Development and Characterization of SPY002, a Novel Extended Half-life Monoclonal Antibody Drug Candidate Targeting TL1A for the Treatment of IBD

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Background

- 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**

- 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).**

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

<table>
<thead>
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<th>Antibody</th>
<th>TL1A</th>
<th>FasL</th>
<th>TRAIL</th>
<th>LIGHT</th>
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<tr>
<td>SPY002-091</td>
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<td>NB²</td>
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<tr>
<td>MK-7240¹</td>
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<td>TEV-48574</td>
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<td>NB²</td>
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</table>

**Table 1: SPY002-091 and other clinical anti-TL1A mAb dissociation constants (Kₐ) for TL1A and related superfamily proteins as determined by surface plasmon resonance. Formerly PRA023; ²NB = no binding.**

**SPY002-091 inhibits TL1A-induced apoptosis and IFNγ 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 IFNγ secretion in primary human whole blood. One of 4 donors shown (right).**

**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.