A Novel Monoclonal Antibody Drug Candidate SPY001 Targeting Integrin α4β7 for the Treatment of IBD Demonstrates Prolonged Half-Life in Non-Human Primates

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SPYRE THERAPEUTICS

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Background

- **Antagonism of the interaction between the cellular adhesion integrin α4β7 and MAdCAM-1** by vedolizumab is safe and effective in the treatment of IBD. **Additional benefit** may be gained from an α4β7 antagonist administered via the **subcutaneous (SC) route at extended intervals (e.g., every 8 to 12 weeks)**.
- **SPY001** binds to the same α4β7 epitope as vedolizumab and includes a **YTE modification** within the Fc region to increase its serum half-life (see Poster P587).

Methods and Results

α4β7 blockade is a validated therapeutic mechanism in IBD

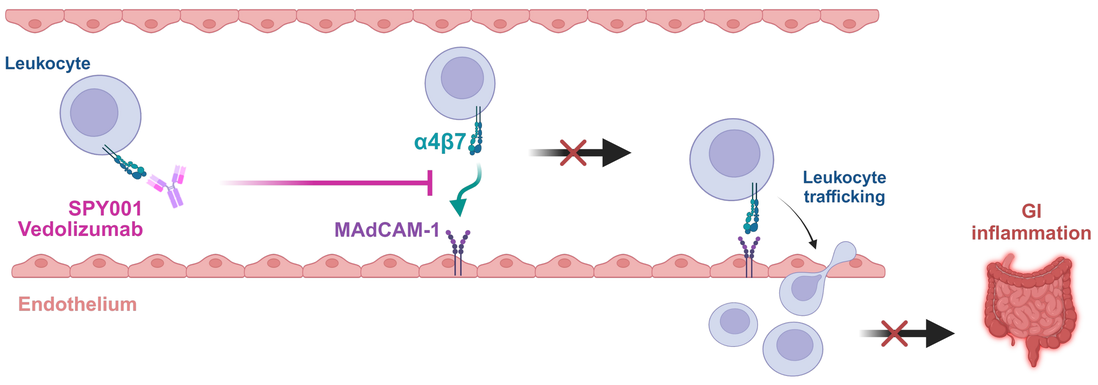


Figure 1: *Binding of SPY001 (or vedolizumab) to α4β7 prevents its association with MAdCAM-1 and is anticipated to inhibit leukocyte trafficking across the endothelium and reduce GI inflammation. Created with BioRender.com.*

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

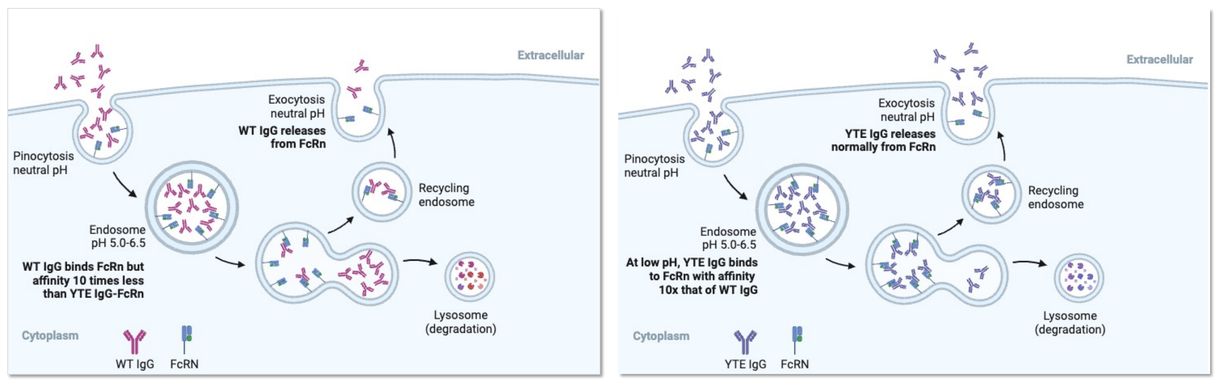
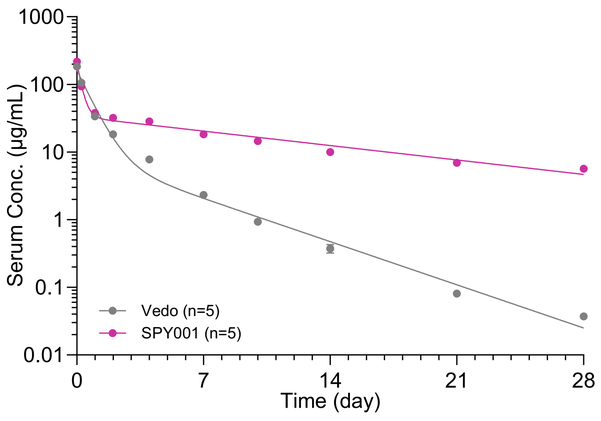


Figure 2*: YTE modification extends half-life by increasing IgG binding affinity to FcRn at low pH, increasing antibody recycling and reducing lysosomal degradation (1). Adapted from "extracellular vesicles" by BioRender.com (2023).*

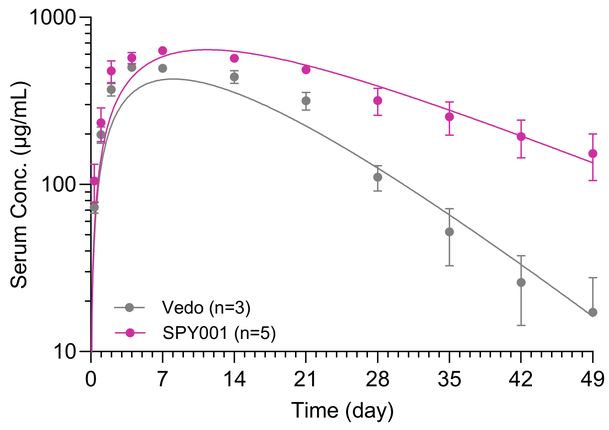
SPY001 has ~3x the half-life of vedolizumab in Tg276 mice expressing human FcRn



PK Parameters Following IV Bolus Administration of SPY001 to Tg276 Mice				
Drug	**Dose (mg/kg)**	**n**	**$t_{1/2}$ (day)**	**AUC_{last} (day*µg/mL)**
Vedo	10	5	4.4 (0.690)	165 (10.5)
SPY001	**10**	**5**	**12.4 (1.32)**	**455 (8.84)**

Figure 3*: Determination of SPY001 and vedolizumab (Vedo) concentration in serum from Tg276 transgenic mice expressing human FcRn following a 10 mg/kg IV dose.*

SPY001 has ~3x the half-life of vedolizumab in NHPs following a SC injection (50 mg/kg)



PK Parameters Following SC Administration of SPY001 to Cyno Monkeys				
Drug	**Dose (mg/kg)**	**n**	**$t_{1/2}$ (day)**	**AUC_{last} (day*µg/mL)**
Vedo	50	3	6.09 (1.52)	8430 (159)
SPY001	**50**	**5**	**21.8 (7.73)**	**18200 (3700)**

Figure 4*: Measurement of SPY001 and vedolizumab (Vedo) serum concentration in cynomolgus monkeys (NHPs) following a single SC dose of 50 mg/kg.*

SPY001 is anticipated to support a SC induction dosing regimen

Target:
Human $C_{avgW0-12}$
SPY001 > Vedo

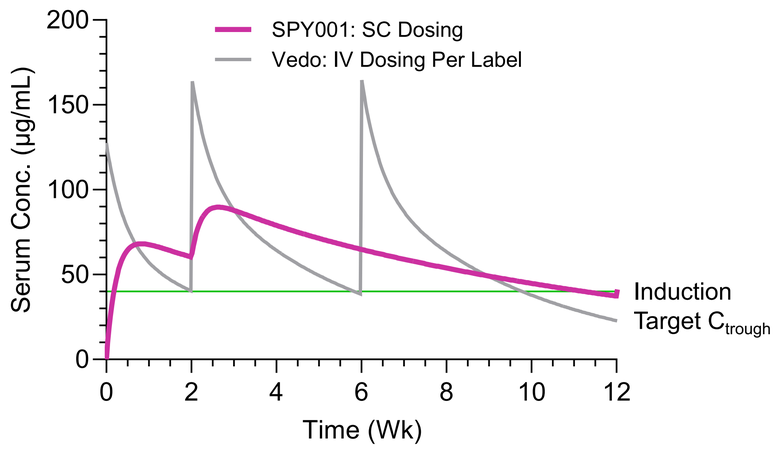


Figure 5*: Simulation of SPY001 and vedolizumab (Vedo) serum concentrations based on dosing SPY001 at W0 and W2 during induction and Vedo as per label (3-5).*

The expected SPY001 human half-life supports Q8-12W SC dosing

Target:
Human SPY001 $t_{1/2}$ ≥35 days

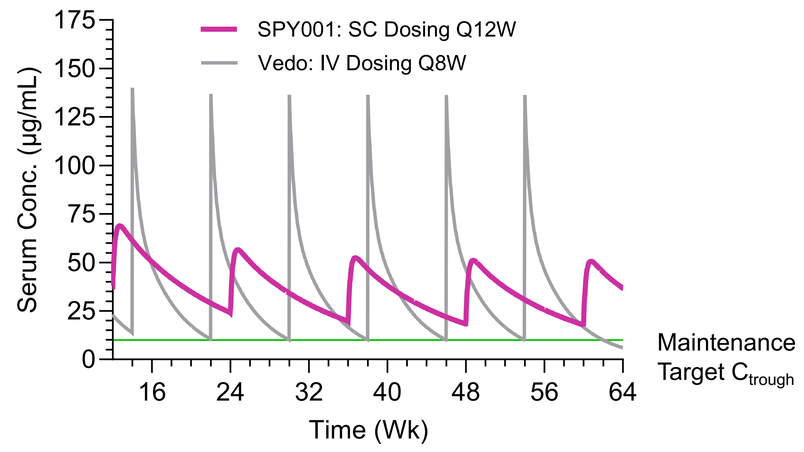


Figure 6*: Simulation of SPY001 and vedolizumab (Vedo) serum concentrations based on dosing at the indicated intervals (3-5).*

Conclusions

- SPY001 is a novel humanized monoclonal IgG1 with an **extended half-life over that of vedolizumab in Tg276 mice and cynomolgus monkeys**.
- 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 dosing**. First-in-human studies are planned for 2024.

References

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Disclosures

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

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