Interim Phase 1 Results for SPY072, a Novel Half-Life Extended Monoclonal Antibody Targeting TL1A, Suggest A Potential for Q3M or Q6M Maintenance Dosing for Rheumatic Disease

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Background

- TL1A is a cytokine that activates T cell subtypes and fibroblast-like synoviocytes.
- Variants in the TL1A gene are associated with RA, PsA, and axSpA, and TL1A expression is increased in each.
- TL1A inhibition is effective in rodent arthritis models.
- SPY072 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.
- SPY072 is being studied in a Phase 1, single ascending dose clinical trial in healthy subjects (NCT06622070).
- SPY072 is also being studied for the treatment of RA, PsA, and axSpA in the **SKYWAY-RD Phase 2 basket study** (NCT07148414).

Methods

- Participants in the U.S. and Canada were randomized 3:1 to receive either SPY072 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 03 July 2025.
- SPY072 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	38 (12)	50.0	77 (12)	26 (2)
300 mg SC	8	40 (11)	87.5	71 (15)	25 (3)
300 mg IV	8	37 (8)	62.5	72 (10)	25 (2)
1000 mg IV	8	34 (10)	62.5	68 (7)	26 (2)
1500 mg IV	8	42 (9)	75.0	67 (11)	25 (2)
Pooled SAD	**40**	**38 (10)**	**67.5**	**71 (12)**	**25 (2)**

SD = standard deviation

- Demographics were well balanced across cohorts and baseline characteristics were consistent with expectations for a phase 1 study in healthy participants.
- With up to 211 days of follow-up, 1 subject (out of 40) discontinued due to physician decision.

SPY072 demonstrated a favorable safety profile

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

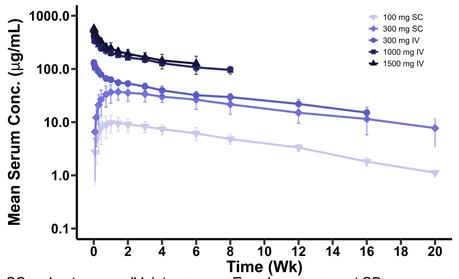
Cohort	N	Subjects with ≥ 1 TEAE	Subjects with ≥ 1 TESAE	Subjects with ≥ 1 treatment-related AE	Subjects with ≥ 1 grade 2 TEAE
100 mg SC	8	2 (25%)	0	0	0
300 mg SC	8	5 (63%)	0	2 (25%)	1 (13%)
300 mg IV	8	5 (63%)	0	0	1 (13%)
1000 mg IV	8	3 (38%)	0	1 (13%)	0
1500 mg IV	8	1 (13%)	0	0	0
Pooled SAD	**40**	**16 (40%)**	**0**	**3 (8%)***	**2 (5%)**

* Treatment-related TEAEs of gastroenteritis, rash, abdominal pain, and non-cardiac chest tightness, all resolved.

- TEAEs were generally mild and unrelated to study drug.
- No serious TEAEs or dose-dependent trends were observed.

SPY072 PK profiles demonstrated half-life extension

Figure 1: SPY072 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: SPY072 PK parameters

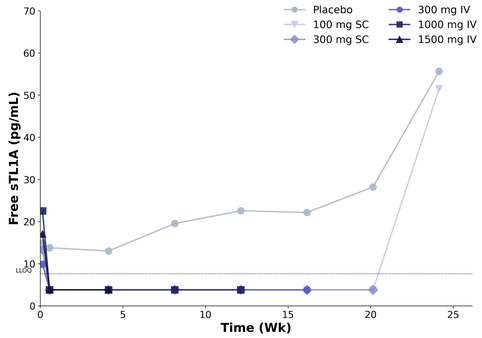
Dose	N	T_{max} (days)*	C_{max} (µg/mL)$	$AUC_{0-\infty}$ (µg·day/mL)$
100 mg SC	6	8.5	10.9 (25.8)	715 (17.7)
300 mg SC	6	12.0	39.1 (28.8)	3590 (38.3)
300 mg IV	6	NR	135 (15.4)	5290 (17.1)
1000 mg IV	6	NR	453 (11.0)	16900 (38.8)
1500 mg IV	6	NR	584 (19.2)	NR

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

- SPY072 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 or lower than first generation anti-TL1As, with no observed impact on PK or PD.

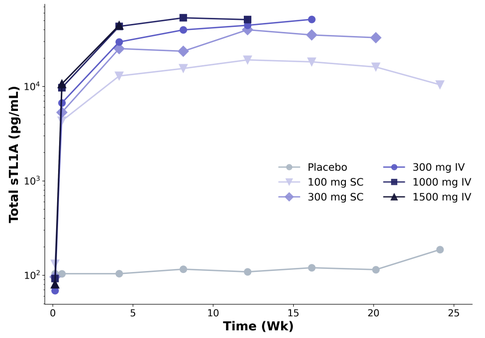
SPY072 demonstrated rapid and sustained target engagement

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 (5-6), 300 mg SC (6), 300 mg IV (4-6), 1000 mg IV (1-6), 1500 mg IV (6)

Figure 3: Total Soluble TL1A



Points are mean values. N: Placebo (2-10), 100 mg SC (6), 300 mg SC (6), 300 mg IV (4-6), 1000 mg IV (1-6), 1500 mg IV (6)

- Rapid and sustained reduction of **free soluble TL1A** was achieved up to 20 weeks of follow-up at the lowest dose.
- 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, SPY072 was **well tolerated**
- SPY002 demonstrated extended half-life and target engagement
- These interim results support the **potential for the treatment of rheumatic disease with SPY072 with quarterly or twice annual dosing.**
- These data support clinical testing of SPY072 in the ongoing **SKYWAY-RD Phase 2 basket** study **in which SPY072 is being evaluated** for the treatment of RA, PsA, and axSpA (NCT07148414).

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