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PROSPECTUS SUPPLEMENT
(To Prospectus Dated May 24, 2024)

Orchestra BioMed Holdings, Inc.

15,000,000 Shares of Common Stock

We are offering 15,000,000 shares of our common stock pursuant to this prospectus supplement and the accompanying base prospectus.

Our common stock is traded on the Nasdaq Global Market under the symbol "OBIO." On November 5, 2026, the last reported sale price of our common stock on the Nasdaq Global Market was $5.62 per share.

Investing in our common stock involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading "Risk Factors" in this prospectus supplement and in the documents incorporated by reference into this prospectus supplement and the accompanying base prospectus.

	Per Share	Total
Public offering price	$5.00	$75,000,000.00
Underwriting discounts and commissions[(1)]	$0.30	$ 4,500,000.00
Proceeds, before expenses, to us	$4.70	$70,500,000.00

(1) See the section titled "Underwriting" for additional information regarding underwriting compensation.

We have granted the underwriters an option for a period of 30 days to purchase up to 2,250,000 additional shares of common stock at the public offering price, less underwriting discounts and commissions. If the underwriters exercise the option in full, the total underwriting discounts and commissions payable by us will be $5,175,000.00 and the total proceeds to us, before expenses, will be $81,075,000.00.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus supplement is truthful or complete. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares of our common stock against payment in New York, New York on or about November 9, 2026.

Piper Sandler **TD Cowen**

BTIG

H.C. Wainwright & Co.

The date of this prospectus supplement is November 5, 2026

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Prospectus

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ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying base prospectus are part of a registration statement that we have filed with the Securities and Exchange Commission (the "SEC"), utilizing a "shelf" registration process, and relates to the offering of our common stock.

We provide information to you about this offering of our common stock in two separate documents that are bound together: (1) this prospectus supplement, which describes the specific details regarding this offering; and (2) the accompanying base prospectus, which provides general information, some of which may not apply to this offering. Generally, when we refer to this "prospectus," we are referring to both documents combined. If information in this prospectus supplement is inconsistent with the accompanying base prospectus, you should rely on this prospectus supplement. To the extent there is a conflict between the information contained in this prospectus supplement, on the one hand, and the information contained in any document incorporated by reference in this prospectus supplement, on the other hand, you should rely on the information in this prospectus supplement, except as provided in the following sentence. If any statement in one of these documents is inconsistent with a statement in another document having a later date — for example, a document incorporated by reference in this prospectus supplement — the statement in the document having the later date modifies or supersedes the earlier statement. Any statement so modified or superseded will not be deemed, except as so modified or superseded, to constitute a part of this prospectus.

You should rely only on the information contained or incorporated by reference in this prospectus supplement, the accompanying base prospectus and any free writing prospectus we may authorize for use in connection with this offering. We and the underwriters have not authorized anyone to provide you with different information. We and the underwriters take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may provide.

The information contained in this prospectus supplement, the accompanying base prospectus, the documents incorporated by reference herein or therein and any free writing prospectus we may authorize for use in connection with this offering, is accurate only as of their respective dates, regardless of the time of delivery of any such document or the time of any sale of our common stock. Our business, financial condition, results of operations and prospects may have changed since those dates. It is important for you to read and consider all information contained in this prospectus supplement, the accompanying base prospectus, the documents incorporated by reference herein and therein and any free writing prospectus that we have authorized for use in connection with this offering, in making your investment decision. You should read this prospectus supplement and the accompanying base prospectus, as well as the documents incorporated by reference herein and therein, the additional information described under the sections titled "Where You Can Find More Information" and "Incorporation of Certain Information by Reference" in this prospectus supplement, and any free writing prospectus that we have authorized for use in connection with this offering, before investing in our common stock.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made.

Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

The accompanying base prospectus and the documents incorporated by reference herein also contain estimates, projections and other information concerning our industry, our business, and the markets for certain diseases, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, studies

and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources.

We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where such offers and sales are permitted. The distribution of this prospectus supplement and the accompanying base prospectus and the offering of our common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying base prospectus must inform themselves about, and observe any restrictions relating to, the offering of our common stock and the distribution of this prospectus supplement and the accompanying base prospectus outside the United States. This prospectus supplement and the accompanying base prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying base prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

As used in this prospectus supplement, unless the context otherwise requires, references to the "Company," "Orchestra," "we," "us" and "our" refer to Orchestra BioMed Holdings, Inc. and its consolidated subsidiaries.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights certain information about us, this offering and selected information contained elsewhere in or incorporated by reference into this prospectus supplement or the accompanying base prospectus. This summary is not complete and does not contain all of the information that you should consider before deciding whether to invest in our common stock. For a more complete understanding of our company and this offering, we encourage you to read and consider carefully the more detailed information in this prospectus supplement and the accompanying base prospectus, including the information incorporated by reference in this prospectus supplement, including the information under the heading "Risk Factors" in this prospectus supplement and in the documents incorporated by reference into this prospectus supplement.

Company Overview

We are a biomedical innovation company accelerating high-impact technologies to patients through risk-reward sharing collaborations with market-leading global medical device companies. Our partnership-enabled business model focuses on forging strategic collaborations with leading medical device companies to drive successful global commercialization of products we develop. We are led by a highly accomplished, multidisciplinary management team and a board of directors with extensive experience in all phases of therapeutic device development. Our business was formed in 2018 by assembling a pipeline of multiple late-stage clinical product candidates originally developed by our founding team.

Our two flagship product candidates — Atrioventricular Interval Modulation Therapy ("AVIM Therapy") and Virtue® Sirolimus AngioInfusion™ Balloon ("Virtue SAB") — are currently undergoing pivotal clinical trials for their lead indications, each representing multi-billion-dollar annual global market opportunities.

AVIM Therapy is a bioelectronic treatment for hypertension ("HTN"), the leading risk factor for death worldwide, and is designed to be delivered by a pacemaker and achieve immediate, substantial and sustained reductions in blood pressure in patients with hypertensive heart disease. We have an exclusive license and strategic collaboration agreement with Medtronic Inc. (an affiliate of Medtronic plc) ("Medtronic"), one of the largest medical device companies in the world and the global leader in cardiac pacing therapies, for the development and commercialization of AVIM Therapy for the treatment of uncontrolled HTN in patients indicated for a cardiac pacemaker. We are actively conducting a double-blind, randomized, global pivotal trial (the "BACKBEAT Trial"). In October 2026, we completed enrollment with 349 randomized patients with uncontrolled HTN who are indicated for a dual-chamber pacemaker. Assuming primary endpoints are met, we and Medtronic intend to submit primary endpoint data as a late-breaking clinical trial presentation at a major cardiovascular conference in the second quarter of 2027, followed by marketing application submissions to the U.S. Food and Drug Administration (the "FDA") and global regulatory agencies. AVIM Therapy has received two FDA Breakthrough Device Designations ("BDDs").

Virtue SAB is a highly differentiated, first-of-its-kind, non-coated drug delivery AngioInfusion balloon system designed to infuse a large liquid dose of our proprietary extended-release formulation of sirolimus, SirolimusEFR™, for the treatment of atherosclerotic artery disease, the leading cause of mortality worldwide. Virtue SAB has been granted BDD by the FDA for the treatment of coronary in-stent restenosis, coronary small vessel disease and below-the-knee peripheral artery disease, in each case, within specified parameters. We are actively enrolling patients in the Virtue SAB in the Treatment of Coronary In-Stent Restenosis Trial (the "Virtue Trial") for our U.S. investigational device exemption pivotal trial comparing Virtue SAB head-to-head with Boston Scientific Corporation's commercially available AGENT™ paclitaxel-coated balloon. Designed to support regulatory approval of Virtue SAB, the Virtue Trial is expected to enroll 740 patients in the United States with enrollment expected to be completed by the end of 2027. We cannot provide assurance that we will be able to complete enrollment of the Virtue Trial in the timeframe we anticipate.

Recent Developments

Certain Unaudited Preliminary September 30, 2026 Financial Results

Although our financial results for the quarter ended September 30, 2026 are not yet finalized, based on currently available information, we expect our cash, cash equivalents and marketable securities to be approximately $102 million as of September 30, 2026.

The preliminary results set forth above are based on management's initial review of our operations for the quarter ended September 30, 2026 and are subject to completion of financial closing procedures. The preliminary financial results in this prospectus supplement have been prepared by, and are the responsibility of, management. Actual results may differ materially from these preliminary results as a result of the completion of financial closing procedures, final adjustments, and other developments arising between now and the time that our financial results are finalized. In addition, these preliminary results are not a comprehensive statement of our financial results for the quarter ended September 30, 2026, should not be viewed as a substitute for full financial statements prepared in accordance with generally accepted accounting principles, and are not necessarily indicative of our results for any future period. Ernst & Young LLP, our independent registered public accounting firm, has not audited, reviewed, compiled, or applied agreed-upon procedures with respect to the preliminary financial results. Accordingly, Ernst & Young LLP does not express an opinion or any other form of assurance with respect thereto.

Corporate Information

We were incorporated in the Cayman Islands in 2020, as a special purpose acquisition company under the name Health Sciences Acquisitions Corporation 2 ("HSAC2"). On January 26, 2023, Orchestra BioMed, Inc. and HSAC2 consummated a business combination pursuant to which, among other things, Orchestra BioMed, Inc. became a wholly owned subsidiary of HSAC2 and HSAC2 deregistered in the Cayman Islands, domesticated as a Delaware corporation and changed its name to Orchestra BioMed Holdings, Inc. (the "Business Combination").

Our principal executive office is located at 150 Union Square Drive, New Hope, PA 18938, and our telephone number is (215) 862-5797. Our website address is www.orchestrabiomed.com. We do not incorporate the information on or accessible through our website into this prospectus supplement, and you should not consider any information on or accessible through our website as part of this prospectus supplement.

THE OFFERING

Common stock offered by us	15,000,000 shares
Option to purchase additional shares of common stock	We have granted the underwriters an option for 30 days from the date of this prospectus supplement to purchase up to additional 2,250,000 shares of our common stock.
Common stock to be outstanding immediately after this offering[(1)]	76,453,382 shares (or 78,703,382 shares if the underwriters exercise in full their option to purchase additional shares of common stock).
Use of proceeds	We estimate that the net proceeds to us from this offering will be approximately $70.0 million, or approximately $80.5 million if the underwriters exercise in full their option to purchase additional shares of common stock, after deducting underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use the net proceeds from this offering, together with our existing cash and cash equivalents, to fund our AVIM Therapy program and the execution of the BACKBEAT Trial and to fund our Virtue SAB program and the Virtue Trial, as well as research and clinical development of other current or additional product candidates, and the remainder for working capital and other general corporate purposes. See the section titled "Use of Proceeds" for more information about the intended use of net proceeds from this offering.
Risk factors	Investing in our common stock involves significant risks. See "Risk Factors" beginning on page S-5 of this prospectus supplement and the information under similar headings in other documents incorporated by reference into this prospectus supplement for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.
Nasdaq Global Market symbol	Our common stock is listed on the Nasdaq Global Market under the symbol "OBIO."

(1) The number of shares of our common stock to be outstanding after this offering is based on 61,453,382 shares of common stock outstanding as of November 4, 2026, and excludes as of November 4, 2026:

- up to 3,242,133 shares of our common stock issuable upon the exercise of stock options outstanding under the Orchestra BioMed, Inc. 2018 Stock Incentive Plan (the "2018 Plan") at a weighted average exercise price of $7.87 per share;
- up to 4,878,599 shares of our common stock issuable upon the exercise of stock options outstanding under the Company's 2023 Equity Incentive Plan (the "2023 Plan") at a weighted average exercise price of $4.52 per share;
- up to 3,360,684 shares of our common stock issuable upon the vesting of restricted stock units ("RSUs") outstanding under the 2023 Plan;
- up to 451,750 shares of our common stock issuable upon the exercise of stock options outstanding under the Orchestra BioMed Holdings, Inc. 2025 New Hire Inducement Plan (the "New Hire Inducement Plan"), at a weighted average exercise price of $4.40 per share;
- up to 482,963 shares of our common stock available for future issuance under the 2023 Plan (which number does not include a possible annual increase on January 1 of each year ending on (and including) January 1, 2032, in an amount equal to the lesser of (i) 4.8% of the total number of shares of our

common stock outstanding on December 31 of the immediately preceding year, (ii) 3,036,722 shares of our common stock, and (iii) such number of shares of our common stock determined by the Board or the compensation committee of our Board prior to January 1st of a given year);

- up to 498,250 shares of our common stock available for future issuance under the New Hire Inducement Plan;
- up to 750,000 shares of our common stock available for future issuance under the Orchestra BioMed Holdings, Inc. 2026 Employee Stock Purchase Plan (the "ESPP");
- approximately 4,000,000 shares of our common stock to be issued as part of the Business Combination if certain earnout milestones are achieved;
- up to 1,666,666 shares of our common stock issuable, subject to certain conditions, upon the conversion of 200,000 shares of Series A Convertible Preferred Stock, $0.0001 par value per share (the "Series A Preferred Stock"), issued to Terumo Medical Corporation on November 7, 2025;
- up to 3,886,331 shares of our common stock issuable upon the exercise of 3,886,331 pre-funded warrants, with an exercise price of $0.0001 per share (the "Pre-Funded Warrants"), issued in the Company's public offering, which closed on August 4, 2025;
- up to 2,000,000 shares of our common stock issuable upon the exercise of 2,000,000 warrants, with an exercise price of $3.67 per share, issued to Ligand Pharmaceuticals Incorporated in a private placement on August 4, 2025;
- up to 750,000 shares of our common stock issuable upon the exercise of the 750,000 private placement warrants, with an exercise price of $11.50 per share (the "HSAC2 Warrant Shares") issued in a private placement to HSAC 2 Holdings, LLC, the sponsor (the "Sponsor") of HSAC2 (the "HSAC2 Warrants") in connection with the initial public offering of HSAC2;
- up to 635,000 shares of our common stock issuable upon the exercise of 635,000 warrants, with an exercise price of $11.50 per share (the "Officer and Director Warrant Shares") that were issued to certain officers and directors of the Company (the "Officer and Director Warrants") in connection with the forfeiture of 750,000 HSAC2 Warrants by the Sponsor as part of the Business Combination (115,000 of the initial 750,000 Officer and Director Warrants were forfeited in connection with the departure of Orchestra's former Chief Financial Officer and one Orchestra director);
- up to 507,841 shares of our common stock issuable upon the exercise of 507,841 private warrants, with a weighted average exercise price of $9.01 per share, issued in connection with the Business Combination in exchange for warrants issued by Orchestra BioMed, Inc., the Company's predecessor and now a wholly owned subsidiary of the Company (the "Orchestra Warrants");
- up to 27,707 shares of our common stock issuable upon the exercise of warrants issued to certain historical lenders of the Company (the "Avenue Warrants"), with an exercise price of $7.67 per share;
- up to 167,598 shares of our common stock issuable upon the exercise of warrants issued to certain lenders of the Company (the "Hercules Warrants"), with an exercise price of $3.58 per share; and
- up to 60,000 shares of our common stock issuable upon the exercise of warrants issued to a certain non-employee consultant of the Company (the "Non-employee Warrants"), with an exercise price of $4.69 per share.

Unless otherwise indicated, all information in this prospectus supplement assumes no exercise of the outstanding options and warrants, or vesting of RSUs described above, and no exercise by the underwriters of their option to purchase additional shares of our common stock. In addition, the number of shares of our common stock outstanding as shown above does not include the $86.2 million of shares of our common stock that are available for sale as of the date of this prospectus supplement pursuant to that certain sales agreement (the "Sales Agreement"), dated as of August 12, 2024, with TD Securities (USA) LLC ("TD Cowen") and the related registration statement of which this prospectus supplement forms a part.

RISK FACTORS

Investing in our common stock involves a high degree of risk. Before making an investment decision, you should carefully consider the risks described below and under "Item 1A. Risk Factors" in our most recent Annual Report on Form 10-K and any subsequent Quarterly Reports on Form 10-Q or Current Reports on Form 8-K, as well as any amendments thereto reflected in subsequent filings with the SEC, each of which are incorporated by reference in this prospectus supplement, and all of the other information included in this prospectus supplement or incorporated herein by reference, including our financial statements and related notes. If any of these risks is realized, our business, financial condition, results of operations and prospects could be materially and adversely affected. In that event, the trading price of our common stock could decline and you could lose part or all of your investment. Additional risks and uncertainties that are not yet identified or that we currently believe to be immaterial may also materially harm our business, financial condition, results of operations and prospects and could result in a complete loss of your investment.

Risks Related to this Offering

We have broad discretion in the use of the net proceeds from this offering and may invest or spend the proceeds in ways with which you do not agree and in ways that may not yield a return on your investment.

Our management will have broad discretion in the application of the net proceeds from this offering, including for any of the purposes described in the section titled "Use of Proceeds," and you will be relying on the judgment of our management regarding such application. You will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used effectively. Our management might not apply the net proceeds in ways that ultimately increase the value of your investment. If we do not invest or apply the net proceeds from this offering in ways that enhance stockholder value, we may fail to achieve expected results, which could cause our stock price to decline. Pending their use, we may invest the net proceeds in a variety of capital preservation instruments, including short-term, investment-grade, interest-bearing instruments and U.S. government securities. These investments may not yield a favorable return to our stockholders.

If you purchase shares of our common stock in this offering, you will incur immediate and substantial dilution in the net tangible book value of your investment.

If you purchase shares of our common stock in this offering, you will incur immediate and substantial dilution in the as adjusted net tangible book value of the common stock that you purchase of $3.68 per share as of June 30, 2026, after giving effect to this offering, because the price that you pay will be substantially greater than the net tangible book value per share of the shares you acquire. Furthermore, the exercise of outstanding stock options and warrants, and the vesting and settlement of RSUs may result in further dilution of your investment. See the section titled "Dilution."

A substantial number of shares of our common stock may be sold in the market following this offering, which may depress the market price for our common stock.

Future sales by us or our stockholders of a substantial number of shares of common stock in the public market, including through this offering, or the perception that these sales might occur, could cause the market price of our common stock to decline and could consequently impair our ability to raise capital through a future sale of, or pay for acquisitions using, our equity securities.

We and our directors and officers have agreed with the underwriters that, for a period of 60 days after the date of this prospectus supplement, we and they will not, directly or indirectly, offer, pledge, sell, contract to sell, grant any option to purchase or otherwise dispose of any shares of our common stock or any securities convertible into or exercisable or exchangeable for our common stock or in any manner transfer all or a portion of the economic consequences associated with the ownership of our common stock, or cause a registration statement covering any shares of common stock to be filed, without the prior written consent of Piper Sandler & Co. and TD Securities (USA) LLC, who may, in their sole discretion and at any time without notice, release all or any portion of the securities subject to those lock-up agreements. In addition, these restrictions are subject to certain important exceptions, and with respect to us, the restrictions

will not apply to, among other things, equity awards made pursuant to our equity incentive plans in effect on the date of this prospectus supplement, and upon the exercise of options or the vesting and settlement of RSUs. See "Underwriting."

The availability of shares for sale or other issuance in the future could reduce the market price of our common stock.

Subject to the listing rules of The Nasdaq Stock Market LLC ("Nasdaq"), our Board has the authority, without action or vote of our stockholders, to issue all or any part of our authorized but unissued shares of common stock, or issue shares of preferred stock, which are convertible into shares of common stock. In the future, we may issue securities to raise cash for acquisitions, as consideration in acquisitions, to pay down debt, to fund capital expenditures or general corporate expenses, in connection with the exercise of stock options or to satisfy our obligations under our incentive plans.

We may also acquire interests in other companies by using a combination of cash, our preferred stock and our common stock or just our common stock. We may also issue securities, including our preferred stock, that are convertible into, exchangeable for, or that represent the right to receive, our common stock. The occurrence of any of these events or any issuance of common stock may dilute your ownership interest in the Company, reduce our earnings per share and have an adverse impact on the price of our common stock.

We may issue preferred stock whose terms could adversely affect the voting power or value of our common stock.

Our governing documents authorize us to issue, without the approval of our stockholders, one or more classes or series of preferred stock having such designations, preferences, limitations and relative rights, including preferences over our common stock respecting dividends and distributions, as our Board may determine. The terms of one or more classes or series of preferred stock could adversely impact the voting power or value of our common stock. For example, we might grant holders of preferred stock the right to elect some number of our directors in all events or on the happening of specified events or the right to veto specified transactions. Similarly, the repurchase or redemption rights or liquidation preferences we might assign to holders of preferred stock could affect the residual value of our common stock.

The terms of any future preferred equity or debt financing may give holders of any preferred securities or debt securities rights that are senior to the rights of our common stockholders or impose more stringent restrictions on our operations.

If we incur additional debt or raise equity through the issuance of preferred stock, the terms of the debt or the preferred stock issued may give the holders rights, preferences and privileges senior to those of holders of our common stock, particularly in the event of liquidation. The terms of the debt may also impose additional and more stringent restrictions on our operations. If we raise funds through the issuance of additional equity, the ownership percentage of our existing stockholders would be diluted.

Changes in tax regulations or their interpretation could negatively impact our cash flows and results of operations.

Changes in tax and other revenue raising laws, regulations, and policies in the jurisdictions where we do business could impose new restrictions, costs, or prohibitions on our practices and negatively impact our results of operations. In addition, interpretation of tax regulations requires us to exercise our judgment and taxing authorities, or our independent registered public accounting firm may reach conclusions about the application of such regulations that differ from our conclusions. Changes to U.S. tax laws, regulations, or interpretations could impact the tax treatment of our earnings and adversely affect our cash flows and financial results.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying base prospectus, the documents that we incorporate by reference herein or therein, and any related free writing prospectus contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act") and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). Any statements about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and may be forward-looking. These statements are often, but are not always, made through the use of words or phrases such as "may," "will," "could," "should," "expects," "intends," "plans," "anticipates," "believes," "estimates," "predicts," "projects," "potential," "continue," and similar expressions, or the negative of these terms, or similar expressions.

Accordingly, these statements involve estimates, assumptions, risks and uncertainties which could cause actual results to differ materially from those expressed in them. Any forward-looking statements are qualified in their entirety by reference to the factors discussed throughout this prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein, and, in particular, those factors referenced in the section "Risk Factors" in such documents.

This prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein contain forward-looking statements that are based on our management's belief and assumptions and on information available to our management as of their respective dates. These statements relate to future events or our future financial performance, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Forward-looking statements include, but are not limited to, statements about:

- our ability to raise financing in the future, including our ability to borrow additional funds under our current debt financing arrangements;
- our success in retaining or recruiting, or changes required in, our officers, key employees or directors;
- our ability and/or the ability of third-party vendors and partners to manufacture our product candidates;
- our ability to source critical components or materials for the manufacture of our product candidates;
- our ability to achieve and sustain profitability;
- our ability to achieve our projected development and commercialization goals;
- the rate of progress, costs and results of our clinical studies and research and development activities, including, among other things, the date by which we expect to complete enrollment of our Virtue Trial;
- market acceptance of our product candidates, if approved;
- our ability to compete successfully with larger companies in a highly competitive industry;
- changes in our operating results, which make future operations results difficult to predict;
- serious adverse events, undesirable side effects that could halt the clinical development, regulatory approval or certification, of our product candidates;
- our ability to manage growth or control costs related to growth;
- economic conditions that may adversely affect our business, financial condition and stock price;
- our reliance on third parties to drive successful marketing and sale of our initial product candidates, if approved;
- our reliance on third parties to manufacture and provide important materials and components for our products and product candidates;

- our and our partners' abilities to obtain necessary regulatory approvals and certifications for our product candidates in an uncomplicated and inexpensive manner;
- our ability to maintain compliance with regulatory and post-marketing requirements;
- adverse medical events, failure or malfunctions in connection with our product candidates and possible subjection to regulatory sanctions;
- healthcare costs containment pressures and legislative or administrative reforms which affect coverage and reimbursement practices of third-party payors;
- our ability to protect or enforce our intellectual property, unpatented trade secrets, know-how and other proprietary technology;
- our ability to obtain necessary intellectual property rights from third parties;
- our ability to protect our trademarks, trade names and build our name recognition;
- our ability to maintain the listing of our common stock on Nasdaq;
- the success of our licensing agreements;
- our public securities' liquidity and trading; and
- our expected use of proceeds from this offering.

These forward-looking statements are neither promises nor guarantees of future performance due to a variety of risks and uncertainties, many of which are beyond our control, which could cause actual results to differ materially from those indicated by these forward-looking statements, including, without limitation the risk factors and cautionary statements described in other documents that we file from time to time with the SEC, specifically under the heading "Item 1A. Risk Factors" in our most recent Annual Report on Form 10-K, under the heading "Item 1A. Risk Factors" in any subsequently filed Quarterly Report on Form 10-Q and the section in this prospectus supplement entitled "Risk Factors."

The forward-looking statements in this prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein represent our views as of their respective dates. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we assume no obligation to update or revise any forward-looking statements except to the extent required by applicable law. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to the dates on which they were made.

This prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein also contain estimates, projections and other information concerning our industry, our business, and the markets for certain diseases, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources.

USE OF PROCEEDS

We estimate that the net proceeds to us from this offering will be approximately $70.0 million, or approximately $80.5 million if the underwriters exercise in full their option to purchase additional shares of common stock, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds from this offering, together with our existing cash and cash equivalents, to fund our AVIM Therapy program and the execution of our BACKBEAT Trial and to fund our Virtue SAB program and the Virtue Trial, as well as research and clinical development of other current or additional product candidates, and the remainder for working capital and other general corporate purposes. The expected use of the net proceeds from this offering represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures will depend on numerous factors, including the factors described under “Risk Factors” in this prospectus supplement and in the documents incorporated by reference herein, as well as the amount of cash used in our operations. We may find it necessary or advisable to use the net proceeds for other purposes, and we will have broad discretion in the application of the net proceeds. Pending the uses described above, we may invest the net proceeds in a variety of capital preservation instruments, including short-term, investment-grade, interest-bearing instruments and U.S. government securities.

Based on the planned use of proceeds described above, we believe that the net proceeds from this offering, together with our existing cash and cash equivalents and marketable securities will be sufficient to enable us to fund our operating expenses and capital expenditure requirements through 2028. We have based this estimate on assumptions that may prove to be incorrect, and we could use our available capital resources sooner than we currently expect. We may satisfy our future cash needs through the sale of equity securities, debt financings, working capital lines of credit, corporate collaborations or license agreements, grant funding, interest income earned on invested cash balances or a combination of one or more of these sources.

DIVIDEND POLICY

We have never declared or paid cash dividends on our capital stock. We intend to retain all available funds and any future earnings to fund the growth and development of our business. We do not intend to pay cash dividends to our stockholders in the foreseeable future. Any future determination to pay dividends will be made at the discretion of the Board subject to applicable laws, and will depend upon, among other factors, our results of operations, financial condition, contractual restrictions and capital requirements. In this regard, the payment of cash dividends is prohibited by the terms of (i) the Loan and Security Agreement dated as of December 30, 2024, as amended, by and among Orchestra BioMed Holdings, Inc., certain of its subsidiaries, the several banks and other financial institutions or entities party thereto, and Hercules Capital, Inc. and (ii) the Loan Agreement, dated July 31, 2025, between Orchestra BioMed Holdings, Inc., certain of its subsidiaries and Medtronic, Inc. Any future debt financing arrangement likely will also contain terms restricting or limiting the amount of dividends that may be declared or paid on our securities. Investors should not purchase our common stock with the expectation of receiving cash dividends.

DILUTION

If you invest in our common stock in this offering, your ownership interest will be diluted to the extent of the difference between the public offering price per share of our common stock in this offering and the as adjusted net tangible book value per share of our common stock immediately after this offering. Our net tangible book value as of June 30, 2026 was approximately $29.4 million, or approximately $0.49 per share of common stock. Net tangible book value per share represents the amount of total tangible assets (total assets less intangible assets) less total liabilities, divided by the number of shares of our common stock outstanding as of June 30, 2026.

After giving effect to the sale of 15,000,000 shares of our common stock in this offering at the public offering price of $5.00 per share, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of June 30, 2026 would have been approximately $99.4 million, or $1.32 per share. This amount represents an immediate increase in net tangible book value of $0.83 per share to our existing stockholders and an immediate dilution in net tangible book value of approximately $3.68 per share to new investors purchasing shares of our common stock in this offering. We determine dilution by subtracting the net tangible book value per share after the offering from the amount of cash that a new investor paid for a share of common stock.

The following table illustrates this dilution on a per share basis:

Public offering price per share		$5.00
Net tangible book value per share as of June 30, 2026	$0.49	
Increase in net tangible book value per share attributable to new investors participating in this offering	$0.83	
As adjusted net tangible book value per share as of June 30, 2026, after giving effect to this offering		$1.32
Dilution per share to new investors participating in this offering		$3.68

If the underwriters exercise in full their option to purchase 2,250,000 additional shares of common stock, the as adjusted net tangible book value will increase to $1.42 per share, representing an immediate increase to existing stockholders of $0.93 per share and an immediate dilution of $3.58 per share to new investors.

The information and the table above is based on 60,105,049 shares of our common stock outstanding as of June 30, 2026, and excludes as of June 30, 2026:

- up to 3,242,474 shares of our common stock issuable upon the exercise of stock options outstanding under our 2018 Plan at a weighted average exercise price of $7.87 per share;
- up to 4,908,597 shares of our common stock issuable upon the exercise of stock options outstanding under our 2023 Plan at a weighted average exercise price of $4.53 per share;
- up to 3,518,226 shares of our common stock issuable upon the vesting of RSUs outstanding under the 2023 Plan;
- up to 333,750 shares of our common stock issuable upon the exercise of stock options outstanding under the New Hire Inducement Plan at a weighted average exercise price of $4.21 per share;
- up to 423,916 shares of our common stock available for future issuance under the 2023 Plan (which number does not include a possible annual increase on January 1 of each year ending on (and including) January 1, 2032, in an amount equal to the lesser of (i) 4.8% of the total number of shares of our common stock outstanding on December 31 of the immediately preceding year, (ii) 3,036,722 shares of our common stock, and (iii) such number of shares of our common stock determined by the Board or the compensation committee of our Board prior to January 1st of a given year);
- up to 616,250 shares of our common stock available for future issuance under the New Hire Inducement Plan;
- up to 750,000 shares of our common stock available for future issuance under the ESPP;

- approximately 4,000,000 shares of our common stock to be issued as part of the Business Combination if certain earnout milestones are achieved;
- up to 1,666,666 shares of our common stock issuable, subject to certain conditions, upon the conversion of 200,000 shares of Series A Preferred Stock;
- up to 3,886,331 shares of our common stock issuable upon the exercise of 3,886,331 Pre-Funded Warrants, with an exercise price of $0.0001 per share;
- up to 2,000,000 shares of our common stock issuable upon the exercise of 2,000,000 warrants, with an exercise price of $3.67 per share, issued to Ligand Pharmaceuticals Incorporated in a private placement on August 4, 2025;
- up to 750,000 HSAC2 Warrant Shares that could be acquired upon the exercise of the HSAC2 Warrants and payment of the exercise price of $11.50 per share;
- up to 635,000 Officer and Director Warrant Shares that could be acquired upon the exercise of the Officer and Director Warrants and payment of the exercise price of $11.50 per share;
- up to 507,841 shares of common stock issuable upon the exercise of the Orchestra Warrants, with a weighted average exercise price of $9.01 per share;
- up to 27,707 shares of common stock issuable upon the exercise of the Avenue Warrants, with an exercise price of $7.67 per share;
- up to 167,598 shares of our common stock issuable upon the exercise of the Hercules Warrants, with an exercise price of $3.58 per share; and
- up to 60,000 shares of our common stock issuable upon the exercise of the Non-employee Warrants, with an exercise price of $4.69 per share.

In addition, we may choose to raise additional capital in the future through the sale of equity or convertible debt securities due to market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. To the extent that any of our outstanding options or warrants are exercised, any of our RSUs vest, new options or RSUs are issued under our equity incentive plans or we issue additional shares of common stock or other equity or convertible debt securities in the future, there will be further dilution to investors participating in this offering. In addition, the number of shares of our common stock outstanding as shown above does not include the $86.2 million of shares of our common stock that are available for sale as of the date of this prospectus supplement pursuant to the Sales Agreement with TD Cowen.

MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES

The following discussion is a summary of the material U.S. federal income tax consequences of the purchase, ownership, and disposition of our common stock issued pursuant to this offering, but does not purport to be a complete analysis of all potential tax effects. The effects of other U.S. federal tax laws, such as estate and gift tax laws, and any applicable state, local, or non-U.S. tax laws are not discussed. This discussion is based on the Internal Revenue Code of 1986, as amended (the "Code"), Treasury Regulations promulgated thereunder, judicial decisions, and published rulings and administrative pronouncements of the Internal Revenue Service (the "IRS"), in each case, as in effect as of the date of this offering. These authorities may change or be subject to differing interpretations. Any such change or differing interpretation may be applied retroactively in a manner that could adversely affect a holder of our common stock. We have not sought and do not currently intend to seek any rulings from the IRS regarding the matters discussed below. There can be no assurance the IRS or a court will not take a contrary position to the discussion below regarding the tax consequences of the purchase, ownership, and disposition of our common stock.

This discussion is limited to holders that hold our common stock as "capital assets" within the meaning of Section 1221 of the Code (generally, property held for investment). This discussion does not address all U.S. federal income tax consequences relevant to a holder's particular circumstances, including the impact of the Medicare contribution tax on net investment income and any alternative minimum tax. In addition, it does not address consequences relevant to holders subject to special rules, including, without limitation:

- U.S. expatriates and former citizens or long-term residents of the United States;
- persons holding our common stock as part of a hedge, straddle or other risk reduction strategy, or as part of a conversion transaction or other integrated investment;
- banks, insurance companies, and other financial institutions;
- real estate investment trusts or regulated investment companies;
- brokers, dealers, or traders in securities or currencies;
- "controlled foreign corporations," "foreign controlled foreign corporations," "passive foreign investment companies," and corporations that accumulate earnings to avoid U.S. federal income tax;
- S corporations, partnerships or other entities or arrangements treated as pass-through entities for U.S. federal income tax purposes (and investors therein);
- tax-exempt organizations or governmental organizations;
- persons deemed to sell our common stock under the constructive sale provisions of the Code;
- "qualified foreign pension funds" as defined in Section 897(l)(2) of the Code and entities all of the interests of which are held by qualified foreign pension funds;
- persons who hold or receive our common stock pursuant to the exercise of any employee stock option or otherwise as compensation; and
- tax-qualified retirement plans.

If a partnership (or other entity or arrangement treated as a partnership for U.S. federal income tax purposes) holds our common stock, the tax treatment of a partner in the partnership will depend on the status of the partner, the activities of the partnership, and certain determinations made at the partner level. Accordingly, entities or arrangements treated as partnerships holding our common stock and the partners in such partnerships should consult their tax advisors regarding the U.S. federal income tax consequences to them.

THIS DISCUSSION IS NOT TAX ADVICE. INVESTORS SHOULD CONSULT THEIR TAX ADVISORS WITH RESPECT TO THE APPLICATION OF THE U.S. FEDERAL INCOME TAX LAWS TO THEIR PARTICULAR SITUATIONS AS WELL AS ANY TAX CONSEQUENCES OF THE PURCHASE, OWNERSHIP, AND DISPOSITION OF OUR COMMON STOCK ARISING UNDER

THE U.S. FEDERAL ESTATE OR GIFT TAX LAWS OR UNDER THE LAWS OF ANY STATE, LOCAL, OR NON-U.S. TAXING JURISDICTION OR UNDER ANY APPLICABLE INCOME TAX TREATY.

Tax Considerations Applicable to U.S. Holders

Definition of a U.S. Holder

For purposes of this discussion, a "U.S. holder" is a beneficial owner of our common stock that, for U.S. federal income tax purposes, is or is treated as any of the following:

- an individual who is a citizen or resident of the United States;
- a corporation (or other entity treated as a corporation for U.S. federal income tax purposes) created or organized under the laws of the United States, any state thereof, or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income tax regardless of its source; or
- a trust that (1) is subject to the primary supervision of a U.S. court and one or more "United States persons" (within the meaning of Section 7701(a)(30) of the Code) have the authority to control all substantial decisions of the trust or (2) has a valid election in effect to be treated as a United States person for U.S. federal income tax purposes.

Distributions

As described in the section titled "Dividend Policy," we do not intend to pay cash dividends to our stockholders in the foreseeable future. However, if we do make distributions of cash or property on our common stock, such distributions will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. Dividends received by a corporate U.S. holder may be eligible for a dividends received deduction, subject to applicable limitations. Dividends received by certain non-corporate U.S. holders, including individuals, are generally taxed at the lower applicable capital gains rate provided certain holding period and other requirements are satisfied.

Amounts not treated as dividends for U.S. federal income tax purposes will constitute a return of capital and first be applied against and reduce a U.S. holder's adjusted tax basis in our common stock, but not below zero. Any excess will be treated as capital gain and will be treated as described below under "— *Tax Considerations Applicable to U.S. Holders — Sale or Other Taxable Disposition*."

Sale or Other Taxable Disposition

Upon the sale, exchange, or other taxable disposition of the common stock, a U.S. holder generally will recognize capital gain or loss equal to the difference between (i) the amount of cash and the fair market value of any property received upon the sale, exchange or other taxable disposition and (ii) such U.S. holder's adjusted tax basis in the common stock. Such capital gain or loss will be long term capital gain or loss if the U.S. holder's holding period in such common stock is more than one year at the time of the sale, exchange or other taxable disposition. Long-term capital gains recognized by certain non-corporate U.S. holders, including individuals, generally will be subject to reduced rates of U.S. federal income tax. The deductibility of capital losses is subject to certain limitations.

Information Reporting and Backup Withholding

A U.S. holder may be subject to information reporting and backup withholding if such holder receives distributions on the common stock (including constructive distributions) or receives proceeds from the sale or other taxable disposition of common stock. Certain U.S. holders are exempt from backup withholding. A U.S. holder will be subject to backup withholding if such holder is not otherwise exempt and such holder:

- fails to furnish the holder's taxpayer identification number, which for an individual is ordinarily such individual's social security number;
- furnishes an incorrect taxpayer identification number;

- is notified by the IRS that the holder previously failed to properly report payments of interest or dividends; or
- fails to certify under penalties of perjury that the holder has furnished a correct taxpayer identification number and that the IRS has not notified the holder that the holder is subject to backup withholding.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules may be allowed as a refund or a credit against a U.S. holder's U.S. federal income tax liability, provided the required information is timely furnished to the IRS. U.S. holders should consult their tax advisors regarding their qualification for an exemption from backup withholding and the procedures for obtaining such an exemption.

Tax Considerations Applicable to Non-U.S. Holders

Definition of a Non-U.S. Holder

For purposes of this discussion, a "non-U.S. holder" is a beneficial owner of our common stock that is neither (i) a U.S. holder nor (ii) an entity treated as a partnership for U.S. federal income tax purposes.

Distributions

As described in the section titled "Dividend Policy," we do not intend to pay cash dividends to our stockholders in the foreseeable future. However, if we do make distributions of cash or property on our common stock, such distributions will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles.

Amounts not treated as dividends for U.S. federal income tax purposes will constitute a return of capital and first be applied against and reduce a non-U.S. holder's adjusted tax basis in our common stock, but not below zero. Any excess will be treated as capital gain and will be treated as described below under "*— Tax Considerations Applicable to Non-U.S. Holders — Sale or Other Taxable Disposition.*" Because we may not know the extent to which a distribution is a dividend for U.S. federal income tax purposes at the time it is made, for purposes of the withholding rules discussed below, we or the applicable withholding agent may treat the entire distribution as a dividend.

Subject to the discussion below on effectively connected income, backup withholding and FATCA (as defined below), dividends paid to a non-U.S. holder will be subject to U.S. federal withholding tax at a rate of 30% of the gross amount of the dividends (or such lower rate specified by an applicable income tax treaty, provided the non-U.S. holder furnishes a valid IRS Form W-8BEN or W-8BEN-E (or other applicable documentation) certifying qualification for such lower rate under an income tax treaty between the United States and the country in which the non-U.S. holder resides or is established). This certification must be provided to the applicable withholding agent prior to the payment of dividends and must be updated periodically. A non-U.S. holder that does not timely furnish the required documentation, but that qualifies for a reduced treaty rate, may obtain a refund of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS. Non-U.S. holders should consult their tax advisors regarding their entitlement to benefits under any applicable tax treaties that may provide for different rules.

If dividends paid to a non-U.S. holder are effectively connected with the non-U.S. holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the non-U.S. holder maintains a permanent establishment in the United States to which such dividends are attributable), then the non-U.S. holder will be exempt from the U.S. federal withholding tax described above. To claim the exemption, the non-U.S. holder must furnish to the applicable withholding agent a valid IRS Form W-8ECI, certifying that the dividends are effectively connected with the non-U.S. holder's conduct of a trade or business within the United States. This certification must be provided to the applicable withholding agent prior to the payment of dividends and must be updated periodically. Any such effectively connected dividends will be subject to U.S. federal income tax on a net income basis at the regular rates in the same manner as if such holder were a resident of the United States. In addition, a non-U.S. holder that is a corporation may be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an

applicable income tax treaty) on its effectively connected dividends, as adjusted for certain items. Non-U.S. holders should consult their tax advisors regarding their entitlement to benefits under any applicable income tax treaty.

Sale or Other Taxable Disposition

Subject to the discussions below regarding backup withholding and FATCA (as defined below), a non-U.S. holder will not be subject to U.S. federal income or withholding tax on any gain realized upon the sale or other taxable disposition of our common stock unless:

- the gain is effectively connected with the non-U.S. holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the non-U.S. holder maintains a permanent establishment in the United States to which such gain is attributable);
- the non-U.S. holder is a nonresident alien individual present in the United States for 183 days or more during the taxable year of the disposition (as calculated pursuant to Section 7701(b) of the Code) and certain other requirements are met; or
- our common stock constitutes a U.S. real property interest ("USRPI"), by reason of our status as a U.S. real property holding corporation ("USRPHC"), for U.S. federal income tax purposes.

Gain described in the first bullet point above will generally be subject to U.S. federal income tax on a net income basis at the regular rates in the same manner as if such holder were a resident of the United States. A non-U.S. holder that is a corporation also may be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on such effectively connected gain, as adjusted for certain items.

A non-U.S. holder described in the second bullet point above will be subject to U.S. federal income tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on any gain realized upon the sale or other taxable disposition of our common stock, which may be offset by certain U.S. source capital losses of the non-U.S. holder (even though the individual is not considered a resident of the United States), provided the non-U.S. holder has timely filed U.S. federal income tax returns with respect to such losses.

With respect to the third bullet point above, we believe we currently are not, and do not anticipate becoming, a USRPHC. Because the determination of whether we are a USRPHC depends, however, on the fair market value of our USRPIs relative to the fair market value of our other business assets and our non-U.S. real property interests, there can be no assurance we currently are not a USRPHC or will not become one in the future. Even if we are or were to become a USRPHC, gain arising from the sale or other taxable disposition of our common stock by a non-U.S. holder will not be subject to U.S. federal income tax if our common stock is "regularly traded," as defined by applicable Treasury Regulations, on an established securities market, and such non-U.S. holder owned, actually and constructively, 5% or less of our common stock throughout the shorter of the five-year period ending on the date of the sale or other taxable disposition or the non-U.S. holder's holding period for such common stock.

Non-U.S. holders should consult their tax advisors regarding potentially applicable income tax treaties that may provide for different rules.

Information Reporting and Backup Withholding

Payments of dividends on our common stock to a non-U.S. holder will not be subject to backup withholding, provided the applicable withholding agent does not have actual knowledge or reason to know the holder is a U.S. holder (as defined above under "*— Tax Considerations Applicable to U.S. Holders — Definition of a U.S. Holder"*) and the holder either certifies its non-U.S. status, such as by furnishing a valid IRS Form W-8BEN, W-8BEN-E, or W-8ECI, or otherwise establishes an exemption. However, information returns are required to be filed with the IRS in connection with any distributions on our common stock paid to the non-U.S. holder, regardless of whether such distributions constitute dividends or whether any tax was actually withheld. In addition, proceeds of the sale or other taxable disposition of our common stock within the United States or conducted through certain U.S.-related brokers generally will not be

subject to backup withholding or information reporting if the applicable withholding agent receives the certification described above and does not have actual knowledge or reason to know that such holder is a U.S. holder or the holder otherwise establishes an exemption. Proceeds of a disposition of our common stock conducted through a non-U.S. office of a non-U.S. broker generally will not be subject to backup withholding or information reporting.

Copies of information returns that are filed with the IRS may also be made available under the provisions of an applicable treaty or agreement to the tax authorities of the country in which the non-U.S. holder resides or is established.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules may be allowed as a refund or a credit against a non-U.S. holder's U.S. federal income tax liability, provided the required information is timely furnished to the IRS.

Additional Withholding Tax on Payments Made to Foreign Accounts

Withholding taxes may be imposed under Sections 1471 to 1474 of the Code (such Sections commonly referred to as the Foreign Account Tax Compliance Act, or "FATCA") on certain types of payments made to non-U.S. financial institutions and certain other non-U.S. entities if certain certification, information reporting and other specified requirements are not met. Specifically, a 30% withholding tax may be imposed on dividends on, or (subject to the proposed Treasury Regulations discussed below) gross proceeds from the sale or other disposition of, our common stock paid to a "foreign financial institution" or a "non-financial foreign entity" (each as defined in the Code), unless (1) the foreign financial institution undertakes certain diligence and reporting obligations, (2) the non-financial foreign entity either certifies it does not have any "substantial United States owners" (as defined in the Code) or furnishes identifying information regarding each substantial United States owner, or (3) the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from these rules. If the payee is a foreign financial institution and is subject to the diligence and reporting requirements in clause (1) above, it must enter into an agreement with the U.S. Department of the Treasury requiring, among other things, that it undertake to identify accounts held by certain "specified United States persons" or "United States owned foreign entities" (each as defined in the Code), annually report certain information about such accounts, and withhold 30% on certain payments to non-compliant foreign financial institutions and certain other account holders. Foreign financial institutions located in jurisdictions that have an intergovernmental agreement with the United States governing FATCA may be subject to different rules.

Under the applicable Treasury Regulations and administrative guidance, withholding under FATCA generally applies to payments of dividends (including deemed dividends) on our common stock. While withholding under FATCA would have applied also to payments of gross proceeds from the sale or other disposition of stock, proposed Treasury Regulations eliminate FATCA withholding on payments of gross proceeds entirely. Taxpayers generally may rely on these proposed Treasury Regulations until final Treasury Regulations are issued. Because we may not know the extent to which a distribution is a dividend for U.S. federal income tax purposes at the time it is made, for purposes of these withholding rules, we or the applicable withholding agent may treat the entire distribution as a dividend.

Prospective investors should consult their tax advisors regarding the potential application of withholding under FATCA to their investment in our common stock.

UNDERWRITING

Subject to the terms and conditions set forth in the underwriting agreement among us, Piper Sandler & Co. and TD Securities (USA) LLC, as the representatives (the "representatives") of the underwriters named below, we have agreed to sell to the underwriters, and each of the underwriters has agreed, severally and not jointly, to purchase from us, at the public offering price less the underwriting discount and commissions set forth on the cover page of this prospectus supplement, the number of shares of common stock listed opposite its name below.

Underwriter	Number of Shares
Piper Sandler & Co.	6,600,000
TD Securities (USA) LLC	5,475,000
BTIG, LLC	2,250,000
H.C. Wainwright & Co., LLC	675,000
Total	15,000,000

The underwriting agreement provides that the obligations of the several underwriters are subject to certain conditions precedent such as the receipt by the underwriters of officers' certificates and legal opinions and approval of certain legal matters by their counsel. The underwriting agreement provides that the underwriters will purchase all of the shares of common stock if any of them are purchased. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the nondefaulting underwriters may be increased or the underwriting agreement may be terminated.

The underwriters are offering the shares of common stock subject to their acceptance of the shares of common stock from us and subject to prior sale. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part. In addition, the underwriters have advised us that they do not intend to confirm sales to any account over which they exercise discretionary authority.

Option to Purchase Additional Shares

We have granted the underwriters an option to purchase up to 2,250,000 additional shares of common stock from us. The underwriters have 30 days from the date of this prospectus supplement to exercise this option to purchase additional shares. If any shares are purchased with this option to purchase additional shares, the underwriters will purchase shares in approximately the same proportion as shown in the table above. If any additional shares of common stock are purchased, the underwriters will offer the additional shares on the same terms as those on which the shares are being offered.

Discounts, Commissions and Expenses

The underwriters have advised us that they propose to offer the shares of common stock to the public at the public offering price set forth on the cover of this prospectus supplement and to certain dealers, which may include the underwriters, at that price less a concession not in excess of $0.18 per share of common stock. After the offering, if all of the shares of common stock are not sold at the public offering price, the public offering price and concession may be reduced by the representatives. No such reduction will change the amount of proceeds to be received by us as set forth on the cover of this prospectus supplement.

The underwriting fee is equal to the public offering price per share of common stock less the amount paid by the underwriters to us per share of common stock. The following table shows the per share and total underwriting discount and commissions to be paid to the underwriters in connection with this offering, assuming both no exercise and full exercise of the underwriters' option to purchase additional shares:

	Per Share	Total Without Option Exercise	Total With Full Option Exercise
Public offering price	$5.00	$75,000,000.00	$86,250,000.00
Underwriting discount and commissions	$0.30	$ 4,500,000.00	$ 5,175,000.00
Proceeds, before expenses, to us	$4.70	$ 70,500,00.00	$81,075,000.00

We estimate that the total fees and expenses payable by us in connection with this offering, excluding underwriting discount and commissions referred to above, will be approximately $550,000. We have also agreed to reimburse the underwriters for certain expenses incurred by them in connection with the offering, in an amount not to exceed $200,000.

Indemnification of Underwriters

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act, or to contribute to payments that the underwriters may be required to make in respect of those liabilities.

Listing

Our common stock is listed on the Nasdaq Global Market under the symbol "OBIO."

No Sales of Similar Securities

We have agreed that we will not (i) offer, sell, contract to sell, pledge, grant any option to purchase, make any short sale or otherwise transfer or dispose of, directly or indirectly, or file with the SEC a registration statement under the Securities Act relating to, any of our securities that are substantially similar to the common stock, including but not limited to any options or warrants to purchase shares of common stock or any securities that are convertible into or exchangeable for, or that represent the right to receive, common stock or any such substantially similar securities, or publicly disclose the intention to make any offer, sale, pledge, disposition or filing, (ii) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of the common stock or any such other securities, whether any such transaction described in clause (i) or (ii) above is to be settled by delivery of common stock or such other securities, in cash or otherwise, (iii) confidentially submit or file any registration statement under the Securities Act in respect of any shares of common stock (other than as contemplated by the underwriting agreement) or (iv) publicly announce the intention to do any of the foregoing, in each case without the prior written consent of Piper Sandler & Co. and TD Securities (USA) LLC, for a period of 60 days after the date of this prospectus supplement; provided, however, that, in each case, such foregoing restrictions will not be required in connection with our (i) issuance or sale of common stock, options to purchase common stock or common stock issuable upon the exercise of options or other equity awards pursuant to any employee or director share option, incentive or benefit plan, share purchase or ownership plan, long-term incentive plan, dividend reinvestment plan, inducement award under Nasdaq listing rules or other compensation plan of ours, as in effect on the date of the underwriting agreement, (ii) issuance or sale of common stock issuable upon exchange, conversion or redemption of securities or the exercise or vesting of warrants, options or other equity awards as in effect on the date of the underwriting agreement, (iii) issuance or sale of common stock or securities convertible into or exchangeable for common stock as consideration for mergers, acquisitions, other business combinations or strategic alliances, joint ventures, marketing or distribution arrangements, collaboration agreements, co-promotion agreements, or intellectual property license agreements occurring after the date of the underwriting agreement, which are not used for capital raising purposes and which aggregate number of shares of common stock issued or sold under this subsection (iii), on an as-converted basis, if applicable, shall not exceed 7.5% of the number of shares of common stock outstanding immediately prior to giving effect to such sale or issuance, and (iv) modification of any outstanding options, warrants or any rights to purchase or acquire common stock outstanding or as in effect as of the date of the underwriting agreement.

Our directors and executive officers (the "lock-up parties") have agreed, subject to certain exceptions, that, without the prior written consent of Piper Sandler & Co. and TD Securities (USA) LLC on behalf of the underwriters, they will not, during the period ending 60 days after the date of this prospectus supplement:

- offer, pledge, announce the intention to sell, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, make any short sale or otherwise transfer or dispose of, directly or indirectly, any shares of common stock or any securities convertible into, exercisable or exchangeable for or that represent the right to receive common stock (including without limitation, common stock which may be deemed to be beneficially owned by the lock-up parties in accordance with the rules and regulations of the SEC and

securities which may be issued upon exercise of a stock option or warrant whether owned as of the date of this prospectus supplement or subsequently acquired) (collectively, the "lock-up shares");

- enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of the lock-up shares;
- make any demand for or exercise any right with respect to, the registration of any common stock or any security convertible into or exercisable or exchangeable for common stock; or
- publicly disclose the intention to do any of the foregoing.

The restrictions described in the immediately preceding paragraph contained in the lock-up agreements with our directors and executive officers do not apply, subject to certain conditions and limitations, to certain transactions, including, among others, transfers or dispositions of such securities:

- (a) as a bona fide gift or gifts, (b) to any trust for the direct or indirect benefit of the lock-up parties or the immediate family of the lock-up parties, (c) if the lock-up party is a trust, transfers to the beneficiary of such trust, (d) transfers by testate succession or intestate succession or (e) pursuant to the underwriting agreement;
- if the lock-up party is a corporation, partnership, limited liability company, trust or other business entity (a) transfers to another corporation, partnership, limited liability company, trust or other business entity that is a direct or indirect affiliate (as defined in Rule 405 promulgated under the Securities Act) of the lock-up party or (b) distributions of shares of common stock or any security convertible into or exercisable for common stock to limited partners, limited liability company members or stockholders of the lock-up party;
- the exercise of stock options granted pursuant to our equity incentive plans and transactions to satisfy tax withholding obligations of the lock-up parties in connection with the vesting or exercise of equity awards outstanding pursuant to our equity incentive plans or to cover the exercise price of outstanding options or warrants;
- the establishment of any contract, instruction or plan that satisfies all of the requirements of Rule 10b5-1(c)(1)(i)(B) under the Exchange Act (collectively a "Rule 10b5-1 Plan");
- transfers of the lock-up shares pursuant to a Rule 10b5-1 Plan entered into prior to the date of the lock-up agreement; or
- transfers of the lock-up shares pursuant to any change of control of the Company which is approved by our Board (including, without limitation, the entering into any lock-up, voting or similar agreement pursuant to which the lock-up parties may agree to transfer, sell, tender or otherwise dispose of shares of common stock or other securities in connection with such transaction, or vote any shares of common stock or other such securities in favor of any such transaction).

Price Stabilization, Short Positions and Penalty Bids

The underwriters have advised us that, pursuant to Regulation M under the Exchange Act, the underwriters participating in the offering may engage in short sale transactions, stabilizing transactions, syndicate covering transactions or the imposition of penalty bids in connection with this offering. These activities may have the effect of stabilizing or maintaining the market price of the common stock at a level above that which might otherwise prevail in the open market. Establishing short sales positions may involve either "covered" short sales or "naked" short sales.

"Covered" short sales are sales made in an amount not greater than the underwriters' option to purchase additional shares of our common stock in this offering. The underwriters may close out any covered short position by either exercising their option to purchase additional shares of our common stock from us or purchasing shares of our common stock in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares from us through the option to purchase additional shares.

"Naked" short sales are sales in excess of the option to purchase additional shares of our common stock. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the shares of our common stock in the open market after pricing that could adversely affect investors who purchase in this offering.

A stabilizing bid is a bid for the purchase of shares of common stock on behalf of the underwriters for the purpose of fixing or maintaining the price of the common stock. A syndicate covering transaction is the bid for or the purchase of shares of common stock on behalf of the underwriters to reduce a short position incurred by the underwriters in connection with the offering. Similar to other purchase transactions, the underwriters' purchases to cover the syndicate short sales may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of our common stock. As a result, the price of our common stock may be higher than the price that might otherwise exist in the open market. A penalty bid is an arrangement permitting the underwriters to reclaim the selling concession otherwise accruing to a syndicate member in connection with the offering if the shares of common stock originally sold by such syndicate member are purchased in a syndicate covering transaction and therefore have not been effectively placed by such syndicate member.

Neither we nor any of the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. The underwriters are not obligated to engage in these activities and, if commenced, any of the activities may be discontinued at any time.

The underwriters may also engage in passive market making transactions in our common stock on the Nasdaq Global Market in accordance with Rule 103 of Regulation M during a period before the commencement of offers or sales of shares of our common stock in this offering and extending through the completion of distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker's bid, that bid must then be lowered when specified purchase limits are exceeded. If passive market making is commenced, it may be discontinued at any time.

Electronic Distribution

A prospectus in electronic format may be made available by e-mail or on the websites or through online services maintained by one or more of the underwriters or their affiliates. In those cases, prospective investors may view offering terms online and may be allowed to place orders online. The underwriters may agree with us to allocate a specific number of shares of common stock for sale to online brokerage account holders. Any such allocation for online distributions will be made by the underwriters on the same basis as other allocations. Other than the prospectus in electronic format, the information on each underwriter's or its affiliates' websites and any information contained in any other website maintained by any of the underwriters or an affiliate is not part of this prospectus supplement, has not been approved and/or endorsed by us or the underwriters and should not be relied upon by investors.

Other Activities and Relationships

The underwriters and certain of their respective affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. The underwriters and certain of their respective affiliates have, from time to time, performed, and may in the future perform, various commercial and investment banking and financial advisory services for us and our affiliates, for which they received or will receive customary fees and expenses. For example, TD Cowen acts as sales agent in connection with the Company's at-the-market program pursuant to the Sales Agreement. In addition, from time to time, certain of the underwriters and their respective affiliates may effect transactions for their own account or the account of customers, and hold on behalf of themselves or their customers, long or short positions in our debt or equity securities or loans, and may do so in the future.

Selling Restrictions

General

Other than in the United States, no action has been taken by us or the underwriters that would permit a public offering of the securities offered by this prospectus supplement in any jurisdiction where action for that purpose is required. The securities offered by this prospectus supplement may not be offered or sold, directly or indirectly, nor may this prospectus supplement or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus supplement comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus supplement. This prospectus supplement does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus supplement in any jurisdiction in which such an offer or a solicitation is unlawful.

European Economic Area

In relation to each Member State of the European Economic Area (each, a "Relevant State"), no securities have been offered or will be offered pursuant to the offering to the public in that Relevant State prior to the publication of a prospectus in relation to the securities which have been approved by the competent authority in that Relevant State or, where appropriate, approved in another Relevant State and notified to the competent authority in that Relevant State, all in accordance with the Prospectus Regulation, except that the securities may be offered to the public in that Relevant State at any time:

(a) to any legal entity which is a qualified investor as defined under Article 2 of the Prospectus Regulation;

(b) to fewer than 150 natural or legal persons (other than qualified investors as defined under Article 2 of the Prospectus Regulation), subject to obtaining the prior consent of the representatives for any such offer; or

(c) in any other circumstances falling within Article 1(4) of the Prospectus Regulation,

provided that no such offer of the securities shall require us or any of the underwriters to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation and each person who initially acquires any securities or to whom any offer is made will be deemed to have represented, acknowledged and agreed to and with each of the underwriters and us that it is a "qualified investor" within the meaning of Article 2(e) of the Prospectus Regulation. In the case of any securities being offered to a financial intermediary as that term is used in the Prospectus Regulation, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the securities acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer of any securities to the public other than their offer or resale in a Relevant State to qualified investors as so defined or in circumstances in which the prior consent of the representatives has been obtained to each such proposed offer or resale.

For the purposes of this provision, the expression "offer to the public" in relation to securities in any Relevant State means the communication in any form and by any means of sufficient information on the terms of the offer and any securities to be offered so as to enable an investor to decide to purchase or subscribe for any securities, and the expression "Prospectus Regulation" means Regulation (EU) 2017/1129.

United Kingdom

No securities have been offered or will be offered pursuant to the offering to the public in the United Kingdom except that the securities may be offered to the public in the United Kingdom at any time:

(a) where (i) the offer is conditional on the admission of the securities to trading on the London Stock Exchange plc's main market (in reliance on the exception in paragraph 6(a) of Schedule 1 of

the POATR) or (ii) the securities being offered are at the time of the offer already admitted to trading on London Stock Exchange plc's main market (in reliance on the exception in paragraph 6(b) of Schedule 1 of the POATR);

(b) to any qualified investor as defined in paragraph 15 of Schedule 1 of the POATR;

(c) to fewer than 150 persons (other than qualified investors as defined in paragraph 15 of Schedule 1 of the POATR), subject to obtaining the prior consent of the representatives for any such offer; or

(d) in any other circumstances falling within Part 1 of Schedule 1 of the POATR.

For the purposes of this provision, the expression an "offer to the public" in relation to the securities in the United Kingdom means the communication to any person which presents sufficient information on: (a) the securities to be offered; and (b) the terms on which they are to be offered, to enable an investor to decide to buy or subscribe for any securities and the expression "POATR" means the Public Offers and Admissions to Trading Regulations 2024.

Any invitation or inducement to engage in investment activity (within the meaning of Section 21 of the Financial Services and Markets Act 2000 (as amended, the "FSMA")) in connection with the issue or sale of the securities may only be communicated or caused to be communicated in circumstances in which Section 21(1) of the FSMA does not apply to us.

All applicable provisions of the FSMA must be complied with in respect to anything done by any person in relation to the shares of our common stock in, from or otherwise involving the United Kingdom.

Canada

The securities may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations. Any resale of the securities must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Germany

Each person who is in possession of this prospectus supplement is aware of the fact that no German securities prospectus (wertpapierprospekt) within the meaning of the German Securities Prospectus Act (Wertpapier-prospektgesetz, or the Prospectus Act) of the Federal Republic of Germany has been or will be published with respect to the securities. In particular, each representative has represented that it has not engaged and has agreed that it will not engage in a public offering in the Federal Republic of Germany within the meaning of the Prospectus Act with respect to any of the securities otherwise than in accordance with the Prospectus Act and all other applicable legal and regulatory requirements.

Hong Kong

The securities have not been and will not be offered or sold in Hong Kong by means of any document other than (i) to "professional investors" as defined in the Securities and Futures Ordinance (Cap. 571) of

Hong Kong (the "SFO") and any rules made thereunder; or (ii) in other circumstances which do not result in the document being a "prospectus" as defined in the Companies (Winding Up and Miscellaneous Provisions) Ordinance (Cap. 32) of Hong Kong (the "CO") or which do not constitute an offer to the public within the meaning of the CO. No advertisement, invitation or document relating to the securities has been or may be issued or has been or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public of Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to the securities which are or are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" as defined in the SFO and any rules made thereunder.

This prospectus supplement has not been registered with the Registrar of Companies in Hong Kong. Accordingly, this prospectus supplement may not be issued, circulated or distributed in Hong Kong, and the securities may not be offered for subscription to members of the public in Hong Kong. Each person acquiring the securities will be required, and is deemed by the acquisition of the securities, to confirm that he is aware of the restriction on offers of the securities described in this prospectus supplement and the relevant offering documents and that he is not acquiring, and has not been offered any securities in circumstances that contravene any such restrictions.

Israel

The securities offered by this prospectus supplement have not been approved or disapproved by the Israel Securities Authority (the "ISA"), nor have such securities been registered for sale in Israel. The securities may not be offered or sold, directly or indirectly, to the public in Israel, absent the publication of a prospectus that has been approved by the ISA. The ISA has not issued permits, approvals or licenses in connection with this offering or publishing this document, nor has it authenticated the details included herein, confirmed their reliability or completeness, or rendered an opinion as to the quality of the securities being offered.

This prospectus supplement does not constitute a prospectus under the Israeli Securities Law, 5728-1968 (the "Israeli Securities Law"), and has not been filed with or approved by the ISA. In Israel, this prospectus supplement is being distributed only to, and is directed only at, and any offer of the securities is directed only at, (i) a limited number of persons in accordance with the Israeli Securities Law and (ii) investors listed in the first addendum (the "Addendum") to the Israeli Securities Law, consisting primarily of joint investment in trust funds, provident funds, insurance companies, banks, portfolio managers, investment advisors, members of the Tel Aviv Stock Exchange, underwriters, venture capital funds, entities with equity in excess of NIS 50 million and "qualified individuals," each as defined in the Addendum (as it may be amended from time to time), collectively referred to as qualified investors (in each case, purchasing for their own account or, where permitted under the Addendum, for the accounts of their clients who are investors listed in the Addendum). Qualified investors are required to submit written confirmation that they fall within the scope of the Addendum, are aware of the meaning of same and agree to it.

Singapore

This prospectus supplement has not been and will not be lodged or registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus supplement and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the securities may not be circulated or distributed, nor may the securities be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to any person in Singapore other than (i) to an institutional investor (as defined in Section 4A of the SFA pursuant to Section 274 of the SFA or (ii) to an accredited investor (as defined in Section 4A of the SFA) pursuant to and in accordance with the conditions specified in Section 275 of the SFA and (where applicable) Regulation 3 of the Securities and Futures (Classes of Investors) Regulations 2018.

Any reference to the "SFA" is a reference to the Securities and Futures Act 2001 of Singapore, as modified or amended from time to time and a reference to any term as defined in the SFA or any provision in the SFA is a reference to that term or provision as modified or amended from time to time including by such of its subsidiary legislation as may be applicable at the relevant time.

The securities are prescribed capital markets products (as defined in the Securities and Futures (Capital Markets Products) Regulations 2018) and Excluded Investment Products (as defined in MAS Notice SFA 04-N12: Notice on the Sale of Investment Products and MAS Notice FAA-N16: Notice on Recommendations on Investment Products).

Switzerland

The offering of the securities in Switzerland is exempt from requirement to prepare and publish a prospectus under the Swiss Financial Services Act ("FinSA") because such offering is made to professional clients within the meaning of the FinSA only and the securities will not be admitted to trading on any trading venue (exchange or multilateral trading facility) in Switzerland. This prospectus supplement does not constitute a prospectus pursuant to the FinSA, and no such prospectus has been or will be prepared for or in connection with the offering of the securities.

United Arab Emirates

This prospectus supplement is strictly private and confidential and is being distributed to a limited number of Professional Investors, within the meaning of the United Arab Emirates (the "UAE") Capital Market Authority's (the "CMA") Board of Directors Decision No. (13/Chairman) of 2021 on the Regulations Manual of the Financial Activities and Status Regularization Mechanisms Rule Book (as amended), and must not be provided to any person other than the original recipient, and may not be reproduced or used for any other purpose. If you are in any doubt about the contents of this prospectus supplement, you should consult an authorized financial adviser.

By receiving this prospectus supplement, the person or entity to whom it has been issued understands, acknowledges and agrees that this prospectus supplement has not been approved by or filed with the UAE Central Bank, the CMA or any other authorities in the UAE, nor have the underwriters received authorization or licensing from the UAE Central Bank, the CMA or any other authorities in the UAE to market or sell securities or other investments within the UAE. No marketing of any financial products or services has been or will be made from within the UAE other than in compliance with the laws of the UAE and no subscription to any securities or other investments may or will be consummated within the UAE. It should not be assumed that any of the underwriters is a licensed broker, dealer or investment adviser under the laws applicable in the UAE, or that any of them advise individuals resident in the UAE as to the appropriateness of investing in or purchasing or selling securities or other financial products. The securities offered pursuant to this prospectus supplement may not be offered or sold directly or indirectly to the public in the UAE and do not constitute a public offer of securities in the UAE in accordance with Federal Decree No. 32 of 2021 on Commercial Companies (as amended) or otherwise.

France

This prospectus supplement (including any amendment, supplement or replacement thereto) is not being distributed in the context of a public offering in France within the meaning of Article L. 411-1 of the French Monetary and Financial Code (Code monétaire et financier).

This prospectus supplement has not been and will not be submitted to the French Autorité des marchés financiers (the "AMF") for approval in France and accordingly may not and will not be distributed to the public in France.

Pursuant to Article 211-3 of the AMF General Regulation, French residents are hereby informed that:

1. the transaction does not require a prospectus to be submitted for approval to the AMF;

2. persons or entities referred to in Point 2°, Section II of Article L.411-2 of the Monetary and Financial Code may take part in the transaction solely for their own account, as provided in Articles D. 411-1, D. 734-1, D. 744-1, D. 754-1 and D. 764-1 of the Monetary and Financial Code; and

3. the financial instruments thus acquired cannot be distributed directly or indirectly to the public otherwise than in accordance with Articles L. 411-1, L. 411-2, L. 412-1 and L. 621-8 to L. 621-8-3 of the Monetary and Financial Code.

This prospectus supplement is not to be further distributed or reproduced (in whole or in part) in France by the recipients of this prospectus supplement. This prospectus supplement has been distributed on the understanding that such recipients will only participate in the issue or sale of our securities for their own account and undertake not to transfer, directly or indirectly, our securities to the public in France, other than in compliance with all applicable laws and regulations and in particular with Articles L. 411-1 and L. 411-2 of the French Monetary and Financial Code.

LEGAL MATTERS

Paul Hastings LLP will pass upon certain legal matters relating to the issuance and sale of the securities offered hereby on behalf of Orchestra BioMed Holdings, Inc. Certain legal matters in connection with this offering will be passed upon for the underwriters by Latham & Watkins LLP.

EXPERTS

The consolidated financial statements of Orchestra BioMed Holdings, Inc. appearing in Orchestra BioMed Holdings, Inc.'s Annual Report (Form 10-K) for the year ended December 31, 2025, have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon included therein, and incorporated herein by reference. Such financial statements are, and audited financial statements to be included in subsequently filed documents will be, incorporated herein in reliance upon the report of Ernst & Young LLP pertaining to such financial statements (to the extent covered by consents filed with the Securities and Exchange Commission) given on the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus supplement is part of a registration statement on Form S-3 that we have filed with the SEC. This prospectus supplement, filed as part of the registration statement, does not contain all the information set forth in the registration statement and its exhibits and schedules, portions of which have been omitted as permitted by the rules and regulations of the SEC. For further information about us, we refer you to the registration statement and to its exhibits and schedules. Certain information in the registration statement has been omitted from this prospectus supplement in accordance with the rules of the SEC.

We are subject to the reporting and information requirements of the Exchange Act and, in accordance therewith, file annual, quarterly and special reports, proxy statements and other information with the SEC. These documents also may be accessed through the SEC's electronic data gathering, analysis and retrieval system, or EDGAR, via electronic means, including the SEC's home page on the Internet (*www.sec.gov*). Written requests for such copies should be directed to Orchestra BioMed Holdings, Inc., 150 Union Square Drive, New Hope, PA, 18938, telephone: (215) 862-5797 and our website is located at *www.orchestrabiomed.com.* Information contained on or accessible through our website is not incorporated by reference into this prospectus supplement and, therefore, is not part of this prospectus supplement.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC's rules allow us to "incorporate by reference" information into this prospectus supplement, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus supplement, and subsequent information that we file with the SEC will automatically update and supersede that information.

This prospectus supplement incorporates by reference the documents set forth below that have previously been filed with the SEC (other than any information therein furnished to, rather than filed with, the SEC):

- our Annual Report on Form 10-K for the year ended December 31, 2025, filed with the SEC on March 12, 2026;
- our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2026 and June 30, 2026, filed with the SEC on May 12, 2026 and August 10, 2026, respectively;
- the information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2025 from our Definitive Proxy Statement on Schedule 14A, filed with the SEC on April 29, 2026;
- our Current Reports on Form 8-K filed with the SEC on January 12, 2026, February 13, 2026, June 23, 2026 and October 1, 2026 (excluding information under Item 7.01); and
- the description of our common stock contained in Exhibit 4.21 to our Annual Report on Form 10-K for the fiscal year ended December 31, 2025 filed with the SEC on March 12, 2026, including any amendment or reports filed for the purpose of updating such description.

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act in this prospectus supplement, prior to the termination of this offering, will also be incorporated by reference into this prospectus supplement and the accompanying base prospectus and deemed to be part of this prospectus supplement and the accompanying base prospectus from the date of the filing of such reports and documents; *provided, however*, unless specifically stated to the contrary, information that we furnish (and that is not deemed "filed" with the SEC) under Items 2.02 and 7.01 of any Current Report on Form 8-K, including the related exhibits under Item 9.01, is not incorporated by reference into this prospectus supplement or the registration statement of which this prospectus supplement is a part.

You may request a free copy of any of the documents incorporated by reference in this prospectus supplement by writing or telephoning us at the following address:

Orchestra BioMed Holdings, Inc.
150 Union Square Drive
New Hope, PA 18938
(215) 862-5797

Exhibits to the filings will not be sent, however, unless those exhibits have specifically been incorporated by reference in this prospectus supplement or the accompanying base prospectus.

You may also access these documents, free of charge on the SEC's website at *www.sec.gov* or on our website at *www.orchestrabiomed.com.* Information contained on our website is not incorporated by reference into this prospectus supplement, and you should not consider any information on or accessible through our website as part of this prospectus supplement.

This prospectus supplement is part of a registration statement we filed with the SEC. We have incorporated exhibits into this registration statement. You should read the exhibits carefully for provisions that may be important to you.

You should rely only on the information incorporated by reference or provided in this prospectus supplement. We have not authorized anyone to provide you with different information. We are not making

an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus supplement or in the documents incorporated by reference is accurate as of any date other than the date on the front of this prospectus supplement or those documents.

Any statement contained in a document that is incorporated by reference will be modified or superseded for all purposes to the extent that a statement contained in this prospectus supplement, or in any other document that is subsequently filed with the SEC and incorporated by reference into this prospectus supplement, modifies or is contrary to that previous statement. Any statement so modified or superseded will not be deemed a part of this prospectus supplement, except as so modified or superseded. Since information that we later file with the SEC will update and supersede previously incorporated information, you should look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus supplement or in any documents previously incorporated by reference have been modified or superseded.

PROSPECTUS



ORCHESTRA BIOMED HOLDINGS, INC.

$300,000,000
Common Stock
Preferred Stock
Debt Securities
Warrants
Rights
Units

We may offer and sell up to $300,000,000 in the aggregate of the securities identified above from time to time in one or more offerings. This prospectus provides you with a general description of the securities.

Each time we offer and sell securities, we will provide a supplement to this prospectus that contains specific information about the offering and the amounts, prices and terms of the securities. The supplement may also add, update or change information contained in this prospectus with respect to that offering. You should carefully read this prospectus and the applicable prospectus supplement before you invest in any of our securities.

We may offer and sell the securities described in this prospectus and any prospectus supplement to or through one or more underwriters, dealers and agents, or directly to purchasers, or through a combination of these methods. If any underwriters, dealers or agents are involved in the sale of any of the securities, their names and any applicable purchase price, fee, commission or discount arrangement between or among them will be set forth, or will be calculable from the information set forth, in the applicable prospectus supplement. See the sections of this prospectus entitled "About this Prospectus" and "Plan of Distribution" for more information. No securities may be sold without delivery of this prospectus and the applicable prospectus supplement describing the method and terms of the offering of such securities.

Investing in our securities involves risks. See the "Risk Factors" beginning on page 7 of this prospectus and any similar section contained in the applicable prospectus supplement concerning factors you should consider before investing in our securities.

We are an "emerging growth company" under applicable federal securities laws and therefore subject to reduced public company reporting requirements.

Our common stock is listed on The Nasdaq Global Market under the symbol "OBIO." On May 14, 2024, the last reported sale price of our common stock on The Nasdaq Global Market was $5.20 per share.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The date of this prospectus is May 24, 2024.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the U.S. Securities and Exchange Commission (the "SEC"), using a "shelf" registration process. By using a shelf registration statement, we may sell securities from time to time and in one or more offerings up to a total dollar amount of $300,000,000 as described in this prospectus. Each time that we offer and sell securities, we will provide a prospectus supplement to this prospectus that contains specific information about the securities being offered and sold and the specific terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement or free writing prospectus may also add, update or change information contained in this prospectus with respect to that offering. If there is any inconsistency between the information in this prospectus and the applicable prospectus supplement or free writing prospectus, you should rely on the prospectus supplement or free writing prospectus, as applicable. Before purchasing any securities, you should carefully read both this prospectus and the applicable prospectus supplement (and any applicable free writing prospectuses), together with the additional information described under the heading "Where You Can Find More Information; Incorporation by Reference."

We have not authorized anyone to provide you with any information or to make any representations other than those contained in this prospectus, any applicable prospectus supplement or any free writing prospectuses prepared by us or on our behalf or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We will not make an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus and the applicable prospectus supplement to this prospectus is accurate only as of the date on its respective cover, that the information appearing in any applicable free writing prospectus is accurate only as of the date of that free writing prospectus, and that any information incorporated by reference is accurate only as of the date of the document incorporated by reference, unless we indicate otherwise. Our business, financial condition, results of operations and prospects may have changed since those dates. This prospectus incorporates by reference, and any prospectus supplement or free writing prospectus may contain and incorporate by reference, market data and industry statistics and forecasts that are based on independent industry publications and other publicly available information. Although we believe these sources are reliable, we do not guarantee the accuracy or completeness of this information and we have not independently verified this information. In addition, the market and industry data and forecasts that may be included or incorporated by reference in this prospectus, any prospectus supplement or any applicable free writing prospectus may involve estimates, assumptions and other risks and uncertainties and are subject to change based on various factors, including those discussed under the heading "Risk Factors" contained in this prospectus, the applicable prospectus supplement and any applicable free writing prospectus, and under similar headings in other documents that are incorporated by reference into this prospectus. Accordingly, investors should not place undue reliance on this information.

When we refer to "Orchestra," "we," "our," "us" and the "Company" in this prospectus, we mean Orchestra BioMed Holdings, Inc. and its consolidated subsidiaries, unless otherwise specified. When we refer to "you," we mean the potential holders of the applicable series of securities.

We have proprietary rights to trademarks, trade names and service marks appearing in this prospectus and the documents incorporated by reference herein that are important to our business. Solely for convenience, the trademarks, trade names and service marks may appear in this prospectus and the documents incorporated by reference herein without the ® and ™ symbols, but any such references are not intended to indicate, in any way, that we forgo or will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensors to these trademarks, trade names and service marks. All trademarks, trade names and service marks appearing in this prospectus and the documents incorporated by reference herein are the property of their respective owners. We do not intend our use or display of other parties' trademarks, trade names or service marks to imply, and such use or display should not be construed to imply, a relationship with, or endorsement or sponsorship of us by, these other parties.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus, any applicable prospectus supplement, any related free writing prospectus and the documents that we incorporate by reference herein or therein contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). Any statements about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and may be forward-looking. These statements are often, but are not always, made through the use of words or phrases such as "may," "will," "could," "should," "expects," "intends," "plans," "anticipates," "believes," "estimates," "predicts," "projects," "potential," "continue," and similar expressions, or the negative of these terms, or similar expressions. Accordingly, these statements involve estimates, assumptions, risks and uncertainties which could cause actual results to differ materially from those expressed in them. Any forward-looking statements are qualified in their entirety by reference to the factors discussed throughout this prospectus, and in particular those factors referenced in the section titled "Risk Factors."

This prospectus contains forward-looking statements that are based on our management's belief and assumptions and on information currently available to our management. These statements relate to future events or our future financial performance, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Forward-looking statements include, but are not limited to, statements about:

- our ability to raise financing in the future;
- our success in retaining or recruiting, or changes required in, our officers, key employees or directors;
- our ability and/or the ability of third-party vendors and partners to manufacture our product candidates;
- our ability to source critical components or materials for the manufacture of our product candidates;
- our ability to achieve and sustain profitability;
- our ability to achieve our projected development and commercialization goals;
- the rate of progress, costs and results of our clinical studies and research and development activities;
- market acceptance of our product candidates, if approved;
- our ability to compete successfully with larger companies in a highly competitive industry;
- changes in our operating results, which make future operations results difficult to predict;
- serious adverse events, undesirable side effects that could halt the clinical development, regulatory approval or certification, of our product candidates;
- our ability to manage growth or control costs related to growth;
- economic conditions that may adversely affect our business, financial condition and stock price;
- our reliance on third parties to drive successful marketing and sale of our initial product candidates, if approved;
- our reliance on third parties to manufacture and provide important materials and components for our products and product candidates;
- our and our partners' abilities to obtain necessary regulatory approvals and certifications for our product candidates in an uncomplicated and inexpensive manner;
- our ability to maintain compliance with regulatory and post-marketing requirements;
- adverse medical events, failure or malfunctions in connection with our product candidates and possible subjection to regulatory sanctions;
- healthcare costs containment pressures and legislative or administrative reforms which affect coverage and reimbursement practices of third-party payors;

- our ability to protect or enforce our intellectual property, unpatented trade secrets, know-how and other proprietary technology;
- our ability to obtain necessary intellectual property rights from third parties;
- our ability to protect our trademarks, trade names and build our names recognition;
- our ability to maintain the listing of our common stock on The Nasdaq Stock Market LLC ("Nasdaq");
- our ability to fund our operations into the second half of 2026 based on our cash, cash equivalents, marketable securities, and potential future payments or revenues discussed under the heading "Liquidity and Capital Resources — Funding Requirements" in Item 2 (Management's Discussion and Analysis of Financial Condition and Results of Operations) of the Company's Quarterly Report on Form 10-Q for quarter ended March 31, 2024, filed with the SEC on May 13, 2024;
- the success of our licensing agreements; and
- our public securities' liquidity and trading.

These forward-looking statements are neither promises nor guarantees of future performance due to a variety of risks and uncertainties, many of which are beyond our control, which could cause actual results to differ materially from those indicated by these forward-looking statements, including, without limitation the risk factors and cautionary statements described in other documents that we file from time to time with the SEC, specifically under "Item 1A. Risk Factors" and elsewhere in our most recent Annual Report on Form 10-K for the year ended December 31, 2023, under the heading "Item 1A. Risk Factors" in any subsequently filed Quarterly Report on Form 10-Q, and the section of any accompanying prospectus supplement entitled "Risk Factors."

The forward-looking statements in this prospectus and the documents incorporated by reference represent our views as of their respective dates. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we assume no obligation to update or revise any forward-looking statements except to the extent required by applicable law. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to the dates on which they were made.

This prospectus, each prospectus supplement and the information incorporated by reference in this prospectus and each prospectus supplement also contain estimates, projections and other information concerning our industry, our business, and the markets for certain diseases, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information.

WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE

Available Information

We file reports, proxy statements and other information with the SEC. The SEC maintains a website that contains reports, proxy and information statements and other information about issuers, such as us, who file electronically with the SEC. The address of that website is *http://www.sec.gov*.

Our website address is *www.orchestrabiomed.com*. The information on or accessible through our website, however, is not, and should not be deemed to be, a part of this prospectus.

This prospectus and any prospectus supplement are part of a registration statement that we filed with the SEC and do not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Forms of the indenture and other documents establishing the terms of the offered securities are or may be filed as exhibits to the registration statement or documents incorporated by reference in the registration statement. Statements in this prospectus or any prospectus supplement about these documents are summaries and each statement is qualified in all respects by reference to the document to which it refers. You should refer to the actual documents for a more complete description of the relevant matters. You may inspect a copy of the registration statement through the SEC's website, as provided above.

Incorporation by Reference

The SEC's rules allow us to "incorporate by reference" information into this prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus, and subsequent information that we file with the SEC will automatically update and supersede that information. Any statement contained in this prospectus or a previously filed document incorporated by reference will be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus or a subsequently filed document incorporated by reference modifies or replaces that statement.

This prospectus and any accompanying prospectus supplement incorporate by reference the documents set forth below that have previously been filed with the SEC (other than any information therein furnished to, rather than filed with, the SEC):

- our Annual Report on Form 10-K for the year ended December 31, 2023, filed with the SEC on March 27, 2024;
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2024, filed with the SEC on May 13, 2024;
- our Current Report on Form 8-K filed with the SEC on March 29, 2024; and
- the description of our Common Stock contained in Exhibit 4.16 to our Annual Report on Form 10-K for the fiscal year ended December 31, 2023 filed with the SEC on March 27, 2024, including any amendment or reports filed for the purpose of updating such description.

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act in this prospectus, prior to the termination of this offering, including all such documents we may file with the SEC after the date of this prospectus and prior to the effectiveness of this prospectus, but excluding any information furnished to, rather than filed with, the SEC, will also be incorporated by reference into this prospectus and deemed to be part of this prospectus from the date of the filing of such reports and documents. Any statements in any such future filings will automatically be deemed to modify and supersede any information in any document we previously filed with the SEC that is incorporated or deemed to be incorporated herein by reference to the extent that statements in the later filed document modify or replace such earlier statements. Any such statement so modified or superseded shall not be deemed to constitute a part of this prospectus, except as so modified or superseded.

You may request a free copy of any of the documents incorporated by reference in this prospectus by writing or telephoning us at the following address:

Orchestra BioMed Holdings, Inc.
150 Union Square Drive
New Hope, PA 18938
(215) 862-5797

Exhibits to the filings will not be sent, however, unless those exhibits have specifically been incorporated by reference in this prospectus or any accompanying prospectus supplement.

THE COMPANY

We are a biomedical innovation company accelerating high-impact technologies to patients through risk-reward sharing partnerships with leading medical device companies. Our partnership-enabled business model focuses on forging strategic collaborations with leading medical device companies to drive successful global commercialization of products we develop. We are led by a highly accomplished, multidisciplinary management team and a board of directors with extensive experience in all phases of therapeutic device development. Our business was formed in 2018 by assembling a pipeline of multiple late-stage clinical product candidates originally developed by our founding team. Our lead product candidate is BackBeat Cardiac Neuromodulation Therapy ("BackBeat CNT") for the treatment of hypertension ("HTN"), the leading risk factor for death worldwide. We have an exclusive license and collaboration agreement (the "Medtronic Agreement") with Medtronic, Inc. (an affiliate of Medtronic plc) ("Medtronic") for the development and commercialization of BackBeat CNT for the treatment of HTN in patients indicated for a cardiac pacemaker. We are also developing the Virtue Sirolimus AngioInfusion Balloon ("Virtue SAB") for the treatment of atherosclerotic artery disease, the leading cause of mortality worldwide. We have a strategic collaboration with Terumo Medical Corporation for the development and commercialization of Virtue SAB for the treatment of coronary and peripheral artery disease.

Corporate Information

On January 26, 2023, we consummated the previously announced business combination contemplated by the Agreement and Plan of Merger, dated as of July 4, 2022 (as amended by Amendment No. 1 to Agreement and Plan of Merger, dated July 21, 2022, and Amendment No. 2 to Agreement and Plan of Merger, dated November 21, 2022, the "Merger Agreement"), by and among Health Sciences Acquisitions Corporation 2, a special purpose acquisition company incorporated as a Cayman Islands exempted company in 2020 ("HSAC2"), HSAC Olympus Merger Sub, Inc., a Delaware corporation and wholly owned subsidiary of HSAC2 ("Merger Sub"), and Orchestra BioMed, Inc. ("Legacy Orchestra"). Pursuant to the Merger Agreement, (i) HSAC2 deregistered in the Cayman Islands in accordance with the Companies Act (2022 Revision) (As Revised) of the Cayman Islands and domesticated as a Delaware corporation in accordance with Section 388 of the Delaware General Corporation Law (the "Domestication") and (ii) Merger Sub merged with and into Legacy Orchestra, with Legacy Orchestra as the surviving company in the merger and, after giving effect to such merger, continuing as a wholly owned subsidiary of Orchestra (the "Merger" and, together with the Domestication and the other transactions contemplated by the Merger Agreement, the "Business Combination"). As part of the Domestication, the Company's name was changed from "Health Sciences Acquisitions Corporation 2" to "Orchestra BioMed Holdings, Inc."

Our principal executive office is located at 150 Union Square Drive, New Hope, PA 18938, and our telephone number is (215) 862-5797. Our website address is www.orchestrabiomed.com. We do not incorporate the information on or accessible through our website into this prospectus, and you should not consider any information on or accessible through our website as part of this prospectus.

RISK FACTORS

Investing in our securities involves risks. Before you make a decision to buy our securities, in addition to the risks and uncertainties discussed above under "Special Note Regarding Forward-Looking Statements" and below in this Risk Factors section, you should carefully consider the specific risks set forth under the heading "Risk Factors" in our Annual Report on Form 10-K for the fiscal year ended December 31, 2023, together with all information contained in this prospectus and any applicable prospectus supplement, and under similar headings in other documents that are incorporated by reference herein or therein. If any of these risks actually occur, it may materially harm our business, financial condition, liquidity and results of operations. As a result, the market price of our securities could decline, and you could lose all or part of your investment. Additionally, the risks and uncertainties described in or incorporated by reference into this prospectus are not the only risks and uncertainties that we face. Additional risks and uncertainties not presently known to us or that we currently believe to be immaterial may become material and adversely affect our business.

USE OF PROCEEDS

We intend to use the net proceeds from the sale of the securities as set forth in the applicable prospectus supplement.

DESCRIPTION OF CAPITAL STOCK

The following description summarizes the most important terms of our securities. The following summary does not purport to be complete and is subject to our certificate of incorporation (the "Charter"), our bylaws (the "Bylaws") and the provisions of applicable law. A copy of the Charter and a copy of the Bylaws are filed as exhibits to the registration statement of which this prospectus forms a part. The stockholders are encouraged to read the applicable provisions of the Delaware General Corporation Law (the "DGCL"), the Charter and the Bylaws in their entirety for a complete description of the rights and preferences of our securities.

Authorized and Outstanding Stock

The Charter authorizes the issuance of (i) 340,000,000 shares of common stock, $0.0001 par value per share (the "Common Stock") and (ii) 10,000,000 shares of preferred stock, $0.0001 par value per share (the "Preferred Stock"). As of May 8, 2024, there were 35,788,497 shares of Common Stock and no shares of Preferred Stock issued and outstanding.

Common Stock

The Charter provides the following with respect to the rights, powers, preferences and privileges of our Common Stock.

Voting Rights

Holders of our Common Stock are entitled to one vote per share of Common Stock held at all meetings of stockholders. The Charter does not provide for cumulative voting for the election of directors.

Dividend Rights

Subject to preferences that may be applicable to any outstanding preferred stock, the holders of our Common Stock are entitled to receive ratably such dividends, if any, as may be declared from time to time by the Company's board of directors (the "Board"), out of funds legally available therefor.

Rights upon Liquidation

In the event of our liquidation, dissolution or winding up, the holders of our Common Stock will be entitled to share ratably in all assets remaining after payment of liabilities, subject to prior distribution rights of Preferred Stock, if any, then outstanding.

No Preemptive or Similar Rights

Holders of our Common Stock have no redemption, conversion or preemptive rights. There are no sinking fund provisions applicable to our Common Stock.

Fully Paid and Non-Assessable

The outstanding shares of our Common Stock are fully paid and non-assessable.

Preferred Stock

As of the date of this prospectus, there are no shares of Preferred Stock outstanding. Pursuant to the Charter, our Board has the authority to issue undesignated Preferred Stock in one or more series and to fix the rights, preferences, privileges and restrictions thereof, including dividend rights, dividend rates, conversion rights, voting rights, terms of redemption, redemption prices, liquidation preferences and the number of shares constituting any series or the designation of such series, without further vote or action by the stockholders.

The issuance of Preferred Stock may have the effect of delaying, deferring or preventing a change in control without further action by the stockholders and may adversely affect the voting and other rights of the holders of our Common Stock. At present, we have no plans to issue any of the Preferred Stock.

Outstanding Warrants

As of May 8, 2024, there are outstanding warrants to acquire up to an aggregate of 1,945,548 shares of Common Stock.

HSAC2 Warrants

There are currently outstanding an aggregate of 750,000 warrants to purchase Common Stock (the "HSAC2 Warrants").

Each HSAC2 Warrant entitles the registered holder to purchase one share of Common Stock at a price of $11.50 per share, subject to adjustment as described in the HSAC2 Warrants, at any time commencing 30 days after the closing of the Business Combination. The HSAC2 Warrants have a net exercise provision under which its holder may, in lieu of payment of the exercise price in cash, surrender the warrant and receive a net amount of shares based on the fair market value of the Common Stock at the time of exercise of the HSAC2 Warrants after deduction of the aggregate exercise price. The HSAC2 Warrants will expire five years after the date on which they first became exercisable, at 5:00 p.m., New York City time.

None of the HSAC2 Warrants will be redeemable by us.

If the number of outstanding shares of Common Stock is increased by a stock dividend payable in shares of Common Stock, then, on the effective date of such stock dividend, or split-up or similar event, the number of shares issuable on exercise of each HSAC2 Warrant will be increased in proportion to such increase in the outstanding shares.

If the number of outstanding shares is decreased by a consolidation, combination, reverse share split or reclassification of Common Stock or other similar event, then, on the effective date of such consolidation, combination, reverse share split, reclassification or similar event, the number of shares issuable on exercise of each HSAC2 Warrant will be decreased in proportion to such decrease in outstanding shares of Common Stock.

Whenever the number of shares of Common Stock issuable upon the exercise of the HSAC2 Warrants is adjusted, as described above, the HSAC2 Warrant exercise price will be adjusted by multiplying the HSAC2 Warrant exercise price immediately prior to such adjustment by a fraction (x) the numerator of which will be the number of shares purchasable upon the exercise of the warrants immediately prior to such adjustment and (y) the denominator of which will be the number of shares so purchasable immediately thereafter.

If, at any time while an HSAC2 Warrant is outstanding, (i) we effect any merger or consolidation with or into another person, (ii) we effect any sale of all or substantially all of our assets or a majority of the Common Stock is acquired by a third party, in each case, in one or a series of related transactions, (iii) any tender offer or exchange offer is completed pursuant to which all or substantially all of the holders of Common Stock are permitted to tender or exchange their shares for other securities, cash or property, or (iv) we effect any reorganization or reclassification of Common Stock or any compulsory share exchange pursuant to which the Common Stock is effectively converted into or exchanged for other securities, cash or property (in any such case, a "Fundamental Transaction"), then the holder of an HSAC2 Warrant shall have the right thereafter to receive, upon exercise of the HSAC2 Warrant, the same amount and kind of securities, cash or property as it would have been entitled to receive upon the occurrence of such Fundamental Transaction if it had been, immediately prior to such Fundamental Transaction, the holder of the number of shares of Common Stock then issuable upon exercise in full of such HSAC2 Warrant.

Officer and Director Warrants

There were formerly 1,500,000 HSAC2 Warrants. As part of the Business Combination, HSAC 2 Holdings, LLC forfeited 50% of its HSAC2 Warrants, comprising 750,000 HSAC2 Warrants, for no consideration, immediately prior to the closing of the Business Combination. Pursuant to the terms of the Merger Agreement, immediately following such forfeiture and prior to the closing of the Business Combination, HSAC2 issued 750,000 warrants to purchase Common Stock to eleven specified employees and directors of Legacy Orchestra (the "Officer and Director Warrants"). However, 90,000 of the initial 750,000 Officer and Director Warrants were forfeited in connection with the departure of the Company's

former Chief Financial Officer and one director of the Company. Accordingly, there are currently 660,000 Officer and Director Warrants outstanding. These Officer and Director Warrants have substantially similar terms to the forfeited HSAC2 Warrants, except that 50% of the Officer and Director Warrants will become exercisable 24 months after the closing of the Business Combination (the "Closing") and the remaining 50% will become exercisable 36 months after the Closing, in each case, subject to the holder's continued employment or service with the Company or one of its subsidiaries through such date.

Legacy Orchestra Warrants that Converted into Company Warrants

At the effective time of the Business Combination, each warrant to purchase shares of the common stock of Legacy Orchestra that was outstanding and unexercised immediately prior to the effective time of the Business Combination was assumed by the Company and represented a warrant to purchase shares of Common Stock on the same terms and subject to the same conditions (including as to vesting and exercisability) as were in effect with respect to such warrants immediately prior to such effective time, with appropriate adjustments to the number of shares of Common Stock underlying such warrant and the exercise price applicable thereto to account for the Business Combination.

Warrants Issued in the Formation Mergers

Warrants to purchase an aggregate of 87,916 shares of Common Stock at an exercise price of $10.22 per share, which Legacy Orchestra issued on May 31, 2018 in connection with the mergers entered into with each of Caliber Therapeutics, Inc. ("Caliber"), BackBeat Medical, Inc. ("Backbeat") and FreeHold Surgical, Inc. pursuant to which Legacy Orchestra was formed in exchange for Caliber and BackBeat warrants that had been issued to designees of Aegis Capital Corp. ("Aegis") with respect to Aegis serving as a placement agent in Caliber and Backbeat capital-raising transactions. Among other things, these warrants have a six-year term that began on January 26, 2023 and became exercisable one year after the closing of the Business Combination.

Warrants Issued to Designees of Aegis for Serving as Placement Agent in Connection with Legacy Orchestra's Series B Preferred Stock and Series B-1 Preferred Stock Financings

Warrants to purchase an aggregate of 319,925 shares of Common Stock at an exercise price of $10.22 per share, which Legacy Orchestra issued to designees of Aegis pursuant to the Placement Agency Agreement entered into with Aegis in connection with Legacy Orchestra's offerings of Series B Preferred Stock and Series B-1 Preferred Stock. Among other things, these warrants have a six-year term that begins on January 26, 2023 and became exercisable one year after the closing of the Business Combination.

Provisions Applicable to All of the Above Company Warrants

All of the warrants above:

- provide for the adjustment of the exercise price and number of shares issuable upon the exercise thereof in the event of certain reclassification of shares, stock dividends or other distributions, capital reorganizations, consolidations, subdivisions, stock splits and combinations;
- have a net exercise provision under which its holder may, in lieu of payment of the exercise price in cash, surrender the warrant and receive a net amount of shares based on the fair market value of the Common Stock at the time of exercise of the warrant after deduction of the aggregate exercise price.

Warrants Issued to Avenue

In June 2022, Legacy Orchestra entered into a loan and security agreement (the "2022 Loan and Security Agreement") with Avenue Venture Opportunities Fund, L.P. ("Avenue I") and Avenue Venture Opportunities Fund II, L.P. ("Avenue II," and, collectively with Avenue I, "Avenue"). Pursuant to the terms of the 2022 Loan and Security Agreement, Legacy Orchestra issued two warrants to Avenue on June 3, 2022 that are exercisable for an aggregate of 100,000 shares of Common Stock at an exercise price of $4.06. These warrants (i) terminate on June 3, 2027, (ii) provide for the adjustment of the exercise price and number of shares issuable upon the exercise thereof in the event of certain reclassifications of shares, stock

dividends or other distributions, consolidations, subdivisions, stock splits and combinations; and (iii) have a net exercise provision under which its holder may, in lieu of payment of the exercise price in cash, surrender the warrant and receive a net amount of shares based on the fair market value of the Common Stock at the time of exercise of the warrant after deduction of the aggregate exercise price.

In connection with the repayment and termination of the 2022 Loan and Security Agreement, we issued two warrants to purchase an aggregate of 27,707 shares of Common Stock at an exercise price of $7.67 to Avenue on October 6, 2023 in lieu of a portion of certain fees we owed pursuant to the 2022 Loan and Security Agreement. These warrants (i) terminate on October 6, 2028, (ii) provide for the adjustment of the exercise price and number of shares issuable upon the exercise thereof in the event of certain reclassifications of shares, stock dividends or other distributions, consolidations, subdivisions, stock splits and combinations; and (iii) have a net exercise provision under which its holders may, in lieu of payment of the exercise price in cash, surrender the warrant and receive a net amount of shares based on the fair market value of the Common Stock at the time of exercise of the warrant after deduction of the aggregate exercise price.

Registration Rights and Lock-Up Agreement

In connection with the Business Combination, we entered into the Amended and Restated Registration Rights Agreement with RTW Master Fund, Ltd., RTW Innovation Master Fund, Ltd. and RTW Biotech Opportunities Ltd (formerly RTW Venture Fund Limited), certain former shareholders of HSAC2 and certain former stockholders of Legacy Orchestra (as amended, the "Second A&R RRA"). Pursuant to the Second A&R RRA and certain other registration obligations of the Company, we filed a registration statement (the "Registration Statement") with respect to the resale of up to 750,000 HSAC2 Warrants exercisable for Common Stock and up to 18,586,201 shares of Common Stock (including up to 1,310,000 shares of Common Stock issuable upon exercise of the HSAC2 Warrants and the Officer and Director Warrants). The Registration Statement, which registers the resale of approximately 52% of our outstanding common stock as of May 8, 2024, was declared effective by the staff of the SEC on May 9, 2024. In addition, subject to certain requirements and customary conditions, including with regard to the number of requests that may be made and when, the relevant stockholders may request to sell all or any portion of their registrable securities in an underwritten offering so long as the total offering price is reasonably expected to exceed, in the aggregate, $25 million. The stockholders party to the Second A&R RRA also have certain "piggy-back" registration rights that require us to include such securities in registration statements that we otherwise file, subject to certain requirements and customary conditions. The Second A&R RRA does not contain liquidated damages provisions or other cash settlement provisions resulting from delays in registering the securities. We will bear the expenses incurred in connection with the filing of any such registration statements. The Second A&R RRA contains customary indemnification provisions.

Anti-Takeover Effects of our Governing Documents under Delaware Law

Certain provisions of Delaware law, along with our Charter and our Bylaws, all of which are summarized below, may have the effect of delaying, deferring or discouraging another person from acquiring control of the Company. These provisions are expected to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed, in part, to encourage persons seeking to acquire control of the Company to first negotiate with our Board. However, these provisions could have the effect of delaying, discouraging or preventing attempts to acquire the Company, which could deprive our stockholders of opportunities to sell their shares of Common Stock at prices higher than prevailing market prices.

Election and Removal of Directors

The size of our Board is currently set at seven directors. The exact number of directors will be fixed from time to time by resolution of the Board. No director may be removed except for cause, and directors may be removed for cause by an affirmative vote of shares representing a majority of the shares then entitled to vote at an election of directors. Any vacancy occurring on the Board and any newly created directorship may be filled only by a majority of the remaining directors in office or by the sole remaining director.

Limits on Written Consents

The Charter and the Bylaws provide that holders of Common Stock will not be able to act by written consent without a meeting.

Special Meetings of Stockholders

The Bylaws provide that special meetings of stockholders may be called only by the chairperson of the Board, our chief executive officer or a majority of the directors.

Advance notice requirements for stockholder proposals and director nominations

The Bylaws provide that stockholders seeking to bring business before an annual meeting of stockholders, or to nominate candidates for election as directors at an annual meeting of stockholders, must provide timely notice of their intent in writing. To be timely, a stockholder's notice will need to be received by the secretary at our principal executive offices not later than the close of business on the 90th day nor earlier than the close of business on the 120th day prior to the first anniversary of the preceding year's annual meeting of stockholders; provided, however, that, in the event that the date of the annual meeting is advanced more than 30 days prior to or delayed by more than 30 days after the anniversary of the preceding year's annual meeting, notice by the stockholder to be timely must be received not earlier than the close of business on the 120th day prior to such annual meeting and not later than the close of business on the later of the 90th day prior to such annual meeting or, if later than the 90th day prior to such annual meeting, the tenth day following the day on which public announcement of the date of such meeting is first made. The Bylaws provide that an adjournment or a postponement of an annual meeting for which notice has been given, or the public announcement thereof has been made, will not commence a new time period (or extend any time period) for the giving of a stockholder's notice as described above. Pursuant to Rule 14a-8 of the Exchange Act, proposals seeking inclusion in the annual proxy statement must comply with the notice periods contained therein. The Bylaws also specify certain requirements as to the form and content of a stockholders' meeting. These provisions may preclude our stockholders from bringing matters before an annual meeting of stockholders or from making nominations for directors at an annual meeting of stockholders.

Authorized but unissued shares

Our authorized but unissued Common Stock and Preferred Stock will be available for future issuances without stockholder approval and could be utilized for a variety of corporate purposes, including future offerings to raise additional capital, acquisitions and employee benefit plans. The existence of authorized but unissued and unreserved Common Stock and Preferred Stock could render more difficult or discourage an attempt to obtain control of the Company by means of a proxy contest, tender offer, merger or otherwise.

Exclusive Forum Selection

The Charter provides that, unless the Company otherwise consents in writing, the Court of Chancery (the "Chancery Court") of the State of Delaware (or, in the event that the Chancery Court does not have subject matter jurisdiction, another state or federal court located within the State of Delaware) will, to the fullest extent permitted by law, be the sole and exclusive forum for resolution of (a) any derivative action or proceeding brought on behalf of the Company, (b) any action, suit or proceeding asserting a claim of breach of a fiduciary duty owed by any director, officer or stockholder of the Company to the Company or to the stockholders of the Company, (c) any action, suit or proceeding arising pursuant to any provision of the DGCL, the Charter or the Bylaws or (d) any action, suit or proceeding asserting a claim against the Company governed by the internal affairs doctrine. If any action the subject matter of which is described in the immediately preceding sentence is filed in a court other than the courts in the State of Delaware (a "Foreign Action") in the name of any stockholder, such stockholder will be deemed to have consented to (x) the personal jurisdiction of the state and federal courts in the State of Delaware in connection with any action brought in any such court to enforce the provisions of the immediately preceding sentence and (y) having service of process made upon such stockholder in any such action by service upon such stockholder's counsel in the Foreign Action as agent for such stockholder.

Notwithstanding the foregoing, unless the Company otherwise consents in writing, the federal district courts of the United States will be the exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act. Any person or entity purchasing or otherwise acquiring any interest in shares of Common Stock shall be deemed to have notice of and consented to the forum provisions in the Charter.

Notwithstanding the foregoing, Section 27 of the Exchange Act creates exclusive federal jurisdiction over all suits brought to enforce any duty or liability created by the Exchange Act or the rules and regulations thereunder. As a result, the exclusive forum provision will not apply to suits brought to enforce any duty or liability created by the Exchange Act or any other claim for which the federal courts have exclusive jurisdiction.

Limitation of Liability and Indemnification of Directors and Officers

Our Charter and Bylaws limit a director's and officer's liability to the fullest extent permitted under the DGCL. The DGCL provides that directors and officers of a corporation will not be personally liable for monetary damages for breach of their fiduciary duties as directors or officers, except for liability:

- for any transaction from which the director or officer derives an improper personal benefit;
- for any act or omission not in good faith or that involves intentional misconduct or a knowing violation of law;
- for a director under Section 174 of the DGCL;
- for any breach of a duty of loyalty to the corporation or its stockholders; or
- for an officer in any action by or in the right of the corporation.

If the DGCL is amended to authorize corporate action further eliminating or limiting the personal liability of directors or officers, then the liability of the directors and officers will be eliminated or limited to the fullest extent permitted by the DGCL, as so amended.

Delaware law and our Bylaws provide that we will, in certain situations, indemnify our directors and officers and may indemnify other employees and other agents, to the fullest extent permitted by law. Any indemnified person is also entitled, subject to certain limitations, to advancement, direct payment, or reimbursement of reasonable expenses (including attorneys' fees and disbursements) in advance of the final disposition of the proceeding.

In addition, we entered into separate indemnification agreements with each of our directors and officers. These agreements, among other things, require us to indemnify our directors and officers for certain expenses, including attorneys' fees, judgments, fines and settlement amounts incurred by a director or officer in any action or proceeding arising out of their services as one of our directors or officers or any other company or enterprise to which the person provides services at our request.

We maintain a directors' and officers' insurance policy pursuant to which our directors and officers are insured against liability for actions taken in their capacities as directors and officers. We believe these provisions in our Charter and Bylaws and these indemnification agreements are necessary to attract and retain qualified persons as directors and officers.

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers, or control persons, in the opinion of the SEC, such indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable.

Listing

Our shares of Common Stock are currently listed on the Nasdaq Global Market under the symbol "OBIO."

Transfer Agent and Registrar

The transfer agent and registrar for our Common Stock is Continental Stock Transfer & Trust Company, located at 17 Battery Place, New York, New York 10004.

DESCRIPTION OF DEBT SECURITIES

The following description, together with the additional information we include in any applicable prospectus supplement or free writing prospectus, summarizes certain general terms and provisions of the debt securities that we may offer under this prospectus. When we offer to sell a particular series of debt securities, we will describe the specific terms of the series in a supplement to this prospectus. We will also indicate in the supplement to what extent the general terms and provisions described in this prospectus apply to a particular series of debt securities.

We may issue debt securities either separately, or together with, or upon the conversion or exercise of or in exchange for, other securities described in this prospectus. Debt securities may be our senior, senior subordinated or subordinated obligations and, unless otherwise specified in a supplement to this prospectus, the debt securities will be our direct, unsecured obligations and may be issued in one or more series.

The debt securities will be issued under an indenture between us and a trustee to be named in the applicable indenture, as trustee. We have summarized select portions of the indenture below. The summary is not complete. The form of the indenture has been filed as an exhibit to the registration statement and you should read the indenture for provisions that may be important to you. In the summary below, we have included references to the section numbers of the indenture so that you can easily locate these provisions. Capitalized terms used in the summary and not defined herein have the meanings specified in the indenture.

As used in this section only, “Orchestra,” “we,” “our” or “us” refer to Orchestra BioMed Holdings, Inc. excluding our subsidiaries, unless expressly stated or the context otherwise requires.

The terms of each series of debt securities will be established by or pursuant to a resolution of our board of directors and set forth or determined in the manner provided in a resolution of our board of directors, in an officer’s certificate or by a supplemental indenture. (Section 2.2) The particular terms of each series of debt securities will be described in a prospectus supplement relating to such series (including any pricing supplement or term sheet).

We can issue an unlimited amount of debt securities under the indenture that may be in one or more series with the same or various maturities, at par, at a premium, or at a discount. (Section 2.1) We will set forth in a prospectus supplement (including any pricing supplement or term sheet) relating to any series of debt securities being offered, the aggregate principal amount and the following terms of the debt securities, if applicable:

- the title and ranking of the debt securities (including the terms of any subordination provisions);
- the price or prices (expressed as a percentage of the principal amount) at which we will sell the debt securities;
- any limit on the aggregate principal amount of the debt securities;
- the date or dates on which the principal of the securities of the series is payable;
- the rate or rates (which may be fixed or variable) per annum or the method used to determine the rate or rates (including, but not limited to, any commodity, commodity index, stock exchange index or financial index) at which the debt securities will bear interest, the date or dates from which interest will accrue, the date or dates on which interest will commence and be payable and any regular record date for the interest payable on any interest payment date;
- the place or places where principal of, and interest, if any, on the debt securities will be payable (and the method of such payment), where the securities of such series may be surrendered for registration of transfer or exchange, and where notices and demands to us in respect of the debt securities may be delivered, and the method of such payment, if by wire transfer, mail or other means;
- the period or periods within which, the price or prices at which and the terms and conditions upon which we may redeem the debt securities;
- any obligation we have to redeem or purchase the debt securities pursuant to any sinking fund or analogous provisions or at the option of a holder of debt securities and the period or periods within

which, the price or prices at which and the terms and conditions upon which securities of the series shall be redeemed or purchased, in whole or in part, pursuant to such obligation;

- the dates on which and the price or prices at which we will repurchase debt securities at the option of the holders of debt securities and other detailed terms and provisions of these repurchase obligations;
- the denominations in which the debt securities will be issued, if other than denominations of $1,000 and any integral multiple thereof;
- whether the debt securities will be issued in the form of certificated debt securities or global debt securities;
- the portion of principal amount of the debt securities payable upon declaration of acceleration of the maturity date, if other than the principal amount;
- the currency of denomination of the debt securities, which may be United States Dollars or any foreign currency, and if such currency of denomination is a composite currency, the agency or organization, if any, responsible for overseeing such composite currency;
- the designation of the currency, currencies or currency units in which payment of principal of, premium and interest on the debt securities will be made;
- if payments of principal of, premium or interest on the debt securities will be made in one or more currencies or currency units other than that or those in which the debt securities are denominated, the manner in which the exchange rate with respect to these payments will be determined;
- the manner in which the amounts of payment of principal of or interest, if any, on the debt securities will be determined, if these amounts may be determined by reference to an index based on a currency or currencies or by reference to a commodity, commodity index, stock exchange index or financial index;
- any provisions relating to any security provided for the debt securities;
- any addition to, deletion of or change in the Events of Default described below in this prospectus or in the indenture with respect to the debt securities and any change in the acceleration provisions described in this prospectus or in the indenture with respect to the debt securities;
- any addition to, deletion of or change in the covenants described in this prospectus or in the indenture with respect to the debt securities;
- any depositaries, interest rate calculation agents, exchange rate calculation agents or other agents with respect to the debt securities;
- the provisions, if any, relating to conversion or exchange of any debt securities of such series, including if applicable, the conversion or exchange price and period, provisions as to whether conversion or exchange will be mandatory, the events requiring an adjustment of the conversion or exchange price and provisions affecting conversion or exchange;
- any other terms of the debt securities, which may supplement, modify or delete any provision of the indenture as it applies to that series, including any terms that may be required under applicable law or regulations or advisable in connection with the marketing of the securities; and
- whether any of our direct or indirect subsidiaries will guarantee the debt securities of that series, including the terms of subordination, if any, of such guarantees. (Section 2.2)

We may issue debt securities that provide for an amount less than their stated principal amount to be due and payable upon declaration of acceleration of their maturity pursuant to the terms of the indenture. We will provide you with information on the federal income tax considerations and other special considerations applicable to any of these debt securities in the applicable prospectus supplement.

If we denominate the purchase price of any of the debt securities in a foreign currency or currencies or a foreign currency unit or units, or if the principal of and any premium and interest on any series of debt securities is payable in a foreign currency or currencies or a foreign currency unit or units, we will provide you

with information on the restrictions, elections, general tax considerations, specific terms and other information with respect to that issue of debt securities and such foreign currency or currencies or foreign currency unit or units in the applicable prospectus supplement.

Transfer and Exchange

Each debt security will be represented by either one or more global securities registered in the name of The Depository Trust Company (the "Depositary"), or a nominee of the Depositary (we will refer to any debt security represented by a global debt security as a "book-entry debt security"), or a certificate issued in definitive registered form (we will refer to any debt security represented by a certificated security as a "certificated debt security") as set forth in the applicable prospectus supplement. Except as set forth under the heading "Global Debt Securities and Book-Entry System" below, book-entry debt securities will not be issuable in certificated form.

Certificated Debt Securities. You may transfer or exchange certificated debt securities at any office we maintain for this purpose in accordance with the terms of the indenture. (Section 2.4) No service charge will be made for any transfer or exchange of certificated debt securities, but we may require payment of a sum sufficient to cover any tax or other governmental charge payable in connection with a transfer or exchange. (Section 2.7)

You may effect the transfer of certificated debt securities and the right to receive the principal of, premium and interest on certificated debt securities only by surrendering the certificate representing those certificated debt securities and either reissuance by us or the trustee of the certificate to the new holder or the issuance by us or the trustee of a new certificate to the new holder.

Global Debt Securities and Book-Entry System. Each global debt security representing book-entry debt securities will be deposited with, or on behalf of, the Depositary, and registered in the name of the Depositary or a nominee of the Depositary. Please see "Global Securities."

Covenants

We will set forth in the applicable prospectus supplement any restrictive covenants applicable to any issue of debt securities. (Article IV)

No Protection in the Event of a Change of Control

Unless we state otherwise in the applicable prospectus supplement, the debt securities will not contain any provisions which may afford holders of the debt securities protection in the event we have a change in control or in the event of a highly leveraged transaction (whether or not such transaction results in a change in control) which could adversely affect holders of debt securities.

Consolidation, Merger and Sale of Assets

We may not consolidate with or merge with or into, or convey, transfer or lease all or substantially all of our properties and assets to any person (a successor person) unless:

- we are the surviving entity or the successor person (if other than Orchestra) is a corporation, partnership, trust or other entity organized and validly existing under the laws of any U.S. domestic jurisdiction and expressly assumes our obligations on the debt securities and under the indenture; and
- immediately after giving effect to the transaction, no Default or Event of Default, shall have occurred and be continuing.

Notwithstanding the above, any of our subsidiaries may consolidate with, merge into or transfer all or part of its properties to us. (Section 5.1)

Events of Default

"Event of Default" means with respect to any series of debt securities, any of the following:

- default in the payment of any interest upon any debt security of that series when it becomes due and payable, and continuance of such default for a period of 30 days (unless the entire amount of the payment is deposited by us with the trustee or with a paying agent prior to the expiration of the 30-day period);

- default in the payment of principal of any security of that series at its maturity;
- default in the performance or breach of any other covenant or warranty by us in the indenture (other than a covenant or warranty that has been included in the indenture solely for the benefit of a series of debt securities other than that series), which default continues uncured for a period of 60 days after there has been given to Orchestra by the trustee or to Orchestra and the trustee by the holders of not less than 25% in principal amount of the outstanding debt securities of that series a written notice specifying such default or breach as provided in the indenture;
- certain voluntary or involuntary events of bankruptcy, insolvency or reorganization of Orchestra;
- any other Event of Default provided with respect to debt securities of that series that is described in the applicable prospectus supplement. (Section 6.1)

No Event of Default with respect to a particular series of debt securities (except as to certain events of bankruptcy, insolvency or reorganization) necessarily constitutes an Event of Default with respect to any other series of debt securities. (Section 6.1) The occurrence of certain Events of Default or an acceleration under the indenture may constitute an event of default under certain indebtedness of ours or our subsidiaries outstanding from time to time.

We will provide the trustee written notice of any Default or Event of Default within 30 days of becoming aware of the occurrence of such Default or Event of Default, which notice will describe in reasonable detail the status of such Default or Event of Default and what action we are taking or propose to take in respect thereof. (Section 6.1)

If an Event of Default with respect to debt securities of any series at the time outstanding occurs and is continuing, then the trustee or the holders of not less than 25% in principal amount of the outstanding debt securities of that series may, by a notice in writing to us (and to the trustee if given by the holders), declare to be due and payable immediately the principal of (or, if the debt securities of that series are discount securities, that portion of the principal amount as may be specified in the terms of that series) and accrued and unpaid interest, if any, on all debt securities of that series. In the case of an Event of Default resulting from certain events of bankruptcy, insolvency or reorganization, the principal (or such specified amount) of and accrued and unpaid interest, if any, on all outstanding debt securities will become and be immediately due and payable without any declaration or other act on the part of the trustee or any holder of outstanding debt securities. At any time after a declaration of acceleration with respect to debt securities of any series has been made, but before a judgment or decree for payment of the money due has been obtained by the trustee, the holders of a majority in principal amount of the outstanding debt securities of that series may rescind and annul the acceleration if all Events of Default, other than the non-payment of accelerated principal and interest, if any, with respect to debt securities of that series, have been cured or waived as provided in the indenture. (Section 6.2) We refer you to the prospectus supplement relating to any series of debt securities that are discount securities for the particular provisions relating to acceleration of a portion of the principal amount of such discount securities upon the occurrence of an Event of Default.

The indenture provides that the trustee may refuse to perform any duty or exercise any of its rights or powers under the indenture unless the trustee receives indemnity satisfactory to it against any cost, liability or expense which might be incurred by it in performing such duty or exercising such right or power. (Section 7.1(e)) Subject to certain rights of the trustee, the holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee or exercising any trust or power conferred on the trustee with respect to the debt securities of that series. (Section 6.12)

No holder of any debt security of any series will have any right to institute any proceeding, judicial or otherwise, with respect to the indenture or for the appointment of a receiver or trustee, or for any remedy under the indenture, unless:

- that holder has previously given to the trustee written notice of a continuing Event of Default with respect to debt securities of that series; and
- the holders of not less than 25% in principal amount of the outstanding debt securities of that series have made written request, and offered indemnity or security satisfactory to the trustee, to the

trustee to institute the proceeding as trustee, and the trustee has not received from the holders of not less than a majority in principal amount of the outstanding debt securities of that series a direction inconsistent with that request and has failed to institute the proceeding within 60 days. (Section 6.7)

Notwithstanding any other provision in the indenture, the holder of any debt security will have an absolute and unconditional right to receive payment of the principal of, premium and any interest on that debt security on or after the due dates expressed in that debt security and to institute suit for the enforcement of payment. (Section 6.8)

The indenture requires us, within 120 days after the end of our fiscal year, to furnish to the trustee a statement as to compliance with the indenture. (Section 4.3) If a Default or Event of Default occurs and is continuing with respect to the securities of any series and if it is known to a responsible officer of the trustee, the trustee shall mail to each Securityholder of the securities of that series notice of a Default or Event of Default within 90 days after it occurs or, if later, after a responsible officer of the trustee has knowledge of such Default or Event of Default. The indenture provides that the trustee may withhold notice to the holders of debt securities of any series of any Default or Event of Default (except in payment on any debt securities of that series) with respect to debt securities of that series if the trustee determines in good faith that withholding notice is in the interest of the holders of those debt securities. (Section 7.5)

Modification and Waiver

We and the trustee may modify, amend or supplement the indenture or the debt securities of any series without the consent of any holder of any debt security:

- to cure any ambiguity, defect or inconsistency;
- to comply with covenants in the indenture described above under the heading “Consolidation, Merger and Sale of Assets”;
- to provide for uncertificated securities in addition to or in place of certificated securities;
- to add guarantees with respect to debt securities of any series or secure debt securities of any series;
- to surrender any of our rights or powers under the indenture;
- to add covenants or events of default for the benefit of the holders of debt securities of any series;
- to comply with the applicable procedures of the applicable depositary;
- to make any change that does not adversely affect the rights of any holder of debt securities;
- to provide for the issuance of and establish the form and terms and conditions of debt securities of any series as permitted by the indenture;
- to effect the appointment of a successor trustee with respect to the debt securities of any series and to add to or change any of the provisions of the indenture to provide for or facilitate administration by more than one trustee; or
- to comply with requirements of the SEC in order to effect or maintain the qualification of the indenture under the Trust Indenture Act. (Section 9.1)

We may also modify and amend the indenture with the consent of the holders of at least a majority in principal amount of the outstanding debt securities of each series affected by the modifications or amendments. We may not make any modification or amendment without the consent of the holders of each affected debt security then outstanding if that amendment will:

- reduce the amount of debt securities whose holders must consent to an amendment, supplement or waiver;
- reduce the rate of or extend the time for payment of interest (including default interest) on any debt security;
- reduce the principal of or premium on or change the fixed maturity of any debt security or reduce the amount of, or postpone the date fixed for, the payment of any sinking fund or analogous obligation with respect to any series of debt securities;

- reduce the principal amount of discount securities payable upon acceleration of maturity;
- waive a default in the payment of the principal of, premium or interest on any debt security (except a rescission of acceleration of the debt securities of any series by the holders of at least a majority in aggregate principal amount of the then outstanding debt securities of that series and a waiver of the payment default that resulted from such acceleration);
- make the principal of or premium or interest on any debt security payable in currency other than that stated in the debt security;
- make any change to certain provisions of the indenture relating to, among other things, the right of holders of debt securities to receive payment of the principal of, premium and interest on those debt securities and to institute suit for the enforcement of any such payment and to waivers or amendments; or
- waive a redemption payment with respect to any debt security. (Section 9.3)

Except for certain specified provisions, the holders of at least a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all debt securities of that series waive our compliance with provisions of the indenture. (Section 9.2) The holders of a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all the debt securities of such series waive any past default under the indenture with respect to that series and its consequences, except a default in the payment of the principal of, premium or any interest on any debt security of that series; provided, however, that the holders of a majority in principal amount of the outstanding debt securities of any series may rescind an acceleration and its consequences, including any related payment default that resulted from the acceleration. (Section 6.13)

Defeasance of Debt Securities and Certain Covenants in Certain Circumstances

Legal Defeasance. The indenture provides that, unless otherwise provided by the terms of the applicable series of debt securities, we may be discharged from any and all obligations in respect of the debt securities of any series (subject to certain exceptions). We will be so discharged upon the irrevocable deposit with the trustee, in trust, of money and/or U.S. government obligations or, in the case of debt securities denominated in a single currency other than U.S. Dollars, government obligations of the government that issued or caused to be issued such currency, that, through the payment of interest and principal in accordance with their terms, will provide money or U.S. government obligations in an amount sufficient in the opinion of a nationally recognized firm of independent public accountants or investment bank to pay and discharge each installment of principal, premium and interest on and any mandatory sinking fund payments in respect of the debt securities of that series on the stated maturity of those payments in accordance with the terms of the indenture and those debt securities.

This discharge may occur only if, among other things, we have delivered to the trustee an opinion of counsel stating that we have received from, or there has been published by, the United States Internal Revenue Service a ruling or, since the date of execution of the indenture, there has been a change in the applicable United States federal income tax law, in either case to the effect that, and based thereon such opinion shall confirm that, the holders of the debt securities of that series will not recognize income, gain or loss for United States federal income tax purposes as a result of the deposit, defeasance and discharge and will be subject to United States federal income tax on the same amounts and in the same manner and at the same times as would have been the case if the deposit, defeasance and discharge had not occurred. (Section 8.3)

Defeasance of Certain Covenants. The indenture provides that, unless otherwise provided by the terms of the applicable series of debt securities, upon compliance with certain conditions:

- we may omit to comply with the covenant described under the heading “Consolidation, Merger and Sale of Assets” and certain other covenants set forth in the indenture, as well as any additional covenants which may be set forth in the applicable prospectus supplement; and
- any omission to comply with those covenants will not constitute a Default or an Event of Default with respect to the debt securities of that series (“covenant defeasance”).

The conditions include:

- depositing with the trustee money and/or U.S. government obligations or, in the case of debt securities denominated in a single currency other than U.S. Dollars, government obligations of the

government that issued or caused to be issued such currency, that, through the payment of interest and principal in accordance with their terms, will provide money in an amount sufficient in the opinion of a nationally recognized firm of independent public accountants or investment bank to pay and discharge each installment of principal of, premium and interest on and any mandatory sinking fund payments in respect of the debt securities of that series on the stated maturity of those payments in accordance with the terms of the indenture and those debt securities; and

- delivering to the trustee an opinion of counsel to the effect that the holders of the debt securities of that series will not recognize income, gain or loss for United States federal income tax purposes as a result of the deposit and related covenant defeasance and will be subject to United States federal income tax on the same amounts and in the same manner and at the same times as would have been the case if the deposit and related covenant defeasance had not occurred. (Section 8.4)

No Personal Liability of Directors, Officers, Employees or Securityholders

None of our past, present or future directors, officers, employees or securityholders, as such, will have any liability for any of our obligations under the debt securities or the indenture or for any claim based on, or in respect or by reason of, such obligations or their creation. By accepting a debt security, each holder waives and releases all such liability. This waiver and release is part of the consideration for the issue of the debt securities. However, this waiver and release may not be effective to waive liabilities under U.S. federal securities laws, and it is the view of the SEC that such a waiver is against public policy.

Governing Law

The indenture and the debt securities, including any claim or controversy arising out of or relating to the indenture or the securities, will be governed by the laws of the State of New York.

The indenture will provide that we, the trustee and the holders of the debt securities (by their acceptance of the debt securities) irrevocably waive, to the fullest extent permitted by applicable law, any and all right to trial by jury in any legal proceeding arising out of or relating to the indenture, the debt securities or the transactions contemplated thereby.

The indenture will provide that any legal suit, action or proceeding arising out of or based upon the indenture or the transactions contemplated thereby may be instituted in the federal courts of the United States of America located in the City of New York or the courts of the State of New York in each case located in the City of New York, and we, the trustee and the holder of the debt securities (by their acceptance of the debt securities) irrevocably submit to the non-exclusive jurisdiction of such courts in any such suit, action or proceeding. The indenture will further provide that service of any process, summons, notice or document by mail (to the extent allowed under any applicable statute or rule of court) to such party's address set forth in the indenture will be effective service of process for any suit, action or other proceeding brought in any such court. The indenture will further provide that we, the trustee and the holders of the debt securities (by their acceptance of the debt securities) irrevocably and unconditionally waive any objection to the laying of venue of any suit, action or other proceeding in the courts specified above and irrevocably and unconditionally waive and agree not to plead or claim any such suit, action or other proceeding has been brought in an inconvenient forum. (Section 10.10)

DESCRIPTION OF WARRANTS

We may issue warrants for the purchase of shares of our common stock or preferred stock or of debt securities. We may issue warrants independently or together with other securities, and the warrants may be attached to or separate from any offered securities. Each series of warrants will be issued under a separate warrant agreement to be entered into between us and the investors or a warrant agent. The following summary of material provisions of the warrants and warrant agreements are subject to, and qualified in their entirety by reference to, all the provisions of the warrant agreement and warrant certificate applicable to a particular series of warrants. The terms of any warrants offered under a prospectus supplement may differ from the terms described below. We urge you to read the applicable prospectus supplement and any related free writing prospectus, as well as the complete warrant agreements and warrant certificates that contain the terms of the warrants.

The particular terms of any issue of warrants will be described in the prospectus supplement relating to the issue. Those terms may include:

- the number of shares of common stock or preferred stock purchasable upon the exercise of warrants to purchase such shares and the price at which such number of shares may be purchased upon such exercise;
- the designation, stated value and terms (including, without limitation, liquidation, dividend, conversion and voting rights) of the series of preferred stock purchasable upon exercise of warrants to purchase preferred stock;
- the principal amount of debt securities that may be purchased upon exercise of a debt warrant and the exercise price for the warrants, which may be payable in cash, securities or other property;
- the date, if any, on and after which the warrants and the related debt securities, preferred stock or common stock will be separately transferable;
- the terms of any rights to redeem or call the warrants;
- the date on which the right to exercise the warrants will commence and the date on which the right will expire;
- United States Federal income tax consequences applicable to the warrants; and
- any additional terms of the warrants, including terms, procedures, and limitations relating to the exchange, exercise and settlement of the warrants.

Holders of equity warrants will not be entitled:

- to vote, consent or receive dividends;
- receive notice as shareholders with respect to any meeting of shareholders for the election of our directors or any other matter; or
- exercise any rights as shareholders of Orchestra.

Each warrant will entitle its holder to purchase the principal amount of debt securities or the number of shares of preferred stock or common stock at the exercise price set forth in, or calculable as set forth in, the applicable prospectus supplement. Unless we otherwise specify in the applicable prospectus supplement, holders of the warrants may exercise the warrants at any time up to the specified time on the expiration date that we set forth in the applicable prospectus supplement. After the close of business on the expiration date, unexercised warrants will become void.

A holder of warrant certificates may exchange them for new warrant certificates of different denominations, present them for registration of transfer and exercise them at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement. Until any warrants to purchase debt securities are exercised, the holder of the warrants will not have any rights of holders of the debt securities that can be purchased upon exercise, including any rights to receive payments of principal, premium or interest on the underlying debt securities or to enforce covenants in the applicable indenture. Until any warrants to purchase common stock or preferred stock are exercised, the holders of the warrants

will not have any rights of holders of the underlying common stock or preferred stock, including any rights to receive dividends or payments upon any liquidation, dissolution or winding up on the common stock or preferred stock, if any.

DESCRIPTION OF RIGHTS

General

We may issue rights to purchase our common stock, preferred stock, units or the other securities described in this prospectus. This prospectus and any accompanying prospectus supplement will contain the material terms and conditions for each right. The accompanying prospectus supplement may add, update or change the terms and conditions of the rights as described in this prospectus.

We will describe in the applicable prospectus supplement the terms and conditions of the issue of rights being offered, the rights agreement relating to the rights and the rights certificates representing the rights, including, as applicable:

- the title of the rights;
- the date of determining the stockholders entitled to the rights distribution;
- the title, aggregate number of shares of our common stock, preferred stock or other securities purchasable upon exercise of the rights;
- the exercise price;
- the currencies in which the rights are being offered;
- the aggregate number of rights issued;
- the date, if any, on and after which the rights will be separately transferable;
- the date on which the right to exercise the rights will commence and the date on which the right will expire; and
- any other terms of the rights, including terms, procedures and limitations relating to the distribution, exchange and exercise of the rights.

Exercise of Rights

Each right will entitle the holder of rights to purchase for cash the principal amount of shares of our common stock, preferred stock, units or other securities at the exercise price provided in the applicable prospectus supplement. Rights may be exercised at any time up to the close of business on the expiration date for the rights provided in the applicable prospectus supplement. After the close of business on the expiration date, all unexercised rights will be void.

Holders may exercise rights as described in the applicable prospectus supplement. Upon receipt of payment and the rights certificate properly completed and duly executed at the corporate trust office of the rights agent or any other office indicated in the prospectus supplement, we will, as soon as practicable, forward the shares of our common stock or preferred stock purchasable upon exercise of the rights. If less than all of the rights issued in any rights offering are exercised, we may offer any unsubscribed securities directly to persons other than stockholders, to or through agents, underwriters, brokers or dealers or through a combination of such methods, including pursuant to standby underwriting arrangements, as described in the applicable prospectus supplement.

DESCRIPTION OF UNITS

We may issue units consisting of any combination of the other types of securities offered under this prospectus in one or more series. We may evidence each series of units by unit certificates that we will issue under a separate agreement. We may enter into unit agreements with a unit agent. Each unit agent will be a bank or trust company that we select. We will indicate the name and address of the unit agent in the applicable prospectus supplement relating to a particular series of units.

The following description, together with the additional information included in any applicable prospectus supplement, summarizes the general features of the units that we may offer under this prospectus. You should read any prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of units being offered, as well as the complete unit agreements that contain the terms of the units. Specific unit agreements will contain additional important terms and provisions and we will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from another report that we file with the SEC, the form of each unit agreement relating to units offered under this prospectus.

If we offer any units, certain terms of that series of units will be described in the applicable prospectus supplement, including, without limitation, the following, as applicable:

- the title of the series of units;
- identification and description of the separate constituent securities comprising the units;
- the price or prices at which the units will be issued;
- the date, if any, on and after which the constituent securities comprising the units will be separately transferable;
- a discussion of certain United States federal income tax considerations applicable to the units; and
- any other terms of the units and their constituent securities.

GLOBAL SECURITIES

Book-Entry, Delivery and Form

Unless we indicate differently in any applicable prospectus supplement or free writing prospectus, the securities initially will be issued in book-entry form and represented by one or more global notes or global securities, or, collectively, global securities. The global securities will be deposited with, or on behalf of, The Depository Trust Company, New York, New York, as depositary ("DTC"), and registered in the name of Cede & Co., the nominee of DTC. Unless and until it is exchanged for individual certificates evidencing securities under the limited circumstances described below, a global security may not be transferred except as a whole by the depositary to its nominee or by the nominee to the depositary, or by the depositary or its nominee to a successor depositary or to a nominee of the successor depositary.

DTC has advised us that it is:

- a limited-purpose trust company organized under the New York Banking Law;
- a "banking organization" within the meaning of the New York Banking Law;
- a member of the Federal Reserve System;
- a "clearing corporation" within the meaning of the New York Uniform Commercial Code; and
- a "clearing agency" registered pursuant to the provisions of Section 17A of the Exchange Act.

DTC holds securities that its participants deposit with DTC. DTC also facilitates the settlement among its participants of securities transactions, such as transfers and pledges, in deposited securities through electronic computerized book-entry changes in participants' accounts, thereby eliminating the need for physical movement of securities certificates. Direct participants in DTC include securities brokers and dealers, including underwriters, banks, trust companies, clearing corporations and other organizations. DTC is a wholly-owned subsidiary of The Depository Trust & Clearing Corporation ("DTCC"). DTCC is the holding company for DTC, National Securities Clearing Corporation and Fixed Income Clearing Corporation, all of which are registered clearing agencies. DTCC is owned by the users of its regulated subsidiaries. Access to the DTC system is also available to others, which we sometimes refer to as indirect participants, that clear through or maintain a custodial relationship with a direct participant, either directly or indirectly. The rules applicable to DTC and its participants are on file with the SEC.

Purchases of securities under the DTC system must be made by or through direct participants, which will receive a credit for the securities on DTC's records. The ownership interest of the actual purchaser of a security, which we sometimes refer to as a beneficial owner, is in turn recorded on the direct and indirect participants' records. Beneficial owners of securities will not receive written confirmation from DTC of their purchases. However, beneficial owners are expected to receive written confirmations providing details of their transactions, as well as periodic statements of their holdings, from the direct or indirect participants through which they purchased securities. Transfers of ownership interests in global securities are to be accomplished by entries made on the books of participants acting on behalf of beneficial owners. Beneficial owners will not receive certificates representing their ownership interests in the global securities, except under the limited circumstances described below.

To facilitate subsequent transfers, all global securities deposited by direct participants with DTC will be registered in the name of DTC's partnership nominee, Cede & Co., or such other name as may be requested by an authorized representative of DTC. The deposit of securities with DTC and their registration in the name of Cede & Co. or such other nominee will not change the beneficial ownership of the securities. DTC has no knowledge of the actual beneficial owners of the securities. DTC's records reflect only the identity of the direct participants to whose accounts the securities are credited, which may or may not be the beneficial owners. The participants are responsible for keeping account of their holdings on behalf of their customers.

So long as the securities are in book-entry form, you will receive payments and may transfer securities only through the facilities of the depositary and its direct and indirect participants. We will maintain an office or agency in the location specified in the prospectus supplement for the applicable securities, where notices and demands in respect of the securities and the indenture may be delivered to us and where certificated securities may be surrendered for payment, registration of transfer or exchange.

Conveyance of notices and other communications by DTC to direct participants, by direct participants to indirect participants and by direct participants and indirect participants to beneficial owners will be governed by arrangements among them, subject to any legal requirements in effect from time to time.

Redemption notices will be sent to DTC. If less than all of the securities of a particular series are being redeemed, DTC's practice is to determine by lot the amount of the interest of each direct participant in the securities of such series to be redeemed.

Neither DTC nor Cede & Co. (or such other DTC nominee) will consent or vote with respect to the securities. Under its usual procedures, DTC will mail an omnibus proxy to us as soon as possible after the record date. The omnibus proxy assigns the consenting or voting rights of Cede & Co. to those direct participants to whose accounts the securities of such series are credited on the record date, identified in a listing attached to the omnibus proxy.

So long as securities are in book-entry form, we will make payments on those securities to the depositary or its nominee, as the registered owner of such securities, by wire transfer of immediately available funds. If securities are issued in definitive certificated form under the limited circumstances described below and unless if otherwise provided in the description of the applicable securities herein or in the applicable prospectus supplement, we will have the option of making payments by check mailed to the addresses of the persons entitled to payment or by wire transfer to bank accounts in the United States designated in writing to the applicable trustee or other designated party at least 15 days before the applicable payment date by the persons entitled to payment, unless a shorter period is satisfactory to the applicable trustee or other designated party.

Redemption proceeds, distributions and dividend payments on the securities will be made to Cede & Co., or such other nominee as may be requested by an authorized representative of DTC. DTC's practice is to credit direct participants' accounts upon DTC's receipt of funds and corresponding detail information from us on the payment date in accordance with their respective holdings shown on DTC records. Payments by participants to beneficial owners will be governed by standing instructions and customary practices, as is the case with securities held for the account of customers in bearer form or registered in "street name." Those payments will be the responsibility of participants and not of DTC or us, subject to any statutory or regulatory requirements in effect from time to time. Payment of redemption proceeds, distributions and dividend payments to Cede & Co., or such other nominee as may be requested by an authorized representative of DTC, is our responsibility, disbursement of payments to direct participants is the responsibility of DTC, and disbursement of payments to the beneficial owners is the responsibility of direct and indirect participants.

Except under the limited circumstances described below, purchasers of securities will not be entitled to have securities registered in their names and will not receive physical delivery of securities. Accordingly, each beneficial owner must rely on the procedures of DTC and its participants to exercise any rights under the securities and the indenture.

The laws of some jurisdictions may require that some purchasers of securities take physical delivery of securities in definitive form. Those laws may impair the ability to transfer or pledge beneficial interests in securities.

DTC may discontinue providing its services as securities depositary with respect to the securities at any time by giving reasonable notice to us. Under such circumstances, in the event that a successor depositary is not obtained, securities certificates are required to be printed and delivered.

As noted above, beneficial owners of a particular series of securities generally will not receive certificates representing their ownership interests in those securities. However, if:

- DTC notifies us that it is unwilling or unable to continue as a depositary for the global security or securities representing such series of securities or if DTC ceases to be a clearing agency registered under the Exchange Act at a time when it is required to be registered and a successor depositary is not appointed within 90 days of the notification to us or of our becoming aware of DTC's ceasing to be so registered, as the case may be;

- we determine, in our sole discretion, not to have such securities represented by one or more global securities; or
- an Event of Default has occurred and is continuing with respect to such series of securities,

we will prepare and deliver certificates for such securities in exchange for beneficial interests in the global securities. Any beneficial interest in a global security that is exchangeable under the circumstances described in the preceding sentence will be exchangeable for securities in definitive certificated form registered in the names that the depositary directs. It is expected that these directions will be based upon directions received by the depositary from its participants with respect to ownership of beneficial interests in the global securities.

Euroclear and Clearstream

If so provided in the applicable prospectus supplement, you may hold interests in a global security through Clearstream Banking S.A., which we refer to as "Clearstream," or Euroclear Bank S.A./N.V., as operator of the Euroclear System, which we refer to as "Euroclear," either directly if you are a participant in Clearstream or Euroclear or indirectly through organizations which are participants in Clearstream or Euroclear. Clearstream and Euroclear will hold interests on behalf of their respective participants through customers' securities accounts in the names of Clearstream and Euroclear, respectively, on the books of their respective U.S. depositaries, which in turn will hold such interests in customers' securities accounts in such depositaries' names on DTC's books.

Clearstream and Euroclear are securities clearance systems in Europe. Clearstream and Euroclear hold securities for their respective participating organizations and facilitate the clearance and settlement of securities transactions between those participants through electronic book-entry changes in their accounts, thereby eliminating the need for physical movement of certificates.

Payments, deliveries, transfers, exchanges, notices and other matters relating to beneficial interests in global securities owned through Euroclear or Clearstream must comply with the rules and procedures of those systems. Transactions between participants in Euroclear or Clearstream, on one hand, and other participants in DTC, on the other hand, are also subject to DTC's rules and procedures.

Investors will be able to make and receive through Euroclear and Clearstream payments, deliveries, transfers and other transactions involving any beneficial interests in global securities held through those systems only on days when those systems are open for business. Those systems may not be open for business on days when banks, brokers and other institutions are open for business in the United States.

Cross-market transfers between participants in DTC, on the one hand, and participants in Euroclear or Clearstream, on the other hand, will be effected through DTC in accordance with the DTC's rules on behalf of Euroclear or Clearstream, as the case may be, by their respective U.S. depositaries; however, such cross-market transactions will require delivery of instructions to Euroclear or Clearstream, as the case may be, by the counterparty in such system in accordance with the rules and procedures and within the established deadlines (European time) of such system. Euroclear or Clearstream, as the case may be, will, if the transaction meets its settlement requirements, deliver instructions to its U.S. depositary to take action to effect final settlement on its behalf by delivering or receiving interests in the global securities through DTC, and making or receiving payment in accordance with normal procedures for same-day fund settlement. Participants in Euroclear or Clearstream may not deliver instructions directly to their respective U.S. depositaries.

Due to time zone differences, the securities accounts of a participant in Euroclear or Clearstream purchasing an interest in a global security from a direct participant in DTC will be credited, and any such crediting will be reported to the relevant participant in Euroclear or Clearstream, during the securities settlement processing day (which must be a business day for Euroclear or Clearstream) immediately following the settlement date of DTC. Cash received in Euroclear or Clearstream as a result of sales of interests in a global security by or through a participant in Euroclear or Clearstream to a direct participant in DTC will be received with value on the settlement date of DTC but will be available in the relevant Euroclear or Clearstream cash account only as of the business day for Euroclear or Clearstream following DTC's settlement date.

Other

The information in this section of this prospectus concerning DTC, Clearstream, Euroclear and their respective book-entry systems has been obtained from sources that we believe to be reliable, but we do not take responsibility for this information. This information has been provided solely as a matter of convenience. The rules and procedures of DTC, Clearstream and Euroclear are solely within the control of those organizations and could change at any time. Neither we nor the trustee nor any agent of ours or of the trustee has any control over those entities and none of us takes any responsibility for their activities. You are urged to contact DTC, Clearstream and Euroclear or their respective participants directly to discuss those matters. In addition, although we expect that DTC, Clearstream and Euroclear will perform the foregoing procedures, none of them is under any obligation to perform or continue to perform such procedures and such procedures may be discontinued at any time. Neither we nor any agent of ours will have any responsibility for the performance or nonperformance by DTC, Clearstream and Euroclear or their respective participants of these or any other rules or procedures governing their respective operations.

PLAN OF DISTRIBUTION

We may sell the securities from time to time pursuant to underwritten public offerings, negotiated transactions, block trades or a combination of these methods or through underwriters or dealers, through agents and/or directly to one or more purchasers. The securities may be distributed from time to time in one or more transactions:

- at a fixed price or prices, which may be changed;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

Each time that we sell securities covered by this prospectus, we will provide a prospectus supplement or supplements that will describe the method of distribution and set forth the terms and conditions of the offering of such securities, including the offering price of the securities and the proceeds to us, if applicable.

Offers to purchase the securities being offered by this prospectus may be solicited directly. Agents may also be designated to solicit offers to purchase the securities from time to time. Any agent involved in the offer or sale of our securities will be identified in a prospectus supplement.

If a dealer is utilized in the sale of the securities being offered by this prospectus, the securities will be sold to the dealer, as principal. The dealer may then resell the securities to the public at varying prices to be determined by the dealer at the time of resale.

If an underwriter is utilized in the sale of the securities being offered by this prospectus, an underwriting agreement will be executed with the underwriter at the time of sale and the name of any underwriter will be provided in the prospectus supplement that the underwriter will use to make resales of the securities to the public. In connection with the sale of the securities, we or the purchasers of securities for whom the underwriter may act as agent, may compensate the underwriter in the form of underwriting discounts or commissions. The underwriter may sell the securities to or through dealers, and those dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters and/or commissions from the purchasers for which they may act as agent. Unless otherwise indicated in a prospectus supplement, an agent will be acting on a best efforts basis and a dealer will purchase securities as a principal, and may then resell the securities at varying prices to be determined by the dealer.

Any compensation paid to underwriters, dealers or agents in connection with the offering of the securities, and any discounts, concessions or commissions allowed by underwriters to participating dealers will be provided in the applicable prospectus supplement. Underwriters, dealers and agents participating in the distribution of the securities may be deemed to be underwriters within the meaning of the Securities Act of 1933, as amended, and any discounts and commissions received by them and any profit realized by them on resale of the securities may be deemed to be underwriting discounts and commissions. We may enter into agreements to indemnify underwriters, dealers and agents against civil liabilities, including liabilities under the Securities Act, or to contribute to payments they may be required to make in respect thereof and to reimburse those persons for certain expenses.

Any common stock will be listed on The Nasdaq Global Market, but any other securities may or may not be listed on a national securities exchange. To facilitate the offering of securities, certain persons participating in the offering may engage in transactions that stabilize, maintain or otherwise affect the price of the securities. This may include over-allotments or short sales of the securities, which involve the sale by persons participating in the offering of more securities than were sold to them. In these circumstances, these persons would cover such over-allotments or short positions by making purchases in the open market or by exercising their over-allotment option, if any. In addition, these persons may stabilize or maintain the price of the securities by bidding for or purchasing securities in the open market or by imposing penalty bids, whereby selling concessions allowed to dealers participating in the offering may be reclaimed if securities sold by them are repurchased in connection with stabilization transactions. The effect of these transactions may be to stabilize or maintain the market price of the securities at a level above that which might otherwise prevail in the open market. These transactions may be discontinued at any time.

We may engage in at the market offerings into an existing trading market in accordance with Rule 415(a)(4) under the Securities Act. In addition, we may enter into derivative transactions with third parties, or sell securities not covered by this prospectus to third parties in privately negotiated transactions. If the applicable prospectus supplement so indicates, in connection with those derivatives, the third parties may sell securities covered by this prospectus and the applicable prospectus supplement, including in short sale transactions. If so, the third party may use securities pledged by us or borrowed from us or others to settle those sales or to close out any related open borrowings of stock, and may use securities received from us in settlement of those derivatives to close out any related open borrowings of stock. The third party in such sale transactions will be an underwriter and, if not identified in this prospectus, will be named in the applicable prospectus supplement (or a post-effective amendment). In addition, we may otherwise loan or pledge securities to a financial institution or other third party that in turn may sell the securities short using this prospectus and an applicable prospectus supplement. Such financial institution or other third party may transfer its economic short position to investors in our securities or in connection with a concurrent offering of other securities.

The specific terms of any lock-up provisions in respect of any given offering will be described in the applicable prospectus supplement.

The underwriters, dealers and agents may engage in transactions with us, or perform services for us, in the ordinary course of business for which they receive compensation.

LEGAL MATTERS

Paul Hastings LLP will pass upon certain legal matters relating to the issuance and sale of the securities offered hereby on behalf of Orchestra BioMed Holdings, Inc. Additional legal matters may be passed upon for us or any underwriters, dealers or agents, by counsel that we will name in the applicable prospectus supplement.

EXPERTS

The consolidated financial statements of Orchestra BioMed Holdings, Inc. appearing in Orchestra BioMed Holdings, Inc.'s Annual Report (Form 10-K) for the year ended December 31, 2023, have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon included therein, and incorporated herein by reference. Such financial statements are, and audited financial statements to be included in subsequently filed documents will be, incorporated herein in reliance upon the report of Ernst & Young LLP pertaining to such financial statements (to the extent covered by consents filed with the Securities and Exchange Commission) given on the authority of such firm as experts in accounting and auditing.

15,000,000 Shares of Common Stock

ORCHESTRA BIOMED HOLDINGS, INC.



PROSPECTUS SUPPLEMENT

Piper Sandler

TD Cowen

BTIG

H.C. Wainwright & Co.

November 5, 2026

Calculation of Filing Fee Tables

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Orchestra BioMed Holdings, Inc.

Table 1: Newly Registered and Carry Forward Securities ☑Not Applicable

	Security Type	Security Class Title	Fee Calculation or Carry Forward Rule	Amount Registered	Proposed Maximum Offering Price Per Unit	Maximum Aggregate Offering Price	Fee Rate	Amount of Registration Fee	Carry Forward Form Type	Carry Forward File Number	Carry Forward Initial Effective Date	Filing Fee Previously Paid in Connection with Unsold Securities to be Carried Forward
Newly Registered Securities												
Fees to be Paid												
Fees Previously Paid												
Carry Forward Securities												
Carry Forward Securities												
				Total Offering Amounts:		$ 0.00		$ 0.00				
				Total Fees Previously Paid:				$ 0.00				
				Total Fee Offsets:				$ 0.00				
				Net Fee Due:				$ 0.00				

Table 2: Fee Offset Claims and Sources ☑Not Applicable

		Registrant or Filer Name	Form or Filing Type	File Number	Initial Filing Date	Filing Date	Fee Offset Claimed	Security Type Associated with Fee Offset Claimed	Security Title Associated with Fee Offset Claimed	Unsold Securities Associated with Fee Offset Claimed	Unsold Aggregate Offering Amount Associated with Fee Offset Claimed	Fee Paid with Fee Offset Source
Rules 457(b) and 0-11(a)(2)												
Fee Offset Claims												
Fee Offset Sources												
Rule 457(p)												
Fee Offset Claims												
Fee Offset Sources												

Table 3: Combined Prospectuses ☑Not Applicable

	Security Type	Security Class Title	Amount of Securities Previously Registered	Maximum Aggregate Offering Price of Securities Previously Registered	Form Type	File Number	Initial Effective Date

Narrative Disclosure

The maximum aggregate offering price of the securities to which the prospectus relates is $75,000,000.00. The prospectus is a final prospectus for the related offering.

The maximum aggregate offering price of that offering is $75,000,000.00 (or up to $86,250,000.00 aggregate offering price if the underwriters' option to purchase additional shares of Common Stock is exercised in full).