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

DIVISION OF
CORPORATION FINANCE

July 9, 2024

E. Rand Sutherland
Chief Executive Officer
Upstream Bio, Inc.
460 Totten Pond Road, Suite 420
Waltham, MA 02451

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

Dear E. Rand Sutherland:

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

Please respond to this letter by providing the requested information and either submitting an amended draft registration statement or publicly filing your registration statement on EDGAR. 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 the information you provide in response to this letter and your amended draft registration statement or filed registration statement, we may have additional comments.

Draft Registration Statement on Form S-1

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.
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.
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.

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.”

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.

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.

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

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.

TSLP Overview, page 3

9. We note you 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.

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

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

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.

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

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.

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.

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.

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.

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.

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

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

Ongoing and planned clinical trials, page 143

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

COPD, page 144

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

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.

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.

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.

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 S-K 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.

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.

Please contact Franklin Wyman at 202-551-3660 or Kevin Kuhar at 202-551-3662 if you have questions regarding comments on the financial statements and related matters. Please contact Jimmy McNamara at 202-551-7349 or Chris Edwards at 202-551-6761 with any other questions.

Sincerely,

Division of Corporation Finance
Office of Life Sciences