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September 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.
Amendment No. 2 to Draft Registration Statement on Form S-1
Submitted August 9, 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 comment 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 originally confidentially submitted on June 12, 2024 and resubmitted on July 18, 2024 and August 9, 2024 (the "Draft Registration Statement"), as set forth in your letter dated August 20, 2024 addressed to E. Rand Sutherland, Chief Executive Officer of the Company (the "Comment Letter"). The Company is concurrently publicly filing the Registration Statement on Form S-1 (the "Registration Statement"), which includes changes that reflect its response to the Staff's comment and other updates.

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

The responses provided herein are based upon information provided to Goodwin Procter LLP by the Company.

Prospectus Summary
Overview, page 1

1. *We note your response to comment 5. Please disclose and quantify any SAEs with respect to the referenced trials for tezepelumab. In addition, please briefly describe interleukin ("IL")-4 receptor alpha antagonist and how this differs from your approach targeting the TSLP pathway.*

   RESPONSE: The Company respectfully acknowledges the Staff's comment and advises the Staff that it has revised the disclosure on pages 2, 3, 119, 121, 130, 135 and 136 with respect to the Staff's request to disclose and quantify SAEs with respect to the referenced trials for tezepelumab. The Company respectfully advises the Staff that tezepelumab (marketed as Tezspire) has been approved by the FDA in severe asthma. In connection with its approval of the drug, the FDA reviewed pooled safety data from the clinical trials of tezepelumab and determined the most notable adverse reactions to be identified on the drug label. In lieu of SAE data from the clinical trials of tezepelumab for severe asthma, the Company has revised its disclosure on pages 121 and 130 to list the potential adverse reactions identified on the FDA-approved Tezspire label, which it believes is the most appropriate source for safety and tolerability information related to tezepelumab in severe asthma patients.

With respect to the Phase 2a proof-of-concept trial of tezepelumab in COPD patients, publicly available data only provides that the SAE profile observed was consistent with that observed in severe asthma trials. To address the Staff's concerns, the Company has disclosed the publicly available adverse events data from this trial on pages 3, 121 and 135. Additionally, to address the Staff's concern, the Company has added disclosure on pages 2, 119 and 136 to highlight the risk that ongoing and future clinical trials of verekitug may result in different clinical activity and tolerability observations.

With respect to the second part of the Staff's comment, the Company has revised its disclosure on pages 1, 2, 119, 124 and 136 to delete references to dupilumab because dupilumab has a different mechanism of action than verekitug and tezepelumab. Dupilumab blocks IL-4 and IL-13, which occur later in the signaling cascade relevant to inflammation. The Company respectfully directs the Staff to Figure 1 on page 126 and the disclosure starting on page 125, which provides an overview of the TSLP signaling pathway and illustrates the later pathways targeted by biologics such as dupilumab.

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.*
William D. Collins, Esq., *Goodwin Procter LLP*

Kathryn W. Clerici, Esq., *Goodwin Procter LLP*
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Charles S. Kim, Esq., *Cooley LLP*