2023

Annual Report

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

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2023

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934 FOR THE TRANSITION PERIOD FROM TO**

Commission File Number: 001-40544

Aerovate Therapeutics, Inc.
(Exact name of Registrant as specified in its Charter)

Delaware **(State or other jurisdiction of incorporation or organization)**	**83-1377888** **(I.R.S. Employer Identification No.)**
930 Winter Street, Suite M-500 **Waltham, MA 02451** **(Address of principal executive offices)**	**02451** **(Zip Code)**

Registrant's telephone number, including area code: (617) 443-2400

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common stock, par value $0.0001 per share	AVTE	The Nasdaq Global Market

Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the Registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. YES ☐ NO ☒

Indicate by check mark if the Registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. YES ☐ NO ☒

Indicate by check mark whether the Registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the Registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. YES ☒ NO ☐

Indicate by check mark whether the Registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the Registrant was required to submit such files). YES ☒ NO ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	☐	Accelerated filer	☐
Non-accelerated filer	☒	Smaller reporting company	☒
		Emerging growth company	☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). YES ☐ NO ☒

As of June 30, 2023 (the last business day of the Registrant's most recently completed second quarter) the aggregate market value of the Registrant's common stock held by non-affiliates of the Registrant was $232.0 million, based on the closing price of the Registrant's common stock as reported on the Nasdaq Global Market of $17.15 per share. In determining the market value of non-affiliate common stock, shares of the Registrant's common stock beneficially owned by officers, directors and affiliates have been excluded. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The number of shares of Registrant's Common Stock outstanding as of March 21, 2024 was 27,862,961.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A relating to the 2024 Annual Meeting of Stockholders within 120 days of the end of the registrant's fiscal year ended December 31, 2023. Portions of such definitive proxy statement are incorporated by reference into Part III of this Annual Report on Form 10-K to the extent stated herein.

Table of Contents

SUMMARY OF THE MATERIAL AND OTHER RISKS ASSOCIATED WITH OUR BUSINESS

Our business is subject to numerous material and other risks and uncertainties that you should be aware of in evaluating our business. These risks include, but are not limited to, the following:

- We are a clinical-stage biopharmaceutical company with a limited operating history.
- We have incurred significant operating losses since our inception and anticipate that we will continue to incur losses for the foreseeable future. We may never achieve or maintain profitability.
- We have no products approved for commercial sale and have not generated any revenue from product sales.
- Our business is entirely dependent on the successful development, regulatory approval and commercialization of AV-101, our only product candidate under development.
- We are conducting our first late-stage clinical trial of AV-101, a dry powder formulation of imatinib for the treatment of PAH administered using a dry powder inhaler, to assess its safety and tolerability. Although we believe that AV-101 has therapeutic potential for PAH based on oral imatinib's results in the Phase 3 IMPRES trial, we are utilizing a novel dry powder formulation which may not achieve better or similar levels of clinical activity or may have similar tolerability challenges as oral imatinib. The results of earlier studies and trials of oral imatinib in PAH patients and our Phase 1 clinical trial of AV-101 in healthy volunteers may not be predictive of future trial results for AV-101.
- If we encounter future difficulties with site activation and patient enrollment in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.
- We face, and will continue to face, significant competition and our failure to effectively compete may prevent us from achieving significant market penetration for AV-101, if approved. Most of our competitors have significantly greater resources than we do and we may not be able to successfully compete.
- We rely, and intend to continue to rely, on qualified third parties to supply all components of AV-101. As a result, we are dependent on several third parties, some of which are sole source suppliers, for the manufacture of AV-101 and our supply chain, and if we experience problems with any of these suppliers, or they fail to comply with applicable regulatory requirements or to supply sufficient quantities at acceptable quality levels or prices, or at all, it would materially and adversely affect our business.
- We rely, and intend to continue to rely, on third parties in the conduct of all of our clinical trials. If these third parties do not successfully carry out their contractual duties, fail to comply with applicable regulatory requirements or meet expected deadlines, we may be unable to obtain regulatory approval for AV-101.
- We have six issued U.S. patents and many pending patent applications with respect to AV-101. We can provide no assurance that any of our other current or future patent applications will result in issued patents. If we cannot protect our patent rights or our other proprietary rights, others may develop products similar or identical to ours, and we may not be able to compete effectively in our market or successfully commercialize any product candidates we may develop.
- We may be unable to obtain regulatory approval for AV-101 under applicable regulatory requirements. The denial or delay of any such approval would delay commercialization of AV-101 and adversely impact our potential to generate revenue, our business and our results of operations.
- AV-101 is a drug-device combination product, which may result in additional regulatory risks.

- We are currently conducting, and may in the future conduct clinical trials for AV-101 outside the United States, and the U.S. Food and Drug Administration, or FDA, European Medicines Agency, or EMA, and applicable foreign regulatory authorities may not accept data from such trials.

- We will need to increase the size of our organization, and we may experience difficulties in managing growth.

- We are highly dependent on our key personnel and anticipate hiring new key personnel. If we are not successful in attracting and retaining highly qualified personnel, our business may be materially and adversely affected.

- Unfavorable global economic or political conditions could adversely affect our business, financial condition or results of operations.

The material and other risks summarized above should be read together with the text of the full risk factors below and in the other information set forth in this Annual Report on Form 10-K, including our consolidated financial statements and the related notes, as well as in other documents that we file with the U.S. Securities and Exchange Commission, or the SEC. If any such material and other risks and uncertainties actually occur, our business, prospects, financial condition and results of operations could be materially and adversely affected. The risks summarized above or described in full under Item 1A of this Annual Report on Form 10-K are not the only risks that we face. Additional risks and uncertainties not currently known to us, or that we currently deem to be immaterial may also materially adversely affect our business, prospects, financial condition and results of operations.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains express or implied forward-looking statements that are based on our management's belief and assumptions and on information currently available to our management. Although we believe that the expectations reflected in these forward-looking statements are reasonable, these statements relate to future events or our future operational or 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 contained in this Annual Report on Form 10-K include, but are not limited to, statements about:

- the initiation, timing, progress, results and cost of our research and development program for AV-101 and our current and future clinical trials, including statements regarding the timing of initiation and completion of studies or trials and related preparatory work and the period during which the results of the trials will become available;
- our expectations regarding the potential market size and size of the potential patient populations for AV-101, if approved for commercial use;
- our clinical and regulatory development plans;
- our expectations with regard to the data to be derived from our ongoing global Phase 2b/Phase 3 clinical trial, or any other product candidates that we may identify or develop;
- the timing or likelihood of regulatory filings and approvals for AV-101;
- our ability to commercialize AV-101, if approved;
- the rate and degree of market acceptance of AV-101, including our expectations regarding prescriber interest in novel agents such as AV-101;
- the pricing and reimbursement of AV-101, if approved;
- the implementation of our business model and strategic plans for our business and AV-101;
- estimates of our future expenses, revenues, capital requirements and our needs for additional financing, and our ability to obtain additional capital;
- the scope of protection we are able to establish and maintain for intellectual property rights covering AV-101, including the projected terms of patent protection;
- regulatory developments in the United States and foreign countries;
- our ability to enter into strategic collaborations, including for the commercialization of AV-101 outside the United States;
- our ability to contract with third-party suppliers, manufacturers and contract research organizations, or CROs, and their ability to perform adequately;
- the success of competing therapies for PAH that are or may become available;
- developments relating to our competitors and our industry, including the impact of government regulation;
- our ability to attract and retain key scientific or management personnel;

- our ability to obtain additional funding for our operations, when needed, including funding necessary to complete further development and commercialization of AV-101, if approved;

- our financial performance; and

- other risks and uncertainties, including those listed under the section titled "Risk Factors."

In some cases, you can identify forward-looking statements by terminology such as "may," "should," "expects," "intends," "plans," "anticipates," "believes," "estimates," "predicts," "potential," "continue" or the negative of these terms or other comparable terminology. These statements are only predictions. You should not place undue reliance on forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, which are, in some cases, beyond our control and which could materially affect results. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed above under "Summary of the Material Risks Associated with Our Business" and under the section titled "Risk Factors" and elsewhere in this Annual Report on Form 10-K. If one or more of these risks or uncertainties occur, or if our underlying assumptions prove to be incorrect, actual events or results may vary significantly from those implied or projected by the forward-looking statements. No forward-looking statement is a guarantee of future performance. You should read this Annual Report on Form 10-K and the documents that we reference in this Annual Report on Form 10-K and have filed with the Securities and Exchange Commission, or the SEC, as exhibits hereto completely and with the understanding that our actual future results may be materially different from any future results expressed or implied by these forward-looking statements.

The forward-looking statements in this Annual Report on Form 10-K represent our views as of the date of this Annual Report on Form 10-K. 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 have no current intention of doing so 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 date of this Annual Report on Form 10-K.

This Annual Report on Form 10-K also contains estimates, projections and other information concerning our industry, our business and the markets for our product candidates. 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 that are assumed in this information. Unless otherwise expressly stated, we obtained this industry, business, market, and other data from our own internal estimates and research as well as 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. While we are not aware of any misstatements regarding any third-party information presented in this Annual Report on Form 10-K, their estimates, in particular as they relate to projections, involve numerous assumptions, are subject to risks and uncertainties and are subject to change based on various factors, including those discussed under the section titled "Risk Factors" and elsewhere in this Annual Report on Form 10-K.

PART I

Item 1. Business.

Unless the context requires otherwise, references in this Annual Report on Form 10-K to "Aerovate", "we", "us" and "our" refer to Aerovate Therapeutics, Inc.

Overview

We are a clinical-stage biopharmaceutical company focused on developing drugs that meaningfully improve the lives of patients with rare cardiopulmonary disease. Our initial focus is on advancing AV-101, our dry powder inhaled formulation of imatinib for the treatment of pulmonary arterial hypertension, or PAH, a devastating disease impacting approximately 70,000 people in the United States and Europe. Imatinib, marketed as Gleevec tablets, was originally developed for the treatment of multiple cancers. Oral imatinib also demonstrated statistically significant improvement on the primary endpoint, six-minute walk distance, and multiple secondary hemodynamic endpoints in PAH patients in an international Phase 3 trial conducted by Novartis but was poorly tolerated due to adverse events, or AEs, and never approved for the treatment of PAH. AV-101, delivered using a dry powder inhaler, is designed to provide lung concentrations at or above those observed with the oral dose while limiting systemic levels of the drug. We have completed a Phase 1 clinical trial in healthy volunteers and AV-101 was generally well-tolerated with no serious adverse events reported. In November 2023, we completed enrollment in the Phase 2b portion and enrolled the first patient in the Phase 3 portion of Inhaled iMatinib Pulmonary Arterial Hypertension Clinical Trial (IMPAHCT), our global Phase 2b/Phase 3 trial of AV-101 in adults with PAH. We have assembled a team with deep expertise in developing innovative PAH and inhaled therapies and commercializing novel drugs.

PAH is an orphan disease with unmet medical need and is characterized by high pressure in the vessels transporting blood from the right side of the heart to the lungs. This high pressure is caused by abnormal cellular hyperproliferation and resistance to apoptosis, driven by improper signaling in cells of the distal pulmonary arteries, which over time results in narrowing of the pulmonary vessels and forces the heart to work harder to pump blood through the lungs. The severe blood flow restriction and strain on the heart becomes increasingly severe over time and ultimately leads to heart failure that is often fatal. We estimate there are between 30,000-40,000 patients treated with approved PAH therapies in the U.S. alone, many of whom are on two or more approved PAH therapies. It is estimated that the combined global sales for PAH products in 2023 was $6.2 billion. Despite the availability of multiple approved therapies, PAH has a five-year survival rate for newly diagnosed and prevalent patients between 61% and 65%. None of the approved therapies directly address the abnormal cellular hyperproliferation of the pulmonary vasculature that causes the increased resistance to blood flow. We believe that novel treatments that primarily address abnormal cellular hyperproliferation may provide therapeutic benefit to PAH patients and lead to improved quality of life.

Our focus on developing AV-101 is driven by historical results from the Phase 3 IMPRES clinical trial of oral imatinib for the treatment of PAH patients. Oral imatinib is a well-characterized targeted kinase inhibitor and approved oncology treatment, but clinical trials also supported its potential for the treatment of PAH. The Phase 3 IMPRES trial was a placebo-controlled clinical trial of oral imatinib, conducted globally by Novartis, in 202 PAH patients whose disease was not adequately controlled by two or all three classes of approved PAH therapies. After 24 weeks of treatment with oral imatinib, patients achieved on average an increase of 32 meters ($p=0.002$) compared to placebo in the distance they could walk in six minutes, a measure known as the 6MWD. A key secondary endpoint in the IMPRES trial was pulmonary vascular resistance, or PVR, which is an objective measure of hemodynamic disease severity in PAH patients. After 24 weeks of treatment with oral imatinib, patients achieved an average PVR improvement (reduction) of 32% ($p<0.001$) compared to placebo with a significant increase in cardiac output ($p<0.001$). The magnitude of improvement in both 6MWD and PVR is notable because no approved PAH drug has shown such an improvement in a Phase 3 trial on top of at least two background therapies. However, treatment with oral imatinib was also associated with significant tolerability issues and adverse events, including nausea, edema, diarrhea and vomiting. Patients taking oral imatinib also experienced serious adverse events, the most frequent of which were anemia (7%), worsening of pulmonary hypertension (6%), dyspnea (6%), peripheral edema (6%), presyncope (5%), diarrhea (3%), device-related infection (3%), subdural hematoma (2%) and syncope (1%). Despite the clinical effects of oral imatinib 26% of patients on oral imatinib, compared to 7% on placebo, discontinued due to AEs by 24 weeks.

Our company was formed to develop an inhaled formulation of imatinib as a means of delivering therapeutically relevant drug concentrations to the lungs while minimizing systemic exposure, which we believe is the source of the observed intolerability of oral imatinib. We have brought together leaders both in the field of PAH drug development as well as in the area of inhaled drug formulation to invent AV-101, a drug/device combination designed to deliver imatinib directly to the lungs. We have completed a Phase 1 clinical trial of AV-101 in 82 healthy adults. Repeat inhaled doses of up to 90 mg were well-tolerated and resulted in systemic plasma levels that were below those observed with the 400 mg oral dose of imatinib (Gleevec) used in the IMPRES trial. According to pharmacokinetic models of lung exposure to imatinib as applied to our Phase 1 dose range, the predicted lung concentrations of imatinib delivered by AV-101 overlapped or surpassed those predicted from the 400 mg dose of oral imatinib in our Phase 1 clinical trial. There were no serious adverse events associated with AV-101. The most common adverse event was a transient cough primarily in the highest dose cohort, which was generally mild, and resolved within 30 minutes of dosing. There were no discontinuations due to cough. The intended Phase 2b dose range with AV-101 will only include doses that use 40% or less of the amount of dry powder that was inhaled at the highest Phase 1 dose and, based on the results of our Phase 1 clinical trial and our modeling, we expect lung concentrations of imatinib delivered by AV-101 in the 35 mg and 70 mg doses, both twice a day, or BID, selected for the Phase 2b portion of our Phase 2b/Phase 3 trial to overlap or surpass the lung concentrations predicted with the 400 mg oral dose in our Phase 1 clinical trial, which was the same target dose used in the Phase 3 IMPRES trial.

In November 2023, we announced completion of enrollment with 202 patients in the Phase 2b portion and enrollment of the first patient in the Phase 3 portion of IMPAHCT, our global double-blinded, placebo-controlled, randomized Phase 2b/Phase 3 trial of AV-101 in adults with PAH on top of standard of care. We are enrolling patients in the Phase 3 portion of this trial and will announce the approximate number of patients we plan to enroll in the Phase 3 portion of the trial based on the topline results of the Phase 2b portion of the trial. The Phase 2b portion of the trial is designed to assess safety, tolerability and inform dose selection for the Phase 3 portion using changes in PVR, an objective measure of the effect of AV-101 on hemodynamic function in PAH patients, as the primary endpoint. We will measure 6MWD as a secondary endpoint in the Phase 2b portion of this trial. We anticipate that topline data from the Phase 2b portion of this trial will be available in June 2024. In the Phase 3 portion of the trial improvement in 6MWD will be the primary endpoint. If the results of the Phase 3 trial show a statistically significant increase in 6MWD, we plan to submit a New Drug Application, or NDA, with the United States Food and Drug Administration, or FDA, and Marketing Authorisation Application, or MAA, with the European Commission for AV-101 for the treatment of PAH. These applications will leverage the existing safety data for Gleevec oral tablets allowing the company to save time and money. If AV-101 is approved, we believe it has the potential to become an important addition to existing therapies for PAH in both the United States and Europe.

We are pursuing a clinical development program utilizing established endpoints for development of previous PAH drugs, as well as enrollment criteria and dosing duration previously studied in oral imatinib PAH trials. At our April 14, 2021 end-of-Phase 1 meeting with the FDA, we received regulatory guidance that our clinical program could support an NDA submission; however, the process of clinical development is inherently uncertain and there can be no guarantee that we will obtain marketing approval. AV-101 has been granted orphan drug designation by the FDA and the EMA for the treatment of PAH. We own four issued U.S. patents and several U.S. and foreign patent applications for patent protection of the composition of the aerosol, drug product, manufacturing and methods of use. We retain worldwide commercial rights to AV-101.

Our Team

Our executive management team has extensive experience in the clinical development and the commercialization of orphan drug indications. Timothy P. Noyes, our Chief Executive Officer, was a senior executive at GelTex Pharmaceuticals, Inc., or GelTex, and Genzyme Corporation, or Genzyme, where he headed all launch planning and the commercialization of Renagel, a treatment for hemodialysis patients that resulted in Genzyme's acquisition of GelTex for more than $1 billion. Benjamin T. Dake, Ph.D., our Founder, President, Chief Operating Officer and Secretary, a cancer biologist, investor and entrepreneur, recognized the potential benefits of developing a lung-targeted imatinib and secured multiple rounds of funding to build the team at Aerovate with experts like Ralph Niven, Ph.D., our Chief Scientific Officer, who has over 30 years of expertise in translational medicine and inhalation dosage forms, and Hunter Gillies, M.B.Ch.B., our Chief Medical Officer, who has led Phase 2 and Phase 3 PAH trials at Pfizer Inc., or Pfizer, and Gilead Sciences, Inc., or Gilead, and has designed and executed PAH trials with several smaller biotechnology companies. George A. Eldridge, our Chief Financial Officer, has served as CFO for several biotechnology companies, leading four of these companies to the public

markets. Marinus Verwijs, our Chief Technical Officer, has over 15 years of product development and manufacturing experience. He has worked on multiple commercial products, leading them from clinical product development to NDA filing and commercial launch. Timothy Pigot, our Chief Commercial Officer, has over 25 years of industry experience working to launch and commercialize a range of products over multiple therapeutic areas. Mr. Pigot gained significant experience in PAH during his 12 years at Gilead and 11 years at Pfizer, where his responsibilities included the launches of Revatio and Letairis for the treatment of PAH. Donna Dea, our Head of Regulatory Affairs, has over 30 years of global regulatory experience designing and implementing regulatory strategies resulting in the approval of treatments for asthma, COPD, rhinitis and others, for which several of these drugs involved inhaled formulations.

Our Strengths

We believe that our company and AV-101 possess the following attributes that may potentially increase the likelihood that we will be successful in developing and commercializing AV-101:

- **Significant efficacy for oral imatinib**. In the global Phase 3 IMPRES trial, oral imatinib demonstrated statistically and clinically significant efficacy following 24 weeks of treatment on top of PAH standard of care. These results were notable for achieving statistically significant improvements in the study's primary efficacy endpoint, 6MWD, and a key secondary endpoint, PVR, but also for hitting statistical significance on other clinically relevant efficacy endpoints on top of standard of care, which included at least two background PAH therapies. The primary endpoint of the Phase 2b portion of our Phase 2b/Phase 3 trial is the change in PVR following 24 weeks of treatment. The primary endpoint of the Phase 3 portion of our Phase 2b/Phase 3 trial is the change in 6MWD following 24 weeks of treatment. Our Phase 2b/Phase 3 trial is designed to treat a similar patient population to the IMPRES trial, patients in WHO Functional Classes II-IV on top of standard of care background PAH therapies.

- **Distinct PAH treatment mechanism**. Unlike approved treatments for PAH, which act primarily through vasodilation (prostacyclin pathway, endothelin pathway, and nitric oxide pathway agents), AV-101 is designed to directly address the abnormal cellular hyperproliferation in the pulmonary vasculature that causes the increased resistance to blood flow and heart failure. We believe AV-101's mechanism uniquely positions our product candidate, if approved, for combination therapy with existing vasodilator treatments.

- **Adaptive development path**. We have designed an innovative global Phase 2b/Phase 3 clinical trial based on an adaptive design that could lead to a potential NDA filing. Our development plan also benefits from our ability to leverage prior toxicology work done with oral imatinib.

- **Improved tolerability based on route of administration**. Our inhaled administration is designed to minimize systemic exposure and limit the safety and tolerability concerns observed in the IMPRES trial of oral imatinib in PAH. Our Phase 1 clinical trial results in healthy volunteers demonstrated that plasma levels of imatinib were significantly lower than those observed with the 400 mg oral dose of imatinib used in the IMPRES trial.

- **Expected comparability of concentrations of drug delivered**. Based on the results of our Phase 1 clinical trial and our modeling, we expect lung concentrations of imatinib delivered by AV-101 in the 35 mg and 70 mg doses, both BID, selected for the Phase 2b portion of our Phase 2b/Phase 3 trial to overlap or surpass the lung concentrations predicted with the 400 mg oral dose in our Phase 1 clinical trial, which was the same target dose used in the Phase 3 IMPRES trial.

- **Powerful barriers to entry**. We have generated strong intellectual property claims and other barriers to entry. We own four issued U.S. patent and several U.S. and foreign patent applications to protect our proprietary imatinib formulation, our drug product and methods of use. In addition, we have obtained exclusive access to a commercially available dry powder delivery device which we believe will create a substantial competitive advantage.

- **Substantial and readily addressable market opportunity.** If AV-101 is approved, we believe there is a substantial medical need and market opportunity for combining AV-101 with existing standard of care, which is often two or three background agents. Beyond this base case, we also believe that AV-101, if approved, could benefit a larger group of PAH patients with earlier-stage disease such as those patients receiving only one other PAH therapy.

- **Strong leadership in PAH**. Our executive management team has extensive experience in the clinical development of treatments for PAH, including Dr. Gillies who has been developing drugs for PAH for more than 20 years and recently ran the AMBITION trial that established the current first-line PAH combination therapy and Dr. Niven's experience in manufacturing and development for inhaled small molecules. In addition, our Clinical Advisory Board includes several of the premier thought leaders in PAH who have extensive experience developing drugs and caring for patients suffering from PAH.

Our Strategy

Our strategy is to develop and commercialize AV-101 for patients suffering from PAH. Key elements of our strategy include our plans to:

- **Complete regulatory discussions for AV-101 in the United States and Europe**. At our April 14, 2021 end-of-Phase 1 meeting with the FDA, we received regulatory guidance that our Phase 2b/Phase 3 trial, if successful, could support a NDA submission using the change in 6MWD compared to placebo as the primary endpoint in the Phase 3 portion of the trial; however, the process of clinical development is inherently uncertain and there can be no guarantee that we will obtain marketing approval even if we successfully achieve our primary endpoint. We have been granted orphan designation for the treatment of PAH from the FDA and from the European Commission in the European Union. We completed the formal process of seeking scientific advice and regulatory guidance from the European Medicines Agency, or EMA, regarding its requirements for regulatory approval and we believe that, if successful, our existing clinical program could support an MAA submission for regulatory approval in Europe.

- **Advance AV-101 through NDA submission**. In November 2023, we announced completion of enrollment in the Phase 2b portion and enrollment of the first patient in the Phase 3 portion of IMPAHCT, our Phase 2b/Phase 3 trial of AV-101 in adults with PAH on top of standard of care PAH therapies. The Phase 2b portion of this trial will be a dose-ranging trial in which PVR will be the primary endpoint and we anticipate that topline data from the Phase 2b portion will be available in June 2024. The Phase 3 portion of the trial will be based on the optimal dose selected in the Phase 2b portion and 6MWD will be the primary endpoint.

- **Commercialize AV-101 directly in the United States**. If AV-101 is approved by the FDA, we intend to commercialize it ourselves in the United States with a specialty sales force focused primarily on pulmonologists and cardiologists treating adult patients suffering from PAH. We will consider entering into collaborations for the development and commercialization of AV-101 in Europe, Asia or other geographic regions, if approved by foreign regulatory authorities.

- **Pursue additional indications for AV-101**. We believe that AV-101 could have clinical applications in other groups of PAH patients, such as those with earlier-stage disease who may be receiving only one other PAH therapy. We also may consider the potential use of AV-101 in other types of pulmonary vascular disease.

- **Expand our pipeline by accessing additional product opportunities**. We plan to search for additional product opportunities available for license or acquisition that could be supported by the commercial infrastructure we build to successfully launch AV-101 in the United States if it is approved for marketing.

PAH Background and Limitations of Current Treatments

PAH is a progressive, life-threatening orphan disease characterized by increased pressure in the pulmonary arteries, vessels responsible for carrying deoxygenated blood from the heart to the lungs. This increased pressure is caused by narrowing of these blood vessels as a result of dysregulation of cells of the arterial wall, leading to excessive growth and proliferation. Over time, blood flow worsens as inflammatory cells are recruited and inflammatory cytokines further stimulate the proliferation of blood vessel cells. This ultimately leads to tissue scarring, fibrosis and blood vessel remodeling, resulting in severe restriction of blood flow (as illustrated in the figure below) and increased risk of developing blood clots and heart failure.

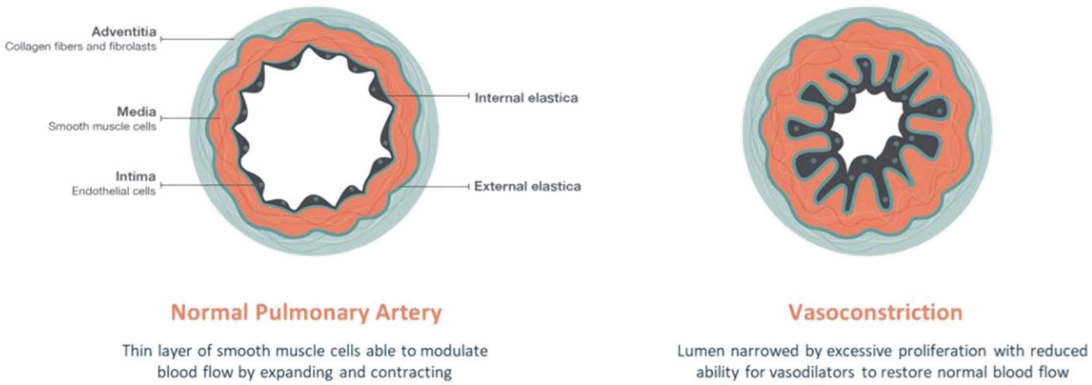

Figure 1. Increased pulmonary resistance is caused by cell proliferation that obstructs blood flow.

This severe restriction of blood flow also causes the heart to work harder to circulate blood through the lungs causing abnormal strain on the right ventricle of the heart resulting in PAH symptoms that worsen over time; these commonly include breathlessness, fatigue, chest pain, fainting or light headedness, as well as abdominal distension. Four PAH functional classes categorize patient symptom severity and ability to carry out physical activity. Higher numbered functional classes indicate worsening symptoms and are associated with higher mortality. The four functional classes established by the World Health Organization, or WHO, are detailed in the figure below.

FIGURE 2. WHO PAH FUNCTIONAL CLASSES

FUNCTIONAL CLASS	DESCRIPTION
I	No limitation of physical activity, and ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.
II	Slight limitation of physical activity, but patients are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
III	Marked limitation of physical activity, but patients are still comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.
IV	Patients are unable to carry out any physical activity without symptoms, and discomfort is increased by any physical activity. Signs of right heart failure manifest, and dyspnea and/or fatigue may even be present at rest.

Prevalence of PAH and Unmet Need

Based on third-party estimates, the number of PAH patients diagnosed is between 30,000 and 40,000 in the United States with an average age at diagnosis of 53 years old and 65% to 80% of those diagnosed being women. The exact prevalence of PAH worldwide is not known but it has been estimated to be between 10 to 52 cases per million. Many drugs have been developed and made commercially available for the treatment of PAH, such as vasodilators, and it is estimated that the combined global sales for PAH products in 2023 was $6.2 billion. While advances in the treatment of PAH using vasodilatory agents over the last two decades have markedly improved survival, PAH patients still face significant disease burden and premature death. The five-year survival rate for newly diagnosed and prevalent patients is between 61% and 65%. Clearly there is unmet need for new therapies beyond the standard of care.

Limitations of Current Therapies for PAH

The current standard of care in PAH consists of drugs that act primarily as pulmonary vasodilators, which relax the muscles in the pulmonary arterial walls, thereby reducing the degree of blood vessel constriction. Although the current standard of care provides some benefit to patients, it is clear from the pathology of PAH that abnormal cellular hyperproliferation causes progressive narrowing of the pulmonary vasculature. This abnormal hyperproliferation is not addressed by therapies currently used to treat PAH.

Three classes of pulmonary vasodilators are currently used to treat PAH: endothelin receptor antagonists, nitric oxide pathway modulators and prostacyclins.

- **Endothelin Receptor Antagonists**. Some treatments currently approved for PAH work by blocking the action of endothelin-1, a potent vasoconstrictor, and are referred to as endothelin receptor antagonists, or ERAs. These drugs include bosentan, macitentan and ambrisentan. All three of these drugs are orally administered and improve blood flow to the lungs as determined by measures of hemodynamics such as pulmonary vascular resistance and cardiac output, which translates to improvements in exercisability as measured by the distance that patients can walk in a fixed period of time (6MWD).

- **Nitric oxide pathway modulators such as PDE5 inhibitors and sGC's**. Nitric oxide is a naturally occurring molecule that is widely recognized as important in a number of biological processes. It causes blood vessels to relax and widen via the second messenger cGMP, resulting in an increase in blood flow. Two common modalities utilize the nitric oxide pathway to result in vasodilation: Phosphodiesterase type 5, or PDE5, inhibitors prevent the breakdown of cGMP and soluble guanylate cyclase stimulators, or sGC's, increase the production of cGMP independent of nitric oxide. Several oral PDE5 drugs are available, such as sildenafil and tadalafil. Additionally, riociguat is the only sGC approved for PAH.

- **Prostacyclin pathway modulators**. Patients with PAH have been shown to have reduced levels of prostacyclin, a naturally occurring lipid that has the effect of relaxing the smooth muscles surrounding arteries, resulting in vasodilation. Prostacyclin analogues, such as iloprost, epoprostenol, and treprostinil, are approved therapies for PAH. Selexipag is an oral prostacyclin-like drug approved for PAH. In addition to the challenges associated with dosing, prostacyclin therapy can be difficult to tolerate. In clinical trials subcutaneous infusion of these agents has shown severe infusion site adverse events requiring narcotics for these symptoms. The oral prostacyclins also have a high incidence of headache and diarrhea, nausea, vomiting, and flushing, which can lead to discontinuations.

PAH patients are often treated with more than one of these drugs and new therapies are typically added to existing therapies rather than replacing drugs that are providing insufficient benefit. Based on both primary research and third party sources, we estimate that a majority of patients are taking two or three FDA approved drugs for the treatment of PAH. Oral therapies are commonly prescribed first-line, typically consisting of an ERA and PDE5 inhibitor. As patients progress in their disease severity, a prostacyclin can typically be added as a third agent. Although these therapies have been shown to improve exercise capacity, quality of life, pulmonary pressure and short-term survival, none of the current treatments are curative

and patients remain on life-long therapy. Despite the availability of multiple agents within each treatment pathway and efforts to treat PAH more aggressively, the long term prognosis for patients with PAH remains poor.

Antiproliferative Medicines as a Novel Approach to Treating PAH

Sotatercept is poised to be the first approved PAH therapy directly targeting the underlying cell proliferation that leads to increased pulmonary arterial pressure, although the concept behind targeting cell proliferation to treat PAH is not new. Sotatercept is a molecule that blocks signaling of members of the TGF-beta family of growth factors. Results from a Phase 3 clinical trial in PAH showed that in patients taking one, two or three standard PAH therapies, sotatercept led to a statistically significant improvement in 6MWD with a safety profile reported to be generally consistent with what was observed with sotatercept in the previous Phase 2 study, providing further support for the therapeutic potential of antiproliferative product candidates in PAH. We are encouraged by these results as they provide independent confirmation of the importance of antiproliferative products as a potentially broad class of PAH therapeutics to complement vasodilators. Despite the significant improvement with sotatercept therapy in multiple efficacy endpoints, it is notable that ~60% of patients did not meet the prespecified multi-component criteria for improvement, ~60% of patients did not achieve "low risk status" on the simplified French risk model and 70% of patients did not improve in New York Heart Association Functional Class status demonstrating the continued significant unmet need in PAH. Similar to the vasodilator field, we believe that PAH patients may benefit from treatment with multiple antiproliferative therapies directed against different targets.

PAH Prescriber Interest in Novel Agents

We conducted primary market research with approximately 150 PAH treating physicians to assess the demand for novel agents for the treatment of PAH. Respondents were presented on a blinded basis with three hypothetical novel agents with efficacy and safety profiles reflective of results seen in PAH clinical trials associated with actual novel agents currently being studied and/or under regulatory review. The majority of prescribers indicated a likelihood to utilize a therapeutic agent with characteristics similar to those of AV-101.

Our Approach, AV-101

We are developing AV-101 as a drug-device combination product that delivers imatinib directly to the lungs via inhalation. The product consists of capsules of particulate imatinib that will be used in conjunction with a dry powder inhaler device. We believe that delivery of imatinib directly to the lungs will maximize the amount of drug in the targeted tissues while minimizing systemic exposure. Furthermore, we believe that delivering imatinib in this way may improve the tolerability of treatment while maintaining imatinib's known effects on exercise capacity and hemodynamics. AV-101 has been granted orphan drug designation by the FDA and the European Commission for the treatment of PAH.

Potential of Imatinib to Treat PAH

The molecule in AV-101, imatinib, has demonstrated improvement on the primary and multiple secondary endpoints in a global Phase 3 trial (IMPRES) conducted by Novartis in PAH patients on top of at least two standard of care PAH drugs. However, when administered orally, serious adverse events, and discontinuations were high and the oral version was never approved for PAH. We believe imatinib is unique amongst tyrosine kinase inhibitors for its specificity and potency. At pharmacologically achievable levels, it inhibits only a handful of kinases, such as PDGFR, KIT, DDR and ABL, which have been implicated in PAH disease processes. Other tyrosine kinase inhibitors that target the same binding pocket are more promiscuous. Recent academic focus on kinase inhibition in PAH has been on PDGFR. However, other kinase inhibitors that hit PDGFR also inhibit the closely related SRC and VEGFR kinases. These drugs have been shown to induce or exacerbate PAH. Thus, we believe clinical success with kinase inhibition in PAH is not dictated by inhibiting PDGFR alone, but rather by the overall kinase inhibition profile. We are encouraged that imatinib, the molecule in AV-101, has shown clinical effects in the IMPRES trial, and we believe inhaled delivery of AV-101 limits systemic exposure and may mitigate the tolerability issues observed with oral imatinib.

Kinase inhibitors have been approved for the treatment of various cancers. Case reports of improvements in PAH in patients receiving oral imatinib, marketed as Gleevec by Novartis, led to several clinical trials designed to test the efficacy

of imatinib for PAH. The IMPRES trial was a randomized, double-blind global Phase 3 trial conducted by Novartis that enrolled 202 PAH patients. Most of these patients had Functional Class II or Class III PAH and were already on at least two background therapies. Patients were randomized to receive oral imatinib or placebo for 24 weeks.

Patients enrolled in the IMPRES trial had reduced exercise capacity compared to healthy adults as measured by the six-minute walk distance, or 6MWD, a simple test that has been used as a primary endpoint for the approval of multiple drugs to treat PAH. The mean baseline 6MWD for patients in this trial was 361 meters, whereas for healthy adults it has been reported to be approximately 600 meters The baseline 6MWD values in these patients upon enrollment was below normal for healthy adults despite the fact that they were all on treatment with at least two PAH therapies and 41% were on triple therapy, the maximal standard of care for PAH. Patients remained on their respective pre-trial PAH therapies throughout the trial.

The target dose of oral imatinib in the IMPRES trial was 400 mg/day which is an approved dose of oral imatinib for the treatment of cancers such as chronic myelogenous leukemia, or CML, and metastatic malignant gastrointestinal stromal tumors, or GIST, containing specific genetic alterations. Treatment of PAH patients with 400 mg oral imatinib led to a significant improvement in 6MWD over baseline compared to placebo. This difference was significant at 12 weeks with significance observed at all consecutive timepoints through the end of the trial at 24 weeks, at which point the oral imatinib-treated patients achieved an average improvement of 32 meters vs placebo in the 6MWD (p=0.002). The magnitude of this improvement is notable because no approved PAH drug has shown such an improvement in a Phase 3 trial on top of at least two background therapies. The most recently approved oral PAH drug in the U.S., Uptravi (Selexipag), showed a 12-meter treatment effect in the Phase 3 GRIPHON trial. The patients in this trial were not as heavily treated as those in the IMPRES trial, with one third on double therapy and none on triple therapy. The figure below shows the improvement over time in 6MWD of PAH patients treated with oral imatinib on at least two standard of care therapies as compared to the placebo group in the Phase 3 IMPRES trial.

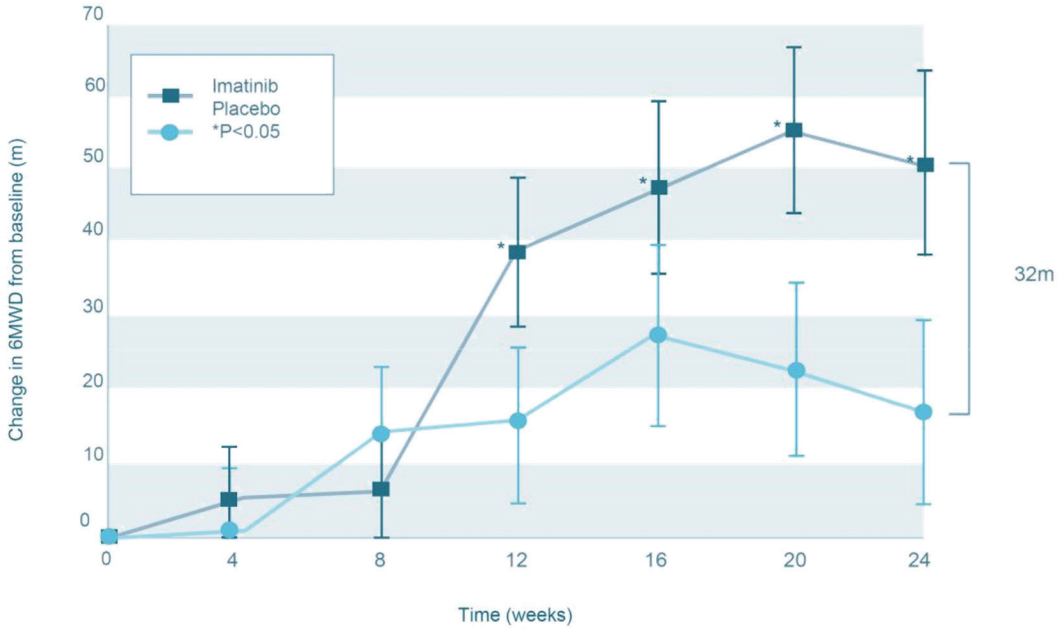

Figure 3. Imatinib led to a significant increase in 6MWD on top of at least two standard of care therapies

The improvement in 6MWD with oral imatinib treatment was observed across all patient subgroups regardless of treatment with other PAH therapies (as seen in the figure below). We believe this observation suggests that oral imatinib improved 6MWD through a mechanism that was independent of patients' background therapies.

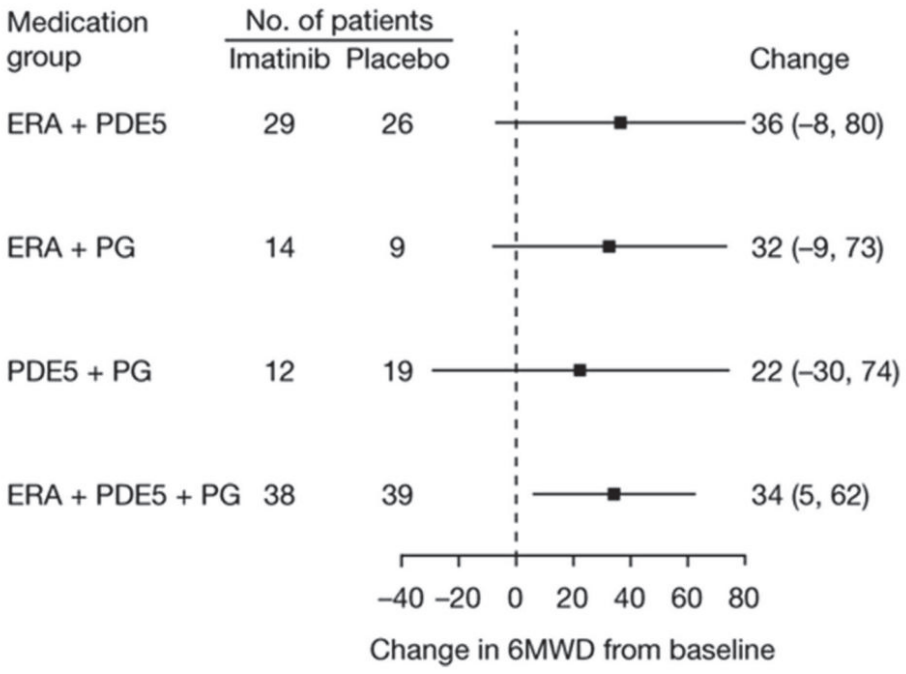

Figure 4. Imatinib led to improvements in 6MWD compared to placebo regardless of patients being treated concurrently with at least two approved PAH therapies

In addition to improvements in 6MWD, patients treated with imatinib had greater improvements in multiple secondary endpoints, including measures of hemodynamics. Importantly, there was a significant improvement at 24 weeks in PVR ($p<0.001$), a measure of how difficult it is for blood to circulate through the lungs. Damaged pulmonary blood vessels make it more difficult for the heart to pump blood through the lungs, leading to increased pulmonary arterial pressure, increased workload on the heart, and if not resolved, heart failure. PVR is frequently used as a quantitative measure in PAH Phase 2 trials to determine the appropriate dose for registrational Phase 3 trials that directly measure changes in patient exercise capacity, such as 6MWD. Patients treated with imatinib had a significant reduction in PVR at 24 weeks, as noted in the blue box in the figure below. PVR was virtually unchanged compared to baseline in placebo treated patients. Consistent with the improvements in PVR, significant improvements compared to placebo treated patients, as shown in the figure below, were also observed in mean pulmonary artery pressure, or mPAP, which was decreased by 5.2 mm Hg; cardiac output, or CO, which was increased by 0.88 liter/min; and right arterial pressure, or RAP, which was decreased by 1.7 mm Hg. An echocardiography sub-study of 74 IMPRES patients showed that patients randomized to oral imatinib showed significant improvements in certain measures of right ventricle function after 24 weeks compared with placebo.

Significant and consistent changes across hemodynamic and echo measures suggest a benefit of imatinib for the treatment of PAH with the potential to result in long-term improvements in pulmonary and cardiac function.

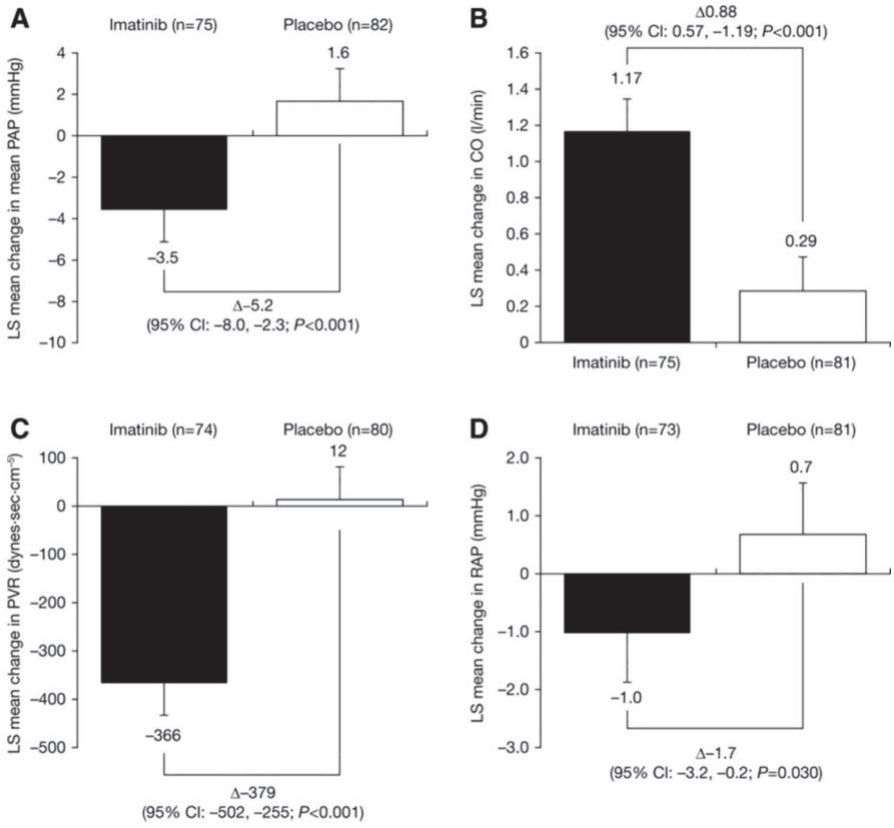

Figure 5. Imatinib treatment led to significant improvements across multiple secondary endpoints including PVR (highlighted), an endpoint frequently used in Phase 2 dose-finding trials (Patients included in analyses of hemodynamic parameters include those who completed the study plus those who discontinued early but had a right heart catheterization performed at discontinuation.)

Long-Term Extension Study

Patients who completed the 24 week trial were eligible to be enrolled in an open label long-term extension study. The improvements in 6MWD achieved at 24 weeks were sustained during this extension and the mean difference in 6MWD compared to baseline improved up to 144 weeks in patients that were able to tolerate the treatment. Although these results were very encouraging, data from the extension trial also highlighted the major limitation in using oral imatinib to treat PAH, which was drug tolerability. Of the 103 patients originally randomized to the imatinib arm of the core trial, only 21 remained on therapy after 180 weeks of dosing. The patients who were able to tolerate the drug long term showed a durable continued improvement in 6MWD.

Safety and Tolerability

The relatively poor tolerability of oral imatinib poses challenges for the potential use in PAH patients. The AEs observed in the IMPRES trial were consistent with the AE profile observed in cancer trials, with the exception of subdural hematoma, and led to a significant number of discontinuations, which limited oral imatinib's potential as a therapy for PAH. Specifically, 44% of patients treated with oral imatinib in the IMPRES trial experienced fluid retention, which is of

particular concern in PAH patients who suffer from heart failure. The figure below lists the AEs reported in the 24-week Phase 3 IMPRES trial of oral imatinib in PAH patients on two or more standard-of-care therapies.

	Imatinib n=103 (%)	Placebo n=98 (%)
Adverse Event	100 (97)	94 (96)
Nausea	57 (55)	23 (24)
Peripheral edema	45 (44)	20 (20)
Diarrhea	36 (35)	19 (19)
Vomiting	31 (30)	10 (10)
Periorbital edema	30 (29)	7 (7)
Headache	25 (24)	22 (22)
Dyspnea	19 (18)	13 (13)
Nasopharyngitis	18 (18)	19 (19)
Hypokalemia	16 (16)	3 (3)
Anemia	14 (14)	3 (3)
Cough	11 (11)	15 (15)
Fatigue	11 (11)	7 (7)
Face edema	10 (10)	1 (1)
Muscle spasms	10 (10)	2 (2)

Figure 6. Adverse events reported in >10% of the Imatinib group in the 24-week IMPRES trial, not including the trial extension

In the IMPRES trial, there were 45 serious adverse events reported in imatinib treated patients, including some that were of particular concern for PAH patients, who already have compromised cardiac function. These included worsening of PAH; anemia; dyspnea, or shortness of breath; peripheral edema; and presyncope, or lightheadedness. Of note, subdural

hematoma occurred in eight patients (two in the core study (1.9%), six in the trial extension (4.2%)) receiving imatinib and anticoagulation.

	Imatinib n=103 (%)	Placebo n=98 (%)
Serious Adverse Event	45 (44)	29 (30)
Worsening of pulmonary hypertension	6 (6)	8 (8)
Anemia	7 (7)	1 (1)
Dyspnea	6 (6)	2 (2)
Peripheral edema	6 (6)	0
Presyncope	5 (5)	0
Diarrhea	3 (3)	2 (2)
Device-related infection	3 (3)	0
Syncope	1 (1)	5 (5)
Subdural hematoma *	2 (2)	0

Figure 7. Serious adverse events reported in the IMPRES 24-week trial publication, not including the trial extension

Patients enrolled in the IMPRES trial that were not able to tolerate 400 mg/day of imatinib did not see a significant improvement in 6MWD after 24 weeks. As shown in the figure below, those patients who were not dosed with 400 mg/day for more than half of the time did not achieve the improvements in 6MWD that were significantly distinguished from those achieved by placebo treated patients. These results suggest that addressing the adverse events and tolerability of imatinib in PAH patients cannot be achieved by lowering the oral dose without sacrificing this improvement. Further development of oral imatinib for the treatment of PAH was discontinued by Novartis.

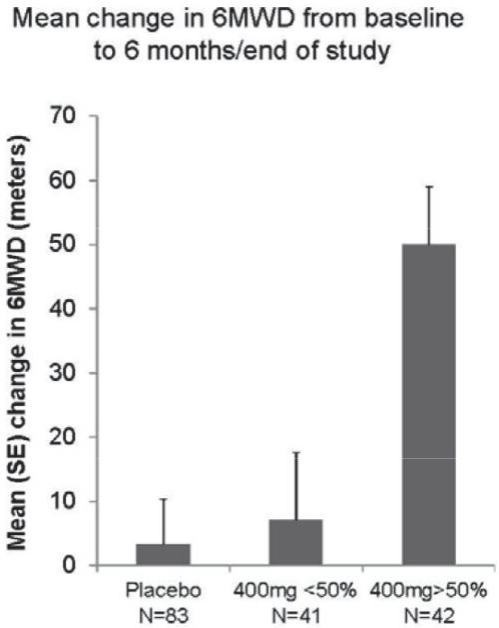

Figure 8. Patients who were dosed with 400 mg/day for less than half of the duration of the trial did not achieve a significant improvement in 6MWD

AV-101, an inhaled formulation of imatinib

AV-101 is designed to deliver imatinib directly to the lungs to maximize the amount of drug in the targeted tissues while minimizing systemic exposure. We believe that delivering imatinib in this way may maintain imatinib's potential therapeutic benefits while improving the tolerability of treatment. The oral version of imatinib, marketed as Gleevec, is delivered as tablets containing imatinib mesylate which is a salt of imatinib. Imatinib mesylate is not readily amenable to being used in an inhaled formulation because it absorbs water from the atmosphere if not stored in a rigorously controlled environment. Moisture uptake would lead to potential stability concerns and a high likelihood of poor delivery performance when inhaled from any dry powder inhaler device. We also believe mesylate salt would be a poor choice for an inhaled PAH therapy for additional reasons: (i) the mesylate group introduces a genotoxic risk; (ii) it increases the formulation risk due to the existence of multiple crystal forms; and (iii) delivery using the mesylate salt has the potential to release the acidic mesylate upon deposition on the lung surface which could lead to transient irritation and increase the propensity for cough. We therefore explored other salt and polymorphs of imatinib to identify a more suitable formulation for an inhaled therapy without altering the active molecule. We discovered a form that exhibited what we believe to be almost ideal physical chemical properties for development as a dry powder for inhalation using capsules in a simple dry powder inhaler, or DPI.

We also believe that dry powder inhalation is the most convenient mode of delivery to the lungs for patients. The prospective advantages of dry powder inhalation include that such formulations (i) can be delivered via a convenient, portable and easy-to-use delivery system; (ii) avoid the cords or batteries or bulky equipment that may be needed with nebulizers; (iii) carry less risk of microbial contamination due to the low moisture content powder; (iv) have better anticipated shelf stability of the drug product compared to a solution dosage form; and (v) can potentially improve lung retention of the powder imatinib compared to an aqueous nebulizer formulation, which may result in reduced dose, dose frequency and peak exposure in the circulation.

AV-101 Phase 1 Clinical Trial

We have completed a placebo-controlled, randomized, double-blinded, single ascending dose and multiple ascending dose Phase 1 clinical trial of AV-101 in 82 healthy adult volunteers. Doses tested in the single ascending dose, or SAD, portion ranged from 1 to 90 mg of AV-101. A 400 mg dose of oral imatinib was included as a comparator. The multiple ascending dose, or MAD, portion tested 10 mg, 30 mg and 90 mg BID (*bis in die*; or twice a day) for seven days. The purpose of the trial was to establish safety and tolerability of AV-101 and to demonstrate that systemic levels of AV-101 were lower than oral imatinib.

All doses resulted in lower systemic plasma levels of imatinib compared to those observed following a single 400 mg oral dose. In the figure below, the blue dashed line shows simulated steady state levels of oral imatinib in the blood extrapolated from the 400 mg cohort in the SAD potion of our Phase 1 clinical trial. These levels are consistent with multiple publications on oral imatinib pharmacokinetics. The other lines show the blood concentrations following the final dose of AV-101 in the MAD portion of our Phase 1 clinical trial, on day 7, when steady state concentrations had been achieved.

The dotted part of the 90 mg dose shows a simulated representation of an additional dose twelve hours later to illustrate steady state BID dosing.

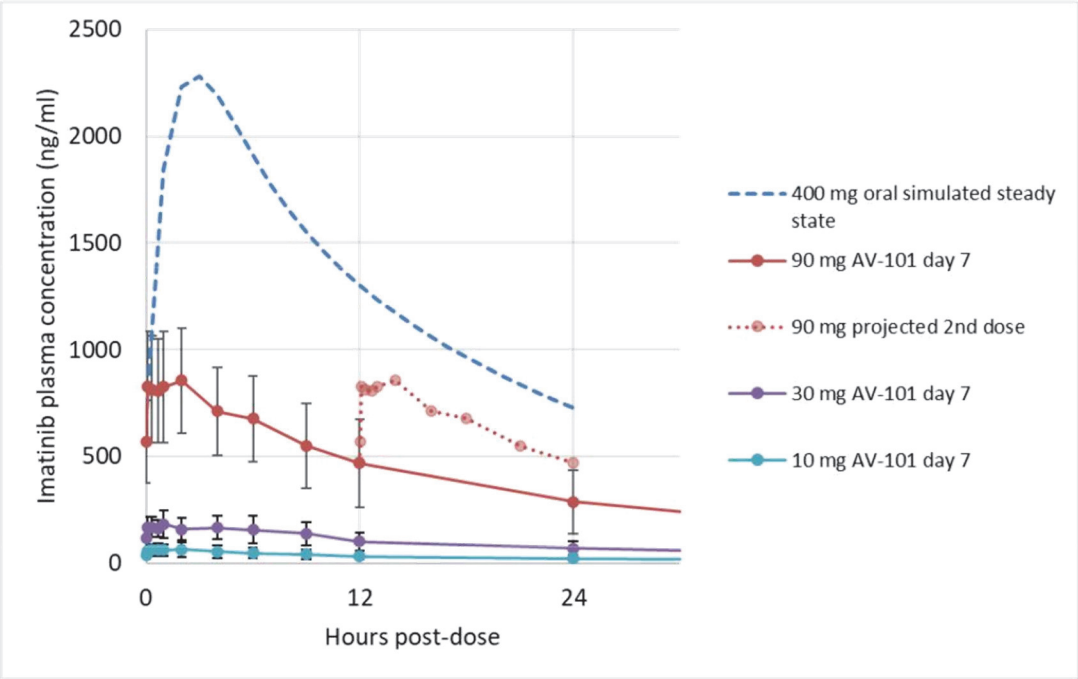

Figure 9. Phase 1 systemic exposure of AV-101 vs 400 mg oral imatinib.

We also predicted lung exposures using a physiologically based pharmacokinetic, or PBPK, model built from a published method to extrapolate lung exposures from blood levels, which was informed by our Phase 1 plasma data. Although there is inherent uncertainty associated with all models that extrapolate data, we expect the exposures of imatinib obtained in the lungs at the dose range we intend to use in the Phase 2b portion of our Phase 2b/Phase 3 trial of 35 mg and 70 mg, all BID, to overlap or surpass lung levels predicted from 400 mg oral imatinib. The dashed blue line in Figure 11 shows lung

exposures extrapolated from published steady state PK data and informed by our Phase 1 plasma data for oral imatinib at 400 mg. The solid lines show extrapolated lung levels of AV-101 doses using our PBPK model.

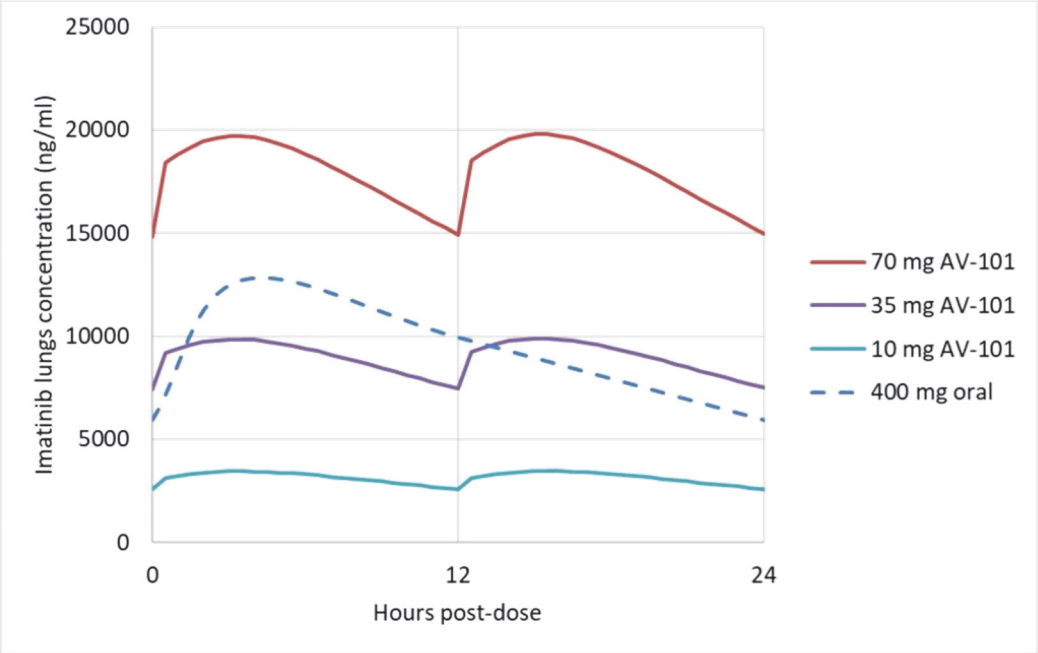

Figure 10. Predicted Phase 2b lung exposures from dosing of 10, 35 and 70 mg AV-101. We expect the lung exposures of imatinib delivered by AV-101 in the dose range to overlap or surpass the predicted lung exposures from 400 mg oral imatinib

Safety and Tolerability in Phase 1 Clinical Trial

There were no serious adverse events reported in our Phase 1 clinical trial. Adverse events reported in the Phase 1 clinical trial were classified as mild or moderate. There were no changes in vital signs including pulmonary function testing and oxygen saturations. Of the less severe adverse events, there was one discontinuation at the highest dose due to vomiting and the most frequent adverse event was a cough that was reported in 55% of volunteers at the highest 90 mg dose. This cough was transient, predominantly mild in nature, resolved on its own within 30 minutes and did not lead to any discontinuations. We believe that the cough may be a function of the total amount of powder delivered in the high Phase 1 dose. The intended dosing for the Phase 2b/Phase 3 trial will use less than 40% of the amount of powder that was inhaled

at the highest Phase 1 dose. The figure below shows the adverse events reported in our Phase 1 MAD trial of AV-101 in healthy volunteers.

Adverse Event n(%)	10 mg (n=8)	30 mg (n=9)	90 mg (n=9)
Cough	1 (13)	1 (11)	5 (56)
Persistent cough	-	-	-
Headache	-	-	4 (44)
Nausea	-	-	2 (22)
Chest discomfort	-	-	2 (22)
Throat irritation	-	1 (11)	1 (11)
Musculoskeletal pain	-	-	2 (22)

Single incidence AEs: Vomiting (discontinued), Dysgeusia, Musculoskeletal chest pain, Nasal congestion, Oropharyngeal pain, Back pain, Abdominal pain, COVID-19, Presyncope, Alanine aminotransferase increased

Figure 11. Adverse events reported in the Phase 1 MAD trial of AV-101 in healthy volunteers

We submitted to the FDA summaries of the safety and tolerability findings from our Phase 1 clinical trial along with the systemic plasma levels for the participants from the trial. We also submitted information on our drug substance and drug product. At our April 2021 meeting, we reached alignment with the FDA that our Phase 2b/Phase 3 trial design was acceptable and could, if successful with strong results, support a NDA submission using the change in 6MWD compared to placebo over 24 weeks as the primary endpoint in the Phase 3 portion of our trial.

AV-101 Phase 2b/Phase 3 IMPAHCT: Inhaled iMatinib Pulmonary Arterial Hypertension Clinical Trial

In December 2021, we announced the initiation of IMPAHCT, our global Phase 2b/Phase 3 trial in adults with Functional Class II through Class IV PAH with inadequate disease control on top of standard of care PAH therapies. In November 2023, we announced completion of enrollment with 202 patients in the Phase 2b portion and enrollment of the first patient in the Phase 3 portion of IMPAHCT. We are enrolling patients in the Phase 3 portion of this trial and will announce the approximate number of patients we plan to enroll in the Phase 3 portion of the trial based on the topline results of the Phase 2b portion of the trial. We anticipate that topline data from the Phase 2b portion of this trial will be available in June 2024. This clinical trial will establish the target dose in the Phase 2b portion then continue into a Phase 3 efficacy trial using the selected dose. The Phase 2b portion of this double-blind, placebo-controlled randomized trial is designed to assess safety and tolerability using change in PVR, an objective measure of the effect of AV-101 on hemodynamic function in PAH patients, as the primary endpoint to inform the selection of the appropriate dose for the Phase 3 portion of the trial. Change in 6MWD compared to placebo will be a secondary endpoint, and all efficacy endpoints will be measured following 24 weeks of treatment. The Phase 3 portion of the trial will use the change in 6MWD compared to placebo at 24 weeks as the primary endpoint. Secondary endpoints in the Phase 2b/Phase 3 trial will include N-terminal pro B-type natriuretic peptide, or NT-proBNP, a biomarker associated with heart failure; hemodynamic parameters; clinical worsening; clinical improvement; change in functional class; change in risk score; and quality of life measures. All patients completing the Phase 2b or Phase 3 portions will be invited to enter a long-term extension trial of AV-101.

Phase 2b/Phase 3 Enrollment and Timing

The Phase 2b/Phase 3 trial employs an operationally seamless, adaptive design consisting of three parts.

- We completed Phase 2b enrollment with 202 patients across four treatment arms, which include three dose groups of AV-101 and one placebo group. The primary endpoint is the change in PVR compared to placebo at 24 weeks. Data from the Phase 2b portion will inform the selection of an optimal dose of AV-101 for Phase 3. We anticipate that topline Phase 2b data will be available in June 2024.

- Part 3 enrollment began in November 2023 with completion of enrollment in the Phase 2b portion of the trial.

- When the optimal dose is selected, Phase 3 will then only enroll across two treatment arms, the optimal dose of AV-101 and the placebo arm. Once the final patient enrolled in the Phase 3 portion has completed 24 weeks on study, the Phase 3 portion of the trial is complete.

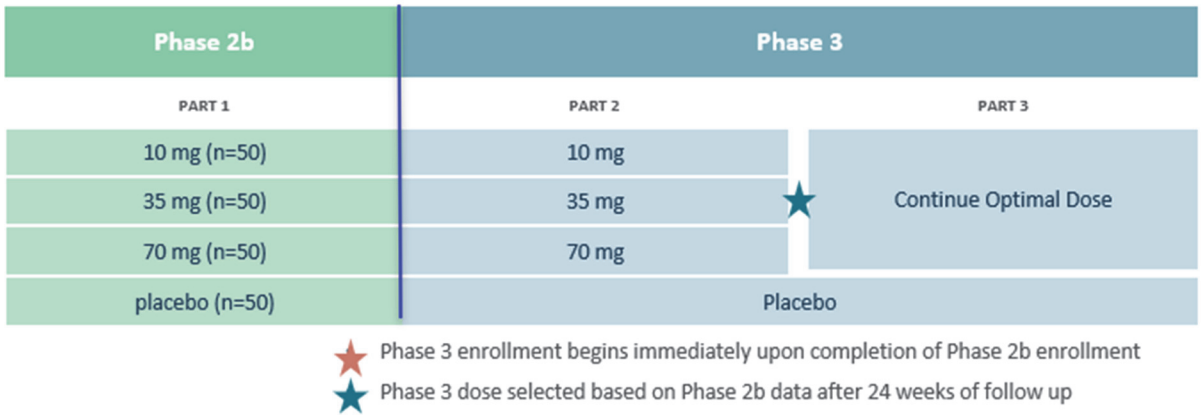

Figure 12. Design of the Phase 2b/Phase 3 trial of AV-101 in adults with PAH

If the results of the Phase 3 portion of this trial show a statistically significant and potentially clinically meaningful benefit in 6MWD, we plan to submit a NDA, with the FDA for AV-101 for the treatment of PAH.

Manufacturing and Supply

We use third-party contract manufacturers for the production of our combination product, AV-101. Our active pharmaceutical ingredient, or API, is generic and can be purchased from multiple commercial vendors in compliance with the FDA's current Good Manufacturing Practice, or current GMP, regulations and European Pharmacopoeia, or EP, standards. To be used in our inhaled product, the API requires an additional manufacturing step, which is completed at our contract manufacturing organization that complies with the FDA's current GMP regulations. The API is converted into drug product for aerosol use by one of our two contract fill/finish providers in the United States. As AV-101 is a drug-device combination product, we have contracted with a third-party to manufacture the single-dose inhaler device that we use for delivering inhaled AV-101 to patients in our Phase 2b/Phase 3 clinical trial.

Release and stability testing to date supports stability of at least 36 months for API under ambient conditions and supports stability of at least 36 months for drug product also under ambient conditions.

Our API, finished product, and single-dose inhaler producers are accepted by the health authorities in all countries that are included in our ongoing global Phase 2b/Phase 3 clinical trial. We are routinely manufacturing clinical supplies to ensure sufficient supplies are positioned at our global distribution partner for distribution to the active clinical sites.

In anticipation of a potential NDA filing, we are manufacturing a minimum of three batches of API, finished product, and single-dose inhaler devices for registration purposes and to test these batches for stability with a goal of establishing a commercial shelf life of at least two years for finished product and bulk API.

Sales and Marketing

Our commercialization strategy is to develop AV-101 into a leading therapy worldwide for the treatment of PAH.

Our Chief Executive Officer and Chief Commercial Officer have significant commercial experience, but beyond that we have not yet established a sales and marketing organization. We intend to recruit our own specialty sales force in the United States focused on promoting AV-101. We plan to target our marketing and sales efforts to pulmonologists and cardiologists who specialize in treating PAH. We believe a specialty sales force of approximately 75-100 representatives, supported by reimbursement specialists and a medical affairs team, will enable us to call on the pulmonologists and cardiologists who specialize in treating PAH.

We believe that the market for AV-101 in the five largest countries in the European Union represents the bulk of the potential European market and that China and Japan represent the bulk of the potential Asian market. We plan to enter one or multiple collaborations to commercialize AV-101 in Europe and Asia.

We believe AV-101 will receive coverage and reimbursement by public and commercial payors, but we cannot guarantee this will happen. For more information regarding these risks, please see "Risk Factors—Risks Related to Commercialization—The successful commercialization of AV-101 will depend in part on the extent to which governmental authorities, private health insurers, and other third-party payors provide coverage and adequate reimbursement levels. Failure to obtain or maintain coverage and adequate reimbursement for AV-101, if approved, could limit our ability to market our product and decrease our ability to generate revenue."

Intellectual Property

Our commercial success depends in part on our ability to obtain and maintain proprietary protection for our products, novel discoveries, drug development technologies and know-how; to operate without infringing on or otherwise violating the proprietary rights of others; and to prevent others from infringing or otherwise violating our proprietary rights. Our policy is to seek to protect our proprietary position by, among other methods, filing or in-licensing U.S. and foreign patents and patent applications related to our products and other proprietary technology, inventions and improvements that are important to the development and implementation of our business. We also rely on trademarks, trade secrets, know-how, continuing technological innovation and potential in-licensing opportunities to develop and maintain our proprietary position.

Our intellectual property portfolio includes issued patents in the United States, pending patent applications in the United States, under the Patent Cooperation Treaty (PCT international applications), and in commercially relevant foreign jurisdictions for our products. The PCT international applications preserve all of our rights to file patent applications in commercially relevant foreign jurisdictions for our products. As of March 20, 2024, we own six U.S. patents, eleven U.S. patent applications, no pending PCT international applications, and thirty foreign patent applications. Our U.S. patent portfolio is expected to expire between May 14, 2040 and February 15, 2042, excluding any extension of patent term that may be available and assuming that the filed patent applications will issue as patents. Our foreign patent portfolio is expected to expire between May 14, 2040 and February 15, 2042, excluding any extension of patent terms that may be available and assuming that filed applications will issue as patents and that the foreign patent terms are calculated similarly to the calculation of U.S. patent terms for the corresponding U.S. portion of the patent portfolio. Our patent portfolio is summarized in the following table.

APPLICATION/ PATENT NO.	RELATED PRODUCT	PROTECTION SOUGHT	PROJECTED EXPIRATION*	JURISDICTION
62/849,054	AV-101	Composition of Matter; Use	N/A	US

11,229,650	AV-101	Composition of Matter; Use	5/14/2040	US
11,806,349	AV-101	Composition of Matter; Use	5/14/2040	US
18/377,561	AV-101	Composition of Matter; Use	5/14/2040	US
20806383.4	AV-101	Composition of Matter; Use; Process	5/14/2040	Europe
202080051359.5	AV-101	Composition of Matter; Use; Process	5/14/2040	China
2021-568694	AV-101	Composition of Matter; Use; Process	5/14/2040	Japan
2020274521	AV-101	Composition of Matter; Use; Process	5/14/2040	Australia
3140641	AV-101	Composition of Matter; Use; Process	5/14/2040	Canada
288111	AV-101	Composition of Matter; Use; Process	5/14/2040	Israel
202117055928	AV-101	Composition of Matter; Use; Process	5/14/2040	India
11202112719X	AV-101	Composition of Matter; Use; Process	5/14/2040	Singapore
10-2021-7041312	AV-101	Composition of Matter; Use; Process	5/14/2040	Republic of Korea
MX/A/2021/104029	AV-101	Composition of Matter; Use; Process	5/14/2040	Mexico
BR1120210230149	AV-101	Composition of Matter; Use; Process	5/14/2040	Brazil
2021/09070	AV-101	Composition of Matter; Use; Process	5/14/2040	South Africa
20210285	AV-101	Composition of Matter; Use; Process	5/14/2040	Bahrain
305/2021	AV-101	Composition of Matter; Use; Process	5/14/2040	Jordan
KW/P/2021/466	AV-101	Composition of Matter; Use; Process	5/14/2040	Kuwait
OM/P/2021/00467	AV-101	Composition of Matter; Use; Process	5/14/2040	Oman
QA/202111/000655	AV-101	Composition of Matter; Use; Process	5/14/2040	Qatar
521430873	AV-101	Composition of Matter; Use; Process	5/14/2040	Saudi Arabia
P6002085/2021	AV-101	Composition of Matter; Use; Process	5/14/2040	UAE
PCT/US20/32872	AV-101	Composition of Matter; Use; Process	N/A	International PCT
62/849,056	AV-101	Composition of Matter; Use	N/A	US
11,298,355	AV-101	Composition of Matter; Use	5/14/2040	US
62/849,058	AV-101	Process	N/A	US
11,413,289	AV-101	Process	5/14/2040	US
11,813,263	AV-101	Process	5/14/2040	US
18/378,949	AV-101	Process	5/14/2040	US
62/849,059	AV-101	Composition of Matter; Use	N/A	US
16/874,128	AV-101	Composition of Matter; Use	5/14/2040	US
62/877,575	AV-101	Composition of Matter; Process	N/A	US
16/874,143	AV-101	Composition of Matter; Process	5/14/2040	US
62/942,408	AV-101	Composition of Matter; Use	N/A	US
11,464,776	AV-101	Composition of Matter; Use	5/14/2040	US
17/963,607	AV-101	Composition of Matter; Use	5/14/2040	US
62/984,037	AV-101	Use; Kit	N/A	US
16/874,168	AV-101	Use; Kit	5/14/2040	US
17/685,704	AV-101	Use; Kit	5/14/2040	US
62/958,481	AV-101	Use	N/A	US
16/874,190	AV-101	Use	5/14/2040	US
PCT/US20/32874	AV-101	Use	N/A	International PCT
20806763.7	AV-101	Use		Europe
63/117,258	AV-101	Composition of Matter; Combination Products; Use	N/A	US
63/150,731	AV-101	Composition of Matter; Combination Products; Use	N/A	US
18/034,558	AV-101	Composition of Matter; Combination Products; Use	11/23/2041	US
2021382051	AV-101	Composition of Matter; Combination Products; Use	11/23/2041	Australia
3199091	AV-101	Composition of Matter; Combination Products; Use	11/23/2041	Canada
202180076594.2	AV-101	Composition of Matter; Combination Products; Use	11/23/2041	China

21895804.9	AV-101	Composition of Matter; Combination Products; Use	11/23/2041	Europe
202317028210	AV-101	Composition of Matter; Combination Products; Use	11/23/2041	India
2023-530592	AV-101	Composition of Matter; Combination Products; Use	11/23/2041	Japan
PCT/US21/60526	AV-101	Composition of Matter; Combination Products; Use	N/A	International PCT
63/149,446	AV-101	Process; Composition of Matter	N/A	US
18/276,396	AV-101	Process; Composition of Matter	2/15/2042	US
2022220017	AV-101	Process; Composition of Matter	2/15/2042	Australia
3211077	AV-101	Process; Composition of Matter	2/15/2042	Canada
202280024931.8	AV-101	Process; Composition of Matter	2/15/2042	China
22753517.6	AV-101	Process; Composition of Matter	2/15/2042	Europe
2023-548863	AV-101	Process; Composition of Matter	2/15/2042	Japan
PCT/US22/16422	AV-101	Process; Composition of Matter	N/A	International PCT
63/619,079	AV-101	Use	N/A	US

* Projected patent expiration dates were calculated for pending U.S. Nonprovisional Applications and Foreign Applications based on filing date. These calculations do not take into account any terminal disclaimers or patent term adjustments that may occur during prosecution or for pharmaceutical patents in Australia. U.S. Provisional and International PCT filings will not issue as patents and therefore do not have a projected expiration date. European filings will issue only in validated European countries and the projected expiration date will apply to those individual country patents.

Our intellectual property estate strategy is designed to provide multiple layers of protection, including: (1) proprietary patent rights with claims directed to our drug product; (2) proprietary patent rights covering methods of treatment using our drug product; and (3) proprietary patent rights covering innovative manufacturing processes.

While we seek broad coverage under our pending patent applications, there is always a risk that a modification of the product or manufacturing process may allow a competitor to avoid infringement claims. In addition, patents, if granted, expire, and we cannot provide any assurance that any patents will be issued from our pending or any future applications or that any issued patents will adequately protect our products.

We have conducted freedom to operate, or FTO, analyses of the current patent landscape with respect to our lead product candidates. In doing so, we have strived to ensure our ability to operate freely within the complex patent landscape of inhalable kinase inhibitors and the use of such products in the field of PAH.

We are also working to develop new formulations of our drug products and new uses for such products, for which we intend to seek patent protection on our own to expand the layers of protection provided by our intellectual property estate.

Patent Protection and Terms

Individual patents extend for varying periods depending on the date of filing of the patent application or the date of patent issuance and the legal term of patents in the countries in which they are obtained. Generally, patents issued from regularly filed applications in the United States are granted a term of 20 years from the earliest effective filing date. In addition, in certain instances, a patent term can be adjusted to recapture a portion of the United States Patent and Trademark Office, or the USPTO, delay in issuing the patent, and extended to recapture a portion of the patent term effectively lost as a result of the FDA regulatory review period of the drug covered by the patent. However, as to the FDA component, the restoration period cannot be longer than five years, the total patent term including the restoration period must not exceed 14 years following FDA approval of the drug, and the extension may only apply to one patent that covers the approved drug (and to only those patent claims covering the approved drug, a method for using it, or a method for manufacturing it). There can be no assurance that any such patent term adjustment or extension will be obtained. The duration of foreign patents

varies in accordance with provisions of applicable local law, but typically is also 20 years from the earliest effective filing date. However, the actual protection afforded by a patent varies on a product-by-product basis, from country to country, and depends upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory-related extensions, the availability of legal remedies in a particular country and the validity and enforceability of the patent.

Furthermore, the patent positions of biotechnology and pharmaceutical products and processes like those we intend to develop and commercialize are generally uncertain and involve complex legal and factual questions. No consistent policy regarding the breadth of claims allowed in such patents has emerged to date in the United States. The patent situation outside the United States is even more uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States and other countries can diminish our ability to protect our inventions and enforce our intellectual property rights, can make it easier to challenge the validity, enforceability or scope of any patents that may issue, and, more generally, could affect the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents or in third-party patents.

Third-Party Patent Filings

Numerous U.S. and foreign issued patents and patent applications owned by third parties exist in the fields in which we are developing products. In addition, because patent applications can take many years to issue, there may be applications unknown to us, which may later result in issued patents that our products or proprietary technologies may infringe. Moreover, we may be aware of patent applications, but incorrectly predict the likelihood of those applications issuing with claims of relevance to us.

Under U.S. law, a person may be able to patent a discovery of a new way to use a previously known compound, even if such compound itself is patented, provided the newly discovered use is novel and non-obvious. Such a method-of-use patent, however, if valid, only protects the use of a claimed compound for the specified methods claimed in the patent. This type of patent does not prevent persons from using the compound for any previously known use of the compound. Further, this type of patent does not prevent persons from making and marketing the compound for an indication that is outside the scope of the patented method.

Trade Secrets and Other Protections

In addition to the protections afforded by patents and other regulatory protections, we may rely, in some circumstances, on trade secrets to protect our technology. Trade secrets may be useful to protect proprietary know-how that is not patentable or which we elect not to patent. Trade secrets may also be useful for processes or improvements for which patents are difficult to enforce.

We also protect our products and proprietary technology through confidentiality agreements with employees, consultants, advisors, contractors and collaborators. These agreements are designed to protect our proprietary information and, in the case of the invention assignment agreements, to grant us ownership of technologies that are developed through a relationship with a third party. These agreements may be breached, and we may not have adequate remedies for any such breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our commercial partners, collaborators, employees and consultants use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems.

Infringement of Third-Party Proprietary Rights

Our commercial success will depend in part on not infringing upon or otherwise violating the intellectual property and proprietary rights of third parties. If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed

to us. We could also be forced, including by court order, to cease commercializing the infringing product or technology. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our products or force us to cease some of our business operations. For more information regarding these risks, please see "Risk Factors—Risks Related to Our Intellectual Property."

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. We face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions.

Some of our potential competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

The key competitive factors that will differentiate AV-101, if approved, are likely to be its efficacy, safety, convenience, price, and the availability of reimbursement from commercial, government and other third-party payors.

We intend to seek approval for AV-101 initially in patients for the treatment of PAH as an add-on therapy to currently approved standard of care. We recognize that physicians have many treatment options for patients already on existing treatments for PAH, including prostanoids available in oral form as Orenitram (United Therapeutics Corporation, or United Therapeutics) and Uptravi (Janssen Pharmaceuticals, Inc., or Janssen), by inhalation as Tyvaso and Tyvaso DPI (United Therapeutics), Ventavis (Janssen), and by infusion as Remodulin (United Therapeutics), Flolan (GlaxoSmithKline plc) and Veletri (Janssen). We believe that AV-101, if approved, could be used prior to or in combination with prostanoids, and in combination with existing front-line agents such as the oral PDE5 inhibitors, including Revatio (Pfizer) and Adcirca (United Therapeutics); the sGC stimulator Adempas (Bayer AG); and oral ERAs, including Tracleer (Janssen), Letairis (Gilead) and Opsumit (Janssen). PAH is also an active indication for investigational drugs, and we may face competition in the future from sotatercept (Acceleron Pharma, Inc., a wholly-owned subsidiary of Merck & Co., Inc.) under review by the FDA and EMA, and/or seralutinib (Gossamer Bio, Inc.). To our knowledge, Aerami Therapeutics, Inc. is developing other formulations of imatinib for PAH, and have completed a Phase 1 clinical trial and indicated they intend to pursue further clinical development.

Government Regulation

United States—FDA Process

In the United States, pharmaceutical products are subject to extensive regulation by the FDA. The FDCA and other federal and state statutes and regulations, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling, and import and export of pharmaceutical products. We, along with third-party contractors, will be required to navigate the various preclinical, clinical and commercial approval requirements of the governing regulatory authorities of the countries in which we wish to conduct studies or seek approval of our product candidates. Failure to comply with applicable United States requirements may subject a company to a variety of administrative or judicial sanctions, such as FDA refusal to approve pending NDAs, withdrawal of an approval, warning or untitled letters, clinical holds, product recalls or withdrawals from the market, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, civil penalties, and criminal prosecution.

FDA approval is required before any new unapproved product or a product with certain changes to a previously approved product, including a new use of a previously approved drug, can be marketed in the United States. The steps required to be completed by the FDA before a drug may be marketed in the United States generally includes the following:

- completion of preclinical laboratory tests, animal studies, and formulation studies performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;

- submission to the FDA of an investigational new drug, or IND, application for human clinical testing, which must become effective before human clinical trials may begin and must be updated annually or when significant changes are made;

- approval by an independent institutional review board, or IRB, or ethics committee at each clinical site before the clinical trial is commenced;

- performance of adequate and well-controlled human clinical trials in accordance with applicable IND regulations, GCP, requirements and other clinical-trial related regulations to establish the safety and efficacy of the proposed drug for each indication;

- preparation and submission to the FDA of a NDA after completion of all pivotal clinical trials, which includes not only the results of the clinical trials, but also, detailed information on the chemistry, manufacture and quality controls for the product candidate and proposed labeling;

- satisfactory completion of an FDA Advisory Committee review, if applicable;

- a determination by the FDA within 60 days of its receipt of an NDA to file the application for review;

- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities at which the proposed drug is produced to assess compliance with current GMP regulations and of selected clinical trial sites to assess compliance with GCPs; and

- FDA review and approval of the NDA to permit commercial marketing of the product for particular indications for use in the United States.

Satisfaction of FDA pre-market approval requirements typically takes many years and the actual time required may vary substantially based upon the type, complexity, and novelty of the product or disease.

Preclinical and Clinical Development

Preclinical tests include laboratory evaluation of product chemistry, formulation, and toxicity, as well as animal trials to assess the characteristics and potential safety and efficacy of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements, including GLPs. The results of preclinical testing are submitted to the FDA as part of an IND application along with other information, including information about the product candidate, chemistry, manufacturing and controls, any available human data or literature to support the use of the product candidate and a proposed clinical trial protocol. Long term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted.

An IND application must become effective before human clinical trials may begin. The IND application automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day period, raises safety concerns or questions relating to one or more proposed clinical trials and places the clinical trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns or questions before the clinical trial can begin. The FDA may also impose clinical holds on a product candidate at any time before or during clinical trials due to safety concerns, non-compliance or other issues affecting the integrity of the trial. Accordingly, submission of an IND application may or

may not result in the FDA allowing clinical trials to commence and, once begun, issues may arise that could cause the trial to be suspended or terminated.

Clinical trials involve the administration of the investigational drug product to human subjects under the supervision of a qualified investigator. Clinical trials must be conducted: (i) in compliance with federal regulations; (ii) in compliance with GCP, an international standard meant to protect the rights and health of clinical research participants and to define the roles of clinical trial sponsors, administrators, and monitors; as well as (iii) under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. Each protocol involving testing on United States patients and subsequent protocol amendments must be submitted to the FDA as part of the IND. Furthermore, an independent IRB or ethics committee for each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and its informed consent form before the clinical trial begins at that site, and must monitor the study until completed. An IRB is charged with protecting the welfare and rights of trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits.

Regulatory authorities, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk or that the trial is unlikely to meet its stated objects. The FDA may order the temporary, or permanent, discontinuation of a clinical trial at any time, or impose other sanctions, if it believes that the clinical trial either is not being conducted in accordance with FDA requirements. Further, an IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB's requirements, or may impose other conditions. Some trials also include oversight by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board, which provides authorization for whether or not a study may move forward at designated check points based on access to certain data from the study and may recommend a clinical trial to be halted if it determines that there is an unacceptable safety risk for subjects or other grounds, such as futility.

Clinical trials to support an NDA for marketing approval are typically conducted in three sequential phases, but the phases may overlap or be combined. In Phase 1 clinical trials, the investigational product is typically introduced into a limited population of healthy human subjects or patients with the target disease or condition. These trials are designed to test the safety, dosage tolerance, pharmacokinetics and pharmacological actions of the investigational product, to identify side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. Phase 2 clinical trials usually involve administering the investigational product to a limited patient population with the specified disease or condition to evaluate the preliminarily efficacy, dosage tolerance, and optimum dosage, and to identify possible adverse effects and safety risks. Phase 3 clinical trials are typically undertaken in a larger number of patients, typically at geographically dispersed clinical trial sites, to provide substantial evidence of clinical efficacy and to further test for safety in an expanded and diverse patient population. These clinical trials are intended to permit the FDA to evaluate the overall benefit-risk relationship of the investigational product and to provide adequate information for the labeling of the product candidate.

In reviewing an NDA, the FDA will consider all information submitted in the NDA, including the results of all clinical trials conducted. In some cases, the FDA may require, or companies may voluntarily pursue, additional clinical trials after a product is approved to gain more information about the product. These so-called Phase 4 studies may be made a condition to approval of the NDA. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication and further document clinical benefit in the case of drugs approved under accelerated approval regulations. Failure to exhibit due diligence with regard to conducting Phase 4 clinical trials could result in the withdrawal of approval for products.

Concurrent with clinical trials, companies may complete additional animal studies and develop additional information about the biological characteristics of the product candidate, and must finalize a process for manufacturing the product in commercial quantities in accordance with current GMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical study investigators. Progress reports detailing the results of the clinical trials, among other information, must be submitted at least annually to the FDA, and written IND safety reports must be submitted to the FDA and the investigators for serious and unexpected suspected adverse events, findings from other studies suggesting a significant risk to humans exposed to the product candidate, findings from animal or in vitro testing that suggest a significant risk for human subjects, and any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

NDA Submission and Review

Assuming successful completion of the required clinical testing in accordance with all applicable regulatory requirements, an NDA application which includes, among other information, the results of product development, preclinical studies and clinical trials are submitted to the FDA. FDA approval of the NDA is required before marketing of the product may begin in the United States. The NDA must include, among other things, the results of all trials and preclinical testing, and other testing and a compilation of data relating to the product's pharmacology, chemistry, manufacture, controls and proposed labeling. The cost of preparing and submitting an NDA is substantial.

The FDA has 60 days from its receipt of an NDA to either issue a Refuse to File Letter or accept the NDA for filing, indicating that it is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of NDAs. Under the Prescription Drug User Fee Act, the FDA has a goal of responding to standard review NDAs within ten months after it accepts the application for filing, or, if the application qualifies for priority review, six months after the FDA accepts the application for filing, but this timeframe can be extended such as by the submission of major amendments by applicants during the review period. The FDA reviews an NDA to determine, among other things, whether the product is safe and effective and the facility in which it is manufactured, processed, packed or held meets standards designed to assure the product's continued safety, purity and potency.

The FDA may refer applications for novel drug products, or drug products that present difficult questions of safety or efficacy, to an advisory committee—typically a panel that includes clinicians and other experts—for review, evaluation, and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. Before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCPs. Additionally, the FDA will inspect the facility or the facilities at which the proposed product is manufactured. If the FDA determines that the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

After the FDA evaluates the NDA and conducts inspections of the manufacturing facilities where the investigational product and/or its drug substance will be produced, it issues either an approval letter or a Complete Response letter. An approval letter authorizes commercial marketing of the drug with approved prescribing information for specific indications. A Complete Response letter indicates that the review cycle of the application is complete and the application is not ready for approval. A Complete Response letter generally outlines the deficiencies in the submission, except that where the FDA determines that the data supporting the application are inadequate to support approval, the FDA may issue the Complete Response letter without first conducting required inspections or reviewing proposed labeling. In issuing the Complete Response letter, the FDA may require substantial additional clinical data and/or other significant, expensive, and time-consuming requirements related to clinical trials, preclinical studies and/or manufacturing. If a Complete Response Letter is issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter, withdraw the application or request a hearing. The FDA has committed to reviewing resubmissions of the NDA addressing such deficiencies in two or six months depending on the type of information included. Even if such data are submitted, however, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval.

If regulatory approval of a product is granted, such approval will be granted for a particular indication(s) and may include limitations on the indicated use(s) for which such product may be marketed. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling or may condition the approval of the NDA

on other changes to the proposed labeling, development of adequate controls and specifications, or a commitment to conduct post-market testing or clinical trials and surveillance to monitor the effects of approved products. As a condition of NDA approval, the FDA may require a risk evaluation and mitigation strategy, or REMS, to help ensure that the benefits of the drug outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The requirement for REMS can materially affect the potential market and profitability of the product. Moreover, product approval may also be conditioned on substantial post-approval testing, such as Phase 4 post-market studies, and surveillance to monitor the product's safety or efficacy, and FDA may limit further marketing of the product based on the results of these post-approval studies. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, require submission and FDA approval of a new NDA or NDA supplement before the change can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs. As with new NDAs, the review process is often significantly extended by the FDA requests for additional information or clarification.

505(b)(2) NDA Approval Process

Section 505(b)(2) of the FDCA provides an alternate regulatory pathway for the FDA to approve a new product and permits reliance for such approval on published literature or an FDA finding of safety and effectiveness for a previously approved drug product. Specifically, section 505(b)(2) permits the filing of an NDA where one or more of the investigations relied upon by the applicant for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference. Typically, 505(b)(2) applicants must perform additional trials to support the change from the previously approved drug and to further demonstrate the new product's safety and effectiveness. The FDA may then approve the new product candidate for all or some of the labeled indications for which the referenced product has been approved, as well as for any new indication sought by the section 505(b)(2) applicant.

Regulation of Combination Products in the United States

Certain products may be comprised of components, such as drug components and device components, that would normally be regulated under different types of regulatory authorities, and frequently by different centers at the FDA. These products are known as combination products. Specifically, under regulations issued by the FDA, a combination product may be:

- a product comprised of two or more regulated components that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

- two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

- a drug, or device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, or device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

- any investigational drug, or device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Under the FDCA and its implementing regulations, the FDA is charged with assigning a center with primary jurisdiction, or a lead center, for review of a combination product. The designation of a lead center generally eliminates the need to

receive approvals from more than one FDA component for combination products, although it does not preclude consultations by the lead center with other components of FDA. The determination of which center will be the lead center is based on the "primary mode of action" of the combination product. Thus, if the primary mode of action of a drug-device combination product is attributable to the drug product, the FDA center responsible for premarket review of the drug product would have primary jurisdiction for the combination product. The FDA has also established an Office of Combination Products to address issues surrounding combination products and provide more certainty to the regulatory review process. That office serves as a focal point for combination product issues for agency reviewers and industry. It is also responsible for developing guidance and regulations to clarify the regulation of combination products, and for assignment of the FDA center that has primary jurisdiction for review of combination products where the jurisdiction is unclear or in dispute.

A combination product with a drug primary mode of action generally would be reviewed and approved pursuant to the drug approval processes under the FDCA. In reviewing the NDA application for such a product, however, FDA reviewers in the drug center could consult with their counterparts in the device center to ensure that the device component of the combination product met applicable requirements regarding safety, effectiveness, durability and performance. In addition, under FDA regulations, combination products are subject to current GMP requirements applicable to both drugs and devices, including the Quality System, or QS, regulations applicable to medical devices.

Post-Approval Requirements

Once an NDA is approved, a product will be subject to pervasive and continuing regulation by the FDA including, among other things, requirements relating to current GMPs, quality controls, record-keeping, reporting of adverse experiences, periodic reporting, product sampling and distribution, and advertising and promotion of the product. For instance, the FDA closely regulates the post-approval marketing and promotion of drugs, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the internet. Drugs may be marketed only for the approved indications and in accordance with the provisions of the approved labeling. Failure to comply with these requirements can result in adverse publicity, warning letters, corrective advertising, and potential civil and criminal penalties. Physicians may prescribe legally available products for uses that are not described in the product's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the practice of medicine by physicians or their choice of treatments. The FDA does, however, regulate manufacturer's communications on the subject of off-label use of their products.

In addition, quality control, drug manufacture, packaging, and labeling procedures must continue to conform to current GMPs after approval. Drug manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA, and certain state agencies for compliance with current GMPs, which impose certain organizational, procedural and documentation requirements with respect to manufacturing and quality assurance activities. Changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from current GMPs and impose reporting requirements upon us and any third-party manufacturers that we may decide to use. NDA holders using contract manufacturers, laboratories or packagers are responsible for the selection and monitoring of qualified firms, and, in certain circumstances, qualified suppliers to these firms. Drug manufacturers and other parties involved in the drug supply chain for prescription drug products must also comply with product tracking and tracing requirements and for notifying the FDA of counterfeit, diverted, stolen and intentionally adulterated products or products that are otherwise unfit for distribution in the United States. The discovery of violative conditions, including failure to conform to current GMP, could result in enforcement actions that interrupt the operation of any such facilities or the ability to distribute products manufactured, processed or tested by them. Accordingly, manufacturers must continue to expend time, money, and effort in the areas of production and quality-control to maintain compliance with current GMPs.

The FDA may withdraw product approvals or request product recalls if a company fails to comply with regulatory standards or is not maintained, if problems occur following initial marketing, or if previously unrecognized problems are subsequently discovered. Later discovery of previously unknown problems with a product, including adverse events of

unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of a product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of existing product approvals;
- product seizure or detention, or refusal of the FDA to permit the import or export of products;
- consent decrees, corporate integrity agreements, debarment or exclusion from federal healthcare programs;
- mandated modification of promotional materials and labeling and the issuance of corrective information;
- the issuance of safety alerts, Dear Healthcare Provider letters, press releases and other communications containing warnings or other safety information about the product; or
- injunctions or the imposition of civil or criminal penalties.

U.S. Patent Term Restoration

Depending upon the timing, duration and specifics of the potential FDA approval of AV-101 and any future product candidates, some of our U.S. patents may be eligible for limited patent term extension. The Hatch-Waxman Amendments permit a patent restoration term, often referred to as patent term extension, of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA plus the time between the submission date of an NDA and the approval of that application. Only one patent applicable to an approved drug is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The USPTO, in consultation with the FDA, reviews and approves or denies the application for any patent term extension or restoration. In the future, we intend to apply for extension of patent term for one of our patents covering AV-101 to add patent life beyond its current expected expiration date.

U.S. Marketing Exclusivity

Market exclusivity provisions under the FDCA can also delay the submission or the approval of certain marketing applications, including 505(b)(2) applications. The FDA provides three years of marketing exclusivity for an NDA (including a 505(b)(2) application), or supplement to an existing NDA, if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application. Three-year exclusivity is typically awarded to innovative changes to a previously-approved drug product, such as new indications, dosage forms or strengths. This three-year exclusivity covers only the modification for which the drug received approval on the basis of the new clinical investigations and does not prohibit the FDA from approving applications for drugs that do not have the innovative change, such as generic copies of the original, unmodified drug product. Three-year exclusivity blocks approval of 505(b)(2) applications and Abbreviated New Drug Applications, or ANDAs, but will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the nonclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness. Orphan drug exclusivity, as described above, may offer a seven-year period of marketing exclusivity, except in certain circumstances. Pediatric exclusivity is another type of

regulatory market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods, including exclusivity attaching to certain patent certifications. This six-month exclusivity, which runs from the end of other exclusivity protection and patent terms, may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued "Written Request" for such a trial, provided that at the time pediatric exclusivity is granted there is not less than nine months of term remaining.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug intended to treat a rare disease or condition—generally a disease or condition with either a patient population that affects fewer than 200,000 individuals in the United States or a patient population greater than 200,000 individuals in the United States and there is no reasonable expectation that the cost of developing and making available the drug will be recovered from sales of the drug in the United States. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the generic identity of the product and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The first NDA applicant to receive FDA approval for a particular active ingredient to treat a particular disease with FDA orphan drug designation is entitled to a seven-year exclusive marketing period in the United States for that product, for that indication. During the seven-year exclusivity period, the FDA may not approve any other applications to market the same product for the same disease, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or if the FDA finds that the holder of the orphan drug exclusivity has not shown that it can assure the availability of sufficient quantities of the orphan drug to meet the needs of the patients with the disease or condition for which the product was designated. Orphan drug exclusivity does not prevent the FDA from approving a different product for the same disease or condition, or the same product for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the NDA or BLA application user fee.

A designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan drug designation. In addition, orphan drug exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition.

Fast Track Designation, Breakthrough Therapy Designation and Accelerated Approval

The FDA is required to facilitate the development, and expedite the review, of drugs that are intended for the treatment of a serious or life-threatening disease or condition which demonstrate the potential to address unmet medical needs for the condition. These programs include fast track designation, priority review and accelerated approval.

A product candidate is eligible for fast track designation if it is intended to treat a serious or life-threatening disease or condition and demonstrates the potential to address unmet medical needs for such disease or condition. Fast track designation applies to the combination of the product and the specific indication for which it is being studied. Under the fast track program, the sponsor of a drug candidate may request that the FDA designate the candidate for a specific indication as a fast track product concurrent with, or after, the filing of the IND for the candidate. The FDA must determine if the product candidate qualifies for fast track designation within 60 days of receipt of the sponsor's request. Fast track designation provides increased opportunities for sponsor interactions with the FDA during preclinical and clinical development, in addition to the potential for rolling review of sections of a the applicant's NDA before the application is complete. This rolling review is available if the applicant provides, and the FDA approves, a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, the FDA's time period goal for reviewing an application does not begin until the last section of the NDA is submitted. Additionally, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Under the FDA's breakthrough therapy program, a sponsor may seek FDA designation of its product candidate as a breakthrough therapy if the product candidate is intended, alone or in combination with one or more other drugs or biologics, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that it may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Breakthrough therapy designation comes with all of the benefits of fast track designation. The FDA may take other actions appropriate to expedite the development and review of the product candidate, including intensive guidance on an efficient product development program beginning as early as Phase 1, and FDA organizational commitment to expedited development, including involvement of senior managers and experienced review staff in a cross-disciplinary review, where appropriate.

Any product submitted to the FDA for marketing, including under the fast track or breakthrough designation program, may also be eligible for other types of FDA programs intended to expedite development and review, such as accelerated approval. Products are eligible for accelerated approval if they can be shown to have an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

In clinical trials, a surrogate endpoint is a measurement of laboratory or clinical signs of a disease or condition that substitutes for a direct measurement of how a patient feels, functions, or survives. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. A product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the conduct of Phase 4, or post-approval, clinical trials to confirm the effect on the clinical endpoint which must be conducted with due diligence and, under the Food and Drug Omnibus Reform Act of 2022, or FDORA, the FDA may require, as appropriate, that such trials be underway prior to approval or within a specific time period after the date accelerated approval is granted. Additionally, under FDORA, the FDA has increased authority for expedited procedures to withdraw a product or indication approved under accelerated approval if, for example, the confirmatory trial fails to verify the predicted clinical benefit of the product. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA unless otherwise informed by the FDA.

Priority Review

A product is eligible for priority review if it has the potential to provide a significant improvement in safety or effectiveness in the treatment, diagnosis or prevention of a serious disease or condition. A priority review means that the goal for the FDA to review an application is six months, rather than the standard review of ten months under current Prescription Drug User Fee Act, or PDUFA, guidelines. Under the current PDUFA agreement, these six and ten month review periods are measured from the "filing" date rather than the receipt date for NDAs for new molecular entities, which typically adds approximately two months to the timeline for review and decision from the date of submission. Most products that are eligible for fast track designation are also likely to be considered appropriate to receive a priority review.

Pediatric Information

Under the Pediatric Research Equity Act, or PREA, NDAs or supplements to NDAs must contain data to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may grant full or partial waivers, or deferrals, for submission of data. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which orphan designation has been granted.

Disclosure of Clinical Trial Information

Sponsors of clinical trials of FDA-regulated products, including drugs and combination products, are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, trial sites and investigators, and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to disclose the results of their clinical trials after completion. Competitors may use this publicly available

information to gain knowledge regarding the progress of development programs. Disclosure of the results of these trials can be delayed until the new product or new indication being studied has been approved. Failure to timely register a covered clinical study or to submit study results as provided for in the law can give rise to civil monetary penalties and also prevent the non-compliant party from receiving future grant funds from the federal government. The Final Rule on ClinicalTrials.gov registration and reporting requirements became effective in 2017, and both the National Institutes of Health and the FDA have signaled the government's willingness to begin enforcing those requirements against non-compliant clinical trial sponsors.

European Union—Process

In the European Union, or EU, our product candidate(s) may also be subject to extensive regulatory requirements governing, among other things, clinical trials and any commercial sales and distribution of our product candidate(s).

Whether or not we obtain FDA approval for a product candidate, we must obtain the requisite approvals from regulatory authorities located in the EU Member States prior to the commencement of clinical trials as well as EU or national regulatory approvals prior to marketing the product candidate(s).

Non-Clinical Studies and Clinical Trials

Similar to the United States, the various phases of non-clinical studies and clinical trials in the EU are subject to significant regulatory controls.

Non-clinical studies are performed to demonstrate the health or environmental safety of new chemical substances. Non-clinical studies must be conducted in compliance with the principles of good laboratory practice, or GLP, as set forth in EU Directive 2004/10/EC. In particular, non-clinical studies, both in vitro and in vivo, must be planned, performed, monitored, recorded, reported and archived in accordance with the GLP principles, which define a set of rules and criteria for a quality system for the organizational process and the conditions for non-clinical studies. These GLP standards reflect the Organization for Economic Co-operation and Development requirements.

Clinical trials of medicinal products in the EU must be conducted in accordance with the EU Clinical Trials Regulation (EU) No 536/2014, or CTR, (which was adopted in April 2014, and repealed the EU Clinical Trials Directive 2001/20/EC on January 31, 2022), and the International Conference on Harmonization, or ICH, guidelines on GCP, as well as the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki. If the sponsor of the clinical trial is not established within the EU, it must appoint an EU entity to act as its legal representative (unless all EU Member States in which the trial is being conducted have chosen not to apply such rule, in which case it may be that only a contact person in the EU is required), who shall be responsible for ensuring compliance with the sponsor's obligations under the CTR and be the addressee for all communications provided for under the CTR. The sponsor must take out a clinical trial insurance policy, and in most EU Member States, the sponsor is liable to provide 'no fault' compensation to any study subject injured in the clinical trial.

The CTR is directly applicable in all Member States (meaning that no national implementing legislation in each EU Member State is required). Under the CTR, there is a centralized application procedure where one national authority takes the lead in reviewing the application and the other national authorities have only limited involvement (instead of submitting applications separately to each national competent authority and ethics committee in the Member States in which the trial will be conducted, as was the case under the previous EU Clinical Trials Directive). The CTR also makes it more efficient for EU Member States to evaluate and authorize applications together, via the Clinical Trials Information System. Medicines used in clinical trials must be manufactured in accordance with GMP. Other national and EU-wide regulatory requirements may also apply.

Disclosure of Clinical Trial Information

The CTR significantly enlarges the publication and transparency obligations for clinical trial sponsors from the previous position under the Clinical Trials Directive. Additionally, the CTR requires that EU Member States adopt specific measures, including penalties, to adequately sanction infringements of the relevant transparency obligations.

Marketing Authorisations

In the EU, medicinal products can only be placed on the market after obtaining a marketing authorisation, or MA. To obtain regulatory approval of a product in the EU, we must submit an MAA. The process for doing this depends, among other things, on the nature of the medicinal product.

Centralized Procedure

Under the centralized procedure, the European Commission issues a single MA, based on the opinion of the European Medicines Agency's, or EMA, Committee for Medicinal Products for Human Use, or CHMP, which is valid across the entire territory of the EU, as well as Iceland, Liechtenstein and Norway (i.e. the European Economic Area, or EEA). The centralized procedure is compulsory for human medicines that are: (i) derived from biotechnology processes; (ii) advanced-therapy medicinal products (i.e. gene therapy, somatic cell-therapy or tissue-engineered medicines); (iii) contain a new active substance indicated for the treatment of certain diseases, such as HIV, AIDS, cancer, diabetes, neurodegenerative diseases, viral diseases or autoimmune diseases and other immune dysfunctions; and (iv) officially designated orphan medicines. For medicines that do not fall within these categories, an applicant has the option of submitting an application for a centralized MA to the EMA if the product contains a new active substance not yet authorized in the EU, or the medicine concerned is a significant therapeutic, scientific or technical innovation, or that the granting of a centralized authorization would be in the interest of public health at the EU-level.

Under the centralized procedure the maximum timeframe for the evaluation of an MAA by the EMA is 210 days, excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP. Clock stops may extend the timeframe of evaluation of an MAA considerably beyond 210 days. Where the CHMP gives a positive opinion, the EMA provides the opinion together with supporting documentation to the European Commission, who makes the final decision to grant an MA, which is issued within 67 days of receipt of the EMA's recommendations. Accelerated assessment may be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and, in particular, from the point of view of therapeutic innovation. Accelerated assessment of an MAA will be performed by the CHMP in no more than 150 days (excluding clock stops) but it is possible that the CHMP may revert to the standard time limit for the centralized procedure if it determines that the application is no longer appropriate to conduct an accelerated assessment. Innovative products that target an unmet medical need (there is no satisfactory method of diagnosis, prevention or treatment in the EU or, if there is, the new medicine will bring a major therapeutic advantage) may be eligible for a number of expedited development and review programs, such as the PRIME scheme, which provides incentives similar to the breakthrough therapy designation in the United States. PRIME is a voluntary scheme aimed at enhancing the EMA's support for the development of medicines that target unmet medical needs. It is based on increased interaction and early dialogue with companies developing promising medicines, to optimize their product development plans and speed up their evaluation to help them reach patients earlier. Product developers that benefit from PRIME designation can expect to be eligible for accelerated assessment but this is not guaranteed. The benefits of a PRIME designation include the appointment of a CHMP rapporteur before submission of an MAA, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review earlier in the application process.

National Authorisation Procedures

There are also two other possible routes to authorize medicinal products in several Member States. National MAs are issued by the national competent authorities of the EU Member States and only cover their respective territory. They are available for products that fall outside the scope of the centralized procedure:

- *Decentralized procedure.* If the product has not received a national MA in any Member State at the time of application, an applicant may apply for simultaneous MAs in more than one EU Member State. Under the decentralized procedure an identical dossier is submitted to the national competent authority of each of the Member States in which an MA is sought, one of which is selected by the applicant as the Reference Member State.

- *Mutual recognition procedure.* Under the mutual recognition procedure, a medicine that has already been authorized in one EU Member State in accordance with the national procedures of that Member State, can be recognized in another Member State.

MAs have an initial duration of five years. After these five years, the authorization may be renewed for an unlimited period on the basis of a reevaluation of the risk-benefit balance.

Similar to the United States, there is a process for authorization of generic/biosimilar versions of innovator medicinal products authorized in the EU. Abridged applications for the authorization of generic/biosimilar versions of medicinal products authorized via the EU centralized procedure can be submitted to the EMA through the centralized procedure referencing the innovator's data.

Data and Market Exclusivity

In the EU, innovative medicinal products approved on the basis of a complete and independent data package qualify for eight years of data exclusivity upon the grant of an MA and an additional two years of market exclusivity. Data exclusivity prevents generic and biosimilar applicants from referencing the innovator's preclinical and clinical trial data contained in the dossier of the reference product when applying for an MA for a period of eight years from the date on which the reference product was first authorized in the EU. During the additional two-year period of market exclusivity, a generic or biosimilar MAA can be submitted and authorized, and the innovator's data may be referenced, but no generic or biosimilar medicinal product can be marketed until the expiration of the market exclusivity period. The overall 10 year period will be extended to a maximum of 11 years if, during the first eight years of those 10 years, the MA holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to authorization, is held to bring a significant clinical benefit in comparison with existing therapies. There is no guarantee that a product will be considered by the EMA to be an innovative medicinal product, and products may not qualify for data exclusivity. Even if a product is considered to be an innovative medicinal product so that the innovator gains the prescribed period of data exclusivity, another company may market another version of the product if such company obtained an MA based on an MAA with a complete and independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Orphan Medicinal Products

The criteria for designating an "orphan medicinal product" in the EU are similar in principle to those in the United States. A medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than 5 in 10,000 persons in the EU when the application is made, or (b) it is unlikely that the marketing of the product, without the benefits derived from orphan status, would generate sufficient return in the EU to justify the necessary investment in its development; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the EU or, if such a method exists, the product in question would be of significant benefit compared to products available for that condition.

In the EU, orphan designation entitles a party to financial incentives such as reduction of fees or fee waivers, regulatory assistance and the possibility to apply for a centralized MA. The application for orphan designation must be submitted before the application for an MA. Orphan designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The grant of an MA for an orphan medicinal product leads to ten years of market exclusivity. During the ten-year market exclusivity period, the EMA cannot accept an MAA, or grant an MA, or accept an application to extend an MA, for the same therapeutic indication, in respect of a "similar medicinal product". A "similar medicinal product" is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. An orphan medicinal product can also obtain an additional two years of market exclusivity in the EU for pediatric studies conducted in compliance with an agreed PIP. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications.

The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the orphan designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify

maintenance of market exclusivity. At any time, an MA may be granted to a similar medicinal product for the same therapeutic indication if: (i) a second applicant can establish that its product, although similar to the authorized product, is safer, more effective or otherwise clinically superior; (ii) the MA holder for the authorized orphan product consents to a second orphan medicinal product application; or (iii) the MA holder for the authorized orphan product cannot supply enough orphan medicinal product.

Pediatric Development

In the EU, MAAs for new medicinal products have to include the results of trials conducted in the pediatric population, in compliance with a pediatric investigation plan, or PIP, agreed with the EMA's Pediatric Committee, or PDCO. The PIP sets out the timing and measures proposed to generate data to support a pediatric indication of the product for which an MA is being sought. The PDCO can grant a deferral of the obligation to implement some or all of the measures of the PIP until there are sufficient data to demonstrate the efficacy and safety of the product in adults. Further, the obligation to provide pediatric clinical trial data can be waived by the PDCO when these data are not needed or appropriate because the product is likely to be ineffective or unsafe in children, the disease or condition for which the product is intended occurs only in adult populations, or when the product does not represent a significant therapeutic benefit over existing treatments for pediatric patients. Once the MA is obtained in all Member States and study results are included in the product information, even when negative, the product is eligible for a six-months supplementary protection certificate, or SPC extension (provided an application for such extension is made at the same time as filing the SPC application for the product, or at any point up to two years before the SPC expires) or, in the case of orphan medicinal products, a two-year extension of the orphan market exclusivity is granted. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted.

Failure to comply with EU and Member State laws that apply to the conduct of clinical trials, manufacturing approval, marketing of such products, both before and after grant of the MA, manufacturing of pharmaceutical products, statutory health insurance, bribery and anti-corruption or with other applicable regulatory requirements may result in administrative, civil or criminal penalties. These penalties could include delays or refusal to authorize the conduct of clinical trials, or to grant an MA, product withdrawals and recalls, product seizures, suspension, withdrawal or variation of the MA, total or partial suspension of production, distribution, manufacturing or clinical trials, operating restrictions, injunctions, suspension of licenses, fines and criminal penalties.

Reform of the Regulatory Framework in the European Union

The European Commission introduced legislative proposals in April 2023 that, if implemented, will replace the current regulatory framework in the EU for all medicines (including those for rare diseases and for children). The European Commission has provided the legislative proposals to the European Parliament and the European Council for their review and approval. In October 2023, the European Parliament published draft reports proposing amendments to the legislative proposals, which will be debated by the European Parliament. Once the European Commission's legislative proposals are approved (with or without amendment), they will be adopted into EU law.

Regulation of Combination Products

The EU regulates medical devices and medicinal products separately, through different legislative instruments, and the applicable requirements will vary depending on the type of drug-device combination product. EU guidance has been published to help manufacturers select the right regulatory framework. In the case of drug-delivery products intended to administer a medicinal product where the device and the medicinal product do not form a single integral product (i.e. where the medicinal product and the device do not form a single product which is intended exclusively for use in the given combination and which is not reusable), the medicinal product is regulated in accordance with the aforementioned rules while the device part is regulated as a medical device and will have to comply with all the requirements set forth by Regulation 2017/745, or the Medical Devices Regulation (which became applicable on May 26, 2021 and repealed the EU Council Directive 93/42/EEC, or the Medical Devices Directive). The dry powder delivery device used with AV-101 is classed as a class IIa device under the Medical Devices Regulation and this will need to be certified under the Medical Devices Regulation in due course as described below. The current CE mark for the delivery device is in accordance with the Medical Devices Directive as a class I device. Under the transitional provisions of the Medical Devices Regulation,

medical devices for which the conformity assessment procedure pursuant to the Medical Devices Directive did not require the involvement of a notified body, for which the declaration of conformity was drawn up prior to May 26, 2021 and for which the conformity assessment procedure pursuant to the Medical Device Regulation requires the involvement of a notified body, may be placed on the market or put into service until December 31, 2028, after which they must be re-certified under the Medical Devices Regulation.

The characteristics of non-integral devices used for the administration of medicinal products may impact the quality, safety and efficacy profile of the medicinal products. To the extent that administration devices are co-packaged with the medicinal product or, in exceptional cases, where the use of a specific type of administration device is specifically provided for in the product information of the medicinal product, additional information may need to be provided in the MAA for the medicinal product on the characteristics of the medical device(s) that may impact on the quality, safety and/or efficacy of the medicinal product. The requirements regarding quality aspects for integral drug-device combination products, including devices that are co-packaged with medicinal products, are outlined in an EMA guideline which came into effect on January 1, 2022.

For a medical device to obtain a CE mark under the Medical Devices Regulation, the device must meet the relevant general safety and performance requirements laid down in Annex I of the Medical Devices Regulation. The most fundamental requirement is that a medical device must be designed and manufactured in such a way that it will not compromise the clinical condition or safety of patients, or the safety and health of users and others. In addition, the device must achieve the performances intended by the manufacturer and be designed, manufactured, and packaged in a suitable manner. To demonstrate compliance with the general safety and performance requirements laid down in Annex I to the Medical Devices Regulation, medical device manufacturers must undergo a conformity assessment procedure, which varies according to the type of medical device and its (risk) classification. Conformity assessment procedures require an assessment of available clinical evidence, literature data for the product, and post-market experience in respect of similar products already marketed. For class IIa medical devices, a conformity assessment procedure requires the intervention of a notified body. Notified bodies are independent organizations designated by EU countries to assess the conformity of devices before being placed on the market. If satisfied that the relevant product conforms to the relevant general safety and performance requirements, the notified body issues a certificate of conformity, which the manufacturer uses as a basis for its own declaration of conformity. The manufacturer may then apply the CE mark to the device, which allows the device to be placed on the market throughout the EU.

As a general rule, demonstration of conformity of medical devices and their manufacturers with the general safety and performance requirements must be based, among other things, on the evaluation of clinical data supporting the safety and performance of the products during normal conditions of use. Specifically, a manufacturer must demonstrate that the device achieves its intended performance during normal conditions of use, that the known and foreseeable risks, and any adverse events, are minimized and acceptable when weighed against the benefits of its intended performance, and that any claims made about the performance and safety of the device are supported by suitable evidence.

The aforementioned EU rules are generally applicable in the EEA.

Brexit and the Regulatory Framework in the United Kingdom

The United Kingdom, or UK formally left the EU (commonly referred to as " Brexit") on January 31, 2020, and the EU and the UK have concluded a trade and cooperation agreement, or TCA, which was provisionally applicable since January 1, 2021 and has been formally applicable since May 1, 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued, but does not provide for wholesale mutual recognition of UK and EU pharmaceutical or medical devices regulations. At present, Great Britain has implemented EU legislation on the marketing, promotion and sale of medicinal products through the Human Medicines Regulations 2012 (as amended) (under the Northern Ireland Protocol, the EU regulatory framework currently continues to apply in Northern Ireland). The medicinal products regulatory regime in Great Britain therefore largely aligns with EU regulations, however it is possible that these regimes will diverge more significantly in future now that Great Britain's regulatory system is independent from the EU and the TCA does not provide for mutual recognition of UK and EU pharmaceutical legislation. The new Medical Devices Regulation is not applicable in Great Britain following Brexit and the current legislation is based on the previous Medical

Devices Directive. However, notwithstanding that there is no wholesale recognition of EU pharmaceutical legislation under the TCA, under a new framework which was put in place by the Medicines and Healthcare products Regulatory Agency, or MHRA, the UK medicines and medical devices regulator, on January 1, 2024, the MHRA may take into account decisions on the approval of MAs from the EMA (and certain other regulators) when considering an application for a Great Britain or UK MA.

On February 27, 2023, the UK government and the European Commission announced a political agreement in principle to replace the Northern Ireland Protocol with a new set of arrangements, known as the "Windsor Framework". This new framework fundamentally changes the existing system under the Northern Ireland Protocol, including with respect to the regulation of medicinal products in the UK. In particular, the MHRA will be responsible for approving all medicinal products destined for the UK market (i.e., Great Britain and Northern Ireland), and the EMA will no longer have any role in approving medicinal products destined for Northern Ireland. A single UK-wide MA will be granted by the MHRA for all medicinal products to be sold in the UK, enabling products to be sold in a single pack and under a single authorization throughout the UK. The Windsor Framework was approved by the EU-UK Joint Committee on March 24, 2023, so the UK government and the EU will enact legislative measures to bring it into law. On June 9, 2023, the MHRA announced that the medicines aspects of the Windsor Framework will apply from January 1, 2025.

Other International Markets—Drug Approval Process

In some international markets (*e.g.*, China or Japan), although data generated in United States or EU trials may be submitted in support of an MAA, additional clinical trials conducted in the host territory, or studying people of the ethnicity of the host territory, may be required prior to the filing or approval of MA within the country.

Pricing and Reimbursement

In the United States and internationally, sales of products that we market in the future, and our ability to generate revenues on such sales, are dependent, in significant part, on the availability and level of reimbursement from third-party payors such as state and federal governments, managed care providers and private insurance plans. Substantial uncertainty exists as to the reimbursement status of newly approved healthcare products by third-party payors.

In the United States no uniform policy of coverage and reimbursement for drug products exists. Accordingly, decisions regarding the extent of coverage and amount of reimbursement to be provided for any of our products will be made on a payor by payor basis. Private third-party payors tend to follow Medicare coverage policies and payment limitations in setting their own reimbursement rate to a substantial degree, but also have their own methods and approval process apart from Medicare determinations. As a result, coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our product candidates to each payor separately, with no assurance that coverage and adequate reimbursement will be obtained. Factors payors consider in determining reimbursement are based on whether the product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

Increasingly, third party payors are implementing cost-cutting and reimbursement initiatives and likely will continue to do so in the future. These include establishing formularies that govern the drugs and biologics that will be offered and also the out-of-pocket obligations of member patients for such products. In addition, net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation

of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. It is possible that future legislation in the United States and other jurisdictions could be enacted which could potentially impact the reimbursement rates for the products we are developing and may develop in the future and also could further impact the levels of discounts and rebates paid to federal and state government entities. Any legislation that impacts these areas could impact, in a significant way, our ability to generate revenues from sales of products that, if successfully developed, we bring to market.

In addition, in some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. In the EU, governments influence the price of medicinal products through their pricing and reimbursement rules and control of national healthcare systems that fund a large part of the cost of those products to consumers. EU Member States are free to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed to by the government. Member States may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market, including volume-based arrangements, caps and reference pricing mechanisms. To obtain reimbursement or pricing approval, some of the Member States may require the completion of clinical trials that compare the cost effectiveness of a particular product candidate to currently available therapies that are considered the local standard of care. Other EU Member States allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription medicines, has become very intense. It is increasingly common in many EU Member States for MA holders to be required to demonstrate the pharmaco-economic superiority of their products as compared to products already subject to pricing and reimbursement in specific countries. In order for drugs to be evaluated positively under such criteria, pharmaceutical companies may need to re-examine, and consider altering, a number of traditional functions relating to the selection, study, and management of drugs, whether currently marketed, under development, or being evaluated as candidates for research and/or development.

Sales and Marketing

Sales, promotion and other activities following product approval are subject to regulation by numerous regulatory authorities in addition to the FDA, including, in the United States, the Centers for Medicare & Medicaid Services, other divisions of the Department of Health and Human Services, the U.S. Department of Justice, and similar foreign, state, and local government authorities.

As described above, the FDA regulates all advertising and promotion activities for products under its jurisdiction both prior to and after approval. A company can make only those claims relating to safety and efficacy that are approved by the FDA in labeling. Physicians may prescribe legally available drugs for uses that are not described in the drug's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties, and often reflect a physician's belief that the off-label use is the best treatment for the patients. The FDA does not regulate the behavior of physicians in their choice of treatments, but FDA regulations do impose stringent restrictions on manufacturers' communications regarding off-label uses. Failure to comply with applicable FDA requirements may subject a company to adverse publicity, enforcement action by the FDA, corrective advertising, consent decrees and the full range of civil and criminal penalties available to the FDA.

Healthcare Laws and Regulations

Pharmaceutical companies are also subject to additional healthcare regulation and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which they conduct their business that may constrain the financial arrangements and relationships through which we research, as well as sell, market and distribute any products for which we obtain marketing authorization. Such laws include, without limitation, state and federal anti-kickback, fraud and abuse, false claims, and transparency laws and regulations related to drug pricing and payments and other transfers of value made to physicians and other healthcare providers. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply, we may be subject to penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, the curtailment or restructuring of operations,

integrity oversight and reporting obligations, exclusion from participation in federal and state healthcare programs and responsible individuals may be subject to imprisonment. Such laws include, but are not limited to:

- the United States federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, offering, receiving or providing any remuneration (including any kickback, bribe, or certain rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, lease, order or recommendation of, any good, facility, item or service, for which payment may be made, in whole or in part, under any United States federal healthcare program, such as Medicare and Medicaid. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. Violations are subject to civil and criminal fines and penalties for each violation, plus up to three times the remuneration involved, imprisonment, and exclusion from government healthcare programs. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act or federal civil money penalties;

- the United States federal civil monetary penalty and civil and criminal false claims laws, including the civil federal False Claims Act, which can be enforced through civil whistleblower or qui tam actions, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, to the United States federal government, claims for payment or approval that are false or fraudulent, knowingly making, using or causing to be made or used, a false record or statement material to a false or fraudulent claim, or from knowingly making a false statement to avoid, decrease or conceal an obligation to pay money to the United States federal government. Manufacturers can be held liable under the federal False Claims Act even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. Pharmaceutical manufacturers can cause false claims to be presented to the United States federal government by engaging in impermissible marketing practices, such as the off-label promotion of a product for an indication for which it has not received FDA approval. In addition, the government may assert that a claim including items and services resulting from a violation of the United States federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act. The federal False Claims Act also permits a private individual acting as a "whistleblower" to bring actions on behalf of the federal government alleging violations of the federal False Claims Act and to share in any monetary recovery;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit a person from knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious, or fraudulent statements or representations in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- the FDCA, which prohibits, among other things, the adulteration or misbranding of drugs, biologics and medical devices;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates, independent contractors or agents of covered entities, that perform services for them that involve the creation, maintenance, receipt, use, or disclosure of, individually identifiable health information relating to the privacy, security and transmission of individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and

seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, there may be additional federal, state and non-U.S. laws which govern the privacy and security of health and other personal information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts;

- the United States Physician Payments Sunshine Act and its implementing regulations, which requires certain manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid, or the Children's Health Insurance Program, with specific exceptions, to report annually to the government information related to certain payments and other transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain other licensed health care professionals, and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members;

- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers;

- federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs;

- analogous United States state laws, including: state anti-kickback and false claims laws, which may apply to our business practices, including but not limited to, research, distribution, sales and marketing arrangements and claims involving healthcare items or services reimbursed by any third-party payor, including private insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the United States federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to file reports relating to pricing and marketing information, which requires tracking gifts and other remuneration and items of value provided to healthcare professionals and entities; and state and local laws requiring the registration of pharmaceutical sales representatives;

- the United States Foreign Corrupt Practices Act of 1977, as amended, which prohibits, among other things, United States companies and their employees and agents from authorizing, promising, offering, or providing, directly or indirectly, corrupt or improper payments or anything else of value to foreign government officials, employees of public international organizations and foreign government owned or affiliated entities, candidates for foreign political office, and foreign political parties or officials thereof; and

- similar healthcare laws in the European Union and other jurisdictions, including reporting requirements detailing interactions with and payments to healthcare providers and laws governing privacy and security of health information, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Similar rigid restrictions are imposed on the promotion and marketing of medicinal products in the EU and other countries. Laws (including those governing promotion, marketing and anti-kickback provisions), industry regulations and professional codes of conduct often are strictly enforced. Even in those countries where we are not directly responsible for the promotion and marketing of our products, inappropriate activity by our international distribution partners can have adverse implications for us.

Healthcare Reform and Legislation

Payors, whether domestic or foreign, or governmental or private, are developing increasingly sophisticated methods of controlling healthcare costs and those methods are not always specifically adapted for new technologies such as gene therapy and therapies addressing rare diseases such as those we are developing. In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the health care system that could impact our ability to sell our products profitably. In particular, in 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the ACA, was enacted, which,

among other things, subjected biologic products to potential competition by lower-cost biosimilars; increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; extended the Medicaid Drug Rebate program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations; subjected manufacturers to new annual fees and taxes for certain branded prescription drugs; created a Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D; and provided incentives to programs that increase the federal government's comparative effectiveness research.

Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. The Budget Control Act of 2011, among other things, included aggregate reductions of Medicare payments to providers up to 2% per fiscal year. Subsequent legislation extended the 2% payment reduction which remains in effect through 2031. In addition, the American Taxpayer Relief Act of 2012 further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. On March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024. Due to the Statutory Pay-As-You-Go Act of 2010, estimated budget deficit increases resulting from the American Rescue Plan Act of 2021, and subsequent legislation, Medicare payments to providers will be further reduced starting in 2025 absent further legislation. These laws and regulations may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Additionally, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy for Part B drugs beginning January 1, 2020.

The Inflation Reduction Act of 2022, includes several provisions that may impact our business to varying degrees, including provisions that reduce the out-of-pocket cap for Medicare Part D beneficiaries to $2,000 starting in 2025; impose new manufacturer financial liability on certain drugs under Medicare Part D, allow the U.S. government to negotiate Medicare Part B and Part D price caps for certain high-cost drugs and biologics without generic or biosimilar competition, require companies to pay rebates to Medicare for certain drug prices that increase faster than inflation, and delay the rebate rule that would limit the fees that pharmacy benefit managers can charge. Further, under the IRA, orphan drugs are exempted from the Medicare drug price negotiation program, but only if they have one orphan designation and for which the only approved indication is for that disease or condition. If a product receives multiple orphan designations or has multiple approved indications, it may not qualify for the orphan drug exemption. The implementation of the IRA is currently subject to ongoing litigation challenging the constitutionality of the IRA's Medicare drug price negotiation program. The effects of the IRA on our business and the healthcare industry in general is not yet known.

There has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent United States Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. President Biden has issued multiple executive orders that have sought to reduce prescription drug costs. In February 2023, HHS also issued a proposal in response to an October 2022 executive order from President Biden that includes a proposed prescription drug pricing model that will test whether targeted Medicare payment adjustments will sufficiently incentivize manufacturers to complete confirmatory trials for drugs approved through FDA's accelerated approval pathway. Although a number of these and other proposed measures may require authorization through additional legislation to become effective, and the Biden administration may reverse or otherwise change these measures, both the Biden administration and Congress have indicated that it will continue to seek new legislative measures to control drug costs.

Further, on May 30, 2018, the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase 1 clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access

program. There is no obligation for a pharmaceutical manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act.

At the state level, individual states are increasingly active in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing.

Data Privacy and Security Laws

Numerous state, federal and foreign laws, including consumer protection laws and regulations, govern the collection, dissemination, use, access to, confidentiality, and security of personal information, including health-related information. In the United States, numerous federal and state laws and regulations, including data breach notification laws, health information privacy and security laws, including HIPAA and federal and state consumer protection laws and regulations (e.g., Section 5 of the Federal Trade Commission Act) that govern the collection, use, disclosure, and protection of health-related and other personal information could apply to our operations or the operations of our partners. In addition, certain state and non-U.S. laws, such as the CCPA, and GDPR, govern the privacy and security of personal information, including health-related information in certain circumstances, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. Failure to comply with these laws, where applicable, can result in the imposition of significant civil and/or criminal penalties and private litigation. Privacy and security laws, regulations, and other obligations are constantly evolving, may conflict with each other to make compliance efforts more challenging, and can result in investigations, proceedings, or actions that lead to significant penalties and restrictions on data processing.

Other Laws and Regulatory Processes

We will become subject to a variety of financial disclosure and securities trading regulations as a public company in the United States, including laws relating to the oversight activities of the SEC and, following the listing of our capital stock on The Nasdaq Global Market, we will be subject to the regulations of The Nasdaq Global Market. In addition, the Financial Accounting Standards Board, or FASB, the SEC and other bodies that have jurisdiction over the form and content of our accounts, our financial statements and other public disclosure are constantly discussing and interpreting proposals and existing pronouncements designed to ensure that companies best display relevant and transparent information relating to their respective businesses.

Our international operations are subject to compliance with the Foreign Corrupt Practices Act, or the FCPA, which prohibits corporations and individuals from paying, offering to pay, or authorizing the payment of anything of value to any foreign government official, government staff member, political party, or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity. We also may be implicated under the FCPA for activities by our partners, collaborators, CROs, vendors or other agents.

Our present and future business has been and will continue to be subject to various other laws and regulations. Various laws, regulations and recommendations relating to safe working conditions, laboratory practices, the experimental use of animals, and the purchase, storage, movement, import and export and use and disposal of hazardous or potentially hazardous substances used in connection with our research work are or may be applicable to our activities. Certain agreements entered into by us involving exclusive license rights or acquisitions may be subject to national or supranational antitrust regulatory control, the effect of which cannot be predicted. The extent of government regulation, which might result from future legislation or administrative action, cannot accurately be predicted.

Human Capital Resources

As of March 22, 2024, we had 51 full-time employees, including 43 in research and development and eight in general and administrative functions. We also contract with a number of consultants to supplement the efforts and responsibilities of our employees. None of our employees are subject to a collective bargaining agreement or represented by a labor or trade union.

Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and new employees, advisors and consultants. The principal purposes of our equity and cash incentive plans are to attract, retain and reward personnel through the granting of stock-based and cash-based compensation awards, in order to increase stockholder value and the success of our company by motivating such individuals to perform to the best of their abilities and achieve our objectives.

We are committed to fostering a diverse workforce and a culture of inclusion. We pursue fair employment practices in every aspect of our business and are dedicated to creating a productive work environment for all our employees. Both at work and in the clinic, we are committed to recruiting individuals that exemplify diversity in culture and life experience and are always striving to grow and improve. As an emerging company operating in a competitive industry, much of our success is rooted in investing in the development of each of our employees. It is our goal to empower all employees to take full advantage of their professional growth opportunities, to lead them to long-term job satisfaction and organizational success. Our people are our greatest competitive advantage and as we grow, we plan to continue to add to our human capital initiatives.

Corporate Information

We were incorporated under the laws of the State of Delaware in July 2018. Our principal corporate office is located at 930 Winter Street, Suite M-500, Waltham, MA 02451, and our telephone number is (617) 443-2400. Our website address is www.aerovatetx.com. Our website and the information contained on, or that can be accessed through, the website will not be deemed to be incorporated by reference in, and are not considered part of, this Annual Report on Form 10-K.

We own various U.S. federal trademark applications and unregistered trademarks, including our company name. All other trademarks or trade names referred to in this Annual Report on Form 10-K are the property of their respective owners.

On July 2, 2021, we closed our initial public offering, or IPO, in which we issued and sold 9,984,463 shares of common stock, including the exercise in full by the underwriters of their option to purchase up to 1,302,321 additional shares of common stock, at a public offering price of $14.00 per share. Including the option exercise, our aggregate net proceeds from the IPO were $126.9 million, net of underwriting discounts, commissions and estimated offering costs.

We are an “emerging growth company” as defined in the Jumpstart Our Business Startups Act of 2012. We will remain an emerging growth company until the earlier of: (i) the last day of the fiscal year (a) following the fifth anniversary of the completion of the IPO, (b) in which we have total annual gross revenue of at least $1.235 billion, or (c) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds $700.0 million as of the prior June 30th, and (ii) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period.

Solely for convenience, the trademarks and trade names in this Annual Report on Form 10-K are referred to without the symbols ® and ™, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

Available Information

Our website address is https://www.aerovatetx.com. Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, including exhibits, proxy and information statements and amendments to those reports filed or furnished pursuant to Sections 13(a), 14, and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, are available through the “Investors” portion of our website free of charge as soon as reasonably practicable after we

electronically file such material with, or furnish it to, the SEC. Information on our website is not part of this Annual Report on Form 10-K or any of our other securities filings unless specifically incorporated herein by reference. In addition, our filings with the SEC may be accessed through the SEC's Interactive Data Electronic Applications system at www.sec.gov. All statements made in any of our securities filings, including all forward-looking statements or information, are made as of the date of the document in which the statement is included, and we do not assume or undertake any obligation to update any of those statements or documents unless we are required to do so by law.

From time to time, we may use our website, LinkedIn or our Twitter account (@AerovateTx) to distribute material information. Our financial and other material information is routinely posted to and accessible on the Investors section of our website, available at www.aerovatetx.com. Investors are encouraged to review the Investors section of our website because we may post material information on that site that is not otherwise disseminated by us. Information that is contained in and can be accessed through our website or our Twitter or LinkedIn posts are not incorporated into, and does not form a part of, this Annual Report.

Our code of conduct, corporate governance guidelines and the charters of our Audit Committee, Compensation Committee and Nominating and Corporate Governance Committee are available through the "Investors" portion of our website.

Item 1A. Risk Factors.

In evaluating the Company and our business, careful consideration should be given to the following risk factors, in addition to the other information set forth in this Annual Report on Form 10-K and in other documents that we file with the SEC. Investing in our common stock involves a high degree of risk. If any of the following risks and uncertainties actually occurs, our business, prospects, financial condition or results of operations could be materially and adversely affected. The risks described below are not intended to be exhaustive and are not the only risks facing the Company. New risk factors can emerge from time to time, and it is not possible to predict the impact that any factor or combination of factors may have on our business, prospects, financial condition or results of operations.

Risks Related to Our Limited Operating History, Financial Position, and Capital Requirements

We are a clinical-stage biopharmaceutical company with a limited operating history.

We are a clinical-stage biopharmaceutical company established in July 2018 with a limited operating history. Since our inception, we have devoted substantially all of our efforts to organizing and staffing our company, research and development of AV-101, our initial product candidate, business planning, raising capital, and providing general and administrative support for these operations. We have limited experience and have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the pharmaceutical industry. We have completed our Phase 1 clinical trial of AV-101. We announced completion of enrollment in the Phase 2b portion and enrollment of the first patient in the Phase 3 portion of our Inhaled iMatinib Pulmonary Arterial Hypertension Clinical Trial (IMPAHCT) Phase 2b/Phase 3 clinical trial for AV-101 in adults with PAH in November 2023. We may explore additional indications for AV-101, but do not intend to conduct research on additional product candidates at this time. We have no products approved for commercial sale and therefore have never generated any revenue from product sales, and we do not expect to in the foreseeable future. We have no other experience as a company conducting clinical trials, submitting applications for regulatory approvals, such as a New Drug Application, or NDA, or commercializing any products.

We have incurred significant operating losses since our inception and anticipate that we will continue to incur losses for the foreseeable future. We may never achieve or maintain profitability.

We have incurred significant operating losses in each year since our incorporation in July 2018, do not expect to become profitable in the near future, and may never achieve profitability. Our net losses were $75.5 million and $51.5 million for the years ended December 31, 2023 and December 31, 2022, respectively. As of December 31, 2023, we had an accumulated deficit of $163.4 million. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We have no products approved for commercial sale, have not generated any revenue from product sales and have incurred losses in each year since our inception in July 2018. Substantially all of our operating

losses have resulted from costs incurred in connection with our research and development program of AV-101 and from general and administrative costs associated with our operations. AV-101 will require substantial additional development time and resources before we would be able to apply for or receive regulatory approvals and begin generating revenue from product sales. We also do not yet have a sales organization or commercial infrastructure and, accordingly, we will incur significant expenses to develop a sales organization or commercial infrastructure in advance of generating any commercial product sales. In addition, as a public company, we will continue to incur additional costs associated with operating that we did not incur as a private company. As a result, we expect to continue to incur significant expenses and operating losses for the foreseeable future, and we anticipate these losses will increase as we continue to develop AV-101 through clinical trials and regulatory submissions. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or when we will become profitable, if at all. Even if we do become profitable, we may not be able to sustain or increase our profitability on a quarterly or annual basis. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' deficit and working capital.

The amount of our future losses is uncertain and our quarterly and annual operating results may fluctuate significantly or may fall below the expectations of investors or securities analysts, each of which may cause our stock price to fluctuate or decline. Our quarterly and annual operating results may fluctuate significantly in the future due to a variety of factors, many of which are outside of our control and may be difficult to predict, including the following:

- the timing and success or failure of the clinical development of AV-101, or any other change in the competitive landscape of our industry, including consolidation among our competitors or partners;
- our ability to successfully open clinical trial sites for AV-101 and recruit and retain subjects for clinical trials, and any delays caused by difficulties in such efforts;
- our ability to obtain regulatory approval for AV-101, and the timing and scope of any such approvals we may receive;
- the timing and cost of, and level of investment in, research and development activities relating to AV-101, which may change from time to time;
- the cost of manufacturing AV-101, should it receive regulatory approval, which may vary depending on the quantity of production and the terms of our agreements with manufacturers;
- the experience of any delays or any issues with any of the above, including but not limited to failed studies, complex results, safety issues or other regulatory challenges;
- our ability to attract, hire and retain qualified personnel;
- the establishment of a sales, marketing, access and distribution infrastructure and the scaling-up manufacturing capabilities, whether alone or with third parties, to commercialize any product candidates for which we may obtain regulatory approval, if any;
- expenditures that we will or may incur to pursue additional indications for AV-101 or develop or acquire additional product candidates;
- the level of demand for AV-101, should it receive regulatory approval, which may vary significantly;
- the risk/benefit profile, cost and reimbursement policies with respect to AV-101, if approved, and existing and potential future therapeutics that compete with AV-101;
- the changing and volatile United States and global economic conditions;

- future accounting pronouncements or changes in our accounting policies; and

- changes to government policies and/or regulation impacting the commercialization of pharmaceutical products.

The cumulative effects of these factors could result in large fluctuations and unpredictability in our quarterly and annual operating results. As a result, comparing our operating results on a period-to-period basis may not be meaningful. This variability and unpredictability could also result in our failing to meet the expectations of industry or financial analysts or investors for any period. If our revenue or operating results fall below the expectations of analysts or investors or below any forecasts we may provide to the market, or if the forecasts we provide to the market are below the expectations of analysts or investors, the price of our common stock could decline substantially. Such a stock price decline could occur even when we have met any previously publicly stated guidance we may provide.

We have no products approved for commercial sale and have not generated any revenue from product sales.

Our ability to become profitable depends upon our ability to generate revenue. To date, we have not generated revenue, and we do not expect to generate any revenue in the near future. We do not expect to generate significant revenue unless and until we obtain regulatory approval of, and begin to sell AV-101. Our ability to generate revenue depends on a number of factors, including, but not limited to, our ability to:

- successfully enroll subjects in, and complete, our ongoing and any future clinical trials for AV-101;

- obtain sufficient safety data required to obtain United States and foreign regulatory approval for AV-101;

- timely file and receive U.S. Food and Drug Administration, or FDA, acceptance of our NDA for AV-101 for review;

- receive regulatory approvals from the FDA and foreign regulatory authorities for AV-101 in order to commence marketing of AV-101;

- establish commercial manufacturing capabilities or make arrangements with third-party manufacturers for clinical supply and commercial manufacturing;

- obtain and maintain patent and trade secret protection or non-patent regulatory exclusivity for AV-101;

- execute a commercial launch of AV-101, if approved, whether alone or in collaboration with others;

- obtain and maintain acceptance of AV-101, if and when approved, by patients, the medical community and third-party payors;

- position AV-101 to effectively compete with other therapies;

- obtain and maintain healthcare coverage and adequate reimbursement;

- enforce and defend intellectual property rights and claims;

- implement measures to help minimize the risk of public health crises, to our employees as well as patients and subjects enrolled in our clinical trials; and

- maintain a continued acceptable safety profile of AV-101 following approval.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize AV-101, which would materially harm our business. If we do not receive regulatory approvals for AV-101, we may not be able to continue our operations.

We will require additional capital to finance our operations, which may not be available on acceptable terms, or at all. If we are unable to raise capital when needed, we would be forced to delay, reduce or terminate our product development or commercialization efforts.

Since our inception, we have invested substantially all of our efforts and financial resources in the development of AV-101 to address the core disease processes of PAH. We believe that we will continue to expend substantial resources for the foreseeable future in connection with the clinical development of AV-101, including in connection with our Phase 2b/Phase 3 clinical trial. These expenditures will include costs associated with clinical trials, obtaining regulatory approvals, manufacturing and supply, as well as commercializing AV-101, if approved for sale. Our overall costs have risen due to the delays in site activation and patient enrollment, and due to our increased headcount to mitigate the effects of staff shortages at clinical trial sites and CROs. In addition, other unanticipated costs may arise. Because the outcome of any clinical trial is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of AV-101.

As of December 31, 2023, we had cash and cash equivalents and short-term investments of $122.4 million. We expect our existing cash, cash equivalents and available-for-sale securities will be sufficient to fund our planned operations into 2026 based upon our current operating plans. However, our operating plans may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned. In addition, we may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans.

Our future capital requirements depend on many factors, including:

- the scope, timing, rate of progress, results and costs of our preclinical studies or clinical trials for AV-101 and any additional product candidates;
- the number and scope of additional product candidates we decide to pursue;
- the extent to which we discover and develop additional product candidates;
- the scope and costs of manufacturing development and commercial manufacturing activities;
- the cost, timing and outcome of regulatory review of AV-101 and any additional product candidates;
- the cost of building a medical affairs and commercial organization including a sales force in anticipation of commercialization of AV-101 and any additional product candidates;
- the cost and timing associated with commercializing AV-101 and any additional product candidates, if approved;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- any product liability or other lawsuits related to AV-101 and any additional product candidates;
- our efforts to enhance operational systems and our ability to attract, hire and retain qualified personnel, including personnel to support the development of AV-101 and any additional product candidates;
- the extent to which we pursue additional indications for AV-101;
- the extent to which we acquire or in-license other product candidates;
- our ability to establish and maintain collaborations on favorable terms, if at all;

- the costs associated with being a public company;

- the potential additional expenses attributable to adjusting our development plans (including any supply related matters) in response to public health crises; and

- the timing, receipt and amount of sales of AV-101 and any additional product candidates, if approved.

Additional funds may not be available when we need them, on terms that are acceptable to us, or at all. If adequate funds are not available to us on a timely basis, we may be required to:

- delay, limit, reduce or terminate clinical studies or other medical and development activities for AV-101; or

- delay, limit, reduce or terminate our efforts to establish manufacturing and sales and marketing capabilities or other activities that may be necessary to commercialize AV-101, or reduce our flexibility in developing or maintaining our sales and marketing strategy.

We also could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our technologies or AV-101 that we would otherwise pursue on our own. We do not expect to realize revenue from sales of AV-101 in the foreseeable future, if at all, and unless and until AV-101 is clinically tested, approved for commercialization and successfully marketed. To date, we have funded our operations through private placements of convertible preferred stock, convertible notes and proceeds from our initial public offering, or IPO. We will be required to seek additional funding in the future and currently intend to do so through public or private equity offerings or debt financings, credit or loan facilities or a combination of one or more of these funding sources.

If we raise additional funds by issuing equity securities, our stockholders will suffer dilution and the terms of any financing may adversely affect the rights of our stockholders. In addition, as a condition to providing additional funds to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. Debt financing, if available, is likely to involve restrictive covenants limiting our flexibility in conducting future business activities, and, in the event of insolvency, debt holders would be repaid before holders of our equity securities received any distribution of our corporate assets. Additionally, global economic instability, higher interest rates and diminished credit availability may limit our ability to obtain debt financing on favorable terms.

Our ability to raise additional funds will depend on financial, economic and other factors, many of which are beyond our control. Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize AV-101. Disruptions in the financial markets in general, and due to public health crises, geopolitical conflicts and economic instability, may make equity and debt financing more difficult to obtain, and may have a material adverse effect on our ability to meet our fundraising needs. We cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all.

Future issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans or pursuant to our Sales Agreement, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.

We registered shares of common stock that we have issued and may issue under our employee equity plans and will file additional registration statements on Form S-8 to register additional shares pursuant to the "evergreen" provisions under our equity compensation plans. Accordingly, these shares are available for sale in the open market, subject to Rule 144 volume limitations applicable to affiliates, and subject to any vesting restrictions and lock-up agreements applicable to these shares.

Additionally, we have sold and may sell additional shares of our common stock pursuant to our ATM Equity Offering℠ Sales Agreement with BofA Securities, Inc., dated April 5, 2023, pursuant to which we may offer and sell, from time to time at our discretion, shares of our common stock having an aggregate offering price of up to $75.0 million, or the ATM Program. The shares of common stock under the ATM Program were registered pursuant to a shelf registration statement

on Form S-3 (File No. 333-266883), declared effective by the Securities and Exchange Commission, or the SEC, on August 23, 2022. As of December 31, 2023, 2,662,721 shares have been sold under the Sales Agreement, generating approximately $44.3 million of net proceeds after deducting commissions to the sales agent and other offering costs, and up to $30.0 million of shares of our common stock remain available for sale from time to time under the ATM Program. If we sell, or the market perceives that we intend to sell, substantial amounts of our common stock under our Form S-3 shelf registration statement or otherwise, the market price of our common stock could decline significantly. Any of the above events could significantly harm our business, prospects, financial condition and results of operations and cause the price of our common stock to decline.

Risks Related to the Development of AV-101

Our business is entirely dependent on the successful development, regulatory approval and commercialization of AV-101, our only product candidate under development.

We have invested substantially all of our efforts and financial resources in the development of AV-101 for the treatment of PAH, which has not been approved for sale or commercial use. Currently, AV-101 is our only product candidate and we have not licensed, acquired, or invented any other product candidates for preclinical or clinical evaluation. This may make an investment in our company riskier than similar companies that have multiple product candidates in active development and that therefore may be able to better sustain a failure of a lead candidate. The success of our business, including our ability to finance our company and generate any revenue in the future, will, at this point, depend entirely on the successful development, regulatory approval and commercialization of AV-101, which may never occur. We may have inadequate financial or other resources to advance AV-101 through the clinical trial process, depending on the requirements of the FDA and similar foreign regulatory agencies. In addition, our clinical development program for AV-101 may not lead to regulatory approval from the FDA and similar foreign regulatory agencies if we fail to demonstrate that AV-101 is safe and effective in our ongoing Phase 2b/Phase 3 clinical trial, and we may therefore fail to commercialize AV-101. Further, interpretation of trial results by the FDA and similar foreign regulatory agencies may vary and AV-101 may not receive regulatory approval even if it is successful in planned and future clinical trials. Any failure to obtain regulatory approval of AV-101 would have a material and adverse impact on our business. Even if we successfully obtain regulatory approvals to market AV-101, our revenue will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval. If the markets or patient subsets that we are targeting are not as significant as we estimate, we may not generate significant revenues from sales of AV-101, even if approved.

We plan to seek regulatory approval to commercialize AV-101 in the United States and in selected foreign countries. The clinical and commercial success of AV-101 will depend on a number of factors, including the following:

- our ability to raise any additional required capital on acceptable terms, or at all;
- timely completion of clinical trials, which may be significantly slower or cost more than we currently anticipate and will depend substantially upon the performance of third-party contractors, as well as timely completion of any preclinical studies that may be required in the future;
- whether we are required by the FDA or similar foreign regulatory agencies to conduct additional clinical trials or other studies beyond those planned to support approval of AV-101;
- our ability to consistently manufacture AV-101 on a timely basis;
- our ability, and the ability of any third parties with whom we contract, to remain in good standing with regulatory agencies and develop, validate and maintain commercially viable manufacturing processes that are compliant with current Good Manufacturing Practices, or current GMPs;
- our ability to demonstrate to the satisfaction of the FDA and similar foreign regulatory authorities the safety, efficacy and acceptable risk-benefit profile of AV-101;

- the prevalence, duration and severity of potential side effects or other safety issues experienced with AV-101;
- the timely receipt of necessary marketing approvals from the FDA and similar foreign regulatory authorities;
- achieving and maintaining, and, where applicable, ensuring that our third-party contractors achieve and maintain, compliance with our contractual obligations and with all regulatory requirements applicable to AV-101;
- the differentiation of AV-101 from other available approved or investigational drugs and treatments of PAH, and the willingness of physicians, operators of hospitals and clinics and patients to adopt and utilize AV-101 administered using a dry powder inhaler, or DPI;
- our ability to successfully develop a commercial strategy and thereafter commercialize AV-101 in the United States and internationally, if approved for marketing, sale and distribution in such countries and territories, whether alone or in collaboration with others;
- the availability of coverage and adequate reimbursement from managed care plans, private insurers, government payors (such as Medicare and Medicaid and similar foreign authorities) and other third-party payors for AV-101;
- patients' ability and willingness to pay out-of-pocket for AV-101 in the absence of coverage and/or adequate reimbursement from third-party payor;
- the convenience of the administration of AV-101 using our DPI;
- acceptance by physicians, payors and patients of the benefits, safety and efficacy of AV-101, if approved;
- patient demand for AV-101, if approved;
- our ability to establish and enforce intellectual property rights in and to AV-101; and
- our ability to avoid third-party patent interference, intellectual property challenges or intellectual property infringement claims.

These factors, many of which are beyond our control, could cause us to experience significant delays or an inability to obtain regulatory approvals or commercialize AV-101. Even if regulatory approvals are obtained, we may never be able to successfully commercialize AV-101. Accordingly, we cannot provide assurances that we will be able to generate sufficient revenue through the sale of AV-101 to continue our business or achieve profitability.

While the scope of regulatory approval generally is similar in other countries, in order to obtain separate regulatory approval in other countries we must comply with numerous and varying regulatory requirements of such countries regarding safety and efficacy. For example, European regulatory authorities generally require a trial comparing the efficacy of the new drug to an existing drug prior to granting approval. Other countries also have their own regulations governing, among other things, clinical trials and commercial sales, as well as pricing and distribution of AV-101, and we may be required to expend significant resources to obtain regulatory approval and to comply with ongoing regulations in these jurisdictions. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in others.

Any outbreak of highly infectious or contagious diseases could seriously harm our research, development, and commercialization efforts, increase our costs and expenses and have a material adverse effect on our business, financial condition, and results of operations.

Public health crises such as pandemics or similar outbreaks could adversely impact our business. The extent to which any outbreak of highly infectious or contagious diseases impacts our operations will ultimately depend on future developments, which are highly uncertain and cannot be predicted with confidence, including the scope, severity, and duration of the

pandemic or outbreak, actions taken to contain the pandemic or mitigate its impact, and the direct and indirect economic effects of the pandemic or outbreak and containment measures, among others. Similar to other biopharmaceutical companies, we may experience protocol deviations, delays in enrolling patients and completing our ongoing global Phase 2b/Phase 3 clinical trial of AV-101, as well as general supply chain delays.

In addition, as a result of medical complications associated with PAH, the patient populations that AV-101 targets may be particularly concerned with public health crises, which may make it more difficult for us to identify patients able to enroll in our current and future clinical trials and may impact the ability of enrolled patients to complete any such trials. Any negative impact public health crises may have on patient enrollment or treatment or the execution of our AV-101 clinical trials could cause costly delays, which could adversely affect our ability to obtain regulatory approval for and to commercialize AV-101, increase our operating expenses, and have a material adverse effect on our financial results. Timely enrollment in planned clinical trials, including our global Phase 2b/Phase 3 clinical trial for AV-101, is dependent upon clinical trial sites being able to actively recruit, screen, enroll, and treat patients in geographies which could be and have been adversely affected by global health matters, such as pandemics.

We are conducting our first late-stage clinical trial of AV-101, a dry powder formulation of imatinib for the treatment of PAH administered using a DPI, to assess its safety and tolerability. Although we believe that AV-101 has therapeutic potential for PAH based on oral imatinib's results in the Phase 3 IMPRES trial, we are utilizing a novel dry powder formulation which may not achieve better or similar levels of clinical activity or may have similar tolerability challenges as oral imatinib. The results of earlier studies and trials of oral imatinib in PAH patients and our Phase 1 clinical trial of AV-101 may not be predictive of future trial results for AV-101.

The results of our Phase 1 clinical trial, as well as clinical testing of oral imatinib in PAH patients by third-parties, may not be predictive of the results of our ongoing Phase 2b/Phase 3 clinical trial. In November 2023, we announced completion of enrollment with 202 patients in the Phase 2b portion, and concurrently announced enrollment of the first patient in the Phase 3 portion, of our Phase 2b/Phase 3 trial of AV-101. We have over 120 clinical sites open and enrolling patients in the Phase 3 portion of the Phase 2b/Phase 3 trial and may continue to activate additional clinical sites globally while enrollment in the Phase 3 portion continues. At this time, we expect to report topline data from the Phase 2b portion of the trial in June 2024. However, it is difficult to predict the timing of topline data availability with certainty due to the timing of the last patient visit in the Phase 2b portion of our trial and the timing to clean and lock the database to report topline results. As we will not know the final size of the Phase 3 portion of our trial until we see the results of the Phase 2b portion of our trial, it is difficult to predict the timing of topline data availability for the Phase 3 portion of our trial with certainty. Our belief that AV-101 has a potential therapeutic benefit for PAH patients is based in part on the Phase 3 IMPRES trial conducted by Novartis AG, or Novartis, which showed oral administration of imatinib, marketed as Gleevec for multiple cancers, led to statistically significant improvements across both primary and secondary endpoints in PAH patients on top of PAH standard of care therapies. Despite the statistically significant improvements in six minute walk distance, or 6MWD, and hemodynamics, there was no difference between oral imatinib and placebo in time to clinical worsening (TTCW), a composite endpoint consisting of death, hospitalization due to worsening PAH, worsening functional class, and a 15% reduction in 6MWD. Oral imatinib was associated with significant adverse events that precluded its approval as a therapy for PAH. AV-101 is our proprietary inhaled dry powder formulation of imatinib that delivers the medicine directly to the lung tissues using a DPI. While we have completed a Phase 1 clinical trial in 82 healthy volunteers in which AV-101 demonstrated lower plasma levels of imatinib compared to 400 mg of oral imatinib and a favorable tolerability profile at a dose of up to 90 mg twice a day, AV-101 has not yet completed a trial in any patients with PAH to assess its efficacy and AV-101 may not have the same clinical activity as oral imatinib seen in the IMPRES trial. We also cannot be certain that AV-101 will continue to show similar tolerability when dosed in PAH patients as it did in healthy volunteers, and we may not be able to demonstrate to the satisfaction of the FDA the safety, efficacy and acceptable risk-benefit profile of AV-101 during our ongoing Phase 2b/Phase 3 clinical trial. As a result, even if AV-101 does achieve lower imatinib plasma concentrations in our Phase 2b/Phase 3 clinical trial, there can be no assurance that AV-101 will exhibit similar tolerability as compared to our Phase 1 clinical trial or improved tolerability as compared to the IMPRES trial of oral imatinib. Product candidates in later stages of clinical trials may fail to show the desired pharmacological properties or safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials. A number of companies in the pharmaceutical and biotechnology industries, including Novartis in the IMPRES trial of oral imatinib, have suffered significant setbacks in Phase 3 clinical trials, even after positive results in earlier clinical trials. These setbacks have been caused by, among other things, preclinical findings made while clinical trials were underway and safety

or efficacy observations made in clinical trials, including previously unreported adverse events. Notwithstanding any promising results in our Phase 1 clinical trial, we cannot be certain that we will not face similar setbacks.

Additionally, we may utilize "open-label" trial designs and plan to use an open-label extension trial in addition to our Phase 2b/Phase 3 clinical trial to collect additional data on AV-101 and may do so as appropriate in the future. An "open-label" clinical trial is one where both the patient and investigator know whether the patient is receiving the investigational product candidate or either an existing approved drug or placebo. Most typically, open-label clinical trials test only the investigational product candidate and sometimes may do so at different dose levels. Open-label clinical trials are subject to various limitations that may exaggerate any therapeutic effect as patients in open-label clinical trials are aware when they are receiving treatment. Open-label clinical trials may be subject to a "patient bias" where patients perceive their symptoms to have improved merely due to their awareness of receiving an experimental treatment. In addition, open-label clinical trials may be subject to an "investigator bias" where those assessing and reviewing the physiological outcomes of the clinical trials are aware of which patients have received treatment and may interpret the information of the treated group more favorably given this knowledge. The results from an open-label trial or extension may not be predictive of future clinical trial results with AV-101 when studied in a controlled environment with a placebo or active control. Currently, we are collecting additional safety information for AV-101 in the long-term extension study eligible to patients who have completed participation in our current Phase 2b/Phase 3 clinical trial. Once an optimal dose has been identified in our Phase 2b/Phase 3 clinical trial, the long-term extension study would qualify as an "open-label" trial design.

As a result of the foregoing, even if we are able to complete any planed and future clinical trials of AV-101, the results may not be sufficient to obtain regulatory approval.

We have experienced and may in the future encounter difficulties with site activation and patient enrollment in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the study until its conclusion. We have experienced and may in the future experience difficulties in site activation delays and patient enrollment in our clinical trials for a variety of reasons as a result of staff shortages and short-term interruptions at clinical trial sites and CROs. We have over 120 clinical sites open and may activate a few new sites while enrolling patients in the Phase 3 portion of IMPAHCT, our ongoing Phase 2b/Phase 3 clinical trial to evaluate the safety and efficacy of different doses of AV-101 in adults with PAH. In November 2023, we announced completion of enrollment with 202 patients in the Phase 2b portion of IMPAHCT and announced enrollment of the first patient in the Phase 3 portion of IMPAHCT. At this time, we expect to report topline data from the Phase 2b portion of the trial in June 2024. However, it is difficult to predict the timing of topline data availability with certainty due to the timing of the last patient visit in the Phase 2b portion of our trial and the timing to clean and lock the database to report topline results. As we will not know the final size of the Phase 3 portion of our trial until we see the results of the Phase 2b portion of our trial, it is difficult to predict the timing of topline data availability for the Phase 3 portion of our trial with certainty. In addition, the ongoing staff shortages and short-term interruptions at clinical trial sites and CROs that caused patient enrollment delays for the Phase 2b portion of our trial and could cause patient enrollment delays for the Phase 3 portion of our trial. The Phase 2b portion of this trial is a dose-ranging trial in which pulmonary vascular resistance is the primary endpoint. The Phase 3 portion of the trial will be based on the optimal dose selected in the Phase 2b portion with 6MWD as the primary endpoint. The enrollment of patients depends on many additional factors, including:

- size and nature of the patient population and process for identifying patients;
- the severity of the disease under investigation;
- the availability and efficacy of approved drugs for the disease under investigation;
- the patient eligibility criteria defined in the protocol;
- the general willingness of patients to enroll in the trial;

- the size of the patient population required for analysis of the trial's primary endpoints;
- the proximity of patients to trial sites;
- the design of the trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience, and to obtain Investigational Review Board, or IRB, approval to conduct our trial at U.S. sites, and similar approvals at sites outside the United States;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment;
- clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new therapies that may be approved for the indications we are investigating;
- competition for patients from other investigational clinical trials in PAH being conducted at the same time as our Phase 2b/Phase 3 trial; and
- the clinical site's ability to obtain and maintain patient consents.

Enrollment risks are heightened with respect to indications that are rare or orphan diseases, which may limit the pool of patients that may be enrolled in our clinical trials. We are developing AV-101 for the treatment of PAH, which is an orphan disease and does not have a large patient population. As a result, we may encounter difficulties enrolling subjects in our clinical trials evaluating AV-101 for the treatment of PAH due, in part, to the small size of this patient population.

In addition, our clinical trials may compete with other clinical trials for product candidates that seek to treat PAH, and this competition will reduce the number and types of patients available to us, because some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Since the number of qualified clinical investigators is limited, we may conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials in such clinical trial sites.

Our overall costs have risen due to the delays in site activation and patient enrollment, and due to our increased headcount to mitigate the effects of staff shortages at clinical trial sites and CROs. Any additional delays in patient enrollment may result in increased costs or may affect the timing or outcome of our ongoing or any future clinical trials, which could prevent completion of these trials and adversely affect our ability to advance the development of AV-101.

Clinical development involves a lengthy and expensive process with an uncertain outcome, and delays can occur for a variety of reasons outside of our control.

Clinical development is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. We have completed our Phase 1 clinical trial of AV-101 in healthy volunteers and announced in November 2023 completion of enrollment with 202 patients in the Phase 2b portion and enrollment of the first patient in the Phase 3 portion of our Phase 2b/Phase 3 dose-ranging clinical trial in adults with PAH. The FDA has agreed in principle with the proposed study design of our Phase 2b/Phase 3 efficacy trial, dose strengths, statistical analysis and that a single efficacy study with strong results could be sufficient to support a 505(b)(2) NDA. However, changes in regulatory requirements and guidance may occur and we may need to amend our clinical trial protocol to reflect these changes with appropriate regulatory authorities. In addition, we may experience delays in completing our ongoing and planned studies and trials of AV-101. Furthermore, we cannot be certain that studies or trials for AV-101 will not require redesign, enroll an adequate number of subjects on time or be completed on schedule, if at all. These factors

may also impact our ability to release data within our anticipated timeframe. Clinical trials can be delayed or terminated for a variety of reasons, including delays or failures related to:

- the FDA or comparable foreign regulatory authorities disagreeing as to the design or implementation of our clinical trials;
- delays in obtaining regulatory authorization to commence a trial;
- reaching agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- obtaining institutional review board, or IRB, approval at each trial site;
- recruiting an adequate number of suitable patients to participate in a trial;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate;
- having subjects complete a trial or return for post-treatment follow-up;
- clinical sites deviating from trial protocol or dropping out of a trial;
- addressing subject safety concerns that arise during the course of a trial;
- adding a sufficient number of clinical trial sites; or
- obtaining sufficient quantities of AV-101 for use in clinical trials from third-party suppliers on a timely basis.

We may experience numerous adverse or unforeseen events during, or as a result of, preclinical studies, if additional studies are required, and clinical trials that could delay or prevent our ability to receive marketing approval or commercialize AV-101, including:

- we may receive feedback from regulatory authorities that requires us to modify the design of our clinical trials or conduct additional studies;
- clinical trials of AV-101 may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon our development program for AV-101;
- the number of patients required for clinical trials of AV-101 may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate, or participants may drop out of these clinical trials at a higher rate than we anticipate;
- we or our third-party contractors may fail to comply with regulatory requirements, fail to maintain adequate quality controls, or be unable to produce sufficient product supply to conduct and complete clinical trials of AV-101 in a timely manner, or at all;
- we or our investigators might have to suspend or terminate clinical trials of AV-101 for various reasons, including non-compliance with regulatory requirements, a finding that AV-101 has undesirable side effects or other unexpected characteristics, or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of AV-101 may be greater than we anticipate;

- the quality of our active pharmaceutical ingredient or other materials necessary to conduct clinical trials of AV-101 may be insufficient or inadequate;

- the FDA may determine that we cannot rely on the Section 505(b)(2) approval pathway for AV-101, in which case we may be required to conduct additional clinical trials and provide additional data and information and meet additional standards for product approval;

- the FDA may determine that we have identified the wrong listed drug(s), or LD, or that approval of a Section 505(b)(2) application for AV-101 is blocked by patent or non-patent exclusivity of the LD or LDs;

- regulators may revise the requirements for approving AV-101, or such requirements may not be as we anticipate; and

- future collaborators may conduct clinical trials in ways they view as advantageous to them but that are sub-optimal for us.

If we are required to conduct additional clinical trials or other testing of AV-101 beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of AV-101 or other testing, if the results of these trials or tests are not positive or are only moderately positive or if there are safety concerns, we may:

- incur unplanned costs;

- be delayed in obtaining marketing approval for AV-101 or not obtain marketing approval at all;

- obtain marketing approval in some countries and not in others;

- obtain marketing approval for indications or patient populations that are not as broad as intended or desired;

- obtain marketing approval with labeling that includes significant use or distribution restrictions or safety warnings, including boxed warnings;

- be subject to additional post-marketing testing requirements, which could be expensive and time consuming; or

- have the treatment removed from the market after obtaining marketing approval.

We could also encounter delays if a clinical trial is suspended or terminated by us, by the IRBs or ethics committees of the institutions in which such trials are being conducted, by the Safety Monitoring Committee, if any, for such clinical trial or by the FDA or other regulatory authorities. Such authorities may suspend or terminate a clinical trial due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site or a manufacturing, processing or storage site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a product candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial.

Further, we are conducting our Phase 2b/Phase 3 clinical trial for AV-101 in adults with PAH globally. This presents additional risks that may delay completion of our clinical trial. These risks include a delay in obtaining or a failure to obtain, regulatory authorization to commence a trial in each country where we plan to conduct the trial, the failure of enrolled patients in foreign countries to adhere to the clinical protocol as a result of differences in healthcare services or cultural customs, managing additional administrative burdens associated with foreign regulatory schemes, as well as political and economic risks relevant to such foreign countries.

Principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and may receive cash or equity compensation in connection with such services. If these relationships and any related

compensation result in perceived or actual conflicts of interest, or a regulatory authority concludes that the financial relationship may have affected the interpretation of the trial, the integrity of the data generated at the applicable clinical trial site may be questioned and the utility of the clinical trial itself may be jeopardized, which could result in the delay or rejection of the marketing application we submit. Any such delay or rejection could prevent or delay us from commercializing AV-101.

If any of our clinical trials of AV-101 are unsuccessful, delayed or terminated, its commercial prospects may be harmed, and our ability to generate revenues from sales of AV-101 will be delayed or not realized at all. In addition, any delays in completing our clinical trials may increase our costs, slow down our AV-101 development and approval process and jeopardize our ability to commence product sales and generate revenues. Any of these occurrences may significantly harm our business, financial condition and prospects. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of AV-101. If AV-101 generally proves to be ineffective, unsafe or commercially unviable, it would have a material and adverse effect on our business, financial condition, results of operations and prospects.

AV-101 may cause undesirable side effects or have other properties that could delay or prevent its regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any.

The results of our preclinical studies or clinical trials may show that AV-101 may cause undesirable side effects, which could interrupt, delay or halt clinical trials, resulting in the denial of regulatory approval by the FDA and other regulatory authorities. In light of widely publicized events concerning the safety risk of certain drug products, regulatory authorities, members of Congress, the Government Accounting Office, medical professionals and the general public have raised concerns about potential drug safety issues. These events have resulted in the withdrawal of drug products, revisions to drug labeling or boxed warnings that further limit use of the drug products and establishment of risk management programs that may, for instance, restrict distribution of drug products. The increased attention to drug safety issues may result in a more cautious approach by the FDA to clinical trials. Data from clinical trials may receive greater scrutiny with respect to safety, which may make the FDA or other regulatory authorities more likely to terminate clinical trials before completion, or require longer or additional clinical trials that may result in substantial additional expense and a delay or failure in obtaining approval or approval for a more limited indication than originally sought.

While AV-101 was generally well-tolerated in our Phase 1 clinical trial, subjects treated with 90 mg of AV-101, the highest dose in this trial, reported a higher frequency of adverse events, including cough at the time of inhalation of the dry powder and headache. However, all adverse events were generally mild and transient with only one discontinuation due to vomiting. The only adverse events experienced by subjects treated at lower doses of AV-101 in the Phase 1 MAD portion of the trial were cough at dosing (1 of 9 patients in the medium dose and 1 of 9 patients at the low dose) and throat irritation (1 patient of 9 at the medium dose). In contrast, the Phase 3 IMPRES trial of oral imatinib in PAH patients demonstrated significant AEs, including nausea, edema, vomiting and diarrhea. Despite the clinical effects of oral imatinib on their disease, 26% of patients on oral imatinib and 7% of placebo patients discontinued due to AEs by 24 weeks of the trial. Further development of oral imatinib for the treatment of PAH was discontinued by Novartis. We believe that delivery of imatinib directly to the lungs through our proprietary dry powder formulation has the potential to maximize the amount of drug in the targeted tissues while minimizing systemic exposure and minimizing the potential for serious adverse events. Nevertheless, if unacceptable side effects arise in our Phase 2b/Phase 3 clinical trial or other trials we may conduct, we, the FDA, or the IRBs at the institutions in which our studies are conducted could suspend or terminate our clinical trials or the FDA or comparable foreign regulatory authorities could order us to cease clinical trials or deny approval of AV-101 for PAH.

If AV-101 receives marketing approval and we or others later identify undesirable side effects caused by such product or by other imatinib products, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw, suspend or limit approvals of the product, or seek an injunction against its manufacture or distribution;

- we may be required to recall a product or change the way such product is administered to patients or conduct additional clinical trials or post-approval studies;

- additional restrictions may be imposed on the marketing of the particular product or the manufacturing processes for the product or any component thereof;

- we may be required to add additional warnings or boxed warnings to our drug labeling or issue safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings or other safety information about the product;

- we may be required to implement a Risk Evaluation and Mitigation Strategy, or REMS, which may include distribution or use restrictions;

- we could be sued and held liable for harm caused to patients;

- we may be subject to fines, injunctions or the imposition of criminal penalties;

- we could be sued and held liable for harm caused to patients;

- the product may become less competitive; and

- our reputation may suffer.

Any of the foregoing events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and result in the loss of significant revenues to us, which would materially and adversely affect our results of operations and business.

Interim, topline and preliminary results from our preclinical studies and clinical trials that we announce or publish from time to time may change as more data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publicly disclose preliminary, interim or topline data from our preclinical studies and clinical trials. These interim updates are based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the topline results that we report may differ from future results of the same studies or trials, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Topline data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, topline data should be viewed with caution until the final data are available. In addition, we may report interim analyses of only certain endpoints rather than all endpoints. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Adverse changes between interim data and final data could significantly harm our business and prospects. Further, additional disclosure of interim data by us or by our competitors in the future could result in volatility in the price of our common stock.

In addition, the information we choose to publicly disclose regarding a particular study or trial is typically selected from a more extensive amount of available information. Investors may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product candidate or our business. If the preliminary or topline data that we report differ from late, final or actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval

for, and commercialize, any of our product candidates may be harmed, which could harm our business, financial condition, results of operations and prospects.

We intend to use the 505(b)(2) regulatory pathway to seek regulatory approval of AV-101, but if the FDA concludes that our marketing application no longer qualifies for the Section 505(b)(2) regulatory pathway, then our application may not be accepted by the FDA for review and approval may be delayed.

We intend to seek FDA approval for AV-101 for PAH through the Section 505(b)(2) regulatory pathway. Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, or FDCA, was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Amendments, and permits the submission of an NDA where at least some of the information required for approval comes from preclinical studies or clinical trials not conducted by or for the applicant and for which the applicant has not obtained a right of reference. The FDA interprets Section 505(b)(2) of the FDCA to permit the applicant to rely upon the FDA's previous findings of safety and efficacy for an approved product. The FDA requires submission of information needed to support any changes to a previously approved drug, such as published data or new studies conducted by the applicant or clinical trials demonstrating safety and efficacy. The FDA could require additional information to sufficiently demonstrate safety and efficacy to support approval. If the FDA later determines AV-101 does not meet the requirements of Section 505(b)(2), or that additional information is needed to support a marketing application for AV-101, we could experience delays in submitting a marketing application or in obtaining marketing approval. Moreover, even if AV-101 is approved under the Section 505(b)(2) regulatory pathway, the approval may be subject to limitations on the indicated uses for which it may be marketed or to other conditions of approval, or may contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the products.

Risks Related to Commercialization

We face, and will continue to face, significant competition and our failure to effectively compete may prevent us from achieving significant market penetration for AV-101, if approved. Most of our competitors have significantly greater resources than we do and we may not be able to successfully compete.

The pharmaceutical industry is highly competitive, with a number of established, large pharmaceutical companies, as well as many smaller companies. Many of these companies have greater financial resources, marketing capabilities and experience in obtaining regulatory approvals for product candidates. There are several pharmaceutical companies, biotechnology companies, public and private universities, government agencies and research organizations actively engaged in research and development of products to target PAH. We expect AV-101 to compete on the basis of, among other things, efficacy, safety, convenience, price, and the availability of reimbursement from commercial, government and other third-party payors. One or more of our competitors may develop products based upon the principles underlying our proprietary technologies earlier than us, obtain approvals for such products from the FDA more rapidly than us or develop alternative products or therapies that are safer, more effective and/or more cost effective than AV-101. We also expect to face competition in our efforts to identify appropriate collaborators or partners to help commercialize AV-101 in our target commercial areas.

If approved, AV-101 is expected to face competition from drug products that are already on the market, as well as those in clinical development for PAH. In particular, we expect that AV-101 will face competition from branded and/or generic prostanoids available in oral form as Orenitram (United Therapeutics Corporation, or United Therapeutics) and Uptravi (Janssen Pharmaceuticals, Inc., or Janssen), by inhalation as Tyvaso and Tyvaso DPI (United Therapeutics), and Ventavis (Janssen) and by infusion as Remodulin (United Therapeutics) Flolan (GSK) and Veletri (Janssen), which are existing drug products indicated for the treatment of PAH. Potential new prostanoid entrants include Yutrepia (Liquidia Corporation) which has received tentative FDA approval pending resolution of ongoing litigation with United Therapeutics, L606 liposomal treprostinil (Liquidia) treprostinil palmitil (Insmed), ralinepag (Arena Pharmaceuticals in collaboration with United Therapeutics). Additional drugs in development for PAH outside of the prostanoid pathway include sotatercept (Acceleron Pharma, Inc., a wholly-owned subsidiary of Merck & Co., Inc., or Merck) under review by the FDA and EMA, MK-5475 (Merck & Co., Inc.), seralutinib (Gossamer Bio, Inc.), KER-012 (Keros Therapeutics Inc.) and LPT-001 (Novartis). Finally, we are aware that Aerami Therapeutics, Inc. announced they intend to develop imatinib for PAH and have completed Phase 1 studies with their formulation.

We believe that AV-101, if approved, could be used prior to or in combination with prostanoids, and in combination with existing front-line agents such as the oral PDE5 inhibitors, including Revatio (Pfizer Inc.) and Adcirca (United Therapeutics); the sGC stimulator Adempas (Bayer AG); and oral ERAs, including Tracleer (Janssen), Letairis (Gilead Sciences, Inc.) and Opsumit (Janssen).

Many of our competitors have significantly greater financial, technical, manufacturing, marketing, sales and supply resources and experience than we do. If we successfully obtain approval for AV-101, we will face competition based on many different factors, including the safety and effectiveness of AV-101, the ease with which AV-101 can be administered and the extent to which patients accept the inhaled route of administration, the timing and scope of regulatory approvals for AV-101, the availability and cost of manufacturing, marketing and sales capabilities, price, reimbursement coverage and patent position. Competing products could present superior treatment alternatives, by being more effective, safer, less expensive or marketed and sold more effectively than AV-101. Competitive products may make any products we develop obsolete or noncompetitive before we recover the expense of developing and commercializing AV-101. Such competitors could also recruit our employees, which could negatively impact our level of expertise and our ability to execute our business plan.

If the FDA or comparable regulatory authorities approve generic versions of AV-101, or do not grant AV-101 a sufficient period of market exclusivity before approving its generic version, our ability to generate revenue may be adversely affected.

Once a NDA is approved, including under the 505(b)(2) pathway, the product covered thereby becomes a "reference listed drug" in the FDA's publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the Orange Book. Manufacturers may seek approval of generic versions of reference listed drugs through submission of Abbreviated New Drug Applications, or ANDAs, and may obtain therapeutical equivalence evaluations for 505(b)(2) pathway drugs under the Food and Drug Omnibus Reform Act's expanded authorities, in the United States. In support of an ANDA, a generic manufacturer need not conduct clinical trials to assess safety and efficacy. Rather, the applicant generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration and conditions of use or labelling as the reference listed drug and that the generic version is bioequivalent to the reference listed drug, meaning it is absorbed in the body at the same rate and to the same extent. Generic products may be significantly less costly to bring to market than the reference listed drug and companies that produce generic products are generally able to offer them at lower prices. Thus, following the introduction of a generic drug, a significant percentage of the sales of any branded product or reference listed drug is typically lost to the generic product.

Generic drug manufacturers may seek to launch generic products following the expiration of any applicable exclusivity period we obtain if AV-101 is approved, even if we still have patent protection. Competition that AV-101 could face from generic versions could materially and adversely affect our future revenue, profitability, and cash flows and substantially limit our ability to obtain a return on the investments we have made in AV-101.

If the market opportunity for AV-101 is smaller than we estimate or if any regulatory approval that we obtain is based on a narrower definition of the patient population, our revenue and ability to achieve profitability will be adversely affected, possibly materially.

The incidence and prevalence for target patient populations of AV-101 has not been established with precision. AV-101 is an inhaled dry powder formulation of antiproliferative imatinib for people who suffer from PAH. A DPI is used to deliver the medicine directly to lung tissues, enabling treatment of the diseased tissues directly while reducing the amount of drug delivered to other organs in the body which can cause unwanted adverse events. Our projections of both the number of people who have PAH, as well as the subset of people with PAH who have the potential to benefit from AV-101, are based on our estimates.

The total addressable market opportunity will ultimately depend upon, among other things, the patient criteria included in the final label, the indications for which AV-101 is approved for sale, acceptance by the medical community and patient access, product pricing and reimbursement. The number of patients with PAH for which AV-101 may be approved as treatment may turn out to be lower than expected, patients may not be otherwise amenable to treatment with our products, or new patients may become increasingly difficult to identify or gain access to, all of which would adversely affect our

results of operations and our business. AV-101 is our only product candidate and therefore our business is dependent on the market opportunity for our product.

The successful commercialization of AV-101 will depend in part on the extent to which governmental authorities, private health insurers, and other third-party payors provide coverage and adequate reimbursement levels. Failure to obtain or maintain coverage and adequate reimbursement for AV-101, if approved, could limit our ability to market our product and decrease our ability to generate revenue.

In the United States and markets in other countries, patients generally rely on third-party payors to be able to afford medical services and pharmaceutical products that receive FDA approval. Our ability to successfully commercialize our product candidates will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. A decision by a third-party payor not to cover or separately reimburse for AV-101, could reduce physician utilization if approved. Assuming there is coverage for AV-101 by a third-party payor, the resulting reimbursement payment rates may not be adequate or may require co-payments that patients find unacceptably high. We cannot be sure that coverage and reimbursement in the United States, the European Union, or EU, or elsewhere will be available for AV-101 and any reimbursement that may become available may not be adequate or may be decreased or eliminated in the future. For more information, see "*Business – Government Regulation – Pricing and Reimbursement"*.

No uniform policy for coverage and reimbursement for products exists among third-party payors in the United States. Therefore, coverage and reimbursement for products can differ significantly from payor to payor. Private third-party payors tend to follow Medicare coverage policies and payment limitations in setting their own reimbursement rates to a substantial degree, but also have their own methods and approval process apart from Medicare determinations. As a result, the coverage determination process is often a time-consuming and costly process that may require us to provide scientific and clinical support for the use of AV-101 to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Furthermore, rules and regulations regarding reimbursement change frequently, in some cases on short notice, and we believe that changes in these rules and regulations are likely.

Moreover, increasing efforts by governmental and other third-party payors in the United States and abroad to cap or reduce healthcare costs have resulted in increasing challenges to prices charged for pharmaceutical products and services, and many third-party payors may refuse to provide coverage and adequate reimbursement for particular drugs when an equivalent generic drug, biosimilar or a less expensive therapy is available. Even if we show improved efficacy or improved convenience of administration with AV-101, pricing of existing third-party therapeutics may limit the amount we will be able to charge for it. These third-party payors may deny or revoke the reimbursement status of AV-101, if approved, or establish prices for it at levels that are too low to enable us to realize an appropriate return on our investment. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize AV-101.

Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that reimbursement will be available for any product candidate that we commercialize and, if reimbursement is available, the level of reimbursement. In addition, many pharmaceutical manufacturers must calculate and report certain price reporting metrics to the government, such as average sales price, or ASP, and best price. Penalties may apply in some cases when such metrics are not submitted accurately and timely. Further, these prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs.

Outside the United States, pharmaceutical products are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe and other countries will likely put pressure on the pricing and usage of medical products. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. Other countries allow companies to fix their own prices for medical products, but monitor and control company profits. Additional foreign price

controls or other changes in pricing regulation could restrict the amount that we are able to charge for AV-101. Accordingly, in markets outside the United States, the reimbursement for AV-101 may be reduced compared with the United States and may be insufficient to generate commercially-reasonable revenue and profits.

Even if AV-101 obtains regulatory approval, it may fail to achieve market acceptance.

Even if AV-101 receives FDA or other regulatory approvals, its commercial success will depend significantly on its adoption and use by physicians and patients for approved indications. The degree of market acceptance of AV-101, if approved, will depend on a number of factors, including:

- the safety and efficacy of AV-101 as compared to other available treatments for PAH;
- patient satisfaction with the results of AV-101 and overall treatment experience, including, the ease and convenience of administration of AV-101;
- the perceived advantages of AV-101 over alternative treatments, such as prostacylins;
- the clinical indications for which AV-101 is approved and patient demand for approved products that treat those indications;
- our ability to manufacture and release adequate commercial supplies on a timely basis;
- the availability of coverage and adequate reimbursement from managed care plans, private insurers, government payors (such as Medicare and Medicaid) and other third-party payors for AV-101;
- the cost of treatment with AV-101 in relation to alternative treatments and patients' ability and willingness to pay out-of-pocket for the product, if approved, in the absence of coverage and/or adequate reimbursement from third-party payors;
- acceptance by physicians, operators of hospitals and clinics and patients of the product as a safe, effective and easy to administer treatment;
- physician and patient willingness to adopt a new therapy over other available therapies for treatment of PAH;
- the prevalence and severity of side effects;
- the effectiveness of our sales, marketing and distribution efforts;
- adverse publicity about AV-101 or favorable publicity about competitive products;
- potential product liability claims; and
- the approval of other new therapies for the same indication.

We cannot assure you that AV-101, if approved, will achieve market acceptance among physicians and patients. Any failure by AV-101, if approved, to achieve market acceptance or commercial success would adversely affect our results of operations.

We currently have no sales organization. If we are unable to establish sales capabilities on our own or through third parties, we may not be able to market and sell AV-101 effectively in the United States and foreign jurisdictions, if approved, or generate product revenue.

We currently employ a Chief Commercial Officer but do not have other employees in our commercial organization. In order to commercialize AV-101, if approved, in the United States and foreign jurisdictions, we must build our marketing, sales, commercial operations, access and distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so. If AV-101 receives regulatory approval, we expect to establish a full commercial organization in the United States with technical expertise and supporting marketing, sales, access and distribution capabilities to commercialize it, which will be expensive and time consuming. As a company, Aerovate has no prior experience in the marketing, sale and distribution of pharmaceutical products and there are significant risks involved in building and managing a sales organization, including our ability to hire, retain, and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel, and effectively manage a geographically dispersed sales and marketing team. Any failure or delay in the development of our internal sales, marketing, commercial operations, access and distribution capabilities would adversely impact the commercialization of AV-101. We may choose to collaborate with third parties that have commercial capabilities, either to augment our own commercial capabilities or in lieu of Aerovate building certain capabilities such as those related to sales or distribution. If we are unable to enter into such arrangements on acceptable terms or at all, we may not be able to successfully commercialize AV-101. If we are not successful in commercializing AV-101, either on our own or through arrangements with one or more third parties, we may not be able to generate product revenue and we would incur significant additional losses.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of AV-101.

We face an inherent risk of product liability as a result of the ongoing clinical testing of AV-101 and will face an even greater risk if we commercialize it. For example, we may be sued if AV-101 allegedly causes injury. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability, and a breach of warranty. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of AV-101. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for AV-101;
- injury to our reputation;
- withdrawal of clinical trial participants;
- costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- regulatory investigations, product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue; and
- the inability to commercialize AV-101.

Our inability to obtain and maintain sufficient product liability insurance at an acceptable cost and scope of coverage to protect against potential product liability claims could prevent or inhibit the commercialization of AV-101. We currently

carry product liability insurance covering our clinical trials, however, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. Our insurance policies also have various exclusions and deductibles, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient funds to pay such amounts. Moreover, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses. If and when we obtain approval for marketing any dose of AV-101, we intend to expand our insurance coverage to include its sale; however, we may be unable to obtain this liability insurance on commercially reasonable terms or at all.

Risks Related to Our Reliance on Third Parties

We rely, and intend to continue to rely, on qualified third parties to supply all components of AV-101. As a result, we are dependent on several third parties, some of which are sole source suppliers, for the manufacture of AV-101 and our supply chain, and if we experience problems with any of these suppliers, or they fail to comply with applicable regulatory requirements or to supply sufficient quantities at acceptable quality levels or prices, or at all, it would materially and adversely affect our business.

We do not own or operate manufacturing facilities for clinical or commercial manufacture of either our proprietary dry-powder formulation of imatinib or the DPI, including the drug substance and packaging. We have limited personnel with experience in drug-device product manufacturing and we lack the capabilities to manufacture either the drug component of AV-101 or the DPI on a clinical or commercial scale. We outsource all manufacturing and packaging of AV-101 to third parties and obtain the DPI from a sole source supplier, and we do not plan to own or operate our own manufacturing and packaging facilities. There can be no assurance that our clinical development product supplies will not be limited, interrupted, or of satisfactory quality or continue to be available at acceptable prices. In addition, any replacement of any of our third-party suppliers could require significant effort and expertise because there may be a limited number of qualified replacements.

Certain of our suppliers are subject to regulatory requirements covering manufacturing, testing, quality control and record keeping relating to AV-101, and are subject to pre-approval and ongoing inspections by the regulatory agencies. Failure by any of our suppliers to comply with applicable regulations may result in long delays and interruptions to our manufacturing capacity while we seek to secure another supplier that meets all regulatory requirements.

Reliance on third-party manufacturers entails risks that we would more directly manage and control, or to which we would not be subject, if we manufactured AV-101 ourselves, including:

- reliance on the third parties for regulatory compliance, quality assurance and hazardous materials handling;
- the possible breach of the manufacturing and quality agreements by the third parties because of factors beyond our control;
- the possibility of termination or nonrenewal of the agreements by the third parties because of our breach of the manufacturing agreement or based on their own business priorities;
- with respect to any manufacturers with which we do not have a long-term agreement, the possibility that the manufacturer decides to stop supplying to us or changes the price or other terms of supply; and
- changes in the products produced by our suppliers, such that they satisfy specifications but have an unanticipated negative impact on the performance of AV-101.

Any of these factors could cause the delay of required approvals or commercialization of AV-101, could prevent us from commercializing it successfully, could cause the suspension of initiation or completion of clinical trials and regulatory submissions, and could lead to higher product costs.

In addition, the facilities used by our contract manufacturing organizations, or CMOs to manufacture AV-101 are subject to various regulatory requirements and may be subject to inspection by the FDA or other regulatory authorities. We do not directly control manufacturing at our CMOs, and are completely dependent on them for compliance with current regulatory requirements. If our CMOs for AV-101 cannot successfully manufacture components of finished product that conforms to our specifications and the regulatory requirements of the FDA or comparable regulatory authorities in foreign jurisdictions, we may not be able to rely on them for the manufacture of AV-101. If we are required to change CMOs for any reason, we will be required to verify that the new CMO maintains facilities and procedures that comply with quality standards and with applicable regulations. We will also need to verify, such as through a manufacturing comparability study, that any new manufacturing process will produce AV-101 according to the specifications previously submitted to the FDA or another regulatory authority. In addition, changes in manufacturers often involve changes in manufacturing procedures and processes, which could require that we conduct bridging studies between our prior clinical supply used in our clinical trials and that of any new manufacturer. We may be unsuccessful in demonstrating the comparability of clinical supplies which could require the conduct of additional clinical trials. In addition, we have limited control over the ability of our CMOs to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable foreign regulatory authority finds our facilities or those of our CMOs inadequate for the manufacture of AV-101 or if such facilities are subject to enforcement action in the future or are otherwise inadequate, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or commercialize AV-101 and the timing of any such approval and commercialization.

Additionally, our CMOs may experience manufacturing difficulties or delays due to resource constraints or as a result of labor shortages, disputes or unstable political environments or on account of global pandemics or similar events. If our CMOs were to encounter any of these difficulties, our ability to provide AV-101 to patients in clinical trials, or to provide product for the treatment of patients once approved, would be jeopardized.

We rely, and intend to continue to rely, on third parties in the conduct of all of our clinical trials. If these third parties do not successfully carry out their contractual duties, fail to comply with applicable regulatory requirements or meet expected deadlines, we may be unable to obtain regulatory approval for AV-101.

We currently do not have the ability to independently conduct any clinical trials. The FDA and comparable foreign regulatory authorities in other jurisdictions require us to comply with regulations and standards, commonly referred to as good clinical practice, or GCP, requirements for conducting, monitoring, recording and reporting the results of clinical trials, in order to ensure that the data and results are scientifically credible and accurate and that the trial subjects are adequately informed of the potential risks of participating in clinical trials. We rely on medical institutions, clinical investigators, contract laboratories and other third parties, such as CROs, to conduct GCP-compliant clinical trials of AV-101 properly and on time. Our global Phase 2b/Phase 3 clinical trial is managed by one CRO and is currently enrolling in over 20 countries and 120 clinical sites. While we have agreements with these third parties, we monitor and control only certain aspects of their activities and have limited influence over their actual performance and the amount or timing of resources that they devote to our programs. Third parties with whom we contract may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. The third parties with whom we contract for execution of our clinical trials play a significant role in the conduct of these trials and the subsequent collection and analysis of data. Although we rely on these third parties to conduct our clinical trials, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with its investigational plan and protocol and applicable laws and regulations, and our reliance on these third parties does not relieve us of our regulatory responsibilities.

If the third parties conducting our clinical trials do not adequately perform their contractual duties or obligations, experience significant business challenges, disruptions or failures, do not meet expected deadlines, terminate their agreements with us or need to be replaced, or if the quality or accuracy of the data they obtain is compromised due to their failure to adhere to our protocols or to GCPs, or for any other reason, we may need to enter into new arrangements with alternative third parties. This could be difficult, costly or impossible, and clinical trials may need to be extended, delayed, terminated or repeated. As a result, we may not be able to obtain regulatory approval in a timely fashion, or at all, for AV-101, our results our business and results of operations and the commercial prospects for AV-101 would be harmed, our costs could increase, and our ability to generate revenues could be delayed. We may also be required to register certain

clinical trials and post the results of completed clinical trials on government-sponsored databases within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

We rely on third parties to supply the raw materials to produce AV-101.

We will rely on independent third parties to supply the raw materials that we use to produce AV-101. As such, we will be dependent upon their services and will not be in a position to control their operations as we might if we directly produced these raw materials. We do not have supplier contracts with these third parties. Although we believe the raw materials used to manufacture our products are readily available and can be obtained from multiple reliable sources on a timely basis, circumstances outside our control may impair our ability to have an adequate supply of raw materials to produce AV-101 which could lead to production delays, interruptions or the need to identify and qualify new raw materials in the production of AV-101.

We may seek to establish collaborations, and, if we are not able to establish them on commercially reasonable terms, or at all, we may have to alter our development and commercialization plans.

Our product development program and the potential commercialization of AV-101 will require substantial cash to fund expenses. We may decide to collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of AV-101.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's own evaluation of a potential collaboration. Such factors a potential collaborator will use to evaluate a collaboration may include the design or results of clinical trials, the likelihood of approval by the FDA or comparable foreign regulatory authorities, the potential market for AV-101, the costs and complexities of manufacturing and delivering AV-101 to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for AV-101. The terms of any additional collaborations or other arrangements that we may establish may not be favorable to us.

We may also be restricted under collaboration agreements from entering into future agreements on certain terms with potential collaborators. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate additional collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of AV-101 for which we are seeking to collaborate, reduce or delay its development program, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop AV-101 or bring it to market and generate product revenue.

In addition, any future collaborations that we enter into may not be successful. The success of our collaboration arrangements will depend heavily on the efforts and activities of our collaborators. Collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaborations. Disagreements between parties to a collaboration arrangement regarding clinical development and commercialization matters can lead to delays in the development process or commercializing the applicable product candidate and, in some cases, termination of the collaboration arrangement. These disagreements can be difficult to resolve if neither of the parties has final decision-making authority. Collaborations with pharmaceutical or biotechnology companies and other third parties often are terminated or allowed to expire by the other party. Any such termination or expiration would adversely affect us financially and could harm our business reputation.

Risks Related to Our Intellectual Property

We have six issued U.S. patents, and many pending patent applications with respect to AV-101. We can provide no assurance that any of our other current or future patent applications will result in issued patents. If we cannot protect our patent rights or our other proprietary rights, others may develop products similar or identical to ours, and we may not be able to compete effectively in our market or successfully commercialize any product candidates we may develop.

Our success depends to a significant degree upon whether we can continue to secure, enforce and defend intellectual property rights that protect our AV-101 product candidate and to operate our business without infringing, misappropriating or otherwise violating the intellectual property rights of others. If we are unable to obtain and maintain sufficient intellectual property protection for AV-101 or other product candidates that we may identify, or if the scope of the intellectual property protection obtained is not sufficiently broad, our competitors and other third parties could develop and commercialize product candidates similar or identical to ours, and our ability to successfully commercialize AV-101 and other product candidates that we may pursue may be impaired. We own six issued U.S. patents with respect to AV-101, and we can provide no assurance that any of our other current or future patent applications will result in issued patents or that any issued patents will provide us with any competitive advantage. Failure to obtain additional issued patents could have a material adverse effect on our ability to develop and commercialize our product candidates. Furthermore, other parties may successfully challenge, invalidate or circumvent our issued patents so that our patent rights do not create an effective competitive barrier or revenue source.

We seek to protect our proprietary position by, among other things, filing patent applications in the United States and abroad related to our proprietary technologies, development programs and product candidates. The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications or to maintain, defend and enforce any patents that may issue from such patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection.

Further, any of our non-provisional patent applications may fail to result in issued patents with claims that cover our proprietary products and technology, including our AV-101 product candidate or any other product candidate in the United States or in other foreign countries, in whole or in part. Although we enter into non-disclosure and confidentiality agreements with parties who have access to patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, contract research organizations, contract manufacturers, consultants, advisors and other third parties, any of these parties may breach these agreement and disclose such results before a patent application is filed, thereby jeopardizing our ability to seek patent protection.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal, technological and factual questions and has, in recent years, been the subject of much debate and litigation throughout the world. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States, or vice versa. As a result, the issuance, scope, validity, enforceability, and commercial value of our patent rights are highly uncertain. The subject matter claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Therefore, our pending and future patent applications may not result in patents being issued in relevant jurisdictions that protect our product candidates, in whole or in part, or which effectively prevent others from commercializing competitive product candidates, and even if our patent applications issue as patents in relevant jurisdictions, they may not issue in a form that will provide us with any meaningful protection for our product candidates or technology, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Additionally, our competitors may be able to circumvent our patents by developing similar or alternative product candidates or technologies in a non-infringing manner.

In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. Without patent protection for our current or future product candidates, we may be open to competition from generic versions of such products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. We may be subject to a third-party pre-issuance submission of prior art to the United States Patent and Trademark Office, or the USPTO, or become involved in opposition, derivation, revocation, reexamination, *inter partes* review, post-grant review or interference proceedings challenging our patent rights or the patent rights of others, or other proceedings in the USPTO or applicable foreign offices that challenge priority of invention or other features of patentability. An adverse determination in any such submission, proceeding or litigation could result in loss of exclusivity or freedom to operate, patent claims being narrowed, invalidated or held unenforceable, in whole or in part, limit the scope or duration of the patent protection of AV-101, all of which could limit our ability to stop others from using or commercializing similar or identical product candidates or technology to compete directly with us, without payment to us, or result in our inability to manufacture or commercialize product candidates or approved products (if any) without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, regardless of the outcome, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates, or could have a material adverse effect on our ability to raise funds necessary to continue our research programs or clinical trials. Such proceedings also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us.

We cannot be certain that the USPTO and courts in the United States or the patent offices and courts in foreign countries will consider the claims in our patents and applications covering our AV-101 product candidate and possible future product candidates as patentable. Method-of-use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products off-label. Although off-label prescriptions may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent, including through legal action.

If we lose or cannot obtain additional patent protection for our AV-101 product candidate or other future product candidates it could have a material adverse impact on our business.

Intellectual property litigation could cause us to spend substantial resources and prevent us from pursuing our programs.

From time to time we may have to defend our intellectual property rights. If we are involved in an intellectual property dispute, we may need to litigate to defend our rights or assert them against others. Disputes can involve arbitration, litigation or proceedings declared by the USPTO or the International Trade Commission or foreign patent authorities. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios.

If we were to initiate legal proceedings against a third party to enforce a patent covering our product candidate, the defendant could counterclaim that our patent is invalid or unenforceable. In patent litigation in the United States and in Europe, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, for example, lack of novelty, obviousness or non-enablement. Third parties might allege unenforceability of our patents because during prosecution of the patent an individual connected with such prosecution withheld relevant information or made a misleading statement. The outcome of proceedings involving assertions of invalidity and unenforceability during patent litigation is unpredictable. With respect to the validity of patents, for example, we cannot be certain that there is no invalidating prior art of which we and the patent examiner were unaware during prosecution, but that an adverse third party may identify

and submit in support of such assertions of invalidity. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidate. Our patents and other intellectual property rights also will not protect our technology if competitors design around our protected technology without infringing our patents or other intellectual property rights.

Because of the expense and uncertainty of litigation, we may not be in a position to enforce our intellectual property rights against third parties.

Because of the expense and uncertainty of litigation, we may conclude that even if a third party is infringing our issued patent, any patents that may be issued as a result of our pending or future patent applications or other intellectual property rights, the risk-adjusted cost of bringing and enforcing such a claim or action may be too high or not in the best interest of our company or our stockholders. In such cases, we may decide that the more prudent course of action is to simply monitor the situation or initiate or seek some other non-litigious action or solution.

Third parties may initiate or threaten legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability and the ability of our strategic partners to develop, manufacture, market and sell our drugs and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. Extensive litigation regarding patents and other intellectual property rights is common in the biotechnology and pharmaceutical industries. We may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our drugs and technology, including interference, derivation, reexamination, post-grant review, opposition, cancellation or similar proceedings before the USPTO or its foreign counterparts. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, resulting in payment of damages. These damages potentially include increased damages and attorneys' fees if we are found to have infringed such rights willfully. Parties making claims against us may seek and obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize our product candidates. We may not be aware of all such intellectual property rights potentially relating to our drugs and their uses. If a third party claims that our AV-101 product candidate or our technology infringe its patents or other intellectual property rights, we or our partners may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We could be required to obtain a license from such third party in order to continue developing and commercializing AV-101 or other product candidates. However, we may not be able to obtain a license to needed intellectual property on commercially reasonable terms, if at all. Even if a license can be obtained on reasonable terms, the rights may be nonexclusive, which would give our competitors access to the same intellectual property rights. We might also be forced to redesign or modify our product candidates so that we no longer infringe the third-party intellectual property rights, which may result in significant cost or delay to us, or which redesign or modification could be impossible or technically infeasible. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or patent applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain. Thus, we do not know with certainty that our drugs or our intended commercialization thereof, does and will not infringe or otherwise violate any third party's intellectual property.

We will not seek to protect our intellectual property rights in all jurisdictions throughout the world and we may not be able to adequately enforce our intellectual property rights even in the jurisdictions where we seek protection.

Filing, prosecuting and defending patents on drugs in all countries and jurisdictions throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those we could obtain in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions.

Competitors may use our technologies in jurisdictions where we do not pursue and obtain patent protection to develop their own products. In addition, competitors may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patent rights or other intellectual property rights may not be effective or sufficient to prevent them from competing. Even if we pursue and obtain issued patents in particular jurisdictions, our patent claims or other intellectual property rights may not be effective or sufficient to prevent third parties from so competing.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to biotechnology. This could make it difficult for us to stop competitors from infringing our patent rights or misappropriating our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. In addition, many countries limit our right to enforce our patent rights against third parties, including government agencies, government contractors, or doctors. In these countries, patents may provide limited or no benefit. We must ultimately seek patent protection on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries.

In addition, proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patent rights at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop.

If we do not obtain additional protection under the Hatch-Waxman Amendments and similar foreign legislation by extending the patent protection for AV-101, our business may be materially harmed.

Depending upon the timing, duration and specifics of the first FDA marketing authorization of AV-101, a United States patent that we own may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments allow the owner of an approved product to extend patent protection for up to five years as compensation for patent term lost during product development and the FDA regulatory review process. During this period of extension, the scope of protection is limited to the approved product and approved uses.

Although we plan on seeking patent term restoration for our products, we may not succeed if, for example, we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we cannot obtain patent term restoration or the term of any such patent restoration is less than we request, our competitors may enter the market and compete against us sooner than we anticipate, and our ability to generate revenue could be materially adversely affected.

We may not identify relevant third-party patents or may incorrectly interpret the relevance, scope or expiration of a third-party patent which might adversely affect our ability to develop, manufacture and market our product candidate.

We cannot guarantee that any of our patent searches or analyses, including but not limited to the identification of relevant patents, analysis of the scope of relevant patent claims or determination of the expiration of relevant patents, are complete or thorough, nor can we be certain that we have identified each and every third-party patent and pending application in the United States, Europe and elsewhere that is relevant to or necessary for the commercialization of AV-101 in any jurisdiction. For example, in the United States, applications filed before November 29, 2000 and certain applications filed after that date that will not be filed outside the United States remain confidential until patents issue. Patent applications in the United States, EU and elsewhere are published approximately 18 months after the earliest filing for which priority is claimed, with such earliest filing date being commonly referred to as the priority date. Therefore, patent applications

covering our product candidates could be filed by others without our knowledge. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover AV-101 or the use of AV-101. After issuance, the scope of patent claims remains subject to construction as determined by an interpretation of the law, the written disclosure in a patent and the patent's prosecution history. Our interpretation of the relevance or the scope of a patent or a pending application may be incorrect, which may negatively impact our ability to market our product candidates. We may incorrectly determine that AV-101 is not covered by a third-party patent or may incorrectly predict whether a third party's pending application will issue with claims of relevant scope. Our determination of the expiration date of any patent in the United States, the EU or elsewhere that we consider relevant may be incorrect, which may negatively impact our ability to develop and market AV-101. Our failure to identify and correctly interpret relevant patents may negatively impact our ability to develop and market AV-101.

If we fail to correctly identify or interpret relevant patents, we may be subject to infringement claims. We cannot guarantee that we will be able to successfully settle or otherwise resolve such infringement claims. If we fail in any such dispute, in addition to being forced to pay monetary damages, we may be temporarily or permanently prohibited from commercializing AV-101. We might, if possible, also be forced to redesign AV-101 in a manner that no longer infringes third-party intellectual property rights. Any of these events, even if we were ultimately to prevail, could require us to divert substantial financial and management resources that we would otherwise be able to devote to our business.

Changes in United States patent law could diminish the value of patents in general, thereby impairing our ability to protect AV-101.

Recent court rulings, including rules from the United States Supreme Court, have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the United States Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

In addition, the America Invents Act, or the AIA, which was passed in September 2011, resulted in significant changes to the U.S. patent system. An important change introduced by the AIA is that, as of March 16, 2013, the United States transitioned from a "first-to-invent" to a "first-to-file" system for deciding which party should be granted a patent when two or more patent applications are filed by different parties claiming the same invention. Under a "first-to-file" system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to a patent on the invention regardless of whether another inventor had made the invention earlier. A third party that files a patent application in the USPTO after that date but before us could therefore be awarded a patent covering an invention of ours even if we made the invention before it was made by the third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application and diligent in filing patent applications, but circumstances could prevent us from promptly filing patent applications on our inventions.

Among some of the other changes introduced by the AIA are changes that limit where a patentee may file a patent infringement suit and providing opportunities for third parties to challenge any issued patent in the USPTO. This applies to all of our U.S. patents, even those issued before March 16, 2013. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in U.S. federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action.

Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. It is not clear what, if any, impact the AIA will have on the operation of our business. However, the AIA and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

We may become involved in opposition, interference, derivation, inter partes review or other proceedings challenging our patent rights, and the outcome of any proceedings are highly uncertain. An adverse determination in any such proceeding

could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights.

There may be significant pressure on the U.S. government and international governmental bodies to limit the scope of patent protection both inside and outside the United States for disease treatments that prove successful, as a matter of public policy regarding worldwide health concerns.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

The USPTO and European and other patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In addition, periodic maintenance and annuity fees on any issued patent are due to be paid to the USPTO and European and other patent agencies over the lifetime of a patent. While an inadvertent failure to make payment of such fees or to comply with such provisions can in many cases be cured by additional payment of a late fee or by other means in accordance with the applicable rules, there are situations in which non-compliance with such provisions will result in the abandonment or lapse of the patent or patent application, and the partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents within prescribed time limits. If we fail to maintain the patents and patent applications covering AV-101 or if we otherwise allow our patents or patent applications to be abandoned or lapse, it can create opportunities for competitors to enter the market, which would hurt our competitive position and could impair our ability to successfully commercialize our product candidates in any indication for which they are approved.

We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.

We generally enter into confidentiality and intellectual property assignment agreements with our employees, consultants, and contractors. These agreements generally provide that inventions conceived by the party in the course of rendering services to us will be our exclusive property. However, those agreements may not be honored and may not effectively assign intellectual property rights to us. Moreover, there may be some circumstances, where we are unable to negotiate for such ownership rights. Disputes regarding ownership or inventorship of intellectual property can also arise in other contexts, such as collaborations and sponsored research. If we are subject to a dispute challenging our rights in or to patents or other intellectual property, such a dispute could be expensive and time consuming. If we were unsuccessful, we could lose valuable rights in intellectual property that we regard as our own. The issuance of a patent is not conclusive as to its inventorship.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

We could in the future be subject to claims that we or our employees have inadvertently or otherwise used or disclosed alleged trade secrets or other confidential information of former employers or competitors. Although we try to ensure that our employees and consultants do not use the intellectual property, proprietary information, know-how or trade secrets of others in their work for us, we may become subject to claims that we caused an employee to breach the terms of his or her non-competition or non-solicitation agreement, or that we or these individuals have, inadvertently or otherwise, used or disclosed the alleged trade secrets or other proprietary information of a former employer or competitor.

While we may litigate to defend ourselves against these claims, even if we are successful, litigation could result in substantial costs and could be a distraction to management. If our defenses to these claims fail, in addition to requiring us to pay monetary damages, a court could prohibit us from using technologies or features that are essential to our product candidates, if such technologies or features are found to incorporate or be derived from the trade secrets or other proprietary information of the former employers. Moreover, any such litigation or the threat thereof may adversely affect our reputation, our ability to form strategic alliances or sublicense our rights to collaborators, engage with scientific advisors

or hire employees or consultants, each of which would have an adverse effect on our business, results of operations and financial condition.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

We rely on trade secrets and confidentiality agreements to protect our unpatented know-how, technology and other proprietary information and to maintain our competitive position. Trade secrets and know-how can be difficult to protect. We seek to protect these trade secrets and other proprietary technology, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, collaborators consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. We cannot guarantee that we have entered into such agreements with each party that may have or has had access to our trade secrets or proprietary technology and processes. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Unauthorized parties may also attempt to copy or reverse engineer certain aspects of our product candidates that we consider proprietary. Monitoring unauthorized uses and disclosures is difficult, and we do not know whether the steps we have taken to protect our proprietary information will be effective.

We also seek to preserve the integrity and confidentiality of our confidential proprietary information by maintaining physical security of our premises and physical and electronic security of our information technology systems, but it is possible that these security measures could be breached. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be materially and adversely harmed.

If we and our partners do not adequately protect the trademarks and trade names for our products, then we and our partners may not be able to build name recognition in our markets of interest and our business may be adversely affected.

Our competitors or other third parties may challenge, infringe or circumvent the trademarks or trade names for our products. We and our partners may not be able to protect these trademarks and trade names. In addition, if the trademarks or trade names for one of our products infringe the rights of others, we or our partners may be forced to stop using the trademarks or trade names, which we need for name recognition in our markets of interest. If we cannot establish name recognition based on our trademarks and trade names, we and our partners may not be able to compete effectively and our business may be adversely affected.

Intellectual property rights do not necessarily address all potential threats to our competitive advantage.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business, or permit us to maintain our competitive advantage. The following examples are illustrative:

- others may make drug products that are similar to AV-101 but that are not covered by the claims of our patents;
- we, or current or future strategic partners, might not have been the first to make the inventions covered by our issued patent or pending patent applications;
- we, or current or future strategic partners, might not have been the first to file patent applications covering our inventions;

- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;

- our pending and future patent applications may not lead to issued patents;

- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors;

- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;

- we may not develop additional proprietary technologies that are patentable; and

- the patents of others may have an adverse effect on our business.

Should any of these events occur, they could significantly harm our business, results of operations and prospects.

Risks Related to Government Regulation

We may be unable to obtain regulatory approval for AV-101 under applicable regulatory requirements. The denial or delay of any such approval would delay commercialization of AV-101 and adversely impact our potential to generate revenue, our business and our results of operations.

We have not previously submitted an NDA or any other marketing application to the FDA or similar filings to comparable foreign regulatory authorities. An NDA or other similar regulatory filing requesting approval to market a product candidate must include extensive preclinical and clinical data and supporting information to establish that the product candidate is safe, effective, pure and potent for each desired indication. The NDA or other similar regulatory filing must also include significant information regarding the chemistry, manufacturing and controls for the product.

The research, testing, manufacturing, labeling, approval, sale, marketing and distribution of pharmaceutical products are subject to extensive regulation by the FDA and other regulatory authorities in the United States and other countries, and such regulations differ from country to country. We are not permitted to market AV-101 in the United States or in any foreign countries until it receives the requisite approval from the applicable regulatory authorities of such jurisdictions.

The FDA or any foreign regulatory bodies can delay, limit or deny approval of AV-101 for many reasons, including:

- our inability to demonstrate to the satisfaction of the FDA or the applicable foreign regulatory body that AV-101 is safe and effective for the requested indication;

- the FDA's or the applicable foreign regulatory agency's disagreement with our trial protocol or the interpretation of data from preclinical studies or clinical trials;

- our inability to demonstrate that the clinical and other benefits of AV-101 outweigh any safety or other perceived risks;

- the FDA's or the applicable foreign regulatory agency's requirement for additional preclinical studies or clinical trials;

- the FDA's or the applicable foreign regulatory agency's non-approval of the formulation, labeling or specifications of AV-101;

- the FDA's or the applicable foreign regulatory agency's failure to approve our manufacturing processes and facilities or the facilities of third-party manufacturers upon which we rely; or

- the potential for approval policies or regulations of the FDA or the applicable foreign regulatory agencies to significantly change in a manner rendering our clinical data insufficient for approval.

Of the large number of pharmaceutical products in development, only a small percentage successfully complete the FDA or other regulatory bodies' approval processes and are commercialized.

Even if we eventually complete clinical testing and receive approval from the FDA or applicable foreign agencies for AV-101, the FDA or the applicable foreign regulatory agency may grant approval contingent on the performance of costly additional clinical trials which may be required after approval. The FDA or the applicable foreign regulatory agency also may approve AV-101 for a more limited indication or a narrower patient population than we originally requested, and the FDA, or applicable foreign regulatory agency, may not approve it with the labeling that we believe is necessary or desirable for the successful commercialization.

Any delay in obtaining, or inability to obtain, applicable regulatory approval would delay or prevent commercialization of AV-101 and would materially adversely impact our business and prospects.

AV-101 is a drug-device combination product, which may result in additional regulatory risks.

Our finished drug product, a proprietary inhaled dry powder formulation and DPI, will be regulated as a drug-device combination product. The DPI we use to administer AV-101 is currently CE marked and used outside the United States but AV-101 would be the first drug to obtain approval with this DPI in the United States. We believe the delivery device we selected will work well with AV-101 and we have conducted human factor studies with this DPI; however, the Phase 2b trial will be the first time we use the device in a clinical trial setting, and the capsules we use with the DPI in Phase 2b will be filled with higher amounts of active pharmaceutical ingredient compared to the Phase 1 clinical trial. There may be additional regulatory risks for drug-device combination products. We may experience delays in obtaining regulatory approval of AV-101 given the increased complexity of the review process when approval of the product and a delivery device is sought under a single marketing application. In the United States, each component of a combination product is subject to the requirements established by the FDA for that type of component, whether a drug, biologic or device. The DPI will be subject to FDA design control device requirements which comprise among other things, design verification, design validation (including human factors testing), and testing to assess performance, cleaning, and robustness. Delays in or failure of the studies conducted by us, or failure of our company, our collaborators, if any, or our third-party providers or suppliers to maintain compliance with regulatory requirements could result in increased development costs, delays in or failure to obtain regulatory approval, and associated delays in AV-101 reaching the market.

We are currently conducting, and may in the future conduct, clinical trials for AV-101 outside the United States, and the FDA, EMA and applicable foreign regulatory authorities may not accept data from such trials.

We have initiated a global Phase 2b/Phase 3 clinical trial of AV-101 in adults with PAH. The acceptance of trial data from clinical trials conducted outside the United States by the FDA, EMA, or applicable foreign regulatory authority may be subject to certain conditions. In cases where data from foreign clinical trials are intended to serve as the basis for marketing approval in the United States, the FDA will generally not approve the application on the basis of foreign data alone unless (i) the data are applicable to the United States population and United States medical practice; (ii) the trials were performed by clinical investigators of recognized competence and pursuant to GCP regulations; and (iii) the data may be considered valid without the need for an on-site inspection by the FDA or, if the FDA considers such an inspection to be necessary, the FDA is able to validate the data through an on-site inspection or other appropriate means. Additionally, the FDA's clinical trial requirements, including sufficient size of patient populations and statistical powering, must be met. Many foreign regulatory bodies have similar approval requirements.

In addition, such foreign trials will be subject to the applicable local laws of the foreign jurisdictions where the trials are conducted. There can be no assurance that the FDA, EMA, or any applicable foreign regulatory authority will accept data from trials conducted outside of the United States. If the FDA, EMA, or any applicable foreign regulatory authority does

not accept such data, it would result in the need for additional trials, which would be costly and time-consuming and delay aspects of our business plan, and which may result in AV-101 not receiving approval or clearance for commercialization in the applicable jurisdiction.

Even if we obtain regulatory approval for AV-101, we will be subject to ongoing regulatory requirements, which may result in significant additional expenses. Additionally, AV-101, if approved, could be subject to labeling and other restrictions, and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with AV-101.

If AV-101 is approved by the FDA or a comparable foreign regulatory authority, it will be subject to extensive and ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping, conduct of post-marketing studies, and submission of safety, efficacy, and other post-market information, including both federal and state requirements in the United States and requirements of comparable foreign regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, establishment registration and listing, as well as continued compliance with current GMPs, and Good Manufacturing Practices, or GMPs, for any clinical trials that we conduct post-approval. Any regulatory approvals that we receive for our product candidates may also be subject to limitations on the approved indicated uses, including the duration of use, for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing studies, including Phase 4 clinical trials, and surveillance to monitor the safety and efficacy of the product. The FDA may also require a REMS in order to approve AV-101, which could entail requirements for a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools.

Manufacturers and manufacturers' facilities are required to comply with extensive FDA and comparable foreign regulatory authority requirements, including ensuring that quality control and manufacturing procedures conform to current GMP regulations and implementing tracking and tracing requirements for certain prescription pharmaceutical products. As such, we and our contract manufacturers will be subject to continual review and inspections to assess compliance with current GMP and adherence to commitments made in any approved marketing application. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, and quality control.

We will have to comply with requirements concerning advertising and promotion for AV-101. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved label. As such, we may not promote AV-101 for indications or uses for which they do not have approval. However, companies may share truthful and not misleading information that is otherwise consistent with a product's FDA approved labeling. We also must submit new or supplemental applications and obtain approval for certain changes to AV-101, if approved, product labeling, or manufacturing process.

If we discover previously unknown problems with AV-101, such as adverse events of unanticipated severity or frequency, or problems with the facility where AV-101 is manufactured, or if the FDA disagrees with the promotion, marketing or labeling of AV-101, the FDA may impose restrictions on it or us, including requiring withdrawal of it from the market. If we fail to comply with applicable regulatory requirements, the FDA and other regulatory authorities may, among other things:

- issue warning letters or other regulatory enforcement action;
- impose injunctions, fines or civil or criminal penalties;
- suspend or withdraw regulatory approval;
- suspend any of our ongoing clinical studies;
- refuse to approve pending applications or supplements to approved applications;

- require revisions to the labeling, including limitations on approved uses or the addition of additional warnings, contraindications or other safety information, including boxed warnings;

- impose a REMS which may include distribution or use restrictions;

- require the conduct of an additional post-market clinical trial or trials to assess the safety of the product;

- impose restrictions on our operations, including closing our contract manufacturers' facilities where regulatory inspections identify observations of noncompliance requiring remediation; or

- restrict the marketing of the product, require a product recall, seizure or detention, or refuse to permit the import or export of the product.

Any government action or investigation of alleged violations of law could require us to expend significant time and resources in response, and could generate negative publicity. Any failure to comply with ongoing regulatory requirements may significantly and adversely affect our ability to commercialize and generate revenue from AV-101. If regulatory sanctions are applied or if regulatory approval is withdrawn, the value of our company and our operating results will be adversely affected.

Moreover, the policies of the FDA and of other regulatory authorities may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of AV-101. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. In addition, if we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may be subject to enforcement action and we may not achieve or sustain profitability.

We may seek priority review designation for AV-101, but we might not receive such designation, and even if we do, such designation may not lead to a faster regulatory review or approval process.

If the FDA determines that a product candidate offers a treatment for a serious condition and, if approved, the product would provide a significant improvement in safety or effectiveness, the FDA may designate the product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months. We may request priority review for AV-101 for the treatment of PAH. The FDA has broad discretion with respect to whether or not to grant priority review status to a product candidate, so even if we believe AV-101 is eligible for such designation or status, the FDA may decide not to grant it. Moreover, a priority review designation does not necessarily result in an expedited regulatory review or approval process or necessarily confer any advantage with respect to approval compared to conventional FDA procedures. Receiving priority review from the FDA does not guarantee approval within the six-month review cycle or at all.

We have received orphan drug designation from the FDA and EMA for AV-101 for treatment of PAH, but we may be unable to obtain additional designations or to maintain the benefits associated with orphan drug status, including the potential for non-patent market exclusivity.

We have obtained orphan drug designation for AV-101 in the United States from the FDA and in the European Union from the EMA. We may not be able to obtain orphan drug designation for additional indications for AV-101 or for future product candidates or maintain the benefits associated with orphan drug designation, including the potential for non-patent market exclusivity. Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a drug or biologic as an orphan drug if it is a product intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals annually in the United States, or a patient population of 200,000 or more in the United States where there is no reasonable expectation that the cost of developing the product will be recovered from sales in the United States. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers.

Similarly, in the European Union, the European Commission, upon the recommendation of the EMA's Committee for Orphan Medicinal Products, may grant orphan designation in respect of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions and either (i) such condition affects not more than 5 in 10,000 persons in the European Union when the application is made or (ii) without incentives, it is unlikely that the marketing of the product would generate sufficient return in the European Union to justify the necessary investment in its development, and, in each case, for which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the product would be a significant benefit to those affected). In the European Union, orphan designation entitles a party to financial incentives such as reduction of fees or fee waivers.

Generally, if a product with an orphan drug designation subsequently receives the first regulatory approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA from approving another marketing application for the same product and indication for that time period, except in limited circumstances. Any competitor developing imatinib in the same indication with orphan drug designation may block our ability to obtain orphan drug exclusivity in the future if the competitor receives marketing approval before we do. The applicable exclusivity period is seven years in the United States and ten years in the European Union. The European Union exclusivity period can be reduced to six years if, at the end of the fifth year, it is established that a product no longer meets the criteria for orphan drug designation, including if the product is sufficiently profitable so that market exclusivity is no longer justified. Legislation has been proposed by the European Commission that, if implemented, has the potential in some cases to shorten the ten-year period of orphan drug exclusivity.

Even if we obtain orphan drug exclusivity for AV-101, that exclusivity may not effectively protect AV-101 from competition because different products can be approved for the same condition. Even after an orphan drug is approved, the FDA or EMA can subsequently approve the same product for the same condition if the FDA or EMA concludes that the later product is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. In addition, a designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. Moreover, orphan drug exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition or if another product with the same active moiety is determined to be safer, more effective, or represents a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a product nor gives the product any advantage in the regulatory review or approval process. Although we have received orphan designation from the EMA, there is no guarantee that such designation will be maintained on grant of a marketing authorization for AV-101.

A fast track designation by the FDA, even if granted for AV-101, may not lead to a faster development or regulatory review or approval process, and does not increase the likelihood that our product candidates will receive marketing approval.

If a product candidate is intended for the treatment of a serious or life-threatening condition and the product candidate demonstrates the potential to address unmet medical needs for this condition, the sponsor may apply for fast track designation by the FDA for a particular indication. We may seek fast track designation for AV-101, but there is no assurance that the FDA will grant this status to AV-101. The FDA has broad discretion whether or not to grant fast track designation, so even if we believe AV-101 is eligible for this designation, there can be no assurance that the FDA would decide to grant it. Even if we do receive fast track designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures, and receiving a fast track designation does not provide assurance of ultimate FDA approval. In addition, the FDA may withdraw fast track designation at any time if it believes that the designation is no longer supported by data from our clinical development program.

A breakthrough therapy designation by the FDA, even if granted for AV-101, may not lead to a faster development, regulatory review or approval process, and each designation does not increase the likelihood that AV-101 will receive regulatory approval in the United States.

We may seek a breakthrough therapy designation for AV-101 for treatment of PAH. A breakthrough therapy is defined as a drug or biologic that is intended, alone or in combination with one or more other drugs or biologics, to treat a serious or

life-threatening disease or condition and preliminary clinical evidence indicates that the drug or biologic may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For product candidates that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Products designated as breakthrough therapies by the FDA may also be eligible for priority review and accelerated approval. Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe AV-101 meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a breakthrough therapy designation for a product candidate may not result in a faster development process, review or approval compared to therapies considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if AV-101 qualifies as a breakthrough therapy, the FDA may later decide that it no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Even if we obtain FDA approval for AV-101 in the United States, we may never obtain approval for or successfully commercialize AV-101 outside of the United States, which would limit our ability to realize its full market potential.

In order to market AV-101 outside of the United States, we must obtain marketing authorizations and comply with numerous and varying regulatory requirements of other countries regarding quality, safety and efficacy. Clinical trials conducted in one country may not be accepted by foreign regulatory authorities, and regulatory approval in one country does not mean that regulatory approval will be obtained in any other country. Approval processes vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking foreign regulatory approval could result in difficulties and costs for us and require additional non-clinical studies or clinical trials, which could be costly and time consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of AV-101 in those countries. We, as a company, do not have experience in obtaining regulatory approval in international markets. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, or if regulatory approval in international markets is delayed, our target market for AV-101 will be reduced and we would not be able to realize the full market potential of AV-101.

Our business operations and current and future relationships with investigators, healthcare professionals, consultants, third-party payors, patient organizations and customers will be subject to applicable healthcare regulatory laws, which could expose us to penalties.

Our business operations and current and future arrangements with investigators, healthcare professionals, consultants, third-party payors, patient organizations and customers, may expose us to broadly applicable fraud and abuse and other healthcare laws, including, without limitation, the federal Anti-Kickback Statute, the federal civil and criminal False Claims Act and Physician Payments Sunshine Act and regulations. These laws may constrain the business or financial arrangements and relationships through which we conduct our operations, including how we research, market, sell and distribute AV-101, if approved. For more information, see "*Business – Government Regulation – Healthcare Laws and Regulation"* in our Annual Report on Form 10-K.

Ensuring that our internal operations and future business arrangements with third parties comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws. If our operations are found to be in violation of any of the laws described above or any other governmental laws that may apply to us, we may be subject to significant penalties, including civil, criminal and administrative penalties, damages, fines, exclusion from government-funded healthcare programs, such as Medicare and Medicaid or similar programs in other countries or jurisdictions, integrity oversight and reporting obligations to resolve allegations of non-compliance, disgorgement, imprisonment, contractual damages, reputational harm, diminished profits and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we expect to do business are found to not be in compliance with applicable laws, they may be subject to significant criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs and imprisonment, which could affect our ability to operate our business. Further, defending against any such

actions can be costly, time-consuming and may require significant personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired.

Healthcare legislative reform measures may have a material adverse effect on our business and results of operations.

The United States and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system that could prevent or delay regulatory approval of our current or future product candidates or any future product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell a product for which we obtain regulatory approval. Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements, (ii) additions or modifications to product labeling, (iii) the recall or discontinuation of our products or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business. For more information, see "*Business – Government Regulation – Pricing and Reimbursement"* in our Annual Report on Form 10-K.

Our revenue prospects could be affected by changes in healthcare spending and policy in the United States and abroad. We operate in a highly regulated industry and new laws, regulations or judicial decisions, or new interpretations of existing laws, regulations or decisions, related to healthcare availability, the method of delivery or payment for healthcare products and services could negatively impact our business, operations and financial condition.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. We cannot predict the initiatives that may be adopted in the future, including repeal, replacement or significant revisions to the ACA. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare and/or impose price controls may adversely affect:

- the demand for our current or future product candidates, if we obtain regulatory approval;
- our ability to set a price that we believe is fair for our products;
- our ability to obtain coverage and reimbursement approval for a product;
- our ability to generate revenue and achieve or maintain profitability;
- the level of taxes that we are required to pay; and
- the availability of capital.

Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors, which may adversely affect our future profitability.

The FDA and other regulatory agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses.

If AV-101 is approved and we are found to have improperly promoted off-label uses of this product, we may become subject to significant liability. The FDA and other regulatory agencies strictly regulate the promotional claims that may be made about prescription products, if approved. In particular, while the FDA permits the dissemination of truthful and non-misleading information about an approved product, a manufacturer may not promote a product for uses that are not approved by the FDA or such other regulatory agencies as reflected in the product's approved labeling. If we are found to have promoted such off-label uses, we may become subject to significant liability. The federal government has levied large civil and criminal fines against companies for alleged improper promotion of off-label use and has enjoined several companies from engaging in off-label promotion. The government has also imposed consent decrees, corporate integrity agreements or permanent injunctions under which specified promotional conduct must be changed or curtailed. If we

cannot successfully manage the promotion of our product candidates, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

Inadequate funding for the FDA, the SEC and other government agencies, including from government-shutdowns, or other disruptions to these agencies' operations, could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory and policy changes. Average review times at the agency have fluctuated in recent years as a result. Disruptions at the FDA and other agencies may also slow the time necessary for new product candidates to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new product candidates to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years the United States government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

Risks Related to Employee Matters and Managing Growth

We will need to increase the size of our organization, and we may experience difficulties in managing growth.

We will need to continue to expand our managerial, operational, finance and other resources in order to manage our operations and clinical trials, continue our development activities and commercialize AV-101. Our management and personnel, systems and facilities currently in place may not be adequate to support this future growth. Our need to effectively execute our growth strategy requires that we:

- effectively manage our clinical trials and the development of AV-101;
- identify, recruit, retain, incentivize and integrate additional employees, including sales personnel;
- manage our internal development and operational efforts effectively while carrying out our contractual obligations to third parties; and
- continue to improve our operational, financial and management controls, reports systems and procedures.

We may be unable to successfully implement these tasks, which could have a material adverse effect on our business, results of operations, financial condition, prospects and stock price.

We are highly dependent on our key personnel and anticipate hiring new key personnel. If we are not successful in attracting and retaining highly qualified personnel, our business may be materially and adversely affected.

Our success depends in part on our continued ability to attract, retain and motivate highly qualified management, clinical and scientific personnel. We are highly dependent upon our senior management, as well as other members of our

management team. The loss of services of any of these individuals could delay or prevent the successful development of AV-101, completion of our ongoing and any future clinical trials or the commercialization of AV-101, if approved.

Competition for qualified personnel in the pharmaceutical and biotechnology fields is intense due to the limited number of individuals who possess the skills and experience required by our industry. We will need to hire additional personnel as we expand our clinical development and if we initiate commercial activities. We may not be able to attract and retain quality personnel on acceptable terms, or at all. In addition, to the extent we hire personnel from competitors, we may be subject to allegations that they have been improperly solicited or that they have divulged proprietary or other confidential information, or that their former employers own their research output.

Our insurance policies may be inadequate and potentially expose us to unrecoverable risks.

We have limited director and officer insurance and product liability insurance policies. Any significant insurance claims would have a material adverse effect on our business, financial condition and results of operations. Insurance availability, coverage terms, including deductibles and pricing, continue to vary with market conditions. We endeavor to obtain appropriate insurance coverage for insurable risks that we identify; however, we may fail to correctly anticipate or quantify insurable risks, we may not be able to obtain appropriate insurance coverage, and insurers may not respond as we intend to cover insurable events that may occur. We have observed rapidly changing conditions in the insurance markets relating to nearly all areas of traditional corporate insurance. Such conditions have resulted in higher premium costs, higher policy deductibles and lower coverage limits. For some risks, we may not have or maintain insurance coverage because of cost or availability.

We may be unable to adequately protect our information systems and infrastructure from cyberattacks and other cybersecurity incidents, which could result in the disclosure or compromise of confidential or proprietary information, including personal data, damage to our reputation, and subject us to significant financial and legal exposure.

We rely on information technology systems that we or our third-party providers operate to process, transmit and store electronic information in our day-to-day operations. In connection with our product discovery efforts, we may collect and use a variety of personal data, such as names, mailing addresses, email addresses, phone numbers and clinical trial information. A successful cyberattack or other cybersecurity incident could result in the theft or destruction of this personal data, intellectual property, other data, or other misappropriation of assets, or otherwise compromise our confidential or proprietary information and disrupt our operations. Cybersecurity incidents are increasing in their frequency, sophistication, level of persistence and intensity, and are being conducted by sophisticated and organized groups and individuals with a wide range of motives and expertise. Cyberattacks could include wrongful conduct by hostile foreign governments, industrial espionage, wire fraud and other forms of cyber fraud, the deployment of harmful malware, denial-of-service, ransomware, social engineering fraud or other means to threaten data security, confidentiality, integrity and availability. We may also face increased cybersecurity risks due to our reliance on internet technology and the number of our employees who are working remotely, which may create additional opportunities for cybercriminals to exploit vulnerabilities. Furthermore, because the techniques used to obtain unauthorized access to, or to sabotage, systems change frequently and often are not recognized until launched against a target, we may be unable to anticipate these techniques or implement adequate preventative measures. We may also experience cybersecurity incidents that may remain undetected for an extended period. A successful cyberattack could cause serious negative consequences for us, including, without limitation, the disruption of operations, the misappropriation of confidential business information, including financial information, trade secrets, financial loss and the disclosure of corporate strategic plans. Although we devote resources to protect our information systems, we realize that cybersecurity incidents are a threat, and there can be no assurance that our efforts will prevent cybersecurity incidents that would result in business, legal, financial or reputational harm to us, or would have a material adverse effect on our results of operations and financial condition. We maintain cybersecurity insurance in the event of a cybersecurity incident; however, the coverage may not be sufficient to cover all financial losses. Any failure to prevent or mitigate cybersecurity incidents or improper access to, use of, or disclosure or compromise of our clinical data or patients' personal data could result in significant liability under state (e.g., state breach notification laws), federal, and international law and may cause a material adverse impact to our reputation, affect our ability to conduct new studies and potentially disrupt our business.

We rely on our third-party providers to implement effective security measures and identify and correct for any such failures, deficiencies or breaches. If we or our third-party providers fail to maintain or protect our information technology systems and data integrity effectively or fail to anticipate, plan for or manage significant disruptions to our information technology systems, we or our third-party providers could have difficulty preventing, detecting and controlling such cyber-attacks and any such incidents could result in the losses described above as well as disputes with physicians, patients and our partners, regulatory sanctions or penalties, increases in operating expenses, other expenses or lost revenues or other adverse consequences, any of which could have a material adverse effect on our business, results of operations, financial condition, prospects and cash flows. Any failure by such third parties to prevent or mitigate cybersecurity incidents or improper access to or disclosure or compromise of such information could have similarly adverse consequences for us. If we are unable to prevent or mitigate the impact of such cybersecurity incidents, we could be exposed to litigation and governmental investigations, which could lead to a potential disruption to our business. By way of example, the California Consumer Privacy Act as amended by the California Privacy Rights Act, or CCPA, provides a private right of action for data breaches impacting California residents.

Risks Related to Ownership of Our Common Stock

Our ability to utilize our net operating loss carryforwards and certain other tax attributes may be limited.

Under Section 382 of the Internal Revenue Code of 1986, as amended, or the Code, if a corporation undergoes an "ownership change" (generally defined as a greater than 50 percentage point change (by value) in the ownership of its equity over a three year period), the corporation's ability to use its pre-change net operating loss carryforwards and certain other pre-change tax attributes to offset its post-change income may be limited. We may have experienced such ownership changes in the past, and we may experience ownership changes in the future or subsequent shifts in our stock ownership, some of which are outside our control. As of December 31, 2023, we had federal net operating loss (NOL) carryforwards of approximately $64.8 million and are accruing additional net operating losses in calendar year 2024, which will be added to the net operating loss carryover balance once the current year is completed. Our ability to utilize our net operating loss carryforwards could be limited by an "ownership change" as described above, which could result in increased tax liability to us. Furthermore, our ability to utilize our NOLs or credits is conditioned upon our attaining profitability and generating United States federal and state taxable income. As a result, the amount of the net operating loss and tax credit carryforwards presented in our financial statements could be limited and may expire unutilized. Federal net operating loss carryforwards generated since our incorporation in July 2018 will not be subject to expiration. However, any such net operating loss carryforwards may only offset 80% of our annual taxable income.

Changes in tax law may adversely affect us or our investors.

The rules dealing with U.S. federal, state and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service, or IRS, and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many changes have been made and changes are likely to continue to occur in the future. For example, under Section 174 of the code, in taxable years beginning after December 31, 2021, expenses that are incurred for research and development in the U.S. are capitalized and amortized, which may have an adverse effect on our cash flow. In addition, it is unclear how these U.S. federal income tax changes will affect state and local taxation.

It cannot be predicted whether, when, in what form, or with what effective dates, new tax laws may be enacted, or regulations and rulings may be enacted, promulgated or issued under existing or new tax laws, which could result in an increase in our or our shareholders' tax liability or require changes in the manner in which we operate in order to minimize or mitigate any adverse effects of changes in tax law or in the interpretation thereof.

Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Our second amended and restated certificate of incorporation and amended and restated bylaws contain provisions that could delay or prevent a change of control of our company or changes in our board of directors that our stockholders might consider favorable. Some of these provisions include:

- a board of directors divided into three classes serving staggered three-year terms, such that not all members of the board of directors will be elected at one time;
- a prohibition on stockholder action through written consent, which requires that all stockholder actions be taken at a meeting of our stockholders;
- a requirement that special meetings of the stockholders may be called only by the board of directors acting pursuant to a resolution approved by the affirmative vote of a majority of the directors then in office, and special meetings of stockholders may not be called by any other person or persons;
- advance notice requirements for stockholder proposals and nominations for election to our board of directors;
- a requirement that no member of our board of directors may be removed from office by our stockholders except for cause and, in addition to any other vote required by law, upon the approval of not less than two-thirds (2/3) of all outstanding shares of our voting stock then entitled to vote in the election of directors;
- a requirement of approval of not less than a majority of all outstanding shares of our voting stock to amend any bylaws by stockholder action and not less than two-thirds (2/3) of all outstanding shares of our voting stock to amend specific provisions of our second amended and restated certificate of incorporation; and
- the authority of the board of directors to issue preferred stock on terms determined by the board of directors without stockholder approval, which preferred stock may include rights superior to the rights of the holders of common stock.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporate Law, which may prohibit certain business combinations with stockholders owning 15% or more of our outstanding voting stock. These anti-takeover provisions and other provisions in our second amended and restated certificate of incorporation and amended and restated bylaws could make it more difficult for stockholders or potential acquirers to obtain control of our board of directors or initiate actions that are opposed by the then-current board of directors and could also delay or impede a merger, tender offer or proxy contest involving our company. These provisions could

also discourage proxy contests and make it more difficult for you and other stockholders to elect directors of your choosing or cause us to take other corporate actions you desire. Any delay or prevention of a change of control transaction or changes in our board of directors could cause the market price of our common stock to decline.

Our amended and restated bylaws designate certain courts as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers, or employees.

Our amended and restated bylaws provide that, unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for any state law claim for (i) any derivative action or proceeding brought on our behalf, (ii) any action asserting a claim of breach of fiduciary duty owed by any of our directors, officers, and employees to us or our stockholders, (iii) any action asserting a claim arising pursuant to any provision of the Delaware General Corporation Law, our second amended and restated certificate of incorporation or our amended and restated bylaws (including the interpretation, validity or enforceability thereof) or (iv) any action asserting a claim that is governed by the internal affairs doctrine, in each case subject to the Court of Chancery having personal jurisdiction over the indispensable parties named as defendants therein, or the Delaware Forum Provision. The Delaware Forum Provision will not apply to any causes of action arising under the Securities Act or the Exchange Act. Our amended and restated bylaws further provide that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States shall be the sole and exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act, or the Federal Forum Provision. In addition, our bylaws provide that any person or entity purchasing or otherwise acquiring any interest in shares of our common stock is deemed to have notice of and consented to the foregoing provisions; provided, however, that stockholders cannot and will not be deemed to have waived our compliance with the federal securities laws and the rules and regulations thereunder.

We recognize that the Delaware Forum Provision in our amended and restated bylaws may impose additional litigation costs on stockholders in pursuing any such claims, particularly if the stockholders do not reside in or near the State of Delaware. Additionally, the forum selection clauses in our amended and restated bylaws may limit our stockholders' ability to bring a claim in a forum that they find favorable for disputes with us or our directors, officers or employees, which may discourage such lawsuits against us and our directors, officers and employees even though an action, if successful, might benefit our stockholders. In addition, while the Delaware Supreme Court ruled in March 2020 that federal forum selection provisions purporting to require claims under the Securities Act be brought in federal court were "facially valid" under Delaware law, there is uncertainty as to whether other courts will enforce our Federal Forum Provision. If the Federal Forum Provision is found to be unenforceable, we may incur additional costs associated with resolving such matters. The Federal Forum Provision may also impose additional litigation costs on stockholders who assert that the provision is not enforceable or invalid. The Court of Chancery of the State of Delaware and the federal district courts of the United States may also reach different judgments or results than would other courts, including courts where a stockholder considering an action may be located or would otherwise choose to bring the action, and such judgments may be more or less favorable to us than our stockholders.

General Risk Factors

Unfavorable global economic or political conditions could adversely affect our business, financial condition or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. A global financial crisis or a global or regional political disruption could cause extreme volatility in the capital markets and lead to diminished liquidity and credit availability, higher interest rates, declines in consumer confidence and economic growth, increases in unemployment rates and uncertainty about economic stability. For instance, the COVID-19 pandemic led to a period of considerable uncertainty and volatility and interest rates in the U.S. have recently increased to levels not seen in decades. In addition, the impact of geopolitical tension, such as a deterioration in the bilateral relationship between the United States and China or the ongoing war in Ukraine and the conflict in the Middle East, including any resulting sanctions, export controls or other restrictive actions, also could lead to disruption, instability, and volatility in the global markets, as well as disruptions to our business and clinical trial sites in China. A severe or prolonged economic downturn or political disruption could result in a variety of risks to our business, including weakened

demand for AV-101, if approved, and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy or political disruption could also strain our manufacturers or suppliers, possibly resulting in supply disruption, or resulting in the inability of any future customers to pay for AV-101, if approved. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the political or economic climate and financial market conditions could adversely impact our business.

Adverse developments affecting the financial services industry, such as actual events or concerns involving liquidity, defaults, or non-performance by financial institutions or transactional counterparties, could adversely affect the Company's current and projected business operations and its financial condition and results of operations.

Actual events involving limited liquidity, defaults, non-performance or other adverse developments that affect financial institutions, transactional counterparties or other companies in the financial services industry or the financial services industry generally, or concerns or rumors about any events of these kinds or other similar risks, have in the past and may in the future lead to market-wide liquidity problems. For example, on March 10, 2023, Silicon Valley Bank, or SVB, was closed by the California Department of Financial Protection and Innovation, which appointed the Federal Deposit Insurance Corporation, or FDIC, as receiver. Similarly, on March 12, 2023, Signature Bank and Silvergate Capital Corp. were each swept into receivership; since then, additional financial institutions have experienced similar failures and have been placed into receivership. It is possible that other banks will face similar difficulty in the future. We had no exposure to the SVB closure and did not experience any adverse impact to our liquidity or to our current and projected business operations, financial condition or results of operations. However, uncertainty remains over liquidity concerns in the broader financial services industry, and there may be additional impacts to our business and our industry that we cannot predict at this time. Similar impacts have occurred in the past, such as during the 2008-2010 financial crisis.

Although we assess our banking and customer relationships as we believe necessary or appropriate, our access to funding sources and other credit arrangements in amounts adequate to finance or capitalize our current and projected future business operations could be significantly impaired by factors that affect the Company, the financial institutions with which the Company has credit agreements or arrangements directly, or the financial services industry or economy in general. These factors could include, among others, events such as liquidity constraints or failures, the ability to perform obligations under various types of financial, credit or liquidity agreements or arrangements, disruptions or instability in the financial services industry or financial markets, or concerns or negative expectations about the prospects for companies in the financial services industry. These factors could involve financial institutions or financial services industry companies with which the Company has financial or business relationships, but could also include factors involving financial markets or the financial services industry generally.

The results of events or concerns that involve one or more of these factors could include a variety of material and adverse impacts on our current and projected business operations and our financial condition and results of operations. These could include, but may not be limited to, the following:

- Delayed access to deposits or other financial assets or the uninsured loss of deposits or other financial assets;
- Delayed or lost access to, or reductions in borrowings available under revolving existing credit facilities or other working capital sources and/or delays, inability or reductions in the company's ability to refund, roll over or extend the maturity of, or enter into new credit facilities or other working capital resources;
- Potential or actual breach of contractual obligations that require the Company to maintain letters of credit or other credit support arrangements; or
- Termination of cash management arrangements and/or delays in accessing or actual loss of funds subject to cash management arrangements.

Any decline in available funding or access to our cash and liquidity resources could, among other risks, adversely impact our ability to meet our operating expenses, financial obligations or fulfill our other obligations, result in breaches of our financial and/or contractual obligations or result in violations of federal or state wage and hour laws. Any of these impacts, or any other impacts resulting from the factors described above or other related or similar factors not described

above, could have material adverse impacts on our liquidity and our current and/or projected business operations and financial condition and results of operations.

In addition, any further deterioration in the macroeconomic economy or financial services industry could lead to losses or defaults by our suppliers, which in turn, could have a material adverse effect on our current and/or projected business operations and results of operations and financial condition. For example, a supplier may determine that it will no longer deal with us as a customer or a supplier could be adversely affected by any of the liquidity or other risks that are described above as factors that could result in material adverse impacts on the Company, including but not limited to delayed access or loss of access to uninsured deposits or loss of the ability to draw on existing credit facilities involving a troubled or failed financial institution. Any supplier bankruptcy or insolvency, or the failure of any customer to make payments when due, or any breach or default by a supplier, or the loss of any significant supplier relationships, could result in material losses to the Company and may have a material adverse impact on our business.

Our business is affected by macroeconomic conditions, including rising inflation, interest rates and supply chain constraints.

Various macroeconomic factors could adversely affect our business and the results of our operations and financial condition, including changes in inflation, interest rates and overall economic conditions and uncertainties such as those resulting from the current and future conditions in the global financial markets. For instance, recent supply chain constraints have led to higher inflation, which if sustained could have a negative impact on our development of AV-101 and future product candidates, as well as our business and results of operations. If inflation or other factors were to significantly increase our business costs, our ability to develop our current pipeline and new therapeutic products may be negatively affected. Interest rates, the liquidity of the credit markets and the volatility of the capital markets could also affect the operation of our business and our ability to raise capital on favorable terms, or at all, in order to fund our operations. Similarly, these macroeconomic factors could affect the ability of our third-party suppliers and manufacturers to manufacture clinical trial materials for our product candidates.

Our employees and independent contractors, including principal investigators, consultants, commercial collaborators, service providers and other vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have an adverse effect on our results of operations.

We are exposed to the risk that our employees and independent contractors, including principal investigators, consultants, any future commercial collaborators, service providers and other vendors may engage in misconduct or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or other unauthorized activities that violate the laws and regulations of the FDA and other similar regulatory bodies, including those laws that require the reporting of true, complete and accurate information to such regulatory bodies; manufacturing standards; United States federal and state fraud and abuse laws, data privacy and security laws and other similar non-United States laws; or laws that require the true, complete and accurate reporting of financial information or data. Activities subject to these laws also involve the improper use or misrepresentation of information obtained in the course of clinical trials, the creation of fraudulent data in our preclinical studies or clinical trials, or illegal misappropriation of product, which could result in regulatory sanctions and cause serious harm to our reputation. It is not always possible to identify and deter misconduct by employees and other third-parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. In addition, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and financial results, including, without limitation, the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, disgorgement, possible exclusion from participation in Medicare, Medicaid and other United States federal healthcare programs or healthcare programs in other jurisdictions, integrity oversight and reporting obligations to resolve allegations of non-compliance, imprisonment, other sanctions, contractual damages, reputational harm, diminished profits and future earnings and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

Actual or perceived failures to comply with United States and foreign privacy and data protection laws, regulations and standards may adversely affect our business, operations and financial performance.

We are subject to or affected by numerous federal, state and foreign laws and regulations, as well as regulatory guidance, governing the collection, use, disclosure, retention, and security of personal information, such as information that we collect about patients and healthcare providers in connection with clinical trials in the United States and abroad. The global data protection landscape is rapidly evolving, and implementation standards and enforcement practices are likely to remain uncertain for the foreseeable future. This evolution may create uncertainty in our business, affect our or any service providers', contractors' or future collaborators' ability to operate in certain jurisdictions or to collect, store, transfer, use and share personal information, necessitate the acceptance of more onerous obligations in our contracts, result in liability or impose additional costs on us. The cost of compliance with these laws, regulations and standards is high and is likely to increase in the future. Any failure or perceived failure by us or our collaborators, service providers and contractors to comply with federal, state or foreign laws or regulations, our internal policies and procedures or our contracts governing processing of personal information could result in negative publicity, diversion of management time and effort and proceedings against us by governmental entities or others. In many jurisdictions, enforcement actions and consequences for noncompliance are rising.

As our operations and business grow, we may become subject to or affected by new or additional data protection laws and regulations and face increased scrutiny or attention from regulatory authorities. In the United States, HIPAA imposes, among other things, certain standards relating to the privacy, security, transmission and breach reporting of individually identifiable health information. Certain states have also adopted comparable privacy and security laws and regulations, some of which may be more stringent than HIPAA. Such laws and regulations will be subject to interpretation by various courts and other governmental authorities, thus creating potentially complex compliance issues for us and our future customers and strategic partners. For example, the CCPA gives California residents expanded rights to access and delete their personal information, opt out of certain personal information sharing, and receive detailed information about how their personal information is used. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches. The CCPA may increase our compliance costs and potential liability. Following the amendment of the CCPA by the California Privacy Rights Act, or CPRA, the CCPA is implemented and enforced by a new California data protection agency, which may result in increased regulatory scrutiny of California businesses in the areas of data protection and security. The effects of the CCPA, as amended by the CPRA, are potentially significant and may require us to modify our data collection or processing practices and policies and to incur substantial costs and expenses in an effort to comply and increase our potential exposure to regulatory enforcement and/or litigation.

Certain other state laws impose similar privacy obligations and we also anticipate that more states will increasingly enact legislation similar to the CCPA. Already, laws similar to the CCPA have been passed in numerous other states. While these laws incorporate many similar concepts of the CCPA, there are also several key differences in the scope, application, and enforcement of the laws that will change the operational practices of regulated entities. In addition, Washington state recently passed a comprehensive health information privacy law. Proposed and newly enacted legislation may add additional complexity, variation in requirements, restrictions and potential legal risk, require additional investment of resources in compliance programs, impact strategies and the availability of previously useful data and could result in increased compliance costs and/or changes in business practices and policies.

Our operations abroad may also be subject to increased scrutiny or attention from data protection authorities. Many countries in these regions have established or are in the process of establishing privacy and data security legal frameworks with which we, our collaborators, service providers, including our CROs, and contractors must comply. For example, the European Union General Data Protection Regulation (with regards to the European Economic Area, or EEA, and the UK GDPR (with regards to the UK), as well as applicable national data protection legislation and requirements. In this document, GDPR refers to both EU GDPR and the UK GDPR, unless specified otherwise. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal information, including requirements relating to having a legal basis for processing personal data, stricter requirements relating to the processing of sensitive data (such as health sensitive data), where required by GDPR obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, requirements to conduct data protection impact assessments for high risk processing and taking certain measures when engaging third-party processors.

Failure to comply with the requirements of the GDPR may result in warning letters, mandatory audits, orders to cease/change the use of data, and financial penalties, including fines of up to 4% of global revenues, or 20,000,000 Euro (£17.5 million for the UK), whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR.

The GDPR provides that EEA Member States may make their own further laws and regulations in relation to the processing of genetic, biometric or health data, which could result in differences between Member States, limit our ability to use and share personal data or could cause our costs to increase, and harm our business and financial condition.

The GDPR also includes restrictions on cross-border transfers of personal data to countries outside the EEA and UK that are not considered by the European Commission or UK Government as providing adequate protection to personal data, including the United States, unless a valid GDPR mechanism (for example, the European Commission approved Standard Contractual Clauses, or SCCs, and the UK International Data Transfer Agreement/Addendum, or UK IDTA) has been put in place. Where relying on the SCCs or UK IDTA for data transfers, we may also be required to carry out transfer impact assessments to assess whether the recipient is subject to local laws which allow public authority access to personal data. . Further, the EU and United States have adopted its adequacy decision for the EU-U.S. Data Privacy Framework ("Framework"), which entered into force on July 11, 2023. This Framework provides that the protection of personal data transferred between the EU and the United States is comparable to that offered in the EEA. This provides a further avenue to ensuring transfers to the United States are carried out in line with GDPR. There has been an extension to the Framework to cover UK transfers to the United States. The Framework could be challenged like its predecessor frameworks. The international transfer obligations under the EEA and UK data protection regimes will require significant effort and cost, and may result in us needing to make strategic considerations around where EEA and UK personal data is transferred and which service providers we can utilize for the processing of EEA and UK personal data. Although the UK is regarded as a third country under the EU GDPR, the European Commission has issued a decision recognizing the UK as providing adequate protection under the EU GDPR, or Adequacy Decision, and, therefore, transfers of personal data originating in the EEA to the UK remain unrestricted. The UK government has confirmed that personal data transfers from the UK to the EEA remain free flowing. The UK Government has also now introduced a Data Protection and Digital Information Bill, UK Bill, into the UK legislative process. The aim of the UK Bill is to reform the UK's data protection regime following Brexit. If passed, the final version of the UK Bill will have the effect of further altering the similarities between the UK and EEA data protection regime and threaten the UK Adequacy Decision from the European Commission. This may lead to additional compliance costs and could increase our overall risk. The respective provisions and enforcement of the EU GDPR and UK GDPR may further diverge in the future and create additional regulatory challenges and uncertainties.

In addition, many jurisdictions outside of Europe are also considering and/or enacting comprehensive data protection legislation. For example, as of August 2020, the Brazilian General Data Protection Law imposes stringent requirements similar to GDPR with respect to personal information collected from individuals in Brazil.

In China, there have also been recent significant developments concerning privacy and data security. On June 10, 2021, the Standing Committee of the PRC National People's Congress published the Data Security Law of the People's Republic of China, or the Data Security Law, which took effect on September 1, 2021. The Data Security Law requires data processing (which includes the collection, storage, use, processing, transmission, provision and publication of data), to be conducted in a legitimate and proper manner. The Data Security Law imposes data security and privacy obligations on entities and individuals carrying out data processing activities and also introduces a data classification and hierarchical protection system based on the importance of data in economic and social development and the degree of harm it may cause to national security, public interests, or legitimate rights and interests of individuals or organizations if such data are tampered with, destroyed, leaked, illegally acquired or illegally used. The appropriate level of protection measures is required to be taken for each respective category of data.

Also in China, on August 20, 2021, the Standing Committee of the National People's Congress of the PRC promulgated the Personal Information Protection Law, or PIPL, which took effect on November 1, 2021. PIPL raises the protection requirements for processing personal information, and many specific requirements of the PIPL remain to be clarified. Fines for PIPL violations range from $7.7 million to up to 5% of the infringing company's previous year's revenues. We

may be required to make further significant adjustments to our business practices to comply with the personal information protection laws and regulations in China.

Although we work to comply with applicable laws, regulations and standards, our contractual obligations and other legal obligations, because the interpretation and application of many privacy and data protection laws (including the GDPR), commercial frameworks, and standards are uncertain, it is possible that these laws, frameworks, and standards may be interpreted and applied in a manner that is inconsistent with our existing data management practices and policies. If so, in addition to the possibility of fines, lawsuits, breach of contract claims, and other claims and penalties, we could be required to fundamentally change our business activities and practices or modify our solutions, which could have an adverse effect on our business. Any inability to adequately address privacy and security concerns, even if unfounded, or comply with applicable privacy and security or data security laws, regulations, and policies, could result in additional cost and liability to us, damage our reputation, inhibit our ability to conduct trials, and adversely affect our business and results of operations.

We are an "emerging growth company" as defined in the JOBS Act and a "smaller reporting company" as defined in the Securities Exchange Act of 1934, as amended, or the Exchange Act, and will be able to avail ourselves of reduced disclosure requirements applicable to emerging growth companies and smaller reporting companies, which could make our common stock less attractive to investors and adversely affect the market price of our common stock.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We will remain an emerging growth company until the earlier of (i) the last day of the fiscal year in which we have total annual gross revenues of $1.235 billion or more; (ii) the last day of the fiscal year following the fifth anniversary of the date of the completion of our IPO; (iii) the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the Securities and Exchange Commission, which means the market value of our common stock that is held by non-affiliates exceeds $700 million as of June 30th. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404;

- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;

- providing only two years of audited financial statements in addition to any required unaudited interim financial statements and a correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure;

- the requirement to provide detailed compensation discussion and analysis in proxy statements and reports filed under the Exchange Act and instead provide a reduced level of disclosure regarding executive compensation; and

- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved and some of the disclosure requirements of the Dodd-Frank Act relating to compensation of executive officers.

Although we are still evaluating the JOBS Act, we currently intend to take advantage of some, but not all, of the available exemptions available to us so long as we qualify as an "emerging growth company." We have taken advantage of reduced reporting burdens in this Annual Report on form 10-K. In particular, we have provided only two years of audited financial statements and have not included all of the executive compensation information that would be required if we were not an emerging growth company. We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have elected to "opt out" of such extended transition period, which means that when a standard is issued or revised and it has different application dates for public or private companies, we will adopt the new or revised standard at the time public companies adopt the new or revised standard.

As a result, changes in rules of United States generally accepted accounting principles or their interpretation, the adoption of new guidance or the application of existing guidance to changes in our business could significantly affect our financial position and results of operations. In addition, our independent registered public accounting firm will not be required to provide an attestation report on the effectiveness of our internal control over financial reporting so long as we qualify as an "emerging growth company," which may increase the risk that material weaknesses in our internal control over financial reporting go undetected. Likewise, so long as we qualify as an "emerging growth company," we may elect not to provide you with certain information, including certain financial information and certain information regarding compensation of our executive officers, that we would otherwise have been required to provide in filings we make with the SEC, which may make it more difficult for investors and securities analysts to evaluate our company. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock, and our stock price may be more volatile and may decline.

Even after we no longer qualify as an emerging growth company, we may still qualify as a "smaller reporting company," which would allow us to continue to take advantage of many of the same exemptions from disclosure requirements, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

We incur increased costs as a result of operating as a public company, and our management is required to devote substantial time to new compliance initiatives.

As a public company, and particularly after we are no longer an "emerging growth company," we will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act of 2002 and rules subsequently implemented by the SEC and Nasdaq have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance.

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting. Management's initial certification under Section 404 of the Sarbanes-Oxley Act was provided with this annual report on Form 10-K for the fiscal year ended December 31, 2023. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we have engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and

challenging. In this regard, we have been and will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that neither we nor our independent registered public accounting firm will be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements. In addition, if we are not able to continue to meet these requirements, we may not be able to remain listed on Nasdaq.

If we fail to establish and maintain proper and effective internal control over financial reporting, our operating results and our ability to operate our business could be harmed.

Ensuring that we have adequate internal financial and accounting controls and procedures in place so that we can produce accurate financial statements on a timely basis is a costly and time-consuming effort that needs to be re-evaluated frequently. Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements in accordance with generally accepted accounting principles. In connection with our IPO, we began the process of documenting, reviewing and improving our internal controls and procedures for compliance with Section 404 of the Sarbanes-Oxley Act, which will require annual management assessment of the effectiveness of our internal control over financial reporting. We have also begun recruiting additional finance and accounting personnel with certain skill sets that we need as a public company.

Implementing any appropriate changes to our internal controls may distract our officers and employees, entail substantial costs to modify our existing processes, and take significant time to complete. These changes may not, however, be effective in maintaining the adequacy of our internal controls, and any failure to maintain that adequacy, or consequent inability to produce accurate financial statements on a timely basis, could increase our operating costs and harm our business. In addition, investors' perceptions that our internal controls are inadequate or that we are unable to produce accurate financial statements on a timely basis may harm our stock price and make it more difficult for us to effectively market and sell our service to new and existing customers.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to the periodic reporting requirements of the Securities Exchange Act of 1934, or the Exchange Act. We designed our disclosure controls and procedures to reasonably assure that information we must disclose in reports we file or submit under the Exchange Act is accumulated and communicated to management, and recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well-conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements due to error or fraud may occur and not be detected.

If securities analysts do not publish research or reports about our business or if they publish negative evaluations of our stock, the price of our stock could decline.

The trading market for our common stock will rely in part on the research and reports that industry or financial analysts publish about us or our business. We do not have control over these analysts. There can be no assurance that existing analysts will continue to provide research coverage or that new analysts will begin to provide research coverage. Although we have obtained analyst coverage, if one or more of the analysts covering our business downgrade their evaluations of our stock, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price to decline.

We may be subject to securities litigation, which is expensive and could divert management attention.

The market price of our common stock may be volatile. The stock market in general, and Nasdaq and biopharmaceutical companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. In the past, companies that have experienced volatility in the market price of their stock have been subject to securities class action litigation. We may be the target of this type of litigation in the future. Securities litigation against us could result in substantial costs and divert our management's attention from other business concerns, which could seriously harm our business.

Item 1B. Unresolved Staff Comments

None.

Item 1C. Cybersecurity

Cyber Risk Management and Strategy

We rely on information technology systems that we or our third-party providers operate to process, transmit and store electronic information in our day-to-day operations. To help protect against risks from cybersecurity threats to these systems, we have implemented cybersecurity processes in accordance with our risk profile and business that are informed by a recognized cybersecurity industry standard.

Our cybersecurity risk management process includes a number of components implemented by internal and external resources, including security monitoring tools, penetration tests and vulnerability assessments, and employee cybersecurity awareness training. We also engage the services of external partners who provide information security services to help maintain our hardware and software, assist with security monitoring on our devices, and help us draft and implement appropriate information security policies.

As part of our cybersecurity risk management process, we take a risk-based approach to the evaluation of third-party vendors based on the criticality and size of the vendor. This process includes a review by our external partners, as appropriate.

Governance Related to Cybersecurity Risks

Our President meets regularly with representatives from our external partners to, as applicable, review aspects of the Company's cybersecurity processes or evaluate risks from cybersecurity threats.

Management, including our President and Chief Financial Officer, reports to the Audit Committee on our major cybersecurity risk exposures, their potential impact on us, and the steps we take to manage them. The Audit Committee considers the Company's cybersecurity risk exposures and the steps that the Company's management has taken to monitor and control such exposures in connection with the Audit Committee's discussion of the Company's risk assessment and management guidelines.

The Audit Committee reviews and discusses, at least annually, the Company's cybersecurity risks, including the Company's information security and risk management programs, controls and procedures, as well as high level review of the threat landscape facing the Company and the Company's strategy to mitigate cybersecurity risks and potential security incidents. The Audit Committee also reviews the recovery and communication plans for any unplanned outage or security incident.

The Audit Committee receives periodic updates from management regarding cybersecurity matters and is notified between such updates regarding significant new cybersecurity threats or incidents. The Audit Committee provides updates to the board of directors regarding such oversight.

Item 2. Properties

Our headquarters is located in Waltham, Massachusetts, where we lease approximately 5,000 square feet of office space. Our Waltham lease expires in December 2025. We also lease approximately 3,500 square feet of office space located in Foster City, California which expires in October 2025. We believe that our existing facilities, as well as facilities available for rent, are sufficient for our current needs and our needs for the foreseeable future.

Item 3. Legal Proceedings

From time to time we may become subject to various legal proceedings and claims that arise in the ordinary course of our business activities. As of the date of this Annual Report on Form 10-K, we are not currently a party to any claim or litigation, the outcome of which, if determined adversely to us, would individually or in the aggregate be reasonably expected to have a material adverse effect on our business. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities.

Our common stock trades under the symbol "AVTE" on The Nasdaq Global Market and has been publicly traded since June 30, 2021. Prior to this time, there was no public market for our common stock.

Holders of Our Common Stock

As of March 22, 2024, there were approximately 13 holders of record of shares of our common stock. This number does not include stockholders for whom shares are held in "nominee" or "street" name.

Dividend Policy

We have never declared or paid any cash dividends on our capital stock. We currently 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 declare dividends will be made at the discretion of our board of directors and will depend on our financial condition, operating results, capital requirements, general business conditions, and other factors that our board of directors may deem relevant. Investors should not purchase our common stock with the expectation of receiving cash dividends

Securities Authorized for Issuance Under Equity Compensation Plans

Information about our equity compensation plans will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2024 Annual Meeting of Stockholders and is incorporated herein by reference.

Recent Sales of Unregistered Equity Securities

None.

Use of Proceeds from our Public Offering of Common Stock

On July 2, 2021, we closed our IPO in which we issued and sold 9,984,463 shares of common stock, including the exercise in full by the underwriters of their option to purchase up to 1,302,321 additional shares of common stock, at a public offering price of $14.00 per share. All of the shares of common stock issued and sold in our IPO were registered under the Securities Act pursuant to a registration statement on Form S-1 (File No. 333-256949), which was declared effective by the SEC on June 29, 2021. Jefferies LLC, Cowen and Company, LLC and Evercore Group L.L.C. acted as joint book-running managers for the IPO.

The aggregate net proceeds to us from the IPO, inclusive of the over-allotment exercise, was approximately $126.9 million, after deducting underwriting discounts and commissions and other offering expenses of approximately $12.9 million. No offering expenses were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning 10% or more of any class of our equity securities or to any other affiliates.

There has been no material change in the planned use of IPO proceeds from that described in our final prospectus filed with the SEC pursuant to Rule 424(b)(4) under the Securities Act on June 30, 2021.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

We did not purchase any of our registered equity securities during the period covered by this Annual Report on Form 10-K.

Item 6. Reserved.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations.

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with our consolidated financial statements and related notes appearing elsewhere in this Annual Report. This discussion contains forward-looking statements that reflect our plans, estimates and beliefs, and involve risks and uncertainties. Our actual results and the timing of certain events could differ materially from those anticipated in these forward-looking statements as a result of several factors, including those discussed in the section titled "Risk Factors" included under Part I, Item 1A and elsewhere in this Annual Report. See "Special Note Regarding Forward-Looking Statements" in this Annual Report.

Overview

We are a clinical-stage biopharmaceutical company focused on developing drugs that meaningfully improve the lives of patients with rare cardiopulmonary disease. Our initial focus is on advancing AV-101, our dry powder inhaled formulation of imatinib for the treatment of pulmonary arterial hypertension, or PAH, a devastating disease impacting approximately 70,000 people in the United States and Europe. Imatinib, marketed as Gleevec tablets, was originally developed for the treatment of multiple cancers. Oral imatinib also demonstrated statistically significant improvement on the primary endpoint, six-minute walk distance, and multiple secondary hemodynamic endpoints in PAH patients in an international Phase 3 trial conducted by Novartis but was poorly tolerated due to adverse events, or AEs, and never approved for the treatment of PAH. AV-101, delivered using a dry powder inhaler, is designed to provide lung concentrations at or above those observed with the oral dose while limiting systemic levels of the drug. We have completed a Phase 1 clinical trial in healthy volunteers and AV-101 was generally well-tolerated with no serious adverse events reported. In November 2023, we completed enrollment in the Phase 2b portion and enrolled our first patient in the Phase 3 portion of Inhaled iMatinib Pulmonary Arterial Hypertension Clinical Trial (IMPAHCT), our global Phase 2b/Phase 3 trial of AV-101 in adults with PAH. We have assembled a team with deep expertise in developing innovative PAH and inhaled therapies and commercializing novel drugs. We do not have any products approved for sale and have incurred significant operating losses since our inception and expect to continue to incur significant operating losses for the foreseeable future.

Recent Developments

At-The-Market Offering

On April 5, 2023, we entered into an ATM Equity Offering℠ Sales Agreement, or the Sales Agreement, with BofA Securities, Inc., or the Agent, pursuant to which we established an "at-the-market" offering program, or ATM Program, to sell, from time to time, at our option, up to an aggregate of $75.0 million of shares of our common stock, through the Agent, as our sales agent. During the year ended December 31, 2023, 2,662,721 shares were sold under the ATM Program, generating approximately $44.3 million of net proceeds after deducting Agent commissions and other offering costs. As of the date of this Annual Report on Form 10-K, approximately $30.0 million of shares remain available for sale from time to time under our ATM Program.

Components of Results of Operations

Revenue

We currently have no products approved for sale, and we have not generated any revenue to date. In the future, we may generate revenue from collaboration or license agreements we may enter into with respect to our drug candidate, as well as product sales from any approved product, which approval we do not expect to occur for at least the next several years, if ever. Our ability to generate product revenue will depend on the successful development and eventual commercialization of AV-101 and any other drug candidates we may pursue. If we fail to complete the development of AV-101 in a timely manner, or to obtain regulatory approval, our ability to generate future revenue and our results of operations and financial position would be materially adversely affected.

Operating Expenses

Research and Development

To date, our research and development expenses have related to the development of AV-101. Research and development expenses are recognized as incurred and payments made prior to the receipt of goods or services to be used in research and development are capitalized until the goods or services are received.

Research and development expenses include:

- external research and development expenses incurred under agreements with contract research organizations, or CROs, and consultants to conduct and support clinical trials of AV-101 and our preclinical studies;
- costs related to manufacturing AV-101 for use in clinical trials; and
- personnel-related costs, including salaries, payroll taxes, employee benefits, and stock-based compensation charges for those individuals involved in research and development efforts.

Our research and development expenses consist principally of direct costs, such as fees paid to CROs, investigative sites and consultants in connection with our clinical trials, preclinical and non-clinical studies, and costs related to manufacturing clinical trial materials. We deploy our personnel related resources across all of our research and development activities. We track direct expenses on a clinical and non-clinical basis.

We plan to substantially increase our research and development expenses for the foreseeable future as we continue the development of AV-101. We cannot determine with certainty the timing of initiation, the duration or the completion costs of current or future clinical trials and nonclinical studies of AV-101 or any future product candidates due to the inherently unpredictable nature of clinical and preclinical development. Clinical and preclinical development timelines, the

probability of success and development costs can differ materially from expectations. We will need to raise substantial additional capital in the future.

Our future clinical development costs may vary significantly based on factors such as:

- per patient trial costs;
- the number of trials required for approval;
- the number of sites included in the trials;
- the countries in which the trials are conducted;
- the length of time required to enroll eligible patients;
- the number of patients that participate in the trials;
- the number of doses evaluated in the trials;
- the drop-out or discontinuation rates of patients;
- potential additional safety monitoring requested by regulatory agencies;
- the duration of patient participation in the trials and follow-up; and
- the efficacy and safety profile of the product candidate.

General and Administrative

General and administrative expenses consist primarily of personnel-related costs, including salaries, payroll taxes, employee benefits, and stock-based compensation charges for those individuals in executive, finance and other administrative functions. Other significant costs include legal fees relating to intellectual property and corporate matters, professional fees for accounting and consulting services, and insurance costs. We anticipate that our general and administrative expenses will increase for the foreseeable future to support our continued research and development activities, pre-commercial preparation activities and commercialization activities for AV-101. We also anticipate increased expenses related to audit, legal, regulatory, and tax-related services associated with maintaining compliance with exchange listing and SEC requirements, director and officer insurance premiums, and investor relations costs associated with operating as a public company.

Results of Operations

Comparison of the Years Ended December 31, 2023 and December 31, 2022

The following table summarizes our results of operations for the years ended December 31, 2023 and December 31, 2022 (in thousands):

	Year Ended December 31,		
	2023	2022	Change
Operating expenses:			
Research and development	$ 64,219	$ 38,622	$ 25,597
General and administrative	17,190	14,615	2,575
Total operating expenses	81,409	53,237	28,172
Loss from operations	(81,409)	(53,237)	(28,172)
Other income (expense):			
Interest income	5,945	1,830	4,115
Other expense	(1)	(79)	78
Total other income	5,944	1,751	4,193
Net loss before income taxes	(75,465)	(51,486)	(23,979)
Provision for income taxes	56	25	31
Net loss	$ (75,521)	$ (51,511)	$ (24,010)

Research and Development Expenses

Research and development expenses for the year ended December 31, 2023 were $64.2 million compared to $38.6 million for the year ended December 31, 2022. The increase of $25.6 million was primarily due to increases of $12.4 million in headcount related costs, $6.0 million in clinical trial costs, $5.6 million in manufacturing costs, and $1.9 million in other miscellaneous costs including travel and professional services, partially offset by lower pre-clinical and regulatory related costs of $0.3 million.

General and Administrative Expenses

General and administrative expenses for the year ended December 31, 2023 were $17.2 million compared to $14.6 million for the year ended December 31, 2022. The increase of $2.6 million was primarily due to a $3.2 million increase in headcount related costs and a $0.6 million increase in travel and other miscellaneous costs, offset by decreases of $0.5 million in insurance costs, $0.4 million in recruiting costs, and $0.3 million in consulting costs.

Total Other Income

Other income for the year ended December 31, 2023 was $5.9 million compared to $1.8 million of other income for the year ended December 31, 2022. The change was primarily due to interest earned on the Company's cash and cash equivalents and short-term investments for the year ended December 31, 2023.

Liquidity and Capital Resources

From our inception through December 31, 2023, we have received aggregate net proceeds of $79.8 million from the sale of shares of our convertible preferred stock and $5.0 million from convertible promissory notes to related parties. In July 2021, we completed our initial public offering, or IPO, with aggregate net proceeds from the offering of $126.9 million, after deducting underwriting discounts and commissions and offering costs.

At-the-Market Offering

On April 5, 2023, we entered into the Sales Agreement with the Agent pursuant to which we can sell, from time to time, at our option, up to an aggregate of $75.0 million of shares of our common stock, through the Agent, as our sales agent. During the year ended December 31, 2023, 2,662,721 shares were sold under the ATM Program, generating approximately $44.3 million of net proceeds after deducting Agent commissions and other offering costs. Since establishment of our ATM Program, we have sold an aggregate of $44.3 million of shares of our common stock, and up to $30.0 million of shares of our common stock remain available for sale from time to time as of the date of this Annual Report on Form 10-K.

Future Funding Requirements

We have prepared operating plans and cash flow forecasts which indicate that our existing cash and cash equivalents and short-term investments on-hand of $122.4 million will be sufficient to fund our planned operations into 2026. However, our forecast of the period of time through which our financial resources will be adequate to support our operations is a forward-looking statement that involves risks and uncertainties, and actual results could vary materially. We have based this estimate on assumptions that may prove to be wrong, and we could deplete our capital resources sooner than we expect. Additionally, the process of conducting clinical trials is costly, and the timing of progress and expenses in these trials is uncertain.

Our future capital requirements will depend on many factors, including:

- the type, number, scope, results, costs and timing of preclinical studies and clinical trials of AV-101, including changes to our development plan based on feedback received from regulatory authorities, and preclinical studies or clinical trials of other potential drug candidates or indications we may choose to pursue in the future;
- the costs and timing of manufacturing for AV-101 or any other product candidates, including commercial scale manufacturing;
- the costs, timing and outcome of regulatory review and approval of AV-101 or any other drug candidates;
- the costs of obtaining, maintaining and enforcing our patents and other intellectual property rights;
- our efforts to enhance operational systems and hire additional personnel to satisfy our obligations as a public company, including enhanced internal controls over financial reporting;
- the costs associated with hiring additional personnel and consultants as our business grows, including additional clinical development personnel;
- the terms and timing of establishing and maintaining collaborations, licenses and other similar arrangements;
- the timing and amount of the milestone or other payments we must make to any future licensors, if we enter into any license agreements;
- the costs and timing of establishing or securing sales and marketing capabilities if AV-101 or any other product candidate is approved;
- our ability to achieve sufficient market acceptance, coverage and adequate reimbursement from third- party payors and adequate market share and revenue for any approved products;
- patients' ability and willingness to pay out-of-pocket costs for any approved products in the absence of coverage and/or adequate reimbursement from third-party payors; and

- costs associated with any products or technologies that we may in-license or acquire.

Until such time, if ever, as we can generate substantial product revenue to support our cost structure, we expect to finance our cash needs through equity offerings, debt financings, or other capital sources, potentially including collaborations, licenses and other similar arrangements. However, we may be unable to raise additional funds or enter into such other arrangements when needed on favorable terms or at all. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be or could be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing and equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise funds through collaborations, or other similar arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or drug candidates or grant licenses on terms that may not be favorable to us and/or may reduce the value of our common stock. Our failure to raise capital or enter into such other arrangements when needed could have a negative impact on our financial condition and on our ability to pursue our business plans and strategies. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market our drug candidates even if we would otherwise prefer to develop and market such drug candidates ourselves.

Contractual Obligations and Commitments

In August 2021, we entered into a lease agreement, or the Waltham Lease, for approximately 5,000 square feet of office space in Waltham, Massachusetts. The term of the Waltham Lease is thirty-nine months, unless extended or earlier terminated pursuant to the terms of the Waltham Lease. In January 2024, we entered into the First Amendment to the Waltham Lease resulting in our lease expiring on December 31, 2025, and subject to scheduled annual increases of $1.00 per rentable square foot during this additional lease term. In obtaining this lease extension, we no longer have the option to extend the Waltham Lease for one additional period of three years.

In April 2022, we entered into a lease agreement, or the Foster City Lease, for approximately 3,500 square feet of office space in Foster City, California. The base rent under the Foster City Lease is $76.80 per rentable square foot, or approximately $22,600 per month and is subject to scheduled annual increases of 3% on each annual anniversary during the lease term. The term of the Foster City Lease is thirty-nine months, unless extended or earlier terminated pursuant to the terms of the Foster City Lease. We have the option to extend the Foster City Lease for one additional period of one year.

As of December 31, 2023, we do not have any other operating lease obligations, long-term debt obligations, capital lease obligations, purchase obligations or long-term liabilities.

We enter into contracts in the normal course of business for contract research services, contract manufacturing services, professional services and other services and products for operating purposes. These contracts generally provide for termination after a notice period, and, therefore, are cancelable contracts and not included above.

Cash Flows

Comparison of the Years Ended December 31, 2023 and December 31, 2022

The following table sets forth a summary of the net cash flow activity for the years ended December 31, 2023 and December 31, 2022 (in thousands):

	Year Ended December 31,	
	2023	2022
Net cash used in operating activities	$ (56,778)	$ (39,122)
Net cash provided by investing activities	11,876	6,926
Net cash provided by financing activities	45,996	396
Net increase (decrease) in cash and cash equivalents	$ 1,094	$ (31,800)

Operating Activities

Net cash used in operating activities for the year ended December 31, 2023 was $56.8 million, consisting primarily of our net loss incurred during the period of $75.5 million adjusted for $8.9 million of noncash charges and $9.7 million for net changes in operating assets and liabilities. Noncash charges consisted primarily of $11.9 million in stock-based compensation expense, partially offset by $3.1 million of amortization of our investments. The net change in operating assets and liabilities related to a $9.8 million increase in accounts payables and accrued liabilities, a $0.5 million increase in prepaid expenses and other current assets, partially offset by a $0.4 million decrease in liabilities and $0.1 million decrease in other long-term assets.

Net cash used in operating activities for the year ended December 31, 2022 was $39.1 million, consisting primarily of our net loss incurred during the period of $51.5 million adjusted for $4.6 million of noncash charges and $7.8 million for net changes in operating assets and liabilities. Noncash charges consisted primarily of $5.5 million in stock-based compensation expense, partially offset by $0.9 million of amortization of our investments. The net change in operating assets and liabilities related to a $5.0 million increase in accounts payables and accrued liabilities, a $4.7 million increase in prepaid expenses and other current assets, partially offset by a $1.9 million decrease in other long-term assets.

Investing Activities

Net cash provided by investing activities for the year ended December 31, 2023 of $11.9 million consisted of maturities of short-term investments of $136.0 million, offset by purchases of short-term investments of $124.0 million and $0.1 million for purchases of property and equipment.

Net cash provided by investing activities for the year ended December 31, 2022 of $6.9 million was comprised of sales and maturities of investments of $154.7 million, offset by purchase of short-term investments of $147.6 million and purchases of property and equipment of $0.2 million to support our research activities and leasehold improvements, furniture and fixtures for our office spaces in Waltham, Massachusetts and Foster City, California.

Financing Activities

Net cash provided by financing activities for the year ended December 31, 2023 consisted of $44.9 million in net proceeds received from sales of common stock under the Sales Agreement, after deducting Agent commissions, $1.3 million of proceeds from stock option exercises and issuances of common stock under our employee stock purchase plan, offset by $0.2 million of payments made for offering costs.

Net cash provided by financing activities for the year ended December 31, 2022 was $0.4 million due to $0.8 million in net proceeds received from stock option exercises and issuances of common stock under our employee stock purchase plan, which were partially offset by $0.4 million of payments made for offering costs.

Critical Accounting Policies and Estimates

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States, or U.S. GAAP. The preparation of our consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets, liabilities, expenses and the related disclosures of contingent liabilities in our consolidated financial statements and accompanying notes. We base our estimates and assumptions on historical experience and other factors that we believe to be reasonable under the circumstances. We evaluate our estimates and judgments on an ongoing basis. Actual results may differ significantly from these estimates under different assumptions, judgments or conditions.

See Note 2 to our consolidated financial statements included in Part II, Item 8 of this Annual Report on Form 10-K for a summary of significant accounting policies and the effect on our consolidated financial statements.

Research and Development Expenses

We are required to estimate our expenses resulting from obligations under contracts with vendors, consultants and CROs, in connection with conducting research and development activities. The financial terms of these contracts are subject to negotiations, which vary from contract to contract and may result in payment flows that do not match the periods over which materials or services are provided under such contracts. We reflect research and development expenses in our consolidated financial statements by matching those expenses with the period in which services and efforts are expended. We account for these expenses according to the progress of the preclinical or clinical study as measured by the timing of various aspects of the study or related activities. We determine clinical trial cost estimates through review of the underlying contracts along with preparation of financial models taking into account discussions with research and other key personnel and outsider service providers as to the progress of studies or other services being conducted. During the course of a study, we adjust our rate of expense recognition if actual results differ from our estimates.

Emerging Growth Company Status

As an emerging growth company under the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, we can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have elected to "opt out" of such extended transition period, which means that when a standard is issued or revised and it has different application dates for public or private companies, we will adopt the new or revised standard at the time public companies adopt the new or revised standard. The decision to opt out of the extended transition period under the JOBS Act is irrevocable.

Recently Issued Accounting Pronouncements

See Note 2 to our consolidated financial statements included in Part II, Item 8 of this Annual Report on Form 10 K for a summary of recently issued accounting pronouncements.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

Interest Rate Risk

We are exposed to market risks in the ordinary course of our business. These risks primarily include interest rate sensitivities related to our cash, cash equivalents and short-term investments. We invest our excess cash primarily in money market funds, commercial paper, corporate debt securities and U.S. Treasury bills. We mitigate credit risk by maintaining a well-diversified portfolio and limiting the amount of investment exposure as to institution, maturity and investment type.

Because of the short-term maturities of our cash equivalents and short-term investments, along with the low risk profile of our investments, we do not believe that an increase in market rates would have any significant impact on the realized value of our investments. An immediate 100 basis point change in interest rates would not have a material effect on the fair market value of our cash equivalents and short-term investments.

Inflation Fluctuation Risk

Inflation generally affects us by increasing our cost of labor. We do not believe that inflation had a material effect on our business, financial condition or results of operations during the years ended December 31, 2023 and December 31, 2022.

Item 8. Financial Statements and Supplementary Data.

The consolidated financial statements required to be filed pursuant to this Item 8 are appended to this Annual Report on Form 10-K. An index of those consolidated financial statements is found in Item 15, Exhibits and Financial Statement Schedules, of this Annual Report on Form 10-K.

Item 9. Changes in and Disagreements With Accountants on Accounting and Financial Disclosure.

None.

Item 9A. Controls and Procedures.

Management's Evaluation of our Disclosure Controls and Procedures

We maintain "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, that are designed to ensure that information required to be disclosed in the reports that we file or submit under the Exchange Act is (i) recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms and (ii) accumulated and communicated to our management, including our principal executive and principal financial officer, as appropriate to allow timely decisions regarding required disclosure. Our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Our disclosure controls and procedures are designed to provide reasonable assurance of achieving their control objectives. Our management, with the participation of our principal executive officer and principal financial officer, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) as of December 31, 2023. Based upon such evaluation, our principal executive officer and principal financial officer have concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of such date.

Management's Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act as a process designed by, or under the supervision of, our principal executive officer and our principal financial officer, and effected by our board of directors, management, and other personnel, to provide reasonable assurance regarding the reliability of our financial reporting and the preparation of financial statements for external purposes in accordance with U.S. GAAP, and includes those policies and procedures that:

- pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of assets;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with U.S. GAAP, and that receipts and expenditures are being made only in accordance with authorizations of management and directors; and
- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on our financial statements.

Under the supervision of and with the participation of our management, including our principal executive officer and principal financial officer, we conducted an evaluation of the effectiveness of our internal control over financial reporting based on the framework provided in Internal Control—Integrated Framework issued by the Committee of Sponsoring

Organizations of the Treadway Commission in (2013 Framework). Based on this evaluation, our management concluded that our internal control over financial reporting was effective as of December 31, 2023.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Attestation Report of the Registered Public Accounting Firm

This Annual Report on Form 10-K does not include an attestation report of our registered public accounting firm due to an exemption established by the JOBS Act for "emerging growth companies."

Changes in Internal Control over Financial Reporting

There was no change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) that occurred during the period covered by this Annual Report on Form 10-K that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

(a)

None.

(b)

Rule 10b5-1 Plans

On November 16, 2023, Benjamin Dake, our President, adopted a trading arrangement that is intended to satisfy the affirmative defense of Rule 10b5-1(c) (the Dake 10b5-1 Plan). Between March 18, 2024 and December 31, 2024, the Dake 10b5-1 Plan provides for the potential sale of approximately 193,530 of our common stock. The plan expires on December 31, 2024, or upon the earlier completion of all authorized transactions under the plan.

On November 17, 2023, Marinus Verwijs, our Chief Technology Officer, adopted a trading arrangement that is intended to satisfy the affirmative defense of Rule 10b5-1(c) (the Verwijs 10b5-1 Plan). Between March 19, 2024 and October 1, 2024, the Verwijs 10b5-1 Plan provides for the potential sale of approximately 42,400 of the our common stock. The plan expires on December 31, 2024, or upon the earlier completion of all authorized transactions under the plan.

On November 24, 2023, Timothy Noyes, our Chief Executive Officer, adopted a trading arrangement that is intended to satisfy the affirmative defense of Rule 10b5-1(c) (the Noyes 10b5-1 Plan). Between April 1, 2024 and July 16, 2025, the Noyes 10b5-1 Plan provides for the potential sale of approximately 280,000 of our common stock. The plan expires on July 31, 2025, or upon the earlier completion of all authorized transactions under the plan.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this Item 10 will be included in our Definitive Proxy Statement to be filed with the Securities and Exchange Commission, or SEC, with respect to our 2024 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 11. Executive Compensation.

The information required by this Item 11 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2024 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

The information required by this Item 12 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2024 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence.

The information required by this Item 13 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2024 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services.

Our independent public accounting firm is KPMG LLP, San Diego, California (PCAOB Auditor ID: 185).

The information required by this Item 14 will be included in our Definitive Proxy Statement to be filed with the SEC with respect to our 2024 Annual Meeting of Stockholders and is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules

1. **All financial statements.**

   The consolidated financial statements of Aerovate Therapeutics, Inc., together with the report thereon of KPMG LLP, an independent registered public accounting firm, are included in this annual report on Form 10-K beginning on page F-1.

2. **Financial statement schedules.**

   All schedules have been omitted because the information required to be set forth therein is not applicable or is shown in the consolidated financial statements or notes thereto.

3. **Exhibits**

   A list of exhibits is set forth on the Exhibit Index immediately preceding the signature page of this annual report on Form 10-K and is incorporated herein by reference.

Item 16. Form 10-K Summary

The Company has elected not to include summary information.

AEROVATE THERAPEUTICS, INC.
INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Stockholders and Board of Directors
Aerovate Therapeutics, Inc.:

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheets of Aerovate Therapeutics, Inc. and subsidiary (the Company) as of December 31, 2023 and 2022, the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for the years then ended, and the related notes (collectively, the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2023 and 2022, and the results of its operations and its cash flows for the years then ended, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits, we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ KPMG LLP

We have served as the Company's auditor since 2019.

San Diego, California
March 25, 2024

AEROVATE THERAPEUTICS, INC.
CONSOLIDATED BALANCE SHEETS
(IN THOUSANDS, EXCEPT SHARE AND PER SHARE AMOUNTS)

	December 31, 2023	December 31, 2022
Assets		
Current assets:		
Cash and cash equivalents	$ 23,491	$ 22,397
Short-term investments	98,948	106,823
Prepaid expenses and other current assets	1,793	2,276
Total current assets	124,232	131,496
Property and equipment, net	288	242
Operating lease right-of-use assets	614	1,003
Other long-term assets	2,284	2,560
Total assets	$ 127,418	$ 135,301
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 2,396	$ 2,575
Accrued and other current liabilities	14,821	4,822
Operating lease liabilities	420	385
Total current liabilities	17,637	7,782
Operating lease liabilities, net of current portion	255	705
Other liabilities	70	71
Total liabilities	17,962	8,558
Commitments and contingencies (Note 5)		
Stockholders' equity:		
Preferred stock, $0.0001 par value; 10,000,000 shares authorized as of December 31, 2023 and December 31, 2022, respectively; no shares issued and outstanding at December 31, 2023 and December 31, 2022, respectively	—	—
Common stock, $0.0001 par value; 150,000,000 shares authorized at December 31, 2023 and December 31, 2022, respectively; 27,762,703 and 24,722,974 shares issued and outstanding at December 31, 2023 and December 31, 2022, respectively	3	2
Additional paid-in capital	272,640	215,110
Accumulated other comprehensive income (loss)	237	(466)
Accumulated deficit	(163,424)	(87,903)
Total stockholders' equity	109,456	126,743
Total liabilities and stockholders' equity	$ 127,418	$ 135,301

See accompanying notes to consolidated financial statements.

AEROVATE THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(IN THOUSANDS, EXCEPT SHARE AND PER SHARE AMOUNTS)

	Year Ended December 31,	
	2023	2022
Operating expenses:		
Research and development	$ 64,219	$ 38,622
General and administrative	17,190	14,615
Total operating expenses	81,409	53,237
Loss from operations	(81,409)	(53,237)
Other income (expense):		
Interest income	5,945	1,830
Other expense:	(1)	(79)
Total other income	5,944	1,751
Net loss before income taxes	(75,465)	(51,486)
Provision for income taxes	56	25
Net loss	$ (75,521)	$ (51,511)
Comprehensive loss:		
Net loss	$ (75,521)	$ (51,511)
Other comprehensive loss:		
Unrealized gain (loss) on securities	703	(407)
Comprehensive loss	$ (74,818)	$ (51,918)
Net loss per share, basic and diluted	$ (2.87)	$ (2.10)
Weighted-average shares of common stock outstanding, basic and diluted	26,331,630	24,472,104

See accompanying notes to consolidated financial statements.

AEROVATE THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(IN THOUSANDS, EXCEPT SHARE AMOUNTS)

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive (Loss) Income	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2021	24,410,393	$ 2	$ 208,867	$ (59)	$ (36,392)	$ 172,418
Unrealized loss on investments	—	—	—	(407)	—	(407)
Stock based compensation	—	—	5,476	—	—	5,476
Issuance of common stock upon exercise of stock options	298,712	—	617	—	—	617
Issuance of common stock under ESPP	13,869	—	150	—	—	150
Net loss	—	—	—	—	(51,511)	(51,511)
Balance at December 31, 2022	24,722,974	$ 2	$ 215,110	$ (466)	$ (87,903)	$ 126,743
Unrealized gain on investments	—	—	—	703	—	703
Stock based compensation	—	—	11,906	—	—	11,906
Issuance of common stock in connection with ATM, net	2,662,721	1	44,282	—	—	44,283
Vesting of restricted stock units	9,913	—	—	—	—	—
Issuance of common stock upon exercise of stock options	338,987	—	986	—	—	986
Issuance of common stock under ESPP	28,108	—	356	—	—	356
Net loss	—	—	—	—	(75,521)	(75,521)
Balance at December 31, 2023	27,762,703	$ 3	$ 272,640	$ 237	$ (163,424)	$ 109,456

See accompanying notes to consolidated financial statements.

AEROVATE THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(IN THOUSANDS)

	Year ended December 31,	
	2023	2022
Cash flow from operating activities:		
Net loss	$ (75,521)	$ (51,511)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation expense	11,906	5,476
Depreciation and amortization expense	96	68
Accretion of discounts and amortization of premiums on investments, net	(3,057)	(910)
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	483	4,677
Other long-term assets	(110)	(1,872)
Accounts payable	(164)	1,368
Accrued and other liabilities	9,999	3,672
Operating lease assets and liabilities, net	(26)	43
Other liabilities	(384)	(133)
Net cash used in operating activities	$ (56,778)	$ (39,122)
Cash flow from investing activities:		
Purchases of short-term investments	(123,982)	(147,623)
Maturities of short-term investments	136,000	154,744
Purchases of property and equipment	(142)	(195)
Net cash provided by investing activities	$ 11,876	$ 6,926
Cash flow from financing activities:		
Proceeds from sale of common stock in connection with ATM, net	44,888	—
Payments for offering costs	(234)	(371)
Proceeds from issuance of common stock under ESPP	356	150
Proceeds from issuance of common stock upon exercise of stock options	986	617
Net cash provided by financing activities	$ 45,996	$ 396
Net increase (decrease) in cash and cash equivalents	1,094	(31,800)
Cash and cash equivalents at the beginning of the year	22,397	54,197
Cash and cash equivalents at the end of the period	$ 23,491	$ 22,397
Supplemental disclosure of noncash investing and financing activities:		
Right-of-use asset obtained in exchange for operating lease liability	$ —	$ 765
Deferred offering costs included in accounts payable	$ —	$ 15

See accompanying notes to consolidated financial statements.

AEROVATE THERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

(1) ORGANIZATION AND SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

(a) Organization and Nature of Operations

Aerovate Therapeutics Inc. ("Aerovate" or the "Company") was incorporated in the state of Delaware in July 2018, and is headquartered in Waltham, Massachusetts. The Company has a wholly owned subsidiary, Aerovate Securities Corporation. The Company is a clinical-stage biopharmaceutical company that is focused on the development of drugs that meaningfully improve the lives of patients with rare cardiopulmonary disease. The Company's initial focus is on advancing AV-101, the Company's dry powder inhaled formulation of imatinib for the treatment of pulmonary arterial hypertension ("PAH"). The Company initiated a global Phase 2b/Phase 3 trial of AV-101 in adults with PAH in December 2021 and announced in November 2023 completion of enrollment of the Phase 2b portion of this trial and enrollment of the first patient in the Phase 3 portion of this trial.

(b) At-the-Market Offering

On April 5, 2023, the Company entered into an ATM Equity Offering℠ Sales Agreement, or the Sales Agreement, with BofA Securities, Inc., or the Agent, pursuant to which the Company can sell, from time to time, at its option, up to an aggregate of $75.0 million of shares of its common stock, through the Agent, as its sales agent. As of December 31, 2023, 2,662,721 shares have been sold under the Sales Agreement, generating approximately $44.3 million of net proceeds after deducting commissions to the sales agent and other offering costs, and up to $30.0 million of shares of the Company's common stock remain available for sale from time to time under the Sales Agreement.

(c) Liquidity and Management Plans

Since inception, the Company has devoted substantially all of its resources to research and development activities, business planning, establishing and maintaining its intellectual property portfolio, hiring personnel, raising capital, and providing general and administrative support for these operations and has not realized revenues from its planned principal operations. The Company has incurred losses and negative cash flows from operations since inception. In addition, the Company expects to incur substantial operating losses for the next several years as it continues its research and development activities. As of December 31, 2023, the Company had cash and cash equivalents and short-term investments of $122.4 million.

Management plans to continue to incur substantial costs in order to conduct research and development activities and additional capital will be needed to undertake these activities. The Company intends to raise such capital through debt or equity financings or other arrangements to fund operations. Management believes that the Company's current cash and cash equivalents and short-term investments will provide sufficient funds to enable the Company to meet its obligations for at least twelve months from the filing date of this report.

(2) BASIS OF PRESENTATION AND SIGNIFICANT ACCOUNTING POLICIES

(a) Basis of Presentation

The consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("U.S. GAAP") and include the Company's wholly owned subsidiary, Aerovate Securities Corporation. All intercompany transactions and balances have been eliminated in consolidation.

(b) Use of Estimates

The preparation of the Company's consolidated financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities as of the date of the consolidated financial statements and the reported amounts of expenses during the reporting period. Reported amounts and note disclosures reflect the overall economic conditions that are most likely to occur and anticipated measures management intends to take. Actual results could differ materially from those estimates. Accounting estimates and management judgements reflected in the consolidated financial statements include: normal recurring accruals, including the accrual for research and development expenses, stock-based compensation, fair value of investments, and operating lease right-of-use assets and lease liabilities. Estimates and assumptions are reviewed quarterly. Any revisions to accounting estimates are recognized in the period in which the estimates are revised and in any future periods affected.

(c) Cash and Cash Equivalents

Cash and cash equivalents include cash in readily available checking accounts, money market funds and commercial paper. The Company considers all highly liquid investments with an original maturity of three months or less from the date of purchase to be cash equivalents.

(d) Short-term Investments

Short-term investments consist of corporate debt securities, commercial paper and U.S. Treasury bills, classified as available-for-sale securities and have maturities of greater than three months. The Company has classified all of its available-for-sale investment securities as current assets on the consolidated balance sheets because these are considered highly liquid securities and are available for use in current operations. The Company carries these securities at fair value and reports unrealized gains and losses as a separate component of accumulated other comprehensive loss. The cost of debt securities is adjusted for amortization of purchase premiums and accretion of discounts to maturity. Such amortization and accretion is included in interest income in the consolidated statements of operations and comprehensive loss. Realized gains and losses on sales of securities are determined using the specific identification method and recorded in other income (expense), net in the consolidated statement of operations and comprehensive loss.

(e) Concentration of Credit Risk

Financial instruments, which potentially subject the Company to concentration of credit risk, consist primarily of cash, cash equivalents and short-term investments. The Company maintains cash, cash equivalents and short-term investments with various high credit quality banks and other financial institutions in the United States. Such deposits may be in excess of federally insured limits. Management believes that the Company is not exposed to significant credit risk due to the financial position of the depository institutions in which those deposits are held. The Company has not experienced any losses on deposits since inception.

(f) Comprehensive Loss

Comprehensive loss consists of net loss and unrealized gains or losses on available-for-sale investments. The Company displays comprehensive loss and its components as part of the consolidated statements of operations and comprehensive loss.

(g) Fair Value Measurements

The accounting guidance defines fair value, establishes a consistent framework for measuring fair value and expands disclosure for each major asset and liability category measured at fair value on either a recurring or non-recurring basis. Fair value is defined as an exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. As such, fair value is a market-based measurement that should be determined based on assumptions that market participants would use

in pricing an asset or liability. As a basis for considering such assumptions, the accounting guidance establishes a three-tier fair value hierarchy, which prioritizes the inputs used in measuring fair value as follows:

Level 1: Observable inputs such as quoted prices in active markets.

Level 2: Inputs, other than the quoted prices in active markets that are observable either directly or indirectly.

Level 3: Unobservable inputs in which there is little or no market data, which require the reporting entity to develop its own assumptions.

The carrying amounts of prepaid expenses and other current assets, accounts payable, accrued liabilities and other current liabilities are reasonable estimates of their fair value due to the short-term nature of these accounts.

(h) Prepaid Expenses and Other Current Assets

Any expenses paid prior to the related services rendered are recorded as prepaid expenses. Such prepaid expenses are expensed in the period the expense is incurred. If the expense is for a service covering multiple periods, it is expensed from the date the services begin and over the period of the service rendered (or contract service period if services rendered dates are not defined).

(i) Property and Equipment, Net

Property and equipment, which consist of leasehold improvements, furniture and fixtures, research equipment, computers and construction-in-progress are stated at cost less accumulated depreciation or accumulated amortization. Depreciation and amortization is calculated using the straight-line method over the estimated useful lives of the assets, which ranges from three to five years. Leasehold improvements are amortized over the remaining life of the lease for leasehold improvements at the time the asset is placed into service.

(j) Impairment of Long-lived Assets

The carrying value of long-lived assets, including property and equipment, are reviewed for impairment whenever events or changes in circumstances indicate that the asset may not be recoverable. An impairment loss is recognized when the total of estimated future undiscounted cash flows, expected to result from the use of the asset and its eventual disposition, are less than its carrying amount. Impairment, if any, would be assessed using discounted cash flows or other appropriate measures of fair value. Through December 31, 2023, there has been no such impairment losses recorded by the Company.

(k) Leases

At the commencement date of a lease, the Company recognizes lease liabilities which represent its obligation to make lease payments, and right-of-use assets ("ROU assets") which represent its right to use the underlying asset during the lease term. The lease liability is measured at the present value of lease payments over the lease term. As the Company's leases typically do not provide an implicit rate, the Company uses an incremental borrowing rate based on the information available at the lease commencement date. The ROU asset is measured at cost, which includes the initial measurement of the lease liability and initial direct costs incurred by the Company and excludes lease incentives. ROU assets are recorded in operating lease ROU assets and lease liabilities are recorded in operating lease liabilities, current and noncurrent in the consolidated balance sheets.

Lease terms may include options to extend or terminate the lease when it is reasonably certain that the Company will exercise that option. Operating lease expense is recognized on a straight-line basis over the lease term. The Company has elected not to separate lease and non-lease components and not recognize lease liabilities and ROU assets for short-term leases with terms of twelve months or less.

(l) Convertible Preferred Stock

The Company records convertible preferred stock at fair value on the dates of issuance, net of issuance costs. Upon the occurrence of certain events that are outside the Company's control, including a deemed liquidation event, holders of the convertible preferred stock can cause redemption for cash. Therefore, convertible preferred stock is classified outside of stockholders' deficit on the balance sheets as events triggering the liquidation preferences are not solely within the Company's control. The carrying values of the convertible preferred stock are adjusted to their liquidation preferences if and when it becomes probable that such a liquidation event will occur.

(m) Research and Development Expenses

Research and development costs are expensed as incurred. Research and development costs consist primarily of salaries and other benefits of research and development personnel, including associated share-based compensation, costs related to research activities, preclinical studies, clinical trial, drug manufacturing and allocated overhead and facility-related expenses. The Company accounts for non-refundable advance payments for goods or services that will be used in future research and development activities as expenses when the goods have been received or when the service has been performed rather than when the payment is made.

Clinical trial costs are a component of research and development expenses. The Company expenses costs for its clinical trial activities performed by third parties, including clinical research organizations and other service providers, as they are incurred, based upon estimates of the work completed over the life of the individual study in accordance with associated agreements. The Company uses information it receives from internal personnel and outside service providers to estimate the clinical trial costs incurred.

(n) Stock-Based Compensation

Stock-based compensation expense represents the cost of the grant-date fair value of employee, officer, director, and non-employee stock option grants and restricted stock units, estimated in accordance with the applicable accounting guidance, recognized using the straight-line method over the vesting period for service-based options and using the graded vesting method for performance-based options. The vesting period generally approximates the expected service period of the awards. Forfeitures are recognized and accounted for as they occur.

The fair value of stock options is estimated using a Black-Scholes option pricing model on the date of grant. This method requires certain assumptions be used as inputs, such as the fair value of the underlying common stock, expected term of the option before exercise, expected volatility of the Company's common stock, expected dividend yield, and a risk-free interest rate. Options and awards granted during the year have a maximum contractual term of ten years. The Company has limited historical stock option activity and therefore estimates the expected term of stock options granted using the simplified method, which represents the average of the contractual term of the stock option and its weighted-average vesting period. The expected volatility of stock options is based upon the historical volatility of a number of publicly traded companies in similar stages of clinical development. The Company has historically not declared or paid any dividends and does not currently expect to do so in the foreseeable future. The risk-free interest rates used are based on the U.S. Department of Treasury ("U.S. Treasury") yield in effect at the time of grant for zero-coupon U.S. Treasury notes with maturities approximately equal to the expected term of the stock options.

(o) Income Taxes

Income taxes are accounted for using the asset and liability method. Under the asset and liability method, deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases and net operating loss ("NOL") and tax credit carryforwards.

Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax

assets and liabilities of a change in tax rates is recognized in income in the period that includes the enactment date. A valuation allowance against deferred tax assets is recorded if, based upon the weight of all available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. The company records uncertain tax positions on the basis of a two-step process whereby (1) management determines whether it is more likely than not that the tax positions will be sustained on the basis of the technical merits of the position and (2) for those tax positions that meet the more-likely-than-not recognition threshold, management recognizes the largest amount of tax benefit that is more than 50 percent likely to be realized upon ultimate settlement with the related tax authority. The company recognizes interest and penalties related to unrecognized tax benefits within income tax expense. Any accrued interest and penalties are included within the related tax liability.

(p) Segment Reporting

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision maker in making decisions on how to allocate resources and assess performance. The Company views its operations and manages its business as one operating segment.

(q) Net Loss Per Share

Basic net loss per share is calculated by dividing the net loss attributable to common stockholders by the weighted-average number of common shares outstanding for the period, without consideration of potential dilutive securities. Diluted net loss per share is computed by dividing the net loss attributable to common stockholders by the sum of the weighted average number of common shares plus the potential dilutive effects of potential dilutive securities outstanding during the period. Potential dilutive securities are excluded from diluted earnings or loss per share if the effect of such inclusion is antidilutive. The Company's potentially dilutive securities, which include convertible preferred stock prior to the conversion of such shares to common stock and outstanding stock options under the Company's equity incentive plan, have been excluded from the computation of diluted net loss per share as they would be anti-dilutive to the net loss per share. For all periods presented, there is no difference in the number of shares used to calculate basic and diluted shares outstanding due to the Company's net loss position.

The following table summarizes the Company's net loss per share:

	Year Ended December 31,	
	2023	2022
Numerator:		
Net loss	$ (75,521)	$ (51,511)
Net loss available to common stockholders	$ (75,521)	$ (51,511)
Denominator:		
Weighted-average common stock outstanding, basic and diluted	26,331,630	24,472,104
Net loss per share, basic and diluted	$ (2.87)	$ (2.10)

Potentially dilutive securities not included in the calculation of diluted net loss per share attributable to common stockholders because to do so would have had an anti-dilutive effect are as follows (in common stock equivalent shares):

	As of December 31,	
	2023	2022
Options to purchase common stock	5,230,344	4,110,219
Unvested restricted stock units	21,968	28,881
	5,252,312	4,139,100

(r) Recently Issued Accounting Pronouncements

In December 2023, the FASB issued ASU No. 2023-09, "Improvements to Income Tax Disclosures." ASU 2023-09 requires disaggregated information about a reporting entity's effective tax rate reconciliation as well as

information on income taxes paid. ASU 2023-09 is effective for public entities with annual periods beginning after December 15, 2024 and for private businesses for annual periods beginning after December 15, 2025, with early adoption permitted. The Company is currently evaluating the impact of this guidance on its financial statement disclosures.

In June 2022, the FASB issued ASU No. 2022-03, Fair Value Measurement (Topic 820) - Fair Value Measurement of Equity Securities Subject to Contractual Sale Restrictions. This standard clarifies that a contractual restriction on the sale of an equity security is not considered part of the unit of account of the equity security and, therefore, is not considered in measuring fair value. This standard will be effective for the Company on January 1, 2024, and is not expected to have an impact on the Company's financial position or results of operations upon adoption.

(3) FAIR VALUE OF FINANCIAL INSTRUMENTS

The following tables summarize the Company's financial assets measured at fair value on a recurring basis and their respective input levels based on the fair value hierarchy (in thousands):

		Fair Value Measurements Using		
	December 31, 2023	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (level 3)
Assets:				
Cash equivalents				
Money market funds	$ 19,787	$ 19,787	$ —	$ —
Total cash equivalents	19,787	19,787	—	—
Short-term investments				
Agency bonds	42,255	—	42,255	—
Commercial Paper	38,386	—	38,386	—
U.S. Treasury bills	10,362	10,362	—	—
Corporate debt securities	7,945	—	7,945	—
Total short-term investments	98,948	10,362	88,586	—
Total fair value of assets	$ 118,735	$ 30,149	$ 88,586	$ —

		Fair Value Measurements Using		
	December 31, 2022	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (level 3)
Assets:				
Cash equivalents				
Money market funds	$ 18,436	$ 18,436	$ —	$ —
Total cash equivalents	18,436	18,436	—	—
Short-term investments				
Commercial paper	55,577	—	55,577	—
U.S. Treasury bills	26,841	26,841	—	—
Agency Bonds	24,405	—	24,405	—
Total short-term investments	106,823	26,841	79,982	—
Total fair value of assets	$ 125,259	$ 45,277	$ 79,982	$ —

Cash Equivalents and Short-Term Investments

Financial assets measured at fair value on a recurring basis consist of the Company's cash equivalents and short-term investments. Cash equivalents consisted of cash, money market funds and commercial paper, and short-term investments consisted of U.S. Treasury bills, agency bonds, corporate debt securities and commercial paper. The Company obtains pricing information from its investment manager and generally determines the fair value of investment securities using standard observable inputs, including reported trades, broker/dealer quotes, and bids and/or offers.

The following tables summarize the Company's short-term investments (in thousands):

		As of December 31, 2023			
	Maturity	Amortized cost	Gross unrealized gains	Gross unrealized losses	Estimated fair value
Agency bonds	2 years or less	42,090	179	(14)	42,255
Commercial paper	2 years or less	38,362	29	(5)	38,386
U.S. Treasury bills	2 years or less	10,334	31	(3)	10,362
Corporate debt securities	2 years or less	7,925	21	(1)	7,945
		$ 98,711	$ 260	$ (23)	$ 98,948

		As of December 31, 2022			
	Maturity	Amortized cost	Gross unrealized gains	Gross unrealized losses	Estimated fair value
Commercial paper	1 year or less	$ 55,645	$ 16	$ (84)	$ 55,577
U.S. Treasury bills	1 year or less	27,108	—	(267)	26,841
Agency bonds	2 years or less	24,536	2	(133)	24,405
		$ 107,289	$ 18	$ (484)	$ 106,823

The following tables summarize the Company's short-term investments with unrealized losses for less than 12 months and 12 months or greater:

	As of December 31, 2023					
	Less than 12 months		12 months or Greater			
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Total Fair Value	Total Unrealized Losses
Commercial paper	$ 6,042	$ (5)	$ —	$ —	$ 6,042	$ (5)
Agency bonds	3,760	(6)	6,579	(8)	10,339	(14)
U.S. Treasury bills	488	(2)	1,007	(1)	1,495	(3)
Corporate debt securities	3,110	(1)	—	—	3,110	(1)
	$ 13,400	$ (14)	$ 7,586	$ (9)	$ 20,986	$ (23)

	As of December 31, 2022					
	Less than 12 months		12 months or Greater			
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Total Fair Value	Total Unrealized Losses
Commercial paper	$ 34,928	$ (84)	$ —	$ —	$ 34,928	$ (84)
U.S. Treasury bills	1,971	(6)	24,833	(261)	26,804	(267)
Agency bonds	22,964	(133)	—	—	22,964	(133)
	$ 59,863	$ (223)	$ 24,833	$ (261)	$ 84,696	$ (484)

The Company considers whether unrealized losses have resulted from a credit loss or other factors. The unrealized losses on the Company's available-for-sale securities as of December 31, 2023 were caused by fluctuations in market value and interest rates as a result of the economic environment and not credit risk. The Company concluded that an allowance for credit losses was unnecessary as of December 31, 2023. It is neither management's intention to sell nor is it more likely than not that the Company will be required to sell these investments prior to recovery of their cost basis or recovery of fair value. Unrealized gains and losses are included in accumulated other comprehensive loss.

Accrued interest receivable is written off through net realized investment gains (losses) at the time the issuer of the bond defaults or is expected to default on payment. Accrued interest receivable related to short-term investments was $0.6 million and $0.3 million as of December 31, 2023 and December 31, 2022, respectively.

(4) BALANCE SHEET COMPONENTS

Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consisted of the following (in thousands):

	December 31, 2023	December 31, 2022
Prepaid expenses	$ 1,168	$ 1,503
Prepaid research and development	375	478
Other current assets	250	295
Total prepaid expenses and other current assets	$ 1,793	$ 2,276

Accrued and Other Current Liabilities

Accrued and other current liabilities consisted of the following (in thousands):

	December 31, 2023	December 31, 2022
Accrued research and development	$ 9,363	$ 2,751
Accrued payroll and other employee benefits	4,368	1,691
Other	1,090	380
Total accrued and other current liabilities	$ 14,821	$ 4,822

(5) COMMITMENTS AND CONTINGENCIES

In August 2021, the Company entered into a lease agreement (the "Waltham Lease") for approximately 5,000 square feet of office space in Waltham, Massachusetts for the Company's corporate headquarters. The Waltham Lease has a term of thirty-nine months ("Lease Term"), unless extended or earlier terminated. The Company has the option to extend the Waltham Lease for one additional period of three years. The Lease Term had an initial abatement period, and the initial base rent payable is approximately $18,000 per month following the abatement period. The initial base rent payable will increase by approximately 2% per year over the Lease Term. The Waltham Lease commencement date was September 1, 2021. In January 2024, the Company entered into the First Amendment to the Waltham Lease resulting in the lease expiring on December 31, 2025, and an increase of $1.00 per rentable square foot during the additional lease term. In obtaining this lease extension, the Company no longer has the option to extend the Waltham Lease for one additional period of three years.

In April 2022, the Company entered into a lease agreement (the "Foster City Lease") for approximately 3,500 square feet of office space in Foster City, California. The Foster City Lease has a term of thirty-nine months, unless extended or earlier terminated. The Company has the option to extend the Foster City Lease for on

additional period of one year. The base rent payable under the Lease Term will be $22,600 per month and will be subject to annual increase of 3% on each anniversary.

As of December 31, 2023, the consolidated balance sheet includes an operating lease right-of-use asset of $0.6 million and operating lease liability of $0.7 million. The total operating lease expense was $0.4 million for both of the years ended December 31, 2023 and 2022.

As of December 31, 2023, the future minimum annual lease payments under the operating leases were as follows (in thousands):

	Total Minimum Lease Payments
2024	$ 466
2025	242
Total operating lease payments	708
Less: Amount representing interest	(33)
Present value of net minimum lease payments	$ 675

The components of operating leases for the years ended December 31, 2023 and December 31, 2022 were as follows (in thousands except lease term and discount rate):

	December 31, 2023	December 31, 2022
Operating lease liabilities:		
Current	420	385
Non-current	255	705
Total lease liabilities	$ 675	$ 1,090
Weighted-average remaining lease term (in years)	1.5	2.4
Weighted-average incremental borrowing rate	6 %	6 %

Legal Proceedings

The Company may from time to time be party to litigation arising in the ordinary course of business. The Company was not subject to any material legal proceedings during the years ended December 31, 2023 and 2022, and no material legal proceedings are currently pending or, to the best of its knowledge, threatened.

(6) STOCKHOLDERS' EQUITY

Under the Company's Amended and Restated Certificates of Incorporation dated August 3, 2020, the Company had a total of 94,052,154 shares of capital stock authorized for issuance, consisting of 50,000,000 shares of common stock, par value of $0.0001 per share, and 44,052,154 shares of convertible preferred stock, par value of $0.0001 per share. Shares of authorized convertible preferred stock were designated as 4,000,000 shares of Series Seed redeemable convertible preferred stock and 40,052,154 shares of Series A redeemable convertible preferred stock.

Common Stock

On July 2, 2021, the Company's certificate of amendment to its certificate of incorporation became effective, which provided 150,000,000 authorized shares of common stock with a par value of $0.0001 per share and 10,000,000 authorized shares of undesignated preferred stock with a par value of $0.0001 per share.

In August 2018, the Company issued 241,467 shares of common stock to RA Capital Healthcare Fund, L.P. at a price of $0.0012 per share. On July 2, 2021, in conjunction with the Company's initial public offering, or IPO, the Company issued 9,984,463 shares of its common stock and all outstanding shares of the Company's redeemable convertible preferred stock were converted into 14,182,854 shares of the Company's common stock.

The holders of the common stock are entitled to one vote for each share of common stock held at all meetings of stockholders.

As of December 31, 2023, the Company had reserved the following shares of common stock for future issuance:

	December 31, 2023
Common stock options granted and outstanding	5,230,344
Shares reserved for issuance under the 2021 Plan	604,363
Reserved for vesting of outstanding restricted stock units	21,968
Reserved for future ESPP issuances	435,252
Total	6,291,927

(7) SHARE-BASED COMPENSATION

(a) Stock Option Plan

The Company's 2021 Stock Option and Incentive Plan (the "2021 Plan") was adopted by the Company's board of directors and approved by the Company's stockholders in June 2021 and became effective as of June 29, 2021. Upon the effectiveness of the 2021 Plan, the Company's 2018 Equity Incentive Plan (the "2018 Plan") was terminated and no further grants may be made thereunder. The Company's 2021 Plan allows for the grant of incentive stock options, non-qualified stock options, stock appreciation rights, stock bonuses, restricted stock, stock units and other forms of awards including cash awards to its officers, directors, employees, consultants and advisors.

As of December 31, 2023, a total of 4,565,333 shares of the Company's common stock were authorized for issuance with respect to awards granted under the 2021 Plan. The share limit will automatically increase on the first trading day in January of each year (commencing with 2022) by an amount equal to the lesser of (1) 4% of the total number of outstanding shares of the Company's common stock on the last trading day in December in the prior year, or (2) such lesser number as determined by the Company's board of directors. Since adoption, the annual increases have accumulated to a total of 3,075,841 shares through January 1, 2024.

Any shares subject to awards granted under the 2021 Plan or the 2018 Plan that are not paid, delivered or exercised before they expire or are canceled or terminated, or otherwise fail to vest, as well as shares used to pay the purchase or exercise price of such awards or related tax withholding obligations, will become available for new award grants under the 2021 Plan.

As of December 31, 2023, 3,931,887 options had been granted under the 2021 Plan, with 604,363 shares authorized under the 2021 Plan available for future issuance. As of December 31, 2023, a total of 1,298,457 options had been granted and were outstanding under the 2018 Plan.

The options that are granted under the 2021 Plan and the 2018 Plan are exercisable at various dates as determined upon grant and terminate within 10 years of the date of grant. The vesting period generally occurs over three to four years.

The following table summarizes the option activity under the 2021 Plan and 2018 Plan for the year ended December 31, 2023:

	Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Vested and expected to vest at December 31, 2022	4,110,219	$ 9.23	8.46	$ 82,490
Granted	1,546,001	22.85		
Exercised	(338,987)	2.91		
Cancelled/Forfeited	(86,889)	9.62		
Outstanding at December 31, 2023	5,230,344	$ 13.66	8.16	$ 49,728
Vested and exercisable at December 31, 2023	2,157,378	11.24	7.81	25,152
Vested and expected to vest at December 31, 2023	5,230,344	$ 13.66	8.16	$ 49,728

The weighted-average grant date fair value of stock option grants was $15.69 and $10.48 per share for the years ended December 31, 2023 and December 31, 2022, respectively. All exercisable options are vested and all outstanding options are vested or expected to vest.

As of December 31, 2023 there was approximately $29.1 million of unrecognized stock-based compensation expense related to nonvested stock-based compensation arrangements granted under the 2021 Plan and 2018 Plan, which is expected to be recognized over a weighted-average period of 2.3 years.

(b) Employee Stock Purchase Plan

The Company's Employee Stock Purchase Plan (the "ESPP") was adopted by the Company's board of directors and stockholders in June 2021 and became effective upon the consummation of the IPO. A total of 230,000 shares of the Company's common stock is initially available for issuance under the ESPP. The share limit will automatically increase on the first trading day in January of each year (commencing with 2022) by an amount equal to the lesser of (1) 1% of the total number of outstanding shares of the Company's common stock on the last trading day in December in the prior year, or (2) such lesser number as determined by the Company's board of directors. The number of shares available under the 2021 Plan increased by 247,229 shares effective January 1, 2023 as determined by the Company's board of directors. The ESPP allows eligible employees to purchase shares of the Company's common stock at a discount through payroll deductions of up to 15% of their eligible compensation, subject to any plan limitations. The ESPP provides for six-month offering periods, and at the end of each offering period, employees are able to purchase shares at 85% of the lower of the fair market value of the Company's common stock on the first trading day of the offering period or on the last trading day of the offering period. As of December 31, 2023, 41,977 shares had been issued under the ESPP, and 435,252 shares authorized under the ESPP Plan were available for issuance.

(c) Restricted Stock Units

As of December 31, 2023, 31,881 restricted stock units had been awarded under the 2021 Plan. A summary of the status of and changes in unvested restricted stock unit activity under the Company's equity award plans for the year ended December 31, 2023, was as follows:

	Units	Weighted-Average Grant Date Fair Value Per Unit
Unvested restricted stock units as of December 31, 2022	28,881	$ 21.62
Granted	3,000	24.58
Vested	(9,913)	21.10
Forfeited	—	—
Unvested restricted stock units as of December 31, 2023	21,968	$ 22.26

Stock-based compensation of restricted stock units is based on the fair value of the Company's common stock on the date of grant and recognized over the vesting period. The vesting period generally occurs over one to four years.

As of December 31, 2023, the Company had unrecognized stock-based compensation expense related to its unvested restricted stock units of $0.9 million, which is expected to be recognized over the remaining weighted-average vesting period of 2.4 years.

(d) Stock-Based Compensation Expense

The Company estimated the fair value of stock options using the Black-Scholes valuation model. The Company accounts for any forfeitures of options when they occur. Previously recognized compensation expense for an award is reversed in the period that the award is forfeited. The fair value of stock options was estimated using the following assumptions:

	Year Ended December 31,	
	2023	2022
Expected term (in years)	5.3 - 6.1	5.5 - 6.1
Expected volatility	73.9 - 91.5 %	73.5 - 76.5 %
Risk-free interest rate	3.5 - 4.8 %	1.6 - 4.3 %
Expected dividend	—	—

Stock-based compensation expense recognized for stock option grants has been reported in the statements of operations and comprehensive loss as follows (in thousands):

	Year Ended December 31,	
	2023	2022
Research and development	$ 6,621	$ 2,129
General and administrative	5,285	3,347
Total	$ 11,906	$ 5,476

Stock-based compensation expense by type of award included within the consolidated statements of operations and comprehensive (loss) income was as follows:

	Year Ended December 31,	
	2023	2022
Stock options	$ 11,494	$ 5,316
Employee stock purchase plan awards	211	62
Restricted stock awards and units	201	98
Total	$ 11,906	$ 5,476

(8) RELATED PARTY TRANSACTIONS

Services Agreement

In August 2018, the Company entered into a services agreement ("Services Agreement") with Carnot, LLC ("Carnot"), an entity owned and controlled by RA Capital Management, L.P. under which Carnot provides research and other services to the Company. RA Capital Management, L.P. is a related party due to its equity ownership of the Company. The Company pays Carnot for services performed and costs incurred. The Services Agreement is for a term of two years. The Company may terminate the Services Agreement by giving 30 days' prior notice and either party can terminate the services agreement for a material breach, if not cured within 30 days following notice by the nonbreaching party.

In July 2019, the Services Agreement with Carnot was amended whereby research and other services are now performed by Carnot Pharma, LLC ("Carnot Pharma"), an entity owned and controlled by RA Capital Management, L.P., and the term was updated to the later of (i) two years from July 15, 2019 and (ii) completion of services under the agreement.

Expenses incurred by the Company under the Services Agreement with Carnot Pharma totaled $0 and less than $0.1 million for the years ended December 31, 2023 and December 31, 2022, respectively, and are presented in the statement of operations and comprehensive loss as research and development and general and administrative expenses. No amount was due to Carnot Pharma, LLC as of December 31, 2023 and December 31, 2022.

(9) INCOME TAXES

Significant components of the Company's net deferred tax assets are as follows (in thousands):

	December 31,	
	2023	2022
Deferred income tax assets:		
NOL carryforwards	$ 16,199	$ 11,781
Research credit carryforwards	5,153	1,601
Capitalized R&D	19,404	8,490
Stock based compensation	1,929	923
Other	1,117	790
Gross deferred tax assets	43,802	23,585
Less: valuation allowance	(43,596)	(23,283)
Total deferred tax assets	206	302
Deferred income tax liabilities:		
Other	(206)	(302)
Total deferred tax liabilities	(206)	(302)
Net deferred tax assets (liabilities)	$ —	$ —

A reconciliation between the provision for income taxes and income taxes computed using the U.S. federal statutory corporate tax rate is as follows (in thousands):

	Years ended December 31,	
	2023	2022
U.S. Federal statutory income tax rate	$ (15,831)	$ (10,829)
State taxes	(3,389)	(2,828)
Permanent and other differences	416	563
Stock-based compensation	1,049	(787)
Research and development credits	(2,676)	(757)
Change in valuation allowance	20,487	14,663
Total tax provision	$ 56	$ 25

The Company had federal NOL carryforwards available of $64.8 million and $46.9 million as of December 31, 2023 and December 31, 2022, respectively, before consideration of limitations under Section 382 of the Internal Revenue Code or Section 382, as further described below. The NOL generated from 2018 onwards of $64.8 million will carryforward indefinitely and be available to offset up to 80% of future taxable income each year. Additionally, the Company had state NOL carryforwards available of $44.1 million and $30.5 million as of December 31, 2023 and December 31, 2022, respectively. The state NOLs may be used to offset future taxable income and will begin to expire in 2038. At December 31, 2023 the Company had federal and state research and development credit carryforwards available of $6.0 million and $1.3 million, respectively. The federal credit carryforwards will begin to expire in 2038, unless previously utilized. The Massachusetts credit carryforwards will begin expiring in 2036, unless previously utilized. The California credits carry forward indefinitely.

The Company has established a full valuation allowance for its deferred tax assets due to uncertainties that preclude it from determining that it is more likely than not that the Company will be able to generate sufficient taxable income to realize such assets. Management assesses the available positive and negative evidence to estimate if sufficient future taxable income will be generated to utilize the existing deferred tax assets. A significant piece of objective negative evidence evaluated was the cumulative loss incurred since inception. Such objective evidence limits the ability to consider other subjective evidence such as the Company's projections for future growth. Based on this evaluation, as of December 31, 2023 and December 31, 2022, a valuation allowance of $43.6 million and $23.3 million, respectively, has been recorded against all of the Company's net deferred tax assets, as the Company has determined that none of the Company's balance of net deferred tax assets is more likely than not to be realized. The amount of the deferred tax assets considered realizable, however, could be

adjusted in the future if objective negative evidence in the form of cumulative losses is no longer present and additional weight may be given to subjective evidence, such as estimates of future taxable income during carryforward periods and the Company's projections for growth.

The future utilization of the Company's NOL and tax credit carryforwards to offset future taxable income may be subject to a substantial annual limitation as a result of changes in ownership by stockholders that hold 5% or more of the Company's common stock. An assessment of such ownership changes under Section 382 and 383 was not completed through December 31, 2023. Utilization of our net operating loss and income tax credit carryforwards may be subject to a substantial annual limitation due to ownership changes that may have occurred or that could occur in the future. These ownership changes may limit the amount of the net operating loss and income tax credit carryover that can be utilized annually to offset future taxable income. The Company will examine the impact of any potential ownership changes in the future.

The following table summarizes the activity related to the Company's gross unrecognized tax benefits at the beginning and end of the years ended December 31, 2023 and December 31, 2022 (in thousands):

	Years ended December 31,	
	2023	2022
Beginning balance of unrecognized tax benefits	$ 993	$ 529
Additions based on tax positions related to the current year	1,127	461
Additions based on tax positions related to the prior year	94	3
Ending balance of unrecognized tax benefits	$ 2,214	$ 993

The unrecognized tax benefit amounts are reflected in the determination of the Company's deferred tax assets. If recognized, none of these amounts would affect the Company's effective tax rate, since it would be offset by an equal corresponding adjustment in the deferred tax asset valuation allowance. The Company does not foresee material changes to its liability for uncertain tax benefits within the next twelve months.

The Company is subject to taxation in the United States and various states. The Company's Federal and state returns are subject to examination, due to the carryforward of unutilized net operating losses and research and development credits.

EXHIBIT INDEX

Exhibit Number	Description
3.1	Second Amended and Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K (File No. 001-40544) filed with the SEC on July 2, 2021).
3.2	Amended and Restated Bylaws of the Registrant (incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K (File No. 001-40544) filed with the SEC on July 2, 2021).
4.1	Form of Specimen Common Stock Certificate (incorporated by reference to Exhibit 4.1 to the Registrant's Registration Statement on Form S-1A (File No. 333-256949) filed with the SEC on June 17, 2021).
4.2	Investors' Rights Agreement among the Registrant and certain of its stockholders, dated August 5, 2020 (incorporated by reference to Exhibit 4.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-256949) filed with the SEC on June 9, 2021).
4.3	Description of Securities (incorporated by reference to Exhibit 4.3 to the Registrant's Annual Report on Form 10-K (File No. 001-40544) filed with the SEC on March 30, 2022).
10.1#	2018 Equity Incentive Plan, and form of award agreements thereunder (incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-256949) filed with the SEC on June 9, 2021).
10.2#	2021 Stock Option and Incentive Plan, and form of award agreements thereunder (incorporated by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form S-1A (File No. 333-256949) filed with the SEC on June 17, 2021).
10.3#	2021 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.3 to the Registrant's Registration Statement on Form S-1A (File No. 333-256949) filed with the SEC on June 17, 2021).
10.4#	Non-Employee Director Compensation Policy (incorporated by reference to Exhibit 10.4 to the Registrant's Registration Statement on Form S-1A (File No. 333-256949) filed with the SEC on June 17, 2021).
10.5#	Form of Indemnification Agreement between the Registrant and each of its directors and executive officers (incorporated by reference to Exhibit 10.5 to the Registrant's Registration Statement on Form S-1A (File No. 333-256949) filed with the SEC on June 17, 2021).
10.6#	Form of Employment Agreement (incorporated by reference to Exhibit 10.6 to the Registrant's Registration Statement on Form S-1A (File No. 333-256949) filed with the SEC on June 17, 2021).
10.7#	Senior Executive Cash Incentive Bonus Plan (incorporated by reference to Exhibit 10.10 to the Registrant's Registration Statement on Form S-1A (File No. 333-256949) filed with the SEC on June 17, 2021).
10.8	Lease, dated August 6, 2021, by and between the Registrant and PDM 930 Unit, LLC (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-40544) filed with the SEC on August 12, 2021).
10.9*	Lease, Amendment, dated January 2, 2024, by and between the Registrant and PDM 930 Unit, LLC.
10.10	Lease, dated April 26, 2022, by and between the Registrant and Hudson Metro Center, LLC (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-40544) filed with the SEC on April 29, 2022).
10.11	ATM Equity Offering[SM] Sales Agreement, dated as of April 5, 2023, by and between Aerovate Therapeutics, Inc. and BofA Securities, Inc. (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-40544) filed with the SEC on April 5, 2023).
19.1*	Aerovate Therapeutics, Inc. Insider Trading Policy.
21.1*	List of Subsidiaries of Registrant (incorporated by reference to Exhibit 21.1 to the Registrant's Annual Report on Form 10-K (File No. 001-40544) filed with the SEC on March 30, 2022).
23.1*	Consent of KPMG LLP, Independent Registered Public Accounting Firm.
24.1*	Power of Attorney (included on signature page).

31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1**	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2**	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
97.1#	Compensation Recovery Policy (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-40544) filed with the SEC on August 14, 2023).
101.INS*	Inline XBRL Instance Document
101.SCH*	Inline XBRL Taxonomy Extension Schema Document
101.CAL*	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF*	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB*	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE*	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File

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* Filed herewith.

\# Indicates a management contract or compensatory plan, contract or arrangement.

** The certifications furnished in Exhibit 32.1 and 32.2 hereto are deemed to accompany this Annual Report on Form 10-K and will not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended. Such certifications will not be deemed to be incorporated by reference into any filings under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, except to the extent that the Registrant specifically incorporates it by reference.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this Annual Report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized**.**

AEROVATE THERAPEUTICS, INC.

Date: March 25, 2024

By: */s/ Timothy P. Noyes*
Timothy P. Noyes
Chief Executive Officer

Each person whose individual signature appears below hereby authorizes and appoints Timothy P. Noyes and George A. Eldridge, and each of them, with full power of substitution and resubstitution and full power to act without the other, as his or her true and lawful attorney-in-fact and agent to act in his or her name, place and stead and to execute in the name and on behalf of each person, individually and in each capacity stated below, and to file any and all amendments to this annual report on Form 10-K and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing, ratifying and confirming all that said attorneys-in-fact and agents or any of them or their or his substitute or substitutes may lawfully do or cause to be done by virtue thereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Annual Report on Form 10-K has been signed below by the following persons on behalf of the Registrant in the capacities and on March 25, 2024.

Name	Title	Date
/s/ Timothy P. Noyes **Timothy P. Noyes**	Chief Executive Officer and Director (Principal Executive Officer)	March 25, 2024
/s/ George A. Eldridge **George A. Eldridge**	Chief Financial Officer (Principal Financial Officer and Principal Accounting Officer)	March 25, 2024
/s/ Habib Dable **Habib Dable**	Director	March 25, 2024
/s/ Allison Dorval **Allison Dorval**	Director	March 25, 2024
/s/ David Grayzel, M.D **David Grayzel, M.D**	Director	March 25, 2024
/s/ Mark Iwicki **Mark Iwicki**	Director	March 25, 2024
/s/ Maha Katabi, Ph.D. **Maha Katabi, Ph. D.**	Director	March 25, 2024
/s/ Joshua Resnick, M.D. **Joshua Resnick, M.D.**	Director	March 25, 2024
/s/ Donald J. Santel **Donald J. Santel**	Director	March 25, 2024

AEROVATE THERAPEUTICS, INC.
CORPORATE AND OTHER INFORMATION

BOARD OF DIRECTORS

Habib J. Dable
Venture Partner, RA Ventures

Allison Dorval
Chief Financial Officer, Verve Therapeutics, Inc.

David Grayzel, M.D.
Partner, Atlas Venture

Mark Iwicki
President & Chief Executive Officer, Kala Pharmaceuticals, Inc.

Maha Katabi, Ph.D.
General Partner, Sofinnova Investments

Timothy P. Noyes
Chief Executive Officer, Aerovate Therapeutics, Inc.

Joshua Resnick, M.D.
Managing Director, RA Capital Management, L.P.

Donald J. Santel
Interim Chief Executive Officer, Tentarix Biotherapeutics, Inc.

EXECUTIVE OFFICERS

Timothy P. Noyes
Chief Executive Officer

Benjamin T. Dake, Ph.D.
President, Founder, and Chief Operating Officer

George A. Eldridge
Chief Financial Officer

Hunter Gillies, M.D.Ch.B.
Chief Medical Officer

Ralph Niven, Ph.D.
Chief Scientific Officer

Timothy J. Pigot
Chief Commercial Officer

Marinus Verwijs, Ph.D.
Chief Technical Officer

CORPORATE INFORMATION

Corporate Headquarters
930 Winter Street, Suite M-500
Waltham, MA 02451

Independent Registered Public Accounting Firm
KPMG LLP
345 Park Avenue
New York City, NY 10154

Transfer Agent
Computershare Trust Company, N.A.
150 Royall Street
Canton, MA 02021

Investor Relations
IR@aerovatetx.com