Spyre Therapeutics Announces Positive Interim Phase 1 Results for Two Next-Generation TL1A Antibody Programs, and Provides Clinical Development Updates Expected to Deliver 9 Phase 2 Readouts

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SPY002 and SPY072 were well tolerated, exhibited PK that supports quarterly or less frequent dosing, and fully engaged TL1A through up to 20 weeks of follow-up; ~75 day half-life demonstrated, more than 3-fold greater than first-generation anti-TL1A antibodies

SKYLINE-UC platform study evaluating three optimized monotherapies and three potentially paradigm-changing combinations in ulcerative colitis, initiated in May 2025

SKYWAY-RD basket study evaluating SPY072 in rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA) announced, with initiation expected in Q3 2025

Management to host a webcast and conference call today at 8:00 a.m. ET

WALTHAM, Mass., June 17, 2025 /PRNewswire/ -- Spyre Therapeutics, Inc. (NASDAQ: SYRE), a clinical-stage biotechnology company advancing best-in-class antibody engineering, dose optimization, and rational therapeutic combinations for the treatment of Inflammatory Bowel Disease ("IBD") and other immune-mediated diseases, today announced positive interim Phase 1 results from its first-in-human trials of SPY002 *(formerly SPY002-091)* and SPY072 *(formerly SPY002-072)*, two investigational, novel, extended half-life monoclonal antibodies targeting TL1A. In addition, the company announced the initiation of its SKYLINE-UC platform trial and unveiled its SKYWAY-RD basket trial evaluating anti-TL1A targeted therapy in three rheumatologic indications.

Interim results from the Phase 1 trials for SPY002 and SPY072, with data reported as of May 30, 2025, met all Phase 1 objectives, supporting their potential to become next-generation anti-TL1A monotherapies in immune-mediated diseases or as elements of combination therapies. Single doses of up to 1500 mg for SPY002 and SPY072 were well tolerated with no serious adverse events reported, exhibited a prolonged half-life supportive of quarterly or less frequent dosing, and suppressed free TL1A through 20 weeks of follow up available for the lowest dose tested.

"These interim results demonstrate clear benefits of our anti-TL1A approach versus first-generation molecules, underscoring the promise and potential of SPY002 and SPY072 as transformational therapies in immune-mediated diseases," said Josh Friedman, M.D., Ph.D., SVP of Clinical Development at Spyre. "We are excited to advance both programs into Phase 2, with the planned addition of SPY002 to our ongoing SKYLINE-UC trial and initiation of a novel basket trial, SKYWAY-RD, with SPY072."

Building on these encouraging Phase 1 results, Spyre is advancing SPY002 into the SKYLINE-UC platform trial – initiated in May 2025 – for ulcerative colitis. SKYLINE-UC is expected to include SPY001 (anti-α4β7), SPY002 (anti-TL1A), SPY003 (anti-IL-23), and combinations thereof under an efficient single master protocol.

SPY072 will be advanced via the newly announced SKYWAY-RD basket trial for three rheumatologic conditions. The SKYWAY-RD study is a Phase 2 basket trial investigating Spyre's improved anti-TL1A as a treatment for RA, PsA, and axSpA and is expected to initiate in Q3 2025.

"The recently initiated SKYLINE-UC platform trial and the planned SKYWAY-RD basket trial leverage innovative and efficient designs to potentially deliver impactful results for the patients, physicians, and caregivers we aim to serve," said Sheldon Sloan, MD, Chief Medical Officer at Spyre. "The SKYLINE-UC study will test optimized versions of the best monotherapies in IBD and combinations of those monotherapies, aiming to identify therapies that deliver a step change in efficacy and convenience compared to today's standard of care. The SKYWAY-RD study will explore safety and efficacy of our anti-TL1A therapy in three rheumatologic diseases with favorable scientific rationale and large patient populations."

In addition to a planned Phase 1 interim readout of SPY003 (anti-IL-23) in the second half of 2025, in 2026 the company expects to readout open-label monotherapy data for its three investigational long-acting antibodies from the SKYLINE-UC trial along with three placebo-controlled readouts for SPY072 in RA, PsA, and axSpA from the SKYWAY-RD trial. In 2027, the company expects to read out placebo-controlled data of its monotherapies and combination therapies from the SKYLINE-UC study.

"Initiation of our Phase 2 SKYLINE-UC trial and planned initiation of our Phase 2 SKYWAY-RD trial marks a significant inflection point as we begin to explore the potential of our pipeline to deliver breakthroughs for patients with hard-to-treat inflammatory diseases," said Cameron Turtle, DPhil, Chief Executive Officer at Spyre. "With cash runway into the second half of 2028, we are well-funded to deliver 9 proof-of-concept readouts over the next two years in markets totaling >$60B of annual revenue. We believe our high-probability science and efficient development program provides the potential for exceptional stockholder value creation."

Anti-TL1A Phase 1 Interim Findings

The SPY002 and SPY072 Phase 1 trials are first-in-human, randomized, double-blind, placebo-controlled trials designed to evaluate safety, PK, and PD in healthy volunteers. To date, each trial has enrolled 40 healthy adult participants into five single-ascending dose (SAD) cohorts. Doses of SPY002 and SPY072 evaluated included 100 mg SC, 300 mg SC, 300 mg IV, 1000 mg IV, and 1500 mg IV. Interim findings from the trial are as follows:

- **Safety – well-tolerated across all dose groups**
  - Single doses of SPY002 and SPY072 up to 1500 mg were well-tolerated with a favorable safety profile consistent with existing third-party data of the anti-TL1A class.
  - The most common (i.e., occurring in more than two subjects) treatment-emergent adverse events (TEAEs) for SPY002 and SPY072 were COVID-19 and nausea, respectively.
  - There were no TEAEs greater than Grade 2, and no AEs led to trial discontinuation.
- **PK – differentiated profile relative to first-generation anti-TL1As**
  - SPY002 half-life is estimated at ~75 days across IV and SC SAD cohorts, more than 3-fold greater than first-generation anti-TL1As.
  - SPY072 showed comparable PK to SPY002 at clinically relevant doses through available follow up; waiting for comparable follow-up to accurately estimate half-life.
  - PK for SPY002 and SPY072 supports potential for chronic dosing in a single SC injection on a quarterly or twice annual basis.
- **PD – complete suppression of free TL1A at the latest time points available**
  - Both SPY002 and SPY072 demonstrated dose-dependent increases in total TL1A as expected.
  - A single 100 mg dose of either SPY002 or SPY072 suppressed free TL1A to below the lower-limit of quantitation (LLOQ) through 20-weeks of follow-up (longest follow-up available with PD data).
- **Immunogenicity – no apparent impact of anti-drug-antibodies was observed on PK or PD**

SKYLINE-UC: Platform Phase 2 trial in Ulcerative Colitis

SKYLINE-UC (NCT07012395) is a Phase 2 randomized and placebo-controlled induction and maintenance platform trial of SPY001, SPY002, SPY003, and pairwise combinations thereof (six investigational agents in total) in patients with moderately to severely active ulcerative colitis with two parts:

- **Part A:** open-label assessment of the safety and preliminary efficacy of monotherapies
  - Investigating a single dose level of each monotherapy as induction and maintenance therapies.
  - Induction data are expected in 2026.
- **Part B:** randomized and placebo-controlled assessment of the safety and efficacy of monotherapies and combination therapies
  - Seamless enrollment expected after completion of enrollment of Part A.
  - Designed to provide dose-ranging data on monotherapies, proof-of-concept and contribution of components for combination therapies.
  - Induction data are expected in 2027.

SKYWAY-RD: Basket Phase 2 trial of anti-TL1A in Three Rheumatologic Conditions

SKYWAY-RD is a planned Phase 2 randomized and placebo-controlled basket trial of SPY072 in patients with moderately to severely active RA, PsA, or axSpA with inadequate response to conventional or advanced therapies.

- **RA sub-study:** Double-blind, placebo-controlled safety and efficacy study of two dose levels of SPY072 through Week 12 with open-label follow-up through Week 36.
- **PsA sub-study:** Double-blind, placebo-controlled safety and efficacy study of a single dose level of SPY072 through Week

16 with open-label follow-up through Week 40.
- **axSpA sub-study:** Double-blind, placebo-controlled safety and efficacy study of a single dose level of SPY072 through Week 16 with open-label follow-up through Week 40.

Topline proof-of-concept data are expected in 2026.

Conference Call and Webcast

Spyre will host a conference call and webcast today, June 17, 2025, at 8:00 a.m. ET to discuss the anti-TL1A Phase 1 interim results and its Phase 2 clinical development plans. A live webcast of the call will be available on the Investor Relations website at https://ir.spyre.com/events-and-presentations. The webcast will be made available for replay on the company's website following completion of the event.

About SPY002

SPY002 is an investigational, extended half-life monoclonal antibody targeting TL1A for the potential treatment of IBD. IBD is a chronic condition characterized by inflammation in the gastrointestinal tract and encompasses two main disorders: ulcerative colitis and Crohn's disease. Together, these conditions affect more than 2.4 million individuals in the United States. In head-to-head preclinical studies, SPY002 demonstrated potency equivalent to or better than first-generation anti-TL1As. Interim data from a Phase 1 trial demonstrated that SPY002 was well tolerated, exhibited prolonged pharmacokinetics, and rapidly and durably suppressed free TL1A. Based on Phase 1 clinical data, the company plans to evaluate SPY002 in its SKYLINE-UC Phase 2 platform study.

About SPY072

SPY072 is an investigational, extended half-life monoclonal antibody targeting TL1A for the potential treatment of rheumatologic diseases including rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. Together, these conditions affect more than 3 million individuals in the United States. In head-to-head preclinical studies, SPY072 demonstrated potency equivalent to or better than first-generation anti-TL1As. Interim data from a Phase 1 trial demonstrated that SPY072 was well tolerated, exhibited prolonged pharmacokinetics, and rapidly and durably suppressed free TL1A. Based on Phase 1 clinical data, the company plans to evaluate SPY002 in a planned SKYWAY-RD Phase 2 basket study.

About Spyre Therapeutics

Spyre Therapeutics is a clinical-stage biotechnology company that aims to create next-generation inflammatory bowel disease (IBD) and other immune-mediated disease products by combining best-in-class antibody engineering, dose optimization, and rational therapeutic combinations. Spyre's pipeline includes investigational extended half-life antibodies targeting α4β7, TL1A, and IL-23.

For more information, please visit http://spyre.com.

Forward-Looking Statements
Certain statements in this press release, other than purely historical information, may constitute "forward-looking statements" within the meaning of the federal securities laws, including for purposes of the safe harbor provisions under the United States Private Securities Litigation Reform Act of 1995, concerning Spyre and other matters. These forward-looking statements include, but are not limited to, express or implied statements relating to Spyre's management team's expectations, hopes, beliefs, intentions or strategies regarding the future including, without limitation, Spyre's ability to achieve the expected benefits or opportunities with respect to its pipeline of product candidates such as the potential efficacy, tolerability, convenience, commercial viability, dosing regimen and safety profile of SPY002 and SPY072 in humans; the potential for SPY002 and SPY072 to become next-generation anti-TL1A therapies in immune-mediated diseases as monotherapies or as elements for combination therapies; Spyre's plans to advance both SPY002 and SPY072 programs into Phase 2 clinical trials; expectations regarding the drug delivery of SPY002 and SPY072, including in the form of a single SC injection; Spyre's ongoing and future clinical development activities, including the expected design and timing of the planned SKYWAY-RD Phase 2 basket trial, including timing of data readouts, timing of each part, cohort and data readout for the ongoing SKYLINE-UC Phase 2 platform trial, enrollment of clinical trials and number of data readouts expected to be delivered in 2026 and 2027; the expected SPY003 readout in the second half of 2025; the potential consistency of the SPY002 and SPY072 Phase 1 trial final data readouts with interim Phase 1 results; the potential therapeutic benefits of Spyre's product candidates as monotherapies or in combinations and their extended half-life, including the expected duration of half-life in comparison to competitor products and the potential efficacy and convenience compared to today's standard of care; the sufficiency of the Company's funding to support the development of its assets, including the expectation of being well-funded to deliver 9 proof-of-concept readouts in 2026 and 2027; the length of time that the Company believes its existing cash resources will fund its operations, including expectations of cash runway extending into the second half of 2028; estimated market sizes and potential growth opportunities; the potential for exceptional stockholder value creation; and the timing and results of clinical trials. In addition, any statements that refer to projections, forecasts or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking statements. The words "opportunity," "potential," "milestones," "pipeline," "can," "goal," "aim," "strategy," "target," "seek," "anticipate," "achieve," "believe," "contemplate," "continue," "could," "estimate," "expect," "intends," "may," "might," "plan," "possible," "predict," "project," "should," "will," "would," and similar expressions (including the negatives of these terms or variations of them) may identify forward-looking statements, but the absence of these words does not mean that a statement is not forward-looking. These forward-looking statements are based

on current expectations and beliefs concerning future developments and their potential effects. There can be no assurance that future developments affecting Spyre will be those that have been anticipated. These forward-looking statements involve a number of risks, uncertainties (some of which are beyond Spyre's control) or other assumptions that may cause actual results or performance to be materially different from those expressed or implied by these forward-looking statements. These risks and uncertainties include, but are not limited, uncertainties and risks arising from regulatory feedback, including potential disagreement by regulatory authorities with the Company's interpretation of data and the Company's planned clinical trials for its product candidates, including the Company's planned SKYWAY-RD Phase 2 clinical trial design; the potential for final data not being consistent with or different than the interim data reported for our programs; the potential impact of Trump Administration policies and changes in law on our business; and those uncertainties and factors described under the heading "Risk Factors," "Risk Factor Summary" and "Note about Forward-Looking Statements" in Spyre's most recent Annual Report on Form 10-K, as supplemented and updated by subsequent Quarterly Reports on Form 10-Q and Current Reports on Form 8-K that the Company has filed or will file with the SEC, as well as discussions of potential risks, uncertainties, and other important factors included in other filings by Spyre from time to time. Should one or more of these risks or uncertainties materialize, or should any of Spyre's assumptions prove incorrect, actual results may vary in material respects from those projected in these forward-looking statements. Nothing in this press release should be regarded as a representation by any person that the forward-looking statements set forth therein will be achieved or that any of the contemplated results of such forward-looking statements will be achieved. You should not place undue reliance on forward-looking statements in this press release, which speak only as of the date they are made and are qualified in their entirety by reference to the cautionary statements herein. Spyre does not undertake or accept any duty to make any updates or revisions to any forward-looking statements. This press release does not purport to summarize all of the conditions, risks and other attributes of an investment in Spyre.

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