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July 18, 2024

Division of Corporation Finance
Office of Life Sciences
United States Securities and Exchange Commission
100 F Street, NE
Washington, D.C. 20549
Attention: Chris Edwards, Jimmy McNamara, Kevin Kuhar and Franklin Wyman

Re: Upstream Bio, Inc.
Draft Registration Statement on Form S-1
Submitted June 12, 2024
CIK No. 0002022626

Dear Ladies and Gentlemen:

This letter is confidentially submitted on behalf of Upstream Bio, Inc. (the "Company") in response to the comments of the staff of the Division of Corporation Finance (the "Staff") of the Securities and Exchange Commission with respect to the Company's Draft Registration Statement on Form S-1 submitted on June 12, 2024 (the "Draft Registration Statement"), as set forth in your letter dated July 9, 2024 addressed to E. Rand Sutherland, Chief Executive Officer of the Company (the "Comment Letter"). The Company is concurrently confidentially submitting Amendment No. 1 to the Draft Registration Statement (the "Amended Draft Registration Statement"), which includes changes that reflect responses to the Staff's comments and other updates.

For reference purposes, the text of the Comment Letter has been reproduced herein with responses below each numbered comment. For your convenience, we have italicized the reproduced Staff comments from the Comment Letter. Unless otherwise indicated, page references in the descriptions of the Staff's comments refer to the Draft Registration Statement, and page references in the responses refer to the Amended Draft Registration Statement. All capitalized terms used and not otherwise defined herein shall have the meanings set forth in the Amended Draft Registration Statement.

The responses provided herein are based upon information provided to Goodwin Procter LLP by the Company. In addition to submitting this letter via EDGAR, we are sending this letter and the Amended Draft Registration Statement (marked to show changes from the Draft Registration Statement) via email.

Prospectus Summary
Overview, page 1

1. *We note your disclosure here, and throughout the prospectus, that verekitug is a "first-in-class antagonist." This term suggests that your product candidate is effective and likely to be approved. Please revise to delete such references throughout your registration statement.*

   RESPONSE: The Company respectfully acknowledges the Staff's comment and directs the Staff to its response to Comment 6 below. Based on the Company's reasonable diligence to date, as described in Comment 6 below, verekitug is the only monoclonal antibody currently in clinical development that targets and inhibits the TSLP receptor, supporting the Company's statement that verekitug is a "first-in-class antagonist of the receptor for TSLP." The Company respectfully disagrees with the Staff's comment that this term suggests effectiveness or likelihood of approval, as it simply means it is the only publicly known antagonist of the receptor for TSLP. The Company also respectfully directs the Staff to the balancing disclosure on pages 7 and 28 that this unique mechanism of action makes it difficult to predict verekitug's likelihood of success and the timing and cost of development and obtaining regulatory approval.

2. *We note your disclosures relating to the regulatory approvals and commercial successes of other companies. Please provide balancing disclosure, as you do on page 36, that such companies may have significantly greater financial resources and expertise such that they may be more successful than you in obtaining regulatory approvals and achieving widespread market acceptance.*

   RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on page 7.

3. *Please clarify, if true, that the $6 to $10 billion estimation refers to global annual peak sales, or otherwise advise and please provide balancing disclosure that you do not have a COPD product in development.*

   RESPONSE: The Company respectfully acknowledges the Staff's comment and directs the Staff to the revised disclosure on pages 1, 115 and 131, which clarifies that the $6 to $10 billion estimation refers to annual peak sales in the United States. The Company also respectfully advises the Staff that it has revised the disclosure on pages 2, 5, 116, 119, 120, 145 and 146 regarding the initiation of development efforts in COPD and directs the Staff to its response to Comment 10 below.

4. *We note your disclosures on page 2, and elsewhere, regarding comparing your product candidate to tezepelumab and dupilumab. Please disclose here, and in the Business section, whether such observations were based on head-to-head trials. In this regard, we note your disclosure on page 35 that "[i]n most cases, [you] do not currently plan to run head-to-head clinical trials evaluating verekitug or any other potential future product candidates against the current standards of care, which may make it more challenging for verekitug or any other potential future product candidates to compete against the current standards of care due to the lack of head-to-head clinical trial data."*

   RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 2, 115, 132, 143 and 144. The Company further respectfully advises the Staff that it does not believe head-to-head clinical trials are necessary to support the development of verekitug, as regulatory authorities would not typically require such a trial to establish the safety and efficacy of a new biologic product.

5. *With respect to the data and observations based on preclinical and clinical trials disclosed in the summary, including those sponsored by others, please disclose whether serious adverse events were observed.*

   RESPONSE: The Company respectfully acknowledges the Staff's comment and directs the Staff to the disclosure starting on page 134 that there was one subject in Cohort D of the Phase 1 SAD clinical trial who experienced a serious treatment-emergent adverse event, nephrolithiasis, which was deemed not related to the study drug by the investigator. No other serious adverse events have been observed by the Company or a third party throughout verekitug's clinical development. Furthermore, the Company respectfully advises the Staff that adverse events, by definition, are occurrences in human subjects in clinical trials, and are not observed in preclinical studies.

6. *Please explain how you determined on page 2 that verekitug is the only monoclonal antibody currently in clinical development that targets and inhibits the TSLP receptor.*

   RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it explored numerous sources, including an industry standard market intelligence database, company press releases and clinicaltrials.gov listings, to gain an understanding of the competitive landscape for product candidates in clinical development involving the TSLP receptor. Based on such evaluation, to our knowledge, verekitug is the only monoclonal antibody currently in clinical development that targets and inhibits the TSLP receptor.

7. *We note that you describe the Phase 2 trial as "pivotal." Please clarify what you mean by pivotal in this instance.*

   RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 2, 5, 116, 119, 120 and 145.

8. *Please define "FPI" in the pipeline table on page 2 and revise the footnote to the table to explain the activities that need to be completed in order to initiate development in COPD.*

   RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the pipeline table appearing on pages 2 and 116 to indicate that development in COPD has been initiated.

TSLP Overview, page 3

9. *We note your statement that you believe verekitug has the potential to be an impactful treatment due to its high potency, extended dosing interval and ability to address unmet needs in multiple diseases characterized by TSLP-driven pathobiology. Please revise to remove these and similar statements, as efficacy determinations are within the sole jurisdiction of the FDA and other similar foreign regulators. You may include information regarding data observed in studies and trials but may not include the company's conclusions based on such data.*

   RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 3 and 117 to clarify that the Company's beliefs about the potential of verekitug are based on preclinical and clinical data observed to date, rather than determinations that have been made by the FDA or similar foreign regulators.

Verekitug: Inhibiting TSLP signaling in severe asthma, CRSwNP and COPD, page 4

10. *Please disclose when you plan to initiate clinical development in COPD.*

    RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 2, 5, 116, 119, 120 and 146.

11. *We note your disclosures regarding results from preclinical and clinical trials demonstrating that verekitug inhibited TSLP signaling, inhibited cytokine production from CD4+ T cells, and demonstrated "rapid, substantial and sustained target engagement" and maintained "maximal inhibition of disease-related biomarkers" in patients with asthma. Please disclose whether such results are statistically significant, or otherwise advise.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff the goal of preclinical studies, among other things, is to assess the biological effect a drug may have in animals and pharmacology models, and thus to predict responses in human patients and identify potential toxicities. As such, these preclinical studies were designed to model and observe these factors, rather than to achieve statistical significance. In addition, the Company respectfully advises the Staff that the Phase 1 SAD and MAD clinical trials were designed as "signal seeking" trials, and not based on a formal statistical hypothesis to achieve statistical significance. The Company has revised its disclosure on pages 2, 4, 5, 116, 118, 131, 133 and 144 to clarify that its preclinical studies and clinical trials completed to date were not designed to support formal statistical comparisons. Furthermore, the Company respectfully advises the Staff that subsequent clinical trials in humans may be designed for statistical significance and that it will report the details of such clinical trials as applicable.

12. *Please disclose the number of volunteers for the Phase 1 SAD trial and Phase 1b MAD trial.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on page 5. The Company also respectfully directs the Staff to the Phase 1 SAD and MAD clinical trial designs described on pages 134 and 137, respectively.

Our Team and Investors, page 5

13. *We note your disclosure on page 6 that you have raised approximately $400 million from "premier biotechnology investors." Please provide balancing disclosure that prospective investors should not rely on such investors' investment decisions, that these investors may have different risk tolerances and that the shares purchased in the referenced financings may have been conducted at a significant discount to the IPO price, if true.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 6 and 119.

Management's Discussion and Analysis of Financial Condition and Results of Operations Critical Accounting Estimates and Significant Judgments Stock-based compensation, page 109

14. *Once you have an estimated offering price range, please explain to us the reasons for any differences between recent valuations of your common stock leading up to the planned offering and the midpoint of your estimated offering price range. This information will facilitate our review of your accounting for stock compensation.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and will supplementally provide the requested information once the estimated offering price range has been determined.

Business
The role of TSLP in severe asthma, CRSwNP, COPD and related inflammatory diseases, page 121

15. *Please revise Figure 2 on page 122 to clarify the diseases you are planning to target with your drug candidate.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised Figure 2 appearing on page 123.

Biologic therapies for severe asthma, page 124

16. *We note your disclosure that the clinical and regulatory progress of tezepelumab represents a "significant derisking" for your own development program. Please remove this statement and any other statements that imply that you will be successful in mitigating risk associated with drug development.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on page 125.

Preclinical Data
Target engagement and inhibition, page 132

17. *With respect to the preclinical studies, please disclose, if true, that Astellas conducted such studies, or otherwise advise. In addition, please disclose if the results were statistically significant, and any observed serious adverse events.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on page 133. The Company also respectfully directs the Staff to the disclosure on pages 4, 118 and 134 stating that the preclinical studies and Phase 1 SAD trial were conducted by Astellas. The Company respectfully acknowledges the Staff's request to disclose whether the results were statistically significant and whether there were any observed serious adverse events, and directs the Staff to its above responses to Comment 11 and Comment 5, respectively.

Phase 1 SAD clinical trial safety and tolerability data, page 135

18. *Please ensure the superscripts are legible in the graphic.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised Figure 8 appearing on page 135.

Ongoing and planned clinical trials, page 143

19. *Please disclose the number of patients enrolled to date in the VIBRANT and VALIANT trial.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and directs the Staff to the disclosure on page 145 stating the estimated number of patients that the Company expects to enroll in each trial. Due to the competitive landscape in which the Company is operating and other ongoing clinical trials in the indications in which the Company is developing its product candidate, the number of patients enrolled to date is highly confidential information and subject to change over time, and as such, the Company does not plan to include this disclosure in its future public filings. The projected timing for announcement of top-line data reflects the Company's assessment of current enrollment status and the time needed for patients to complete the assessments in each trial. Accordingly, the Company has revised the disclosure on page 145 to clarify the basis for the projected top-line data readouts for the VIBRANT and VALIANT trials.

COPD, page 144

20. *Please clarify whether the "additional endpoints" will be primary or secondary, or otherwise advise.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on page 146.

Intellectual Property, page 146

21. *We note your disclosures relating to your owned patent families. We also note your disclosure on page 149 regarding licensing certain intellectual property from Lonza. Please disclose, if material, whether you license any patents. To the extent you do, please disclose the type of patent protection (e.g., composition of matter, use, or process), the patent expiration dates, and the applicable jurisdictions. In addition, please clarify what indications the Lonza license covers.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that the Lonza License Agreement does not include a license of patents that it considers to be material to its business or pipeline and as such, the current disclosure starting on page 147 remains accurate and complete. The material intellectual property rights licensed from Lonza under the Lonza License Agreement relate to manufacturing know-how that is not specific to an indication.

Asset purchase and license agreements, page 148

22. *With respect to the Maruho and Lonza license agreements, please disclose the payments received or made to date, any expiration dates, and any potential development, regulatory and commercial milestone payments.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 98, 107, 150 and 151 to include all payments received or made to date under the Maruho License Agreement and Lonza License Agreement, as applicable. The license granted to the Company under each agreement does not have a specified expiration date. In addition, the Company respectfully directs the Staff to its disclosure starting on page 149 discussing the Company's obligation to develop the Maruho License Product for use in Japan, which will result in development and regulatory expenses to be reimbursed by Maruho, and describing the royalty payments due to Lonza under the Lonza License Agreement. There are no other potential development, regulatory or commercial milestone payments under the Maruho License Agreement or Lonza License Agreement that are not described in the Amended Draft Registration Statement.

Executive Compensation
Executive compensation arrangements, page 185

23. *We note your disclosure that you have entered into employment agreements with each of your named executive officers. Please describe the material terms of such agreements with your current CEO and CFO. In addition, please file the employment or offer letter agreements with your executive officers as exhibits pursuant to Item 601(b)(10) of Regulation S-K or tell us why you believe such filing is not required.*

RESPONSE: The Company acknowledges the Staff's request to file the employment or offer letter agreements with its executive officers as exhibits, and respectfully advises the Staff that prior to effectiveness of the registration statement, the Company intends to enter into new employment agreements with its executive officers that supersede and replace their existing offer letters in all respects. The Company undertakes to update the registration statement to include appropriate disclosure regarding these new employment agreements in the Executive Compensation section as requested, and to file such agreements, pursuant to Item 601(b)(10), prior to the effectiveness of the registration statement.

Certain relationships and related party transactions, page 195

24. *We note your disclosure on page 95 that Maruho, for which you have an exclusive license agreement, is a related party. We also note on page 175 that Atsushi Sugita, who has served on your Board of Directors since 2021, is also the President and CEO of Maruho. Please disclose any related party transactions under Item 404(a) of Regulation SK or otherwise advise. Also, please tell us whether any other officers, directors or principal shareholders are affiliated with Maruho. Finally, please provide, if material, corresponding risk factor disclosure.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised page 201 to disclose the Maruho License Agreement as a related party transaction. Other than Mr. Sugita, no officers, directors or principal shareholders of the Company are affiliated with Maruho.

The Company respectfully directs the Staff to the risk factors entitled "*Our existing research and development arrangement as well as any future collaborations with third parties for the development and commercialization of verekitug or any other potential future product candidates may not be successful, which could adversely affect our ability to advance verekitug or any other potential future product candidates*" starting on page 42, discussing risks associated with the Maruho License Agreement and similar potential future arrangements and collaborations, and "*Our executive officers, directors, principal stockholders and their respective affiliates own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval*" appearing on page 74, discussing risks associated with the influence of its directors, officers and principal stockholders. The Company respectfully advises the Staff that there are no additional material risks associated with the Maruho License Agreement due to Maruho's status as a related party or Mr. Sugita's affiliation with Maruho that are not described in the Amended Draft Registration Statement.

General

25. *Please supplementally provide us with copies of all written communications, as defined in Rule 405 under the Securities Act, that you, or anyone authorized to do so on your behalf, present to potential investors in reliance on Section 5(d) of the Securities Act, whether or not they retain copies of the communications.*

RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that the Company will undertake to provide the Staff with any such written communications that the Company, or any authorized to do so on behalf of the Company, has presented or will present to potential investors in reliance on Section 5(d) of the Securities Act.

If you should have any questions concerning the enclosed matters, please contact the undersigned at (617) 570-1329.

Sincerely,

/s/ Gabriela Morales-Rivera
Gabriela Morales-Rivera, Esq.

cc: E. Rand Sutherland, M.D., M.P.H., *Upstream Bio, Inc.*
Michael Paul Gray, M.B.A., *Upstream Bio, Inc.*
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