

INITIAL STATEMENT OF BENEFICIAL OWNERSHIP OF SECURITIES

OMB APPROVAL	
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Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person* <u>Chimovits Erez</u> (Last) (First) (Middle) UPSTREAM BIO, INC. 890 WINTER STREET, SUITE 200 (Street) WALTHAM MA 02451 (City) (State) (Zip)	2. Date of Event Requiring Statement (Month/Day/Year) 10/10/2024	3. Issuer Name and Ticker or Trading Symbol <u>Upstream Bio, Inc. [UPB]</u>	
		4. Relationship of Reporting Person(s) to Issuer (Check all applicable) <input checked="" type="checkbox"/> Director <input checked="" type="checkbox"/> 10% Owner Officer (give title below) Other (specify below)	5. If Amendment, Date of Original Filed (Month/Day/Year) 6. Individual or Joint/Group Filing (Check Applicable Line) <input checked="" type="checkbox"/> Form filed by One Reporting Person <input type="checkbox"/> Form filed by More than One Reporting Person

Table I - Non-Derivative Securities Beneficially Owned

1. Title of Security (Instr. 4)	2. Amount of Securities Beneficially Owned (Instr. 4)	3. Ownership Form: Direct (D) or Indirect (I) (Instr. 5)	4. Nature of Indirect Beneficial Ownership (Instr. 5)
Common Stock	251,760	I	By OrbiMed Israel Partners II, L.P. ⁽¹⁾⁽²⁾
Common Stock	1,007,040	I	By OrbiMed Private Investments VIII, LP ⁽²⁾⁽³⁾

Table II - Derivative Securities Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 4)	2. Date Exercisable and Expiration Date (Month/Day/Year)		3. Title and Amount of Securities Underlying Derivative Security (Instr. 4)		4. Conversion or Exercise Price of Derivative Security	5. Ownership Form: Direct (D) or Indirect (I) (Instr. 5)	6. Nature of Indirect Beneficial Ownership (Instr. 5)
	Date Exercisable	Expiration Date	Title	Amount or Number of Shares			
Series A redeemable convertible preferred stock	(4)	(4)	Common Stock	524,500	(4)	I	By OrbiMed Israel Partners II, L.P. ⁽¹⁾⁽²⁾
Series A redeemable convertible preferred stock	(4)	(4)	Common Stock	2,098,000	(4)	I	By OrbiMed Private Investments VIII, LP ⁽²⁾⁽³⁾
Series B redeemable convertible preferred stock	(4)	(4)	Common Stock	197,456	(4)	I	By OrbiMed Israel Partners II, L.P. ⁽¹⁾⁽²⁾
Series B redeemable convertible preferred stock	(4)	(4)	Common Stock	789,833	(4)	I	By OrbiMed Private Investments VIII, LP ⁽²⁾⁽³⁾

Explanation of Responses:

1. Shares held by OrbiMed Israel Partners II, L.P. ("OIP II"). OrbiMed Israel GP II, L.P. ("OrbiMed Israel GP II") is the general partner of OIP II, and OrbiMed Advisors Israel II Limited ("OrbiMed Israel II") is the general partner of OrbiMed Israel GP II. By virtue of such relationships, OrbiMed Israel GP II and OrbiMed Israel II may be deemed to have voting power and investment power over the securities held by OIP II and as a result, may be deemed to have beneficial ownership over such securities. OrbiMed Israel II exercises this investment and voting power through a management committee comprised of Carl L. Gordon, David P. Bonita, and the Reporting Person, each of whom disclaims beneficial ownership of the shares held by OIP II.

2. Each of the Reporting Person, OrbiMed Israel GP II, OrbiMed Israel II, OrbiMed Capital GP VIII LLC ("GP VIII"), and OrbiMed Advisors LLC ("OrbiMed Advisors") disclaims beneficial ownership of the securities reported herein for purposes of Rule 16a-1(a) under the Securities Exchange Act of 1934, as amended (the "Exchange Act"), except to the extent of his or its pecuniary interest therein, if any. This report shall not be deemed an admission that any such entity or person is a beneficial owner of such securities for purposes of Section 16 of the Exchange Act, or for any other purpose.

3. Shares held by OrbiMed Private Investments VIII, LP ("OPI VIII"). GP VIII is the general partner of OPI VIII, and OrbiMed Advisors is the managing member of GP VIII. The Reporting Person is an employee of OrbiMed Advisors. By virtue of such relationships, GP VIII and OrbiMed Advisors may be deemed to have voting power and investment power over the securities held by OPI VIII and as a result, may be deemed to have beneficial ownership over such securities. OrbiMed Advisors exercises voting and investment

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.

4. Each share of Series A redeemable convertible preferred stock and Series B redeemable convertible preferred stock (collectively, the "Preferred Stock") is convertible into Common Stock on a 1.049-for-one basis at the option of the holder, and will convert automatically upon closing of the Issuer's initial public offering into the number of shares shown in column 3 without payment of consideration. The Preferred Stock has no expiration date.

Remarks:

Exhibit 24 - Power of Attorney

/s/ Michael Gray,
Attorney-in-Fact

10/10/2024

** Signature of Reporting
Person

Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, see Instruction 5 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

LIMITED POWER OF ATTORNEY

The undersigned hereby constitutes and appoints each of E. Rand Sutherland, Michael Paul Gray and Gabriela Morales-Rivera, signing singly, and with full power of substitution, the undersigned's true and lawful attorney-in-fact to:

(1) execute for and on behalf of the undersigned, in the undersigned's capacity as an officer, director, and/or securityholder of Upstream Bio, Inc., a Delaware corporation (the "Company"), from time to time the following U.S. Securities and Exchange Commission ("SEC") forms: (i) Form ID, including any attached documents (such as Update Passphrase Authentication), to effect the assignment of codes to the undersigned to be used in the transmission of information to the SEC using the EDGAR System; (ii) Form 3, Initial Statement of Beneficial Ownership of Securities, including any attached documents; (iii) Form 4, Statement of Changes in Beneficial Ownership of Securities, including any attached documents; (iv) Form 5, Annual Statement of Beneficial Ownership of Securities in accordance with Section 16(a) of the Securities Exchange Act of 1934, as amended, and the rules thereunder, including any attached documents; (v) Schedules 13D and 13G; and (vi) amendments of each thereof, in accordance with the Securities Exchange Act of 1934, as amended, and the rules thereunder, including any attached documents;

(2) do and perform any and all acts for and on behalf of the undersigned which may be necessary or desirable to complete and execute any such Form 3, 4 or 5, Schedule 13D or 13G, or any amendment(s) thereto and timely file such form(s) with the SEC and any securities exchange, national association or similar authority; and

(3) take any other action of any type whatsoever in connection with the foregoing which, in the opinion of such attorney-in-fact, may be of benefit to, in the best interest of, or legally required by, the undersigned, it being understood that the documents executed by such attorney-in-fact on behalf of the undersigned pursuant to this Power of Attorney shall be in such form and shall contain such terms and conditions as such attorney-in-fact may approve in such attorney-in-fact's discretion.

The undersigned hereby grants to each such attorney-in-fact, acting singly, full power and authority to do and perform any and every act and thing whatsoever requisite, necessary or proper to be done in the exercise of any of the rights and powers herein granted, as fully to all intents and purposes as the undersigned might or could do if personally present, with full power of substitution or revocation, hereby ratifying and confirming all that such attorney-in-fact, or such attorney-in-fact's substitute or substitutes, shall lawfully do or cause to be done by virtue of this power of attorney and the rights and powers herein granted. The undersigned acknowledges that the foregoing attorneys-in-fact, in serving in such capacity at the request of the undersigned, are not assuming, nor is the Company assuming, any of the undersigned's responsibilities to comply with Section 16 or Regulation 13D-G of the Securities Exchange Act of 1934, as amended. The undersigned hereby agrees to indemnify the attorneys-in-fact and the Company from and against any demand, damage, loss, cost or expense arising from any false or misleading information provided by the undersigned to the attorneys-in-fact.

This Power of Attorney shall remain in full force and effect until the undersigned is no longer required to file such forms with respect to the undersigned's holdings of and transactions in securities issued by the Company, unless earlier revoked by the undersigned in a signed writing delivered to the foregoing attorneys-in-fact. This Power of Attorney supersedes any prior power of attorney in connection with the undersigned's capacity as an officer and/or director of the Company. This Power of Attorney shall expire as to any individual attorney-in-fact if such attorney-in-fact ceases to be an employee of the Company.

IN WITNESS WHEREOF, the undersigned has caused this Power of Attorney to be executed as of October 10, 2024.

/s/ Erez Chimovits, M.B.A., M.Sc.

Signature

Erez Chimovits, M.B.A., M.Sc.

Print Name
