SPYRE THERAPEUTICS

CORPORATE OVERVIEW

March 2024

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Engineering for 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[1]	Preclinical	Phase 1	Phase 2	Phase 3
α4β7	SPY001		*Phase 1 interim data expected YE24*		
TL1A	SPY002		*Phase 1 interim data expected 1H25*		
IL-23	SPY003		*DC expected mid-2024*		
Novel MOA	SPY004				
α4β7 + TL1A	SPY120				
α4β7 + IL-23	SPY130				
TL1A + IL-23	SPY230				

[1]Spyre exercised its option to license worldwide rights from Paragon Therapeutics, Inc. for SPY001 and SPY002. Spyre continues to hold an exclusive 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.

Potential best-in-class lead programs

DESIGN ATTRIBUTES

SPY001 (α4β7)

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

Interim HV PK data expected YE 2024

SPY002 (TL1A)

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

Interim HV PK data expected 1H 2025

COMBINATIONS

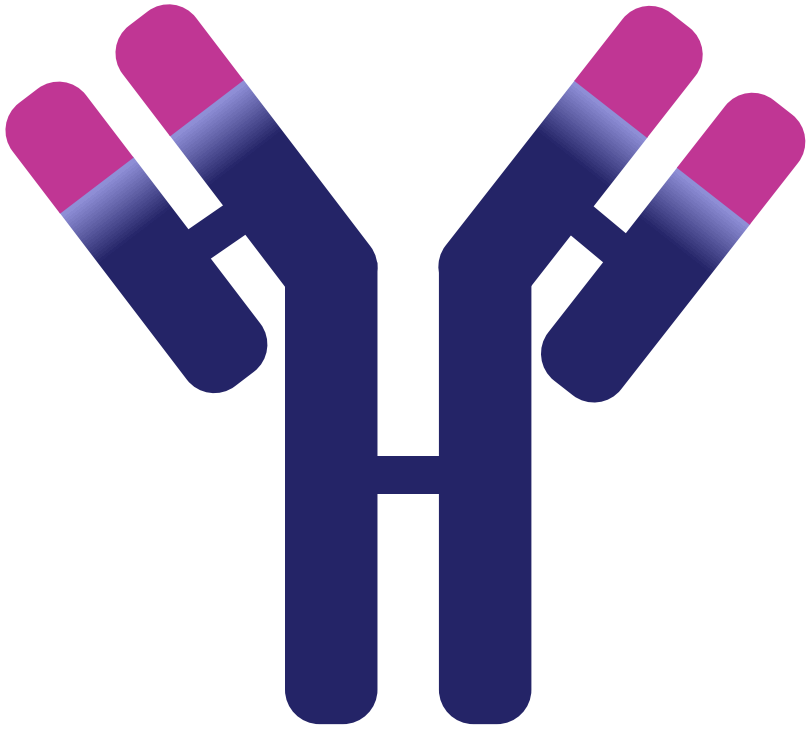
- ✓ ONLY KNOWN PORTFOLIO WITH α4β7, TL1A, AND IL-23
- ✓ POTENTIAL TO ADDRESS ORTHOGONAL BIOLOGY
- ✓ TARGETING UNIFIED Q8-12W SC DOSING

Study initiation expected in 2025

SPY001:

Potential best-in-class α4β7 antibody

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



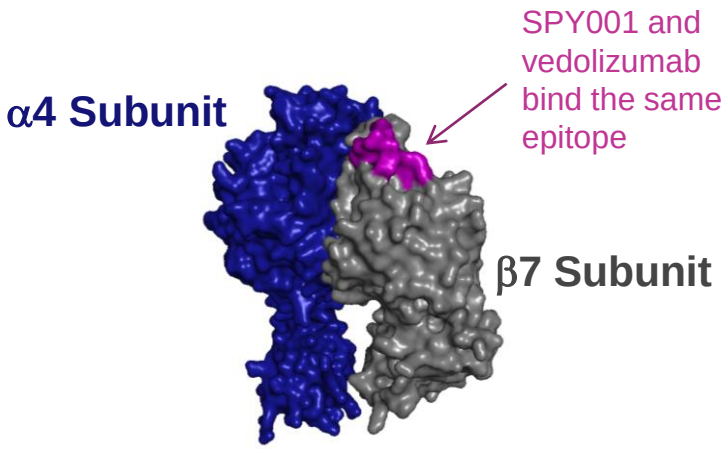
SPY001

- Identical epitope target as vedolizumab based on modeling
- Comparable potency and selectivity as vedolizumab in preclinical studies
- Half-life extension through validated Fc modification to enable Q8-12W SC dosing

Source: Data on file

SPY001 potency & selectivity matches vedolizumab

SPY001 & vedolizumab epitope



Potent and selective binding to α4β7

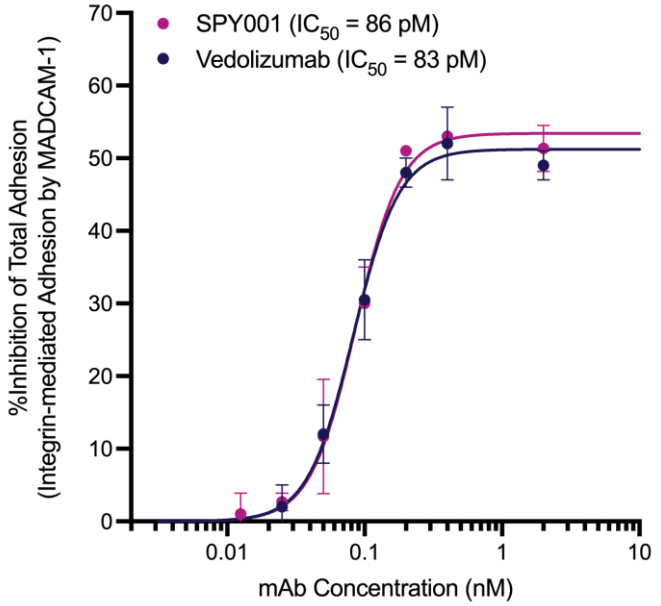
Antibody	α4β7[1]	α4β1	αEβ7
SPY001	K_D <1 nM	NB[2]	NB[2]
Vedolizumab	K_D <1 nM	NB[2]	NB[2]

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

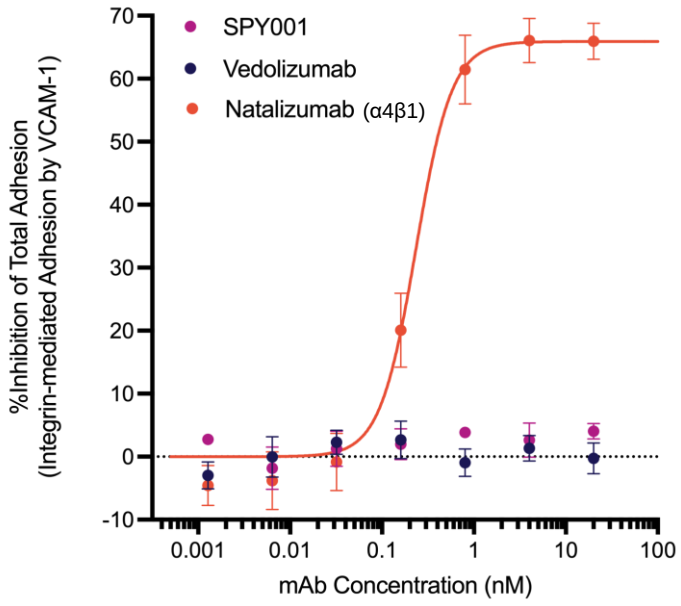
Source: Data on file.

Potent and selective inhibition of cellular adhesion

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

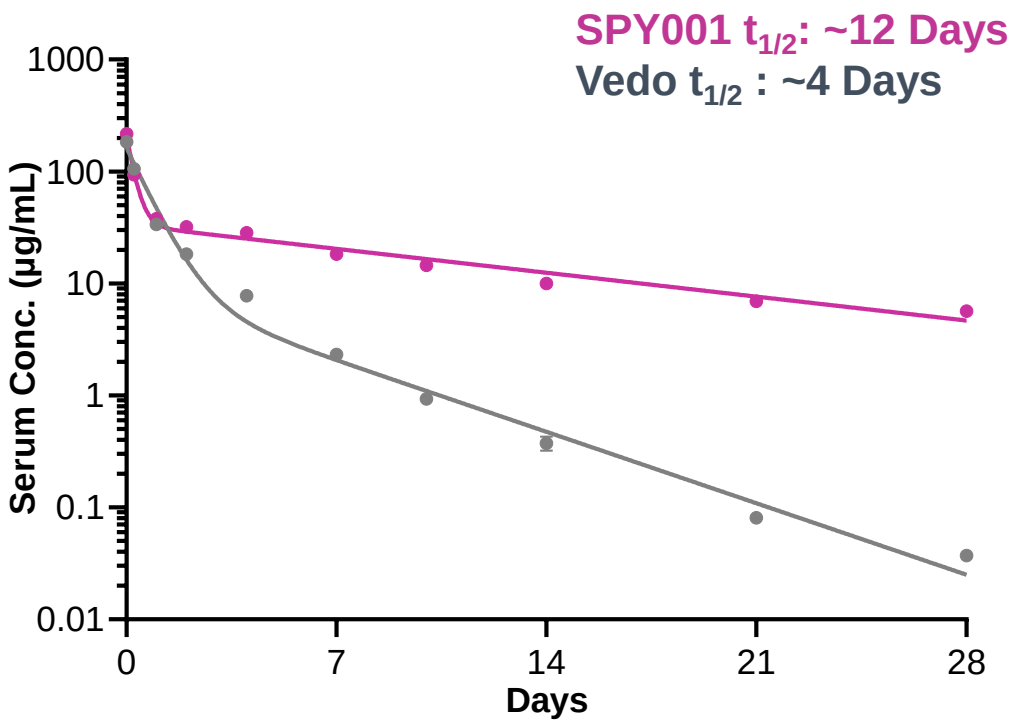


No inhibition of unwanted VCAM-1-mediated (CNS) cellular adhesion

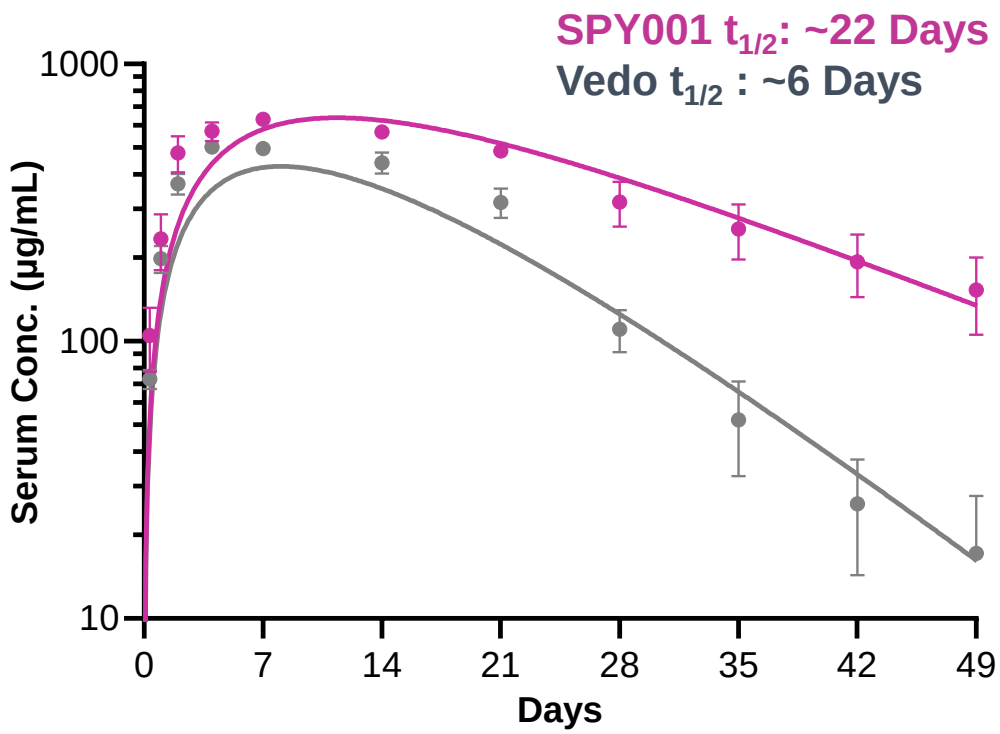


SPY001 has exhibited >3x the half-life of vedolizumab in preclinical models

>3x increased half-life in Tg276 mice vs vedolizumab



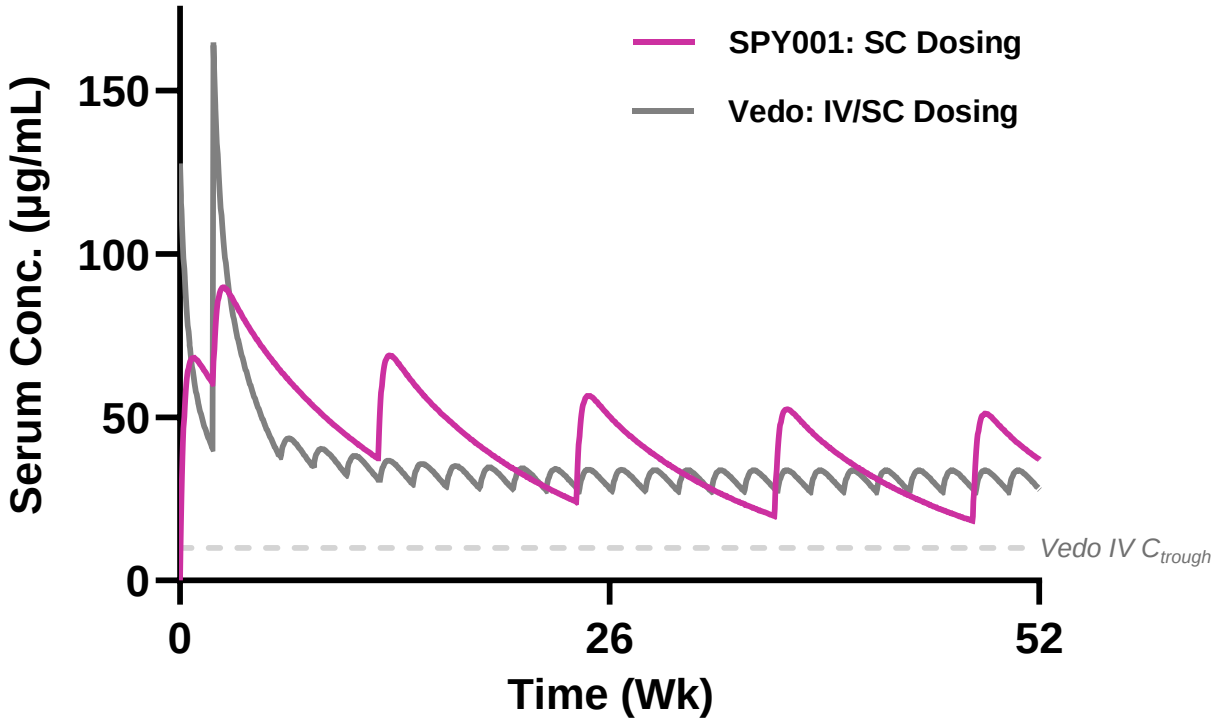
>3x increased half-life in NHPs vs vedolizumab



Source: Data on file. N=5 per group per study

SPY001 is designed to have a superior maintenance profile for patients

PK simulation of SPY001 vs. vedolizumab



SPY001 SC

Potential for as few as
4-6 INJECTIONS
per year in maintenance

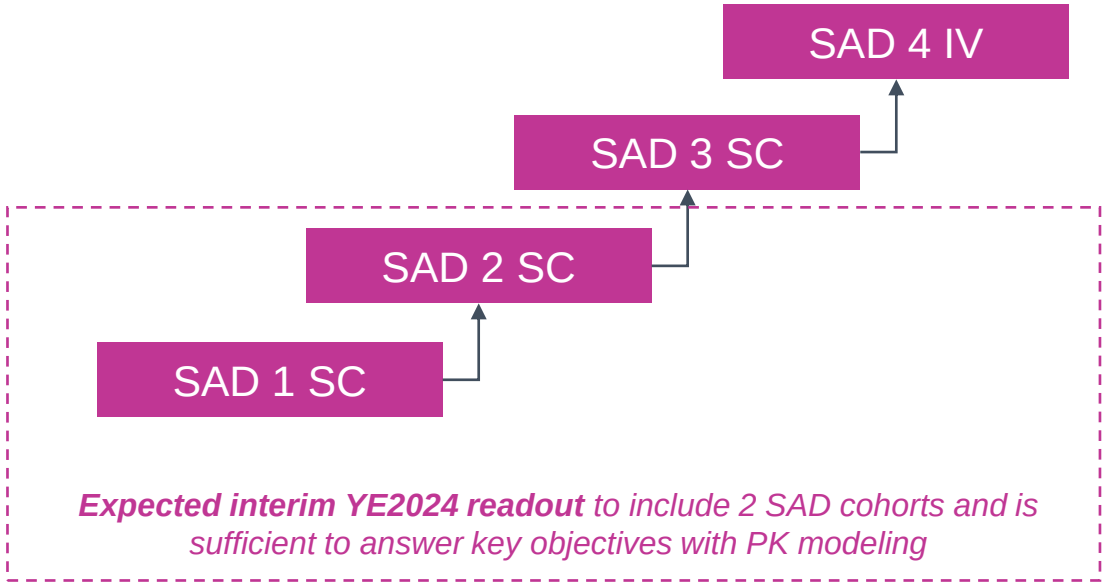
~150 mg/mL
SC concentration

VEDO SC

26 INJECTIONS
per year in maintenance

SPY001 Phase 1 trial expected to initiate in H1 2024

Single-ascending dose



Expected interim YE2024 readout *to include 2 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

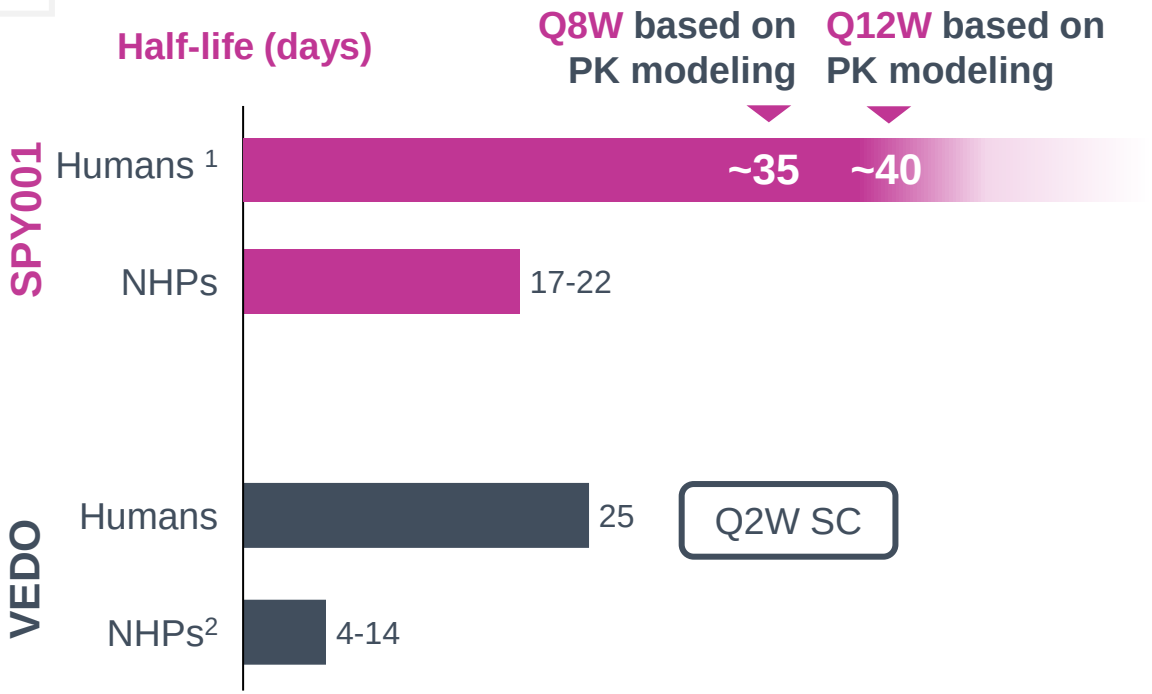
We aim to demonstrate the following for SPY001 in the expected YE2024 interim Phase 1 readout

1	≥35-day half-life enables ≥Q8-12W SC maintenance dosing based on PK model
2	Potential to address vedo's slow onset of action with higher induction exposures
3	Establish SPY001 has favorable safety profile and is well-tolerated
4	Minimal to no impact on ADA rates vs vedolizumab

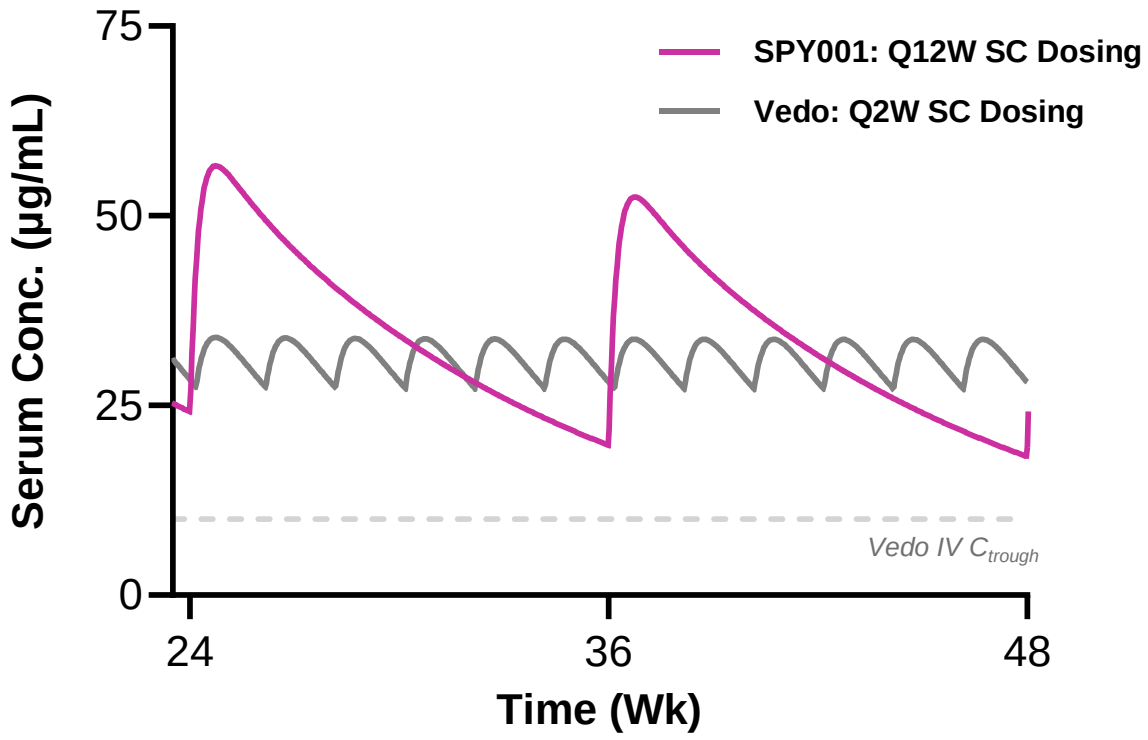
Phase 1 interim PK will serve as confirmation of Q8-12W SPY001 maintenance dosing, as predicted by NHP data

SPY001 human half-life predictions

1



Maintenance PK simulations

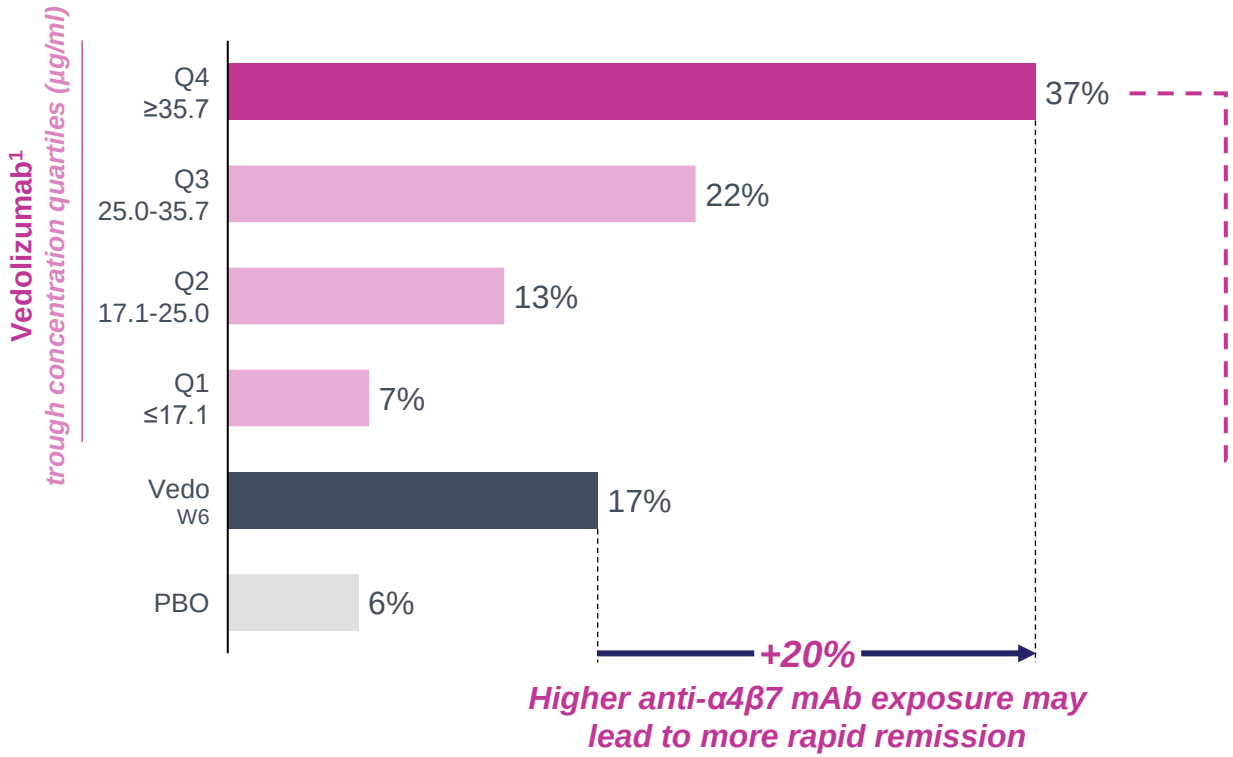


Source: [1]Human YTE mAb half-life is on average 3.1x of NHP half-life; Haraya, Kenta, and Tatsuhiko Tachibana. BioDrugs (2023); Rosario, M, et. al. (2017); *Feagan, et. al. (2013); [2]Range of half-life observed in vedolizumab NHP studies (BLA review) and internal Spyre preclinical studies*

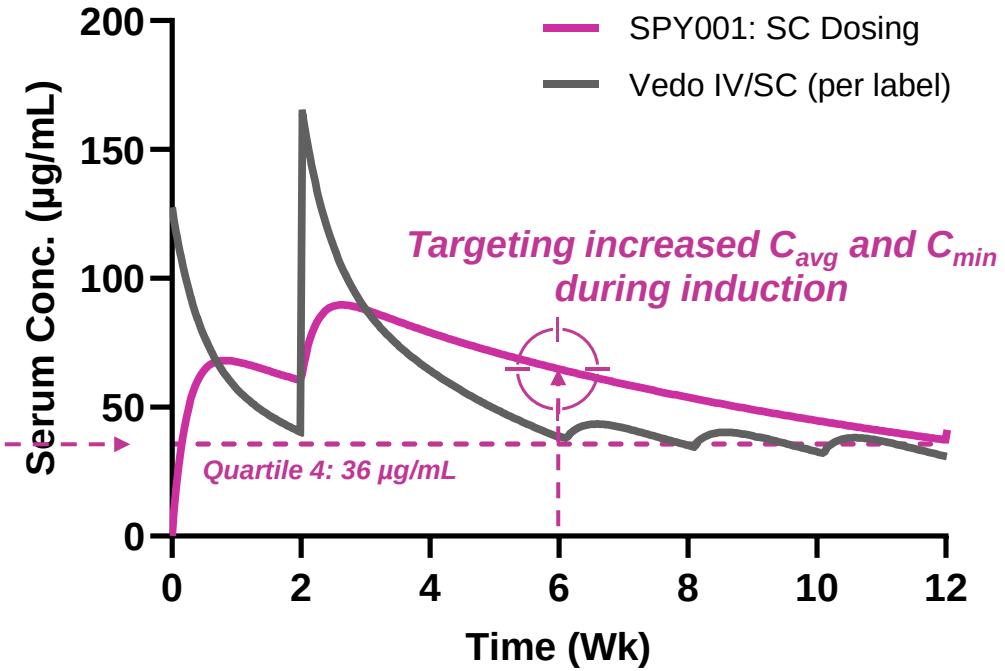
Interim PK data expected to enable Phase 2 dose selection to maximize efficacy potential of SPY001

Potential Upside: Greater remission w/ higher exposure

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



Induction PK simulations



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

Phase 1 is intended to establish that SPY001 has a favorable safety profile and low ADA rate, similar to vedolizumab

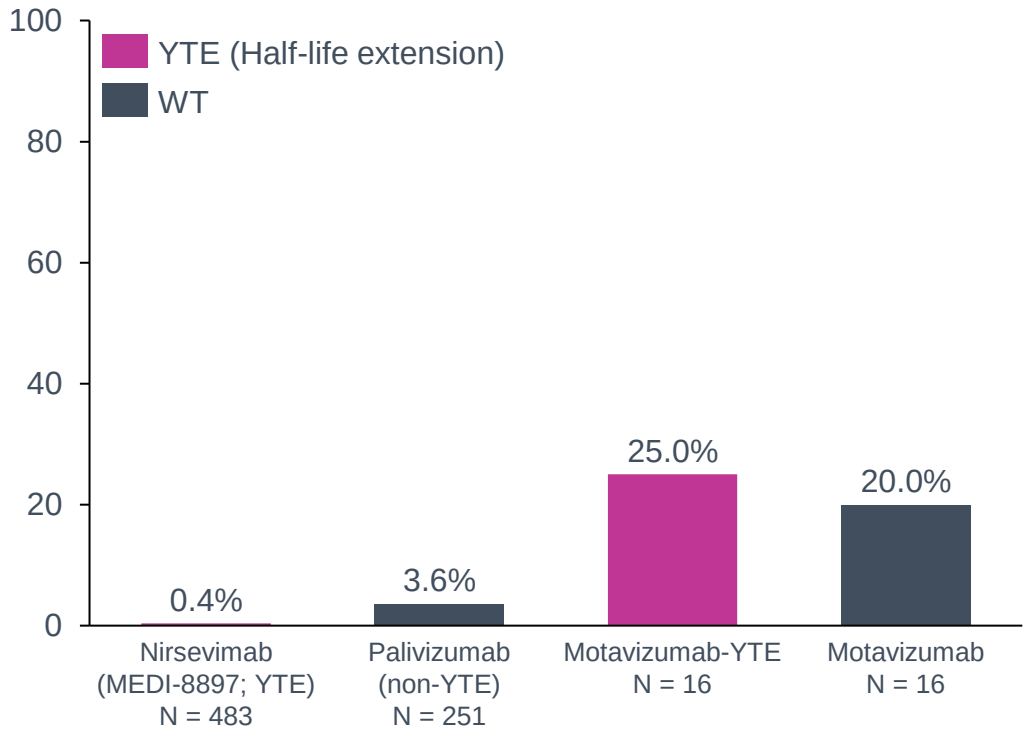
Vedo is well tolerated with low immunogenicity[1]

3

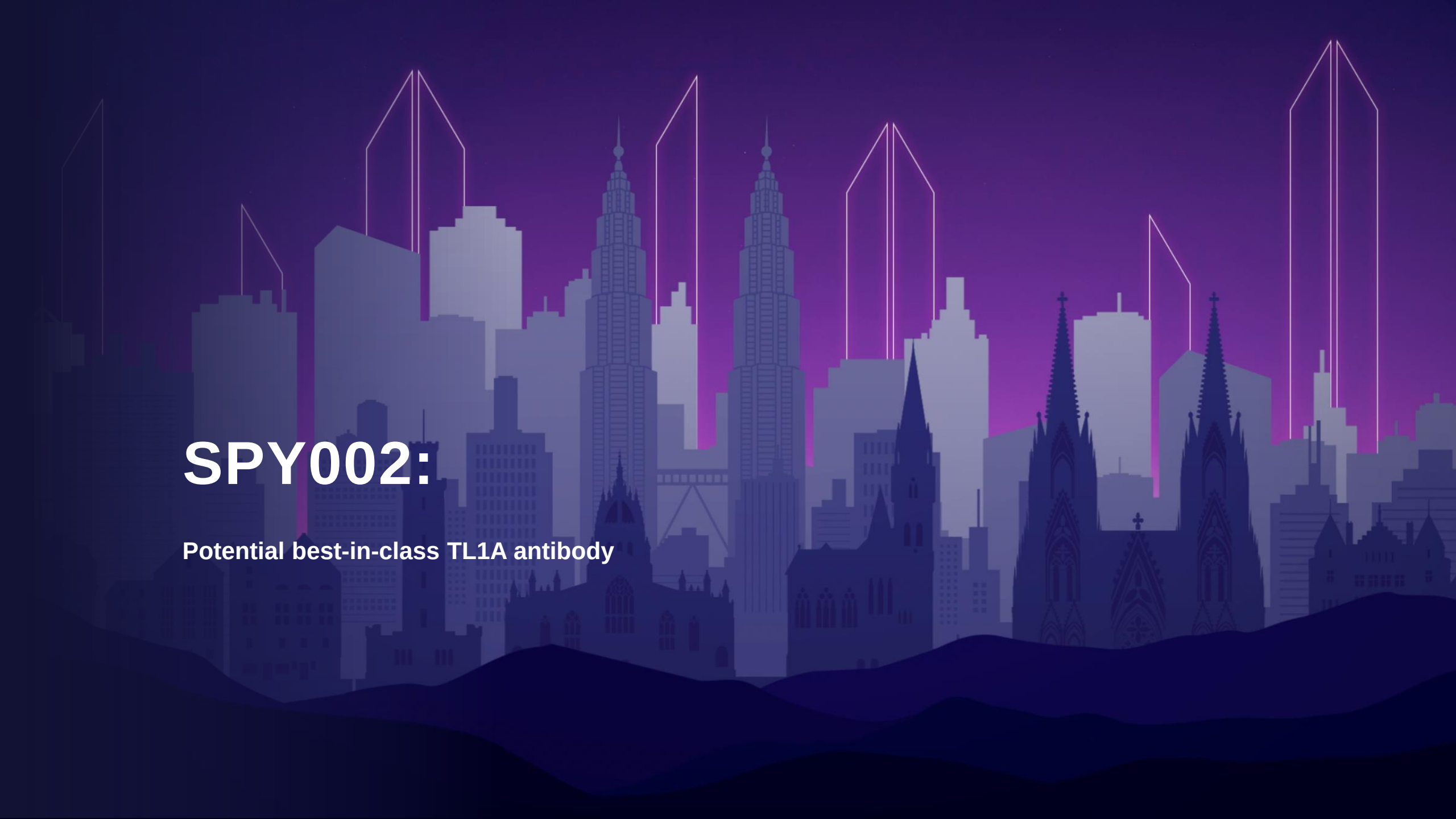
	Vedolizumab	Placebo
Infection rates	**0.85** per patient-year	**0.70** per patient-year
Serious infection rates	**0.07** per patient-year	**0.06** per patient-year
Adverse reaction rates	**52%** (N=1434)	**45%** (N=297)
Malignancy rates	**0.4%** (N=1434)	**0.3%** (N=297)
Infusion reactions	**4%** (N=1434)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

ADA rates are similar for YTE and WT antibodies[2,3]

4



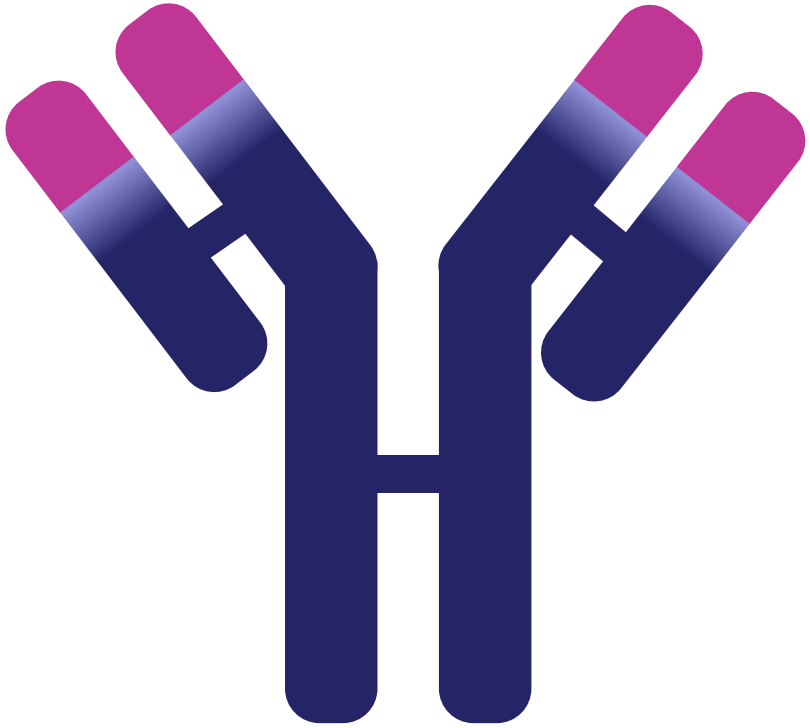
Source: [1]Entyvio prescribing information; SPY001 clinical safety data to be collected in planned clinical trials; [2]Rocca, A, et al. Int J of Mol Sci, 2021; [3]Domachowske NEJM 2022



SPY002:

Potential best-in-class TL1A antibody

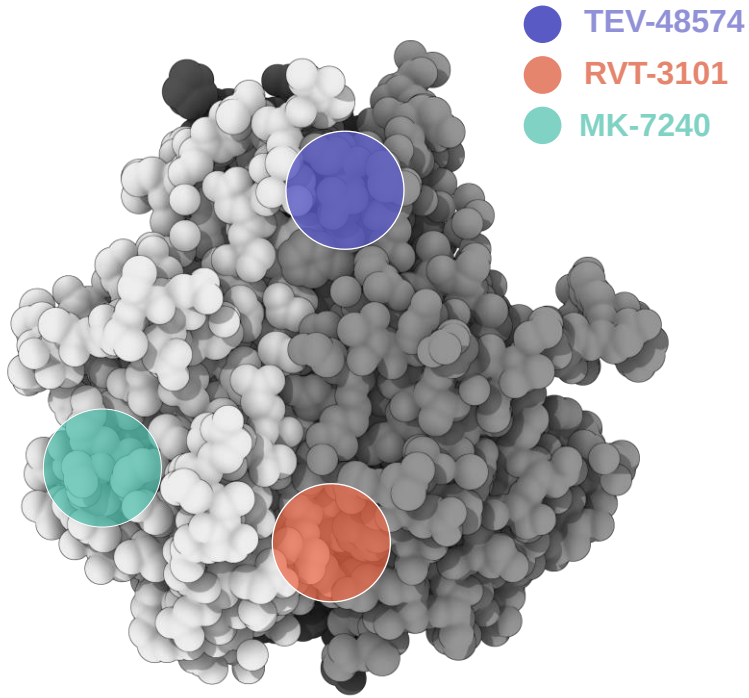
SPY002 is designed to achieve an optimal anti-TL1A profile



SPY002

- Novel epitope with dual monomer and trimer binding based on CryoEM and biochemical assays
- Subnanomolar potency against all forms of TL1A in preclinical models
- Half-life extension through validated Fc modification to enable Q8-12W SC dosing

Spyre is advancing two development candidates with distinct epitopes and binding properties



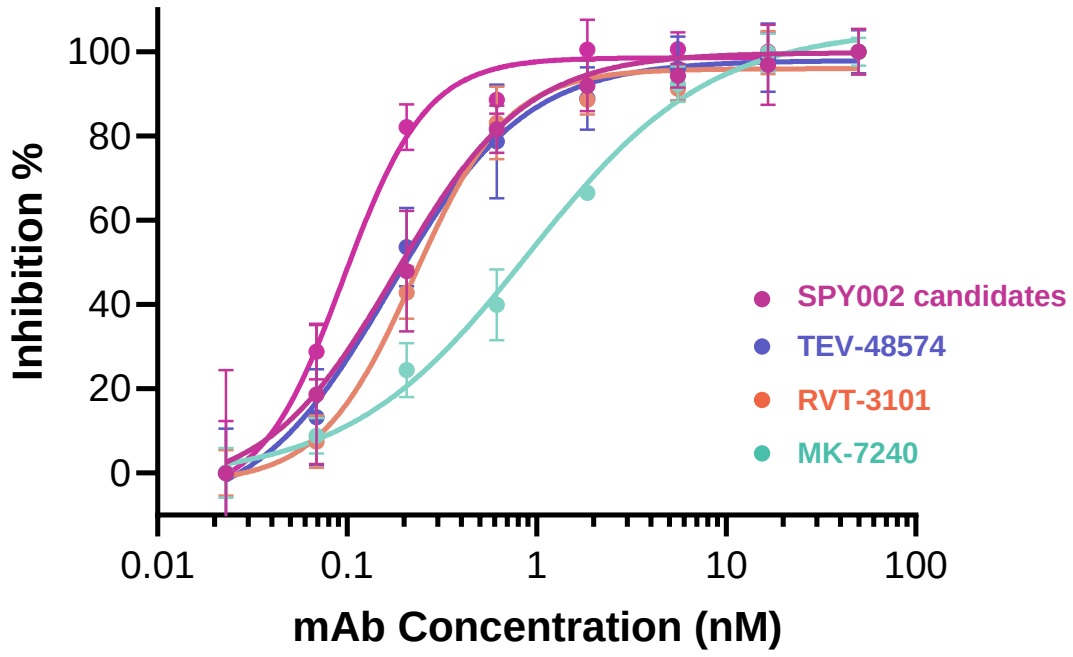
- *Epitope locations were resolved by CryoEM*
- *Illustrative locations are overlayed with the crystal structure of trimeric TL1A*

SPY002 DC-1 AND DC-2

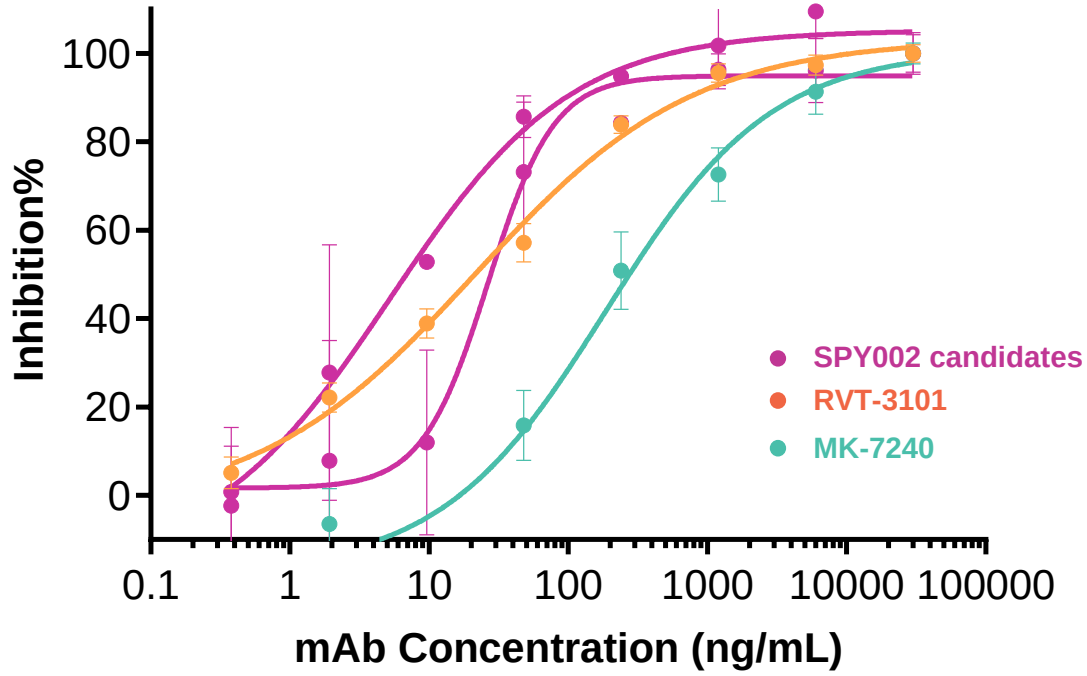
- **Novel epitopes**, both of which bind to a **single TL1A monomer** unit
- Each DC has a **distinct epitope and unique biochemical properties**
- **K_D < 300 pM**
- Fully human IgG1 mAb

SPY002 candidates have comparable or better preclinical potency compared to first-gen. anti-TL1As

Comparable or superior inhibition of TF-1 apoptosis



Comparable or superior inhibition of IFNγ secretion

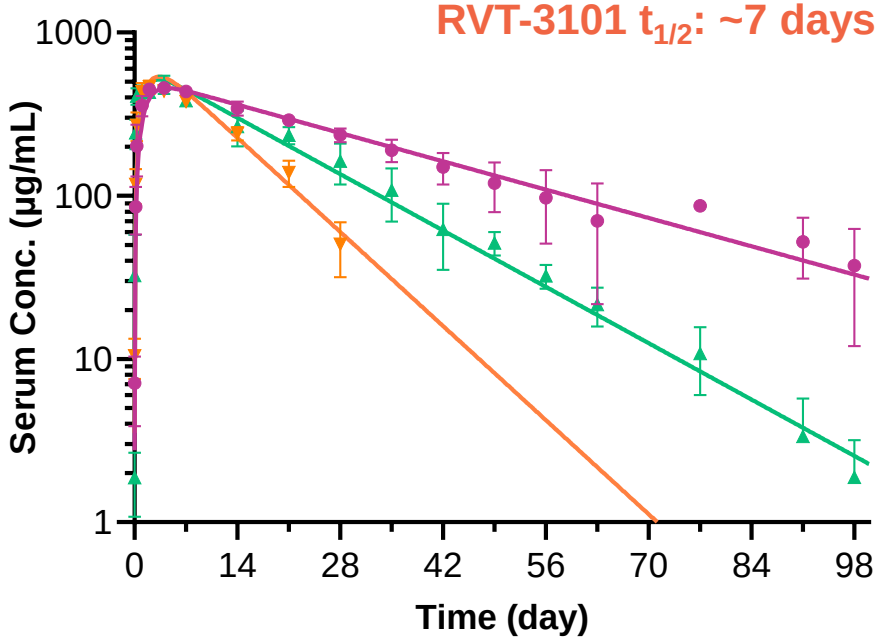


Note: TEV-48574 not benchmarked in IFN$_\gamma$ secretion assay

SPY002 candidates exhibit increased half-life compared to first-generation anti-TL1As in NHPs

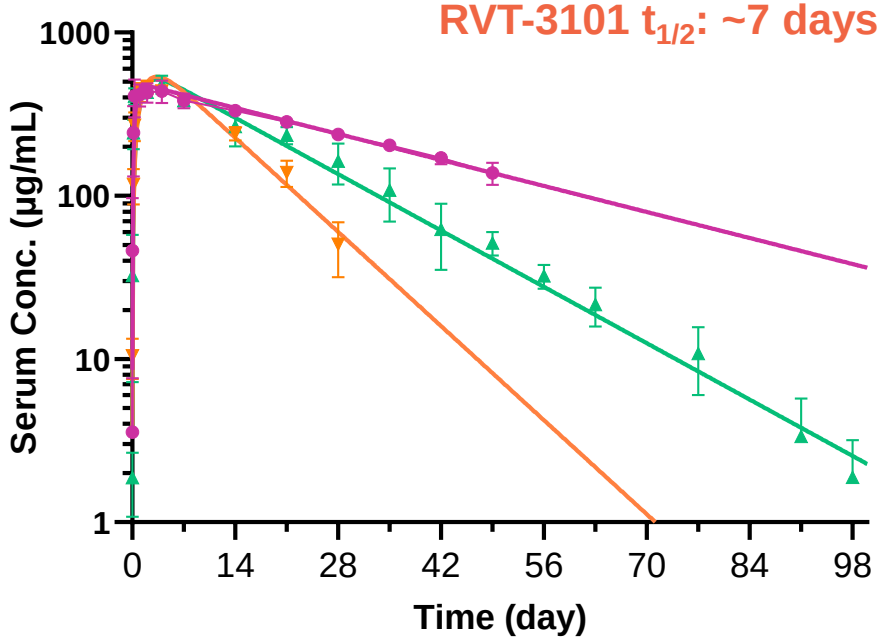
SPY002 DC1: 2-3x Increased Half-life in NHPs

SPY002 $t_{1/2}$: ~24 days
MK-7240 $t_{1/2}$: ~12 days
RVT-3101 $t_{1/2}$: ~7 days



SPY002 DC2: >2-3x Increased Half-life in NHPs

SPY002 $t_{1/2}$: ~26 days
MK-7240 $t_{1/2}$: ~12 days
RVT-3101 $t_{1/2}$: ~7 days



Note: No titers for RVT-3101 were detected after day 28; TEV-48574 not compared in these models given low human half-life (7-10 days); ECCO 2024 abstract P633; 98-day PK for SPY002 DC2 pending (study in progress)

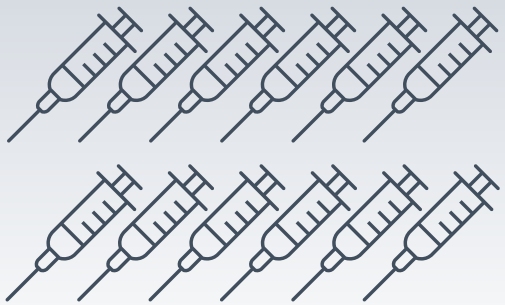
SPY002 is designed to have a superior maintenance profile for patients

First-generation TL1As

At least:

12 INJECTIONS[1]

per year

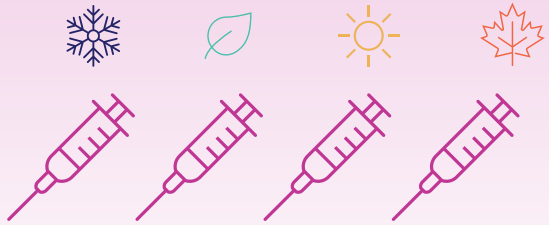


SPY002 SC

Potential for as little as:

4 INJECTIONS[2]

per year



~200 mg/mL

SC concentration

Note: [1]Expected dosing regimen based on publicly available information from Phase 2 programs; [2]Assumption based on 2-3x extended half-life observed in NHPs

We believe SPY002 is the most advanced unencumbered TL1A in development

Announcement dates:

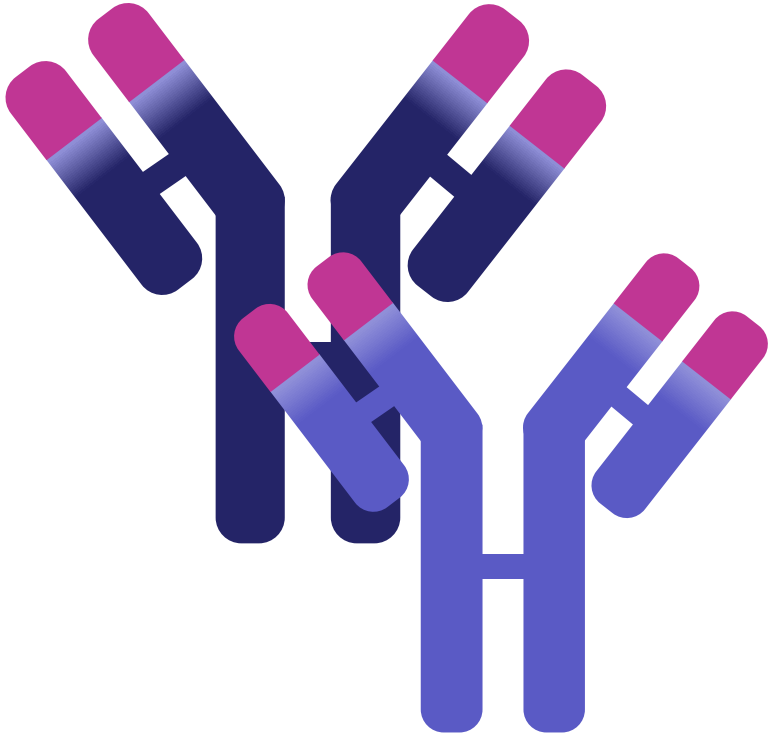
April 16, 2023	Oct 3, 2023	Oct 23, 2023
MERCK / Prometheus Biosciences	sanofi / teva	Roche / roivant / Telavant
$10.8B acquisition	**50-50 licensing deal**	**$7.1B acquisition**
Global rights	$0.5B upfront +$1B in milestones North America, Japan, Asia rights	+$150M near-term milestone U.S. and Japan rights

Source: Company press releases

Therapeutic combinations

A paradigm shift in the treatment of IBD

Spyre is unique in its portfolio approach to evaluating multiple combination regimens



SPY120 • SPY130 • SPY230

- **Only known portfolio with α4β7, TL1a, and IL-23 inhibitors**
- **Potential to address orthogonal biology**
- **Unified Q8-12W SC dosing potential across targets**

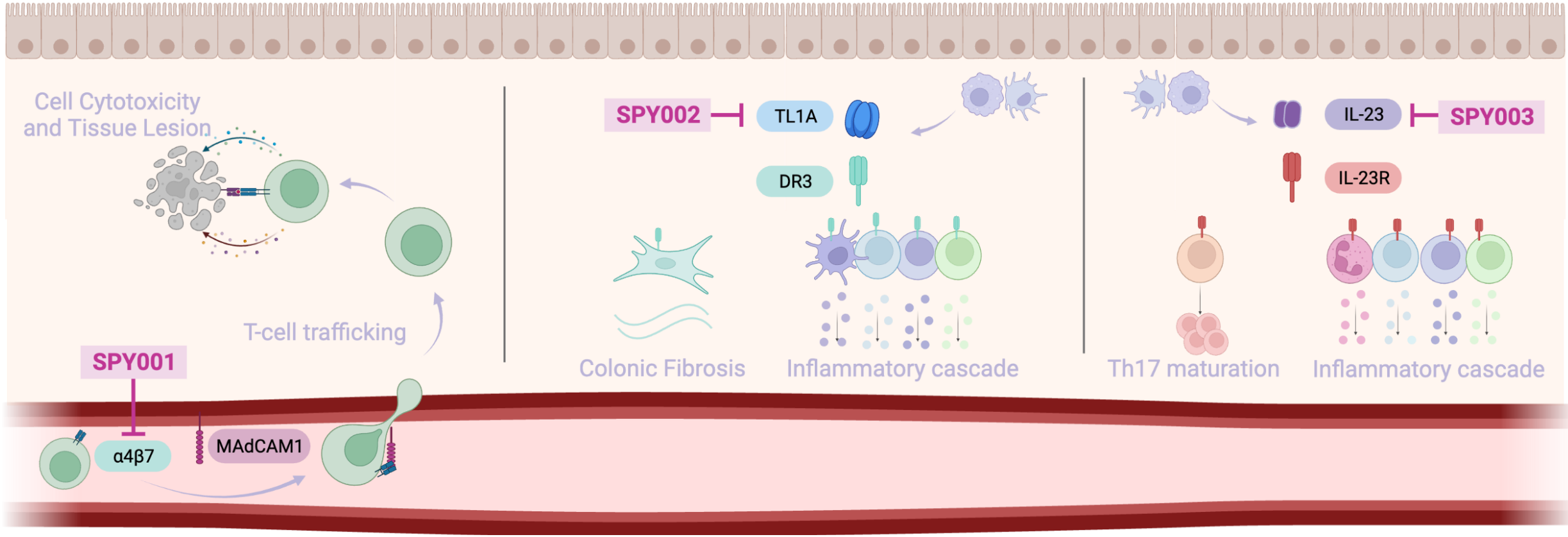
Spyre portfolio addresses the diverse pathophysiology of IBD

MOA

Blockade of **α4β7** prevents circulating immune cells from entering inflammatory gut tissues

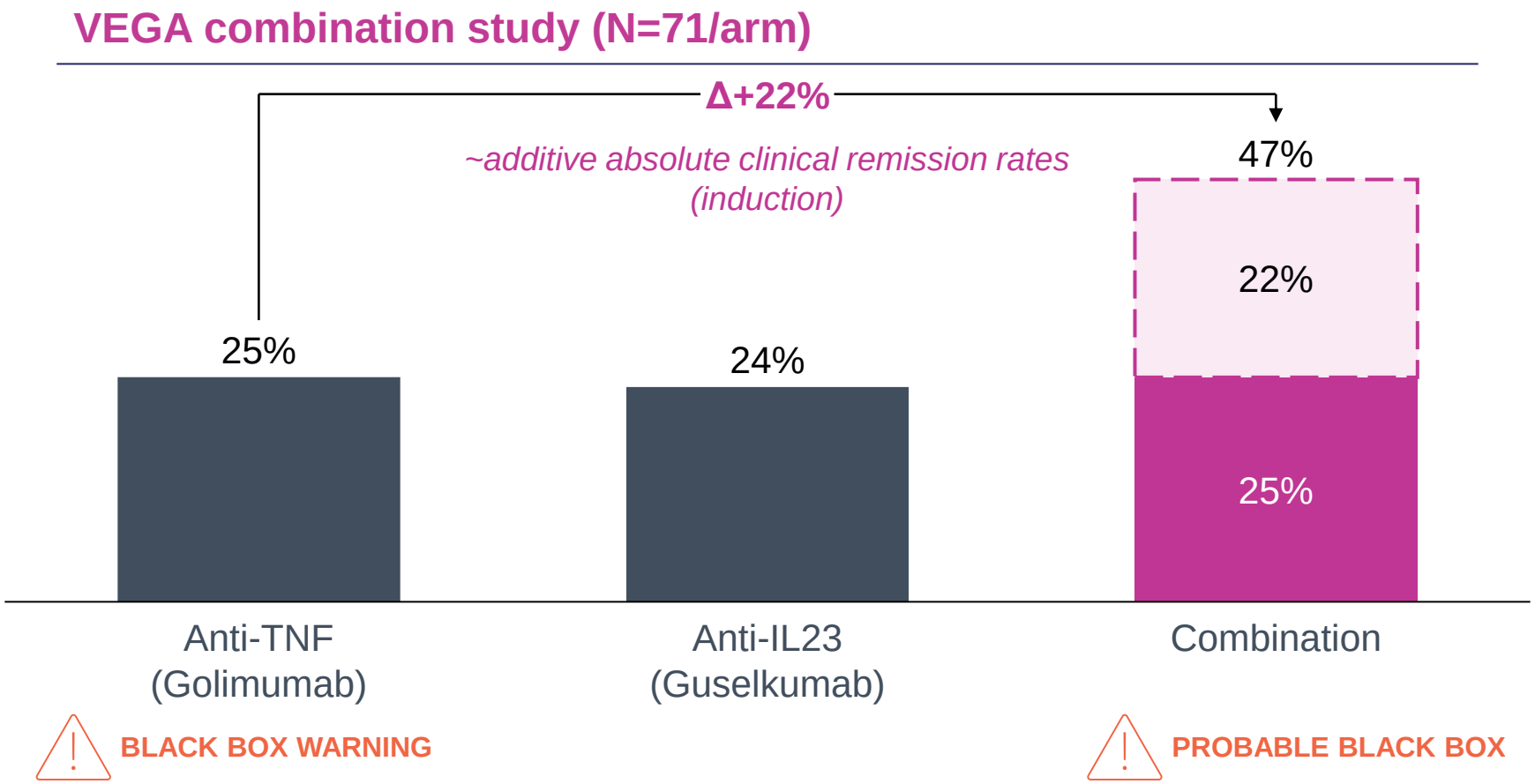
Neutralization of **TL1A** suppresses inflammation within gut tissue and blocks immune cell activation

Neutralization of **IL-23** inhibits cascade of various proinflammatory cytokines



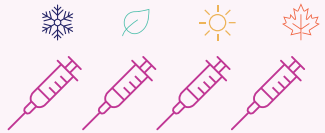
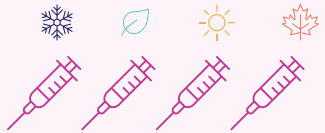
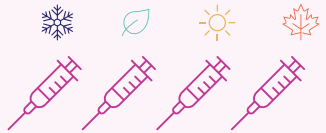
Sypre is a pioneer in developing potential best-in-class mAbs against three top targets with the goal of enabling superior combinations for IBD

JNJ's VEGA study demonstrated power of combination therapy

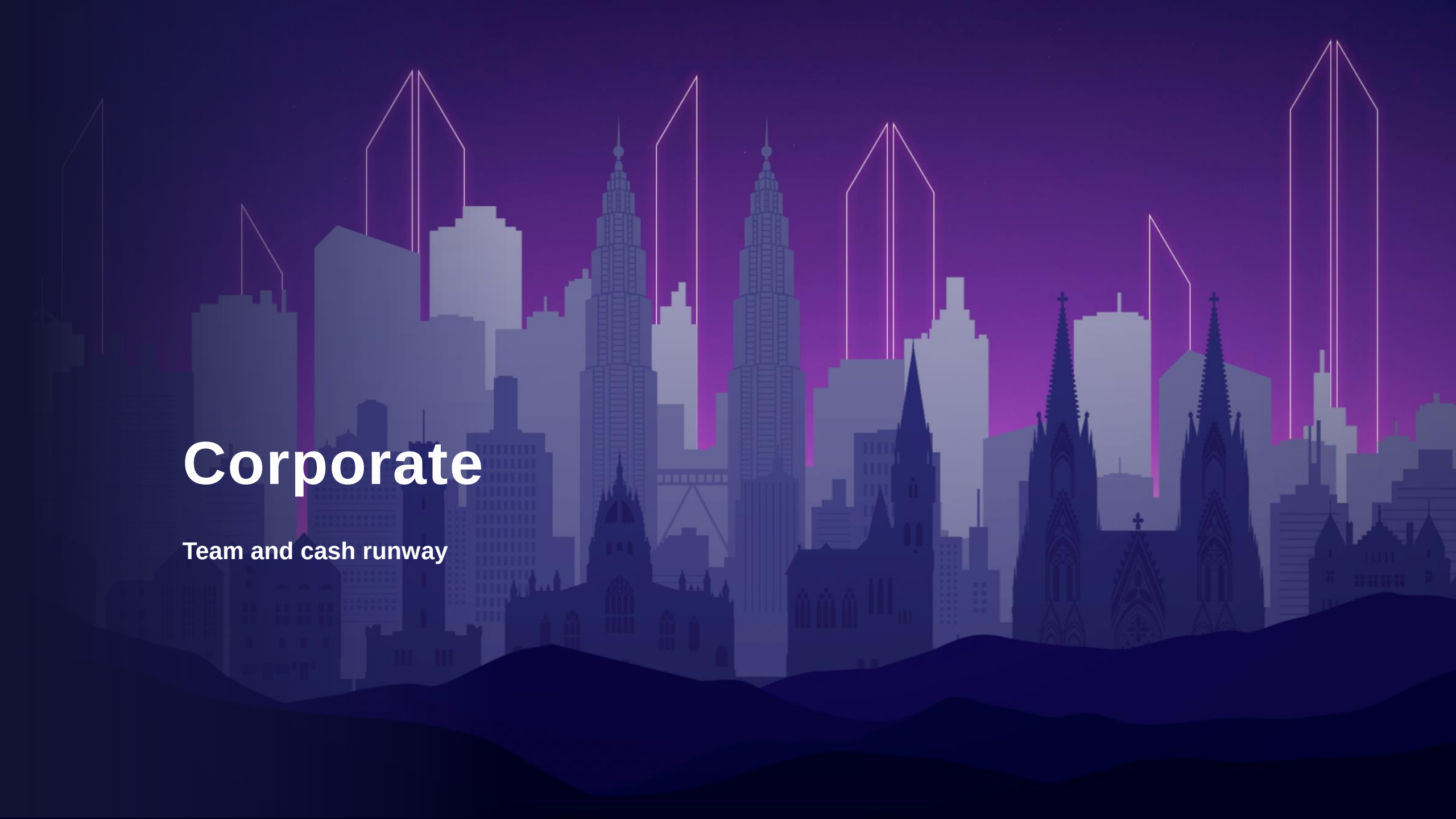


NOTE: In VEGA, only guselkumab (IL-23) was continued in maintenance for the combo arm in a treat-through design; Spyre plans to use combinations in maintenance. Maintenance remission rates for the anti-TNF arm, anti-IL23 arm, and induction combination arm were 21%, 31%, and 48%, respectively.; Feagan, 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

	SPY120	SPY130	SPY230	JNJ-4804
Targets	α4β7 + IL-23	α4β7 + TL1A	TL1A + IL-23	TNF + IL-23
Expected maintenance regimen				
Target format	Co-formulation	Co-formulation	Co-formulation	Co-formulation
Anti-cytokine + anti-lymphocyte trafficking	✓	✓		✗
No black box warning	✓	✓	✓	✗

Source: Company materials



Corporate

Team and cash runway

Leadership

Scott Burrows
Chief Financial Officer

Brian Connolly
Chief Technical Officer

Melissa Cooper
SVP, People

Paul Fehlner
SVP, Chief Intellectual Property Counsel

Joshua Friedman
SVP, Clinical Development

Janet Gunzner-Toste
SVP, Operations

MiRa Huyghe
SVP, Development Operations

Heidy King-Jones
Chief Legal Officer and Corporate Secretary

Justin LaFountaine
SVP, Corporate Development

Deanna Nguyen
SVP, Clinical Development

Andrew Spencer
SVP, Preclinical Research and Development

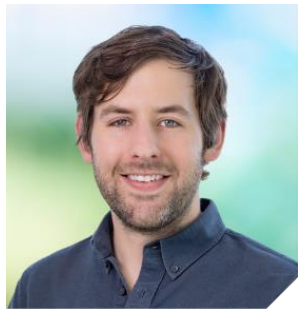
Cameron Turtle
Chief Executive Officer

Board of Directors

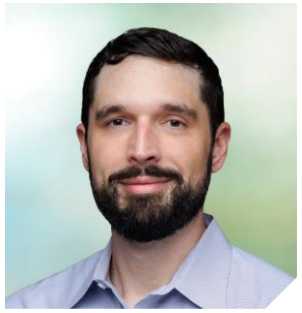
Jeffrey Albers

Russell J. Cox

Peter Harwin



Michael Henderson



Tomas Kiselak

Mark McKenna

Laurie Stelzer

Cameron Turtle

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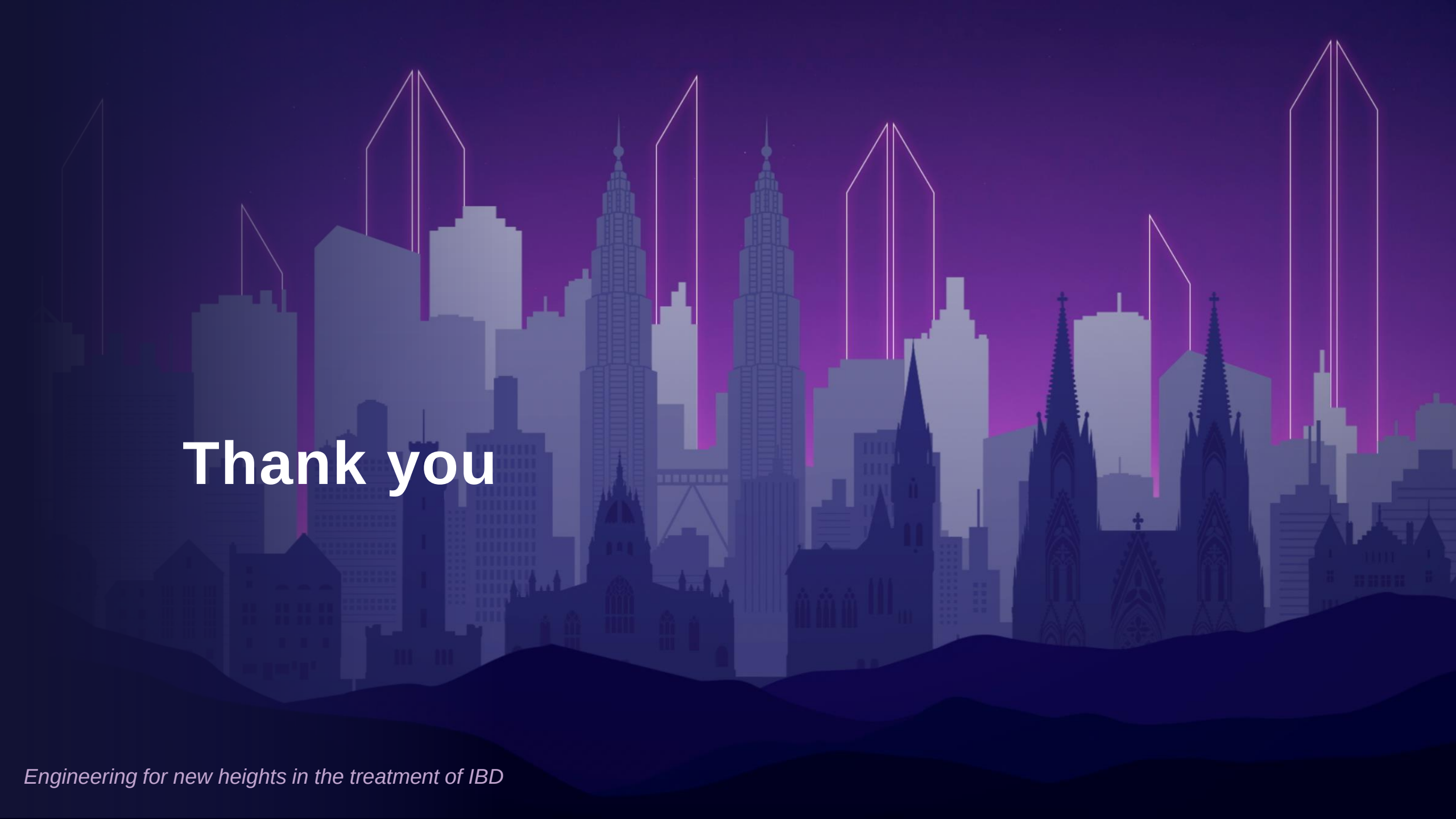
Cash and anticipated milestones

$509M 12/31/2023 proforma cash[1]
Expected runway well into **2027**

65.2M
Shares outstanding[2]

	2024	2025
SPY001 (α4β7)	IND/CTA	PHASE 1 INTERIM DATA PHASE 1 FULL DATA PHASE 2 INITIATION
SPY002 (TL1A)		IND/CTA PHASE 1 INTERIM DATA
SPY003 (IL-23)		IND/CTA
COMBINATIONS		PHASE 2 INITIATION
EXTERNAL EVENTS		TEV-48574 P2b Interim MORF057 P2b/DUET UC-CD P2b MK-7240 SSc-ILD P2

Notes: Anticipated milestones as of March 2024; [1]Proforma cash includes cash, cash equivalents, restricted cash & marketable securities as of 12/31/23 of $340M plus estimated net proceeds of $169M from PIPE offering which closed in March 2024; [2]Shares outstanding on a pro forma and as-converted basis, which (i) gives effect to the full conversion of the Company's preferred stock, (ii) disregards beneficial ownership limitations that may limit the ability of certain holders of preferred stock to convert into common stock, and (iii) assumes the exercise of all outstanding pre-funded warrants.



Engineering for new heights in the treatment of IBD