aeglea™

SPYRE THERAPEUTICS

# CORPORATE OVERVIEW

Q3 2023

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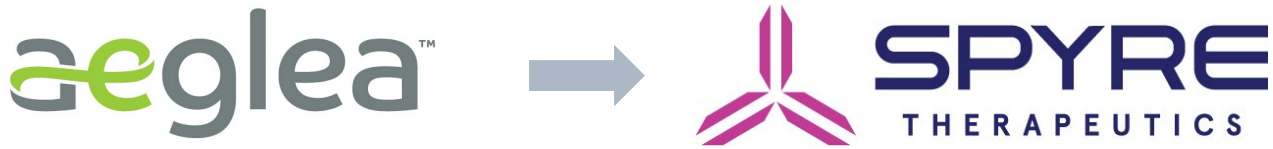
# Aeglea-Spyre Transaction highlights




**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.

**Management and BOD:** Continuing leadership includes Jonathan D. Alspaugh, President and Chief Financial Officer, and Cortney Caudill, Chief Product Officer, and will be joined by Cameron Turtle, DPhil, Chief Operating Officer. Peter Harwin, Managing Member, Fairmount Funds, and Tomas Kiselak, Managing Member, Fairmount Funds, join Russell Cox, Chairman of the Board of Aeglea, Hunter Smith, Board Member and Audit Chair, Allison Lawton, Board Member, and Ivana Magovčević-Liebisch, Board Member. Michael Henderson, CEO of Apogee Therapeutics, will be joining as an Independent Director.

**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.

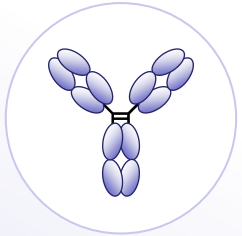
# Capitalization

| As of 6/20/2023 | |
|---|---|
| Shares of common stock outstanding | 65.4 million |
| Pre-funded warrants | 28.9 million |
| **Merger consideration** | |
| Shares of common | 13.0 million |
| Shares of preferred | 0.4 million |
| Preferred conversion ratio | 1:1000 |
| Total pre-financing common equivalent | 472.2 million |
| **Concurrent financing** | |
| Shares of preferred | 0.7 million |
| Common equivalent | 721.5 million |
| **Total capitalization (Common)** | **1,193.6 million** |

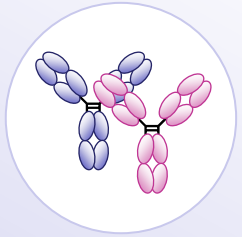
- Shares of common stock and preferred stock were issued to Spyre security holders in exchange for all of Spyre's outstanding equity interests.
- Shares of preferred stock were issued to Spyre stockholders and to investors in the $210 million private placement.
- Each share of preferred stock will automatically convert into 1,000 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.

# Spyre aims to transform the treatment of IBD

SPYRE THERAPEUTICS



***Opportunity for best-in-class Long-acting antibodies***
SC with Q8-12W dosing



***Rational therapeutic combinations***



***Precision patient selection***

## PARALLEL LEAD PROGRAMS AGAINST HIGH VALUE TARGETS

| TARGET | PROGRAM | DISCOVERY | IND-ENABLING | CLINICAL |
|---|---|---|---|---|
| *α4β7*<br>*Same MOA as vedolizumab* | SPY001 | | | *HV PK/PD data expected YE24* |
| *TL1A*<br>*Same MOA as PRA023* | SPY002 | | | *HV PK/PD data expected 1H25* |
| *IL-23* | SPY003 | | | |
| *Novel MOA* | SPY004 | | | |
| *α4β7 + IL-23* | SPY130 | | | |
| *α4β7 + TL1A* | SPY120 | | | |
| *TL1A + IL-23* | SPY230 | | | |

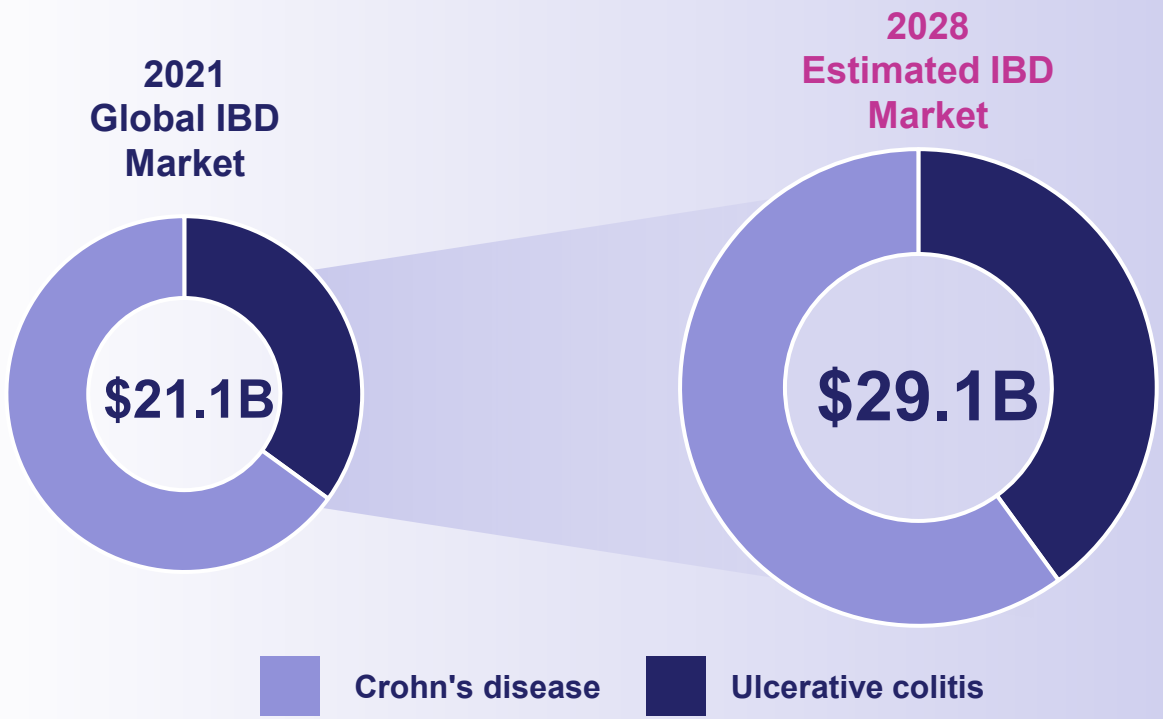
# Inflammatory bowel disease is a growing $21B market in which biologics are the preferred modality

**~1.7M**
IBD patients diagnosed in the US.

IBD makes up **22% of the global $100B+ I&I market.**

**Biologics are the preferred modality** for moderate-to-severe patients due to superior benefit-risk profile.

**$29B+**
estimated IBD market globally in 2028.




**IBD represents a multi-billion dollar market opportunity for best-in-class biologics.**

*Sources: Global Data, Evaluate Pharma, UpToDate, SVB Leerink.*

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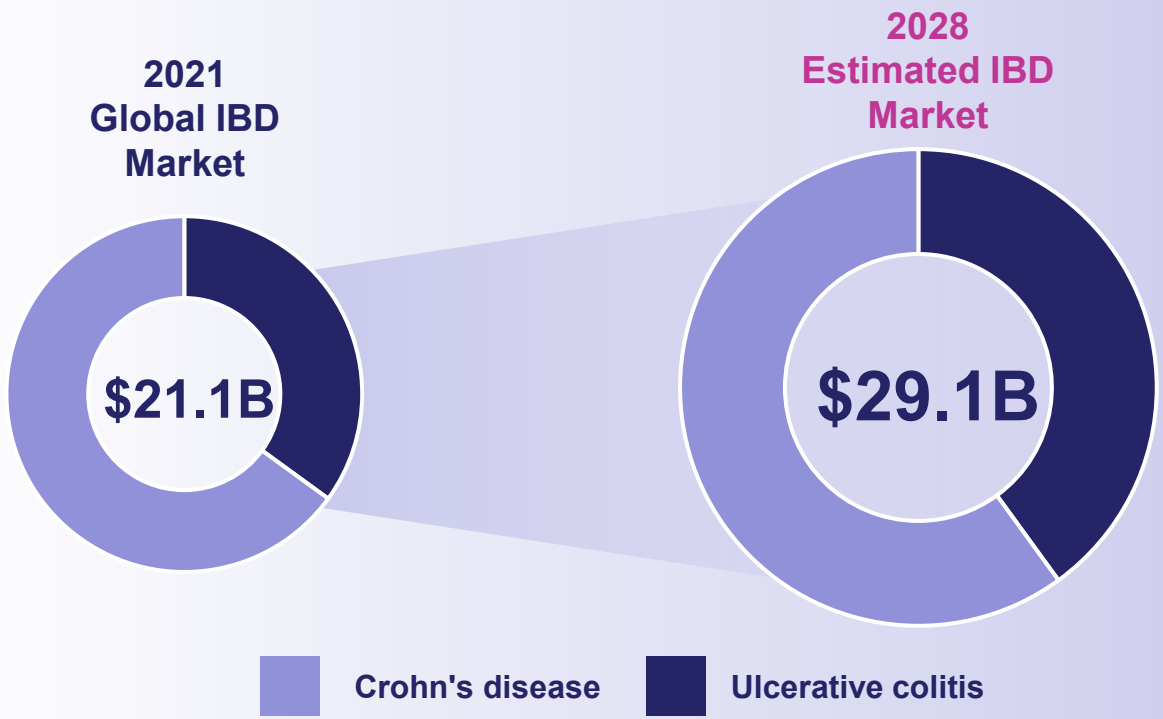


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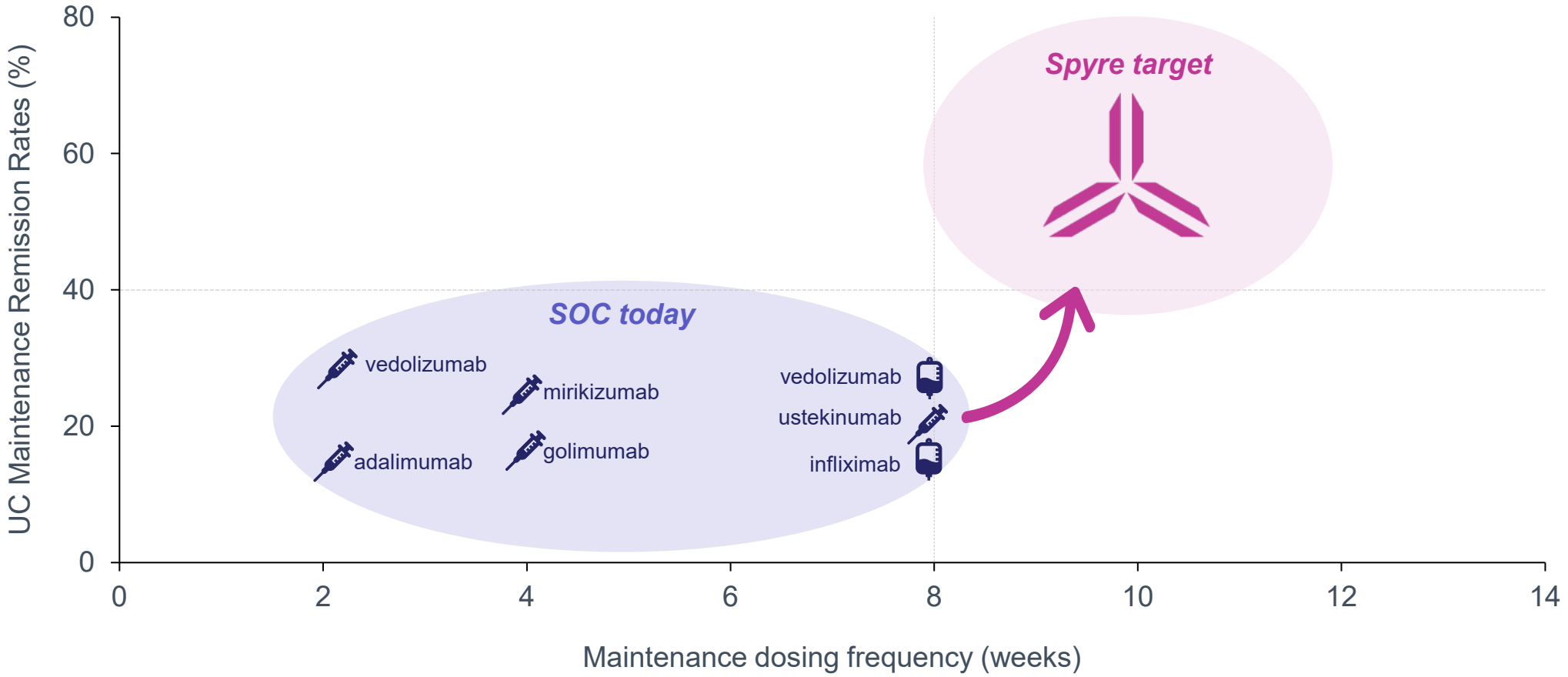
# Despite advances, new approaches are needed to break the efficacy ceiling and improve convenience of biologics

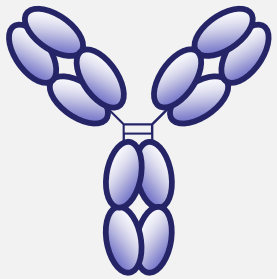



*Summary data for select agents that randomize patients post response to induction; data from labels, company reports.*
*Vedolizumab approved in US as Q8W IV – Q2W SC approval pending following CRL in 2019. TL1A maintenance data not available.*
*Orals not shown (pbo-adj maintenance remission rates): Jaks - tofacitinib (27%), upadacitinib (30% 15mg, 40% 30mg); S1Ps: ozanimod (19%); etrasimod (25% - P3 Treat-through design).*

# Spyre's strategy to address unmet needs in IBD

***Three strategic pillars in an effort to create the preeminent IBD company***

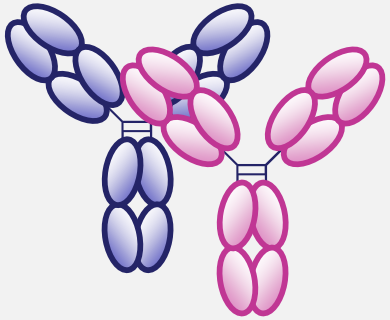
**1**



**Best-in-class mAb engineering**

*With half-life extension technology*

**2**



**Rational therapeutic combinations**

**3**



**Precision patient selection**

# Spyre mAbs exploit validated biology with modifications designed for best-in-class properties

1 2 3

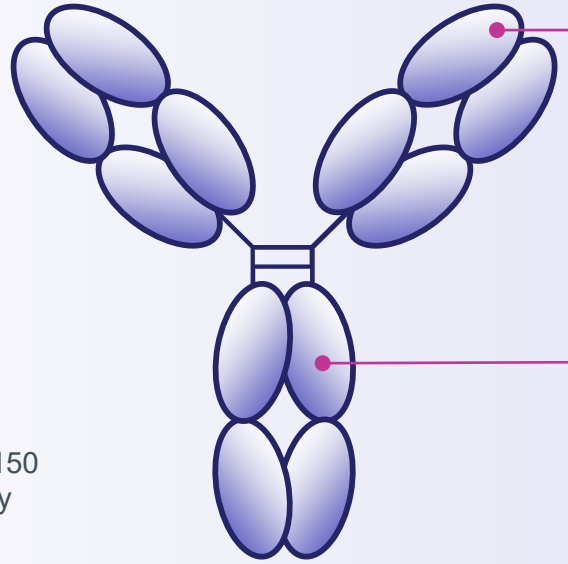
## Spyre mAbs introduce significant improvements over 1st generation mAbs

**Epitopes maintained**

- Validated pharmacology
- Equivalent or better potency

**High concentration SQ**

- Ability to formulate at >150 mg/mL with low viscosity
- Citrate-free formulation



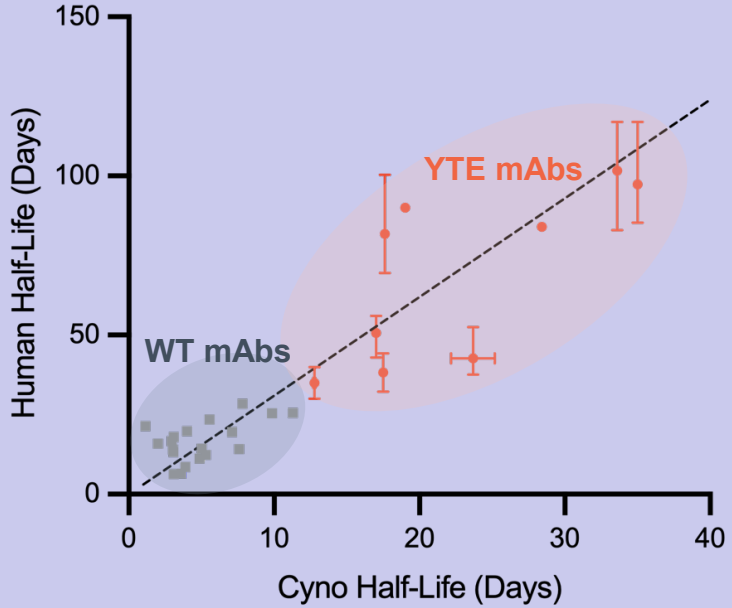
**Potential for IP into 2040s**

- Novel dosing profile
- Improved manufacturability
- Coverage of diverse back-up series

**Significantly extended half-life**

- Q8-Q12W dosing based on validated half-life extension technology

**CLINICAL PRECEDENT**

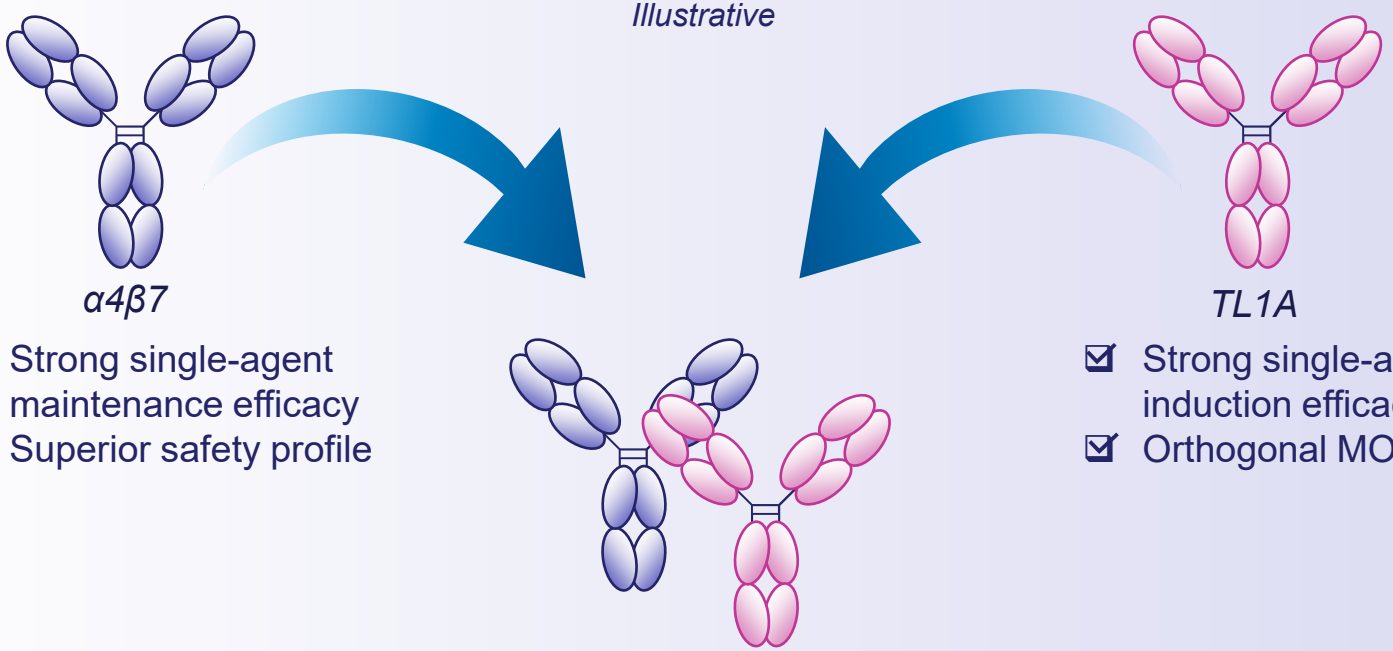


# Spyre is rapidly developing combination products given clinical evidence of substantial efficacy enhancement

1 2 3

## Rational therapeutic combinations

*Illustrative*



*α4β7*

- ☑ Strong single-agent maintenance efficacy
- ☑ Superior safety profile

*TL1A*

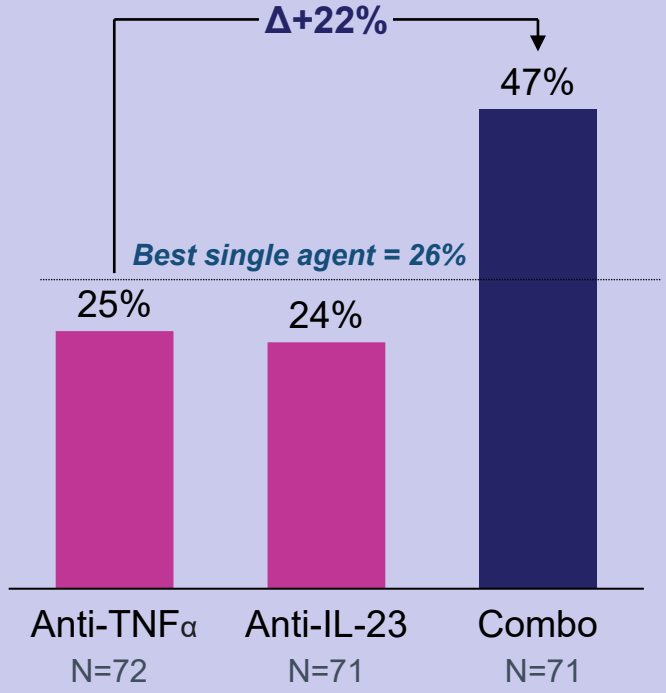
- ☑ Strong single-agent induction efficacy
- ☑ Orthogonal MOA

- ☑ **Enhanced induction and maintenance efficacy**

## CLINICAL PRECEDENT

***JNJ VEGA Ph2a study***

Clinical remission at 12 weeks

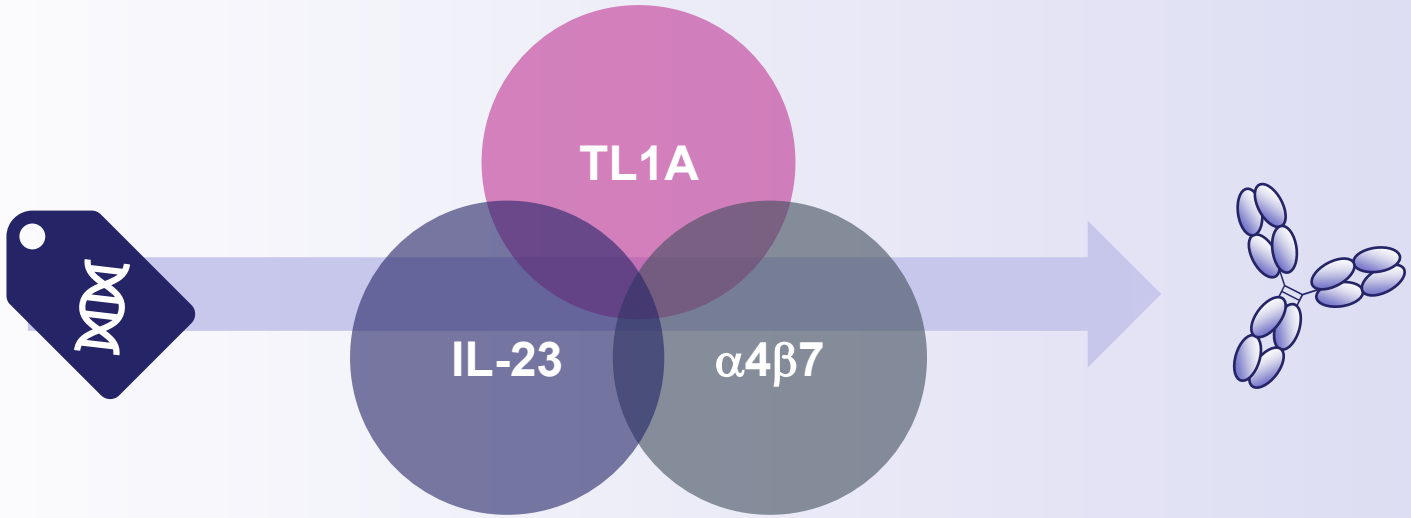



*Source: Feagan, B. G. et al. Lancet Gastroenterol. Hepatol. 8, 307–320 (2023)*

# Spyre leverages genetically-driven patient selection to match disease drivers with therapeutic targets

1 2 3

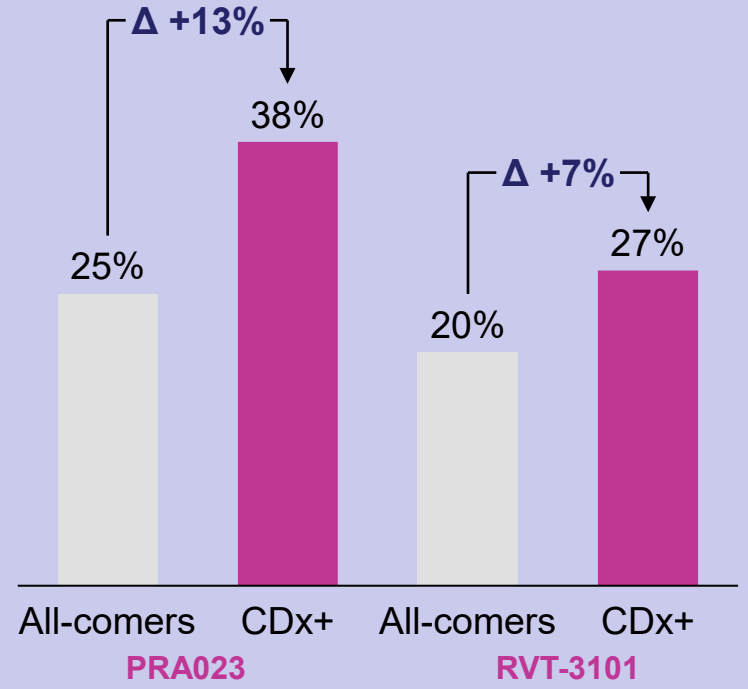
## Genetic companion diagnostic (CDx) leveraging large-scale human genomic datasets




## CLINICAL PRECEDENT

***TL1A studies***

UC clinical remission at 12 weeks



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



Co-lead programs

| STRATEGY | TARGET | PROGRAM[1] | DISCOVERY | IND-ENABLING | CLINICAL |
|---|---|---|---|---|---|
| Best-in-class mAbs (Extended half-life) | *α4β7* Same MOA as vedolizumab | SPY001 ● | | *IND/CTN expected 2Q24* | *HV PK/PD data expected YE24* |
| | *TL1A* Same MOA as PRA023 | SPY002 ● | | *IND/CTN expected 2H24* | *HV PK/PD data expected 1H25* |
| | *IL-23* | SPY003 | | | |
| | *Novel MOA* | SPY004 | | | |
| Rational combinations | *α4β7 + IL-23* | SPY130 | | | |
| | *α4β7 + TL1A* | SPY120 | | | |
| | *TL1A + IL-23* | SPY230 | | | |

[1]*Spyre holds an option to license worldwide rights from Paragon Therapeutics, Inc. for all programs. SPY003 license is restricted to IBD, all other program licenses are indication agnostic*

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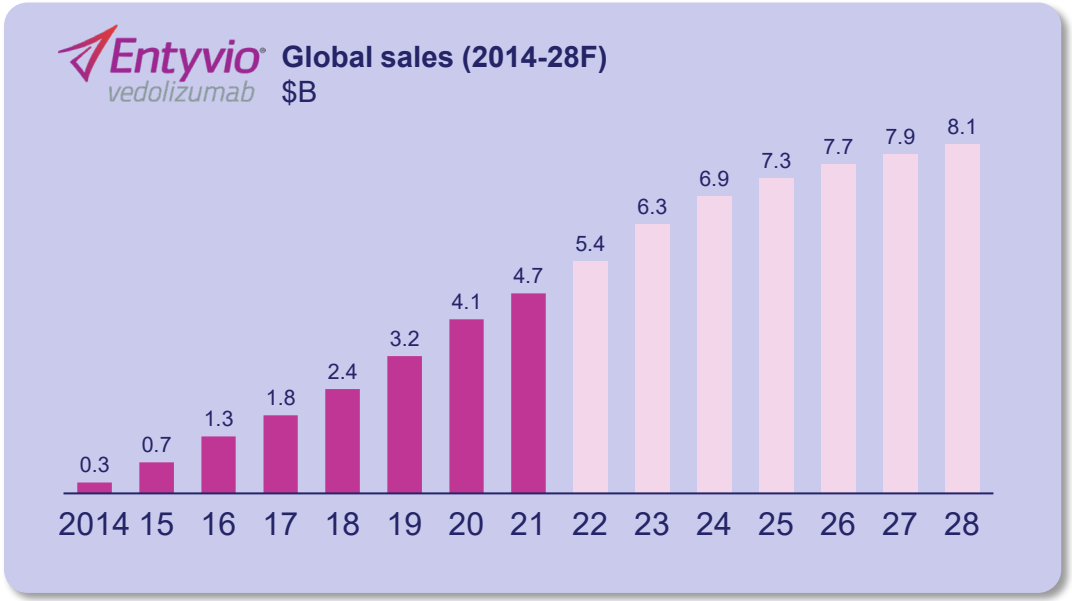
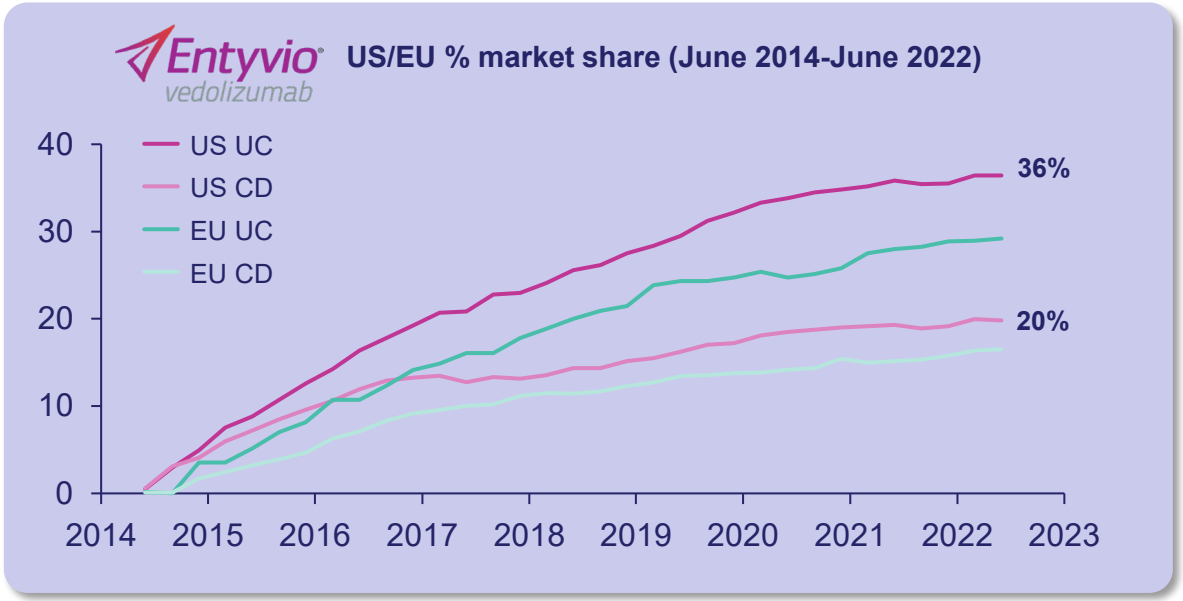
# Vedolizumab is a mega-blockbuster product in IBD

*"Biologic of choice for UC is Entyvio."* – US KOL

- Vedolizumab estimated $5.4B revenues WW in FY22.[1]
- Projected to sell **$7.5-9.0B** at peak WW.[1]
- Significant market share: **~36% of UC market** share and ~20% of CD market share in US.[1]



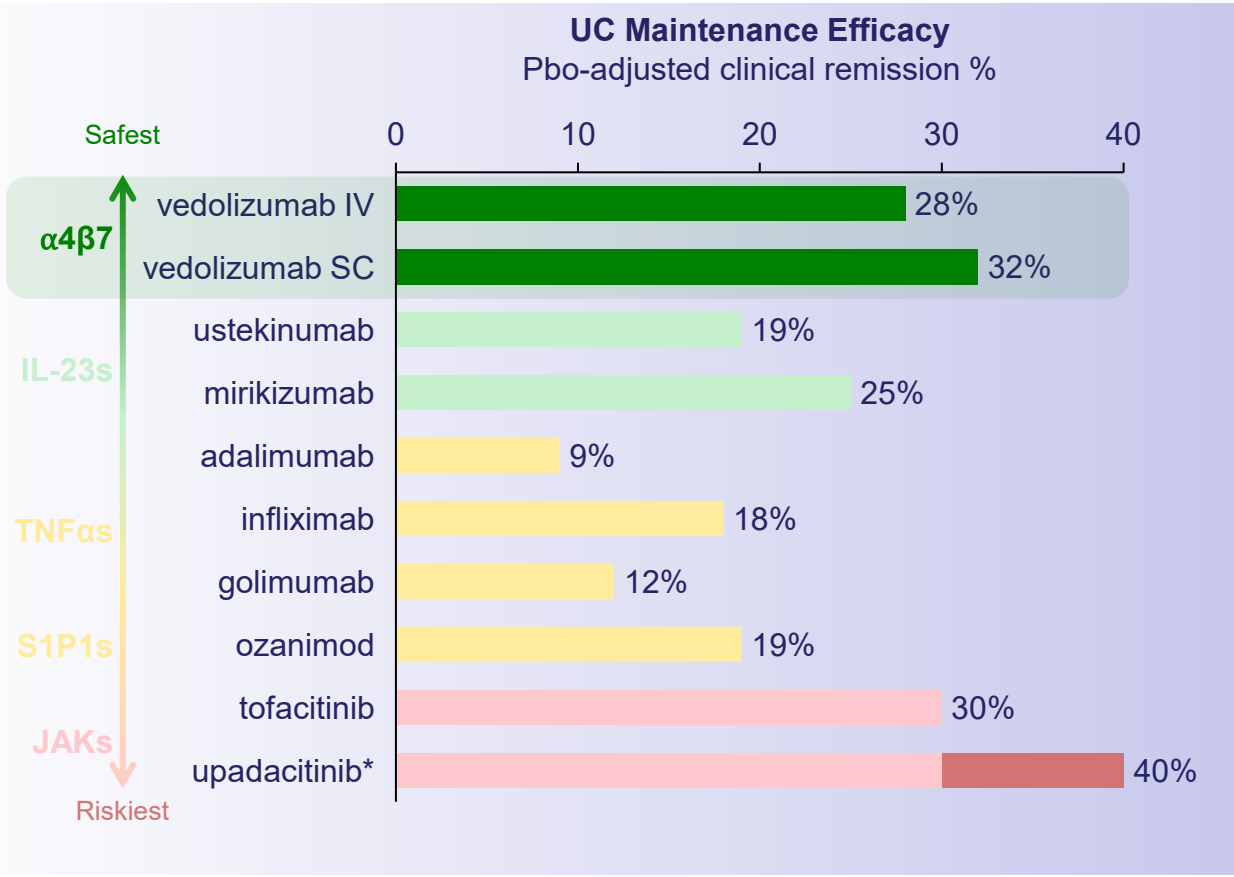

*1. Takeda JPM 2023 presentation. Note that Takeda's FY22 is April 2022-March 2023.*

*Sales forecast in figure: EvaluatePharma consensus*

# Vedolizumab maintenance efficacy and exquisite safety make it preferred biologic in moderate-to-severe UC

*"Entyvio (vedolizumab) is the safest drug and one of the most effective for UC."* – US KOL

- Vedolizumab specifically binds α4β7 integrin, selectively blocking gut lymphocyte trafficking.
- **Leading maintenance efficacy data in UC** replicated in two P3 studies; efficacy on par with upadacitinib 15mg dose; **superior head-to-head vs adalimumab** (Humira) in UC.
- Clean safety profile since approval in 2014.
- **#1 biologic in IBD** bio-naïve patients in the US.[1]




1. Takeda JPM 2023 presentation.

*Figure data sources: Vedolizumab IV and SC data from VISIBLE 1 P3 study. Ustekinumab, adalimumab, infliximab, golimumab, ozanimod, tofacitinib, upadacitinib data from labels. Mirikizumab data from phase 3 LUCENT-2 study. *Upadacitinib data shown in lighter red is 15mg preferred dose, darker red higher 30mg dose. Maintenance studies shown included patients who achieved clinical response at induction.*

# SPY001 is designed to be a best-in-class anti-α4β7 mAb



| | Entyvio® IV vedolizumab | Entyvio® SC* vedolizumab *Not approved in the US | SPY001 |
|---|---|---|---|
| **Highly potent** *Proven epitope* | ✓ | ✓ | ✓ |
| **Selective** *No α4β1 binding, no VCAM-1 adhesion blocking* | ✓ | ✓ | ✓ |
| **Favorable safety profile** | ✓ | ✓ | ✓ |
| **High maintenance efficacy** | ✓ | ✓ | ✓ |
| **Convenient SC dosing** *Q8W or Q12W+* | Q8W ***IV infusion*** | Q2W SC | ✓ |
| **Convenient formulation** *High concentration, citrate free* | Lyophilized | Citrate formulation | ✓ |
| **Rapid efficacy onset** | | | Potential upside |
| **Patient selection approach** *Genetic CDx* | | | Potential upside |

**Entyvio SC US BLA resubmitted April 2023 following CRL in 2019.*

SPYRE

# SPY001 exploits validated α4β7 biology with modifications designed for best-in-class properties

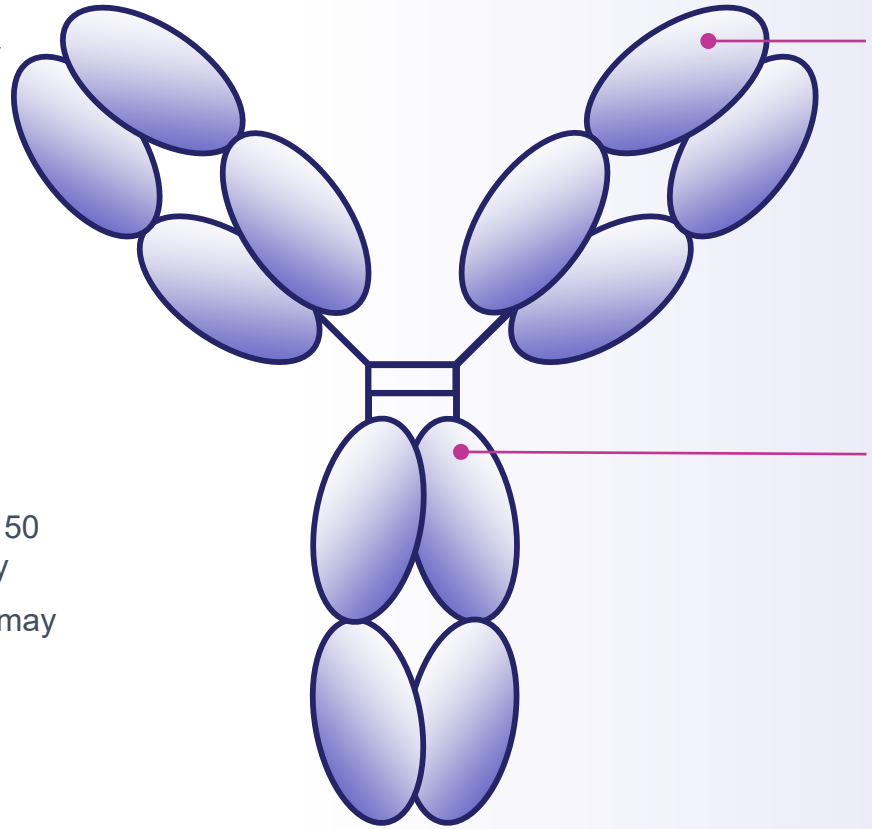
## Spyre mAbs introduce significant improvements over 1st generation mAbs

**Epitope maintained**

- Validated pharmacology
- Equivalent potency

**High concentration SC**

- Ability to formulate at >150 mg/mL with low viscosity
- Citrate-free formulation may improve patient comfort



SPY001

**Potential for IP into 2040s**

- Diverse coverage of lead and backup series

**Significantly extended half-life**

- Q8-Q12W dosing based on validated half-life extension technology

**SPY001 target profile:**

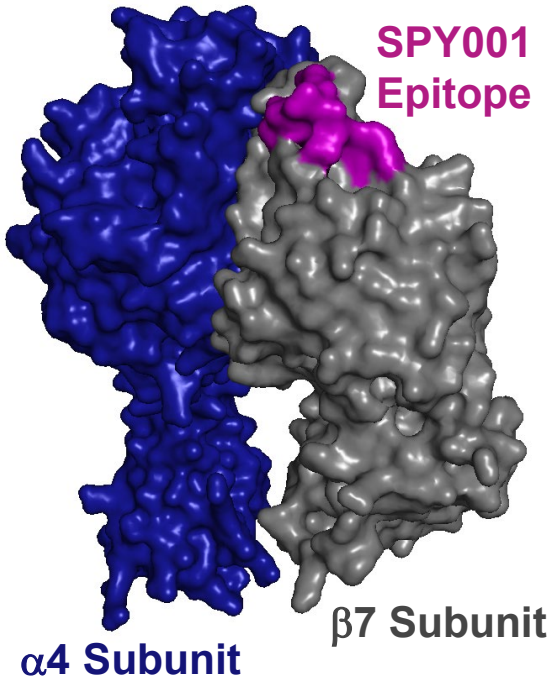
- ✓ Efficacy ≥ vedolizumab
- ✓ Citrate-free subcutaneous 300 mg dose
- ✓ Q8W or Q12W dosing interval

# SPY001 is as potent and selective as vedolizumab

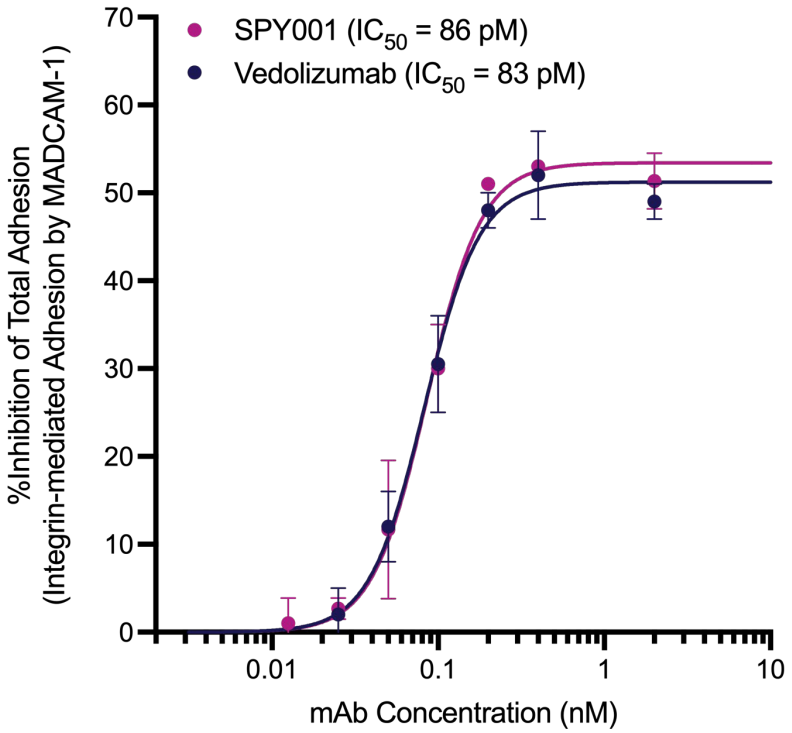
SPY001 binds the same α4β7 epitope as vedolizumab.

SPY001 is comparable to vedolizumab in potency…

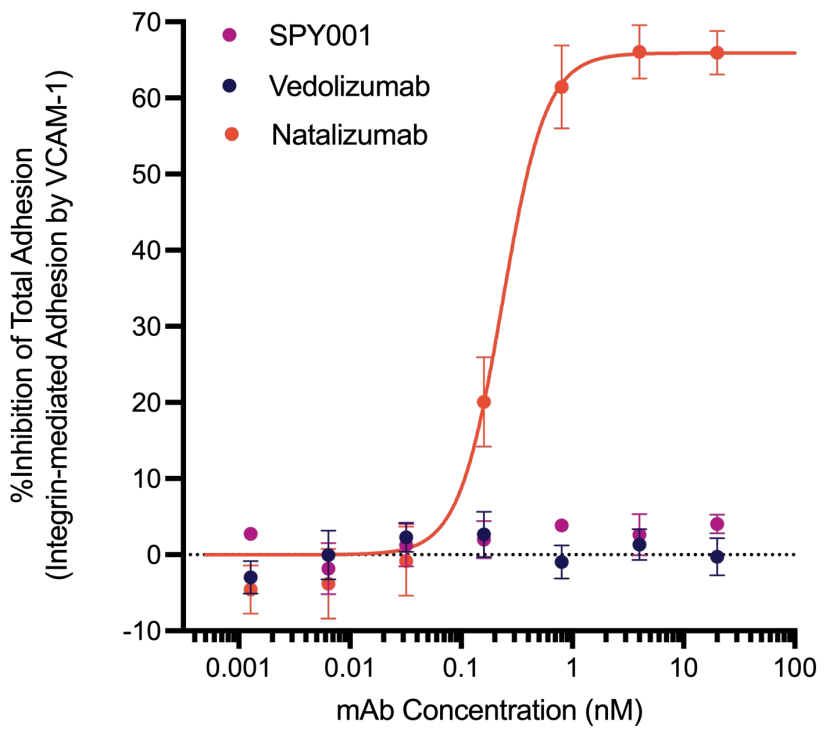
…and avoids unwanted interactions with α4β1.



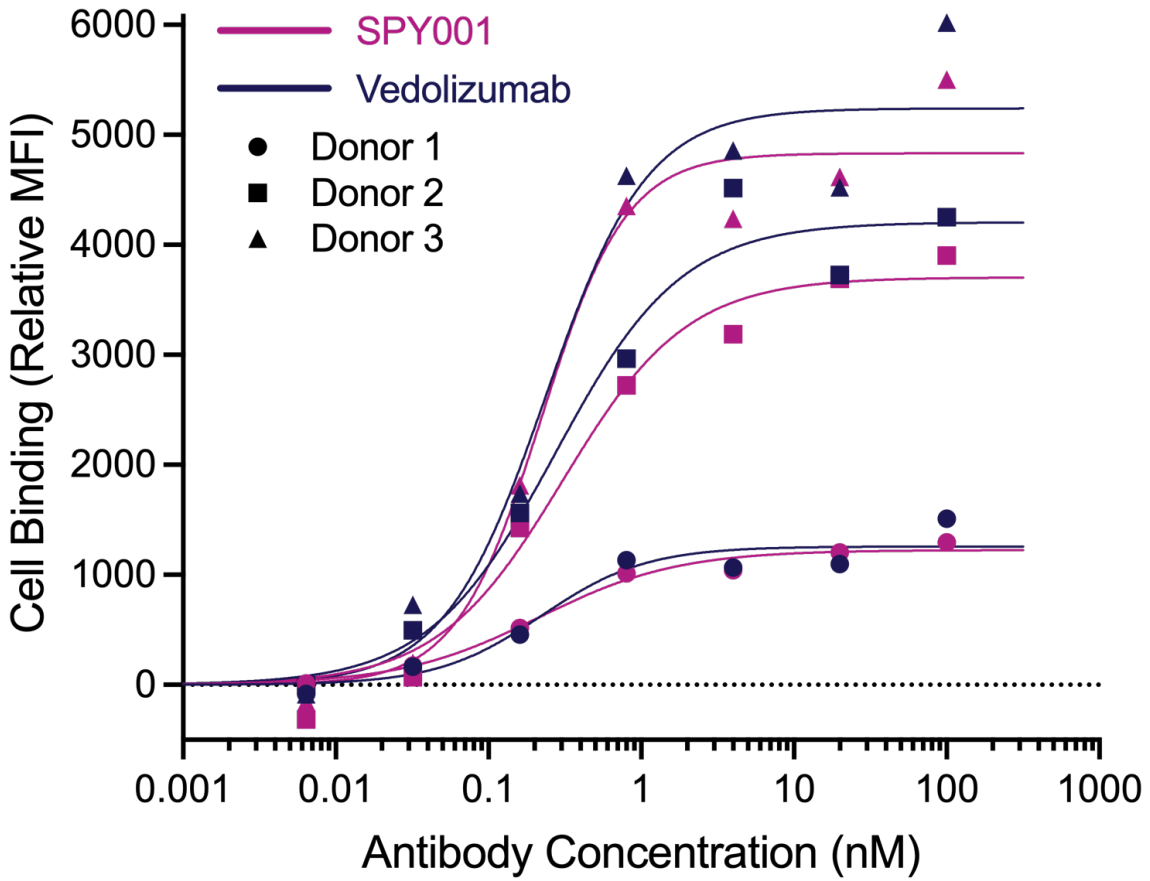

## Blocking MADCAM-1 Adhesion




## Blocking VCAM-1 Adhesion



# SPY001 binds to memory T-helper cells as well as vedolizumab



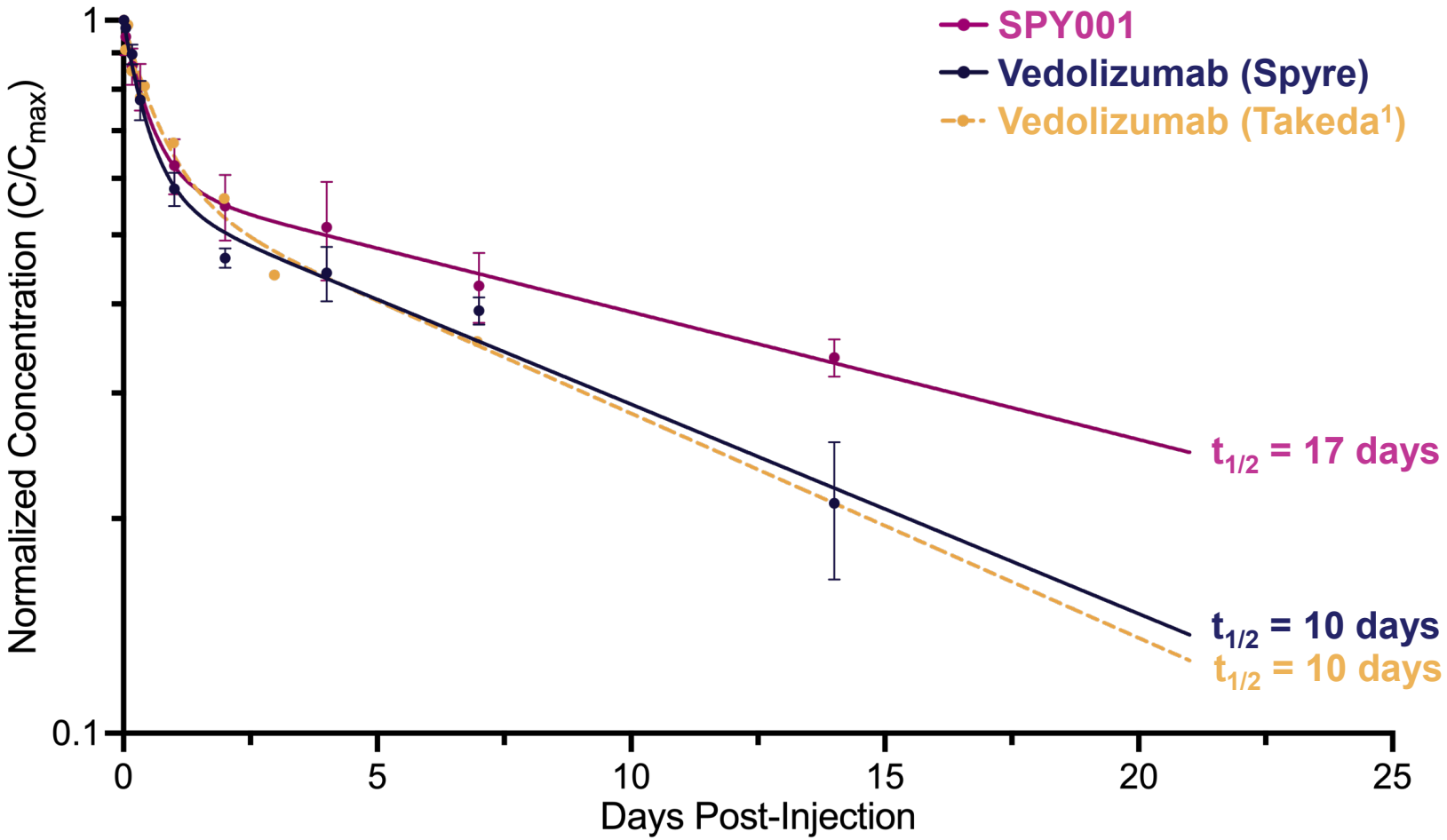

| | Vedolizumab $EC_{50}$ (nM) | SPY001 $EC_{50}$ (nM) |
|---|---|---|
| **Donor 1** | 0.22 | 0.21 |
| **Donor 2** | 0.27 | 0.30 |
| **Donor 3** | 0.24 | 0.22 |

- PBMCs from three human donors were isolated and stained with either vedolizumab or SPY001, as well as a basic immunophenotyping T-cell panel.
- Both vedolizumab and SPY001 exhibited binding on the memory T-helper CD3+CD4+CD45RO+ population.
- $EC_{50}$ values for both antibodies corresponded well with what has previously been reported for binding to the same population: $EC_{50}$ ~ 0.3 nM.[1]

*1. Soler, et. al. (2009)*

# SPY001 has exhibited a 17-day half-life in NHPs, nearly 2x the half-life of vedolizumab observed in multiple studies

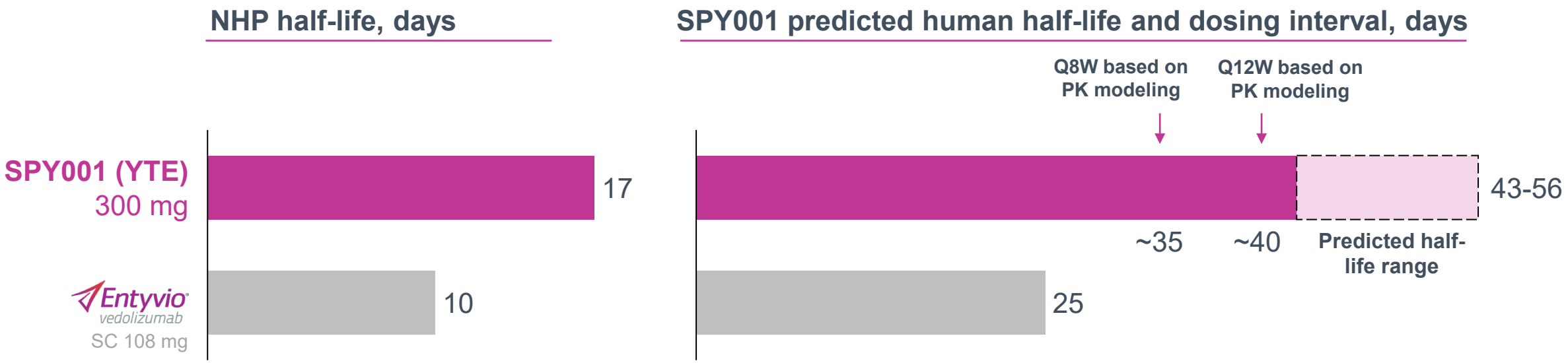
## Pharmacokinetics in NHP, IV Bolus




- **β-elimination half-life of SPY001 observed at ~17 days, 70% longer than observed for vedolizumab.**
- Spyre vedolizumab data matches half-life observed in Takeda studies.[1,2]

NOTE: [1]BLA 125476, Vedolizumab. [2]Crawford, D. and Friedman, M. (2019). In all cases, PK data was normalized to $C_{max}$ and fit to a biphasic exponential decay curve from which the β-elimination half-life was determined.
SOURCE: Data on file.

# SPY001 NHP half-life and increased dose suggest potential for significant improvement over Entyvio




- YTE modification typically increases mAb half-life by 2-4x versus wild-type in both NHP and human.
- Human YTE mAb half-life is on average 3.1x of NHP half-life.

*Source:* Rosario, M, et. al. (2017).

# SPY001 is specifically formulated to maximize dosing without sacrificing patient comfort

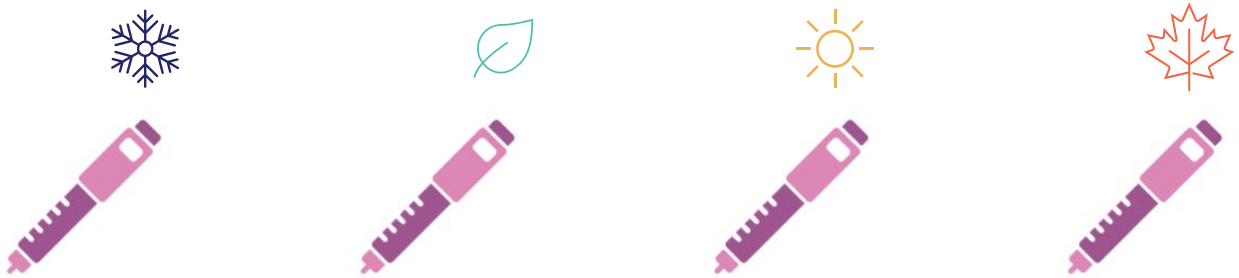
**Vedolizumab SC**
**108 mg**
**20 mM Citrate**



**26** injections per year

Potential injection site pain

**SPY001 SC**
**300 mg**
**Citrate Free**



**Seasonal** or every other month injections

Improved patient comfort

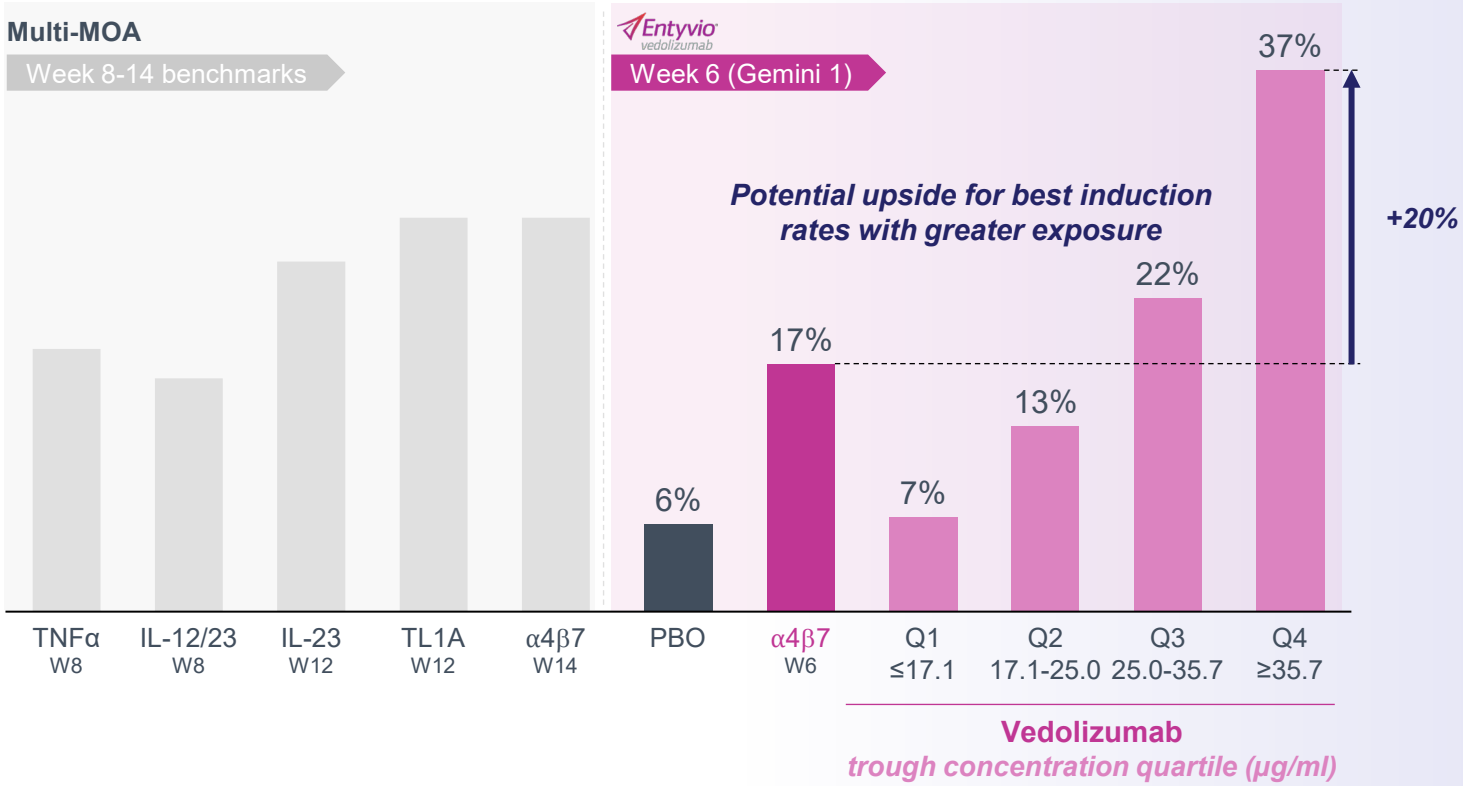
*Note: Vedolizumab SC approved in EU. US BLA resubmitted April 2023 following CRL in 2019.*

# Vedolizumab appears underdosed in induction; opportunity for SPY001 to achieve superior time to onset

Induction

## UC induction clinical remission rates

%




- Slow onset of vedolizumab efficacy may be explained by insufficient dosing. Clear exposure-efficacy relationship[1] observed at Week 6:
  - **Highest quartile achieved a remarkable 37.1% remission rate.**
  - **Lowest exposure quartile did not separate from placebo.**
- FDA noted "significant exposure-response relationship" and recommended exploring higher doses to improve remission rates.[2]

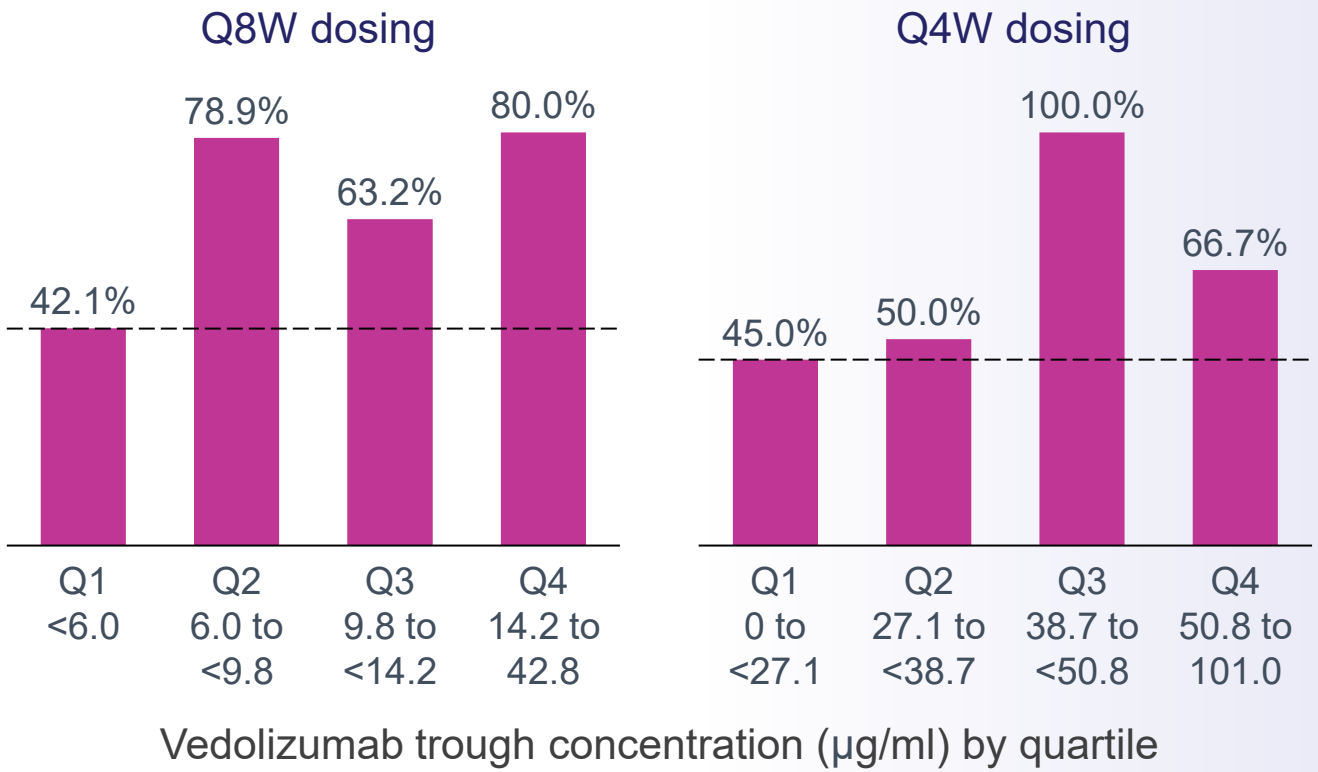
**Superior time to onset could position SPY001 as the preferred starting therapy vs. vedolizumab**

*1. Rosario, M., et. al. (2017). 2. Vedolizumab FDA Clinical Pharmacology Review. Figure sources: Multi-MOA benchmark data from adalimumab label (TNFα), ustekinumab label (IL-12/23), mirikizumab LUCENT-1 study (IL-23), PRA023 P2b (TL1A), and vedolizumab VARSITY study (α4β7). Vedolizumab exposure-response data from Rosario, M., et. al. (2017).*

# Once induction is achieved, very low exposures of vedolizumab are sufficient to maintain remission

Maintenance

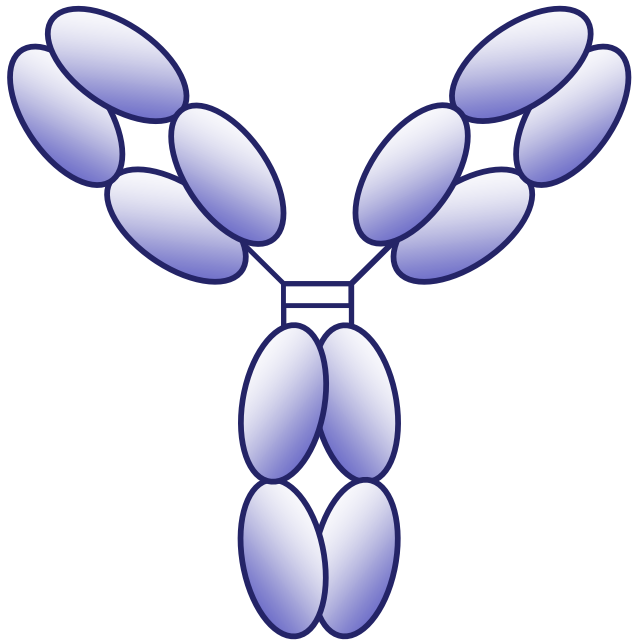
**Vedolizumab maintenance of clinical remission by exposure quartile**
% at week 52 (GEMINI 1)




- Minimal difference in maintenance of clinical remission between vedolizumab IV Q4W (44.8%) or Q8W (41.8%).
- **$C_{trough}$ ≥ 6 µg/mL is a conservative target to maintain long-term efficacy with potent anti-α4β7 mAbs**.

*Source: Feagan, et. al. (2013).*

# SPY001 is a potentially best-in-class anti-α4β7 mAb with near-term de-risking studies anticipated



SPY001

## PROGRAM SUMMARY

**Preferred target in large market**

Vedolizumab is the preferred biologic in UC with >$5B in annual sales

**Clinically validated pharmacology**

SPY001 observed to maintain vedolizumab's epitope with similar potency

**Designed for differentiation**

Q8W+ dosing, faster time to onset, patient-friendly formulation

**Promising early data**

SPY001 observed to match vedolizumab's potency and selectivity and has ~2x half-life in NHPs

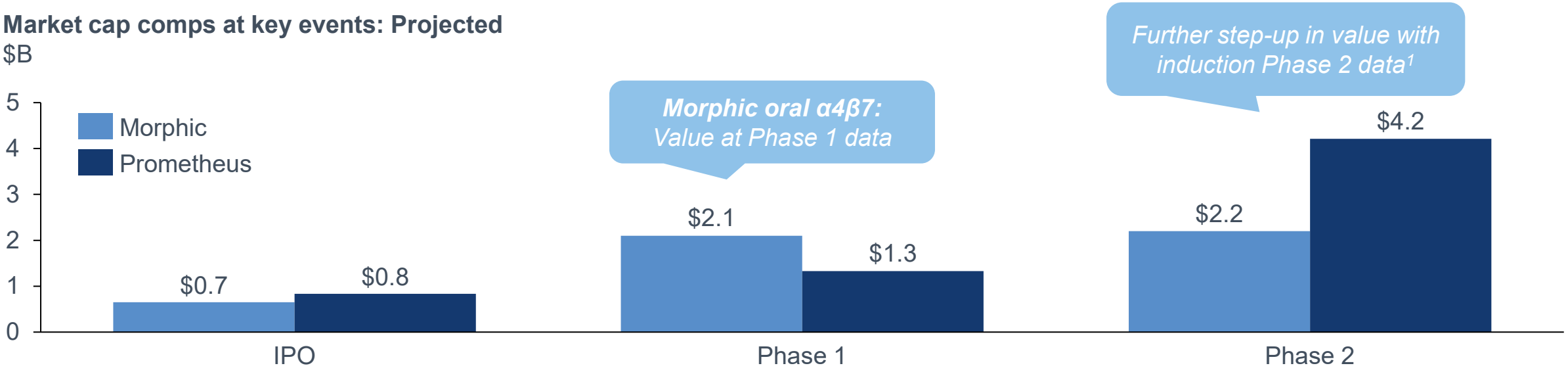
## UPCOMING CATALYSTS

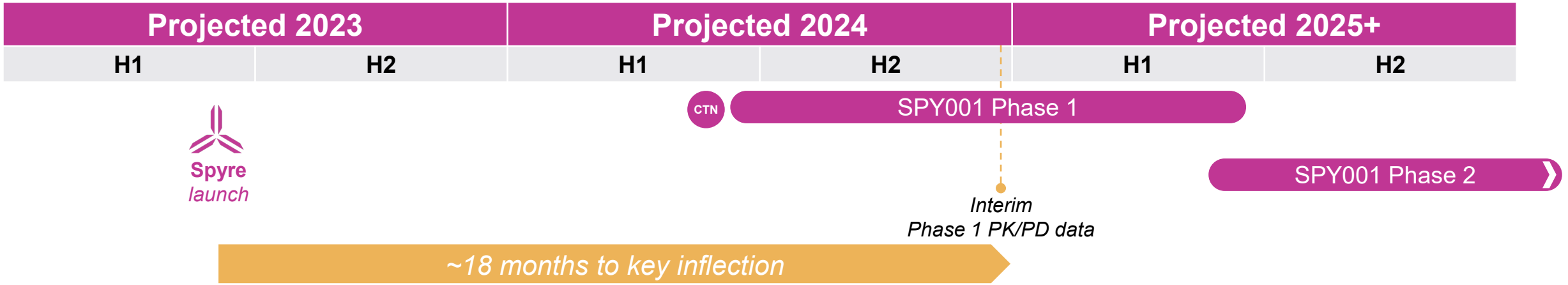
**2Q2024**
IND/CTN

**YE2024**
Human PK/PD

# Key value inflection in ~18 months with Phase 1 PK data anticipated to validate SPY001 as “long-acting Vedo”

**Market cap comps at key events: Projected**




*Source: FactSet 30-d average market caps after event date.*

*1 Morphic Phase 2a single arm UC data; Prometheus RCT (UC) and single arm (CD) Phase 2.; Prometheus ultimately acquired for $10.8B after Phase 2 data*

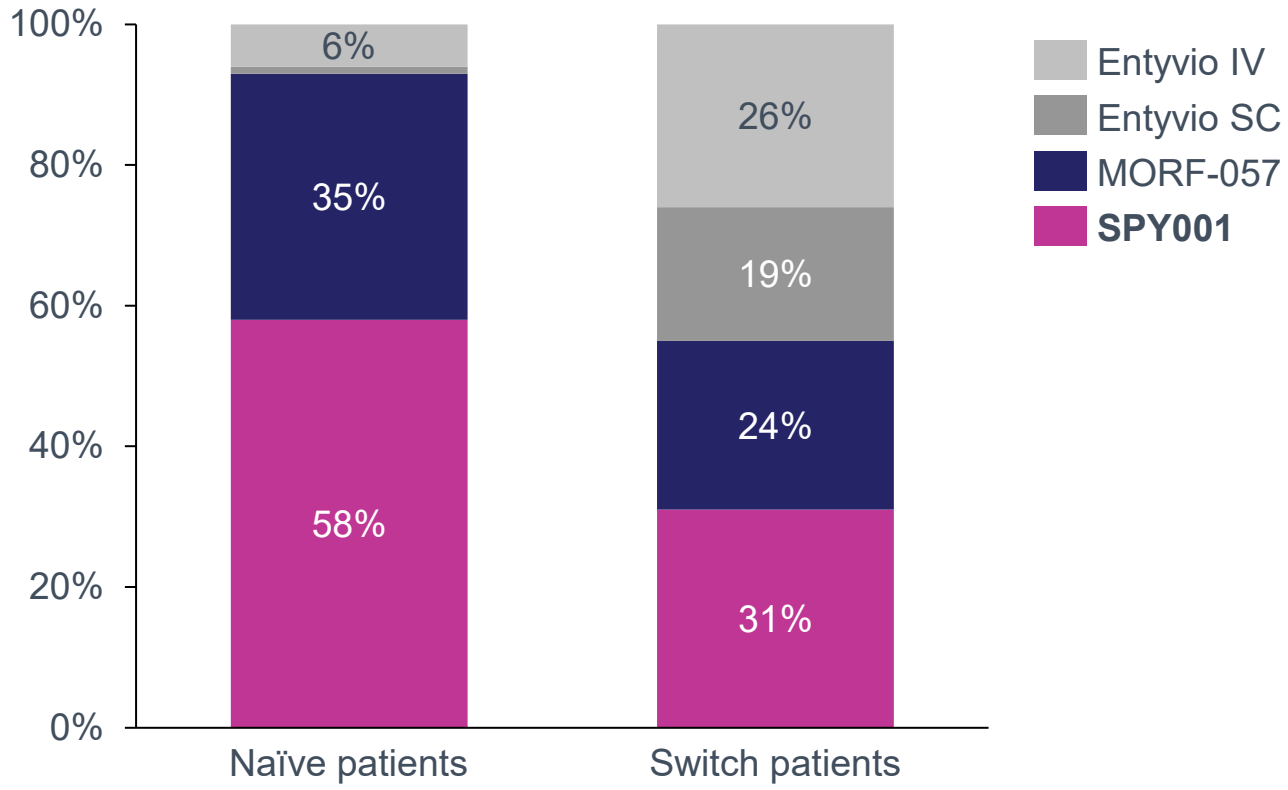
# The base case* SPY001 profile was conservatively compared to Takeda's Entyvio and Morphic's MORF-057

| Agent | SPY001 | Entyvio IV | Entyvio SC | MORF-057 |
|---|---|---|---|---|
| MOA | α4β7 monoclonal antibody | α4β7 monoclonal antibody | α4β7 monoclonal antibody | α4β7 antagonist small molecule |
| Indication | Treatment of moderately to severely active ulcerative colitis patients | | | |
| Administration (in maintenance) | Subcutaneous Q12W (autoinjector) | Intravenous Q8W | Subcutaneous Q2W (autoinjector) | Oral BID |
| Efficacy (primary endpoints) | Induction clinical remission at week 12: 20% (absolute)<br>Maintenance remission at week 52: 40% (absolute) | | | |
| Safety | Clean safety profile / manageable AE profile expected for class | | | |

*Note: *Comparable efficacy to Entyvio*

# Assuming equivalent efficacy and safety, a quarterly injectable would be the preferred profile

**Preference class share in naïve and experienced patients**
Percent (n=14)




*Source: Expert calls with N=14 gastroenterologists conducted in May 2023*

*"Oral agents typically have an advantage except in this case … one shot every three months will have the advantage"*

*U.S. KOL*

*"Infrequent injections are more beneficial than orals, patients will forget to take the orals daily"*

*U.S. KOL*

*"The denominator will also increase with this profile, I would expect more patients to go to [SPY001] rather than Stelara after TNF failure"*

*U.S. KOL*

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



Co-lead programs

| STRATEGY | TARGET | PROGRAM | DISCOVERY | IND-ENABLING | CLINICAL |
|---|---|---|---|---|---|
| Best-in-class mAbs (Extended half-life) | *α4β7* Same MOA as vedolizumab | SPY001 | | *IND/CTN expected 2Q24* | *HV PK/PD data expected YE24* |
| | ***TL1A*** *Same MOA as PRA023* | SPY002 | | ***IND/CTN expected 2H24*** | ***HV PK/PD data expected 1H25*** |
| | *IL-23* | SPY003 | | | |
| | *Novel MOA* | SPY004 | | | |
| Rational combinations | *α4β7 + IL-23* | SPY130 | | | |
| | *α4β7 + TL1A* | SPY120 | | | |
| | *TL1A + IL-23* | SPY230 | | | |

# TL1A has emerged as one of the most promising targets in both UC and CD

- TL1A is involved in chronic inflammation and fibrosis pathways and is genetically associated with IBD.
- Clinical results from first-generation anti-TL1A antibodies suggest potential for highest induction efficacy across target classes and the utility of companion diagnostics to identify hyper-responders.

**Phase 2 results in UC and CD with PRA023 was a key factor in Prometheus' $10.8B acquisition by Merck.**

**First-generation anti-TL1A antibodies provide blueprint for a next-generation best-in-class agent from Spyre.**

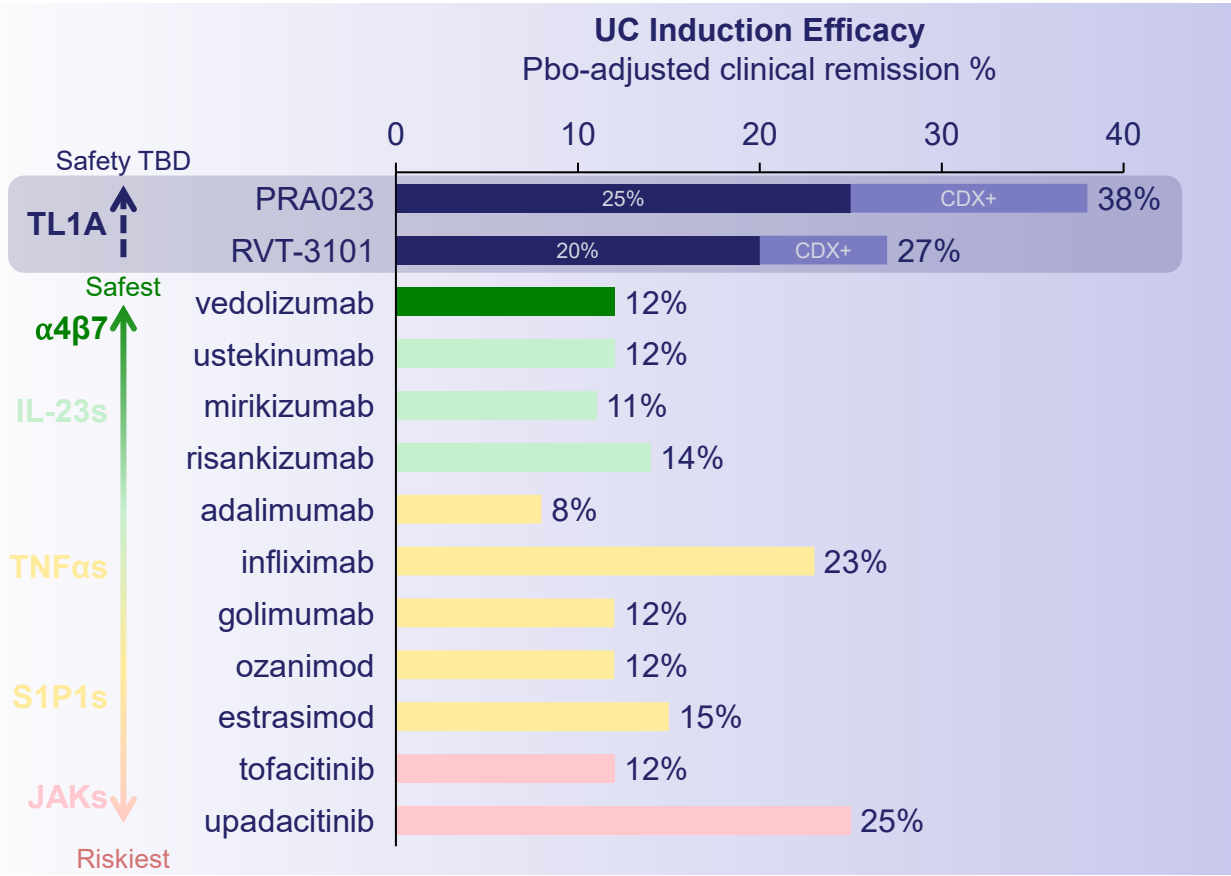



*Figure data sources: PRA023 P2b study. RVT-3101 P2b study. Vedolizumab GEMINI 1 P3 study. Ustekinumab, adalimumab, infliximab, risankizumab golimumab, ozanimod, tofacitinib, upadacitinib data from labels. Mirikizumab data from phase 3 LUCENT-1 study. Etrasimod data average of ELEVATE UC 12 and 52 studies.*

# SPY002 is designed to be a best-in-class anti-TL1A mAb



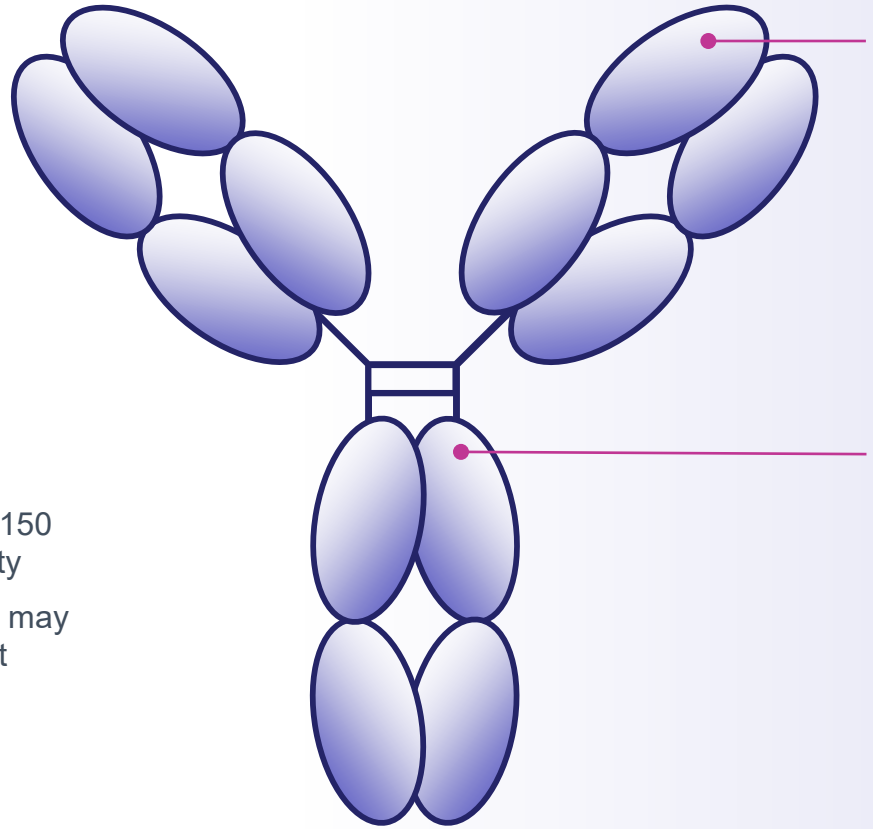
| | PRA023 | RVT-3101 | TEV-48574 | SPY002 |
|---|---|---|---|---|
| **Complete TL1A blockade** *Monomers and trimers* | ✓ | ○ | ○ | ✓ |
| **Highly potent** *Kd below 150 pM* | ○ | ✓ | ✓ | ✓ |
| **Infrequent SC dosing** *Q8W or Q12W+* | ○ *Q4W[1]* | ○ *Q4W* | ○ *Q2W[3]* | ✓ |
| **Convenient formulation** *High concentration* | ✓ | ○ *100 mg/ml, ~45% BA* | ? *Subcutaneous infusion* | ✓ |
| **High remission rates** | ✓ | ✓ | ? | ↗ *Potential upside w/ increased exposure* |
| **Favorable safety profile** | ✓ | ✓ | ✓ | ✓ |
| **Immunogenicity** *<20% ADA[1]* | ✓ | ○ *>48% ADA (8% neutralizing)[2]* | ✓ | ✓ |

*1. Prometheus PRA023 P2 ARTEMIS-UC and P2a APOLLO-CD data readouts, December 7, 2022. Q4W IV tested in Phase 2, Phase 3 SC dosing to be determined*
*2. Roivant RVT-3101 Release Deck, January 4, 2023.*
*3. Teva's TEV-48574 TL1A is currently in Phase 2 IBD studies, but limited information has been disclosed to date on attributes. Dosed Q2W in asthma study.*

# SPY002 exploits biology that has been validated by PRA023 and is designed to be best-in-class

## Spyre mAbs introduce significant improvements over the 1st generation mAbs

**PRA023 clinically validates pharmacology and therapeutic effect of MOA**



SPY002

**Novel IP for composition of matter into 2040s**

**Significantly extended half-life**

- Q8-Q12W dosing based on validated half-life extension technology

**High concentration SC**

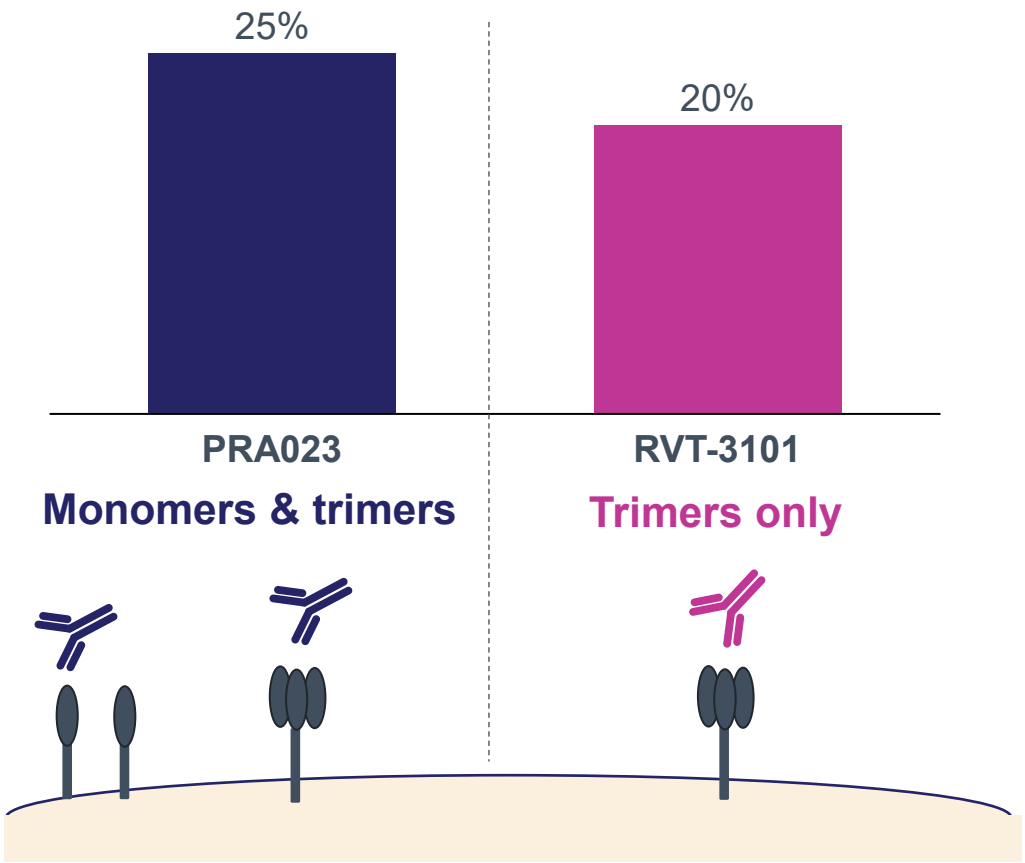
- Ability to formulate at >150 mg/mL with low viscosity
- Citrate-free formulation may improve patient comfort

**SPY002 target profile:**

- ✓ Efficacy ≥ PRA023
- ✓ Subcutaneous 300 mg dose
- ✓ Q8W or Q12W dose with citrate-free, patient-friendly formulation

# Spyre is evaluating both trimeric and monomeric/trimeric TL1A blockade for SPY002

**UC induction clinical remission rates**
Pbo-adjusted %




- Though PRA023 performed numerically better in a cross-trial comparison, it has yet to be determined whether monomeric/trimeric blockade is superior.
- Known biology suggests only trimeric blockade is necessary for effect.

**Spyre is advancing both monomeric/trimeric and trimeric-only TL1A mAbs to DC selection.**

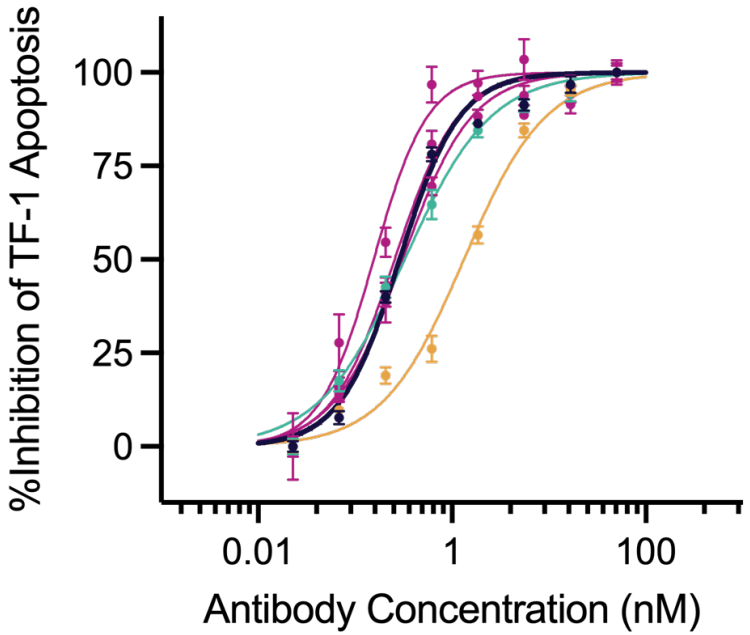
**Redundancy provides highest probability of creating a best-in-class therapeutic.**

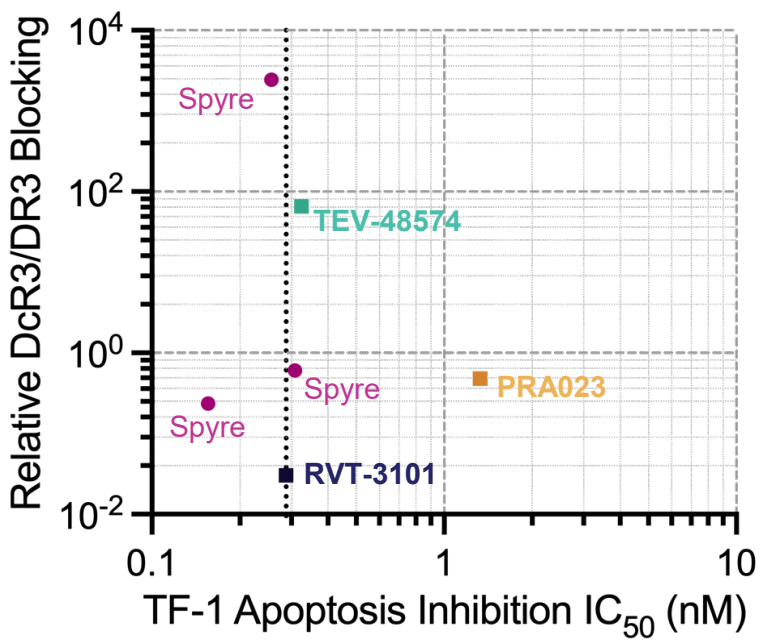
*Figure sources: Prometheus PRA023 P2 ARTEMIS-UC data release, December 7, 2022. Roivant RVT-3101 Release Deck, January 4, 2023.*

# De novo TL1A lead clones are highly potent and characteristically diverse

Example Spyre clones observed to be more potent than leading competitors

…with diverse profiles of monomer binding and/or DcR3 sparing



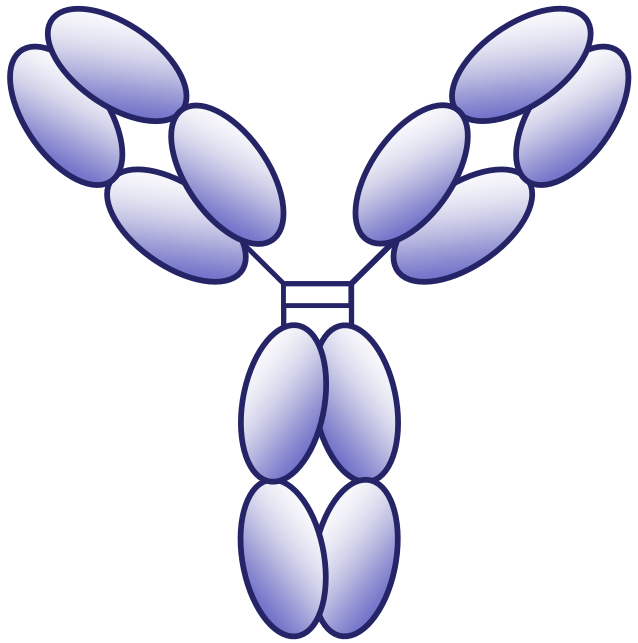

**Spyre has multiple lead clones that have demonstrated superior potency as compared to PRA023.**

**Diverse clones identified matching specificity profile with competitive antibodies.**

**Development candidate to optimize against trimer and monomers, selectivity against decoy receptor.**

**Specialized reagents required to generate monomeric/trimeric TL1A mAbs, likely limiting fast-follower competition**

# SPY002 is a potentially best-in-class anti-TL1A mAb with near-term de-risking studies anticipated



SPY002

## PROGRAM SUMMARY

**Attractive target in a large market**

Existing investigational products have demonstrated excellent clinical efficacy in UC and CD

**Clinically validated pharmacology**

SPY002 conserves the validated epitope to maximize TL1A blockade

**Designed for differentiation**

Q8W+ dosing and formulation improvements

**Promising early data**

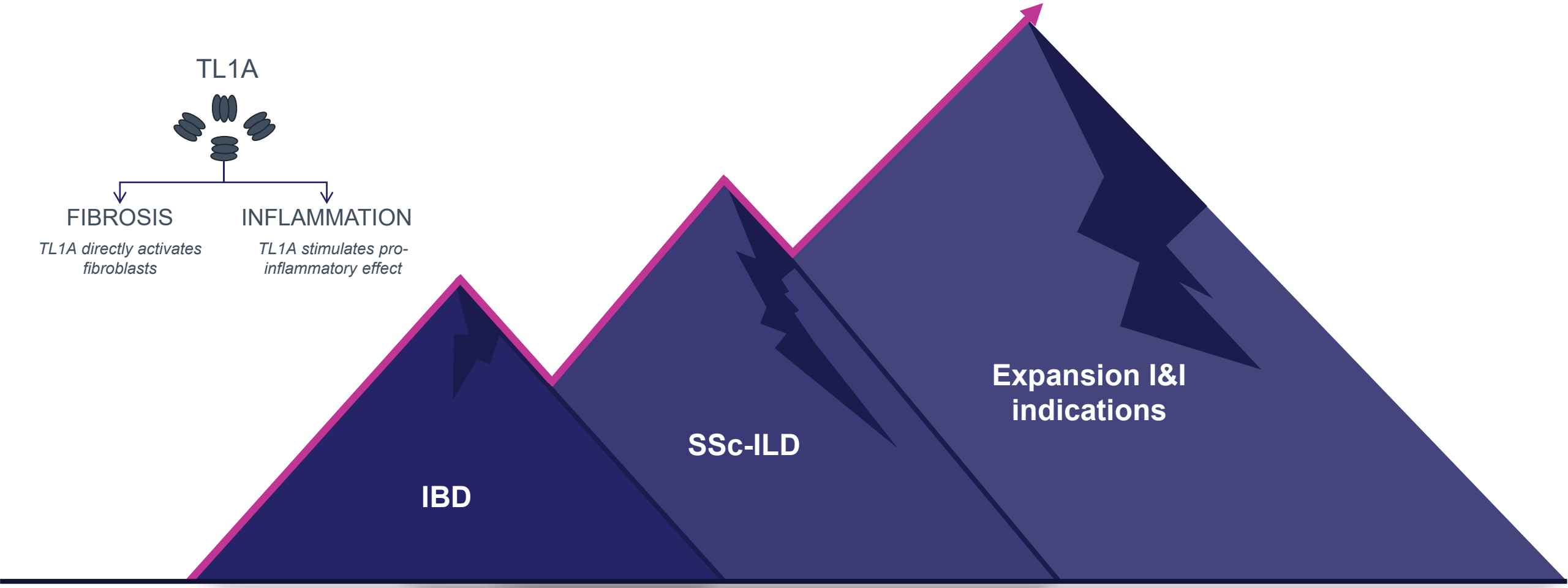
SPY002 observed to bind to monomers and trimers with picomolar potency

## UPCOMING CATALYSTS

**2H2024**
IND/CTN

**1H2025**
Human PK/PD

# TL1A: Potential I&I indication expansion with dual anti-fibrotic and anti-inflammatory mechanism



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



● Co-lead programs

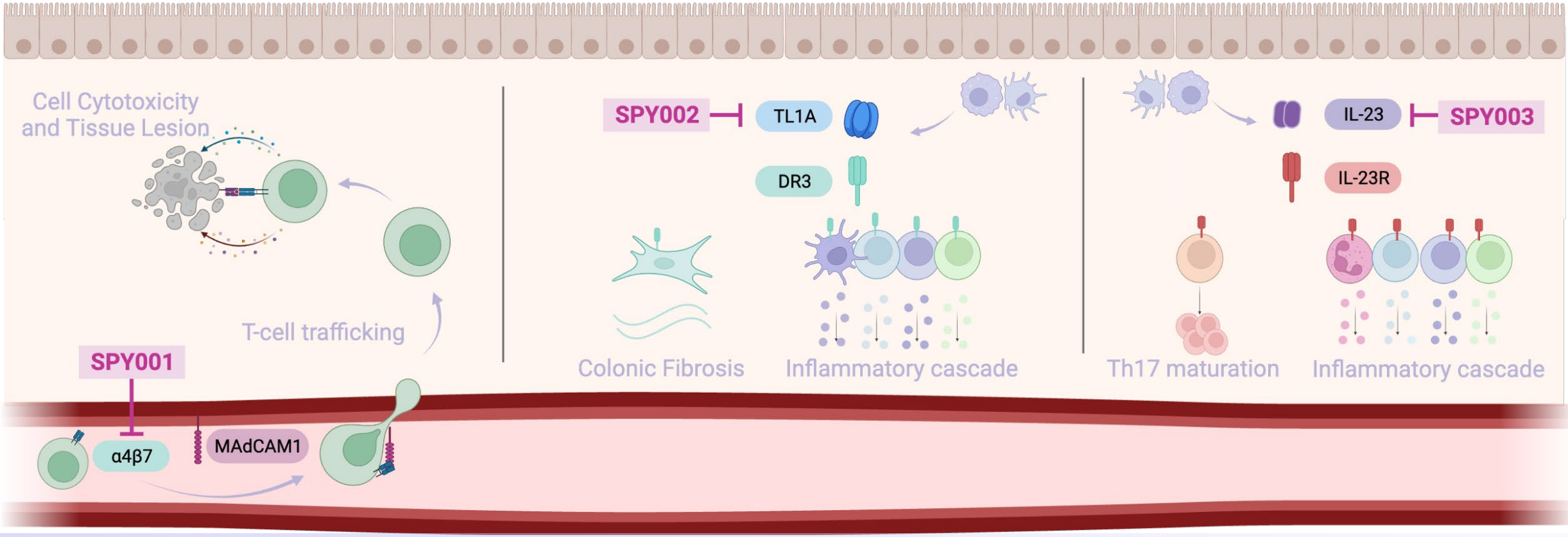
| STRATEGY | TARGET | PROGRAM | DISCOVERY | IND-ENABLING | CLINICAL |
|---|---|---|---|---|---|
| Best-in-class mAbs (Extended half-life) | *α4β7* Same MOA as vedolizumab | SPY001 ● | | IND/CTN expected 2Q24 | HV PK/PD data expected YE24 |
| | *TL1A* Same MOA as PRA023 | SPY002 ● | | IND/CTN expected 2H24 | HV PK/PD data expected 1H25 |
| | *IL-23* | SPY003 | | | |
| | *Novel MOA* | SPY004 | | | |
| Rational combinations | *α4β7 + IL-23* | SPY130 | | | |
| | *α4β7 + TL1A* | SPY120 | | | |
| | *TL1A + IL-23* | SPY230 | | | |

# Spyre portfolio addresses the diverse pathophysiology of IBD

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

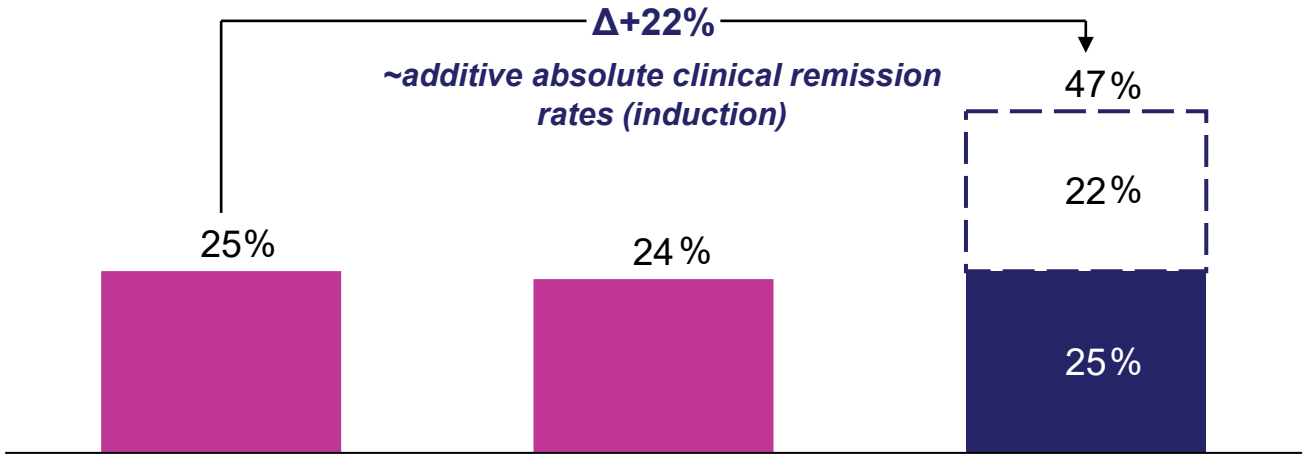
Neutralization of **TL1A** suppresses inflammation within the gut tissue and blocks immune cell activation

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




**Spyre is a pioneer in developing best-in-class mAbs against three top targets to enable superior combinations for IBD**

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

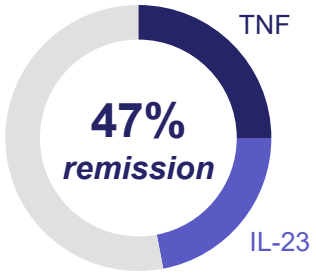
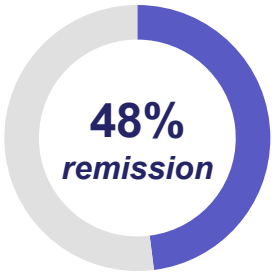
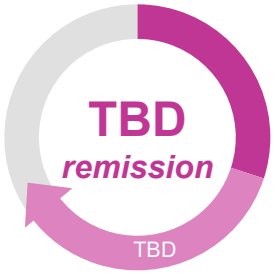
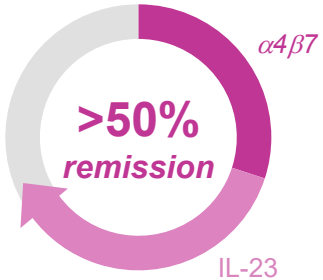



| | Golimumab (TNFα) | Guselkumab (IL-23) | Combination |
|---|---|---|---|
| N= | 72 | 71 | 71 |
| Maintenance remission* | 28% | 31% | 48% |
| Safety | Poor (class effect) | Well tolerated | Mixed |

- Despite non-optimal components, JNJ combination (JNJ-78934804) delivered superior UC efficacy compared to any single agent.
- Spyre aims to build on this success with combinations of best-in-class mAbs from superior MOAs.

*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.*

# Spyre could create optimal combinations in IBD to safely and conveniently maximize efficacy

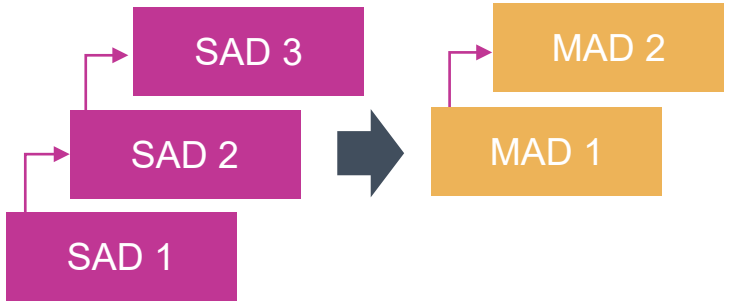
| Program | UC Induction | UC Maintenance | Safety | Dosing |
|---|---|---|---|---|
| **JNJ-4804**<br>*TNFα + IL-23* |  |  | *TNFα **black-box** safety warning*<br><br>*Broad immunosuppression* | Q4W |
| **SPY120**<br>*α4β7 + TL1A* |  |  | *Gut-selective α4β7 backbone*<br>+<br>*Encouraging TL1A safety profile* | **Q8-12W** |
| **SPY130**<br>*α4β7 + IL-23* |  |  | *Gut-selective α4β7 backbone*<br>+<br>*2nd safest class in IBD* | **Q8-12W** |

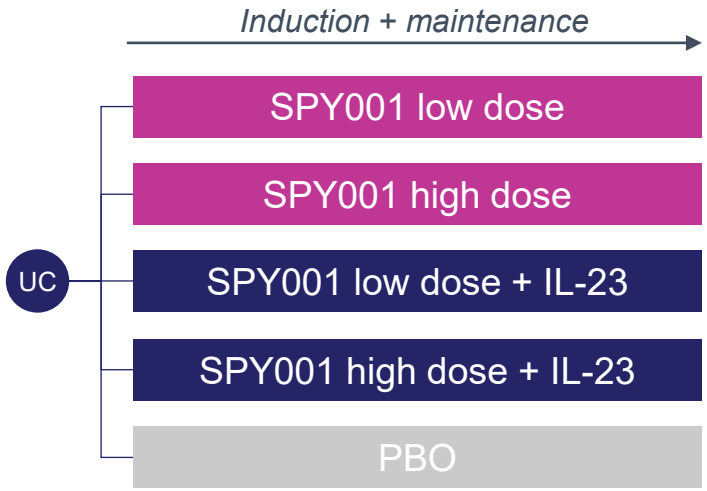
*The figures above are for Illustrative purposes only, assuming combinations result in additive efficacy*

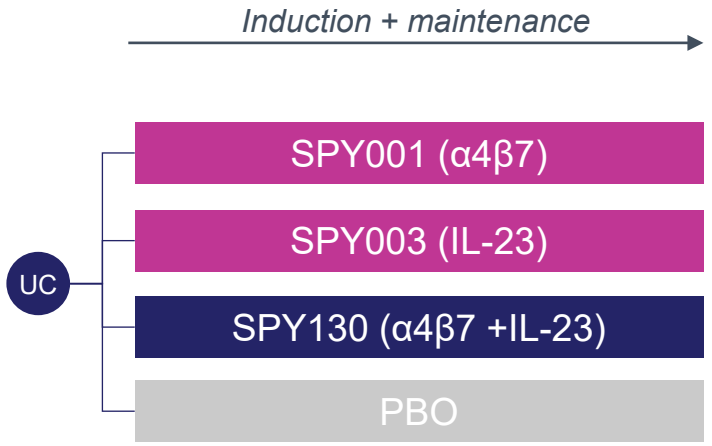
# We plan to rapidly advance combination programs in parallel with monotherapies in Phase 2

*Illustrative example*

| Phase 1 | Phase 2 | Phase 3 |
|---|---|---|
| Monotherapy safety and PK/PD in healthy volunteers | Co-administered, dose-ranging combination in IBD patients | Co-formulated combination of wholly owned investigational agents in IBD patients |



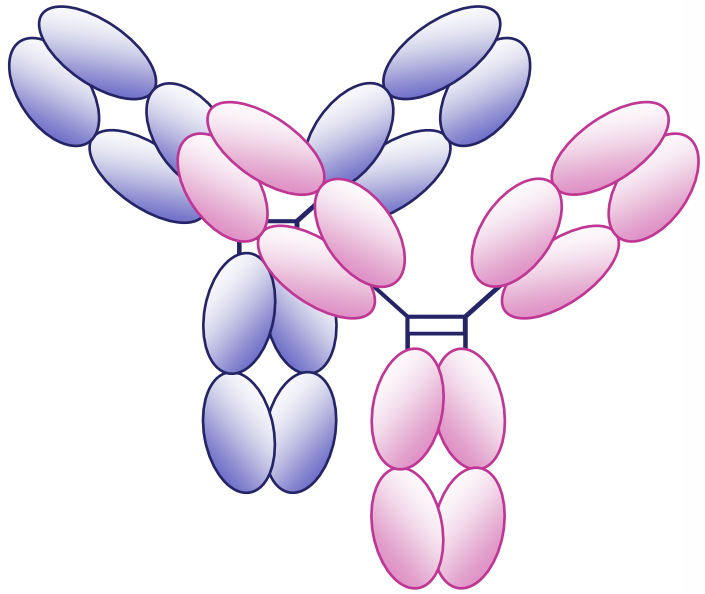




**Comparable development strategy to be pursued with SPY002 (TL1A) combinations**

*Preliminary; pending regulatory feedback*

# Spyre is developing potentially best-in-class combinations to maximize efficacy for patients with IBD



**SPY130**
**SPY120**
**SPY230**

## PROGRAM SUMMARY

**Established combination precedent**

JNJ VEGA study demonstrated unprecedented efficacy despite sub-optimal combination components

**Ideal building blocks**

Spyre's best-in-class engineered mAbs provide optionality for multiple rational combinations

**Rapid proof-of concept**

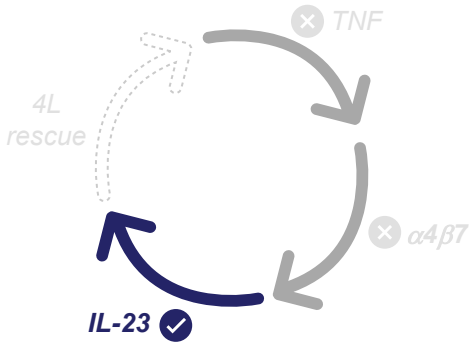
Parallel progression of portfolio of mAbs will allow evaluation of combinations in Phase 2 studies

## UPCOMING CATALYSTS

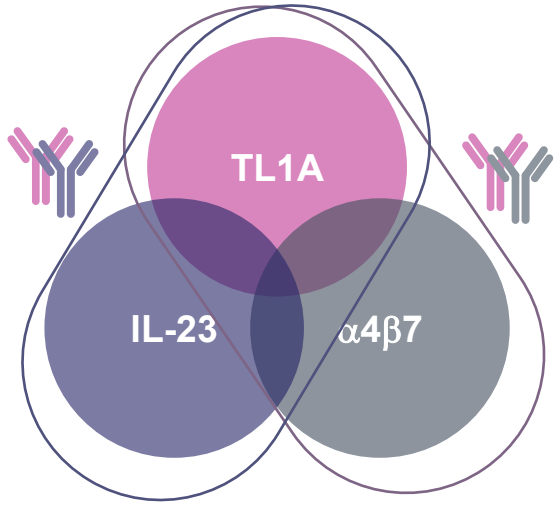
**2025**
Ph2 initiation with SPY001 backbone

# We aim to develop companion diagnostics to augment our therapeutic combinations and monotherapies

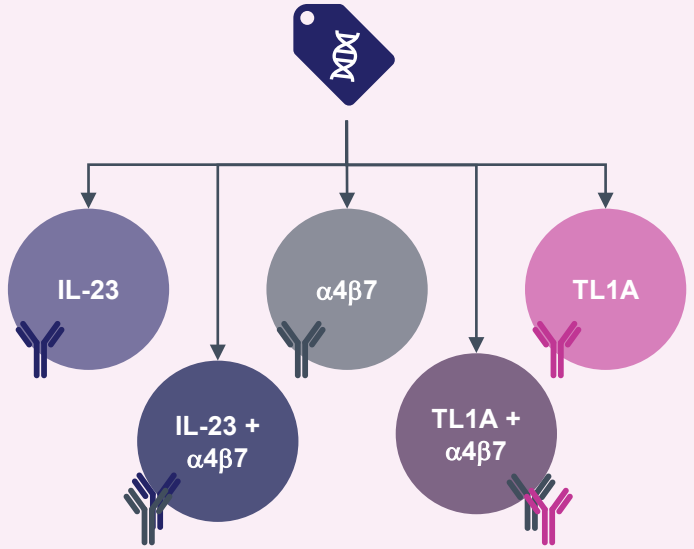
**IBD patients cycle though multiple biologics with modest remission rates**




**We believe the future of IBD includes combination therapies and precision approaches to break the therapeutic ceiling**



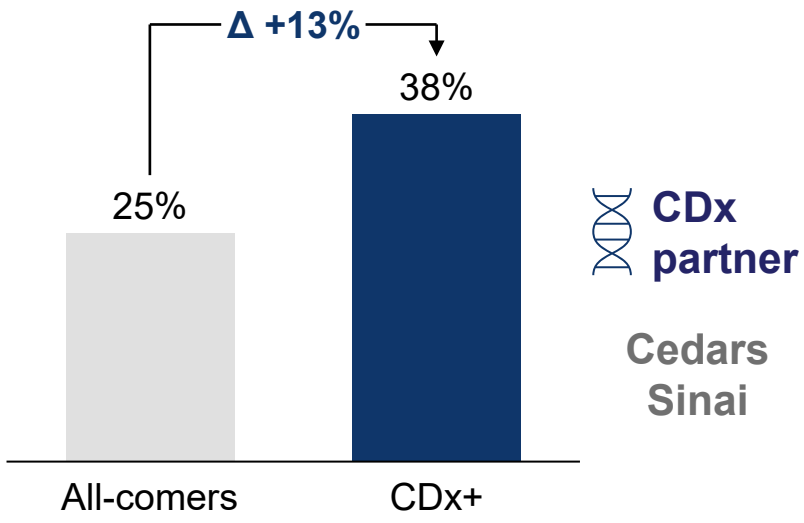

## Precision immunology



# Prometheus and Roivant demonstrated POC that a genetic CDx can identify responders to TL1A

**Prometheus Biosciences** **PRA023**
TL1A

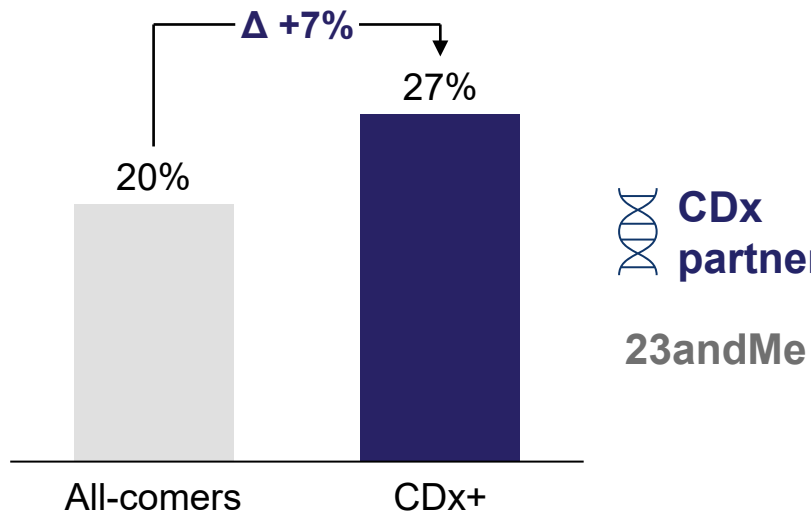
**UC clinical remission at 12 weeks**




**CDx partner**
Cedars Sinai

**Roivant** **RVT-3101**
TL1A

**UC clinical remission at 12 weeks**




**CDx partner**
23andMe

Spyre aims to develop genetic companion diagnostics across a portfolio of best-in-class therapeutics

*Source: Company materials*

SPYRE THERAPEUTICS

# Corporate

# Leadership and BOD

## Management team



**Cameron Turtle**
*Chief Operating Officer*



**Jonathan Alspaugh**
*President and CFO*



**Cortney Caudill**
*Chief Product 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

| | 2023 | 2024 Expected | 2025 Expected |
|---|---|---|---|
| **SPY001** (SC, extended half-life α4β7) | | **2Q – IND/CTN**<br>**YE – POC PK in HVs** | **Full PK in HVs**<br>**Phase 2 initiation** |
| **SPY002** (SC, extended half-life **TL1A**) | | **1H – R&D Day**<br>**2H – IND/CTN** | **PK in HVs** |
| **SPY003** (SC, extended half-life **IL-23**) | | **1H – R&D Day** | **IND/CTN** |
| **SPY004** (SC, extended half-life **novel target**) | | **1H – R&D Day Target disclosure** | |
| **Combinations** (SC, extended half-life) | | | **Phase 2 initiation** |
| **Key external catalysts** | ✓ **RVT-3101 P2 maintenance data (2Q)**<br>**PRA023 UC cohort 2 data**<br>**PRA023 UC/CD P2 OLE data** | **PRA023 SSc-ILD P2 data (1H)**<br>PRA023 4th indication announcement<br>**DUET-UC & DUET-CD data**<br>**TEV-48574 CD P2b interim data (2H)** | |

**$200M expected to fund broad pipeline into 2026 through multiple key value creation events**

# I&I companies with compelling science have maintained value even in market downturns

| | IPO Raise | Market Cap ($M) Min — IPO — Today — Max | Stage at IPO (Pre / Ph1 / Ph2 / Ph3) | Lead program status at fundraising |
|---|---|---|---|---|
| Prometheus Biosciences | $219 | 566 — 9,196 | ● ● | • Lead anti-TL1A program in P1, <2 years to P2 RCT data in UC and P1b data in CD. |
| MORPHIC | $104 | 406 — 2,680 | ● | • Lead α4β7 integrin inhibitor for IBD 1 year from IND.<br>• αvβ6 integrin inhibitor for IPF 6 months from IND. |
| DICE | $235 | 500 — 1,607 | ● | • CTN for lead IL-17 SM program, <3 months to psoriasis P1 initiation.<br>• Preclinical data showing IL17 inhibition & efficacy matching Cosentyx. |
| ventyx BIOSCIENCES | $174 | 496 — 2,679 | ● | • Lead Tyk2 inhibitor P1 MAD initiation in <1Q, P2 POC following year.<br>• S1P1R program to initiate P2 that quarter. |
| PLIANT | $166 | 150 — 1,798 | ● ● ● | • P2a IPF initiated following P1a/b completion.<br>• P2a initiated; PSC IND submitted, <6mos to P2a start. |
| SPYRE THERAPEUTICS | TBD | If 2023… | | • Two development candidates with NHP PK. |
| | | If 2024… | | • Expect 2 INDs filed with P1 trials initiating, PK/PD data for SPY001. |
| | | If 2025… | | • Expect SPY001 and SPY002 enabled for rapid development as potentially best-in-class SC therapeutics for IBD. |

NOTE: "Today" market cap as of *April 17, 2023*
*SOURCE: FactSet. Company S-1s.*

**Initial financing rounds expected to generate valuable milestones.**

# Acquisitions illustrate value of validated targets in I&I, which have supported multiple transactions >$1B per Spyre program

| Acquirer | Target | Deal economics (year) | Status of lead asset | We believe Spyre programs could be at comparable stage by | | |
|---|---|---|---|---|---|---|
| | | | | 2025 | 2026 | 2027 |
| MERCK | PANDION THERAPEUTICS | **$1.85B (2021)** | Proof-of-mechanism in P1a (HVs); potential for UC & autoimmune indications. | SPY001<br>SPY002 | SPY003<br>SPY004 | |
| sanofi | kymab | **$1.435B total (2021)**<br>• $1.1B upfront<br>• $350M milestone | Positive data from a randomized P2a study for KY1005 (OX40L) | | SPY001<br>SPY002 | |
| MERCK | Prometheus Biosciences | **$10.8B (2023)** | Positive topline P2b RCT data in UC and open-label single-arm P2 data in CD. | | SPY001 | SPY002<br>Combos |
| Takeda | nimbus THERAPEUTICS | **$6.0B (2022)**<br>• $4.0B upfront<br>• $2.0B milestones | Positive topline P2b data in psoriasis for NDI-034858 (TYK2); potential in immune-mediated diseases, including IBD. | | | |
| Pfizer | ARENA PHARMACEUTICALS | **$6.7B (2021)** | Positive P2 data in UC for etrasimod. | | | |

**Comparable acquisitions illustrate optionality that exists for potential exits.**

*SOURCE: Press releases.*

# Thank you

# Spyre antibodies were developed by our partners at Paragon

**Paragon Therapeutics** was founded in 2021 by Fairmount.

**21** **Professionals with deep expertise** in antibody engineering and drug development from across the industry.

**Capabilities augmented** by facilities and scientists at FairJourney Biologics and contract research organizations across the globe.

**12** **Programs** currently in development with lead program on track to enter clinical trials in 3Q23, less than 2 years from ideation.

**Launched first spinout,** Apogee Therapeutics, in 2022, which went public in July 2023 in a $345M IPO.

PARAGON THERAPEUTICS



**Evan Thompson**
*COO*



**Hussam Shaheen**
*SVP Biotherapeutics*



**Jason Oh**
*VP Biology*



**Shawn Russell**
*VP CMC*



**Cyrus Stacey**
*VP Quality*



**Neta Batscha**
*VP Operations & Strategy*

# Diverse expertise in antibody discovery and engineering enables potentially best-in-class therapeutics

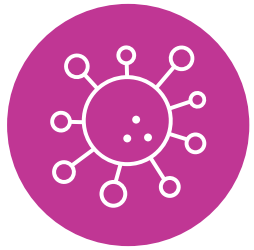
## Antibody engineering expertise in a variety of techniques to fulfill the needs of a wide range of programs



Cross-species immunization



Hybridoma approaches



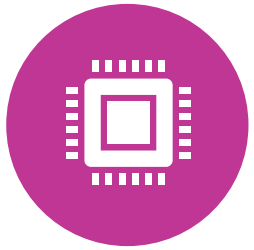
Single B-cell cloning



Phage display



Yeast display



In-silico design

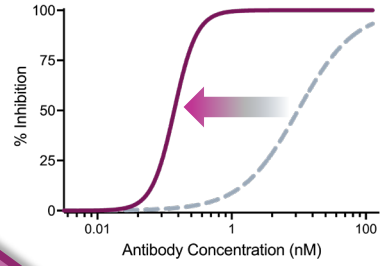
**Established workflows and CRO relationships enable fast and reliable antibody discovery to generate novel drug candidates with best-in-class properties**

# Paragon aims to engineer best-in-class antibodies by optimizing across five key properties

1

## Potency

*Targeting the best epitope and maximizing in vitro responses*




2

## Safety

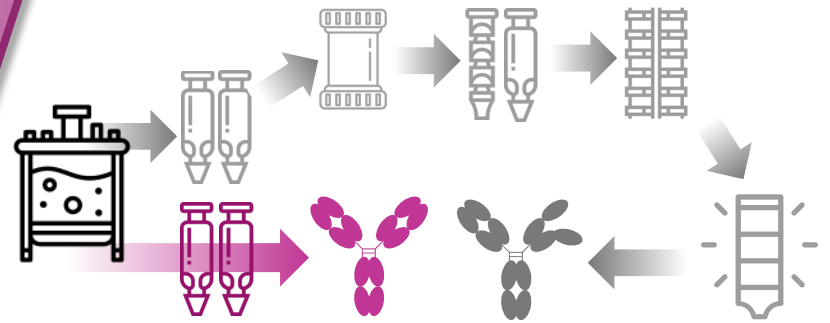
*Target specificity and low immunogenicity*



3

## Manufacturability

*Plug-and-play manufacturing and highly stable*



4

## Formulatability

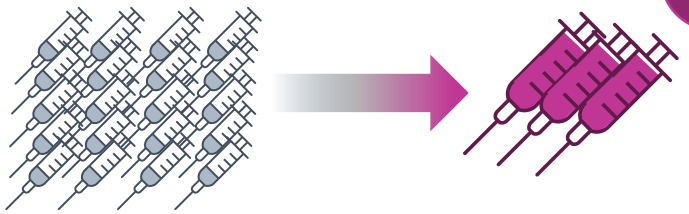
*More drug and less pain*



5

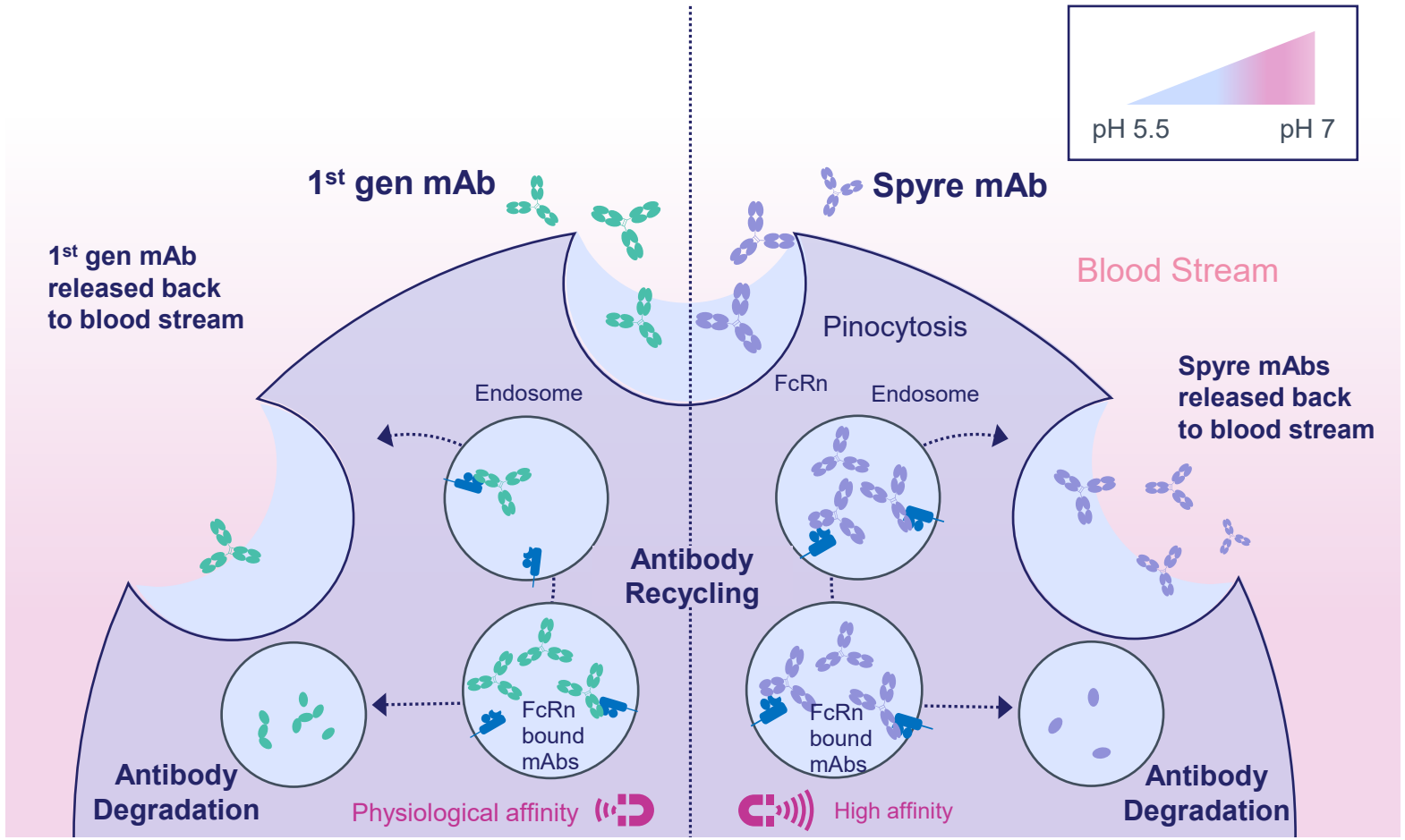
## Pharmacokinetics

*Longer half-life for fewer shots*



SPYRE

# Spyre mAbs employ proven half-life extension technology

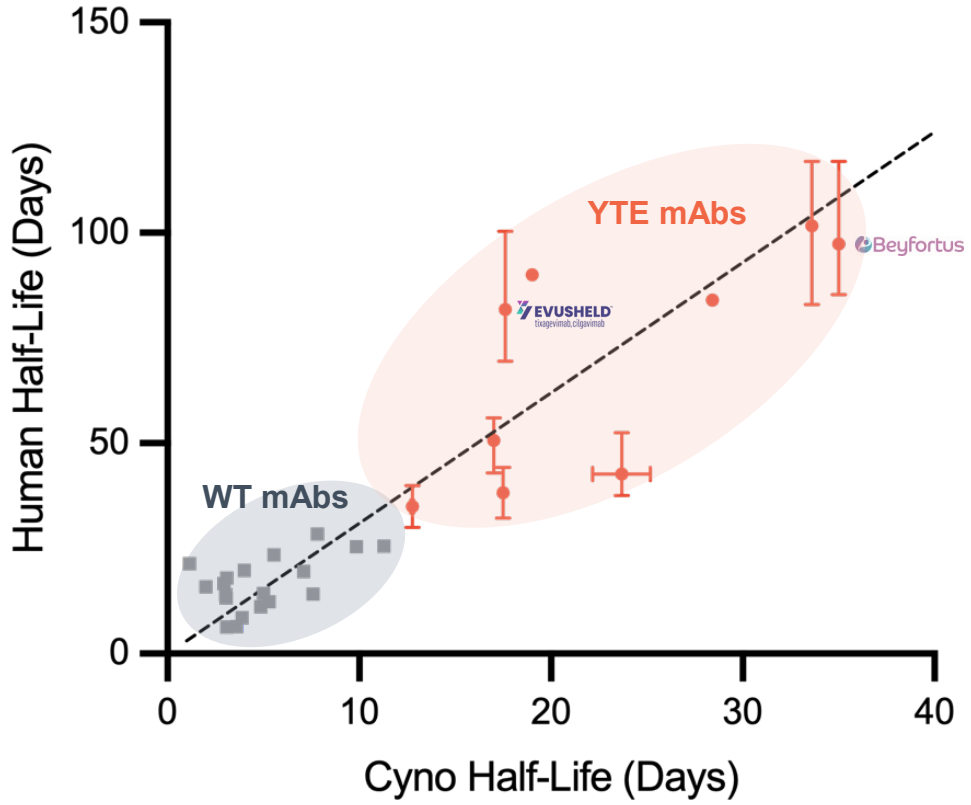



- Spyre mAbs designed to be recycled back into circulation more readily
- Drug exists at much higher levels for longer duration of effect
- Fewer injections decrease patient burden and can improve compliance and penetration

SOURCE: Adapted from Ko S et al *BioDrugs* 2021

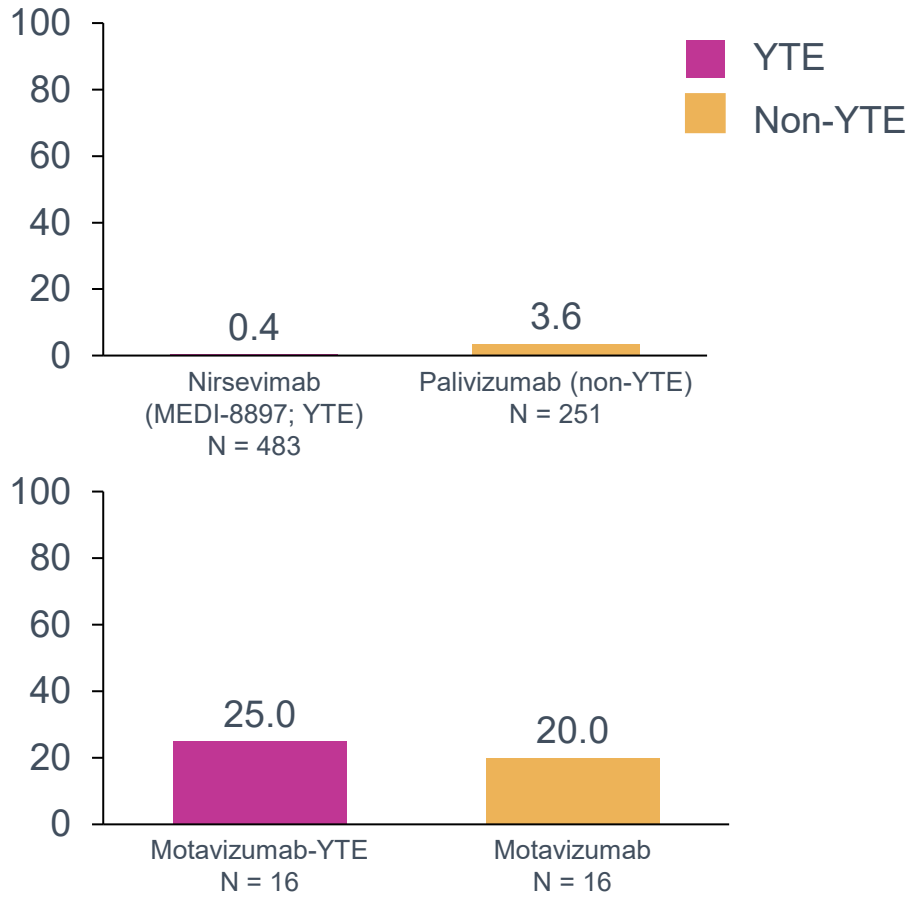
# YTE technology shown to significantly prolong half-life and without increasing immunogenicity

## YTE mAbs have extended half-lives in NHPs and humans




**Extent of half-life extension dependent on target (soluble vs. membrane bound)**

## ADA rates are similar for YTE and non-YTE antibodies[1,2]




*Source: 1) Rocca, A, et al. Int J of Mol Sci, 2021; 2) Domachowske NEJM 2022*