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

DIVISION OF
CORPORATION FINANCE

July 25, 2024

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

Re: Upstream Bio, Inc.
Amendment No. 1 to Draft Registration Statement on Form S-1
Submitted July 18, 2024
CIK No. 0002022626

Dear E. Rand Sutherland:

We have reviewed your amended 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. Unless we note otherwise, any references to prior comments are to comments in our July 9, 2024 letter.

Amendment No. 1 to Draft Registration Statement on Form S-1

Prospectus Summary
Overview, page 1

1. We note your response to comment 1 and re-issue. Please revise to delete references to verekitug being a “first-in-class antagonist” throughout your registration statement.
2. Please tell us the basis or source for the statement that tezepelumab is projected to reach over $3.0 billion in peak global annual sales for severe asthma alone.
3. We note your response to comment 2 and re-issue. Please include the balancing disclosure in the Overview section that the referenced 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.

4. We note your response to comment 6 in which you state that the Company's due diligence has allowed you to conclude that "verekitug is the only monoclonal antibody currently in clinical development that targets and inhibits the TSLP receptor". In light of your due diligence, please tell us why this statement is true given that public records indicate that Uniquity Bio's solritug, a monoclonal antibody targeting TSLP, has completed phase 1 trials.

5. We note your response to comment 5 and re-issue in part. With respect to the references to clinical trials conducted by other companies, please disclose whether serious adverse events were observed.

Business
Ongoing and planned clinical trials, page 145

6. We note your response to comment 19. Currently the progress arrow representing the indications for severe asthma and CRSwNP shows that the Phase 2 trials are more than halfway finished, but that patient enrollment is ongoing and has not yet been completed. Please tell us, with a view toward disclosure, why this represents an accurate depiction of the Phase 2 trials or alternatively, please revise to reduce the length of the progress arrow to accurately reflect the actual status of your pipeline candidate as of the latest practicable date.

Asset purchase and license agreements
License agreement with Lonza, page 151

7. We note your response to comment 22 and re-issue in part. Please disclose, if true, in the prospectus that the Lonza agreement is perpetual, or otherwise advise.

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

cc: Gabriela Morales-Rivera