Blockade of the interaction of TL1A with its cognate receptor DR3 has been shown to ameliorate disease activity in patients with CD and UC.

SPY002-091 is a novel, extended half-life, fully human IgG1 mAb that binds TL1A with high affinity and specificity and potently inhibits TL1A-mediated signaling.

**Methods and Results**

**SPY002-091** binds a novel epitope on a single TL1A subunit, with some RVT-3101 & TEV-48574 overlap

- **SPY002-091**
  - Potency of 150 pM
  - Binds single TL1A subunit
  - Epitope overlaps the DR3 binding interface, resulting in potent functional blockade of signaling

![Figure 2: Epitopes for TL1A antibodies were resolved by CryoEM; illustrative locations are overlayed with the crystal structure of trimeric TL1A (PDB: 2000).](image)

**SPY002-091** demonstrates potent and selective binding to human TL1A in vitro

<table>
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<tr>
<th>Antibody</th>
<th>TL1A</th>
<th>FasL</th>
<th>TRAIL</th>
<th>LIGHT</th>
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<td>NB²</td>
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</table>

*Table 1: SPY002-091 and other clinical anti-TL1A mAb dissociation constants (Kd) for TL1A and related superfamily proteins as determined by surface plasmon resonance.*

¹Formerly PRA223; NB = no binding.

**SPY002-091** inhibits TL1A-induced apoptosis and IFN-γ secretion with comparable or lower IC₅₀ values vs. other clinical stage anti-TL1A mAbs

![Figure 4: Inhibition of TL1A-induced TF-1 cell apoptosis (left) and IFN-γ secretion in primary human whole blood. One of 4 donors shown (right).](image)

**SPY002-091** has an extended half-life in both NHPs and mice compared to clinical stage anti-TL1A mAbs

![Figure 5: Serum concentration of SPY002-091 after one SC dose in cynomolgus monkeys (left) or an IV bolus dose in Tg276 transgenic mice expressing human FcRn (right).](image)

**Conclusions**

- **SPY002-091** exhibits high selectivity and affinity for TL1A, demonstrates effective blockade of the TL1A interaction with DR3, and potently inhibits downstream cellular signaling.
- With an extended half-life in NHPs, **SPY002-091** demonstrates the potential for effective and safe treatment of CD and UC as a monotherapy or combination backbone, with the advantage of infrequent SC dosing (Q8-12W).

First-in-human studies are planned for 2024.

**Disclosures**

EZ, DR, RV, HS, JM, JM, 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.