A Novel Monoclonal Antibody Drug Candidate SPY001 Targeting Integrin α4β7 for the Treatment of IBD: In Vitro Properties and Non-human Primate Pharmacokinetics and Safety

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SPYRE THERAPEUTICS

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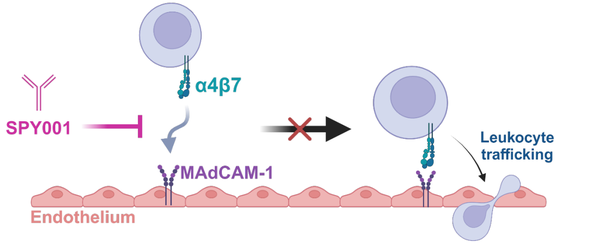
Background

- Antagonism of the interaction between the cellular adhesion integrin **α4β7** and endothelial ligand mucosal addressin cell-adhesion molecule-1 **(MAdCAM-1)** has proven to be well-tolerated and effective in the treatment of **Crohn's disease (CD) and ulcerative colitis (UC)**.



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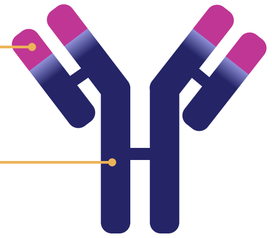
About SPY001

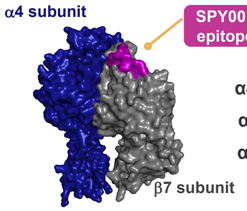


- Identical epitope target as vedolizumab with comparable potency and selectivity
- Half-life extension through validated Fc modification to enable Q8W-Q12W SC dosing
- IND-enabling tox studies completed with **NOAEL (160 mg/kg) at the highest dose tested**

Phase 1 study ongoing with interim data YE24

Methods and Results

SPY001 exhibits potent and selective α4β7 binding



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

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

Figure 1: *Predicted binding site for SPY001 (left); dissociation constants for SPY001 and vedolizumab (vedo) for α4β7 and related integrins by surface plasmon resonance (right).*

SPY001 is a potent & selective inhibitor of α4β7-mediated cellular adhesion

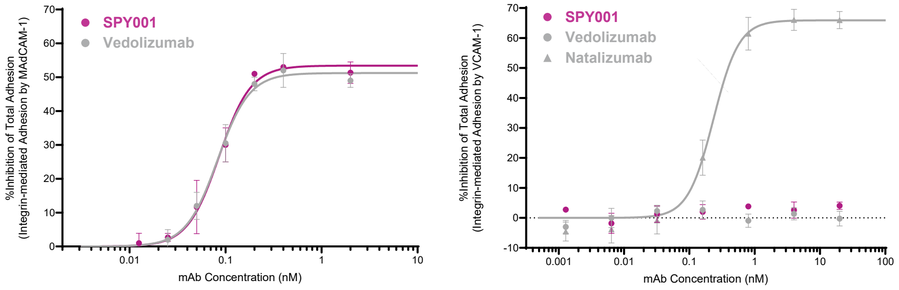


Figure 2: *SPY001 and vedolizumab both inhibit α4β7-mediated cellular adhesion to MAdCAM-1 (left); neither SPY001 nor vedolizumab inhibit α4β1-mediated cellular adhesion via VCAM-1 (right).*

SPY001 includes a YTE modification in the Fc region for extended half-life

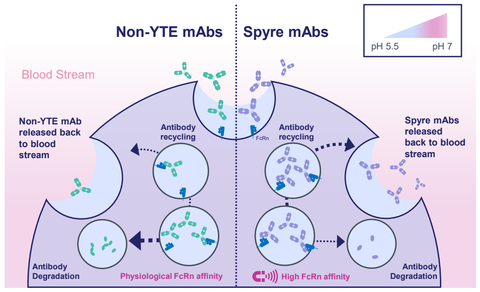


Figure 3: *YTE modification extends half-life by increasing IgG binding affinity to FcRn at low pH, increasing antibody recycling and reducing lysosomal degradation.*

SPY001 exhibits a ~3-fold extended half-life in Tg276 mice and NHPs

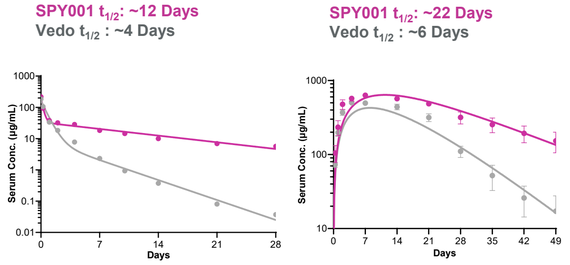


Figure 4: *Measurement of SPY001 and vedolizumab (vedo) serum concentrations in Tg276 transgenic mice expressing human FcRn following a single 10 mg/kg IV dose (left) and in cynomolgus monkeys (NHPs) following a single 50 mg/kg SC dose (right).*

The projected SPY001 human half-life supports Q8W to Q12W SC maintenance dosing

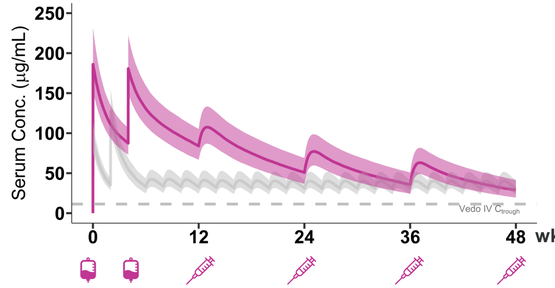


Figure 5: *Simulated PK profiles of SPY001 (IV at W0, W4; SC at W12 and Q12W) and vedolizumab (IV at W0, W2; SC dose Q2W). Based on average $t_{1/2}$ extension of ~3x with YTE and published human vedolizumab $t_{1/2}$ of 25 days. Solid line: simulated median; Shaded area: interquartile range. Stochastic simulations: n=2,000 virtual subjects.*

Conclusions

- **SPY001** is a novel humanized monoclonal IgG1 with an **extended half-life compared to vedolizumab** in Tg276 mice and cynomolgus monkeys that is **currently being tested in a Phase 1 clinical trial**.
- SPY001 offers the **potential for effective and safe treatment of CD and UC as a monotherapy or combination backbone**, with the advantage of **infrequent SC maintenance dosing**.

References

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Disclosures

EZ, DR, RV, SO, JO, and HS are employees of Paragon Therapeutics. JF, DN, MR, OB, and AS are employees of Spyre Therapeutics. All authors own equity in Paragon Therapeutics and/or Spyre Therapeutics.

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