Development and Characterization of SPY003, a Novel Extended Half-Life Monoclonal Antibody Drug Candidate Targeting IL-23 for the Treatment of IBD

B. Kwan, M. Alam[1], J. Milligan[1], S. Oliveira[1], J. Friedman[2], D. Nguyen[2], M. Rose[2], A. Spencer[2] , J. Oh[1], H. Shaheen[1]

[1]Paragon Therapeutics, Waltham MA, United States; [2]Spyre Therapeutics, Waltham MA, United States

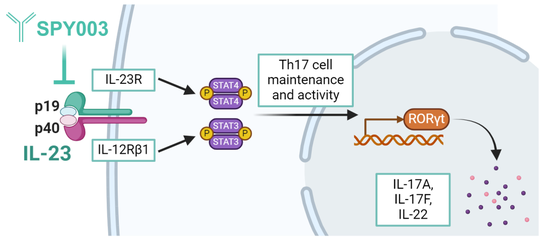
SPYRE THERAPEUTICS

MP118

October 12 – 15
ueg.eu/week

Background

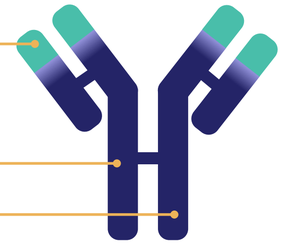
- **IL-23 inhibition** has been proven to be well-tolerated and effective in the treatment of **Crohn's disease (CD) and ulcerative colitis (UC)**.



Created with BioRender.com

About SPY003

- Similar epitope target as risankizumab with comparable potency and selectivity
- Half-life extension through validated Fc modification to enable Q3M-Q6M SC dosing
- Effector-null human IgG1 Fc
- IND-enabling tox studies initiated



Phase 1 expected to start in Q1 2025

Methods and Results

SPY003 binds to a similar epitope on the p19 subunit of IL-23 as risankizumab

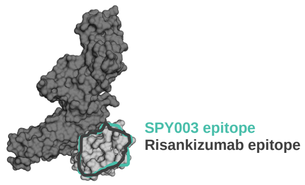
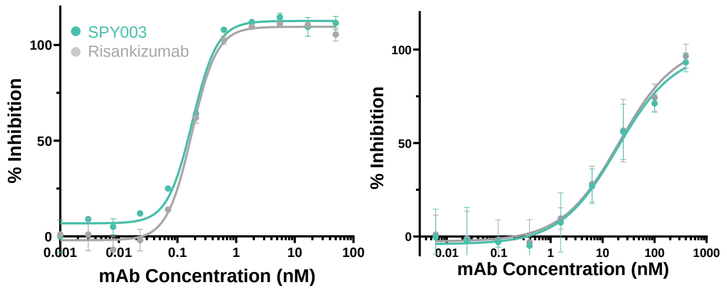


Figure 1: *The SPY003 epitope was resolved by negative stain EM; illustrative location is overlayed with the crystal structure IL-23. The p19 subunit is shown in light grey.*

SPY003 exhibits similar potency to risankizumab in multiple assays



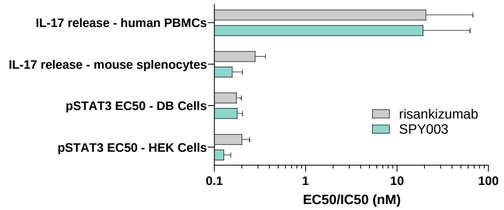


Figure 2: *SPY003 and risankizumab potently inhibit pSTAT signaling in DB cells (left) and IL-17 secretion in IL-23-stimulated human peripheral blood mononuclear cells (PBMCs; center). These findings are replicated across multiple assays (right).*

SPY003 includes a YTE modification in the Fc region for extended half-life

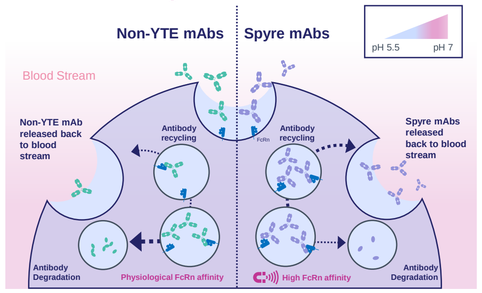


Figure 3: *YTE modification extends half-life by increasing IgG binding affinity to FcRn at low pH, increasing antibody recycling and reducing lysosomal degradation.*

SPY003 exhibits increased half-life in non-human primates compared to risankizumab

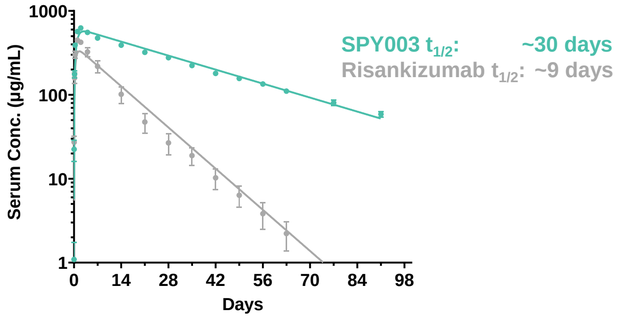


Figure 4: *Measurement of SPY003 or risankizumab half-life in cynomolgus monkeys following a single 50 mg/kg SC dose. N = 5 per group at final timepoints.*

The projected SPY003 human half-life supports Q3M to Q6M SC maintenance dosing

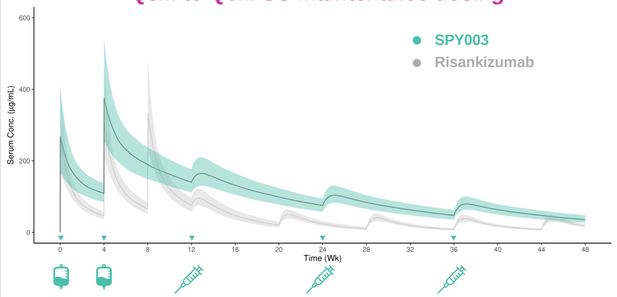


Figure 5: *Simulated PK profiles of SPY003 (IV at W0, W4; SC at W12 and Q12W) and risankizumab (IV at W0, W4, W8; SC dose Q8W) Based on average $t_{1/2}$ extension of ~3x with YTE and published human risankizumab $t_{1/2}$ of 23 days. Solid line: simulated median; Shaded area: IQR. Stochastic simulations: n=2,000 virtual subjects.*

Conclusions

- **SPY003** exhibits **high selectivity and affinity** for IL-23 and **potently inhibits** downstream cellular signaling.
- SPY003 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

1. D'Haens, G. *et al.* Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. *Lancet* **399**, 2015–2030 (2022).
2. Ferrante, M. *et al.* Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. *Lancet* **399**, 2031–2046 (2022).
3. Louis, E. *et al.* Risankizumab for Ulcerative Colitis. *JAMA* **332**, (2024).
4. Haraya K, Tachibana T. Translational Approach for Predicting Human Pharmacokinetics of Engineered Therapeutic Monoclonal Antibodies with Increased FcRn-Binding Mutations. *BioDrugs*. **37**(1):99-108.

Disclosures
BK, MA, JM, SO, JO, and HS are employees of Paragon Therapeutics. JF, DN, MR, and AS are employees of Spyre Therapeutics. All authors own equity in Paragon Therapeutics and/or Spyre Therapeutics.

Acknowledgements
The authors wish to thank Dr. Li Yan for pharmacokinetic analysis.