UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

DIVISION OF
CORPORATION FINANCE

February 16, 2024

Cameron Turtle
Chief Executive Officer
Spyre Therapeutics, Inc.
221 Crescent Street
Building 23, Suite 105
Waltham, MA 02453

Re: Spyre Therapeutics, Inc.
Amendment No. 1 to Registration Statement on Form S-1
Filed February 5, 2024
File No. 333-276251

Dear Cameron Turtle:

We have reviewed your registration statement and have the following comments.

Please respond to this letter by amending your registration statement and providing the requested information. If you do not believe a comment applies to your facts and circumstances or do not believe an amendment is appropriate, please tell us why in your response.

After reviewing any amendment to your registration statement and the information you provide in response to this letter, we may have additional comments.

Amendment No. 1 to Registration Statement on Form S-1 filed February 5, 2024

Prospectus Summary
Company Overview, page 4

1. We note your response to prior comment 6. Please revise to address the part of that comment requesting certain balancing disclosures to be included in the Summary.

Risk Factor Summary, page 10

2. Please revise your summary risk factors to disclose, if true, that additional time may be required to obtain regulatory approval for your product candidates and future product candidates because of their status as combination therapies. In this regard, we note your disclosure on page 88 that the FDA indicated it intends to assess each potential combination on a case-by-case basis.

Our Relationship with Paragon and Parapyre, page 53

3. Please revise the last paragraph of this section to clarify how the provisions of the Papyre Option Obligation relate to the term of the Paragon Agreement. In this regard, we note based on your disclosure on page F-40 that the Parapyre Option Obligation provides for an annual equity grant of options for Parapyre to purchase 1% of the then outstanding shares of Spyre's common stock, on a fully diluted basis, on the last business day of each calendar year "during the term of the Paragon Agreement."

Business, page 73

4. In your Business section, please revise your disclosure where appropriate to:
   - Better explain the meaning of "complementary diagnostics" and explain how such term differs from "companion diagnostics," including with respect to the regulatory approval pathways.
   - Discuss the advantages and disadvantages of potentially using patient selection strategies based on development and use of a complementary diagnostic. Explain how your plan to develop and use a complementary diagnostic may impact your overall clinical development plan, including your clinical trial design and regulatory strategy, as well as your commercialization strategy, if ultimately approved.

Our Strategy, page 73

5. With respect to the patient selection and complementary diagnostics pillar of your development strategy, please revise in an appropriate place to explain what a genetic- or biomarker-based complementary diagnostic is, and how you plan to develop and use such complementary diagnostics to match treatment targets to IBD sub-populations to implement a precision immunology approach.

Our Combination Therapy Approach, page 74

6. You disclose that you plan to investigate combinations of your proprietary antibody therapies in preclinical studies in 2024 and in clinical studies beginning in 2025.
   - Please revise to clarify that commencement of clinical trials is subject to approval of an IND or equivalent foreign regulatory submission.
   - Further, you state that your preclinical studies and preclinical trials involving your combination therapies are expected to initially include SPY120. Please disclose when you plan to submit an IND or foreign regulatory submission for SPY120 or otherwise advise. Also, please make conforming revisions to the section captioned "SPY120 – combination anti-4ß7 and anti-TL1A mAbs" on page 79.

Our Portfolio, page 75

7. We note your response to prior comment 23. Your response letter and other disclosures suggest that SPY-003 and at least some of your combination product candidates are not currently material to your business given the early stage of discovery. With respect to SPY003, we note:

- Your disclosures regarding SPY003 are limited in comparison with your discussion of co-lead product candidates SPY001 and SPY002.
- Your disclosure on page 19 indicates that you are investing a majority of your efforts and financial resources into optioned co-lead product candidates SPY001 and SPY002.
- It appears that under the terms of the Paragon Agreement, (a) Paragon has granted you only a limited license to the antibody technology arising from the non-optioned research programs solely to evaluate the Option and for the purpose of allowing you to determine whether to exercise the Option with respect to each such program; and (b) unless and until you exercise the Option with respect to SPY003, the execution of a SPY003 License Agreement will not occur.
- You state in the response letter and on page 79 that (i) the Company is still in the process of narrowing down potential clones to select a development candidate for SPY003, which is not expected to occur until at least mid-2024, if at all; and (ii) the Company will not exercise the Option to acquire IP rights for the SPY003 program until after such candidate nomination occurs.

In addition to the foregoing, we note the following with respect to your combination product candidates:

- Your disclosures regarding your combination product programs remain limited in comparison with your discussion of co-lead product candidates SPY001 and SPY002.
- You disclose on page 79 that each of SPY130 and SPY230 include combination with non-optioned SPY003, for which no development candidate has been nominated.
- You disclose on page 74 that with respect to your combination therapies, your preclinical studies and clinical trials planned for 2024 and 2025, respectively, are expected to initially include SPY120, which combines optioned product candidates SPY001 and SPY002.

As such, please limit the product candidates and programs included in your pipeline table to those that are currently material to you and your operations, and for which you have exercised the Option to exclusively license all of Paragon's right, title, and interest in, including all intellectual property license rights thereto. Please remove the references to SPY003 and combination programs that include SPY003 from your pipeline table. We will not object to your discussion of your development plans for SPY003. SPY004, and your combination programs including SPY003 in the narrative discussion in the Business section.

SPY001 - anti-4ß7 mAb, page 76

8. You state on page 76: "The JDC is the decision-making body for SPY001 and our other pipeline programs prior to the execution of the SPY-001 License Agreement and we will control and lead the development process once the SPY001 License Agreement is executed." For the avoidance of doubt, please clarify whether you will control and lead the development process for each of SPY002, non-optioned programs SPY003 and

SPY004, and each of the combination programs once the SPY001 license agreement is executed, or otherwise revise.

9. We note your response to prior comment 26, which we reissue with respect to portions of the second bullet. In this subsection and in others as appropriate, please further revise your discussion of completed preclinical studies to disclose when preclinical studies were conducted, as well as the number of tests conducted in each study.

10. Please review and revise the Figures includes in this section to ensure that the text in each, including subscript or other notations, are clearly legible without need for magnification.

Notes to the Financial Statements
8. Paragon Agreement, page F-58

11. We acknowledge your response to comment 33. Please revise your disclosure on pages F-56 and F-59 to clarify that the $22.0 million is also upon the achievement of regulatory milestones as your current disclosure only refers to development and clinical milestones.

General

12. Please file the offer letter with Ms. King-Jones as an exhibit to the registration statement, or tell us why you believe it is not required to be filed.

We remind you that the company and its management are responsible for the accuracy and adequacy of their disclosures, notwithstanding any review, comments, action or absence of action by the staff.

Refer to Rules 460 and 461 regarding requests for acceleration. Please allow adequate time for us to review any amendment prior to the requested effective date of the registration statement.

Please contact Christine Torney at 202-551-3652 or Vanessa Robertson at 202-551-3649 if you have questions regarding comments on the financial statements and related matters. Please contact Lauren Sprague Hamill at 303-844-1008 or Jason Drory at 202-551-8342 with any other questions.

Sincerely,

Division of Corporation Finance
Office of Life Sciences

cc: Branden Berns