Spyre Therapeutics Announces Positive Interim Results from Phase 1 Healthy Volunteer Trial for SPY001, Its Novel Half-Life Extended anti-α4β7 Antibody for the Treatment of Inflammatory Bowel Disease, with a Half-Life of >90 Days Supporting the Potential for Both Q3M & Q6M Maintenance Dosing

November 12, 2024

SPY001 was well tolerated with a favorable safety profile consistent with the anti-α4β7 class

SPY001 pharmacokinetics exceeded expectations with a ~4-fold increase relative to vedolizumab, supporting potential Q6M maintenance dosing with a single subcutaneous (SC) injection

Planned Phase 2 induction regimen targets drug concentrations in quartile 4 of vedolizumab's exposure-response relationship, which has the potential to increase or accelerate efficacy

Single, lowest dose of SPY001 led to complete saturation of α4β7 receptors through Week 12 (longest follow-up available for pharmacodynamic data)

Company plans to initiate a platform Phase 2 trial in mid-2025 that will include SPY001, followed by SPY002 (TL1A), SPY003 (IL-23), and combinations thereof, providing three optimized monotherapy readouts and three potentially paradigm-changing combination readouts under an efficient single master protocol

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

WALTHAM, Mass., Nov. 12, 2024 /PRNewswire/ -- Spyre Therapeutics, Inc. (NASDAQ: SYRE) (the "Company" or "Spyre"), a clinical-stage biotechnology company utilizing best-in-class antibody engineering, rational therapeutic combinations, and precision medicine approaches to target improved efficacy and convenience in the treatment of inflammatory bowel disease ("IBD"), today announced positive interim Phase 1 data from its first-in-human trial of SPY001, an investigational novel, extended half-life monoclonal antibody targeting α4β7. SPY001 was well tolerated with pharmacokinetic ("PK") data demonstrating a half-life of >90 days and pharmacodynamic ("PD") data demonstrating complete target engagement at all time points available.

Interim results from the trial, with data as of October 30, 2024, exceeded the Company's expectations and support the potential for SPY001 to become a next-generation anti-α4β7 therapy and backbone for paradigm-changing combination therapies in IBD. The PK and PD results support optimized Phase 2 dosing including (i) increased induction exposures with the potential to improve or accelerate efficacy compared to other anti-α4β7 treatments and (ii) maintenance dosing on a potential Q3M and Q6M frequency via a single subcutaneous injection. Across single doses of up to 1000 mg and multiple doses of up to 600 mg, SPY001 was well-tolerated with no serious adverse events reported and all adverse events being mild in severity. Based on these data, and subject to regulatory feedback, the Company plans to initiate a Phase 2 platform trial in mid-2025 that will ultimately include SPY001, SPY002 (TL1A), SPY003 (IL-23) and combinations thereof, providing three optimized monotherapy readouts and three potentially paradigm-changing combination readouts under an efficient single master protocol.

"These interim data exceeded our expectations for SPY001 and support its potential to become both a differentiated monotherapy and an ideal backbone for combination therapy in IBD," said Cameron Turtle, DPhil, Chief Executive Officer of Spyre. "We look forward to initiating Phase 2 trials next year that explore SPY001's safety and efficacy in IBD patients. Alongside our half-life-extended antibodies targeting TL1A and IL-23, we believe the Spyre portfolio is uniquely positioned to develop products that could substantially improve upon today's standard of care in IBD."

Key SPY001 Phase 1 Interim Findings

The SPY001 Phase 1 trial is a first-in-human, randomized, double-blind, placebo-controlled trial designed to evaluate safety and PK of SPY001 in healthy volunteers. To date, the trial has enrolled 56 healthy adult participants into five single-ascending dose (SAD) and two multiple-ascending dose (MAD) cohorts. Doses of SPY001 evaluated in the trial included single doses of 100 mg SC, 300 mg SC, 600 mg SC, 1,000 mg SC, and 1,000 mg IV and multiple doses of 300 mg SC and 600 mg IV. Findings from the interim SAD and MAD portions of the Phase 1 trial are as follows:

- **Safety – well-tolerated across all dose groups**
  - Single doses of SPY001 up to 1,000 mg and multiple doses of 600 mg were well tolerated with a favorable safety profile consistent with existing third-party data of the anti-α4β7 class
  - The most common (i.e., occurring in more than one subject) treatment-emergent adverse events ("TEAEs") were headache and nasopharyngitis.
  - There were no Grade 2 or above TEAEs or serious adverse events ("SAEs"). No AEs led to trial discontinuation
- **PK – meaningfully differentiated profile relative to vedolizumab**

- Half-life estimate is >90 days in the 300mg SC cohort and >100 days in the 600mg SC cohort, ~4-fold greater than vedolizumab's 25-day human half-life
    - SPY001 half-life supports potential for maintenance dosing via a single subcutaneous injection on a Q3M and Q6M basis using a high-concentration, citrate-free formulation
- Dose-proportionality and limited intrasubject variability observed across key parameters (e.g., C_{max}, AUC), support planned Phase 2 induction dosing to evaluate exposures of SPY001 in 4th quartile of vedolizumab's exposures to potentially achieve greater clinical remission rates and/or more rapid clinical effect
- No apparent impact of anti-drug antibodies observed on pharmacokinetic exposures

- **PD – complete saturation of α4β7 receptor occupancy to latest time point available**
    - Single 300 mg dose of SPY001 saturated α4β7 receptor occupancy up to Day 57 (longest follow-up available with pharmacodynamic data)
    - Exploratory immunophenotyping in progress, expected to be shared at upcoming academic conferences

Spyre expects to share data from additional cohorts and longer follow-up from existing cohorts at future medical meetings.

Platform Phase 2 trial in Ulcerative Colitis

Pending regulatory feedback, Spyre plans to advance SPY001 into a double-blind, randomized, placebo-controlled, Phase 2 platform trial with a master protocol in patients with moderately-to-severely active ulcerative colitis. The platform trial is designed to efficiently evaluate each of Spyre's monotherapy and combination therapies against a common placebo control. The trial is also intended to evaluate the contribution of each monotherapy component to the safety and efficacy of Spyre's combination therapies.

This Phase 2 ulcerative colitis trial is expected to initiate in mid-2025 with SPY001 and placebo arms, with SPY002, SPY003, and combination arms to be added following clinical data, nonclinical data, and regulatory feedback. The trial is expected to enroll approximately 500 subjects across treatment arms and consist of a 12-week, placebo-controlled induction period followed by a 38-week maintenance period.

Updated portfolio guidance for maintenance dosing

Given the PK results of SPY001, the Company is updating its guidance for maintenance dosing across the portfolio to Q3M-Q6M for monotherapies and combinations. Updated guidance highlights Spyre's unique ability to target a product profile with potentially best-in-indication efficacy and convenience.

Conference Call and Webcast

Spyre will host a conference call and webcast today, November 12, 2024, at 8:00 a.m. ET to discuss the SPY001 Phase 1 interim results. 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 SPY001

SPY001 is an investigational novel, extended half-life monoclonal antibody targeting α4β7 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. In the United States, it is estimated that approximately 2.4 million individuals currently have IBD. SPY001 targets the same epitope as vedolizumab and demonstrates equivalent potency and selectivity as vedolizumab in head-to-head preclinical studies. Interim data from a Phase 1 trial demonstrated that SPY001 was well tolerated and exhibited a human half-life of >90 days, a ~4-fold increase relative to vedolizumab. This half-life supports potential for both Q3M and Q6M SC maintenance dosing in a single autoinjector compared to vedolizumab's Q2W SC profile. Based on initial Phase 1 clinical data, the company plans to initiate a Phase 2 platform trial in ulcerative colitis in mid-2025.

About Spyre Therapeutics

Spyre Therapeutics is a clinical-stage biotechnology company that aims to create next-generation of inflammatory bowel disease (IBD) products by combining best-in-class antibody engineering, rational therapeutic combinations, and precision medicine approaches. 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

This press release contains "forward-looking" statements within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. All statements contained in this press release, other than statements of historical fact are forward-looking statements. These forward-looking statements include statements regarding the Company's business strategy, including the Company's ability to develop best-in-class therapeutics for IBD that meaningfully improve both efficacy and convenience compared to today's standard of care, the SPY001 phase 1 trial final data readout, the efficacy, safety and tolerability of SPY001 and its other product candidates, the planned induction and maintenance dosing regimen for SPY001 and its other product candidates, the potential for increased or accelerated efficacy, the therapeutic benefits of its product candidates as monotherapies or in combinations and their extended half-life, the expected design and timing of the platform Phase 2 trial, and

that the human PK data is not based on head-to-head clinical trials and differences exist between trial design and patient populations which could confound the results. The words "believe," "may," "will," "potentially," "estimate," "continue," "anticipate," "predict," "target," "intend," "could," "would," "should," "project," "plan," "expect," the negatives of these terms, and similar expressions that convey uncertainty of future events or outcomes are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. 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, final clinical trial data readouts and clinically trial designs, including the planned Phase 2 trial to be materially different from those expressed or implied by these forward-looking statements. These risks and uncertainties include, but are not limited to the final SPY001 Phase I trial data readouts not being consistent with or being different than the interim Phase I SPY001 results reported in this press release, 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 Phase 2 clinical trial design and those uncertainties and factors described under the heading "Risk Factors" and "Note about Forward-Looking Statements" in Spyre's most recent Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission, 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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