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

SCHEDULE 13D

Under the Securities Exchange Act of 1934

Upstream Bio, Inc.

(Name of Issuer)

Common Stock

(Title of Class of Securities)

91678A107

(CUSIP Number)

**OrbiMed Advisors LLC
OrbiMed Capital GP VIII LLC
OrbiMed Israel GP II, L.P.
OrbiMed Advisors Israel II Limited**

**601 Lexington Avenue, 54th Floor
New York, NY 10022
Telephone: (212) 739-6400**

(Name, Address and Telephone Number of Person Authorized to
Receive Notices and Communications)

October 15, 2024

(Date of Event which Requires Filing of this Statement)

If the filing person has previously filed a statement on Schedule 13G to report the acquisition that is the subject of this Schedule 13D, and is filing this schedule because of §§240.13d-1(e), 240.13d-1(f) or 240.13d-1(g), check the following box.

Note: Schedules filed in paper format shall include a signed original and five copies of the schedule, including all exhibits. See §240.13d-7(b) for other parties to whom copies are to be sent.

* The remainder of this cover page shall be filled out for a Reporting Person's initial filing on this form with respect to the subject class of securities, and for any subsequent amendment containing information which would alter disclosures provided in a prior cover page.

The information required on the remainder of this cover page shall not be deemed to be "filed" for the purpose of Section 18 of the Securities Exchange Act of 1934 ("Act") or otherwise subject to the liabilities of that section of the Act but shall be subject to all other provisions of the Act (however, see the Notes).

CUSIP No. 91678A107

1	Names of Reporting Persons. OrbiMed Advisors LLC	
2	Check the Appropriate Box if a Member of a Group (See Instructions). (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC Use Only	
4	Source of Funds (See Instructions) AF	
5	Check if Disclosure of Legal Proceedings Is Required Pursuant to Items 2(d) or 2(e) <input type="checkbox"/>	
6	Citizenship or Place of Organization Delaware	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	Sole Voting Power 0
	8	Shared Voting Power 4,554,873
	9	Sole Dispositive Power 0
	10	Shared Dispositive Power 4,554,873
11	Aggregate Amount Beneficially Owned by Each Reporting Person 4,554,873	
12	Check if the Aggregate Amount in Row (11) Excludes Certain Shares (See Instructions) <input type="checkbox"/>	
13	Percent of Class Represented by Amount in Row (11) 8.9%*	
14	Type of Reporting Person (See Instructions) IA	

* This percentage is calculated based upon 51,341,695 shares of common stock, par value \$0.001 per share, outstanding of Upstream Bio, Inc. (the "Issuer") following the closing of the Issuer's initial public offering, as set forth in the Issuer's Rule 424(b)(4) Prospectus filed with the Securities and Exchange Commission on October 11, 2024, without giving effect to an additional 2,250,000 shares that may be issued and sold by the Issuer to the underwriters pursuant to the underwriters' option.

CUSIP No. 91678A107

1	Names of Reporting Persons. OrbiMed Capital GP VIII LLC	
2	Check the Appropriate Box if a Member of a Group (See Instructions). (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC Use Only	
4	Source of Funds (See Instructions) AF	
5	Check if Disclosure of Legal Proceedings Is Required Pursuant to Items 2(d) or 2(e) <input type="checkbox"/>	
6	Citizenship or Place of Organization Delaware	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	Sole Voting Power 0
	8	Shared Voting Power 4,554,873
	9	Sole Dispositive Power 0
	10	Shared Dispositive Power 4,554,873
11	Aggregate Amount Beneficially Owned by Each Reporting Person 4,554,873	
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14	Type of Reporting Person (See Instructions) OO	

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CUSIP No. 91678A107

1	Names of Reporting Persons. OrbiMed Advisors Israel II Limited	
2	Check the Appropriate Box if a Member of a Group (See Instructions). (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC Use Only	
4	Source of Funds (See Instructions) AF	
5	Check if Disclosure of Legal Proceedings Is Required Pursuant to Items 2(d) or 2(e) <input type="checkbox"/>	
6	Citizenship or Place of Organization Cayman Islands	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	Sole Voting Power 0
	8	Shared Voting Power 1,138,716
	9	Sole Dispositive Power 0
	10	Shared Dispositive Power 1,138,716
11	Aggregate Amount Beneficially Owned by Each Reporting Person 1,138,716	
12	Check if the Aggregate Amount in Row (11) Excludes Certain Shares (See Instructions) <input type="checkbox"/>	
13	Percent of Class Represented by Amount in Row (11) 2.2%*	
14	Type of Reporting Person (See Instructions) CO	

* This percentage is calculated based upon 51,341,695 shares of common stock, par value \$0.001 per share, outstanding of Upstream Bio, Inc. (the "Issuer") following the closing of the Issuer's initial public offering, as set forth in the Issuer's Rule 424(b)(4) Prospectus filed with the Securities and Exchange Commission on October 11, 2024, without giving effect to an additional 2,250,000 shares that may be issued and sold by the Issuer to the underwriters pursuant to the underwriters' option.

CUSIP No. 91678A107

1	Names of Reporting Persons. OrbiMed Israel GP II, L.P.	
2	Check the Appropriate Box if a Member of a Group (See Instructions). (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC Use Only	
4	Source of Funds (See Instructions) AF	
5	Check if Disclosure of Legal Proceedings Is Required Pursuant to Items 2(d) or 2(e) <input type="checkbox"/>	
6	Citizenship or Place of Organization Cayman Islands	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	Sole Voting Power 0
	8	Shared Voting Power 1,138,716
	9	Sole Dispositive Power 0
	10	Shared Dispositive Power 1,138,716
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Item 1. Security and Issuer

This Statement on Schedule 13D (this “Statement”) relates to the common stock, par value \$0.001 per share (the “Shares”), of Upstream Bio, Inc., a corporation organized under the laws of Delaware (the “Issuer”), with its principal executive offices located at 890 Winter Street, Suite 200, Waltham, MA 02451. The Shares are listed on the NASDAQ Global Select Market under the ticker symbol “UPB”. Information given in response to each item shall be deemed incorporated by reference in all other items, as applicable.

On October 15, 2024, the Issuer completed its initial public offering pursuant to which the Issuer agreed to issue and sell 15,000,000 Shares to the participants in the offering (the “IPO”). In addition, the Issuer granted the underwriters of the IPO an option to purchase, at the public offering price less any underwriting discounts and commissions, up to an additional 2,250,000 Shares. The purchase price for each Share was \$17.00. As a result of the IPO, the Issuer’s total number of outstanding Shares increased to 51,341,695 (without giving effect to the additional 2,250,000 shares that may be issued and sold by the Issuer to the underwriters pursuant to the underwriters’ option).

Item 2. Identity and Background

(a) This Statement is being filed by OrbiMed Advisors LLC (“OrbiMed Advisors”), OrbiMed Capital GP VIII LLC, (“GP VIII”), OrbiMed Advisors Israel II Limited (“Advisors II”), and OrbiMed Israel GP II, L.P. (“Israel GP”) (collectively, the “Reporting Persons”).

(b) — (c), (f) OrbiMed Advisors, a limited liability company organized under the laws of Delaware and a registered investment adviser under the Investment Advisers Act of 1940, as amended, is the managing member or general partner of certain entities as more particularly described in Item 6 below. OrbiMed Advisors has its principal offices at 601 Lexington Avenue, 54th Floor, New York, New York 10022.

GP VIII, a limited liability company organized under the laws of Delaware, is the general partner of a limited partnership, as more particularly described in Item 6 below. GP VIII has its principal offices at 601 Lexington Avenue, 54th Floor, New York, New York 10022.

Advisors II, an exempted company organized under the laws of the Cayman Islands, is the general partner of Israel GP. Advisors II has its principal offices at 5 Hahoshlim Street, Building B, 1st Floor, Herzliya Pituach, Israel.

Israel GP, an exempted limited partnership organized under the laws of the Cayman Islands, is the general partner of a limited partnership, as more particularly described in Item 6 below, Israel GP has its principal offices at 5 Hahoshlim Street, Building B, 1st Floor, Herzliya Pituach, Israel.

The directors and executive officers of OrbiMed Advisors, GP VIII, Advisors II, and Israel GP are set forth on Schedules I, II, III, and IV, respectively, attached hereto. Schedules I through IV set forth the following information with respect to each such person:

- (i) name;
- (ii) business address;
- (iii) present principal occupation of employment and the name, principal business and address of any corporation or other organization in which such employment is conducted; and
- (iv) citizenship.

(d) — (e) During the last five years, neither the Reporting Persons nor any Person named in Schedules I or II has been (i) convicted in a criminal proceeding (excluding traffic violations or similar misdemeanors) or (ii) a party to a civil proceeding of a judicial or administrative body of competent jurisdiction and as a result of such proceeding was or is subject to a judgment, decree or final order enjoining future violations of, or prohibiting or mandating activities subject to, federal or state securities laws or finding any violation with respect to such laws.

Item 3. Source and Amount of Funds or Other Consideration

In October 2021, Advisors II and Israel GP, pursuant to their authority under the limited partnership agreement of OrbiMed Israel Partners II, L.P. (“OIP II”), as more particularly described in Item 6 below, caused OIP II to purchase 275,000 shares of the Issuer’s Series A redeemable convertible preferred stock (“Series A Shares”) and OrbiMed Advisors and GP VIII, pursuant to their authority under the limited partnership agreement of OrbiMed Private Investments VIII, L.P. (“OPI VIII”), as more particularly described in Item 6 below, caused OPI VIII to purchase 1,100,000 Series A Shares, each at a price of \$10.00 per Series A Share.

In October 2022, Advisors II and Israel GP, pursuant to their authority under the limited partnership agreement of OIP II, and OrbiMed Advisors and GP VIII, pursuant to their authority under the limited partnership agreement of OPI VIII, caused OIP II and OPI VIII to purchase 225,000 and 900,000 Series A Shares, respectively, at a price of \$10.00 per Series A Share.

In June 2023, Advisors II and Israel GP, pursuant to their authority under the limited partnership agreement of OIP II, and OrbiMed Advisors and GP VIII, pursuant to their authority under the limited partnership agreement of OPI VIII, caused OIP II and OPI VIII to purchase 47,058 and 188,235 shares of the Issuer’s Series B redeemable convertible preferred stock (“Series B Shares”), respectively, at a price of \$17.00 per Series B Share.

In April 2024, Advisors II and Israel GP, pursuant to their authority under the limited partnership agreement of OIP II, and OrbiMed Advisors and GP VIII, pursuant to their authority under the limited partnership agreement of OPI VIII, caused OIP II and OPI VIII to purchase 141,176 and 564,705 Series B Shares, respectively, at a price of \$17.00 per Series B Share.

Each Series A Share and Series B Share automatically converted into Shares on a one-for-1.049 basis immediately prior to the closing of the IPO.

On and prior to the closing of the IPO, OrbiMed Advisors and GP VIII, pursuant to their authority under the limited partnership agreement of OPI VIII, caused OPI VIII to purchase 660,000 Shares in the IPO, and Advisors II and Israel GP, pursuant to their authority under the limited partnership agreement of OIP II, caused OIP II to purchase 165,000 Shares in the IPO.

The source of funds for such purchases was the working capital of OPI VIII and OIP II, respectively.

Item 4. Purpose of Transaction

This Statement relates to the acquisition of Shares by the Reporting Persons. The Shares acquired by the Reporting Persons were acquired for the purpose of making an investment in the Issuer and not with the intention of acquiring control of the Issuer’s business on behalf of the Reporting Persons’ respective advisory clients.

The Reporting Persons from time to time intend to review their investment in the Issuer on the basis of various factors, including the Issuer’s business, financial condition, results of operations and prospects, general economic and industry conditions, the securities markets in general and those for the Issuer’s Shares in particular, as well as other developments and other investment opportunities. Based upon such review, the Reporting Persons will take such actions in the future as the Reporting Persons may deem appropriate in light of the circumstances existing from time to time. If the Reporting Persons believe that further investment in the Issuer is attractive, whether because of the market price of Shares or otherwise, they may acquire Shares or other securities of the Issuer either in the open market or in privately negotiated transactions. Similarly, depending on market and other factors, the Reporting Persons may determine to dispose of some or all of the Shares currently owned by the Reporting Persons or otherwise acquired by the Reporting Persons either in the open market or in privately negotiated transactions.

Except as set forth in this Schedule 13D, the Reporting Persons have not formulated any plans or proposals which relate to or would result in: (a) the acquisition by any person of additional securities of the Issuer or the disposition of securities of the Issuer, (b) an extraordinary corporate transaction, such as a merger, reorganization or liquidation, involving the Issuer or any of its subsidiaries, (c) a sale or transfer of a material amount of the assets of the Issuer or any of its subsidiaries, (d) any change in the present Board of Directors or management of the Issuer, including any plans or proposals to change the number or term of directors or to fill any existing vacancies on the board, (e) any material change in the Issuer's capitalization or dividend policy of the Issuer, (f) any other material change in the Issuer's business or corporate structure, (g) any change in the Issuer's charter or bylaws or other instrument corresponding thereto or other action which may impede the acquisition of control of the Issuer by any person, (h) causing a class of the Issuer's securities to be deregistered or delisted from a national securities exchange or to cease to be authorized to be quoted in an inter-dealer quotation system of a registered national securities association, (i) a class of equity securities of the Issuer becoming eligible for termination of registration pursuant to Section 12(g)(4) of the Act or (j) any action similar to any of those enumerated above.

Item 5. Interest in Securities of the Issuer

(a) — (b) The following is based upon 51,341,695 Shares outstanding following the closing of the IPO, as set forth in the Issuer's Rule 424(b)(4) Prospectus filed with the Securities and Exchange Commission on October 11, 2024, without giving effect to an additional 2,250,000 Shares that may be issued and sold by the Issuer to the underwriters pursuant to the underwriters' option.

As of the date of this filing, OPI VIII, a limited partnership organized under the laws of Delaware, holds 4,554,873 Shares, constituting approximately 8.9% of the issued and outstanding Shares. GP VIII is the general partner of OPI VIII, pursuant to the terms of the limited partnership agreement of OPI VIII, and OrbiMed Advisors is the managing member of GP VIII, pursuant to the terms of the limited liability company agreement of GP VIII. As a result, OrbiMed Advisors and GP VIII share power to direct the vote and disposition of the Shares held by OPI VIII and may be deemed directly or indirectly, including by reason of their mutual affiliation, to be the beneficial owners of the Shares held by OPI VIII. OrbiMed Advisors exercises this investment and voting power through a management committee comprised of Carl L. Gordon, Sven H. Borho, and W. Carter Neild, each of whom disclaims beneficial ownership of the Shares held by OPI VIII.

In addition, OrbiMed Advisors and GP VIII, pursuant to their authority under the limited partnership agreement of OPI VIII, caused OPI VIII to enter into the agreements referred to in Item 6 below.

As of the date of this filing, OIP II, an exempted limited partnership organized under the laws of the Cayman Islands, holds 1,138,716 Shares, constituting approximately 2.2% of the issued and outstanding Shares. Israel GP is the general partner of OIP II, pursuant to the terms of the limited partnership agreement of OIP II, and Advisors II is the general partner of Israel GP, pursuant to the terms of the limited partnership agreement of Israel GP. As a result, Advisors II and Israel GP share power to direct the vote and disposition of the Shares held by OIP II and may be deemed, directly or indirectly, including by reason of their mutual affiliation, to be the beneficial owners of the Shares held by OIP II. Advisors II exercises this investment and voting power through an investment committee comprised of Carl L. Gordon, David Bonita, and Erez Chimovits, each of whom disclaims beneficial ownership of the Shares held by OIP II.

In addition, Advisors II and Israel GP, pursuant to their authority under the limited partnership agreement of OIP II, caused OIP II to enter into the agreements referred to in Item 6 below.

(c) Except as disclosed in Item 3, the Reporting Persons have not effected any transactions during the past sixty (60) days in any Shares.

(d) Not applicable.

(e) Not applicable.

Item 6. Contracts, Arrangements, Understandings or Relationships with Respect to Securities of the Issuer

In addition to the relationships between the Reporting Persons described in Items 2 and 5 above, GP VIII is the general partner of OPI VIII, pursuant to the terms of the limited partnership agreement of OPI VIII. Pursuant to this agreement and relationship, GP VIII has discretionary investment management authority with respect to the assets of OPI VIII. Such authority includes the power to vote and otherwise dispose of securities held by OPI VIII. The number of outstanding Shares of the Issuer attributable to OPI VIII is 4,554,873 Shares. GP VIII, pursuant to its authority under the limited partnership agreement of OPI VIII, may be considered to hold indirectly 4,554,873 Shares.

In addition to the relationships between the Reporting Persons described in Items 2 and 5 above, OrbiMed Advisors is the managing member of GP VIII, pursuant to the terms of the limited liability company agreement of GP VIII. Pursuant to this agreement and relationship, OrbiMed Advisors and GP VIII have discretionary investment management authority with respect to the assets of OPI VIII. Such authority includes the power of GP VIII to vote and otherwise dispose of securities held by OPI VIII. The number of outstanding Shares attributable to OPI VIII is 4,554,873 Shares. OrbiMed Advisors, pursuant to its authority under the terms of the limited liability company agreement of GP VIII may also be considered to hold indirectly 4,554,873 Shares.

In addition to the relationships between the Reporting Persons described in Items 2 and 5 above, Israel GP is the general partner of OIP II, pursuant to the terms of the limited partnership agreement of OIP II, and Advisors II is the general partner of Israel GP, pursuant to the terms of the limited partnership agreement of Israel GP. Pursuant to these agreements and relationships, Advisors II and Israel GP have discretionary investment management authority with respect to the assets of OIP II. Such authority includes the power to vote and otherwise dispose of securities held by OIP II. The number of outstanding Shares of the Issuer attributable to OIP II is 1,138,716 Shares. Israel GP, pursuant to its authority under the limited partnership agreement of OIP II, and Advisors II, pursuant to its authority under the limited partnership agreement of Israel GP, may each be considered to hold indirectly 1,138,716 Shares.

Erez Chimovits (“Chimovits”), an employee of OrbiMed Advisors and a director of Advisors II, is a member of the Board of Directors of the Issuer and, accordingly, OrbiMed Advisors, GP VIII, Advisors II, Israel GP may have the ability to affect and influence control of the Issuer. From time to time, Chimovits may receive stock options or other awards of equity-based compensation pursuant to the Issuer’s compensation arrangements for non-employee directors. Pursuant to an agreement with OrbiMed Advisors, GP VIII, Advisors II, and Israel GP, Chimovits is obligated to transfer any securities issued under any such stock options or other awards, or the economic benefit thereof, to OrbiMed Advisors, GP VIII, Advisors II, and Israel GP, who will in turn ensure that such securities or economic benefits are provided to OPI VIII and OIP II.

Investors’ Rights Agreement

In addition, OPI VIII, OIP II, and certain other stockholders of the Issuer entered into an Amended and Restated Investors’ Rights Agreement with the Issuer, dated as of June 6, 2023 (the “Investors’ Rights Agreement”). Pursuant to the Investors’ Rights Agreement and subject to the terms and conditions therein, the parties agreed that:

Demand Registration Rights

At any time beginning 180 days following the effective date of the registration statement of the IPO, the holders of at least a majority of the Issuer’s registrable securities may request that the Issuer file a registration statement under the Securities Act of 1933, as amended (the “Securities Act”) on a Form S-1 at the Issuer’s expense, subject to certain exceptions, with an anticipated aggregate offering price, net of offering expenses, of not less than \$5 million, in which case the Issuer will be required to effect the registration as soon as practicable, and in any event within 60 days after the date of such registration request. The Issuer is not obligated to effect more than two of these registrations.

Form S-3 Registration Rights

At any time after the Issuer is qualified to file a registration statement on Form S-3 under the Securities Act, and subject to limitations and conditions specified in the Investors’ Rights Agreement, holders of at least 30% of the registrable securities under the Investors’ Rights Agreement may request that the Issuer prepare and file a registration statement on Form S-3 at the Issuer’s expense covering the Shares of such holders having an anticipated aggregate offering price, net of offering expenses, of at least \$1 million, in which case the Issuer will be required to effect the registration as soon as practicable, and in any event within 45 days after receiving such request. The Issuer is not obligated to effect more than one of these registrations in any 12-month period.

Piggyback Registration Rights

Whenever the Issuer proposes to file a registration statement under the Securities Act, other than with respect to certain excluded registrations, OPI VIII and OIP II will each be entitled to notice of the registration and have the right, subject to limitations that the underwriters may impose on the number of Shares included in the registration, to include the Shares held by them in the registration.

Lock-Up Agreement

In addition, in connection with the IPO, OPI VIII, OIP II, and Chimovits each entered into a lock-up agreement (the “Lock-Up Agreement”) with the Issuer’s underwriters pursuant to which, among other things, OPI VIII, OIP II, and Chimovits each agreed not to, except in limited circumstances, directly or indirectly, from the date of the Lock-Up Agreement until 180 days after the date of the final prospectus supplement relating to the IPO: (i) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend, or otherwise transfer or dispose of any Shares or any securities convertible into or exercisable or exchangeable for Shares; (ii) enter into any hedging, swap or other agreement or transaction that transfers, in whole or in part, any of the economic consequences of ownership of the Shares or securities convertible into or exercisable or exchangeable for Shares, whether settled by delivery of Shares, in cash or otherwise; (iii) make any demand for, or exercise any right with respect to, the registration of any Shares or securities convertible into or exercisable or exchangeable for Shares; or (iv) publicly disclose the intention to do any of the foregoing.

The foregoing description of the Investors’ Rights Agreement and the Lock-Up Agreement do not purport to be complete and are qualified in their entirety by reference to the full text of the Investors’ Rights Agreement and the Lock-Up Agreement, which are filed as Exhibits 2 and 3, respectively, and incorporated herein by reference.

Item 7. Material to Be Filed as Exhibits

Exhibit	Description
1.	Joint Filing Agreement among OrbiMed Advisors LLC, OrbiMed Capital GP VIII LLC, OrbiMed Advisors Israel II Limited, and OrbiMed Israel GP II, L.P.
2.	Amended and Restated Investors’ Rights Agreement, among the Issuer and certain of its stockholders, dated June 6, 2023 (incorporated by reference to Exhibit 4.2 to the Issuer’s Registration Statement on Form S-1/A (File No. 333-282197) filed with the SEC on October 7, 2024).
3.	Form of Lock-Up Agreement (incorporated by reference to Exhibit A to Exhibit 1.1 to the Issuer’s Registration Statement on Form S-1/A (File No. 333-282197) filed with the SEC on October 7, 2024).

Signature

After reasonable inquiry and to the best of my knowledge and belief, I certify that the information set forth in this statement is true, complete and correct.

Dated: October 17, 2024

ORBIMED ADVISORS LLC

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Member

ORBIMED CAPITAL GP VIII LLC

By: ORBIMED ADVISORS LLC, its managing member

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Member of OrbiMed Advisors LLC

ORBIMED ADVISORS ISRAEL II LIMITED

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Director

ORBIMED ISRAEL GP II, L.P.

By: ORBIMED ADVISORS ISRAEL II LIMITED., its general partner

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Director of OrbiMed Advisors Israel II Limited

SCHEDULE I

The names and present principal occupations of each of the executive officers and directors of OrbiMed Advisors LLC are set forth below. Unless otherwise noted, each of these persons is a United States citizen and has a business address of 601 Lexington Avenue, 54th Floor, New York, NY 10022.

<u>Name</u>	<u>Position with Reporting Person</u>	<u>Principal Occupation</u>
Carl L. Gordon	Member	Member OrbiMed Advisors LLC
Sven H. Borho German and Swedish Citizen	Member	Member OrbiMed Advisors LLC
W. Carter Neild	Member	Member OrbiMed Advisors LLC
Geoffrey C. Hsu	Member	Member OrbiMed Advisors LLC
C. Scotland Stevens	Member	Member OrbiMed Advisors LLC
David P. Bonita	Member	Member OrbiMed Advisors LLC
Peter A. Thompson	Member	Member OrbiMed Advisors LLC
Matthew S. Rizzo	Member	Member OrbiMed Advisors LLC
Trey Block	Chief Financial Officer	Chief Financial Officer OrbiMed Advisors LLC

SCHEDULE II

The business and operations of OrbiMed Capital GP VIII LLC are managed by the executive officers and directors of its managing member, OrbiMed Advisors LLC, set forth on Schedule I attached.

SCHEDULE III

The names and present principal occupations of each of the executive officers and directors of OrbiMed Advisors Israel II Limited are set forth below. Unless otherwise noted, each of these persons is a United States citizen and has a business address of 5 Hahoshlim Street, Building B, 1st Floor, Herzliya Pituach, Israel.

<u>Name</u>	<u>Position with Reporting Person</u>	<u>Principal Occupation</u>
Carl L. Gordon	Director	Director OrbiMed Advisors Israel II Limited
David P. Bonita	Director	Director OrbiMed Advisors Israel II Limited
Erez Chimovits	Director	Director OrbiMed Advisors Israel II Limited

SCHEDULE IV

The business and operations of OrbiMed Israel GP II, L.P. are managed by the executive officers and directors of its general partner, OrbiMed Advisors Israel II Limited, set forth on Schedule III attached.

EXHIBIT INDEX

Exhibit	Description
1.	Joint Filing Agreement among OrbiMed Advisors LLC, OrbiMed Capital GP VIII LLC, OrbiMed Advisors Israel II Limited, and OrbiMed Israel GP II, L.P.
2.	Amended and Restated Investors' Rights Agreement, among the Issuer and certain of its stockholders, dated June 6, 2023 (incorporated by reference to Exhibit 4.2 to the Issuer's Registration Statement on Form S-1/A (File No. 333-282197) filed with the SEC on October 7, 2024).
3.	Form of Lock-Up Agreement (incorporated by reference to Exhibit A to Exhibit 1.1 to the Issuer's Registration Statement on Form S-1/A (File No. 333-282197) filed with the SEC on October 7, 2024).

JOINT FILING AGREEMENT

The undersigned hereby agree that the Statement on Schedule 13D, dated October 15, 2024, with respect to the common stock of Upstream Bio, Inc. is filed on behalf of each of us pursuant to and in accordance with the provisions of Rule 13d-1(k) under the Securities Exchange Act of 1934, as amended. Each of the undersigned agrees to be responsible for the timely filing of this Statement, and for the completeness and accuracy of the information concerning itself contained therein. This Joint Filing Agreement may be executed in any number of counterparts, all of which taken together shall constitute one and the same instrument.

IN WITNESS WHEREOF, the undersigned have executed this Joint Filing Agreement as of the 17th day of October, 2024.

ORBIMED ADVISORS LLC

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Member

ORBIMED CAPITAL GP VIII LLC

By: ORBIMED ADVISORS LLC, its managing member

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Member of OrbiMed Advisors LLC

ORBIMED ADVISORS ISRAEL II LIMITED

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Director

ORBIMED ISRAEL GP II, L.P.

By: ORBIMED ADVISORS ISRAEL II LIMITED, its general partner

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Director of OrbiMed Advisors Israel II Limited
