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

DIVISION OF
CORPORATION FINANCE

January 18, 2024

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

Re: Spyre Therapeutics, Inc.
Registration Statement on Form S-1
Filed December 22, 2023
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.

Registration Statement on Form S-1 filed December 22, 2023

Company Overview, page 4

1. On page 4 and in your Business section, please revise your disclosure to:
   - Disclose the meaning of "combinations of proprietary antibodies," "patient enrichment strategies," and "companion diagnostics;"
   - With reference to your disclosure on page F-58, explain how you plan to develop your portfolio of individual treatments to create therapeutic combination candidates, and clarify whether you plan to develop any of your candidates for use both as monotherapies and combination therapies;
   - Explain how you plan to develop and use each of patient enrichment strategies and companion diagnostics in your development strategy; and
   - Explain how your plan to use combination candidates and patient enrichment strategies via companion diagnostics may "enhance efficacy" in your programs. Further, please qualify your statements on pages 4, 49, and 66 to clarify that your

ability to execute your strategy to "enhance efficacy" is currently aspirational.

2. With respect to your strategy to use patient enrichment strategies via companion diagnostics:
   - Please disclose in an appropriate place in the Summary and Business sections whether you anticipate that any or all of your programs will require you to develop and obtain FDA approval of a companion diagnostic.
   - Include balancing disclosure regarding any material risks or challenges that the development and/or use of companion diagnostics might pose to your business and/or development strategy.

3. Please revise to qualify the following statement that appears on pages 4 and 66: "We have purposely engineered our product candidates to bind potently and selectively to target epitopes with extended half-lives." In this regard, we note your disclosure on page 48 indicating that potent binding and selectivity are "the aim" of your product engineering.

4. We note that your statement on page 17 that your success is "dependent on observing a longer half-life of your programs in humans than other mAbs currently marketed and in development" lacks sufficient context in the Summary and Business sections.
   - Please revise pages 4 and 66 to clearly describe your strategy to engineer "long-acting" product candidates that will exhibit extended pharmacokinetic half-lives.
   - In your revisions, please also specifically explain the meaning of the term "extended half-life" and how your focus on half-life extension relates to potential dosing convenience or otherwise advise.

5. We note your stated intention to deliver your product candidates through self-administered, subcutaneous injection via a pre-filled pen. Please revise your Summary and Business sections to disclose whether you anticipate that your product candidates may be regulated by the FDA as drug/device combination products. Explain the implications of drug/device combination product classification with respect to the regulatory approval process, including how this process differs from the process of obtaining FDA approval for drugs.

6. Please balance the discussion of your Company's development strategy and candidate programs by prominently highlighting in the Summary that:
   - the drug and/or device development process is inherently uncertain, your development approach is unproven, preclinical evidence to support your approach is preliminary and limited, and you have yet to test any product candidate in humans; and
   - there can be no guarantee that you will be able to develop product candidates that will be found to be safe and effective so as to obtain necessary regulatory approvals.

Risk Factor Summary, page 9

7. We note your stated plan to use patient enrichment strategies via companion diagnostics in

your product development. If material, please add summary risk and corresponding risk factor disclosure addressing the risks and challenges related to your proposed use of companion diagnostic tools needed to leverage your strategy.

8. Given your stated intention to deliver your product candidates through injection via a pre-filled pen, please add summary risk and corresponding risk factor disclosure discussing any risks or challenges related to the development and/or regulatory approval of your product candidates if the FDA may consider your product candidates to be drug/device combination products.

Risk Factors

We will need to raise additional capital..., page 11

9. On page 12, please remove the reference to being subject to the limitations set forth in Instruction I.B.6 of Form S-3, or otherwise advise.

We have historically incurred losses, have a limited operating history..., page 13

10. In the first sentence of the third paragraph, please revise to clarify whether the reference to "conducting clinical trials" pertains only to your legacy product candidates. In this regard, it appears from your disclosure throughout that all of your current programs are in preclinical stages of development and have not yet been tested in humans.

11. We note your disclosure that the holders of your Series B Preferred Stock may be entitled to require you to settle their shares of Series B Preferred Stock for cash at a price per share equal to the fair value of the Series B Preferred Stock, as described in your Series B Certificate of Designation. Please revise your disclosure to describe how the fair value is determined and quantify the aggregate amount of the potential cash redemption as of a recent date or otherwise advise.

Our Certificate of Incorporation provides that..., page 42

12. We note the exclusive forum provisions in your certificate of incorporation and bylaws. Please clarify whether these provisions apply to actions arising under the Securities Act or Exchange Act. In that regard, please note that while Section 27 of the Exchange Act creates exclusive federal jurisdiction over all suits brought to enforce any duty or liability created by the Exchange Act, Section 22 of the Securities Act creates concurrent jurisdiction for federal and state courts over all suits brought to enforce any duty or liability created by the Securities Act or the rules and regulations thereunder.

Our Relationship with Paragon and Parapyre, page 49

13. We note your disclosure describing the Parapyre Option Obligation, "which provided for an annual equity grant of options to purchase 1% of the then outstanding shares of Pre-Merger 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 ." Please update your disclosure

to clarify the term of the Paragon Agreement.

Research and Development Expenses, page 53

14. Please revise the disclosure to break out the dollar amount of external research and development expenses incurred for each period presented. Alternatively, disaggregate research and development expenses by nature or type of expense for each period presented .

Management's Discussion and Analysis of Financial Condition and Results of Operations
Future Funding Requirements and Operational Plan, page 59

15. Please update the final paragraph in this section consistent with your disclosure in the "Recent Developments" section and elsewhere regarding shareholder approval of the conversion of your Series A Preferred Stock. In addition, please update your "Recent Developments" section to discuss the December 2023 SPA for Series B Preferred Stock.

Contractual Obligations and Other Commitments, page 63

16. You state here and on page 66 that as of the date of this prospectus, the Option remains unexercised with respect to three research programs under the Paragon Agreement.
    - Such disclosures are inconsistent with statements on pages 17, 49, and 116 indicating that you exercised your Option for the PSY001 and SPY002 programs in July 2023 and December 2023, respectively, and the remaining two options for the SPY003 and SPY004 programs remain outstanding. Please reconcile or advise.
    - Also, please update this section as appropriate to clarify the current status of your expected obligations under the Paragon Agreement based on your exercise of the Option to date.

Management's Discussion and Analysis of Financial Condition and Results of Operations
Contractual Obligations and Other Commitments, page 63

17. You disclose that as of the date of the filing of this prospectus, the Option remains unexercised with respect to the three remaining research programs under the Paragon Agreement. However, on pages 48 and 49 you disclose that in December 2023 you exercised the Option for the SPY002 program. Please clarify.

Business
Company Overview, page 66

18. We note your disclosure "[f]or more information on the Paragon Agreement, see discussion under the heading “*Paragon Agreement*” below." However, we are unable to locate the heading. Please revise your disclosure to describe all the material terms of the Paragon Agreement as amended.

Our Strategy, page 66

19. We note your statements on pages 66 and 67 that your antibodies have "best-in-class" potential. Given the development stage of your programs and length of the drug approval process, it is premature and inappropriate to speculate or imply that any Spyre product candidates will ultimately be approved or become best-in-class. Please remove these statements and any similar statements throughout.

20. Please revise in an appropriate place to explain what a genetic- or biomarker-based companion diagnostic is, and how you plan to develop and use such companion diagnostics to match treatment targets to IBD sub-populations.

21. With respect to the half-life extension pillar of your development strategy, please revise your Business section in the appropriate place(s) to:
    - explain the basic operation of half-life extension technologies including YTE and LS amino acid substitutions, and describe your efforts to develop programs using such technologies, as mentioned on page 18;
    - explain how your focus on half-life extension/optimization has the potential to confer a more favorable dosing schedule for your programs, assuming they successfully complete clinical development; and
    - if material, describe the non-human primate study referenced on page 18, including quantitative information regarding the range of results observed regarding the increased half-life properties of your programs or otherwise.

Our Portfolio, page 67

22. Please remove or revise your statement that you are advancing a "broad pipeline" of antibodies for the treatment of IBD, or advise. In this regard, we note your disclosure that you are initially focused and substantially dependent on the success of the SPY001 and SPY002 programs that each address IBD. We also refer to disclosure on page F-36 stating that the Company determined that the pipeline candidates within its portfolio are "similar in nature."

23. We note the inclusion of SPY003, SPY004 and combination programs SPY120, SPY130 and SPY230 in your pipeline table. In this regard:
    - It is seemingly premature to highlight the SPY003 and SPY004 programs in the pipeline table given your disclosure that you are investing a majority of your efforts and financial resources into optioned co-lead programs SPY001 and SPY002, disclosure that you have not exercised the Option with respect to SPY003 and SPY004, and your limited disclosures regarding SPY003 and SPY004 in the registration statement. Please remove SPY003 and SPY004 from the table, or explain why these programs are currently material to your business so as to warrant inclusion therein.
    - It is also seemingly premature to highlight your combination programs in the pipeline table given that your individual programs appear to be in early preclinical stages, certain of your combination programs purport to involve combination

with SPY003 (IL-23) which you have not yet exercised the Option on, and you have provided only limited disclosures regarding your combination programs in the registration statement. Please remove your combination programs from the pipeline table or advise as to the materiality of each such program.

Please note that we do not object to your narrative discussion of SPY003, SPY004, and your combination programs in the Business section.

24. Please also revise the pipeline table on page 67 as follows:
- Disclose the indication for which you are currently developing each program.
- Disclose whether you have nominated a development candidate for each program.
- Revise the columns so they are clearly delineated from each other. Include columns of equal width for each of Phase 1, Phase 2 and Phase 3 of clinical testing.
- The table should not be used to prematurely project or imply successful completion of the stages required prior to regulatory approval. To the extent that you disclose the next anticipated milestone for a candidate in the table, only provide the next material step in the regulatory review process (e.g., development candidate nomination, intended timing of IND submissions, etc.). The narrative discussion following the pipeline table is more appropriate for discussing aspirational plans for your product candidates beyond the immediate next step, such as expected interim data from any future Phase 1 trials.
- Ensure the font and type used is clearly legible. For example only, we note that the information currently presented under the column titled "Clinical" is not clearly readable even with enhanced pixelation.
- With respect to footnote 1 to the table, revise to explain that the SPY001 and SPY002 License Agreements are still being finalized and clarify the expected timing for entering into these agreements.

25. In the narrative discussion following the pipeline table, you discuss the potential timing of Phase 1 clinical trials of SPY001 and SPY002 without addressing the necessary submission of INDs to the FDA. For each of SPY001 and SPY002, clarify when you plan to submit an IND and specify the indication(s) to be covered.

26. Please expand your narrative disclosure following the pipeline table to provide a more fulsome discussion of each of your individual and combination programs and clarify the status of development activities to date. In your revisions, please:
- Clarify your role and involvement in completed or ongoing development efforts, as well as that of your research partners.
- Include descriptions of material preclinical studies conducted to date or in-process, including who conducted such studies and when, the number of tests conducted, and the number of animal subjects used in each test. Include quantitative information regarding the range of results observed.
- Clearly describe the remaining material steps to be completed for each program before advancing that program into the clinic (e.g., product candidate nomination, regulatory submissions, etc.) and the remaining clinical steps to be taken to develop

and commercialize your product candidates.

27. Provide the basis for all statements regarding your program observations. By way of example only, we note your statements that SPY001 and SPY002 are "highly potent, highly selective" antibodies and that SPY002 lead clones "exhibit extended pharmacokinetic half-lives relative to competitive molecules in clinical development." Include clarifying disclosure that your preliminary study results are not based on head-to-head studies but rather on your preclinical models.

SPY003 - anti-IL-23 mAb, page 68

28. Please revise the reference on page 68 to SPY003 as "[your] third program" in light of your other disclosure indicating that your Option to acquire intellectual property license rights related to the SPY003 and SPY004 programs remains unexercised. Alternatively, please clearly highlight in this section and the section captioned "SPY004" that while you hold the Option to acquire intellectual property license rights related to the SPY003 and SPY004 programs, such Option remains unexercised.

Our Precision Immunology Approach, page 69

29. You state that you are in discussions with potential partners with access to large scale IBD biobanks to support CDx development across your portfolio.
    - Please revise to define "CDx development;" and
    - Briefly explain how you plan to work with potential partners to leverage biobank access in support of the precision immunology pillar of your development strategy.

Government Regulation, page 71

30. As appropriate, please revise this discussion to include a description of the regulation of drug/device combination products and companion diagnostics, or advise.

Executive Officers, page 97

31. We note that the table on page 97 appears to reflect that as of December 11, 2023, Dr. Turtle serves as your Chief Operating Officer. However, disclosure elsewhere indicates that on November 22, 2023, Dr. Turtle was promoted from COO to Chief Executive Officer. Please update your disclosure as appropriate, or advise.

Certain Relationships and Related Transactions, page 115

32. Please revise your disclosure under the first bullet on page 116 to disclose and quantify all material payments you expect to be obligated to pay Paragon upon and following the execution of the SPY001 License Agreement and SPY002 License Agreement, which you state on page 48 are currently being finalized on previously agreed terms. In this regard, we refer you to page F-59, which references expected fees for the nomination of development candidates and milestone payments upon the first dosing of a human patient

in a Phase 1 trial.

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

33. With regards to the SPY001 License Agreement, the disclosure refers to specific development and clinical milestone payments totaling $22 million. However, on page 63 you disclose that the $22 million is based on specific clinical and regulatory milestones. Please clarify the nature of these potential milestone payments

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 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