

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

OMB APPROVAL	
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Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

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

Check this box to indicate that a transaction was made pursuant to a contract, instruction or written plan for the purchase or sale of equity securities of the issuer that is intended to satisfy the affirmative defense conditions of Rule 10b5-1(c). See Instruction 10.

1. Name and Address of Reporting Person* <u>ORBIMED ADVISORS LLC</u> (Last) (First) (Middle) 601 LEXINGTON AVENUE 54TH FLOOR (Street) NEW YORK NY 10022 (City) (State) (Zip)	2. Issuer Name and Ticker or Trading Symbol <u>Upstream Bio, Inc. [UPB]</u>	5. 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)
	3. Date of Earliest Transaction (Month/Day/Year) 10/15/2024	
4. If Amendment, Date of Original Filed (Month/Day/Year)		

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	10/15/2024		C		721,956	A	(1)	973,716	I	See Footnote(2)(4)
Common Stock	10/15/2024		P		165,000	A	\$17	1,138,716	I	See Footnote(2)(4)
Common Stock	10/15/2024		C		2,887,833	A	(1)	3,894,873	I	See Footnote(3)(4)
Common Stock	10/15/2024		P		660,000	A	\$17	4,554,873	I	See Footnote(3)(4)

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

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Series A redeemable convertible preferred stock	(1)	10/15/2024		C		524,500		(1)	(1)	Common Stock	524,500	(1)	0	I	See Footnote(2)(4)
Series A redeemable convertible preferred stock	(1)	10/15/2024		C		2,098,000		(1)	(1)	Common Stock	2,098,000	(1)	0	I	See Footnote(3)(4)
Series B redeemable convertible preferred stock	(1)	10/15/2024		C		197,456		(1)	(1)	Common Stock	197,456	(1)	0	I	See Footnote(2)(4)
Series B redeemable convertible preferred stock	(1)	10/15/2024		C		789,833		(1)	(1)	Common Stock	789,833	(1)	0	I	See Footnote(3)(4)

1. Name and Address of Reporting Person* <u>ORBIMED ADVISORS LLC</u> (Last) (First) (Middle) 601 LEXINGTON AVENUE 54TH FLOOR (Street) NEW YORK NY 10022 (City) (State) (Zip)		
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1. Name and Address of Reporting Person*		
OrbiMed Capital GP VIII LLC		
(Last)	(First)	(Middle)
601 LEXINGTON AVENUE 54TH FLOOR		
(Street)		
NEW YORK	NY	10022
(City) (State) (Zip)		
1. Name and Address of Reporting Person*		
OrbiMed Advisors Israel II Ltd		
(Last)	(First)	(Middle)
5 HAHOSHLIM STREET, BUILDING B 1ST FLOOR		
(Street)		
HERZLIYA PITUACH	L3	4672408
(City) (State) (Zip)		
1. Name and Address of Reporting Person*		
OrbiMed Israel GP II, L.P.		
(Last)	(First)	(Middle)
5 HAHOSHLIM STREET, BUILDING B 1ST FLOOR		
(Street)		
HERZLIYA PITUACH	L3	4672408
(City) (State) (Zip)		

Explanation of Responses:

- Each share of Series A redeemable convertible preferred stock and Series B redeemable convertible preferred stock automatically converted into shares of the Issuer's common stock on a one-for-1.049 basis immediately prior to the closing of the Issuer's initial public offering and have no expiration date.
- These securities are held of record by OrbiMed Israel Partners II, L.P. ("OIP II"). OrbiMed Israel GP II, L.P. ("Israel GP") is the general partner of OIP II, and OrbiMed Advisors Israel II Limited ("Advisors II") is the general partner of Israel GP. By virtue of such relationships, Israel GP and Advisors II may be deemed to have voting and investment power over the securities held by OIP II and, as a result, may be deemed to have beneficial ownership over such securities. Advisors II exercises voting and investment power through an investment committee comprised of Carl L. Gordon, David P. Bonita, and Erez Chimovits ("Chimovits"), each of whom disclaims beneficial ownership of the securities held by OIP II.
- These securities are held of record by OrbiMed Private Investments VIII, LP ("OPI VIII"). OrbiMed Capital GP VIII LLC ("GP VIII") is the general partner of OPI VIII, and OrbiMed Advisors LLC ("OrbiMed Advisors") is the managing member of GP VIII. 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 securities held by OPI VIII.
- Each of Advisors II, Israel GP, OrbiMed Advisors, and GP VIII 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 its pecuniary interest therein, if any. OrbiMed Advisors, GP VIII, Advisors II, and Israel GP have designated a representative, Chimovits, an employee of OrbiMed Advisors and a director of Advisors II, to serve on the Issuer's board of directors. This report shall not be deemed an admission that any such person or entity is a beneficial owner of such securities for the purpose of Section 16 of the Exchange Act, or for any other purpose.

/s/ Carl L. Gordon, Member of OrbiMed Advisors LLC	10/17/2024
/s/ Carl L. Gordon, Member of OrbiMed Capital GP VIII LLC	10/17/2024
/s/ Carl L. Gordon, Director of OrbiMed Advisors Israel II Limited	10/17/2024
/s/ Carl L. Gordon, Director of OrbiMed Israel GP II, L.P.	10/17/2024

** 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 4 (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.