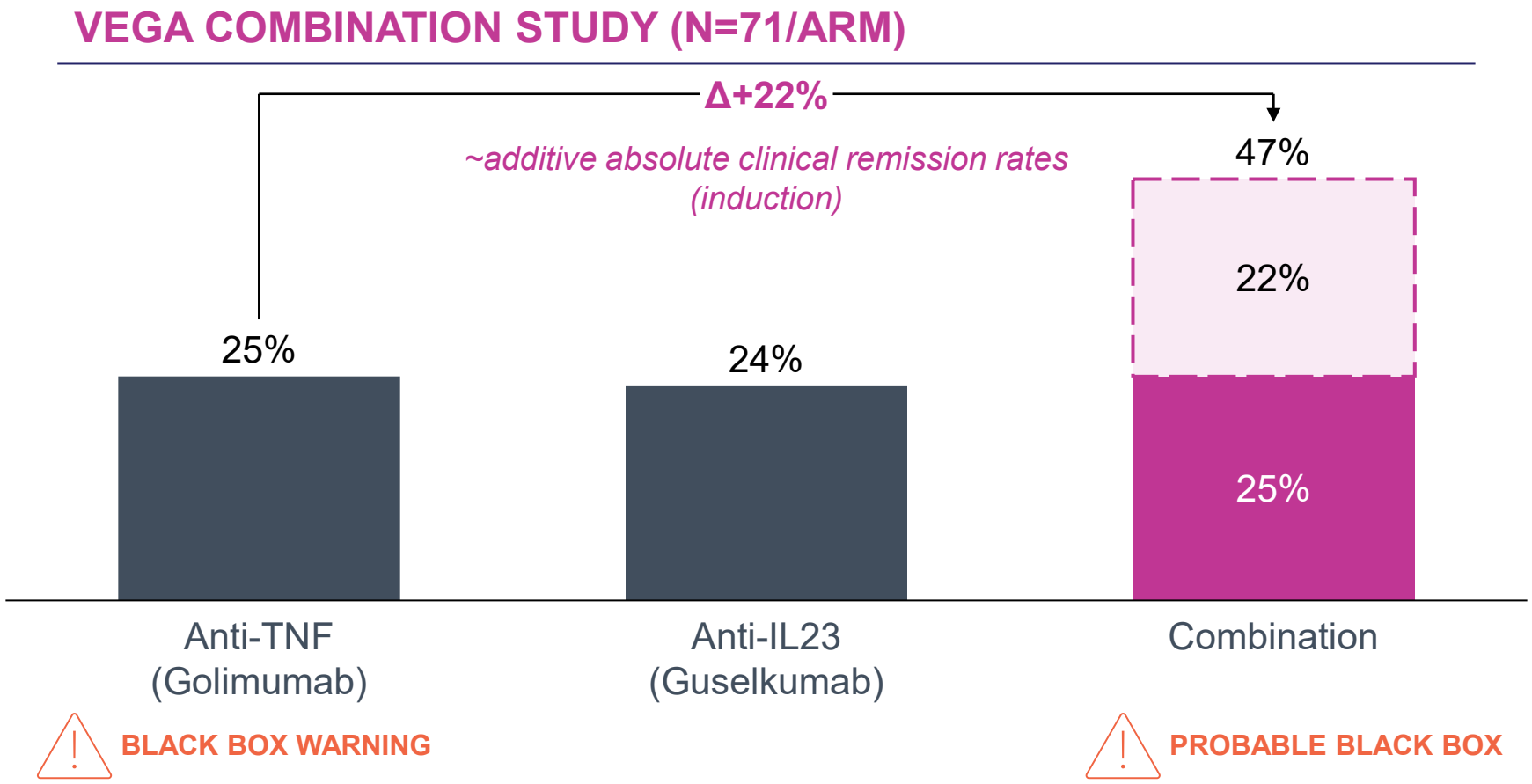
Neutralization of TL1A suppresses inflammation within gut tissue and blocks immune cell activation

Neutralization of IL-23 inhibits cascade of various proinflammatory cytokines



Sypre is a pioneer in developing potential best-in-class mAbs against three top targets with the goal of enabling superior combinations for IBD

JNJ's VEGA study demonstrated power of combination therapy despite relative weakness of components



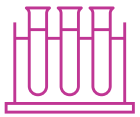
NOTE: In VEGA, only guselkumab (IL-23) was continued in maintenance for the combo arm in a treat-through design; Spyre plans to use combinations in maintenance. Maintenance remission rates for the anti-TNF arm, anti-IL23 arm, and induction combination arm were 28%, 31%, and 48%, respectively.; Feagan, B. G. et al. Lancet Gastroenterol. Hepatol. 8, 307–320 (2023).

Spyre aims to build on this success with combinations of potentially best-in-class mAbs from favorable MOAs

	SPY130	SPY120	SPY230	JNJ-’4804
Targets	α4β7 + IL-23	α4β7 + TL1A	TL1A + IL-23	TNF + IL-23
Format	Co-formulation	Co-formulation	Co-formulation	Co-formulation
Monotherapies lack black box warning	✓	✓	✓	
Anti-cytokine + anti-lymphocyte trafficking	✓	✓		
Half-life extension Q8-12W dosing	✓	✓	✓	

Source: Company materials

Combination programs summary



COMBINATION OF POTENTIALLY BEST-IN-CLASS MONOTHERAPY BUILDING BLOCKS



TARGETING UNIFIED Q8-12W DOSING FOR OPTIMIZED PATIENT CONVENIENCE



DEVELOPING PATIENT SELECTION APPROACHES TO IDENTIFY RESPONDERS



SPY130 Phase 2 study initiation expected in 2025

CORPORATE

TEAM AND CASH RUNWAY



Leadership and BOD

Management team



Cameron Turtle
Chief Operating Officer



Scott Burrows
Chief Financial Officer



Heidy King-Jones
Chief Legal Officer



Josh Friedman
SVP, Clinical Development



Janet Gunzner-Toste
SVP, Operations



Andy Spencer
SVP, Preclinical R&D



Justin LaFountaine
VP, Corporate Development

Board of Directors



Russell J. Cox
Chairman



Hunter C. Smith
Board of Directors



Ivana Magovčević-Liebisch
Board of Directors



Alison Lawton
Board of Directors



Peter Harwin
Board of Directors



Tomas Kiselak
Board of Directors



Michael Henderson
Board of Directors

Cash and anticipated milestones

CASH RUNWAY

$236.7M as of 6/30/2023

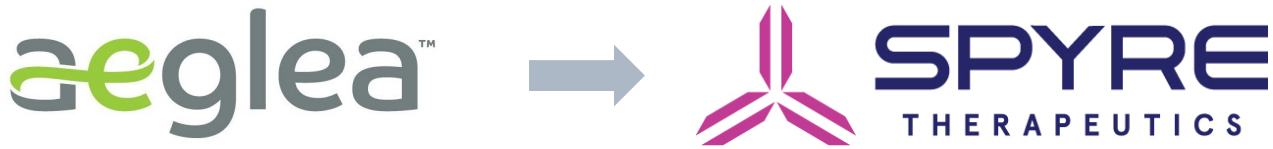
expected to fund pipeline into 2026 through multiple key value creation events

CATALYSTS[1]	2024 EXPECTED	2025 EXPECTED
SPY001 (α4β7)	1H - IND/CTN 2H - PHASE 1 INTERIM DATA	PHASE 1 FULL DATA PHASE 2 INITIATION
SPY002 (TL1A)	2H - IND/CTN	PHASE 1 INTERIM DATA
SPY003 (IL-23)		IND/CTN
COMBINATIONS		PHASE 2 INITIATION
EXTERNAL EVENTS	1H – PRA023 SSc-ILD P2 2H - TEV-48574 P2b 2H – DUET UC/CD P2b	MORF057 P2b

Note: [1]As of October 23, 2023

Thank you

Aeglea-Spyre Transaction highlights



Structure: The acquisition of Spyre was structured as a stock-for-stock transaction whereby all of Spyre's outstanding equity interests were exchanged for a combination of shares of Aeglea common stock and a newly created non-voting Series A convertible preferred stock.

Financing: Concurrent with the acquisition of Spyre, Aeglea closed a $210 million private placement with a group of institutional accredited investors led by Fairmount Funds and joined by a robust syndicate of dedicated biotechnology investors as well as additional undisclosed institutional investors.

Primary use of proceeds: The proceeds from the private placement are expected to be primarily used to advance the Spyre pipeline and deliver the following anticipated milestones: two INDs for SPY001 and SPY002 in 2024, HV PK/PD data for SPY001 in 2H2024, and HV PK/PD data for SPY002 in 1H2025. Proceeds are expected to provide cash runway into 2026.

Capitalization

As of 6/20/2023*	
Shares of common stock outstanding	2.6 million
Pre-funded warrants	1.2 million
Merger consideration	
Shares of common	0.5 million
Shares of preferred	0.4 million
Preferred conversion ratio	1:40
Total pre-financing common equivalent	18.9 million
Concurrent financing	
Shares of preferred	0.7 million
Common equivalent	28.9 million
Total capitalization (Common)	**47.7 million**

- Shares of common stock and preferred stock were issued to Spyre Therapeutics Inc. security holders in exchange for all of Spyre's outstanding equity interests.
- Shares of preferred stock were issued to Spyre Therapeutics Inc. stockholders and to investors in the $210 million private placement.
- Each share of preferred stock will automatically convert into 40 shares of common stock upon stockholder approval, subject to certain beneficial ownership restrictions set by each holder.
- Please refer to the company's SEC filings for additional information.

**Note: All figures have been retroactively adjusted to reflect the company's 1-for-25 reverse stock split that will be effective as of 12:01 a.m. Eastern Time on September 8, 2023.*