Interim Phase 1 Results for SPY002, a Novel Half-Life Extended Monoclonal Antibody Targeting TL1A, Suggest a Potential for Q3M or Q6M Maintenance Dosing for Inflammatory Bowel Disease

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Background

- In Phase 2 studies, first-generation antibodies targeting TL1A have been **effective** in patients with **Crohn's disease (CD) and ulcerative colitis (UC)**.
- SPY002 is a novel investigational, **extended half-life,** fully human IgG1 mAb that binds TL1A with **high affinity and specificity** and potently inhibits TL1A-mediated signaling.
- SPY002 is being studied in a Phase 1, single ascending dose clinical trial in healthy subjects (NCT06672718).
- SPY002 is also being studied in the SKYLINE-UC Phase 2 platform study in UC, which includes treatment arms with SPY002 as a monotherapy and in combination with anti-α4β7 or anti-IL-23 mAbs (NCT07012395).

Methods

- Participants were recruited in the U.S. and randomized 3:1 to receive either SPY002 or placebo in SAD cohorts.
- Blood and safety information were collected for AE, PK, PD, and ADA assessment. All data shown are latest available as of 17 July 2025.
- SPY002 pharmacodynamics were measured using assays of serum soluble total and free TL1A.

Results

Table 1: Demographics and baseline characteristics

Cohort	N	Age, years Mean (SD)	Female Percent	Weight, kg Mean (SD)	BMI, kg/m² Mean (SD)
100 mg SC	8	45 (14)	88%	71 (9)	26 (3)
300 mg SC	8	35 (7)	50%	72 (17)	26 (3)
300 mg IV	8	34 (4)	38%	73 (13)	25 (2)
1000 mg IV	8	34 (13)	63%	67 (9)	25 (2)
1500 mg IV	8	38 (13)	50%	72 (11)	26 (3)
Pooled SAD	**40**	**37 (11)**	**58%**	**71 (12)**	**26 (3)**

SD = standard deviation

- Demographics were well-balanced across cohorts.
- Baseline characteristics were consistent with expectations for a phase 1 study in healthy participants.
- With up to 233 days of follow-up, 1 subject (out of 40) discontinued due to being lost to follow-up.

SPY002 demonstrated a favorable safety profile

Table 2: Interim, blinded treatment-emergent adverse events (TEAEs)

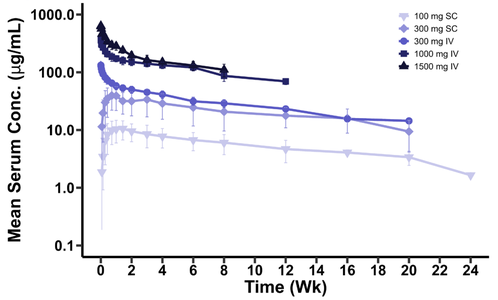
Cohort	N	Subjects with ≥ 1 TEAE	Subjects with ≥ 1 TESAE	Subjects with ≥ 1 treatment-related AE	Subjects with ≥ 1 grade 2 TEAE
100 mg SC	8	3 (38%)	0	2 (25%)	0
300 mg SC	8	2 (25%)	0	0	0
300 mg IV	8	3 (38%)	0	0	0
1000 mg IV	8	3 (38%)	0	0	0
1500 mg IV	8	0	0	0	0
Pooled SAD	**40**	**11 (28%)**	**0**	**2 (5%)***	**0**

* Treatment-related TEAEs of headache and migraine, both resolved.

- TEAEs were generally mild and unrelated to study drug.
- TEAEs occurring in 2 or more participants were COVID-19 and diarrhea.
- No treatment-emergent serious adverse events (TESAEs) or dose-dependent trends were observed.

SPY002 PK profiles demonstrated half-life extension

Figure 1: SPY002 PK profiles



SC=subcutaneous; IV=intravenous. Error bars represent SD.
Values below LLOQ (1 µg/mL) treated as missing for calculations of the mean.

Table 3: SPY002 PK parameters

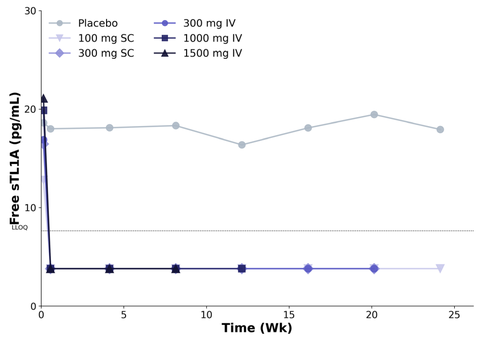
Dose	N	T_{max} (days)*	C_{max} (µg/mL)$	$AUC_{0-\infty}$ (µg·day/mL)$
100 mg SC	5#	12.7	10.5 (32.3)	1082 (18.0)
300 mg SC	5#	5	44.6(34.9)	4266 (36.0)
300 mg IV	6	NR	135(17.9)	5190 (11.8)
1000 mg IV	6	NR	372 (14.3)	15000 (17.8)
1500 mg IV	6	NR	645 (17.4)	NR

** Median. $ Mean (CV%). #Outlier excluded. NR=not reported*

- SPY002 exhibited a differentiated PK profile, with a half-life of > 3x compared to first generation anti-TL1As, supporting quarterly or twice annual SC maintenance dosing.
- ADA rates were comparable to or lower than first generation anti-TL1As, with no observed impact on PK or PD.

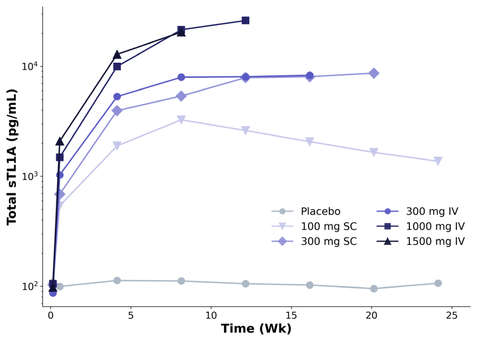
SPY002 demonstrated rapid and sustained target engagement

Figure 2: Free Soluble TL1A



Points are median values. Values below LLOQ of 8 pg/mL plotted as one-half of LLOQ. N: Placebo (2-10), 100 mg SC (6), 300 mg SC (4-6), 300 mg IV (1-6), 1000 mg IV (6), 1500 mg IV (6)

Figure 3: Total Soluble TL1A



Points are mean values. N: Placebo (2-10), 100 mg SC (5-6), 300 mg SC (4-6), 300 mg IV (5-6), 1000 mg IV (6), 1500 mg IV (6)

- Rapid and sustained reduction of **free soluble TL1A** was achieved up to 24 weeks of follow-up.
- Rapid, dose-dependent, sustained increases of **total (free + bound) soluble TL1A** were observed up to 24 weeks of follow-up.

Conclusions

- In a Phase 1 study of healthy participants, SPY002 was **well tolerated.**
- SPY002 demonstrated extended half-life and target engagement.
- These interim results support the **potential for the treatment of CD and UC with SPY002 as a monotherapy or combination backbone**, with **quarterly or twice annual maintenance dosing.**
- These data support clinical testing of SPY002 in the ongoing **SKYLINE-UC Phase 2 UC platform study as a monotherapy and in combination with anti-α4β7 or anti-IL-23 monoclonal antibodies**.

References

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Disclosures: All Spyre Therapeutics, Inc. authors own equity in Spyre Therapeutics, Inc.. BW is an employee of Cinlanian, LLC.