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

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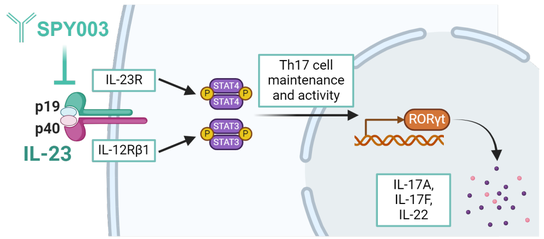
SPYRE THERAPEUTICS

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)**.

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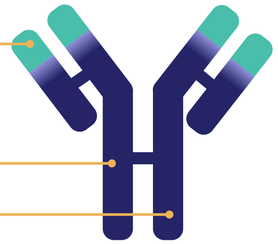
### About SPY003



- 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

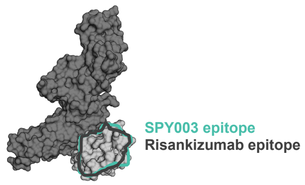
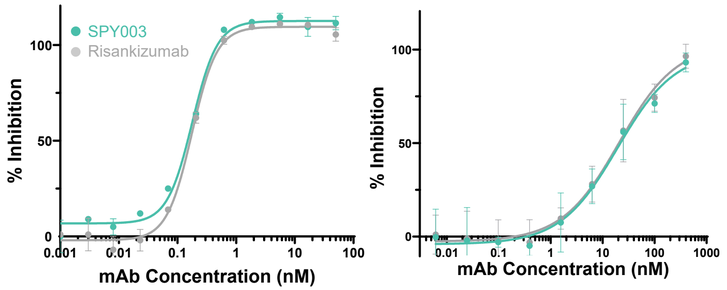



***Figure 1:*** *The SPY003 epitope was resolved by negative stain EM; illustrative location is overlayed with the crystal structure IL-23. The p19 subunit is shown in light grey.*

### SPY003 exhibits similar potency to risankizumab in multiple assays



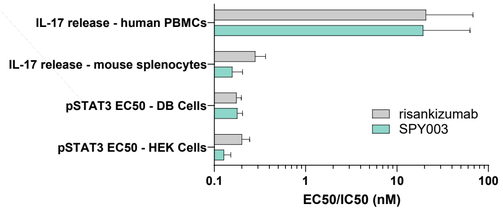




***Figure 2:*** *SPY003 and risankizumab potently inhibit pSTAT signaling in DB cells (left) and IL-17 secretion in IL-23-stimulated human peripheral blood mononuclear cells (PBMCs; center). These findings are replicated across multiple assays (right).*

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

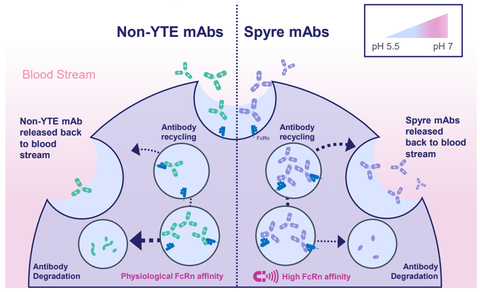



***Figure 3:*** *YTE modification extends half-life by increasing IgG binding affinity to FcRn at low pH, increasing antibody recycling and reducing lysosomal degradation.*

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

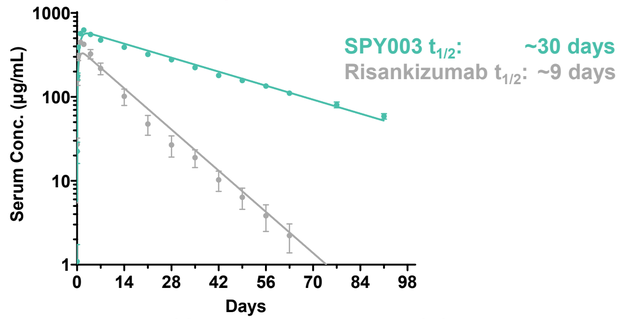



***Figure 4:*** *Measurement of SPY003 or risankizumab half-life in cynomolgus monkeys following a single 50 mg/kg SC dose. N = 5 per group at final timepoints.*

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

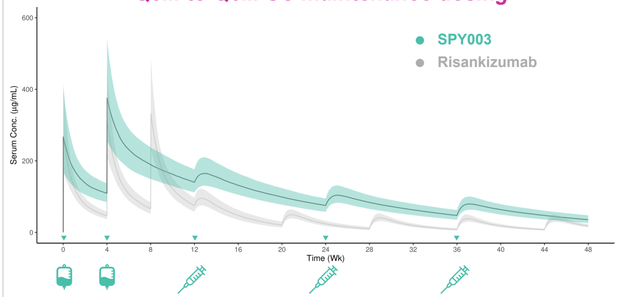



***Figure 5:*** *Simulated PK profiles of SPY003 (IV at W0, W4; SC at W12 and Q12W) and risankizumab (IV at W0, W4, W8; SC dose Q8W) Based on average $t_{1/2}$ extension of ~3x with YTE and published human risankizumab $t_{1/2}$ of 23 days. Solid line: simulated median; Shaded area: IQR. Stochastic simulations: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