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

SCHEDULE 14A INFORMATION
Proxy Statement Pursuant to Section 14(a) of the Securities Exchange Act of 1934
(Amendment No.)

Filed by the Registrant ☒

Filed by a Party other than the Registrant ☐

Check the appropriate box:

☐ Preliminary Proxy Statement

☐ Confidential, for Use of the Commission Only (as permitted by Rule 14a-6(e)(2))

☒ Definitive Proxy Statement

☐ Definitive Additional Materials

☐ Soliciting Material under §240.14a-12

UPSTREAM BIO, INC.
(Name of Registrant as Specified in Its Charter)

(Name of Person(s) Filing Proxy Statement, if other than the Registrant)

Payment of Filing Fee (Check all boxes that apply)

☒ No fee required

☐ Fee paid previously with preliminary materials

☐ Fee computed on table in exhibit required by Item 25(b) per Exchange Act Rules 14a-6(i)(1) and 0-11

UPSTREAM BIO, INC.
890 Winter Street, Suite 200
Waltham, MA 02451

NOTICE OF 2025 ANNUAL MEETING OF STOCKHOLDERS
To be held on June 10, 2025

Notice is hereby given that the 2025 Annual Meeting of Stockholders of Upstream Bio, Inc. (the "Annual Meeting") will be held virtually on June 10, 2025 at 8:00 a.m. Eastern Time, via live webcast. You may attend the meeting online at www.virtualshareholdermeeting.com/UPB2025, where you will be able to vote electronically and submit questions. You will need the 16-digit control number included with the Notice of Internet Availability of Proxy Materials (the "Notice") being mailed to you separately in order to attend the Annual Meeting.

Stockholders of record at the close of business on April 14, 2025, the record date for the Annual Meeting, are entitled to notice of, and to vote at, the Annual Meeting or any adjournment or postponement of the Annual Meeting. The Annual Meeting will be held for the following purposes:

1. To elect two class I directors to our board of directors, each to serve until the 2028 annual meeting of our stockholders, and until his or her respective successor has been duly elected and qualified, or until his or her earlier death, resignation or removal;
2. To ratify the appointment of PricewaterhouseCoopers LLP ("PwC") as our independent registered public accounting firm for the fiscal year ending December 31, 2025; and
3. To transact any other business properly brought before the Annual Meeting or any continuation, adjournment or postponement of the Annual Meeting.

You can find more information on each of the matters to be voted on at the Annual Meeting, including information regarding the nominees for election to our board of directors, in the accompanying proxy statement (the "Proxy Materials"). The board of directors recommends a vote "FOR" the election of each of the nominees for class I directors and "FOR" the ratification of the appointment of our independent registered public accounting firm for the fiscal year ending December 31, 2025.

This year, the Company is following the Securities and Exchange Commission's "Notice and Access" rule that allows companies to furnish their proxy materials to stockholders by posting them online. As a result, we are mailing the Notice to our stockholders instead of a paper copy of the Proxy Materials and our annual report to our stockholders for the fiscal year ended December 31, 2024 (the "2024 Annual Report"). We are mailing the Notice on or about April 17, 2025, and it contains instructions on how to access both the Proxy Materials and the 2024 Annual Report online. This method provides our stockholders with expedited access to Proxy Materials and not only lowers the cost of printing and distribution but also reduces the environmental impact of the Annual Meeting. If you would like to receive a paper copy of the Proxy Materials by mail, free of charge, please follow the instructions on the Notice.

To attend the Annual Meeting, please visit www.virtualshareholdermeeting.com/UPB2025. You will not be able to attend the Annual Meeting in person.

Whether or not you expect to attend the Annual Meeting online, we encourage you to read the Proxy Materials and vote your shares as promptly as possible to ensure your representation and the presence of a quorum at the Annual Meeting as described in the instructions included in the Notice by voting online at www.proxyvote.com. If you requested and received a paper copy of the Proxy Materials, you can vote by signing, dating and returning the enclosed proxy card, calling 1-800-690-6903 and following the recorded instructions, or visiting www.proxyvote.com. If you vote your shares online or by telephone, you will need to enter the 16-digit control number provided in the Notice.

Your vote is important regardless of the number of shares you own. If you attend the Annual Meeting online, you may vote your shares during the Annual Meeting virtually even if you previously voted your proxy. Your proxy is revocable in accordance with the procedures set forth in the Proxy Materials.

If your shares are held in "street name," that is, held for your account by a broker or other nominee, you will receive instructions from the holder of record that you must follow for your shares to be voted.

By order of the board of directors,



Allison C. Ambrose
General Counsel and Secretary

Waltham, Massachusetts
April 17, 2025

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UPSTREAM BIO, INC.
890 Winter Street, Suite 200
Waltham, MA 02451

PROXY STATEMENT
FOR THE 2025 ANNUAL MEETING OF STOCKHOLDERS
To be held on June 10, 2025

This proxy statement ("Proxy Statement") contains information about the 2025 Annual Meeting of Stockholders (the "Annual Meeting") of Upstream Bio, Inc., which will be held virtually on June 10, 2025 at 8:00 a.m. Eastern Time, via live webcast. The board of directors of Upstream Bio, Inc. ("board of directors" or "board") is using this Proxy Statement to solicit proxies for use at the Annual Meeting. In this Proxy Statement, the terms "Upstream Bio," "we," "us," and "our" refer to Upstream Bio, Inc. The mailing address of our principal executive office is Upstream Bio, Inc., 890 Winter Street, Suite 200, Waltham, MA 02451.

All properly submitted proxies will be voted in accordance with the instructions contained in those proxies. If no instructions are specified, the proxies will be voted in accordance with the recommendation of our board of directors with respect to each of the matters set forth in the accompanying Notice of the 2025 Annual Meeting of Stockholders. You may revoke your proxy at any time before it is exercised at the Annual Meeting by giving our corporate secretary written notice to that effect.

We will make this Proxy Statement and our annual report to stockholders for the fiscal year ended December 31, 2024 (our "2024 Annual Report") available to stockholders on or about April 17, 2025.

We are an "emerging growth company" under applicable federal securities laws and therefore permitted to conform with certain reduced public company reporting requirements. As an emerging growth company, we provide in this Proxy Statement the scaled disclosure permitted under the Jumpstart Our Business Startups Act of 2012, including the compensation disclosures required of a "smaller reporting company," as that term is defined in Rule 12b-2 promulgated under the Securities Exchange Act of 1934, as amended (the "Exchange Act"). In addition, as an emerging growth company, we are not required to conduct votes seeking approval, on an advisory basis, of the compensation of our named executive officers or the frequency with which such votes must be conducted, and we are not required to provide pay versus performance disclosure under Item 402(v) of Regulation S-K. We will remain an "emerging growth company" until the earliest of (i) the last day of the fiscal year following the fifth anniversary of our initial public offering, which was completed in October 2024; (ii) the last day of the fiscal year in which our total annual gross revenue is equal to or more than $1.235 billion; (iii) the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the Securities and Exchange Commission (the "SEC"). Even after we are no longer an "emerging growth company," we may remain a "smaller reporting company."

Important Notice Regarding the Availability of Proxy Materials for
the Annual Meeting of Stockholders to be Held on June 10, 2025:

This Proxy Statement and our 2024 Annual Report are
available for viewing, printing and downloading at https://materials.proxyvote.com/91678A

A copy of our 2024 Annual Report, as filed with the SEC, except for exhibits, will be furnished without charge to any stockholder upon written request to Upstream Bio, Inc., 890 Winter Street, Suite 200, Waltham, MA 02451, Attention: Corporate Secretary. This Proxy Statement and our 2024 Annual Report are also available on the SEC's website at www.sec.gov and on the Investors page of our website at investors.upstreambio.com.

UPSTREAM BIO, INC.
PROXY STATEMENT
FOR THE 2025 ANNUAL MEETING OF STOCKHOLDERS

GENERAL INFORMATION

When are this Proxy Statement and the accompanying materials scheduled to be sent to stockholders?

We have elected to provide access to our Proxy Materials to our stockholders online. Accordingly, on or about April 17, 2025, we will begin mailing the Notice. Our Proxy Materials, including the Notice of the 2025 Annual Meeting of Stockholders, this Proxy Statement and the accompanying proxy card or, for shares held in street name (i.e., held for your account by a broker or other nominee), a voting instruction form, and our 2024 Annual Report will be mailed or made available to stockholders online on or about the same date.

Why did I receive a Notice instead of a full set of proxy materials?

Pursuant to rules adopted by the SEC, for most stockholders, we are providing access to our Proxy Materials online rather than printing and mailing our Proxy Materials. We believe following this process will expedite the receipt of such materials and will help lower our costs and reduce the environmental impact of the materials relating to the Annual Meeting. Therefore, the Notice will be mailed to holders of record and beneficial owners of our common stock, par value $0.001 per share ("common stock"), starting on or about April 17, 2025. The Notice provides instructions as to how stockholders may access and review our Proxy Materials, including the Notice of the 2025 Annual Meeting of Stockholders, this Proxy Statement, the proxy card and our 2024 Annual Report, on the website referred to in the Notice or, alternatively, how to request a copy of the Proxy Materials, including a proxy card, be sent to them by mail. The Notice also provides voting instructions. In addition, stockholders of record may request to receive the Proxy Materials in printed form by mail or electronically by e-mail on an ongoing basis for future stockholder meetings. Please note that, while our Proxy Materials are available at the website referenced in the Notice, and our Notice of the 2025 Annual Meeting of Stockholders, this Proxy Statement and our 2024 Annual Report are available on our website, no other information contained on either website is incorporated by reference in or considered to be a part of this Proxy Statement.

Who is soliciting my vote?

Our board of directors is soliciting your vote for the Annual Meeting, including at any continuations, adjournments or postponements thereof.

When is the record date for the Annual Meeting?

The record date for determination of stockholders entitled to vote at the Annual Meeting is the close of business on April 14, 2025.

How many votes can be cast by all stockholders?

There were 53,688,703 shares of our common stock outstanding on April 14, 2025, all of which are entitled to vote with respect to all matters to be acted upon at the Annual Meeting. Each stockholder of record is entitled to one vote for each share of our common stock held by such stockholder. None of our shares of undesignated preferred stock were outstanding as of April 14, 2025.

Who is entitled to vote?

Registered Stockholders. If shares of our common stock are registered directly in your name with our transfer agent, you are considered the stockholder of record with respect to those shares. As the stockholder of record, you have the right to grant your voting proxy directly to the individuals listed on the proxy card or vote on your own behalf at our virtual Annual Meeting. Throughout this Proxy Statement, we refer to these registered stockholders as "stockholders of record."

"Street Name" Stockholders. If shares of our common stock are held on your behalf in a brokerage account or by a bank or other nominee, you are considered to be the beneficial owner of shares that are held in "street name," and the Proxy Materials were forwarded to you by your broker or nominee, who is considered the stockholder of record with respect to those shares. As the beneficial owner, you have the right to direct your broker, bank or other nominee as to how to vote your shares. Beneficial owners are also invited to attend our virtual Annual Meeting. However, since a beneficial owner is not the stockholder of record, you may not vote your shares of our common stock on your own behalf at the Annual Meeting unless you follow your broker's procedures for obtaining a legal proxy. Note you should also be receiving a voting instruction form for you to use from your broker. Throughout this Proxy Statement, we refer to stockholders who hold their shares through a broker, bank or other nominee as "street name" stockholders.

How do I vote?

If you are a stockholder of record, there are several ways for you to vote your shares:

- *Online*. You may vote at www.proxyvote.com, 24 hours a day, seven (7) days a week. You will need the 16-digit control number included on your Notice. Votes submitted online must be received by 11:59 p.m. Eastern Time on June 9, 2025.
- *By Telephone*. You may vote by calling 1-800-690-6903, 24 hours a day, seven (7) days a week. You will need the 16-digit control number included on your Notice. Votes submitted by telephone must be received by 11:59 p.m. Eastern Time on June 9, 2025.
- *By Mail*. If you requested and received a paper copy of the Proxy Materials you may vote by mail by completing, signing and dating the enclosed proxy card and returning it in the enclosed prepaid envelope. Votes submitted through the mail must be received by June 9, 2025.
- *By QR Code*. You may vote by scanning the QR code on your proxy card with your mobile device. Votes submitted by QR code must be received by 11:59 p.m. Eastern Time on June 9, 2025.
- *During the Annual Meeting*. You may vote during the Annual Meeting by going to www.virtualshareholdermeeting.com/UPB2025. You will need the 16-digit control number included on your proxy card.

If the Annual Meeting is adjourned or postponed, the deadlines above may be extended.

The voting deadlines and availability of telephone and online voting for "street name" stockholders will depend on the voting processes of the organization that holds your shares. Therefore, we urge you to carefully review and follow the voting instruction card and any other materials that you receive from that organization. **If you hold your shares of Upstream Bio, Inc. common stock in multiple accounts, you should vote your shares as described in each set of Proxy Materials you receive.**

Can I vote by proxy?

If you will not be attending the Annual Meeting, you may vote by proxy. You can vote by proxy online by following the instructions provided in the enclosed proxy card. Proxies submitted by mail must be received by June 9, 2025.

If you submit a proxy without giving voting instructions, your shares will be voted in the manner recommended by the board of directors on all matters presented in this Proxy Statement, and as the persons named as proxies in the proxy card may determine in their discretion with respect to any other matters properly presented at the Annual Meeting. You may also authorize another person or persons to act for you as proxy in a writing, signed by you or your authorized representative, specifying the details of such authority. The original writing must be given to each of the named proxies, although it may be sent to them by electronic transmission if, from that transmission, it can be determined that the transmission was authorized by you.

If any other matters are properly presented for consideration at the Annual Meeting, including, among other things, consideration of a motion to adjourn the Annual Meeting to another time or place (including, without limitation, for the purpose of soliciting additional proxies), the persons named in your proxy and acting thereunder will have discretion to vote on those matters in accordance with their best judgment. We do not currently anticipate that any other matters will be raised at the Annual Meeting.

How can I virtually attend the Annual Meeting?

To attend and participate in the Annual Meeting, stockholders will need to access the live webcast of the meeting. To do so, stockholders of record will need to visit www.virtualshareholdermeeting.com/UPB2025, and "street name" stockholders will need to follow the instructions provided in the voting instructions form by the broker, bank or other nominee that holds their shares.

The live webcast of the Annual Meeting will begin promptly at 8:00 a.m. Eastern Time on June 10, 2025. We encourage stockholders to login to the virtual meeting website and access the webcast before the Annual Meeting's start time. You should allow ample time in advance of the meeting.

Additionally, questions regarding how to attend and participate via the Internet can be answered by following the assistance instructions included on the virtual meeting website (www.virtualshareholdermeeting.com/UPB2025) or by calling the phone number provided on the virtual meeting website on the day of the Annual Meeting.

If you wish to submit a question during the Annual Meeting, you may log into, and submit a question on, the virtual meeting platform using the unique link provided to you on your proxy card and following the instructions there. Our Annual Meeting will be governed by the Annual Meeting's Rules of Conduct, which will address the ability of stockholders to ask questions during the meeting and rules for how questions will be recognized and addressed. The Annual Meeting's Rules of Conduct will be available during the meeting on the virtual meeting website (www.virtualshareholdermeeting.com/UPB2025).

How do I revoke my proxy?

You may revoke your proxy by (1) following the instructions on the Notice and entering a new vote by mail that we receive by June 9, 2025 or online by 11:59 p.m. Eastern Time on June 9, 2025, (2) attending and voting at the Annual Meeting (although attendance at the Annual Meeting will not automatically revoke a proxy), or (3) by filing an instrument in writing revoking the proxy or another duly executed proxy bearing a later date with our corporate secretary. Any written notice of revocation or subsequent proxy card must be received by our corporate secretary prior to the taking of the vote at the Annual Meeting. Such written notice of revocation or subsequent proxy card should be hand delivered to our corporate secretary or sent to our principal executive offices at Upstream Bio, Inc., 890 Winter Street, Suite 200, Waltham, MA 02451, Attention: Corporate Secretary.

"Street name" stockholders must contact their broker, bank, or nominee to find out how to change their vote.

How is a quorum reached?

Our Second Amended and Restated Bylaws ("bylaws") provide that the presence in person or by remote communication, or represented by proxy, of the holders of a majority in voting power of the outstanding shares of stock entitled to vote shall be necessary and sufficient to constitute a quorum for the transaction of business at the Annual Meeting. Under the General Corporation Law of the State of Delaware, shares that are voted "abstain" or "withheld" and "broker non-votes" are counted as present for purposes of determining whether a quorum is present at the Annual Meeting. If a quorum is not present, the meeting may be adjourned until a quorum is obtained.

How is the vote counted?

Under our bylaws, to be elected, each of the directors nominated in Proposal No. 1 must receive a plurality of the votes properly cast for Proposal No. 1. You may vote for all the director nominees, withhold authority to vote your shares for all the director nominees or withhold authority to vote your shares with respect to any one or more of the director nominees. Withholding authority to vote your shares with respect to one or more director nominees will have no effect on the outcome of the election of such director(s). Broker non-votes are not considered votes cast and will have no effect on the outcome of the election of directors. A broker non-vote occurs when a nominee holding shares for a beneficial owner does not vote on a particular proposal because the nominee does not have discretionary voting power with respect to that item and has not received instructions from the beneficial owner.

Under our bylaws, any proposal other than an election of directors is decided by the affirmative vote of a majority of the votes properly cast for and against such matter, except where a larger vote is required by law, by our Third Amended and Restated Certificate of Incorporation ("certificate of incorporation"), or our bylaws. Abstentions and broker-non votes will be treated as shares present for the purpose of determining the presence of a quorum for the transaction of business at the Annual Meeting, but will not be counted as votes cast and will have no effect on the outcome of the vote for such proposal.

For "street name" stockholders, your brokerage firm is required to vote your shares according to your instructions. If you do not give instructions to your brokerage firm, the brokerage firm will still be able to vote your shares with respect to "discretionary" items, but will not be allowed to vote your shares with respect to "non-discretionary" items.

Proposal No. 1 is a "non-discretionary" item. If you do not instruct your broker how to vote your shares with respect to this proposal, your broker may not vote for this proposal, and those shares will be counted as broker non-votes. Proposal No. 2 is considered to be a discretionary item, and your brokerage firm will be able to vote your shares on this proposal even if it does not receive instructions from you. Accordingly, we do not anticipate that there will be any broker non-votes on Proposal No. 2; however, any broker non-votes will not be counted as votes cast and will therefore have no effect on the outcome of this proposal.

Who pays the cost for soliciting proxies?

We are making this solicitation and will pay the entire cost of preparing and distributing the Notice and our Proxy Materials and soliciting votes. If you choose to access the Proxy Materials or vote over the Internet, you are responsible for any Internet access charges that you may incur. Our officers and employees may, without compensation other than their regular compensation, solicit proxies through further mailings, personal conversations, e-mails, or otherwise. We have hired Broadridge Financial Solutions, Inc. to assist us in the distribution of Proxy Materials. Proxy solicitation expenses that we will pay include those for preparation, mailing, returning, and tabulating the proxies.

How may stockholders submit matters for consideration at next year's annual meeting?

The required notice must be in writing and received by our corporate secretary at our principal executive offices not later than the close of business on February 10, 2026, nor earlier than the close of business on March 12, 2026 (not less than 90 days nor more than 120 days prior to the first anniversary of the Annual Meeting). However, in the event that the date of next year's annual meeting is advanced by more than 30 days or delayed by more than 60 days from the first anniversary of the Annual Meeting, a stockholder's notice must be received no earlier than the 120th day prior to such annual meeting and not later than the close of business on the later of (A) the 90th day prior to such annual meeting and (B) the tenth day following the day on which notice of the date of such annual meeting was mailed or public disclosure of the date of such annual meeting was made, whichever first occurs. In addition, to comply with the SEC's universal proxy rules, stockholders who intend to solicit proxies in support of director nominees other than our nominees must provide notice to us in accordance with the additional requirements of Rule 14a-19(b), which, among other things, requires that notice be postmarked or transmitted electronically to our principal executive offices by no later than April 27, 2025 for director nominations to be brought before the Annual Meeting, which is ten calendar days following the date of this proxy statement, which is the day on which public announcement of the date of the Annual Meeting is first being made. For director nominations to be brought before

the 2026 annual meeting, notice must be postmarked or transmitted electronically to our principal executive offices by no later than April 11, 2026, which is 60 days before the one-year anniversary date of the Annual Meeting, except that if the 2026 annual meeting is more than 30 days before or after the anniversary date of the Annual Meeting, then notice must be provided by the later of 60 days prior to the date of the 2026 annual meeting or the tenth day following the day on which public announcement of the date of the annual meeting is first made.

In addition, any stockholder proposal intended to be included in the proxy statement for the next annual meeting of our stockholders in 2026 must also satisfy the requirements of SEC Rule 14a-8 under the Exchange Act, and be received not later than December 18, 2025. If the date of the annual meeting is moved by more than 30 days from the date contemplated at the time of the previous year's proxy statement, then notice must be received within a reasonable time before we begin to print and send proxy materials. If that happens, we will publicly announce the deadline for submitting a proposal in a document filed with the SEC.

How can I get help if I have trouble checking in or listening to the meeting online?

If you encounter any difficulties accessing the virtual meeting during the check-in or meeting time, please refer to the instructions on the virtual meeting website and the phone number made available on the day of the meeting on the virtual meeting website.

How can I know the voting results?

We plan to announce preliminary voting results at the Annual Meeting. Final voting results will be published in a Current Report on Form 8-K ("Form 8-K") that we expect to file with the SEC within four business days after the Annual Meeting. If final voting results are not available to us in time to file a Form 8-K within four business days after the Annual Meeting, we intend to file a Form 8-K to publish preliminary results and, within four business days after the final results are known to us, amend such Form 8-K to publish the final results.

PROPOSAL NO. 1 – ELECTION OF CLASS I DIRECTORS

Our board of directors currently consists of seven members. In accordance with the terms of our certificate of incorporation and bylaws, our board of directors is divided into three classes, with members of each class serving staggered three-year terms. The members of the classes are divided as follows:

- the class I directors are Erez Chimovits, M.B.A., M.Sc. and Marcella Kuhlman Ruddy, M.D., M.S., and their terms will expire at the Annual Meeting;
- the class II directors are H. Edward Fleming, Jr., M.D. and Liam Ratcliffe, M.B.Ch.B., Ph.D., M.B.A., and their terms will expire at the annual meeting of stockholders to be held in 2026; and
- the class III directors are E. Rand Sutherland, M.D., Ronald C. Renaud, Jr., M.B.A. and Daniella Beckman, and their terms will expire at the annual meeting of stockholders to be held in 2027.

Upon the expiration of the term of a class of directors, directors in that class will be eligible to be elected for a new three-year term at the annual meeting of stockholders in the year in which their term expires. This year, the term of our class I directors, Mr. Chimovits and Dr. Ruddy, is expiring.

Our certificate of incorporation and bylaws provide that the authorized number of directors may be changed only by resolution of our board of directors. Our certificate of incorporation also provides that our directors may be removed only for cause by the affirmative vote of the holders of not less than two-thirds (2/3) of the voting power of the outstanding shares then entitled to vote at an election of directors, and that any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, may be filled only by the affirmative vote of a majority of our directors then in office, even if less than a quorum.

In selecting board members, we identify members who (i) possess relevant experience and expertise to enable him or her to be able to offer germane advice and guidance to management; (ii) have proven achievement and competence in his or her field; (iii) have the ability to exercise sound business judgment; (iv) have an understanding of the fiduciary responsibilities required of a director; (v) are committed to devoting time and energy to the affairs of the Company; (vi) have a diverse personal background, perspective and experience; (vii) are committed to vigorously representing the long-term interests of the Company's stockholders; and (viii) have the highest personal integrity and ethics.

In addition to the information presented below regarding each of the nominees and continuing directors' specific experience, qualifications, attributes and skills that our board of directors and our nominating and corporate governance committee considered in determining that he or she should serve as a director, we also believe that each of our directors has demonstrated business acumen, integrity and an ability to exercise sound judgment, as well as a commitment of service to Upstream Bio and our board of directors.

Nominees for Election as Class I Directors

The following table identifies our director nominees, their positions and offices, the year of commencement of their service with us, and their ages as of April 14, 2025:

Name	Positions and Offices Held with Upstream Bio	Director Since	Age
Erez Chimovits, M.B.A., M.Sc.	Director	2021	61
Marcella Kuhlman Ruddy, M.D., M.S.	Director	2023	62

Erez Chimovits, M.B.A., M.Sc. has served on our board of directors since October 2021. Mr. Chimovits is a Partner at OrbiMed, an investment firm, where he has served in various roles of increasing responsibility since November 2010. Mr. Chimovits previously served on the boards of directors of Adicet Bio, Inc. from January 2016 until March 2021, BiomX, Inc. from December 2015 until October 2020, LogicBio Therapeutics, Inc. from January 2016 until December 2020, and Novus Therapeutics, Inc. (now Eledon Pharmaceuticals, Inc) from June 2017 until September 2020. Mr. Chimovits served as Chief Executive Officer of NasVax Ltd. (now SciSparc Ltd.) from January 2007 to November 2010. Previously, Mr. Chimovits served as President of Compugen USA Inc., a

subsidiary of Compugen Ltd., from January 2001 to January 2007, and as Executive Vice President in Commercial Operations from December 1999 to January 2007. Mr. Chimovits holds an M.B.A., M.Sc. in Microbiology, and B.Sc. from Tel Aviv University. We believe Mr. Chimovits is qualified to serve as a member of our board of directors because of his professional background in the biopharmaceutical industry.

Marcella Kuhlman Ruddy, M.D., M.S. has served on our board of directors since January 2023. Since July 2021, Dr. Ruddy has served as Chief Medical Officer at Tectonic Therapeutic, Inc. From June 2016 until June 2021, Dr. Ruddy was at Regeneron Pharmaceuticals, Inc. where she was the Head of Clinical Development for the Immunology/Inflammation Therapeutic Area. Previously, Dr. Ruddy held positions of increasing responsibility, including Head of Early Clinical Development for Immunology, from November 2004 until June of 2014 at Merck & Company, Inc. ("Merck"). From November 2015 until June 2016, Dr. Ruddy served as Vice President, Clinical Development and Head of Pharmacovigilance at Alnylam Pharmaceuticals, Inc. From June 2014 until November 2014, Dr. Ruddy served as Vice President of Clinical Immunology at EMD Serono, Inc., Merck's healthcare business. From June 1996 until October 2004, Dr. Ruddy held a staff position in the Pulmonary Unit at Massachusetts General Hospital/Harvard Medical School where she founded and directed the Adult Cystic Fibrosis Program. Dr. Ruddy has served on the board of directors of Sionna Therapeutics, Inc. ("Sionna Therapeutics") since January 2025. Dr. Ruddy holds a B.A. from Princeton University and a M.D. and M.S. from Washington University, St. Louis and completed her Internal Medicine and Pulmonary fellowship training at Harvard Medical School affiliated hospitals. We believe Dr. Ruddy is qualified to serve as a member of our board of directors because of her extensive experience in both drug development and the biopharmaceutical industry.

The proxies will be voted in favor of the above nominees unless a contrary specification is made on the proxy. The nominees have indicated a willingness to continue to serve as directors, if elected. If any nominee becomes unable or unwilling to serve, however, the proxies may be voted for a substitute nominee selected by our board of directors.

Vote Required

To be elected, each director nominee must receive a plurality of the votes properly cast for the election of directors. Withheld votes and broker non-votes will have no effect on the outcome of this proposal.

Board Recommendation

The board of directors recommends that stockholders vote "FOR" the election of Mr. Chimovits and Dr. Ruddy as class I directors, to serve for a three-year term ending at the annual meeting of stockholders to be held in 2028.

Directors Continuing in Office

The following table identifies our continuing directors, and sets forth their positions and offices, the year of commencement of their service with us, and their ages as of April 14, 2025:

Name	Position and Offices Held with Upstream Bio	Director Since	Class and Year in Which Term Will Expire	Age
H. Edward Fleming, Jr., M.D.	Director	2023	Class II – 2026	62
Liam Ratcliffe, M.B.Ch.B., Ph.D., M.B.A.	Director	2021	Class II – 2026	61
E. Rand Sutherland, M.D.	Chief Executive Officer and Director	2024	Class III – 2027	55
Ronald C. Renaud, Jr., M.B.A.	Director	2021	Class III – 2027	56
Daniella Beckman	Director	2024	Class III – 2027	46

Class II Directors (Term Expires at 2026 Annual Meeting)

H. Edward Fleming, Jr., M.D. has served on our board of directors since June 2023. Since November 2022, Dr. Fleming has served as the Executive Vice President of Enavate Sciences where he works closely to invest in and build therapeutic companies. From January 1997 until August 2022, Dr. Fleming held multiple positions at McKinsey & Company ("McKinsey"), most recently as Senior Partner and global leader of McKinsey's research and development practice. Dr. Fleming has served on the boards of directors of CRISPR Therapeutics AG since June 2021 and Sionna Therapeutics since March 2024. Dr. Fleming holds a B.A. in Chemistry from Harvard University, his M.D. from Vanderbilt University, and completed internal medicine training at Johns Hopkins Hospital and subspecialty training in Pulmonary and Critical Care Medicine at the University of California, San Francisco. We believe Dr. Fleming is qualified to serve on our board of directors because of his experience in the healthcare industry, including working closely with biopharmaceutical companies on strategy, operational performance and research and development innovation.

Liam Ratcliffe, M.B.Ch.B., Ph.D., M.B.A. has served on our board of directors since October 2021. Since April 2019, Dr. Ratcliffe has served as Head of Biotechnology at Access Industries, a privately held industrial group. From September 2008 until March 2019, Dr. Ratcliffe held various positions at New Leaf Venture Partners, most recently as Managing Director. From January 1997 until August 2008, Dr. Ratcliffe was Worldwide Head of Clinical Research and Development at Pfizer Inc. Dr. Ratcliffe has served as a member of the boards of directors of Disc Medicine, Inc. since September 2019 and Eliem Therapeutics, Inc. since October 2019. Previously, Dr. Ratcliffe served as a member of the boards of directors of Arvinas, Inc. from October 2015 until August 2022, Passage Bio, Inc. from September 2019 until March 2022, Unum Therapeutics, Inc. from March 2018 until April 2019, Deciphera Pharmaceuticals, Inc. from September 2017 until March 2019, Aptinyx, Inc. from June 2018 until April 2019 and Edge Therapeutics, Inc. (now PDS Biotechnology Corp.) from October 2015 until November 2018. Dr. Ratcliffe holds an M.B.Ch.B. and a Ph.D. in immunology from University of Cape Town and an M.B.A. from the University of Michigan. We believe Dr. Ratcliffe is qualified to serve as a member of our board of directors because of his extensive clinical development and venture capital experience in the life sciences industry.

Class III Directors (Term Expires at 2027 Annual Meeting)

E. Rand Sutherland, M.D. has served as our Chief Executive Officer and on our board of directors since April 2024. From May 2022 until June 2023, Dr. Sutherland served as Chief Executive Officer of Seeker Biologics Inc., a privately held biotechnology company. Dr. Sutherland served as President of Translate Bio, Inc. ("Translate Bio") from March 2021 until its acquisition by Sanofi in September 2021. From February 2014 to March 2021, Dr. Sutherland served in various research and development and medical affairs roles at Sanofi, most recently as Senior Vice President and Global Head of Medical Affairs for Sanofi Genzyme from July 2018 to March 2021. Previously, Dr. Sutherland was Professor of Medicine at the University of Colorado and Chief of Pulmonary and Critical Care Medicine at National Jewish Health in Denver, where he treated patients and led an NIH-funded translational research program in severe asthma. Dr. Sutherland has served as a director of Krystal Biotech, Inc. since January 2022. He previously served on the board of directors of Allakos Inc. from August 2023 until May 2024. Dr. Sutherland holds a B.A. from Oberlin College, an M.P.H. from the Harvard School of Public Health and an M.D. from the University of Chicago. Dr. Sutherland completed his post-doctoral training in Internal Medicine at the University of California, San Francisco, where he also served as Chief Medical Resident, followed by a fellowship in Pulmonary and Critical Care Medicine at the University of Colorado. We believe Dr. Sutherland is qualified to serve as a member of our board of directors because of his scientific and professional background, and his familiarity with our Company as Chief Executive Officer.

Ronald C. Renaud, Jr., M.B.A. is Chair of our board of directors and has served on our board of directors since November 2021. Since October 2024, Mr. Renaud has served as President and Chief Executive Officer and a member of the board of directors at Kailera Therapeutics, Inc. Prior to this, Mr. Renaud served as President and Chief Executive Officer and a member of the board of directors of Cerevel Therapeutics Holdings, Inc. from June 2023 until August 2024. Prior to this, Mr. Renaud was a partner at Bain Capital Life Sciences from September 2022 through June 2023. Prior to this, he served as Chair and Chief Executive Officer of Translate Bio from 2014 until its acquisition by Sanofi in September 2021. Prior to this, Mr. Renaud was at Idenix Pharmaceuticals, Inc. from 2007 through 2014, where he served as Chief Financial Officer, Chief Business Officer and, finally, President and Chief Executive Officer at the time of its acquisition by Merck. Prior to this, Mr. Renaud was a biotechnology equity

research analyst at J.P. Morgan, Schwab Soundview and Bear Stearns from January 2000 until February 2006. Mr. Renaud also served in various positions at Amgen Inc. from April 1994 until December 1999. Mr. Renaud previously served on the boards of Atara Biotherapeutics, Inc. from April 2020 until December 2022, Ikena Oncology, Inc. from March 2018 until December 2022, Chimerix, Inc. from December 2014 until November 2021, and Akebia Therapeutics, Inc. from September 2014 until December 2018. Mr. Renaud holds a B.A. from St. Anselm College and an M.B.A. from the Marshall School of Business at the University of Southern California. We believe Mr. Renaud is qualified to serve on our board of directors because of his leadership and management experience and his extensive knowledge of the biopharmaceutical industry.

Daniella Beckman has served on our board of directors since October 2024. Ms. Beckman has served as the Chief Financial Officer of Tango Therapeutics, Inc. since September 2019, where she previously served as interim Chief Financial Officer from October 2016 to September 2019. From November 2015 to September 2019, she provided consulting and interim chief financial officer services for early-stage biotechnology companies. From June 2011 until August 2014, Ms. Beckman served as Chief Financial Officer of Idenix Pharmaceuticals, Inc., where she previously served as Corporate Controller from March 2008 until June 2011. Ms. Beckman has served on the boards of directors of Blueprint Medicines Corporation since December 2021 and Vor Biopharma Inc. since July 2020, and previously served on the boards of directors of 5:01 Acquisition Corp. from October 2020 to October 2022 and Translate Bio from October 2017 to September 2021. Ms. Beckman holds a B.S. from Boston University. We believe Ms. Beckman is qualified to serve as a member of our board of directors because of her financial expertise and leadership experience in the biopharmaceutical industry.

PROPOSAL NO. 2 – RATIFICATION OF THE APPOINTMENT OF PRICEWATERHOUSECOOPERS LLP AS UPSTREAM BIO'S INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM FOR THE FISCAL YEAR ENDING DECEMBER 31, 2025

Upstream Bio's stockholders are being asked to ratify the appointment by the audit committee of the board of directors of PwC as the Company's independent registered public accounting firm for the fiscal year ending December 31, 2025. PwC has served as Upstream Bio's independent registered public accounting firm since 2022.

The audit committee is solely responsible for selecting Upstream Bio's independent registered public accounting firm for the fiscal year ending December 31, 2025. Stockholder approval is not required to appoint PwC as Upstream Bio's independent registered public accounting firm. However, the board of directors believes that submitting the appointment of PwC to the stockholders for ratification is good corporate governance. If the stockholders do not ratify this appointment, the audit committee will consider whether it is appropriate to select another independent registered public accounting firm. If the selection of PwC is ratified, the audit committee, at its discretion, may direct the appointment of a different independent registered public accounting firm at any time it decides that such a change would be in the best interest of Upstream Bio and its stockholders.

A representative of PwC is expected to be present at the Annual Meeting and will have an opportunity to make a statement if he or she desires to do so, and to respond to appropriate questions from our stockholders.

Principal Accountant Fees and Services

Upstream Bio incurred the following fees from PwC for the fiscal years ended December 31, 2024 and 2023:

Fee Category	2024 ($)	2023 ($)
Audit Fees[(1)]	2,040,000	250,000
Audit-Related Fees	—	—
Tax Fees	—	—
All Other Fees[(2)]	2,125	—
Total Fees	2,042,125	250,000

(1) Audit Fees consist of fees billed for professional services performed by PwC for the audit of our annual consolidated financial statements, the review of interim consolidated financial statements, review of the registration statement on Form S-1 and the delivery of comfort letters for our initial public offering, review of the registration statement on Form S-8, and related services that are normally provided in connection with statutory and regulatory filings or engagements.
(2) All Other Fees consist of fees billed for our subscription to PwC software used in connection with the preparation of our financial statements.

Audit Committee Pre-approval Policy and Procedures

Our audit committee has adopted a pre-approval policy relating to the approval of all audit and non-audit services that are to be performed by our independent registered public accounting firm. This policy provides that we will not engage our independent registered public accounting firm to render audit or non-audit services unless our audit committee either pre-approves the specific service or pre-approves a specified category of services that are expected to be provided to us by our independent registered public accounting firm during the next 12 months. Any such pre-approval details the particular service or type of services to be provided and is also generally subject to a maximum dollar amount.

During the fiscal years ended December 31, 2024 and 2023, all audit and non-audit services provided to us by PwC were pre-approved in accordance with the pre-approval policy described above.

Vote Required

To ratify the appointment of PwC as our independent registered public accounting firm for the fiscal year ending December 31, 2025, the affirmative vote of a majority of the votes properly cast for and against Proposal No. 2 is required. Abstentions will have no effect on the outcome of this proposal. This proposal is considered to be a discretionary item, and your broker will be able to vote on this proposal even if it does not receive instructions from you. Accordingly, we do not anticipate that there will be any broker non-votes on this proposal; however, any broker non-votes will not be counted as votes cast and will therefore have no effect on the outcome of this proposal.

Board Recommendation

The board of directors recommends voting "FOR" Proposal No. 2 to ratify the appointment of PwC as Upstream Bio's independent registered public accounting firm for the fiscal year ending December 31, 2025.

CORPORATE GOVERNANCE

Director Nomination Process

Our nominating and corporate governance committee is responsible for identifying individuals qualified to serve as directors, consistent with criteria approved by our board, and recommending such persons to be nominated for election as directors, except where we are legally required by contract, law or otherwise to provide third parties with the right to nominate.

The process followed by our nominating and corporate governance committee to identify and evaluate director candidates includes requests to board members and others, including search firms or other advisors, for recommendations, meetings from time to time to evaluate biographical information and background material relating to potential candidates, including review of detailed questionnaires and comprehensive background checks, and interviews of selected candidates by management, recruiters, members of the committee and our board. The nominating and corporate governance committee meets as a group to discuss and evaluate the qualities and skills of each candidate, both on an individual basis and taking into account the overall composition and needs of our board of directors. Based on the results of the evaluation process, the nominating and corporate governance committee recommends candidates for the board of directors' approval to fill a vacancy or as director nominees for election to the board of directors by our stockholders each year in the class of directors whose term expires at the relevant annual meeting.

The qualifications, qualities and skills that our nominating and corporate governance committee believes must be met by a committee recommended nominee for a position on our board of directors are as follows:

- Nominees should have relevant experience and expertise to enable him or her to be able to offer germane advice and guidance to management.
- Nominees should have proven achievement and competence in the nominee's field and the ability to exercise sound business judgment.
- Nominees should have an understanding of the fiduciary responsibilities that are required of a member of the board of directors and the commitment of time and energy necessary to diligently carry out those responsibilities.
- Nominees should have a diverse personal background, perspective and experience.
- Nominees should have a commitment to vigorously represent the long-term interests of our stockholders.

Stockholders may recommend individuals to the nominating and corporate governance committee for consideration as potential director candidates. Any such stockholder proposals should be submitted to our corporate secretary at our principal executive offices no later than the close of business on the 90th day nor earlier than the close of business on the 120th day prior to the one-year anniversary of the date of the preceding year's annual meeting and should include appropriate biographical and background material to allow the nominating and corporate governance committee to properly evaluate the potential director candidate and the number of shares of our stock beneficially owned by the stockholder proposing the candidate. Stockholder proposals should be addressed to Upstream Bio, Inc., 890 Winter Street, Suite 200, Waltham, MA 02451, Attention: Corporate Secretary. Assuming that biographical and background material has been provided on a timely basis in accordance with our bylaws, any recommendations received from stockholders will be evaluated in the same manner and using the same criteria as potential nominees proposed by the nominating and corporate governance committee and/or recommended by our board of directors. If our board of directors determines to nominate a stockholder recommended candidate and recommends his or her election, then his or her name will be included on our proxy card for the next annual meeting of stockholders. See "Stockholder Proposals" for a discussion of submitting stockholder proposals.

Director Independence

Applicable rules of the Nasdaq Stock Market ("Nasdaq") require a majority of a listed company's board of directors to be comprised of independent directors within one year of listing. In addition, the Nasdaq rules require that, subject to specified exceptions, each member of a listed company's audit, compensation and nominating and corporate governance committees be independent and that audit committee members also satisfy independence criteria set forth in Rule 10A-3 under the Exchange Act and that compensation committee members satisfy independence criteria set forth in Rule 10C-1 under the Exchange Act. Under applicable Nasdaq rules, a director will only qualify as an "independent director" if, in the opinion of the listed company's board of directors, that person does not have a relationship that would interfere with the exercise of independent judgment in carrying out the responsibilities of a director. In order to be considered independent for purposes of Rule 10A-3, a member of an audit committee of a listed company may not, other than in his or her capacity as a member of the audit committee, the board of directors, or any other board committee, accept, directly or indirectly, any consulting, advisory, or other compensatory fee from the listed company or any of its subsidiaries or otherwise be an affiliated person of the listed company or any of its subsidiaries. In addition, in affirmatively determining the independence of any director who will serve on a company's compensation committee, Rule 10C-1 under the Exchange Act requires that a company's board of directors must consider all factors specifically relevant to determining whether a director has a relationship to such company which is material to that director's ability to be independent from management in connection with the duties of a compensation committee member, including: the source of compensation to the director, including any consulting, advisory or other compensatory fee paid by such company to the director, and whether the director is affiliated with the company or any of its subsidiaries or affiliates.

Our board of directors has determined that all members of the board of directors are independent directors, including for purposes of the rules of Nasdaq and the SEC, except for Dr. Sutherland, due to his role as the Chief Executive Officer of the Company. In making such determination, our board of directors considered the relationships that each non-employee director has with us and all other facts and circumstances that our board of directors deemed relevant in determining their independence, including the beneficial ownership of our capital stock by each non-employee director, as well as the association of our directors with holders of five percent or more of our common stock. There are no family relationships among any of our directors or executive officers.

Board Committees

Our board of directors has established an audit committee, a compensation committee and a nominating and corporate governance committee. Each of our board committees operate under a charter that satisfies the applicable standards of the SEC and Nasdaq, which is reviewed by the respective committee at least annually A current copy of the charter for each of the audit committee, compensation committee, and nominating and corporate governance committee is posted on the corporate governance section of our website at *investors.upstreambio.com/corporate-governance*.

Audit Committee

Ms. Beckman, Dr. Fleming, and Dr. Ratcliffe serve on the audit committee, which is chaired by Ms. Beckman. Our board of directors has determined that each member of the audit committee is "independent" for audit committee purposes as that term is defined by the rules of the SEC and Nasdaq, and that each has sufficient knowledge in financial and auditing matters to serve on the audit committee. Our board of directors has designated Ms. Beckman as an "audit committee financial expert," as defined under the applicable rules of the SEC. During the fiscal year ended December 31, 2024, the audit committee met three times. The audit committee's responsibilities include:

- appointing, approving the compensation of, and assessing the independence of our independent registered public accounting firm;
- pre-approving auditing and permissible non-audit services, and the terms of such services, to be provided by our independent registered public accounting firm;
- reviewing the overall audit plan with our independent registered public accounting firm and members of management responsible for preparing our financial statements;

- reviewing and discussing with management and our independent registered public accounting firm our annual and quarterly financial statements and related disclosures as well as critical accounting policies and practices used by us;
- coordinating the oversight and reviewing the adequacy of our internal control over financial reporting;
- establishing policies and procedures for the receipt and retention of accounting-related complaints and concerns;
- recommending, based upon the audit committee's review and discussions with management and our independent registered public accounting firm, whether our audited financial statements shall be included in our Annual Report on Form 10-K;
- monitoring the integrity of our financial statements and our compliance with legal and regulatory requirements as they relate to our financial statements and accounting matters;
- preparing the audit committee report required by SEC rules to be included in our annual proxy statement;
- reviewing all related person transactions for potential conflict of interest situations and approving all such transactions;
- reviewing quarterly earnings releases; and
- reviewing our major risk exposures, including financial, operational, cybersecurity, competition, legal and regulatory exposures.

All audit and non-audit services to be provided to us by our independent registered public accounting firm, other than de minimis non-audit services, must be approved in advance by our audit committee.

Compensation Committee

Mr. Chimovits, Dr. Ratcliffe, and Mr. Renaud serve on the compensation committee, which is chaired by Mr. Renaud. Our board of directors has determined that each member of the compensation committee is "independent" as defined in the applicable Nasdaq rules. During the fiscal year ended December 31, 2024, the compensation committee met three times. The compensation committee's responsibilities include:

- annually reviewing and recommending to the board of directors the corporate goals and objectives relevant to the compensation of our Chief Executive Officer;
- evaluating the performance of our Chief Executive Officer in light of such corporate goals and objectives and based on such evaluation (i) reviewing and recommending to the board of directors the cash compensation of our Chief Executive Officer, and (ii) reviewing and recommending to the board of directors grants and awards to our Chief Executive Officer under equity-based plans;
- reviewing and approving the compensation of our other executive officers;
- developing and implementing compensation policies and plans;
- overseeing and administering our compensation and similar plans;
- evaluating and assessing potential and current compensation advisors in accordance with the independence standards identified in the applicable Nasdaq listing rules;
- retaining and approving the compensation of any compensation advisors;
- reviewing and recommending to the board of directors our policies and procedures for the grant of equity-based awards;
- reviewing and recommending to the board of directors the compensation of our directors;
- preparing our compensation committee report if and when required by SEC rules;

- reviewing and discussing annually with management our Compensation Discussion and Analysis, if and when required, to be included in our annual proxy statement; and
- reviewing and approving the retention or termination of any consulting firm or outside advisor to assist in the evaluation of compensation matters.

The compensation committee may establish and delegate authority to one or more subcommittees consisting of one or more of its members to carry out its responsibilities. For example, the compensation committee has delegated authority to the Chief Executive Officer (i) to grant equity-based awards under any incentive-compensation plans and equity-based plans to employees, including newly hired and current employees, and consultants serving at or below the level of Senior Vice President, subject to any equity grant guidelines or limits, or vesting policy approved by the board of directors and (ii) to make other cash compensation awards for employees serving at or below the level of Senior Vice President, subject to approved guidelines and established limits. Additionally, to the extent permitted by applicable law and the provisions of any employee benefit plan, the compensation committee may delegate any of its duties, responsibilities or authority in connection with any employee benefit plan to members of management as the compensation committee deems appropriate.

Compensation Consultant

The compensation committee has engaged Alpine Rewards ("Alpine") as its independent compensation consultant. When requested, Alpine consultants attend meetings of our compensation committee, including executive sessions in which executive compensation-related matters are discussed without the presence of our management. Alpine reports to our compensation committee and not to our management, although Alpine meets with our management for purposes of gathering information for its analyses and recommendations.

Nominating and Corporate Governance Committee

Mr. Chimovits, Dr. Fleming, and Dr. Ruddy serve on the nominating and corporate governance committee, which is chaired by Dr. Ruddy. Our board of directors has determined that each member of the nominating and corporate governance committee is "independent" as defined in the applicable Nasdaq rules. During the fiscal year ended December 31, 2024, the nominating and corporate governance committee met one time. The nominating and corporate governance committee's responsibilities include:

- developing and recommending to the board of directors criteria for board and committee membership, including any specific qualities or skills, and reassessing such criteria on an ongoing basis;
- establishing procedures for identifying and evaluating board of director candidates, including nominees recommended by stockholders;
- identifying individuals qualified to become members of the board of directors;
- recommending to the board of directors the persons to be nominated for election as directors and to each of the board's committees;
- developing and recommending to the board of directors a code of business conduct and ethics and a set of corporate governance guidelines;
- reviewing and discussing with the board of directors succession plans for our key officers; and
- overseeing the evaluation of our board of directors, its committees and management.

Board and Committee Meetings Attendance

The full board of directors met seven times during 2024. During 2024, each member of the board of directors attended in person or participated via teleconference in at least 75% of the aggregate of (i) the total number of meetings of the board of directors (held during the period for which such person has been a director), and (ii) the total number of meetings held by all committees of the board of directors on which such person served (during the periods that such person served).

Director Attendance at Annual Meeting of Stockholders

Directors are responsible for attending the annual meeting of stockholders to the extent practicable.

Compensation Committee Interlocks and Insider Participation

None of the members of the compensation committee is currently, or has been at any time, one of our officers or employees. None of our officers currently serves, or has served during the last calendar year, as a member of the board of directors or compensation committee of any entity that has one or more executive officers serving as a member of our board of directors or compensation committee.

Policy on Trading, Pledging and Hedging of Company Stock

We have adopted an insider trading policy which governs transactions in our securities by the Company and its directors, officers, employees, and consultants that we believe is reasonably designed to promote compliance with insider trading laws, rules and regulations, and listing standards applicable to the Company. A copy of our insider trading policy is filed with our 2024 Annual Report as Exhibit 19.1.

Certain transactions in our securities (such as purchases and sales of publicly traded put and call options, and short sales) create a heightened compliance risk or could create the appearance of misalignment between management and stockholders. In addition, securities held in a margin account or pledged as collateral may be sold without consent if the owner fails to meet a margin call or defaults on the loan, thus creating the risk that a sale may occur at a time when an officer or director is aware of material, non-public information or otherwise is not permitted to trade in Company securities. Our insider trading policy expressly prohibits short sales and derivative transactions of our stock and purchases or sales of puts, calls, or other derivative securities of the Company or any derivative securities that provide the economic equivalent of ownership of any of the Company's securities or an opportunity, direct or indirect, to profit from any change in the value of the Company's securities or engage in any other hedging transaction with respect to the Company's securities, at any time, by our executive officers, directors and employees.

Rule 10b5-1 Trading Plan Policy

We have adopted a Rule 10b5-1 trading plan policy, which permits our officers, directors, employees and certain other persons to enter into trading plans complying with Rule 10b5-1 under the Exchange Act. Generally, under these trading plans, the individual relinquishes control over the transactions once the trading plan is put into place and can only put such plans into place while the individual is not in possession of material non-public information. Accordingly, sales under these plans may occur at any time, including possibly before, simultaneously with, or immediately after significant events involving our company.

Compensation Recovery Policy

In accordance with the requirements of the SEC and Nasdaq listing rules, we maintain a compensation recovery policy (the "clawback policy"). The clawback policy provides that in the event we are required to prepare a restatement of financial statements due to material noncompliance with any financial reporting requirement under securities laws, we must (subject to certain limited exceptions described in the clawback policy and permitted under the SEC and Nasdaq listing rules) recover any incentive-based compensation that was based upon the attainment of a financial reporting measure and that was received by any current or former executive officer during the three-year period preceding the date that the restatement was required if such compensation exceeds the amount that the executive officer would have received based on the restated financial statements. A copy of our compensation recovery policy is filed with our 2024 Annual Report as Exhibit 97.1.

Code of Business Conduct and Ethics

We have adopted a written code of business conduct and ethics that applies to our directors, officers and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. A current copy of the code is posted on the corporate governance section of our website, which is located at

https://investors.upstreambio.com/corporate-governance/documents-charters. If we make any substantive amendments to, or grant any waivers from, the code of business conduct and ethics for any officer or director, we will disclose the nature of such amendment or waiver on our website or in a current report on Form 8-K.

Board Leadership Structure and Board's Role in Risk Oversight

Currently, the role of chairperson of the board of directors is separated from the role of Chief Executive Officer. Our Chief Executive Officer is responsible for recommending strategic decisions and capital allocation to the board of directors and to ensure the execution of the recommended plans. Mr. Renaud is our current chairperson of the board of directors. The chairperson of the board of directors is responsible for leading the board of directors in its fundamental role of providing advice to and independent oversight of management. Our board of directors recognizes the time, effort and energy that the Chief Executive Officer is required to devote to his position in the current business environment, as well as the commitment required to serve as our chairperson, particularly as the board of directors' oversight responsibilities continue to grow. While our bylaws and Corporate Governance Guidelines do not require that our chairperson and Chief Executive Officer positions be separate, our board of directors believes that having separate positions is the appropriate leadership structure for us at this time and demonstrates our commitment to good corporate governance.

Risk is inherent to every business, and how well a business manages risk can ultimately determine its success. We face a number of risks, including risks relating to our financial condition, development and commercialization activities, operations, strategic direction and intellectual property. Management is responsible for the day-to-day management of risks we face, while our board of directors, as a whole and through its committees, has responsibility for the oversight of risk management. In its risk oversight role, our board of directors has the responsibility to satisfy itself that the risk management processes designed and implemented by management are adequate and functioning as designed.

The role of the board of directors in overseeing the management of our risks is conducted primarily through committees of the board of directors, as disclosed in the descriptions of each of the committees above and in the charters of each of the committees. The full board of directors (or the appropriate board committee in the case of risks that are under the purview of a particular committee) discusses with management our major risk exposures, their potential impact on us, and the steps we take to manage them. When a board committee is responsible for evaluating and overseeing the management of a particular risk or risks, the chairperson of the relevant committee reports on the discussion to the full board of directors during the committee reports portion of the next board meeting. This enables the board of directors and its committees to coordinate the risk oversight role, particularly with respect to risk interrelationships.

Communication with the Directors of Upstream Bio

Any interested party with concerns about our company may report such concerns to the board of directors as a whole, or to individual directors on the board of directors, by submitting a written communication to the attention of such director at the following address:

c/o Upstream Bio, Inc.
890 Winter Street, Suite 200
Waltham, MA 02451
United States

The audit committee oversees the procedures for the receipt, retention, and treatment of complaints received by Upstream Bio regarding accounting, internal accounting controls, or audit matters, and the confidential, anonymous submission by employees of concerns regarding questionable accounting or auditing matters or potential violations of the federal securities laws. We have also established a toll-free telephone number for the reporting of such activity, which is (833) 805-1073, which permits submissions on a confidential and anonymous basis.

Executive Officers Who Are Not Directors

The following table identifies our executive officers who are not directors, their current positions, the year of commencement of their service with us, and their ages as of April 14, 2025:

Name	Position Held with Upstream Bio	Officer Since	Age
Michael Paul Gray, M.B.A	Chief Financial and Operating Officer	2024	54
Aaron Deykin, M.D.	Chief Medical Officer and Head of Research and Development	2022	59
Adam Houghton, Ph.D., M.B.A.	Chief Business Officer	2021	54
Allison Ambrose, J.D.	Sr. Vice President, General Counsel	2024	40

Michael Paul Gray, M.B.A. has served as our Chief Financial Officer and Chief Operating Officer since March 2024. Mr. Gray was Chief Financial Officer and Chief Operating Officer of Carmot Therapeutics, Inc. from June 2023 until February 2024. Mr. Gray was Chief Financial Officer and Chief Operating Officer of Imara, Inc. from April 2019 until March 2023 and Chief Financial Officer and Chief Operating Officer of Arsanis, Inc. from March 2016 until March 2019. Prior to this, Mr. Gray held a number of leadership positions at Curis, Inc., including most recently as Chief Financial Officer and Chief Business Officer from February 2013 until February 2016. Mr. Gray previously served on the board of directors of Therapeutics Acquisition Corporation, from May 2020 until its merger in July 2021. Mr. Gray holds a B.S. in business administration (accounting) from Bryant College and an M.B.A. in corporate finance and entrepreneurial management from the F.W. Olin Graduate School of Business at Babson College.

Aaron Deykin, M.D. has served as our Chief Medical Officer and Head of Research and Development since April 2022. From March 2020 until April 2022, Dr. Deykin was Senior Vice President of Clinical Sciences overseeing Biostatistics, Statistical Programming, Biomarkers, Clinical Pharmacology, Epidemiology, and Clinical Operations for Biogen, Inc.'s ("Biogen") pipeline globally. Prior to this, Dr. Deykin held other roles of increasing responsibility at Biogen, was a member of the faculty of Medicine at Harvard Medical School and a member of the Pulmonary and Critical Care faculty at Brigham and Women's Hospital. In that capacity, he treated patients with asthma and other advanced respiratory diseases while leading the medical activities of the Lung Transplantation Program, directing the Pulmonary Function Testing Laboratory and serving as the Associate Director of the Asthma Research Center. Dr. Deykin has been awarded board certification in Internal Medicine, Pulmonary Disease, and Critical Care Medicine, and holds an M.D. from Harvard Medical School and a B.A. from Dartmouth College.

Adam Houghton, Ph.D., M.B.A. has served as our Chief Business Officer since October 2021. From March 2019 until September 2021, Dr. Houghton was Vice President, Corporate Strategy, and Head of AbbVie Ventures, AbbVie Inc.'s corporate venture investment group and served as Senior Director and Head, Immunology Search and Evaluation from February 2015 until March 2019. Prior to this, Dr. Houghton was Senior Director and Head of Search and Evaluation at Biogen from July 2017 until February 2018. From November 2013 until February 2015, Dr. Houghton was Senior Director, Global External Research and Development, BioMedicines and Tailored Therapeutics at Eli Lilly and Company. Prior to this, Dr. Houghton was Section Head, Bone and Inflammation Drug Discovery at Procter & Gamble Pharmaceuticals from April 2000 until July 2005 and Research Assistant at Zeneca (now AstraZeneca) from October 1988 until September 1994. Dr. Houghton holds a B.S. from Manchester Metropolitan University, a Ph.D. in Cell and Molecular Biology from the University of Sheffield, performed post-doctoral research at Yale School of Medicine and holds an M.B.A. from Xavier University.

Allison Ambrose, J.D. has served as our Sr. Vice President, General Counsel since December 2024. Prior to joining us, Ms. Ambrose served as general counsel of Skyhawk Therapeutics, Inc., a biotechnology company, from June 2024 to December 2024. Prior to that, Ms. Ambrose served as vice president and deputy general counsel from March 2023 to June 2024 and as senior director, senior corporate counsel from March 2021 to March 2023 at Ginkgo Bioworks Holdings, Inc., a publicly traded biotechnology company. Previously, Ms. Ambrose served as senior director, lead counsel from June 2020 to March 2021 and as director, senior corporate counsel from April 2019 to June 2020 at Orchard Therapeutics plc, a gene therapy company acquired by the global pharmaceutical company Kyowa Kirin Co., Ltd. in January 2024. Earlier in her career, Ms. Ambrose served as an attorney at Ropes

& Gray LLP. Ms. Ambrose holds B.A. degrees in English and Sociology from the University of Tennessee and a J.D. from Georgetown University Law Center.

The principal occupation and employment during the past five years of each of our executive officers was carried on, in each case except as specifically identified in this Proxy Statement, with a corporation or organization that is not a parent, subsidiary or other affiliate of us. There is no arrangement or understanding between any of our executive officers and any other person or persons pursuant to which he or she was or is to be selected as an executive officer.

There are no material legal proceedings to which any of our directors, executive officers, or affiliates is a party adverse to us or our subsidiary or in which any such person has a material interest adverse to us or our subsidiary.

Director Compensation

2024 Director Compensation Table

The following table presents the total compensation paid by us to non-employee members of our board of directors during the fiscal year ended December 31, 2024. Other than as set forth in the table and described more fully below, we did not pay any compensation, make any equity awards or non-equity awards to, or pay any other compensation to any of the members of our board of directors in 2024 for their services as members of the board of directors. Dr. Sutherland, our Chief Executive Officer, does not, and Ms. Truex, our former Chief Executive Officer, did not, receive any compensation from us for their service on our board of directors. See the section titled "Executive Compensation" for more information on the compensation paid to or earned by Dr. Sutherland and Ms. Truex as an employee for the year ended December 31, 2024.

Name	Fees Earned or Paid in Cash ($)	Option Awards($)[1]	Total ($)
Ronald C. Renaud, Jr., M.B.A.[2]	80,440	735,852	816,292
Marcella Kuhlman Ruddy, M.D., M.S.[3]	40,516	216,910	257,426
H. Edward Fleming, Jr., M.D.[4]	11,556	216,910	228,466
Liam Ratcliffe, M.B.Ch.B., Ph.D., M.B.A.[5]	11,776	216,910	228,686
Erez Chimovits, M.B.A., M.Sc.[6]	11,226	216,910	228,136
Danielle Beckman[7]	12,106	446,876	458,982
Andy Wardle, M.B.Ch.B., M.B.A.[8][9]	—	—	—
Atshushi Sugita, M.B.A.[8][10]	—	—	—
Dayton Misfeldt[8][11]	—	—	—

(1) Amounts reflect the aggregate grant date fair value of option awards granted during 2024 in accordance with our Non-employee Director Compensation Policy, described below, calculated in accordance with the provisions of Financial Accounting Standards Board ("FASB") Accounting Standards Codification ("ASC") Topic 718, *Compensation-Stock Compensation*. Such grant date fair values do not take into account any estimated forfeitures. The assumptions used in the grant date fair value of the awards in this column are described in Note 10 to our audited financial statements included in our 2024 Annual Report. The amounts reported in this column reflect the accounting cost for these options and do not correspond to the actual economic value that may be received by our directors upon the exercise of the options or any sale of the underlying shares of common stock.
(2) Mr. Renaud held options to purchase 443,497 shares as of December 31, 2024.
(3) Dr. Ruddy held options to purchase 81,237 shares as of December 31, 2024.
(4) Dr. Fleming held options to purchase 17,096 shares as of December 31, 2024.
(5) Dr. Ratcliffe held options to purchase 17,096 shares as of December 31, 2024.
(6) Mr. Chimovits held options to purchase 17,096 shares as of December 31, 2024.
(7) Ms. Beckman joined the board of directors in October 2024. Ms. Beckman held options to purchase 34,681 shares as of December 31, 2024.
(8) The director resigned from the board of directors effective immediately prior to our initial public offering.
(9) Dr. Wardle held no shares as of December 31, 2024.
(10) Mr. Sugita held no shares as of December 31, 2024.
(11) Mr. Misfeldt held no shares as of December 31, 2024.

Non-Employee Director Compensation

In connection with our initial public offering in October 2024, we adopted a non-employee director compensation policy in order to enable us to attract and retain, on a long-term basis, highly qualified non-employee directors. Under the policy, our non-employee directors will be eligible to receive cash retainers (which will be payable quarterly in arrears and prorated for partial years of service) and equity awards as set forth below:

Annual Retainer for Board of Directors		
Members	$	40,000
Additional retainer for non-executive chair	$	30,000
Audit Committee:		
Members (other than chair)	$	15,000
Retainer for chair	$	7,500
Compensation Committee		
Members (other than chair)	$	12,000
Retainer for chair	$	6,000
Nominating and Corporate Governance Committee		
Members (other than chair)	$	10,000
Retainer for chair	$	5,000

In addition, the non-employee director compensation policy provides that, upon initial election to our board of directors, each non-employee director will be granted a one-time stock option award to purchase 34,681 shares of our common stock (the "Initial Grant"). The Initial Grant will vest in equal monthly installments over three years from the date of grant, subject to continued service on our board through the applicable vesting date. The Initial Grant will expire ten years from the date of grant and have an exercise price per share equal to the fair market value of our common stock on the date of grant.

Furthermore, on the date of each annual meeting of stockholders, each non-employee director who continues as a non-employee director (other than a director receiving an Initial Grant) following such meeting will be granted an annual stock option award to purchase 17,096 shares of our common stock (the "Annual Grant"). The Annual Grant will vest in full upon the earlier of the following annual meeting of the stockholders or the first anniversary of the date of grant and have an exercise price per share equal to the fair market value of our common stock on the date of grant.

Finally, upon the effectiveness of the registration statement with respect to our initial public offering, each non-employee director then serving on our board (except Daniella Beckman who received an Initial Grant upon her appointment to the board of directors) received an Annual Grant, which shall vest in full on the earlier of the first anniversary of the date of grant or the next annual meeting of stockholders.

All awards granted under the non-employee director compensation policy will vest in full upon the occurrence of a "sale event" as defined in our 2024 stock option and incentive plan.

The aggregate amount of compensation, including both equity compensation and cash compensation, paid to any non-employee director for service as a non-employee director in a calendar year period will not exceed $1,000,000 in the first calendar year such individual becomes a non-employee director and $750,000 in any other calendar year.

We will reimburse all reasonable out-of-pocket expenses incurred by non-employee directors in attending meetings of the board of directors and committees thereof.

EXECUTIVE COMPENSATION

The following discussion contains forward-looking statements that are based on our current plans, considerations, expectations and determinations regarding our future compensation programs. The actual amount and form of compensation and the compensation policies and practices that we adopt in the future may differ materially from currently planned programs as summarized in this discussion.

As an emerging growth company and smaller reporting company, we have opted to comply with the executive compensation disclosure rules applicable to "smaller reporting companies," as such term is defined in the rules promulgated under the Securities Act. The compensation provided to our named executive officers for the fiscal year ended December 31, 2024 is detailed in the 2024 Summary Compensation Table and accompanying footnotes and narrative that follow. Our named executive officers for the fiscal year ended December 31, 2024 are:

E. Rand Sutherland, M.D., our Chief Executive Officer;

Michael Paul Gray, M.B.A., our Chief Financial Officer and Chief Operating Officer;

Allison Ambrose, J.D., our Sr. Vice President, General Counsel; and

Samantha Truex, our Former Chief Executive Officer*.

* Ms. Truex stepped down as our Chief Executive Officer in March 2024.

To date, the compensation of our named executive officers has consisted of a combination of base salary, cash bonuses and long-term incentive compensation in the form of stock options. Our named executive officers, like all of our full-time employees, are eligible to participate in our health and welfare benefit plans and 401(k) plan.

2024 Summary Compensation Table

The following table shows the total compensation earned by, or paid to, our named executive officers for services rendered to us in all capacities during the fiscal year ended December 31, 2024 and, if applicable, the fiscal year ended December 31, 2023.

Name and Principal Position	Year	Salary ($)	Bonus ($)	Option Awards[1] ($)	Non-Equity Incentive Plan Compensation[2] ($)	All Other Compensation[3] ($)	Total ($)
E. Rand Sutherland, M.D. *Chief Executive Officer*[4]	2024	407,955	—	8,375,648	315,000	10,350	9,108,953
Michael Paul Gray, M.B.A. *Chief Financial Officer and Chief Operating Officer*[5]	2024	352,667	—	2,401,910	184,000	—	2,938,577
Allison Ambrose, J.D. *Sr. Vice President, General Counsel*[6]	2024	17,292	42,500 [7]	1,474,045 [9]	—	— [10]	1,533,837
Samantha Truex *Former Chief Executive Officer*[8]	2024	113,208	—	120,381 [9]	—	638,917 [10]	872,507
	2023	475,000	—	943,227	235,125	9,900	1,663,252

(1) The amounts reported in this column represent the aggregate grant date fair value of stock options granted to the named executive officers during the applicable fiscal year, as calculated in accordance with FASB ASC Topic 718. Such grant date value does not take into account any estimated forfeitures related to service-based vesting conditions. The assumptions used in the grant date fair value of the awards in this column are described in Note 10 to our audited financial statements included in our 2024 Annual Report. The amounts reported in this column reflect the accounting cost for these stock option awards and do not correspond to the actual economic value that may be received by our named executive officers upon the exercise of the stock option awards or any sale of the underlying shares. These awards are described in more detail under "Narrative Disclosure to Summary Compensation Table – Equity-Based Compensation" below.

(2) The amounts reported represent annual performance bonuses earned based on achievement of company performance during the year ended December 31, 2024. For more information on these bonuses, see description of the annual performance bonuses under the section titled "Narrative Disclosure to Summary Compensation Table—2024 Cash Bonuses" below.

(3) The amounts reported represent an employer matching contribution on the employee's behalf under our 401(k) plan.

(4) Dr. Sutherland commenced employment as our Chief Executive Officer in April 2024. Accordingly, the salary reported represents the salary earned for his partial year of employment.

(5) Mr. Gray commenced employment as our Chief Financial Officer and Chief Operating Officer in March 2024. Accordingly, the salary reported represents the salary earned for his partial year of employment

(6) Ms. Ambrose commenced employment as our Sr. Vice President, General Counsel in December 2024. Accordingly, the salary reported represents the salary earned for her partial year of employment. In addition, due to her commencement date in December, Ms. Ambrose was not eligible to earn a cash bonus for 2024.

(7) The amount reported represents a signing bonus paid to Ms. Ambrose in connection with the commencement of her employment pursuant to the terms of her employment agreement, as described below under "Executive Compensation Arrangements-- Employment Agreements."

(8) Ms. Truex ceased being our Chief Executive Officer in March 2024.

(9) Amounts include the incremental fair value associated with the acceleration of options and extension of the exercise period of Ms. Truex's stock options in connection with the termination of her employment, as described below under "Executive Compensation Arrangements—Separation Agreement with Samantha Truex."

(10) Amounts include compensation Ms. Truex received in connection with her termination of employment: (i) $380,792 of salary continuation, (ii) $222,300 representing her target bonus, (iii) $23,176 in COBRA continuation and (iv) $9,871 in reimbursement of legal fees, as described below under "Executive Compensation Arrangements—Separation Agreement with Samantha Truex." Additionally, amount includes $2,779 for an employer matching contribution on the employee's behalf under our 401(k) plan.

Narrative Disclosure to Summary Compensation Table

Compensation Philosophy

Our executive compensation philosophy is to provide a competitive and market-based total compensation program to attract, motivate, and retain our executive team. Our compensation is based heavily on performance, which aligns with our goal to drive long-term growth and value creation.

2024 Base Salaries

Our named executive officers each receive a base salary to compensate them for services rendered to our Company. The base salary payable to each named executive officer is intended to provide a fixed component of compensation reflecting the executive's skill set, experience, role and responsibilities. Base salaries are expected to be reviewed annually, typically in connection with our annual performance review process, approved by our board of directors or the compensation committee of the board of directors, and may be adjusted from time to time to realign salaries with market levels after taking into account individual responsibilities, performance and experience.

The annual base salaries for each of our named executive officers for the fiscal year ended December 31, 2024 are set forth in the table below:

Name		Annual Base Salary
E. Rand Sutherland, M.D.	$	630,000
Michael Paul Gray, M.B.A.	$	460,000
Allison Ambrose, J.D.	$	415,000
Samantha Truex	$	494,000

2024 Cash Bonuses

For the fiscal year ended December 31, 2024, Dr. Sutherland and Mr. Gray were eligible to earn an annual cash bonus determined by our board of directors in its sole discretion, based on achievement of certain corporate performance milestones primarily focused on the advancement of our program and completion of financing strategies. The target annual bonus for Dr. Sutherland and Mr. Gray for the fiscal year ended December 31, 2024 was equal to the percentage of the executive's respective annual base salary specified below:

Name	Target Bonus Percentage
E. Rand Sutherland, M.D.	50%
Michael Paul Gray, M.B.A.	40%

In the fourth quarter of 2024, our board of directors determined that we had achieved 100% of our corporate goals for 2024 and, accordingly, in the first quarter of 2025, paid each of our named executive officers a bonus as specified in the Summary Compensation Table above.

Ms. Ambrose commenced employment with us in December 2024 and, accordingly, was not eligible to earn a performance bonus for 2024. Commencing in 2025, Ms. Ambrose will be eligible to earn a performance bonus, with a target equal to 35% of her base salary. Ms. Truex was not eligible to earn a performance bonus for 2024.

Equity-Based Compensation

We believe that equity grants provide our executives with a strong link to our long-term performance, create an ownership culture and help to align the interests of our executives and our stockholders. In addition, we believe that equity grants promote executive retention because they incentivize our executive officers to remain in our employment during the vesting period. To date, we have granted our named executive officers stock option awards.

For additional information regarding outstanding equity awards held by our named executive officers as of December 31, 2024, see the "Outstanding Equity Awards at 2024 Fiscal Year End" table below.

401(k) Plan

We maintain a retirement savings plan ("401(k) plan") that is intended to qualify for favorable tax treatment under Section 401(a) of the Code, and contains a cash or deferred feature that is intended to meet the requirements of Section 401(k) of the Code. U.S. employees are generally eligible to participate in the 401(k) plan, subject to certain criteria. Participants may make pre-tax and certain after-tax (Roth) salary deferral contributions to the plan from their eligible earnings up to the statutorily prescribed annual limit under the Code. Participants who are 50 years of age or older may contribute additional amounts based on the statutory limits for catch-up contributions. Participant contributions are held in trust as required by law. We make matching contributions equal to 50% of each participant's elective deferrals on the first 6% of the participant's compensation.

Policy Regarding Timing of Awards of Options and Other Option-Like Instruments

Our compensation committee generally grants annual equity awards, including stock option grants to our named executive officers, in the first quarter of each fiscal year. In addition, new hires receive stock option grants at the time of their hiring. During 2024 and following our initial public offering, our compensation committee did not take into account any material nonpublic information when determining the timing and terms of equity incentive awards, and we did not time the disclosure of material nonpublic information for the purpose of affecting the value of executive compensation. During 2024, we did not grant stock options to our named executive officers during any period beginning four business days before and ending one business day after the filing or furnishing of a Form 10-Q, 10-K or 8-K that discloses material nonpublic information.

Outstanding Equity Awards at 2024 Fiscal Year End

The following table lists all outstanding equity awards held by our named executive officers as of December 31, 2024. Equity awards granted prior to our initial public offering were under our 2021 Stock Option and Grant Plan (as amended from time to time, the "2021 Plan") and equity awards granted following our initial public offering were granted under our 2024 Stock Option and Incentive Plan (the "2024 Plan").

	Option Awards[1]				
Name	Vesting Commencement Date	Number of Securities Underlying Unexercised Options (#) Exercisable	Number of Securities Underlying Unexercised Options (#) Unexercisable	Option Exercise Price ($)	Option Expiration Date
E. Rand Sutherland, M.D.	04/01/2024	—	866,704	5.69	04/03/2034
	04/05/2024	—	1,053,799	6.59	04/24/2034
Michael Paul Gray, M.B.A.	03/26/2024	—	445,040	5.69	03/26/2034
	04/05/2024	—	152,450	5.69	03/26/2034
Allison Ambrose, J.D.	12/16/2024	—	100,000	19.01	12/15/2034
Samantha Truex	10/13/2021	368,490	—	3.45	03/22/2026
	02/14/2023	116,255	—	3.45	03/22/2026
	03/02/2023	9,563	—	4.27	03/22/2026
	08/10/2023	38,245	—	4.87	03/22/2026

(1) Each stock option vests as follows: 25% of the shares subject to the stock option vested on the one year anniversary of the vesting commencement date, and the remaining 75% of the shares subject to the stock option vest on a monthly basis thereafter, in each case, subject to the NEO's continuous service relationship with the company through each applicable vesting date. Each stock option is subject to acceleration in the event of a qualified termination within the change in control period, as described below under "—Executive Compensation Arrangements—Executive Severance Plan."

Executive Compensation Arrangements

We have entered into an employment agreement with each of our named executive officers. Each employment agreement or offer letter provides for "at-will" employment and the compensation and benefits described below. In addition, each of our current named executive officers is eligible to participate in our severance and change in control plan.

Employment Agreements

We have entered into employment agreements with each of our current named executive officers (each, an "Employment Agreement," and collectively, the "Employment Agreements"). Under the Employment Agreements, each of the executive officers will serve in their respective roles on an at-will basis. The Employment Agreements set forth the initial base salary of each named executive officer, target annual bonus eligibility and compliance with restrictive covenants. In addition, each such executive is eligible to participate in our severance and change in control plan, as further described below. In addition, pursuant to Ms. Ambrose's Employment Agreement, Ms. Ambrose received a signing bonus of $42,500, which she shall be required to repay if she is terminated for cause or resigns without good reason prior to the first anniversary of her start date.

Executive Severance Plan

On August 19, 2024, our board of directors adopted the Executive Severance Plan (the "Severance Plan"), which became effective upon the effectiveness of the registration statement of which this prospectus forms a part, in which our currently employed named executive officer and certain other executives are expected to participate. The benefits provided in the Severance Plan replaces any severance for which such named executive officer may be eligible under their existing severance and change in control agreements (unless otherwise specified).

The Severance Plan provides that upon a termination by us for any reason other than for Cause, death or Disability, or resignation for Good Reason, each as defined in the Severance Plan (a "Qualifying Termination"), in each case outside of the period commencing three months prior to and ending on the first month anniversary following a Change in Control, as defined in the Severance Plan (the "Change in Control Period"), eligible participants will be entitled to receive, subject to the execution and delivery of a release of claims in favor of the company and continued compliance with all applicable restrictive covenants, (a) 12 months of continued base salary (or the annual base salary in effect for the year immediately prior to the year in which the date of termination occurs) ("Base Salary") for the Chief Executive Officer, nine months for each other chief executive other than the Chief Executive Officer, and six months for each senior vice president of the Company, and (b) an amount equal to the monthly employer contribution that we would have made to provide health insurance for the applicable participant if he or she had remained employed by us while receiving payments of Base Salary.

The Severance Plan also provides that upon a Qualifying Termination within the Change in Control Period, an eligible participant will be entitled to receive, in lieu of the payments and benefits above and subject to the execution and delivery of a release of claims in favor of the company and continued compliance with all applicable restrictive covenants, (a) a lump sum payment equal to the sum of (i) 18 months' Base Salary for the Chief Executive Officer, 12 months' Base Salary for each chief executive other than the Chief Executive Officer and nine months' Base Salary for each senior vice president (such periods, the "CIC Periods") and (ii) 1.5 times the target annual bonus in effect immediately prior to the date of termination (or immediately prior to the change in control if higher) for the Chief Executive Officer, 1.0 times for each chief executive other than the Chief Executive Officer and 0.75 times for each senior vice president, (b) an amount equal to the monthly employer contribution, based on the premiums as of the date of termination, that we would have made to provide health insurance for the applicable participant if he or she had remained employed by us for the duration of the applicable CIC Period and (c) for all outstanding and unvested equity awards of the company that are subject to time-based vesting held by the participant, full accelerated vesting of such awards.

The payments and benefits provided under the Severance Plan in connection with a Change in Control may not be eligible for a federal income tax deduction by us pursuant to Section 280G of the Code. These payments and benefits may also subject an eligible participant, including named executive officers, to an excise tax under Section 4999 of the Code. If the payments or benefits payable in connection with a Change in Control would be subject to the excise tax imposed under Section 4999 of the Code, then those payments or benefits will be reduced if such reduction would result in a higher net after-tax benefit to the participant.

Separation Agreement with Samantha Truex

Ms. Truex's employment was terminated as of March 22, 2024. In connection with such termination, we entered into a separation agreement with Ms. Truex, dated as of March 13, 2024 (the "Truex Separation Agreement"), including a release of claims, providing for (i) continued payment of her then current base salary for a period of twelve months, (ii) if Ms. Truex was participating in the Company's group health plan immediately prior to the termination date and timely elected continuation coverage under COBRA, a monthly payment equal to the monthly employer contribution that the Company would have made to provide health insurance to Ms. Truex had Ms. Truex remained employed by the Company for up to twelve months, (iii) a single lump sum payment equal to 100% of Ms. Truex's target bonus for 2024, (iv) acceleration of her then outstanding and unvested time-based equity awards granted on August 14, 2023, such that options to purchase 36,458 shares vested as of the date of termination, (v) an extension of the exercise period of Ms. Truex's vested options from 90 days to 24 months from the date of termination, provided that such period may be shortened consistent with the provisions of the applicable equity documents in the event of a change of control or sale event and (vi) a reimbursement of legal fees of up to $10,000 incurred in connection with the review of the Truex Separation Agreement.

Equity Compensation Plan Information

The following table provides information as of December 31, 2024 with respect to the shares of our common stock that may be issued under our existing equity compensation plans:

Plan category	Number of securities to be issued upon exercise of outstanding options, warrants and rights		Weighted-average exercise price of outstanding options, warrants and rights	Number of securities remaining available for future issuance under equity compensation plans (excluding securities reflected in first column)	
Equity compensation plans approved by security holders	6,490,571	(1)	5.54	3,409,073	(2)(3)
Equity compensation plans not approved by security holders	—		—	—	
Total	6,490,571		5.54	3,409,073	

1. Consists of the 2021 Plan, the 2024 Plan, and the Upstream Bio, Inc. 2024 Employee Stock Purchase Plan (the "2024 ESPP").

2. Shares of our common stock available for issuance as of December 31, 2024 pursuant to the 2024 Plan excludes the 2,680,169 shares that were added to the 2024 Plan as a result of the automatic annual increase on January 1, 2025. The 2024 Plan provides that the number of shares reserved and available for issuance under the 2024 Plan will automatically increase on January 1, 2024 and each January 1 thereafter, by five percent of the outstanding number of shares of common stock on the immediately preceding December 31 or such lesser number of shares as determined by the compensation committee. The Company no longer makes grants under the 2021 Plan. The shares of common stock underlying any awards under the 2024 Plan and the 2021 Plan that are forfeited, cancelled, held back upon exercise or settlement of an award to satisfy the exercise price or tax withholding, reacquired by the Company prior to vesting, satisfied without the issuance of stock, expire or are otherwise terminated (other than by exercise) will be added back to the shares of common stock available for issuance under the 2024 Plan.

3. The 2024 ESPP provides that the number of shares of common stock that may be issued under the 2024 ESPP shall cumulatively increase beginning on January 1, 2025 and each January 1 thereafter through January 1, 2034, by the least of (i) 976,934 shares of common stock, (ii) one percent of the outstanding number of shares of common stock on the immediately preceding December 31 or (iii) such number of shares of common stock as determined by the administrator of the 2024 ESPP. No shares were added to the 2024 ESPP on January 1, 2025.

CERTAIN RELATIONSHIPS AND RELATED PARTY TRANSACTIONS

Certain Relationships and Transactions

Other than the compensation agreements and other arrangements described under "Executive Compensation" and "Director Compensation" in this Proxy Statement and the transactions described below, since January 1, 2023, there has not been and there is not currently proposed, any transaction or series of similar transactions to which we were, or will be, a party in which the amount involved exceeded, or will exceed, $120,000 (or, if less, 1% of the average of our total asset amounts at December 31, 2023 and 2024) and in which any director, executive officer, holder of five percent or more of any class of our capital stock or any member of the immediate family of, or entities affiliated with, any of the foregoing persons, had, or will have, a direct or indirect material interest.

Series A Redeemable Convertible Preferred Stock Financing

Milestone closings

In February 2023, in connection with the second milestone closing of our Series A redeemable convertible preferred stock financing, we issued and sold an aggregate of 8,000,000 shares of Series A redeemable convertible preferred stock at a purchase price of $10.00 per share for an aggregate purchase price of $80.0 million. Each share of our Series A redeemable convertible preferred stock automatically converted into 1.049 shares of our common stock immediately prior to the completion of our initial public offering. The following table summarizes purchases of our Series A redeemable convertible preferred stock by related persons:

Participant	Shares of series A redeemable convertible preferred stock	Total purchase price ($)
AI Upstream LLC[(1)]	1,200,000	12,000,000
Altshuler Shaham Provident Fund and Pension Ltd.[(2)]	1,000,000	10,000,000
Decheng Capital Global Life Sciences Fund IV, L.P.[(3)]	1,000,000	10,000,000
HBM Healthcare Investments (Cayman) Ltd.[(4)]	800,000	8,000,000
Maruho Deutschland GmbH[(5)]	1,000,000	10,000,000
Omega Fund VII, L.P.[(6)]	600,000	6,000,000
OrbiMed Israel Partners II, L.P.[(7)]	200,000	2,000,000
OrbiMed Private Investments VIII, L.P.[(7)]	800,000	8,000,000
Samsara BioCapital, L.P.[(8)]	600,000	6,000,000
TCG Crossover Fund I, L.P.[(9)]	800,000	8,000,000

(1) AI Upstream LLC, an entity affiliated with Access Industries, is a holder of five percent or more of our capital stock. Dr. Ratcliffe is head of biotech at Access Industries and a member of our board of directors.
(2) Altshuler Shaham Provident Fund and Pension Ltd. is a holder of five percent or more of our capital stock.
(3) Decheng Capital Global Life Sciences Fund IV, L.P., an entity affiliated with Decheng Capital, is a holder of five percent or more of our capital stock. Dayton Misfeldt, an affiliate of Decheng Capital, was a member of our board of directors at the time of the transaction. Mr. Misfeldt resigned from our board of directors effective immediately prior to our initial public offering.
(4) HBM Healthcare Investments (Cayman) Ltd. is a holder of five percent or more of our capital stock.
(5) Maruho Deutschland GmbH was a holder of five percent or more of our capital stock at the time of the transaction. Atshushi Sugita, an affiliate of Maruho, was a member of our board of directors at the time of the transaction. Mr. Sugita resigned from our board of directors effective immediately prior to our initial public offering.
(6) Omega Fund VII, L.P. was a holder of five percent or more of our capital stock at the time of the transaction.
(7) Entities affiliated with OrbiMed hold five percent or more of our capital stock. Mr. Chimovits is a partner at OrbiMed and a member of our board of directors.
(8) Samsara BioCapital, L.P. was a holder of five percent or more of our capital stock at the time of the transaction.
(9) TCG Crossover Fund I, L.P. is a holder of five percent or more of our capital stock.

Series B Redeemable Convertible Preferred Stock Financing

First closing

In June 2023, we issued and sold an aggregate of 2,941,170 shares of our Series B redeemable convertible preferred stock at a purchase price of $17.00 per share for an aggregate purchase price of $50.0 million. Each share of our Series B redeemable convertible preferred stock automatically converted into 1.049 shares of our common stock immediately prior to the completion of our initial public offering. The following table summarizes purchases of our Series B redeemable convertible preferred stock by related persons:

Participant	Shares of series B redeemable convertible preferred stock	Total purchase price ($)
AI Upstream LLC[1]	279,411	4,749,987
Altshuler Shaham Provident Fund and Pension Ltd.[2]	183,823	3,124,991
BCLS Fund III Investments, LP[3]	433,823	7,374,991
Decheng Capital Global Life Sciences Fund IV, L.P.[4]	110,294	1,874,998
HBM Healthcare Investments (Cayman) Ltd.[5]	147,058	2,499,986
Omega Fund VII, L.P. [6]	110,294	1,874,998
OrbiMed Israel Partners II, L.P.[7]	47,058	799,986
OrbiMed Private Investments VIII, L.P.[7]	188,235	3,199,995
Samsara BioCapital, L.P.[8]	117,647	1,999,999
TCG Crossover Fund I, L.P.[9]	161,764	2,749,988
Entities affiliated with Enavate Sciences[10]	514,705	8,749,985
Venrock Healthcare Capital Partners EG, L.P.[11]	308,361	5,242,137
Venrock Healthcare Capital Partners III, L.P.[11]	114,052	1,938,884
VHCP Co-Investment Holdings III, LLC[11]	11,410	193,970

(1) AI Upstream LLC, an entity affiliated with Access Industries, is a holder of five percent or more of our capital stock. Dr. Ratcliffe is head of biotech at Access Industries and a member of our board of directors.
(2) Altshuler Shaham Provident Fund and Pension Ltd. is a holder of five percent or more of our capital stock.
(3) BCLS Fund III Investments, LP, an entity affiliated with Bain Capital Life Sciences, acquired five percent or more of our capital stock at the time of the transaction.
(4) Decheng Capital Global Life Sciences Fund IV, L.P., an entity affiliated with Decheng Capital, is a holder of five percent or more of our capital stock. Dayton Misfeldt, an affiliate of Decheng Capital, was a member of our board of directors at the time of the transaction. Mr. Misfeldt resigned from our board of directors effective immediately prior to our initial public offering.
(5) HBM Healthcare Investments (Cayman) Ltd. is a holder of five percent or more of our capital stock.
(6) Omega Fund VII, L.P. was a holder of five percent or more of our capital stock at the time of the transaction.
(7) Entities affiliated with OrbiMed hold five percent or more of our capital stock. Mr. Chimovits is a partner at OrbiMed and a member of our board of directors.
(8) Samsara BioCapital, L.P. was a holder of five percent or more of our capital stock at the time of the transaction.
(9) TCG Crossover Fund I, L.P. was a holder of five percent or more of our capital stock at the time of the transaction.
(10) UpStream Aggregator, LP, an entity affiliated with Enavate Sciences, acquired five percent or more of our capital stock as a result of the transaction. Dr. Fleming is an executive vice president at Enavate Sciences and a member of our board of directors.
(11) Entities affiliated with Venrock Healthcare Capital Partners acquired five percent or more of our capital stock as a result of the transaction. Andy Wardle, an affiliate of Venrock Healthcare Capital Partners, is a former member of our board of directors. Dr. Wardle resigned from our board of directors effective immediately prior to our initial public offering.

Series B option closing

In April 2024, in connection with the Series B option closing of our Series B redeemable convertible preferred stock financing, we issued and sold an aggregate of 8,823,523 shares of our Series B redeemable convertible preferred stock at a purchase price of $17.00 per share for an aggregate purchase price of $150.0 million. Each share of our Series B redeemable convertible preferred stock automatically converted into 1.049 shares of our common stock immediately prior to the completion of our initial public offering. The following table summarizes purchases of our Series B redeemable convertible preferred stock by related persons:

Participant	Shares of series B redeemable convertible preferred stock	Total purchase price ($)
AI Upstream LLC[(1)]	838,235	14,249,995
Altshuler Shaham Provident Fund and Pension Ltd.[(2)]	551,470	9,374,990
BCLS Fund III Investments, LP [(3)]	1,301,470	22,124,990
Decheng Capital Global Life Sciences Fund IV, L.P.[(4)]	330,882	5,624,994
HBM Healthcare Investments (Cayman) Ltd.[(5)]	441,176	7,499,992
OrbiMed Israel Partners II, L.P.[(6)]	141,176	2,399,992
OrbiMed Private Investments VIII, L.P.[(6)]	564,705	9,599,985
TCG Crossover Fund I, L.P.[(7)]	485,294	8,249,998
Entities affiliated with Enavate Sciences[(8)]	1,544,117	26,249,989
Venrock Healthcare Capital Partners EG, L.P.[(9)]	989,508	16,821,636
Venrock Healthcare Capital Partners III, L.P.[(9)]	283,590	4,821,030
VHCP Co-Investment Holdings III, LLC[(9)]	28,372	482,324

(1) AI Upstream LLC, an entity affiliated with Access Industries, is a holder of five percent or more of our capital stock. Dr. Ratcliffe is head of biotech at Access Industries and a member of our board of directors.
(2) Altshuler Shaham Provident Fund and Pension Ltd. is a holder of five percent or more of our capital stock.
(3) BCLS Fund III Investments, LP, an entity affiliated with Bain Capital Life Sciences, held five percent or more of our capital stock at the time of the transaction.
(4) Decheng Capital Global Life Sciences Fund IV, L.P., an entity affiliated with Decheng Capital, is a holder of five percent or more of our capital stock. Mr. Misfeldt is a partner at Decheng Capital and a former member of our board of directors.
(5) HBM Healthcare Investments (Cayman) Ltd. is a holder of five percent or more of our capital stock.
(6) Entities affiliated with OrbiMed hold five percent or more of our capital stock. Mr. Chimovits is a partner at OrbiMed and a member of our board of directors.
(7) TCG Crossover Fund I, L.P. is a holder of five percent or more of our capital stock.
(8) UpStream Aggregator, LP, an entity affiliated with Enavate Sciences, held five percent or more of our capital stock at the time of the transaction. Dr. Fleming is an executive vice president at Enavate Sciences and a member of our board of directors.
(9) Entities affiliated with Venrock Healthcare Capital Partners acquired five percent or more of our capital stock as a result of the transaction. Andy Wardle, an affiliate of Venrock Healthcare Capital Partners, is a former member of our board of directors. Dr. Wardle resigned from our board of directors effective immediately prior to our initial public offering.

Participation in our Initial Public Offering

In October 2024, we completed our initial public offering of 17,250,000 shares of its common stock at a public offering price of $17.00 per share, resulting in gross proceeds to Upstream of $293.3 million, before deducting underwriting discounts and commissions and other offering expenses. Certain of our five percent or greater stockholders, including certain affiliates of our directors, purchased an aggregate of 3,650,000 shares of our common stock in our initial public offering at the initial public offering price. The following table sets forth the number of shares of our common stock purchased by such holders and their affiliates and the aggregate purchase price paid for such shares.

Participant	Shares of common stock	Total purchase price ($)
AI Upstream LLC[(1)]	1,175,000	19,975,000
Entities affiliated with Orbimed[(2)]	825,000	14,025,000
Entities affiliated with Bain Capital Life Sciences[(3)]	475,000	8,075,000
TCG Crossover Fund I, L.P.[(4)]	325,000	5,525,000
Entities affiliated with Enavate Sciences[(5)]	300,000	5,100,000
FMR LLC[(6)]	3,750,000	63,750,000
Entities affiliated with Samsara[(7)]	250,000	4,250,000
Decheng Capital Global Life Sciences Fund IV, L.P.[(8)]	200,000	3,400,000
Entities affiliated with Omega[(9)]	100,000	1,700,000

(1) AI Upstream LLC, an entity affiliated with Access Industries, is a holder of five percent or more of our capital stock. Dr. Ratcliffe is head of biotech at Access Industries and a member of our board of directors.
(2) Entities affiliated with OrbiMed hold five percent or more of our capital stock. Mr. Chimovits is a partner at OrbiMed and a member of our board of directors.
(3) Entities affiliated with Bain Capital Life Sciences held five percent or more of our capital stock at the time of the transaction.
(4) TCG Crossover Fund I, L.P. is a holder of five percent or more of our capital stock.
(5) Entities affiliated with Enavate Sciences held five percent or more of our capital stock at the time of the transaction. Dr. Fleming is an executive vice president at Enavate Sciences and a member of our board of directors.
(6) As a result of this transaction, FMR LLC is a holder of five percent or more of our capital stock.
(7) Entities affiliated with Samsara held five percent or more of our capital stock at the time of the transaction.
(8) Decheng Capital Global Life Sciences Fund IV, L.P., an entity affiliated with Decheng Capital, holds five percent or more of our capital stock. Mr. Misfeldt is a partner at Decheng Capital and a former member of our board of directors.
(9) Entities affiliated with Omega held five percent or more of our capital stock at the time of the transaction.

Agreements with Our Stockholders

Maruho License Agreement

In October 2021, we entered into a license agreement with Maruho Co. Ltd ("Maruho") (as amended, the "Maruho License Agreement"), under which we granted Maruho an exclusive, irrevocable, perpetual, royalty-free, sublicensable (subject to our right of first negotiation) license. Mr. Sugita, a former member of our board of directors, is president and chief executive officer of Maruho, which is a co-founder of our company. Under the Maruho License Agreement, Maruho is responsible for and controls, at its sole expense, (i) the preparation, filing, prosecution, obtaining and maintaining all regulatory approvals in Japan and (ii) the promotion, marketing, sale and commercialization in Japan.

Pursuant to the Maruho License Agreement, we maintain our responsibility for and control the global research and development of the Maruho license product, including in Japan. We will conduct specified clinical trial activities for Japan as part of our global research and development plan. Maruho will reimburse us for the costs of these research and development activities, including the cost of drug supply. Apart from reimbursement of qualifying research and development expenses, Maruho is not obligated to make any future payments under the Maruho License Agreement.

During the years ended December 31, 2024 and 2023, we received payments from Maruho in the amount of $1.9 million and $2.7 million, respectively.

Investors' Rights Agreement

In connection with our redeemable convertible preferred stock financings, we entered into an investors' rights agreement with the purchasers of our redeemable convertible preferred stock and certain holders of our common stock. The investors' rights agreement provides certain holders of our capital stock with the right to demand that we file a registration statement, subject to certain limitations, and to request that their shares be covered by a registration statement that we are otherwise filing.

Indemnification Agreements

We have entered into agreements to indemnify our directors and executive officers. These agreements, among other things, require us to indemnify these individuals for certain expenses (including attorneys' fees), judgments, fines and settlement amounts reasonably incurred by such person in any action or proceeding, including any action by or in our right, on account of any services undertaken by such person on behalf of our company or that person's status as a member of our board of directors or executive officer to the maximum extent allowed under Delaware law.

Policies for Approval of Related Person Transactions

Our board of directors has adopted a written related person transaction policy providing for the review and oversight of all transactions involving over $120,000 in which the Company is a participant and a related person has a direct or indirect interest. A related person for purposes of this policy is a director, executive officer, director nominee, holder of five percent or more of our voting securities, or any immediate family member of the foregoing persons. The audit committee is responsible for reviewing the material facts of all such transactions and will take into account, among other factors that it deems appropriate, whether the transaction is on terms no less favorable to the Company than terms generally available in a transaction with an unaffiliated third-party under the same or similar circumstances, whether the transaction is otherwise consistent with the interests of the Company and its stockholders, and the extent of the related person's interest in the transaction. The audit committee has also determined that certain types of transactions are not subject to further review by the committee, and accordingly are deemed to be pre-approved under the policy.

PRINCIPAL STOCKHOLDERS

The following table sets forth information, to the extent known by us or ascertainable from public filings, with respect to the beneficial ownership of our common stock as of April 14, 2025 by:

- each of our directors;
- each of our named executive officers;
- all of our directors and executive officers as a group; and
- each person, or group of affiliated persons, who is known by us to beneficially owner of 5.0% or more of our common stock.

The column entitled "Shares Beneficially Owned" is based on a total of 53,688,703 shares of our common stock outstanding as of April 14, 2025.

Beneficial ownership is determined in accordance with the rules and regulations of the SEC and includes voting or investment power with respect to our common stock. Shares of our common stock subject to options that are currently exercisable or exercisable within 60 days of April 14, 2025 are considered outstanding and beneficially owned by the person holding the options for the purpose of calculating the percentage ownership of that person but not for the purpose of calculating the percentage ownership of any other person. Except as otherwise noted, the persons and entities in this table have sole voting and investing power with respect to all of the shares of our common stock beneficially owned by them, subject to community property laws, where applicable. Except as otherwise indicated in the table below, addresses of named beneficial owners are in care of Upstream Bio, Inc., 890 Winter Street, Suite 200, Waltham, MA 02451.

Name of Beneficial Owner	Shares Beneficially Owned	Percentage of Shares Beneficially Owned
Five Percent or Greater Stockholders:		
FMR LLC [1]	7,176,187	13.37%
Entities affiliated with OrbiMed [2]	5,693,589	10.60%
AI Upstream LLC [3]	5,494,410	10.23%
Altshuler Shaham Provident Fund and Pension Ltd. [4]	3,393,822	6.32%
Decheng Capital Global Life Sciences Fund IV, L.P. [5]	3,285,293	6.12%
TCG Crossover Fund I, L.P. [6]	2,801,763	5.22%
HBM Healthcare Investments (Cayman) Ltd. [7]	2,715,056	5.06%
Named Executive Officers and Directors:		
E. Rand Sutherland M.D., Chief Executive Officer and Director [8]	591,396	1.09%
Michael Paul Gray, M.B.A., Chief Financial Officer and Chief Operating Officer [9]	186,453	*
Allison Ambrose, J.D., Sr. Vice President, General Counsel [10]	1,562	*
Samantha Truex, former Chief Executive Officer [11]	513,802	*
Ronald C. Renaud, Jr., M.B.A. [12]	271,951	*
Daniella Beckman [13]	7,706	*
Erez Chimovits, M.B.A., M.Sc. [14]	5,710,685	10.63%
H. Edward Fleming, Jr., M.D. [15]	17,096	*
Liam Ratcliffe, M.B.Ch.B., Ph.D., M.B.A. [16]	17,096	*
Marcella Kuhlman Ruddy, M.D., M.S. [17]	54,273	*
All Current Executive Officers and Directors as a Group (11 Persons)[18]	7,527,937	13.56%

*Represents beneficial ownership of less than one percent.

(1) Information herein is based on a Schedule 13G/A filed with the SEC on February 12, 2025 by FMR LLC and Abigail P. Johnson. Consists of 7,176,187 shares of common stock held by FMR LLC. All of the shares of common stock are beneficially owned, or may be deemed to be beneficially owned, by FMR LLC, certain of its subsidiaries and affiliates, and other companies. Members of the Johnson family,

including Abigail P. Johnson, are the predominant owners, directly or through trusts, of Series B voting common shares of FMR LLC, representing 49% of the voting power of FMR LLC. The Johnson family group and all other Series B shareholders have entered into a shareholders' voting agreement under which all Series B voting common shares will be voted in accordance with the majority vote of Series B voting common shares. Accordingly, through their ownership of voting common shares and the execution of the shareholders' voting agreement, members of the Johnson family may be deemed, under the Investment Company Act of 1940, to form a controlling group with respect to FMR LLC. The address for each of the entities and individuals identified in this footnote is c/o FMR LLC, 245 Summer Street, Boston, MA 02210.

(2) Information herein is based on a Schedule 13D filed with the SEC on October 17, 2024 by OrbiMed Advisors LLC ("OrbiMed Advisors"), OrbiMed Capital GP VIII LLC ("GP VIII"), OrbiMed Advisors Israel II Limited ("Advisors Israel") and OrbiMed Israel GP II, L.P. ("Israel GP"). Consists of 4,554,873 shares of common stock held by OrbiMed Private Investments VIII, LP ("OPI VIII") and 1,138,716 shares of common stock held by OrbiMed Israel Partners II, L.P. ("OIP II"). Israel GP is the general partner of OIP II and Advisors Israel is the general partner of Israel GP. By virtue of such relationships, Israel GP and Advisors Israel may be deemed to have investment and voting power with respect to the shares held by OIP II and as a result, may be deemed to have beneficial ownership over such securities. Advisors Israel exercises this investment and voting power through a management committee comprised of Carl L. Gordon, David P. Bonita and Erez Chimovits, each of whom disclaims beneficial ownership of the shares held by OIP II. GP VIII is the general partner of OPI VIII and OrbiMed Advisors is the managing member of GP VIII. By virtue of such relationships, GP VIII and OrbiMed Advisors may be deemed to have investment and voting power with respect to the shares held by OPI VIII and as a result, may be deemed to have beneficial ownership over such securities. 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. Mr. Chimovits is an employee of OrbiMed and a member of our board of directors. The address for each of the entities and individuals identified in this footnote is c/o OrbiMed Advisors LLC, 601 Lexington Avenue 54th Floor, New York, NY 10022.

(3) Information herein is based on a Schedule 13D filed with the SEC on October 22, 2024 by AI Upstream LLC ("AI Upstream"), AI Biotechnology LLC ("AI Biotechnology"), Access Industries Holdings LLC ("AIH"), Access Industries Management, LLC ("AIM") and Len Blavatnik (collectively, the "Access Reporting Persons"). Consists of 5,494,410 shares of common stock held by AI Upstream. The shares held by AI Upstream may be deemed to be beneficially owned by AI Biotechnology, AIH, AIM and Mr. Blavatnik because (i) Mr. Blavatnik controls AIM and AIH, (ii) AIM controls AIH, (iii) AIH owns all of the voting units of AI Biotechnology and (iv) AI Biotechnology owns all of the voting units of AI Upstream. Each of the Access Reporting Persons (other than AI Upstream), and each of their affiliated entities and the officers, partners, members and managers thereof, disclaims beneficial ownership of the shares held by AI Upstream, except to the extent of its or his pecuniary interest therein. Liam Ratcliffe, M.B.Ch.B., Ph.D., M.B.A. is head of biotechnology at Access Industries, Inc., an affiliate of AI Upstream, and a member of our board of directors. The address for each of the Access Reporting Persons is c/o Access Industries, Inc., 40 West 57th Street, 28th Floor, New York, NY 10019.

(4) Information herein is based on our final prospectus filed with the SEC pursuant to Rule 424(b)(4) on October 11, 2024. The address of each of the Altshuler entities is 19 A Habarzel St. Ramat Hahayal, Tel Aviv, 6971026, Israel.

(5) Information herein is based on a Schedule 13G filed with the SEC on February 14, 2025 by Decheng Capital Global Life Sciences Fund IV, L.P. ("Decheng Fund IV"), Decheng Capital Management IV (Cayman), LLC ("Decheng Fund GP"), Decheng Capital Global Healthcare Fund (Master), LP ("Decheng Healthcare"), Decheng Capital Global Healthcare GP, LLC ("Decheng Healthcare GP") and Xiangmin Cui. Consists of (i) 3,085,293 shares of common stock held by Decheng Fund IV and (ii) 200,000 shares of common stock held by Decheng Healthcare. Decheng Fund GP is the general partner of Decheng Fund IV and shares voting and investment authority over the shares held by Decheng Fund IV. Decheng Healthcare GP is the general partner of Decheng Healthcare and shares voting and investment authority over the shares held by Decheng Healthcare. Dr. Cui is the manager of Decheng Fund GP and the indirect managing member and ultimate beneficial owner of Decheng Healthcare GP. Dr. Cui shares voting and investment authority over the shares held by each of Decheng Fund IV and Decheng Healthcare. Dayton Misfeldt is a partner at Decheng Capital LLC, the service company of Decheng Fund IV, and a former member of our board of directors. The address for each of the entities and individuals identified in this footnote is 3000 Sand Hill Road, Building 2, Suite 110, Menlo Park, CA 94025.

(6) Information herein is based on a Schedule 13G filed with the SEC on February 14, 2025 by TCG Crossover Fund I, L.P. ("TCG Crossover I"), TCG Crossover GP I, LLC ("TGC Crossover GP I") and Chen Yu. Consists of 2,801,763 shares of common stock held by TCG Crossover Fund I. TCG Crossover GP I is the general partner of TCG Crossover I and may be deemed to have voting, investment, and dispositive power with respect to these securities. Chen Yu is the sole managing member of TCG Crossover GP I and may be deemed to share voting, investment and dispositive power with respect to these securities. The address for each of the entities and individuals identified in this footnote is 705 High St., Palo Alto, CA 94301.

(7) Information herein is based on a Schedule 13G filed with the SEC on February 13, 2025 by HBM Healthcare Investments (Cayman) Ltd. ("HBM Healthcare"). Consists of 2,715,056 shares of common stock held by HBM Healthcare. Voting and investment power over the shares held by HBM Healthcare is exercised by its board of directors, which consists of Jean-Marc Lesieur, Richard H. Coles, Sophia Harris, Dr. Andreas Wicki, Dr. Mark Kronenfeld and Richard Paul Woodhouse, none of whom has individual voting or investment power with respect to the shares. The address for each of the entities and individuals identified in this footnote is Governors Square, 23 Lime Tree Bay Avenue, PO Box 30852, Grand Cayman, KY1-1204, Cayman Islands.

(8) Consists of 591,396 shares of common stock issuable upon the exercise of options exercisable within 60 days of April 14, 2025 held by Dr. Sutherland.

(9) Consists of 186,453 shares of common stock issuable upon the exercise of options exercisable within 60 days of April 14, 2025 held by Mr. Gray.

(10) Consists of 1,562 shares of common stock issuable upon the exercise of options exercisable within 60 days of April 14, 2025 held by Ms. Ambrose.

(11) Consists of (i) 29,057 shares of common stock and (ii) 484,745 shares of common stock issuable upon the exercise of options exercisable within 60 days of April 14, 2025 held by Ms. Truex.

(12) Consists of 271,951 shares of common stock issuable upon the exercise of options exercisable within 60 days of April 14, 2025 held by Mr. Renaud.

(13) Consists of 7,706 shares of common stock issuable upon the exercise of options exercisable within 60 days of April 14, 2025 held by Ms. Beckman.

(14) Consists of (i) 17,096 shares of common stock issuable upon the exercise of options exercisable within 60 days of April 14, 2025 held by Mr. Chimovits and (ii) 5,693,589 shares of common stock held by entities affiliated with OrbiMed, as described in note 2 above.

(15) Consists of 17,096 shares of common stock issuable upon the exercise of options exercisable within 60 days of April 14, 2025 held by Dr. Fleming.
(16) Consists of 17,096 shares of common stock issuable upon the exercise of options exercisable within 60 days of April 14, 2025 held by Dr. Ratcliffe.
(17) Consists of 54,273 shares of common stock issuable upon the exercise of options exercisable within 60 days of April 14, 2025 held by Dr. Ruddy.
(18) Consists of (i) 5,693,589 shares of common stock held by entities affiliated with OrbiMed over which Mr. Chimovits may be deemed to have beneficial ownership, as described in note 2 above, and (ii) 1,834,348 shares of common stock issuable upon the exercise of options exercisable within 60 days of April 14, 2025 held by our current executive officers, Dr. Sutherland, Mr. Gray, Ms. Ambrose, Dr. Deykin and Dr. Houghton, and current directors.

REPORT OF THE AUDIT COMMITTEE

The audit committee is appointed by the board of directors to assist the board of directors in fulfilling its oversight responsibilities with respect to (1) the integrity of Upstream Bio's financial statements and financial reporting process and systems of internal controls regarding finance, accounting, and compliance with legal and regulatory requirements, (2) the qualifications, independence, and performance of Upstream Bio's independent registered public accounting firm, (3) the performance of Upstream Bio's internal audit function, if any, and (4) other matters as set forth in the charter of the audit committee approved by the board of directors.

Management is responsible for the preparation of Upstream Bio's financial statements and the financial reporting process, including its system of internal control over financial reporting and its disclosure controls and procedures. The independent registered public accounting firm is responsible for performing an audit of Upstream Bio's financial statements in accordance with the standards of the Public Company Accounting Oversight Board (PCAOB) and issuing a report thereon. The audit committee's responsibility is to monitor and oversee these processes.

In connection with these responsibilities, the audit committee reviewed and discussed with management and the independent registered public accounting firm the audited consolidated financial statements of Upstream Bio for the fiscal year ended December 31, 2024. The audit committee also discussed with the independent registered public accounting firm the matters required to be discussed by the PCAOB's Auditing Standard No. 1301, *Communication with Audit Committees*. In addition, the audit committee received written communications from the independent registered public accounting firm confirming their independence as required by the applicable requirements of the PCAOB and has discussed with the independent registered public accounting firm their independence.

Based on the reviews and discussions referred to above, the audit committee recommended to the board of directors that the audited consolidated financial statements of Upstream Bio be included in Upstream Bio's Annual Report on Form 10-K for the fiscal year ended December 31, 2024 that was filed with the SEC. The information contained in this report shall not be deemed to be (1) "soliciting material," (2) "filed" with the SEC, (3) subject to Regulations 14A or 14C of the Exchange Act, or (4) subject to the liabilities of Section 18 of the Exchange Act. This report shall not be deemed incorporated by reference into any of our other filings under the Exchange Act or the Securities Act, except to the extent that we specifically incorporate it by reference into such filing.

THE AUDIT COMMITTEE OF THE BOARD OF DIRECTORS OF UPSTREAM BIO, INC.

Daniella Beckman, Chairperson
H. Edward Fleming, Jr., M.D.
Liam Ratcliffe, M.B.Ch.B., Ph.D., M.B.A.

April 17, 2025

HOUSEHOLDING

Some banks, brokers and other nominee record holders may be participating in the practice of "householding" proxy statements and annual reports. This means that only one copy of our documents, including the 2024 Annual Report to stockholders and Proxy Statement, may have been sent to multiple stockholders in your household. We will promptly deliver a separate copy of either document to you upon written or oral request to Upstream Bio, Inc., 890 Winter Street, Suite 200, Waltham, MA 02451, Attention: Corporate Secretary, telephone: (781) 208-2466. If you want to receive separate copies of the proxy statement or annual report to stockholders in the future, or if you are receiving multiple copies and would like to receive only one copy per household, you should contact your bank, broker or other nominee record holder, or you may contact us at the above address and phone number.

STOCKHOLDER PROPOSALS

A stockholder who would like to have a proposal considered for inclusion in our 2026 proxy statement must submit the proposal in accordance with the procedures outlined in Rule 14a-8 of the Exchange Act so that it is received by us no later than December 18, 2025, which is 120 days prior to April 17, 2026. However, if the date of the 2025 annual meeting of stockholders is changed by more than 30 days from the date of the previous year's meeting, then the deadline is a reasonable time before we begin to print and send our proxy statement for the 2026 annual meeting of stockholders. SEC rules set standards for eligibility and specify the types of stockholder proposals that may be excluded from a proxy statement. Stockholder proposals should be addressed to Upstream Bio, Inc., 890 Winter Street, Suite 200, Waltham, MA 02451, Attention: Corporate Secretary.

If a stockholder wishes to propose a nomination of persons for election to our board of directors or present a proposal at an annual meeting but does not wish to have the proposal considered for inclusion in our proxy statement and proxy card, our bylaws establish an advance notice procedure for such nominations and proposals. Stockholders at an annual meeting may only consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of the board of directors or by a stockholder of record on the record date for the meeting, who is entitled to vote at the meeting and who has delivered timely notice in proper form to our corporate secretary of the stockholder's intention to bring such business before the meeting.

The required notice must be in writing and received by our corporate secretary at our principal executive offices not less than 90 days nor more than 120 days prior to the first anniversary of the preceding year's annual meeting. However, in the event that the date of the annual meeting is advanced by more than 30 days or delayed by more than 60 days from the first anniversary of the preceding year's annual meeting, a stockholder's notice must be received no earlier than the 120th day prior to such annual meeting and not later than the close of business on the later of (A) the 90th day prior to such annual meeting and (B) the tenth day following the day on which notice of the date of such annual meeting was mailed or public disclosure of the date of such annual meeting was made, whichever first occurs. For stockholder proposals to be brought before the 2026 annual meeting of stockholders, the required notice must be received by our corporate secretary at our principal executive offices no earlier than February 10, 2026 and no later than March 12, 2026. Stockholder proposals and the required notice should be addressed to Upstream Bio, Inc., 890 Winter Street, Suite 200, Waltham, MA 02451, Attention: Corporate Secretary.

To comply with the SEC's universal proxy rules, stockholders who intend to solicit proxies in support of director nominees other than our nominees must provide notice to us in accordance with the additional requirements of Rule 14a-19(b), which, among other things, requires that notice be postmarked or transmitted electronically to our principal executive offices by no later than April 27, 2025 for director nominations to be brought before the Annual Meeting, which is ten calendar days following the date of this proxy statement, which is the day on which public announcement of the date of the Annual Meeting is first being made. For director nominations to be brought before the 2026 annual meeting, notice must be postmarked or transmitted electronically to our principal executive offices by no later than April 11, 2026, which is 60 days before the one-year anniversary date of the Annual Meeting, except that if the 2026 annual meeting is more than 30 days before or after the anniversary date of the Annual Meeting, then notice must be provided by the later of 60 days prior to the date of the 2026 annual meeting or the tenth day following the day on which public announcement of the date of the annual meeting is first made.

OTHER MATTERS

Our board of directors does not know of any other matters to be brought before the Annual Meeting. If any other matters not mentioned in this Proxy Statement are properly brought before the meeting, the individuals named in the enclosed proxy intend to use their discretionary voting authority under the proxy to vote the proxy in accordance with their best judgment on those matters.

UPSTREAM BIO, INC.
890 WINTER STREET, SUITE 200
WALTHAM, MA 02451

SCAN TO VIEW MATERIALS & VOTE

Before The Meeting

VOTE BY INTERNET - Go to **www.proxyvote.com**
Use the Internet to transmit your voting instructions and for electronic delivery of information up until 11:59 p.m. Eastern Time on June 9, 2025. Have your proxy card in hand when you access the web site and follow the instructions to obtain your records and to create an electronic voting instruction form.

VOTE BY PHONE - 1-800-690-6903
Use any touch-tone telephone to transmit your voting instructions up until 11:59 p.m. Eastern Time on June 9, 2025. Have your proxy card in hand when you call and then follow the instructions.

VOTE BY MAIL
Mark, sign and date your proxy card and return it in the postage-paid envelope we have provided or return it to Vote Processing, c/o Broadridge, 51 Mercedes Way, Edgewood, NY 11717.

VOTE BY QR CODE
You may vote by scanning the QR code above with your mobile device. Votes submitted by scanning the QR code must be received by no later than 11:59 p.m. Eastern Time on June 9, 2025.

During The Meeting

VOTE BY INTERNET - Go to **www.virtualshareholdermeeting.com/UPB2025**
You may attend the meeting via the Internet and vote during the meeting. Have the information that is printed in the box marked by the arrow available and follow the instructions.

TO VOTE, MARK BLOCKS BELOW IN BLUE OR BLACK INK AS FOLLOWS:

V71354-P27279 KEEP THIS PORTION FOR YOUR RECORDS

THIS PROXY CARD IS VALID ONLY WHEN SIGNED AND DATED. DETACH AND RETURN THIS PORTION ONLY

UPSTREAM BIO, INC.

The board of directors recommends you vote FOR the following proposal:

	For All	Withhold All	For All Except
1. To elect two class I directors to Upstream's board of directors, each to serve until the 2028 annual meeting of Upstream's stockholders, and until his or her respective successor has been duly elected and qualified, or until his or her earlier death, resignation or removal.	☐	☐	☐

To withhold authority to vote for any individual nominee(s), mark "For All Except" and write the number(s) of the nominee(s) on the line below.

_____

Nominees:

01) Erez Chimovits, M.B.A., M.Sc.
02) Marcella Kuhlman Ruddy, M.D., M.S.

The board of directors recommends you vote FOR the following proposal:

	For	Against	Abstain
2. To ratify the appointment of PricewaterhouseCoopers LLP as Upstream's independent registered public accounting firm for the fiscal year ending December 31, 2025.	☐	☐	☐

NOTE: In their discretion, the proxies are authorized to vote upon such other business as may properly come before the meeting or any continuation, adjournment or postponement thereof.

Please sign exactly as your name(s) appear(s) hereon. When signing as attorney, executor, administrator, or other fiduciary, please give full title as such. Joint owners should each sign personally. All holders must sign. If a corporation or partnership, please sign in full corporate or partnership name by authorized officer.

Signature [PLEASE SIGN WITHIN BOX] Date

Signature (Joint Owners) Date

Important Notice Regarding the Availability of Proxy Materials for the Annual Meeting:
The Notice, Proxy Statement and 2024 Annual Report are available at www.proxyvote.com.

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UPSTREAM BIO, INC.
ANNUAL MEETING OF STOCKHOLDERS
June 10, 2025 8:00 AM ET
THIS PROXY IS SOLICITED BY THE BOARD OF DIRECTORS

The stockholder(s) hereby appoint(s) E. Rand Sutherland, M.D. and Michael Paul Gray, M.B.A., or either of them, as proxies, each with the power to appoint his substitute, and hereby authorize(s) them to represent and to vote, as designated on the reverse side of this ballot, all of the shares of common stock of UPSTREAM BIO, INC. that the stockholder(s) is/are entitled to vote at the Annual Meeting to be held at 8:00 AM ET on June 10, 2025, virtually at www.virtualshareholdermeeting.com/UPB2025, and any continuation, adjournment or postponement thereof.

This proxy, when properly executed, will be voted in the manner directed herein. If no such direction is made, this proxy will be voted in accordance with the board of directors' recommendations.

CONTINUED AND TO BE SIGNED ON REVERSE SIDE