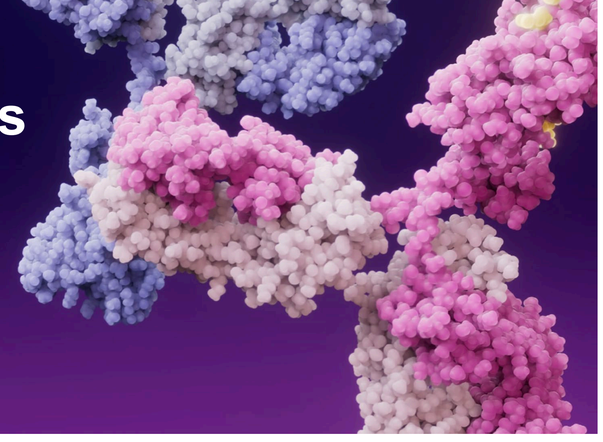
SKYLINE-UC: the First Platform Study in Ulcerative Colitis Assessing Efficacy and Safety of Three Long-acting Antibodies Administered as Single Agents and in Combinations

Silvio Danese[1], Vipul Jairath[2], JD Lu[3], Matthew Zinder[3], Yulia Vugmeyster[3], Joshua R. Friedman[3], MiRa Huyghe[3], Brian Connolly[3], Sheldon Sloan[3], Deanna D. Nguyen[3]

[1]University Vita-Salute San Raffaele, Gastroenterology, Milan, Italy; [2]Western University, Medicine - Epidemiology and Biostatistics, London ON, Canada; [3]Spyre Therapeutics, Waltham, United States



SPYRE THERAPEUTICS

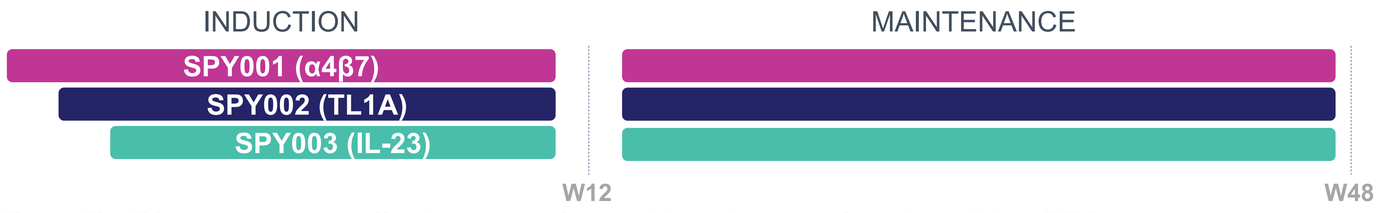
P0978

Objective

Evaluate the efficacy and safety of investigational long-acting antibodies, including 3 monotherapies and 3 advanced combination therapies, for moderately to severely active UC in adults

Figure 1: Platform Study Design

Part A: Open-label monotherapy evaluation (N=~100)

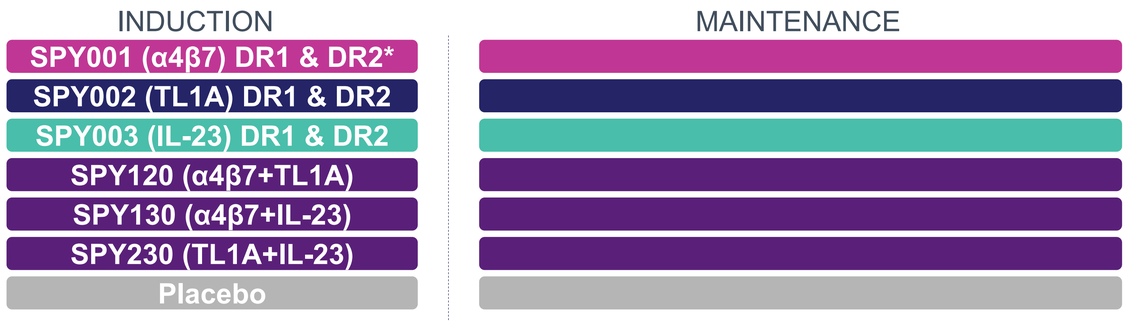


OBJECTIVES

- Monotherapy POC

Part B: Placebo-controlled factorial combination evaluation (N=~550)

Seamless enrollment *after completion of enrollment in Part A*



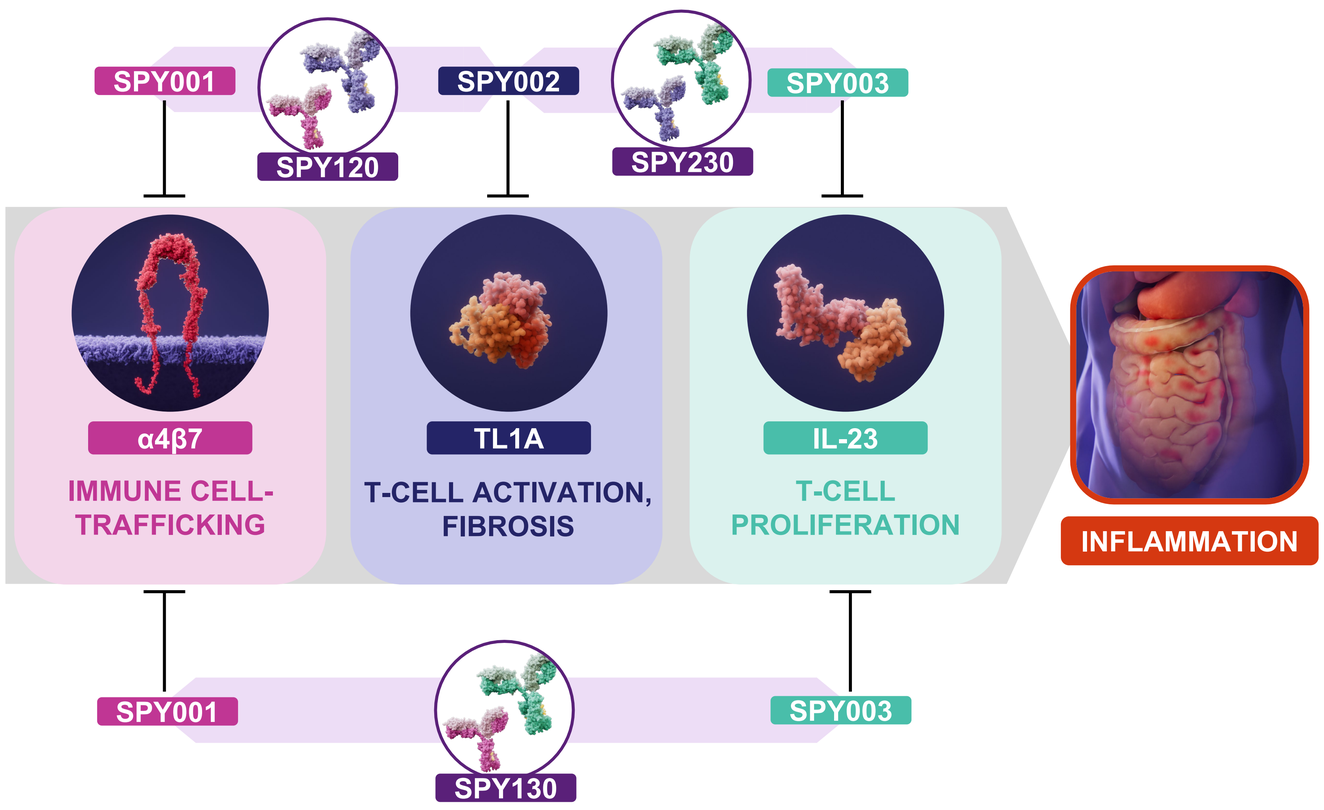
- Monotherapy dose optimization
- Combination POC compared to placebo & monotherapies

*Note: * Dosing Regimen 1 and 2 (DR1 and DR2)*

Background

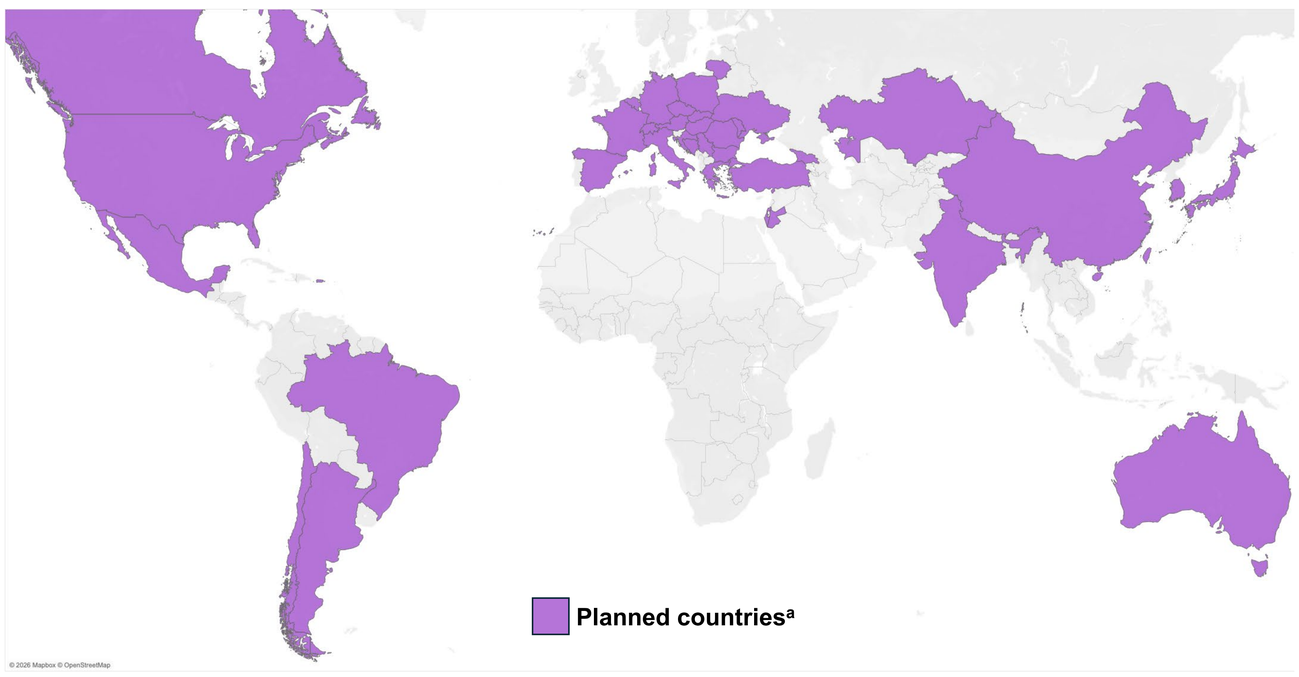
- SPY001, SPY002, and SPY003 are investigational, half-life extended monoclonal antibodies to α4β7, TL1A, and IL-23, respectively (Figure 2).[1,2,3]
- Interim Phase 1 data from each antibody suggest the potential for Q3M or Q6M maintenance dosing.[1,2,3]
- Preclinical data suggest additive-to-synergistic efficacy for the pairwise combinations of these mechanisms in mouse models of colitis.[4,5]
- The aim of this study is to assess the efficacy and safety of SPY001, SPY002, and SPY003 as single agents & in pairwise combinations (SPY120 [SPY001 & SPY002], SPY130 [SPY001 & SPY003], SPY230 [SPY002 & SPY003]) in UC.

Figure 2: Mechanisms of action



SKYLINE-UC evaluates complementary mechanisms targeting key inflammatory pathways in ulcerative colitis. SPY001 targets α4β7 to inhibit immune cell trafficking to the gut, SPY002 targets TL1A to modulate T-cell activation and fibrosis-associated pathways, and SPY003 targets IL-23 to inhibit T-cell differentiation, proliferation, and downstream inflammatory signaling. These mechanisms act at distinct points in the inflammatory cascade, allowing combination strategies that target multiple pathways responsible for intestinal inflammation.

Figure 3: Planned study locations



[a] Countries with planned or active investigational sites participating in the SKYLINE-UC platform study. Status in some geographies is pending final regulatory and ethics approval. See https://clinicaltrials.gov/study/NCT07012395 for the most up-to-date information.

Methods

- This ongoing platform study is designed for operational efficiency and scientific rigor in evaluating multiple interventions.
- Study includes an open-label Part A and a randomized, placebo-controlled Part B (Figure 1) that begins seamlessly enrolling after enrollment of Part A with flexibility on cohort enrollment period given platform design.
- Shared placebo and monotherapy comparators minimize overall trial size and patient exposure to placebo.
- A master protocol defines common elements, including eligibility criteria and assessment schedules.
- Key eligibility criteria include:
  - Adults (≥18 years) with a confirmed diagnosis of moderately to severely active UC for ≥3 months prior to enrollment
  - Active disease at screening, defined by modified Mayo score 5–9, rectal bleeding subscore ≥1, and endoscopic subscore ≥2
  - Inadequate response, loss of response, or intolerance to at least one conventional or approved advanced UC therapy
- Participants may be eligible for participation in a long-term extension (LTE) study based on protocol-defined criteria.
- Additional evaluations include pharmacokinetics, immunogenicity, and exploratory biomarker assessments.

Table 1: Key endpoints

Part	Primary Endpoint	Key Secondary Endpoints
A	Change in RHI at W12	Clinical remission at W12 Endoscopic improvement at W12 Change in mMS at W12
B	Clinical remission at W12	Endoscopic improvement at W12 Clinical response at W12 Histological improvement at W12 HEMI at W12 Clinical remission at W48

Clinical remission: stool frequency ≤1 and rectal bleeding = 0. Clinical response: ≥2-point and ≥30% decrease from baseline in modified Mayo score and ≥1-point decrease from baseline in rectal bleeding subscore or absolute rectal bleeding subscore ≤1. Endoscopic improvement: Mayo endoscopic subscore ≤1 (excluding friability). Histological improvement: improvement in histologic disease activity by validated histologic scoring criteria. HEMI: concurrent endoscopic and histologic improvement. RHI: Robarts Histopathology Index. mMS: modified Mayo score.

Conclusions

- Evaluating 6 interventions as a platform study is predicted to reduce sample size by 45% vs. investigating the same hypotheses in 3 separate combination studies.
- Part A data are anticipated to be available in 2026; Part B data are anticipated to be available in 2027.

For more information, scan the QR code or go to https://clinicaltrials.gov/study/NCT07012395

References

1. Nguyen, D. *et al. DDW*, Su1871 (2025).
2. Vugmeyster, Y. *et al. UEGW*, MP728 (2025).
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Disclosures

S.D. has received consulting fees from AbbVie, Alimentiv, Allergan, Amgen, Applied Molecular Transport, AstraZeneca, Athos Therapeutics, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Dr Falk Pharma, Eli Lilly, Enthera, Ferring Pharmaceuticals Inc., Gilead, Hospira, Inotrem, Janssen, Johnson & Johnson, Morphic, MSD, Mundipharma, Mylan, Pfizer, Roche, Sandoz, Sublimity Therapeutics, Takeda, Teladoc Health, TiGenix, UCB Inc., Vial, and Vifor. S.D. has received speaker's fees from AbbVie, Amgen, Ferring Pharmaceuticals Inc., Gilead, Janssen, Mylan, Pfizer, and Takeda.
V.J. has received consulting/advisory board fees from AbbVie, Alimentiv, Asieris, Astra Zeneca, Attovia, Biomebank, Boehringer Ingelheim, Caldera Therapeutics, Calluna, Celltrion, Domain Therapeutics, Eli Lilly, Enthera, Ensho, Exeliom Biosciences, Ferring Ventures, Flagship Pioneering, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genentech, Gilead, Granite Bio, Janssen, Merck, Metacrine, Mountainfield, MRM Health, Nxera, Organon, OSE Immunotherapeutics, Pandion, Pendopharm, Pfizer, Prometheus Biosciences, Roche, Salvina, Sanofi, Shattuck Labs, Sorriso, Spyre, Synedgen, Takeda, Teva, Thabor Therapeutics, Union Therapeutics, Ventus, Ventyx, Vividion, Xencor, and Zealand. V.J. has received speaker's fees from Abbvie, Ferring, Eli Lilly, Pfizer, and Takeda.
J.D.L., M.Z., Y.V., J.R.F., M.H., S.S., and D.D.N. are employees of Spyre Therapeutics, Inc. and own equity in Spyre Therapeutics, Inc.
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