

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

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

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>Houghton Adam</u> (Last) (First) (Middle) <u>UPSTREAM BIO, INC.</u> <u>890 WINTER STREET, SUITE 200</u> (Street) <u>WALTHAM</u> <u>MA</u> <u>02451</u> (City) (State) (Zip)	2. Issuer Name and Ticker or Trading Symbol <u>Upstream Bio, Inc. [UPB]</u> Foreign Trading Symbol 3. Date of Earliest Transaction (Month/Day/Year) <u>09/16/2026</u> 4. If Amendment, Date of Original Filed (Month/Day/Year)	5. Relationship of Reporting Person(s) to Issuer (Check all applicable) Director 10% Owner ☒ Officer (give title below) Other (specify below) <u>Chief Business Officer</u> 6. Individual or Joint/Group Filing (Check Applicable Line) ☒ Form filed by One Reporting Person Form filed by More than One Reporting Person
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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	09/16/2026		S ⁽¹⁾		700	D	\$5.49	22,901	D	

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)
						Date Exercisable	Expiration Date	Title	Amount or Number of Shares			

Explanation of Responses:

1. The Issuer has adopted a "sell-to-cover" policy to satisfy the tax withholding obligations of the Reporting Person. The sales reported on this Form 4 represent the number of shares required to be sold by the Reporting Person to cover tax withholding obligations in connection with the vesting of restricted stock units. Such sales were automatic and not at the discretion of the Reporting Person.

/s/ Allison Ambrose,
Attorney-in-Fact 09/17/2026

** 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.