Spyre Therapeutics Reports Fourth Quarter and Full Year 2024 Financial Results and Provides Corporate Update

Reported positive interim pharmacokinetic ("PK") and safety data in Phase 1 trial of SPY001 in November 2024 and strengthened the balance sheet with a $230 million public offering

Continued execution towards expected milestones across portfolio, with interim Phase 1 data readouts for SPY002 and SPY003 on-track for the second quarter and second half of 2025, respectively

Remain on track for initiation of Phase 2 platform trial in ulcerative colitis ("UC") in mid-2025 with SPY001 (α4β7), followed by SPY002 (TL1A), SPY003 (IL-23), and combinations thereof, with initial monotherapy results expected in 2026

Announced indication expansion into rheumatoid arthritis ("RA") with SPY002, with expected Phase 2 trial initiation in mid-2025 and top-line results in 2026

$603 million of cash, cash equivalents, and marketable securities as of December 31, 2024, with expected runway into the second half of 2028

Waltham, Mass, February 27, 2025 - Spyre Therapeutics, Inc. ("Spyre" or the "Company") (NASDAQ:SYRE), a clinical-stage biotechnology company utilizing best-in-class antibody engineering, dose optimization, and rational therapeutic combinations to target improved efficacy and convenience in the treatment of inflammatory bowel disease ("IBD") and other immune-mediated diseases, today announced its fourth quarter and full year 2024 financial results and provided program and corporate updates.

“In 2024, we initiated first-in-human studies for three of our next-generation antibodies and delivered outstanding interim Phase 1 results for SPY001, which underscore our portfolio's potential to revolutionize the treatment of IBD. Looking ahead, we are progressing our suite of therapeutics into a groundbreaking Phase 2 platform study in ulcerative colitis, which is designed to test both monotherapies and combination therapies with the potential for unified quarterly subcutaneous dosing in maintenance," said Cameron Turtle, DPhil., Chief Executive Officer. "Additionally, the expansion of SPY002 into a Phase 2 rheumatoid arthritis trial this year represents a key step in addressing a pressing unmet need in a disease that affects millions across the globe. We are well-positioned and well-capitalized to deliver a series of value-inflecting catalysts, including three Phase 1 readouts expected in 2025 and four Phase 2 proof-of-concept readouts expected in 2026."

Development Pipeline Overview and Update

The Company's approach combines best-in-class antibody engineering, dose optimization, and rational therapeutic combinations with the goal of maximizing efficacy, safety, and convenience in the treatment of IBD and other immune-mediated diseases. IBD is a chronic condition characterized by inflammation within the gastrointestinal tract, including two main disorders: UC and Crohn's disease ("CD"). In the United States, it is estimated that approximately 2.4 million individuals are diagnosed with IBD. RA is a chronic inflammatory autoimmune condition that primarily affects the joints but also other parts of the body. It is characterized by pain, stiffness, and swelling of one or more joints and can progress from mild swelling of the joints in early stages to severe deformations of the feet, ankles, and hands in late/severe stages. RA affects more than 1.5 million individuals in the United States.

The Company has four programs in nonclinical and clinical development, three of which are targets in IBD validated by third parties. The fourth program is an undisclosed target. All three validated targets offer the potential for safe and effective treatment of UC and CD, with infrequent, subcutaneous maintenance dosing as a monotherapy or in rational combinations. The Company is also planning to study its anti-TL1A program in additional indications outside IBD, beginning with RA.

SPY001 – a highly potent and selective investigational monoclonal antibody targeting α4β7, engineered with half-life extension technology and formulated at high concentration with the goal of maximizing efficacy and enabling infrequent, subcutaneous maintenance dosing.

- In November 2024, interim healthy volunteer data from a Phase 1 trial were presented, demonstrating a favorable safety profile, a meaningfully differentiated PK profile relative to vedolizumab with half-life estimates greater than 90 days supporting potential Q6M maintenance dosing, and complete occupancy of α4β7 receptors out to 12 weeks at a single dose of 300mg.
- Longer-term data from this Phase 1 trial will be presented at a medical meeting later this year. Based on these interim results, Spyre plans to advance SPY001 to a Phase 2 clinical trial in UC patients in mid-2025.

SPY002 – a program with two highly potent and selective, investigational anti-TL1A monoclonal antibodies, engineered with half-life extension technology and formulated at high concentration with the goal of maximizing efficacy and enabling infrequent, subcutaneous maintenance dosing. The Company believes TL1A has emerged as one of the most promising targets in IBD and broader immunology indications.

- In January 2025, the Company announced its intent to study one of its anti-TL1A antibodies in RA, with Phase 2 trial initiation expected in mid-2025 and topline results in 2026. With class-leading potency and half-life established in preclinical studies, SPY002 has the potential to become the first-in-class and best-in-class anti-TL1A treatment for RA.
- In December 2024, the Company initiated first-in-human ("FIH") trials of both SPY002 candidates, with healthy volunteer interim data expected in the second quarter of 2025. If successful, the Company expects one or more SPY002 candidates would then advance to Phase 2 clinical trials.
- In October 2024, preclinical data for both SPY002 development candidates were presented at the United European Gastroenterology Week ("UEGW") Congress demonstrating superior or comparable in vitro potency to first-generation anti-TL1As, as well as a pharmacokinetic half-life of 24 days in non-human primates ("NHPs"), which represents a two to three-fold increase compared to these same first-generation anti-TL1As.

SPY003 – a highly potent and selective investigational monoclonal antibody targeting the p19 subunit of IL-23, engineered with half-life extension technology and formulated at high concentration with the goal of maximizing efficacy and enabling infrequent, subcutaneous maintenance dosing.

- In October 2024, preclinical data for SPY003 were presented for the first time at UEGW, demonstrating comparable potency to risankizumab, as well as a pharmacokinetic half-life of 30 days in NHPs, greater

than three-fold compared to risankizumab. These data also demonstrated that SPY003 exhibits high selectivity and affinity for IL-23 and potently inhibits downstream cellular signaling.
- SPY003 remains on track to initiate a FIH trial in the first quarter of 2025, with healthy volunteer interim data expected in the second half of 2025.

Rational Combinations – the Company plans to investigate combinations of our proprietary antibodies in nonclinical studies and clinical trials in order to evaluate whether combination therapy can potentially lead to best-in-class efficacy in IBD, with less frequent dosing.

- In February 2025, new preclinical data for SPY120 were presented at the 20th Congress of the European Crohn's and Colitis Organisation, demonstrating that the combined inhibition of TL1A and α4β7 is superior to either monotherapy in mouse models of colitis and that coadministration of SPY001 and SPY002 demonstrated no drug effects on PK in NHPs.
- In October 2024, preclinical data for SPY130 and SPY230 were presented at UEGW, demonstrating enhanced efficacy and pharmacodynamics with SPY003 in combination with SPY001 and with SPY002.
- The Company expects to initiate a Phase 2 clinical trial in 2025 that is intended to include each of its rational combinations, as well as all three of its lead monotherapy programs.

Recent Corporate Updates

- In December 2024, Spyre was added to the Nasdaq Biotechnology Index.
- In November 2024, the Company raised $230 million in gross proceeds from a public offering of common stock with broad participation from both new and existing investors, extending cash runway into the second half of 2028.
- In October 2024, the Company announced the appointment of Sheldon Sloan, M.D., M. Bioethics, as Chief Medical Officer. Dr. Sloan's 25+ years of experience in both large pharmaceutical and small biotech companies, featuring an extensive track record of program leadership in the field of Inflammation and Immunology, will be invaluable to guide the Company as it advances its potentially best-in-class IBD portfolio.

Fourth Quarter 2024 Financial Results

Cash Position: As of December 31, 2024, Spyre had cash, cash equivalents, and marketable securities of $603.1 million. Net cash used in operating activities was $37.2 million for the fourth quarter of 2024. In November 2024, the Company raised $230 million in gross proceeds, before deducting $14.2 million in underwriting discounts, commissions, and other offering expenses, from a public offering of common stock.

Research and Development (R&D) expenses: R&D expenses totaled $50.5 million for the fourth quarter of 2024 and $33.7 million for the fourth quarter of 2023. The increase was primarily driven by nonclinical and clinical development, as well as manufacturing expenses, for the Company's pipeline candidates.

General and Administrative (G&A) expenses: G&A expenses totaled $10.8 million for the fourth quarter of 2024 and $14.1 million for the fourth quarter of 2023. The decrease was driven by higher stock compensation expense related to the Spyre acquisition in the fourth quarter of 2023.

Other income (expense): Other income totaled $5.0 million for the fourth quarter of 2024 primarily driven by interest earned on the Company's cash and marketable securities. For the fourth quarter of 2023, other expense totaled $17.3 million, primarily driven by an increase in the Company's CVR liability related to the increased likelihood of certain milestone payments related to pegzilarginase reimbursement in European markets, partially offset by interest earned on the Company's cash and marketable securities.

Net Loss: Net loss totaled $56.3 million and $63.2 million for the fourth quarters of 2024 and 2023, respectively, which includes non-cash stock compensation expense of $9.2 million and $17.3 million for the fourth quarters of 2024 and 2023, respectively.

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.

Safe Harbor / 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 future results of operations and financial position; its business strategy, including the Company's ability to successfully develop best-in-class and/or first-in-class therapeutics for IBD, RA, or other immune-mediated diseases that meaningfully improve both efficacy and convenience compared to today's standard of care; the SPY001 Phase 1 trial final data readouts not being consistent with or being different than the interim Phase 1 results; the sufficiency of the Company's funding to support the development of its assets, including expectations of cash runway extending into the second half of 2028; the length of time that the Company believes its existing cash resources will fund its operations; estimated market sizes and potential growth opportunities; its nonclinical and future clinical development activities; clinical trial designs and related regulatory feedback; further clinical evaluation of therapeutic combinations; the potential efficacy, tolerability, convenience, commercial viability and safety profile of its product candidates, including in combinations; the planned dosing regimen for SPY001 and our other product candidates, including the potential for a Q6M dosing profile; the potential therapeutic benefits and economic value of its product candidates as monotherapies or in combinations and their extended half-life; the timing for initiation of nonclinical studies and clinical trials, including the commencement of FIH and Phase 2 trials; and the planned expansion of SPY002 into RA, including timing thereof. 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 are subject to a number of risks, uncertainties and assumptions, including the expected or potential impact of macroeconomic conditions, including U.S. elections inflationary pressures, rising interest rates, general economic slowdown or a recession, changes in monetary policy, the prospect of a shutdown of the U.S. federal government, volatile market conditions, financial institution instability, as well as geopolitical instability, including the ongoing military conflict in Ukraine, conflict in Israel and surrounding areas, and geopolitical tensions in China on the Company's operations, the potential impacts of the BIOSECURE Act bill if passed into law and those risks described in the Company’s Quarterly Reports on Form 10-Q, Annual Reports on Form 10-K, as well as in other filings and reports that the Company makes from time to time with the Securities and Exchange Commission. Moreover, the Company operates in a very competitive and rapidly changing environment, and new risks emerge from time to time. It is not possible for the Company’s management to predict all risks, nor can the Company assess the impact of all factors on the business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements it may make. In light of these risks, uncertainties, and assumptions, the forward-looking events and circumstances discussed in this press release may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements.

You should not rely upon forward-looking statements as predictions of future events. Although the Company believes that the expectations reflected in the forward-looking statements are reasonable, the Company cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur. The Company undertakes no obligation to update publicly any forward-looking statement for any reason after the date of this press release to conform these statements to actual results, to reflect changes in the Company's expectations, or otherwise, except as required by law. You should read press release with the understanding that the Company's actual results, levels of activity, performance, events, outcomes, and the timing of results and outcomes, and other circumstances may be materially different from what the Company expects.

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Spyre Therapeutics, Inc.
Consolidated Balance Sheets
(Unaudited, in thousands, except share and per share amounts)

	December 31, 2024	December 31, 2023
ASSETS		
CURRENT ASSETS		
Cash and cash equivalents	$ 89,423	$ 188,893
Marketable securities	513,665	150,384
Prepaid expenses and other current assets	5,386	2,251
Total current assets	608,474	341,528
Restricted cash	—	322
Other non-current assets	10	9
TOTAL ASSETS	$ 608,484	$ 341,859
LIABILITIES AND STOCKHOLDERS' EQUITY		
CURRENT LIABILITIES		
Accounts payable	$ 666	$ 896
CVR liability	25,080	1,390
Accrued and other current liabilities	27,711	13,108
Related party accounts payable	603	16,584
Total current liabilities	54,060	31,978
Non-current CVR liability	36,620	41,310
TOTAL LIABILITIES	90,680	73,288
Commitments and Contingencies		
Series B non-voting convertible preferred stock, $0.0001 par value; 150,000 shares authorized, issued, and outstanding as of December 31, 2023.	—	84,555
STOCKHOLDERS' EQUITY		
Series A non-voting convertible preferred stock, $0.0001 par value; 1,086,341 shares authorized as of December 31, 2024 and December 31, 2023; 346,045 and 437,037 shares issued and outstanding as of December 31, 2024 and December 31, 2023, respectively.	146,425	184,927
Series B non-voting convertible preferred stock, $0.0001 par value; 271,625 shares authorized and 16,667 shares issued and outstanding as of December 31, 2024.	9,395	—
Preferred stock, $0.0001 par value; 8,642,034 shares and 8,763,659 shares authorized as of December 31, 2024 and December 31, 2023, respectively; no shares issued and outstanding as of December 31, 2024 and December 31, 2023.	—	—
Common stock, $0.0001 par value; 400,000,000 shares authorized as of December 31, 2024 and December 31, 2023; 60,257,023 shares and 36,057,109 shares issued and outstanding as of December 31, 2024 and December 31, 2023, respectively.	13	10
Additional paid-in capital	1,334,223	763,191
Accumulated other comprehensive income	180	302
Accumulated deficit	(972,432)	(764,414)
TOTAL STOCKHOLDERS' EQUITY	517,804	184,016
TOTAL LIABILITIES, CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY	$ 608,484	$ 341,859

Spyre Therapeutics, Inc.
Consolidated Statements of Operations
(Unaudited, in thousands, except share and per share amounts)

	Three Months Ended December 31,		Twelve Months Ended December 31,	
	2024	2023	2024	2023
Revenue:				
Development fee and royalty	$ —	$ —	$ —	$ 886
Total revenue	—	—	—	886
Operating expenses:				
Research and development [1]	50,482	33,682	162,790	89,504
General and administrative	10,771	14,072	45,776	39,946
Acquired in-process research and development	—	—	—	130,188
Gain on sale of in-process research and development asset	—	(1,840)	—	(16,449)
Total operating expenses	61,253	45,914	208,566	243,189
Loss from operations	(61,253)	(45,914)	(208,566)	(242,303)
Other (expense) income:				
Interest income	5,776	4,126	21,312	6,147
Change in fair value of forward contract liability	—	—	—	(83,530)
Other (expense) income, net	(818)	(21,392)	(20,713)	(19,130)
Total other (expense) income	4,958	(17,266)	599	(96,513)
Loss before income tax expense	(56,295)	(63,180)	(207,967)	(338,816)
Income tax (expense) benefit	(1)	—	(51)	26
Net loss	$ (56,296)	$ (63,180)	$ (208,018)	$ (338,790)
Net loss per share, basic and diluted, Series A Preferred Stock	$ (32.28)	$ (49.17)	$ (127.21)	$ (550.28)
Weighted-average Series A non-voting convertible preferred stock outstanding, basic and diluted	346,045	860,495	374,387	434,612
Net loss per share, basic and diluted, Series B Preferred Stock	$ (32.28)	$ (49.18)	$ (127.21)	$ (550.29)
Weighted-average Series B non-voting convertible preferred stock outstanding, basic and diluted	16,667	34,239	85,208	8,630
Net loss per share, basic and diluted, common	$ (0.81)	$ (1.23)	$ (3.18)	$ (13.76)
Weighted-average common shares outstanding, basic and diluted	55,259,227	15,607,898	47,027,638	6,897,065

(1) Includes $6.1 million and $41.2 million in related party expenses for the three and twelve months ended December 31, 2024, respectively, and $27.7 million and $48.5 million related party expenses for the three and twelve months ended December 31, 2023, respectively.