Interim PK Data for SPY001, a Novel Half-Life Extended Monoclonal Antibody Targeting α4β7, Suggest a Potential for Q3M or Q6M Maintenance Dosing for Inflammatory Bowel Disease

D. Nguyen[1], L. Yan[1], K. Hew[1], P. Patel[1], R. McLean[1], R. Himes[1], T. Das[1], M. Huyghe[1], B. Connolly[1], J. Friedman[1]

[1]Spyre Therapeutics, Inc., Waltham MA, United States

SPYRE THERAPEUTICS

Su1871

Background

- Antagonism of α4β7 has been approved as a treatment for Crohn's disease (CD) and ulcerative colitis (UC).
- SPY001 is an investigational, half-life extended monoclonal antibody directed against α4β7 that shows comparable *in vitro* potency and selectivity to the approved drug vedolizumab[1].
- SPY001 is being studied in a Phase 1, randomized, double-blind, placebo-controlled, single- and multiple-dose clinical trial to assess its safety, tolerability, and pharmacokinetics in healthy subjects (NCT06448247).

Methods

- Participants were randomized 3:1 to receive either active or placebo in SAD or MAD cohorts.
- Participants were recruited from the U.S. and Canada; ongoing ethno-bridging cohorts are not included here.
- Blood and safety information were collected for AE, PK, PD, and ADA assessment. All data shown are latest available as of 03/19/2025.
- α4β7 binding was assessed using PBMCs stained with biotinylated MAdCAM-1 followed by streptavidin-PE and surface markers of immune cell subsets; gene expression was evaluated by qRT-PCR.

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	52 (9)	0%	77 (8)	26 (3)
300 mg SC	8	46 (14)	13%	87 (17)	27 (5)
600 mg SC	8	54 (7)	38%	72 (17)	25 (4)
1000 mg SC	8	40 (6)	25%	75 (9)	26 (3)
1000 mg IV	8	36 (9)	50%	81 (9)	28 (3)
Pooled SAD	**40**	**46 (11)**	**25%**	**79 (13)**	**26 (4)**
300 mg SC	8	45 (10)	25%	71 (12)	24 (3)
600 mg IV	8	38 (8)	13%	84 (10)	28 (4)
Pooled MAD	**16**	**41 (10)**	**19%**	**78 (13)**	**26 (4)**

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 275 days of follow-up, 1 subject (out of 56) discontinued after Day 141 for personal reasons.

SPY001 demonstrated a favorable safety profile

Table 2: Summary of interim, blinded treatment-emergent adverse events (TEAEs)

Cohort	N	At least one TEAE	At least one TESAE	At least one Drug-related AE	At least one ≥ Grade 2 TEAE
100 mg SC	8	1 (13%)	0	0	0
300 mg SC	8	5 (63%)	0	0	0
600 mg SC	8	4 (50%)	0	0	0
1000 mg SC	8	3 (38%)	0	1 (13%)*	1 (13%)#
1000 mg IV	8	2 (25%)	0	0	0
Pooled SAD	**40**	**15 (38%)**	**0**	**1 (3%)**	**1 (3%)**
300 mg SC	8	4 (50%)	0	0	0
600 mg IV	8	3 (38%)	0	0	0
Pooled MAD	**16**	**7 (44%)**	**0**	**0**	**0**

* Injection site discomfort starting 6 hours after 4 SC injections and resolved 2 hours later without intervention. # Dyspepsia.

- Treatment-emergent adverse events (TEAEs) were generally mild and generally unrelated to study drug.
- The most common TEAEs were headache and nasopharyngitis; no treatment-emergent serious adverse events (TESAEs) or dose-dependent trends were observed.

SPY001 demonstrated rapid and sustained target engagement

Figure 3: PD of SPY001 in SAD cohorts

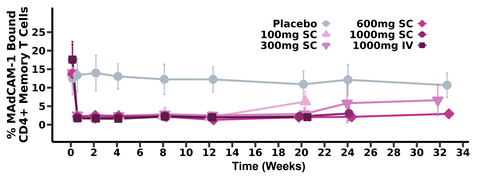
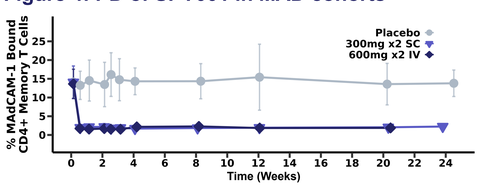


Figure 4: PD of SPY001 in MAD cohorts



Mean. Error bars represent standard deviations.

- Rapid and sustained saturation of α4β7 was observed through 32-weeks of follow-up with a single 600mg SC dose.
- In MAD cohorts, rapid and sustained saturation was achieved through up to 24 weeks (longest follow-up available).

SPY001 interim population PK demonstrated a half-life >3x of vedolizumab

Figure 1: SPY001 PK profiles following SAD administration in healthy volunteers

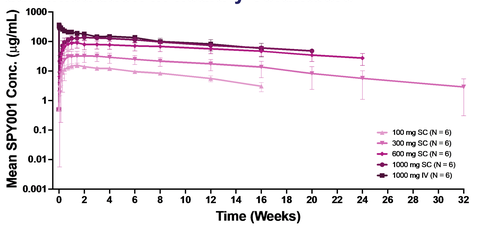
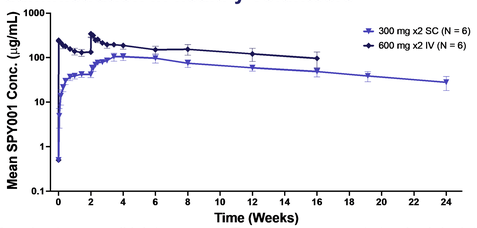


Figure 2: SPY001 PK profiles following MAD administration in healthy volunteers



SC=subcutaneous; IV=intravenous. Error bars represent standard deviations.

Table 3: SPY001 PK parameters following SAD administration in healthy volunteers

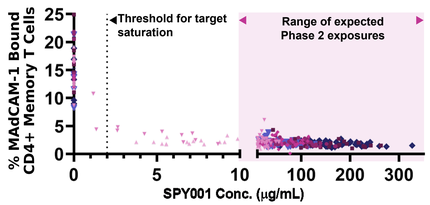
Dose	N	T_{max} (days)*	C_{max} (µg/mL)$	$AUC_{0-\infty}$ (µg·day/mL)$
100 mg SC	6	10	16.1 (2.93)	1160 (259)
300 mg SC	6	8	36.2 (16.3)	3930 (2120)
600 mg SC	6	10	92.9 (31.9)	12600 (5040)
1000 mg SC	6	14	141 (24.4)	18000 (1660)
1000 mg IV	6	0	362 (63.3)	19100 (6350)

* Median. $ Mean (SD).

- Terminal $t_{1/2}$ derived from population PK modeling was ~80 days, >3x vedolizumab's 25-day $t_{1/2}$.
- SPY001 half-life supports quarterly or biannual maintenance dosing.
- ADA rates were low and comparable to vedolizumab[2] with no observed impact on PK or PD.

Full saturation of α4β7 observed above 2 µg/mL SPY001

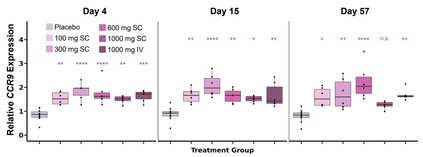
Figure 5: Target engagement at varying serum concentrations of SPY001



- SPY001 demonstrated exposure-dependent target engagement, with full saturation at concentrations >2 µg/mL, which is far below expected clinical trough concentrations.

SPY001 resulted in increased CCR9+ cells in the blood

Figure 6: *CCR9* mRNA in whole blood in subjects receiving SPY001 or placebo



*P<0.05; **P<0.005; ***P<0.0005; ****P<0.00005 vs. Placebo (t-test with Bonferroni correction for multiple comparisons)

- CCR9 gene expression is correlated with α4β7 expression in peripheral blood cells.
- CCR9 mRNA increased with SPY001, likely due to increased proportions of $\alpha4\beta7^+$ cells in the periphery.

Conclusions

- In a Phase 1 study of healthy participants, SPY001 was **well tolerated,** had an **~80-day half-life based on population PK model** (**>3x** compared to **vedolizumab**), and demonstrated full **target engagement at serum levels far below expected clinical trough concentrations.**
- SPY001 offers the **potential for the treatment of CD and UC as a monotherapy or combination backbone**, with the potential for **quarterly or biannual maintenance dosing.**
- These data support clinical testing of SPY001 in a **Phase 2 UC platform** study planned to start in **mid-2025, in which SPY001 will be evaluated as a monotherapy and in combination with anti-TL1A or anti-IL-23 monoclonal antibodies.**

References

1. Zhu, E. *et al.* A Novel Monoclonal Antibody Drug Candidate SPY001 Targeting Integrin α4β7 for the Treatment of IBD: In Vitro Properties and Non-Human Primate Pharmacokinetics and Safety. *UEGW*, PP1103 (2024).
2. T. Wyant, L. Yang, R. A. Lirio, M. Rosario, Vedolizumab Immunogenicity With Long-Term or Interrupted Treatment of Patients With Inflammatory Bowel Disease. The Journal of Clinical Pharmacology 61, 1174–1181 (2021).

Disclosures: All authors are employees of Spyre Therapeutics, Inc. and own equity in Spyre Therapeutics, Inc.