Interim Phase 1 Results for SPY003, a Novel Half-Life Extended Monoclonal Antibody Targeting IL-23, Suggest Potential for Q3M or Q6M Maintenance Dosing for Inflammatory Bowel Disease

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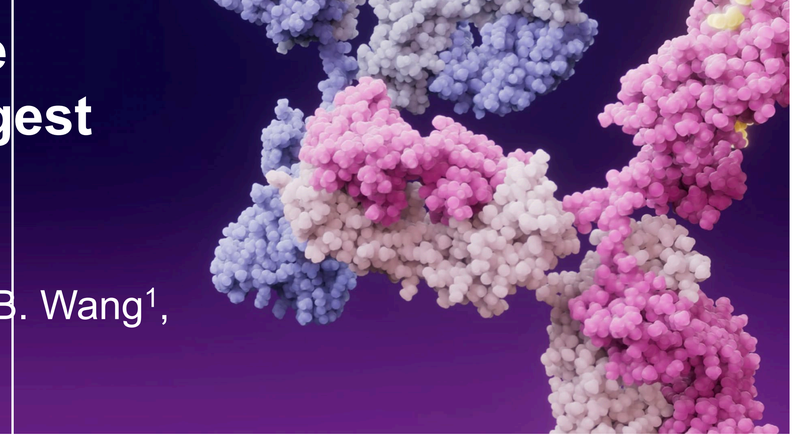


SPYRE THERAPEUTICS

P0834

Background

- Anti-IL-23 antibodies have been **approved** to treat **Crohn's disease (CD) and ulcerative colitis (UC)**.
- SPY003 is an investigational, **extended half-life**, fully humanized IgG1 monoclonal antibody that specifically binds to the p19 subunit of IL-23 at an epitope similar to that of risankizumab.[1]
- SPY003 is being studied in the **SKYLINE-UC** Phase 2 platform study in UC, which includes treatment arms with SPY003 as a monotherapy and in combination with anti-α4β7 or anti-TL1A mAbs (NCT07012395).
- Here, we report interim safety, tolerability, PK, and PD data from the ongoing Phase 1, first-in-human study of SPY003 in healthy volunteers (NCT06873724).

Methods

- Participants in the single ascending dose (SAD) and multiple dose (MD) cohorts were recruited in Canada and were randomized 3:1 to receive either SPY003 or placebo.
- Participants in the Chinese ethnobridging (Eb) cohort were recruited in the US and were randomized with a 4:1 active:placebo ratio.
- Blood, ECG, urine, and safety information were collected for AE, PK, PD, and ADA assessment.
- SPY003 PD were assessed using TruCulture® assays for surrogate IL-23-dependent biomarkers, including IL-17A, IL-17F, and IL-22.

Results

Table 1: Demographics and baseline characteristics

Cohort		N	Age, years Mean (SD)	Female Percent	Weight, kg Mean (SD)	BMI, kg/m² Mean (SD)
SAD	200 mg IV	6	34 (10)	67%	70 (14)	25 (2)
	600 mg SC	6	38 (11)	67%	73 (14)	25 (3)
	600 mg IV	7	37 (3)	14%	77 (9)	27 (2)
	1200 mg IV	6	35 (9)	33%	72 (7)	24 (2)
	Pooled SAD	**25**	**36 (8)**	**44%**	**73 (11)**	**25 (2)**
MD	1200 mg IV	6	37 (10)	50%	70 (14)	24 (4)
Pbo	SAD placebo	10	35 (10)	30%	76 (15)	25 (4)
	MD placebo	2	34 (13)	100%	67 (13)	26 (1)

SD = standard deviation. Data cutoff as of 03 Nov 2025.

- Demographics were well-balanced across cohorts.
- Baseline characteristics were consistent with expectations for a phase 1 study in healthy participants.

SPY003 demonstrated a favorable safety profile

Table 2: Interim, unblinded 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
SAD	200 mg IV	6	4 (67%)	0	0	0
	600 mg SC	6	1 (17%)	0	0	1 (17%)
	600 mg IV	7	2 (29%)	0	1 (14%)	0
	1200 mg IV	6	2 (33%)	0	1 (17%)	1 (17%)
	Pooled SAD	**25**	**9 (36%)**	**0**	**2 (8%)***	**2 (8%)**
MD	1200 mg IV	6	1 (17%)	0	0	0
Pbo	SAD placebo	10	3 (30%)	0	0	1 (10%)
	MD placebo	2	0	0	0	0

** Treatment-related TEAEs included 1 case of infusion reaction and 1 case of pruritus, both Grade 1 and resolved without medication. Data cutoff as of 03 Nov 2025.*

- TEAEs were generally mild and unrelated to study drug.
- No treatment-emergent serious adverse events (TESAEs) or dose-dependent trends were observed.
- The 1200 mg IV Eb cohort (N=8) and the 600 mg SC high concentration formulation cohort (N=6) similarly demonstrated a favorable safety profile.
- Headache (mild, transient, not on dosing day), occurring in 5 out of 45 participants dosed with SPY003 (11%), was the only TEAE occurring in 2 or more participants.

SPY003 interim PK demonstrated a half-life >3x of risankizumab

Figure 1: SPY003 PK profiles

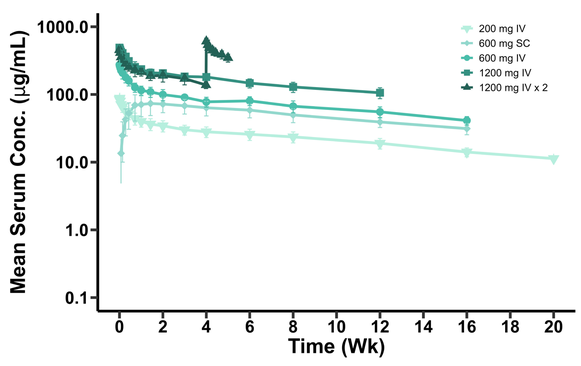


Table 3: SPY003 PK parameters after a single dose

Dose	T_{max} (days)*	C_{max} (µg/mL)$	$AUC_{0-\infty}$ (µg·day/mL)$
200 mg IV	0.105 (0.104, 0.271)	89.0 (16.2)	4420 (754)
600 mg SC	12.0 (4.98, 21.0)	78.0 (24.4)	9150 (1650)
600 mg IV	0.0209 (0.0208, 0.0209)	276 (55.0)	13800 (2940)
1200 mg IV	0.0417 (0.0417, 0.132)	497 (52.0)	28000 (6030)

** Median (Min, Max). $ Mean (SD). Data cutoff as of 29 Aug 2025.*

- SPY003 exhibited a differentiated PK profile, with a half life of >3x of risankizumab's (21-28 days[2-4]), supporting quarterly or twice annual maintenance dosing (data cutoff as of 29 Aug 2025).
- The PK profiles in the Eb and the main 1200 mg IV cohorts were similar (data cutoff as of 01 Dec 2025).
- ADA rates were low with no observed impact on PK or PD (data cutoff as of 25 Aug 2025).

SPY003 demonstrated targeted biological activity

Figure 2: SPY003 PD assay on IL-23-related cytokines

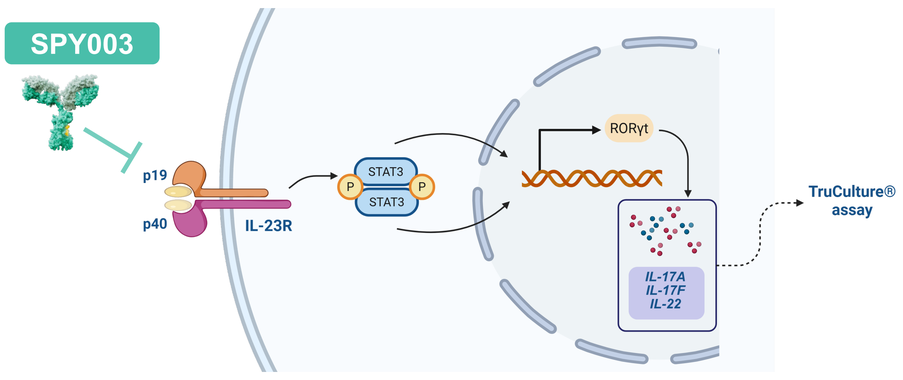
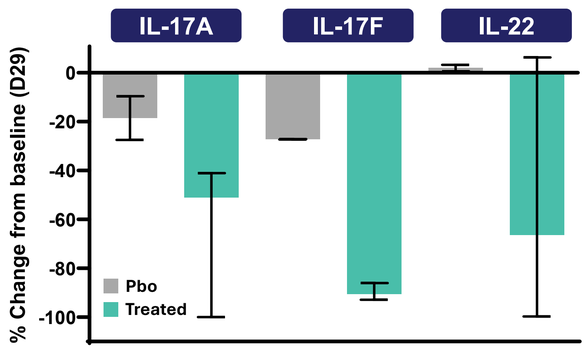


Figure 3: Cytokine change from baseline



- IL-17A, IL-17F, and IL-22 are canonical downstream cytokines associated with IL-23-driven T_H17 responses.
- In the TruCulture® assay, inhibition of IL-17A, IL-17F, and IL-22 production was observed in samples obtained at Day 29 following SPY003 dosing in both SAD and MD cohorts.

Data shown are median values for the proteins measured +/- IQR. BLQ are plotted as one-half of LLOQ for each analyte. Percent change from baseline was calculated per subject where (Day 29/Baseline -1) x 100. ; N: Placebo (5) & Treated (13, inclusive of SAD: 7 + MD: 6). Data cutoff as of 12 Dec 2025.

Conclusions

- In a Phase 1 study of healthy participants, SPY003 was **well tolerated**, had a **half-life of >3x of risankizumab**, and demonstrated **targeted biological activity**.
- These interim results support the **potential for the treatment of CD and UC with SPY003 as an investigational monotherapy or advanced combination therapy component**, with **quarterly or twice annual maintenance dosing**.
- These data support clinical testing of SPY003 in the ongoing **SKYLINE-UC Phase 2 UC platform study as a monotherapy and in combination with anti-α4β7 or anti-TL1A monoclonal antibodies** [see Spyre poster P0978 for further details[5]].

References

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Disclosures

B.W. is an employee of Cinlanian, LLC. All other authors are employees of Spyre Therapeutics, Inc. and own equity in Spyre Therapeutics, Inc.