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

FORM 10-Q

(Mark One)

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

For the quarterly period ended June 30, 2022

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

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 is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

As of August 11, 2022, the registrant had 24,448,144 shares of common stock, $0.0001 par value per share, outstanding.

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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.
- The ongoing COVID-19 pandemic, or a similar pandemic, epidemic, or outbreak of an infectious disease, may materially and adversely affect our business and our financial results and could cause a disruption to the development of AV-101. As a result of medical complications associated with pulmonary arterial hypertension (PAH), the patient populations that AV-101 targets may be particularly susceptible to COVID-19, 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.
- 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 pulmonary arterial hypertension, or PAH, patients and our Phase 1 clinical trial of AV-101 may not be predictive of future trial results for AV-101.
- If we encounter difficulties with site initiation 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 two issued U.S. patents and many pending patent applications with respect to AV-101 (of which two have recently received a notice of allowance). 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 plan to conduct clinical trials for AV-101 outside the United States, and the U.S. Food and Drug Administration, European Medicines Agency, 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 Quarterly Report on Form 10-Q, including our condensed consolidated financial statements and the related notes, as well as in other documents that we file with the U.S. Securities and Exchange Commission ("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 Quarterly Report on Form 10-Q 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 Quarterly Report on Form 10-Q 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 Quarterly Report on Form 10-Q 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 planned 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 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;
- the rate and degree of market acceptance of AV 101;
- 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;
- the effect of the ongoing COVID-19 pandemic, including mitigation efforts and economic effects, on any of the foregoing or other aspects of our business operations, including but not limited to our clinical trials and any future studies or trials; 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 under the section titled "Risk Factors" and elsewhere in this Quarterly Report on Form 10-Q. 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 Quarterly Report on Form 10-Q and the documents that we reference in this Quarterly Report on Form 10-Q and have filed with the SEC thereto 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 Quarterly Report on Form 10-Q represent our views as of the date of this Quarterly Report on Form 10-Q. 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 Quarterly Report on Form 10-Q.

This Quarterly Report on Form 10-Q 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 Quarterly Report on Form 10-Q, 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 Quarterly Report on Form 10-Q.

PART I-FINANCIAL INFORMATION

Item 1. Financial Statements.

Aerovate Therapeutics, Inc.
Condensed Consolidated Balance Sheets
(Unaudited)
(in thousands, except share and per share amounts)

	June 30, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 27,457	$ 54,197
Short-term investments	124,531	113,178
Prepaid expenses and other current assets	1,461	6,958
Total current assets	153,449	174,333
Property and equipment, net	316	186
Operating lease right-of-use asset	1,188	542
Other long-term assets	731	302
Total assets	$ 155,684	$ 175,363
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 2,068	$ 1,208
Accrued and other current liabilities	1,341	1,150
Operating lease liability	347	192
Total current liabilities	3,756	2,550
Operating lease liabilities, net of current portion	862	382
Other liabilities	13	13
Total liabilities	4,631	2,945
Commitments and contingencies (Note 5)		
Stockholders' equity:		
Preferred stock, $0.0001 par value; 10,000,000 shares authorized as of June 30, 2022 and December 31, 2021, respectively; no shares issued and outstanding at June 30, 2022 and December 31, 2021, respectively	—	—
Common stock, $0.0001 par value; 150,000,000 shares authorized at June 30, 2022 and December 31, 2021, respectively; 24,418,434 and 24,410,393 shares issued and outstanding at June 30, 2022 and December 31, 2021, respectively	2	2
Additional paid-in capital	211,129	208,867
Accumulated other comprehensive loss	(785)	(59)
Accumulated deficit	(59,293)	(36,392)
Total stockholders' equity	151,053	172,418
Total liabilities and stockholders' equity	$ 155,684	$ 175,363

See accompanying notes to unaudited interim condensed consolidated financial statements.

Aerovate Therapeutics, Inc.
Condensed Consolidated Statements of Operations and Comprehensive Loss
(Unaudited)
(in thousands, except share and per share amounts)

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Operating expenses:				
Research and development	$ 8,363	$ 4,327	$ 15,618	$ 6,523
General and administrative	3,852	1,447	7,615	2,031
Total operating expenses	12,215	5,774	23,233	8,554
Loss from operations	(12,215)	(5,774)	(23,233)	(8,554)
Other income (expense):				
Interest income	230	2	338	2
Other expense	(6)	(3)	(6)	(4)
Total other income (expense)	224	(1)	332	(2)
Net loss	$ (11,991)	$ (5,775)	$ (22,901)	$ (8,556)
Comprehensive loss:				
Net loss	$ (11,991)	$ (5,775)	$ (22,901)	$ (8,556)
Other comprehensive loss:				
Unrealized loss on securities	(141)	—	(726)	—
Comprehensive loss	$ (12,132)	$ (5,775)	$ (23,627)	$ (8,556)
Net loss per share, basic and diluted	$ (0.49)	$ (23.80)	$ (0.94)	$ (35.29)
Weighted-average shares of common stock outstanding, basic and diluted	24,410,503	243,076	24,410,448	243,076

See accompanying notes to unaudited interim condensed consolidated financial statements.

Aerovate Therapeutics, Inc.
Condensed Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)
(Unaudited)
(in thousands, except share amounts)

	Series A Redeemable Convertible Preferred Stock		Series Seed Redeemable Convertible Preferred Stock		Common Stock		Additional Paid-In	Accumulated Other Comprehensive	Accumulated	Total Stockholders' Equity
	Shares	Amount	Shares	Amount	Shares	Amount	Capital	Loss	Deficit	(Deficit)
Balance at December 31, 2021	—	$ —	—	$ —	24,410,393	$ 2	$ 208,867	$ (59)	$ (36,392)	$ 172,418
Unrealized loss on investments	—	—	—	—	—	—	—	(585)	—	(585)
Stock based compensation	—	—	—	—	—	—	1,024	—	—	1,024
Net loss	—	—	—	—	—	—	—	—	(10,910)	(10,910)
Balance at March 31, 2022	—	$ —	—	$ —	24,410,393	$ 2	$ 209,891	$ (644)	$ (47,302)	$ 161,947
Unrealized loss on investments	—	—	—	—	—	—	—	(141)	—	(141)
Stock based compensation	—	—	—	—	—	—	1,224	—	—	1,224
Issuance of common stock upon exercise of stock options	—	—	—	—	8,041	—	14	—	—	14
Net loss	—	—	—	—	—	—	—	—	(11,991)	(11,991)
Balance at June 30, 2022	—	$ —	—	$ -	24,418,434	$ 2	$ 211,129	$ (785)	$ (59,293)	$ 151,053

	Series A Redeemable Convertible Preferred Stock		Series Seed Redeemable Convertible Preferred Stock		Common Stock		Additional Paid-In	Accumulated Other Comprehensive	Accumulated	Total Stockholders' Equity
	Shares	Amount	Shares	Amount	Shares	Amount	Capital	Loss	Deficit	(Deficit)
Balance at December 31, 2020	6,489,534	$ 12,285	4,000,000	$ 4,000	243,076	$ —	$ 63	$ —	$ (13,407)	$ (13,344)
Issuance of Series A redeemable convertible preferred stock at $1.893 per share, net of issuance costs of $13	4,224,274	7,983	—	—	—	—	—	—	—	—
Accretion of Series A redeemable convertible preferred stock to redemption value	—	13	—	—	—	—	—	—	(13)	(13)
Stock based compensation	—	—	—	—	—	—	23	—	-	23
Net loss	—	—	—	—	—	—	—	—	(2,781)	(2,781)
Balance at March 31, 2021	10,713,808	$ 20,281	4,000,000	$ 4,000	243,076	$ —	$ 86	$ —	$ (16,201)	$ (16,115)
Issuance of Series A redeemable convertible preferred stock at $1.893 per share, net of issuance costs of $9	29,338,346	55,529	—	—	—	—	—	—	—	—
Accretion of Series A redeemable convertible preferred stock to redemption value	—	9	—	—	—	—	—	—	(9)	(9)
Stock based compensation	—	—	—	—	—	—	321	—	—	321
Net loss	—	—	—	—	—	—	—	—	(5,775)	(5,775)
Balance at June 30, 2021	40,052,154	$ 75,819	4,000,000	$ 4,000	243,076	$ —	$ 407	$ —	$ (21,985)	$ (21,578)

See accompanying notes to unaudited interim condensed consolidated financial statements.

Aerovate Therapeutics, Inc.
Condensed Consolidated Statements of Cash Flows
(Unaudited)
(in thousands)

	Six months ended June 30,	
	2022	**2021**
Cash flow from operating activities:		
Net loss	$ (22,901)	$ (8,556)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation expense	2,248	344
Depreciation and amortization expense	28	4
Accretion of discounts and amortization of premiums on investments, net	(32)	—
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	5,493	(56)
Other long-term assets	(428)	(74)
Accounts payable	875	563
Accrued and other liabilities	191	(5)
Operating lease assets and liabilities, net	(11)	–
Net cash used in operating activities	(14,537)	(7,780)
Cash flow from investing activities:		
Purchases of short-term investments	(71,791)	—
Sales and maturities of short-term investments	59,744	—
Purchases of property and equipment	(158)	(40)
Net cash used in investing activities	(12,205)	(40)
Cash flow from financing activities:		
Proceeds from sale of Series A redeemable convertible preferred stock, net of issuance costs	—	63,512
Payments for deferred offering costs	—	(1,115)
Proceeds from issuance of common stock upon exercise of stock options	2	—
Net cash provided by financing activities	2	62,397
Net (decrease) increase in cash	(26,740)	54,577
Cash and cash equivalents at the beginning of the year	54,197	4,573
Cash and cash equivalents at the end of the period	$ 27,457	$ 59,150
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	$ 1	$ 1,901

See accompanying notes to unaudited interim condensed consolidated financial statements.

AEROVATE THERAPEUTICS, INC.
NOTES TO UNAUDITED INTERIM CONDENSED CONSOLIDATED FINANCIAL STATEMENTS

(1) ORGANIZATION AND NATURE OF OPERATIONS

(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 Phase 2b/Phase 3 trial of AV-101 in PAH patients in December 2021.

(b) 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 June 30, 2022, the Company had cash and cash equivalents and short-term investments of $152.0 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 accompanying unaudited condensed consolidated financial statements as of June 30, 2022 and for the three and six months ended June 30, 2022 and 2021 have been prepared in conformity with generally accepted accounting principles ("GAAP") in the United States of America for interim financial information and pursuant to Article 10 of Regulation S-X of the Securities Act of 1933, as amended (the Securities Act). Accordingly, they do not include all of the information and notes required by GAAP for complete financial statements. These unaudited condensed consolidated financial statements include only normal and recurring adjustments that the Company believes are necessary to fairly state the Company's financial position and the results of its operations and cash flows.

The results for the three and six months ended June 30, 2022 are not necessarily indicative of the results expected for the full fiscal year or any subsequent interim period. The condensed consolidated balance sheet as of December 31, 2021 has been derived from the audited financial statements at that date but does not include all disclosures required by GAAP for complete financial statements. Because all of the disclosures required by GAAP for complete financial statements are not included herein, these unaudited condensed consolidated financial statements and the notes accompanying them should be read in conjunction with the Company's audited financial statements for the year ended December 31, 2021. Any reference in these notes to applicable guidance is meant to refer to the authoritative GAAP as found in the Accounting Standards Codification ("ASC") and Accounting Standards Update ("ASU") of the Financial Accounting Standards Board ("FASB").

(b) Reverse Stock Split

On June 22, 2021, the Company effected a 1-for-3.1060103 reverse stock split (the "Reverse Stock Split") of its issued and outstanding common stock. Accordingly, the conversion ratio for the Company's outstanding convertible preferred stock was proportionately adjusted such that the common stock issuable upon conversion of such preferred stock was decreased in proportion to the Reverse Stock Split. The par value of the common stock was not adjusted as a result of the Reverse Stock Split. All references to common stock, options to purchase common stock, early exercised options, share data, per share data, convertible preferred stock (to the extent presented on an as-converted to common stock basis) and related information contained in these financial statements have been retrospectively adjusted to reflect the effect of the Reverse Stock Split for all periods presented.

(c) 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. The full extent to which the COVID-19 pandemic will directly or indirectly impact our business, results of operations, and financial condition will depend on future developments that are highly uncertain, including as a result of new information that may emerge concerning COVID-19 and the actions taken to contain or treat it, as well as the economic impact on local, regional, national and international markets. 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 and fair value of investments. 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.

(d) 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 (in thousands, except share and per share amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Numerator:				
Net loss	$ (11,991)	$ (5,775)	$ (22,901)	$ (8,556)
Accretion of Series A redeemable convertible preferred stock to redemption value	—	(9)	—	(22)
Net loss available to common stockholders	$ (11,991)	$ (5,784)	$ (22,901)	$ (8,578)
Denominator:				
Weighted-average common stock outstanding, basic and diluted	24,410,503	243,076	24,410,448	243,076
Net loss per share, basic and diluted	$ (0.49)	$ (23.80)	$ (0.94)	$ (35.29)

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 June 30,	
	2022	2021
Options to purchase common stock	3,953,390	2,770,954
Unvested restricted stock units	1,631	—
Series Seed redeemable convertible preferred stock	—	1,287,825
Series A redeemable convertible preferred stock	—	12,895,029
	3,955,021	16,953,808

(e) Recently Issued and Recently Adopted Accounting Pronouncements

From time to time, new accounting pronouncements are issued by the FASB or other standard setting bodies that are adopted by the Company as of the specified effective date. The Company has evaluated recently issued accounting pronouncements and does not believe any will have a material impact on the Company's condensed consolidated financial statements or related financial statement disclosures.

(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		
	June 30, 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	$ 16,286	$ 16,286	$ —	$ —
Commercial paper	5,991	—	5,991	—
Total cash equivalents	22,277	16,286	5,991	—
Short-term investments				
U.S. Treasury bills	32,147	32,147	—	—
Corporate debt securities	1,991	—	1,991	—
Commercial paper	84,905	—	84,905	—
Agency bond	5,488	—	5,488	—
Total short-term investments	124,531	32,147	92,384	—
Total fair value of assets	$ 146,808	$ 48,433	$ 98,375	$ —

	December 31, 2021	Fair Value Measurements Using: 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	$ 39,653	$ 39,653	$ —	$ —
Commercial paper	14,448	—	14,448	—
Total cash equivalents	54,101	39,653	14,448	—
Short-term investments				
U.S. Treasury bills	25,135	25,135	—	—
Corporate debt securities	10,715	—	10,715	—
Commercial paper	77,328	—	77,328	—
Total short-term investments	113,178	25,135	88,043	—
Total fair value of assets	$ 167,279	$ 64,788	$ 102,491	$ —

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 money market funds and commercial paper, and short-term investments consisted of U.S. Treasury bills, 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):

	Maturity	As of June 30, 2022: Amortized cost	Gross unrealized gains	Gross unrealized losses	Estimated fair value
Corporate debt securities	1 year or less	$ 2,001	$ —	$ (10)	$ 1,991
Commercial paper	1 year or less	85,197	—	(292)	84,905
U.S. Treasury bills	2 years or less	32,620	—	(473)	32,147
Agency bond	2 years or less	5,498	—	(10)	5,488
		$ 125,316	$ —	$ (785)	$ 124,531

	Maturity	As of December 31, 2021: Amortized cost	Gross unrealized gains	Gross unrealized losses	Estimated fair value
Corporate debt securities	1 year or less	$ 10,726	$ —	$ (11)	$ 10,715
Commercial paper	1 year or less	77,328	9	(9)	77,328
U.S. Treasury bills	2 years or less	25,183	—	(48)	25,135
		$ 113,237	$ 9	$ (68)	$ 113,178

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 June 30, 2022 and December 31, 2021 were caused by fluctuations in market value and interest rates as a result of the economic environment and not credit risk. As of June 30, 2022 and December 31, 2021, no allowance for credit losses was recorded. During the six months ended June 30, 2022, the Company did not recognize any impairment losses related to its short-term investments. 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. The Company excludes accrued interest from both the fair value and the amortized cost basis of the available-for-sale debt securities for the purposes of identifying and measuring an impairment and to not measure an allowance for expected credit losses for accrued interest receivables. 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. It is the Company's policy to present the accrued interest receivable balance as part of prepaid expenses and other current assets in the balance sheets. Accrued interest receivable related to short-term investments was $0.1 million as of June 30, 2022 and December 31, 2021.

(4) BALANCE SHEET COMPONENTS

Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consisted of the following (in thousands):

	June 30, 2022	December 31, 2021
Prepaid research and development	$ 820	$ 5,233
Prepaid expenses	415	1,485
Other current assets	226	240
Total prepaid expenses and other current assets	$ 1,461	$ 6,958

Accrued and Other Current Liabilities

Accrued and other current liabilities consisted of the following (in thousands):

	June 30, 2022	December 31, 2021
Accrued payroll and other employee benefits	$ 817	$ 790
Accrued research and development	373	217
Other	151	143
Total accrued and other current liabilities	$ 1,341	$ 1,150

(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 has an initial abatement period, and the initial base rent payable will be 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 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 June 30, 2022, the future minimum annual lease payments under the operating leases were as follows (in thousands):

2022	$ 147
2023	449
2024	489
2025	242
Total operating lease payments	1,327
Less: Amount representing interest	(118)
Present value of net minimum lease payments	$ 1,209
Operating lease liabilities:	
Current	347
Non-current	862
Total lease liabilities	$ 1,209
Weighted-average remaining lease term (in years)	3.0
Weighted-average incremental borrowing rate	6%

Supplemental cash flow information related to cash paid for amounts included in the measurement of operating lease liabilities was as follows (in thousands):

	Six months ended June 30,	
	2021	2020
Cash paid included in operating cash flows	$ 113	$ —

Rent expense was as follows (in thousands):

	Three months ended June 30,		Six months ended June 30,	
	2022	2021	2022	2021
Operating lease	$ 92	$ —	$ 142	$ —
Short-term lease	11	—	46	—
Total rent expense	$ 103	$ —	$ 188	$ —

(6) STOCKHOLDERS' EQUITY

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 June 30, 2022, the Company had reserved the following shares of common stock, on an as-converted basis, for future issuance:

	June 30, 2022
Common stock options granted and outstanding	3,953,390
Reserved for exercise of outstanding stock options	1,552,307
Reserved for vesting of outstanding restricted stock units	1,631
Reserved for future ESPP issuances	230,000
Total	**5,737,328**

(7) STOCK-BASED COMPENSATION

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 June 30, 2022, a total of 3,576,415 shares of the Company's common stock is 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. Effective January 1, 2022, the number of shares available under the 2021 Plan increased by 976,415 shares, as determined by the Company's board of directors.

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 June 30, 2022, 2,022,477 options had been granted and 1,631 restricted stock units had been awarded under the 2021 Plan, with 1,552,307 shares authorized under the 2021 Plan available for future issuance. As of June 30, 2022, a total of 1,930,913 options had been granted 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 six months ended June 30, 2022:

	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, 2021	3,454,374	$ 6.85	9.42	$ 19,378
Granted	507,057	$ 13.08	9.79	
Exercised	(8,041)	1.74		
Cancelled/Forfeited	—	—		
Outstanding at June 30, 2022	3,953,390	$ 7.66	9.02	$ 31,633
Vested and exercisable at June 30, 2022	875,657	$ 5.91	8.80	$ 8,533
Vested and expected to vest at June 30, 2022	3,953,390	$ 7.66	9.02	$ 31,633

The weighted-average grant date fair value of stock option grants was $8.73 per share for the six months ended June 30, 2022. All exercisable options are vested and all outstanding options are vested or expected to vest.

(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 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 June 30, 2022, no shares had been issued under the ESPP, and the full number of shares authorized under the ESPP Plan was available for issuance purposes upon the effectiveness of the ESPP.

(c) 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:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Expected term (in years)	5.5 - 6.1	5.8 - 6.1	5.5 - 6.1	5.8 - 6.1
Expected volatility	73.8 - 76.5%	68.7 - 69.6%	73.6 - 76.5%	68.7 - 69.6%
Risk-free interest rate	2.5 - 3.4%	1.0 - 1.2%	1.6 - 3.4%	1.0 - 1.2%
Expected dividend	—	—	—	—

Stock-based compensation expense recognized for all equity awards has been reported in the statements of operations and comprehensive loss as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Research and development	$ 445	$ 101	$ 701	$ 113
General and administrative	779	220	1,547	231
Total	$ 1,224	$ 321	$ 2,248	$ 344

As of June 30, 2022, there was approximately $14.8 million of total 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 approximately 3.0 years.

(d) Restricted Stock Units

A summary of the status of and changes in unvested restricted stock unit activity under the Company's equity award plans for the six months ended June 30, 2022 was as follows:

	Units	Weighted-Average Grant Date Fair Value Per Unit
Unvested restricted stock units as of December 31, 2021	–	–
Granted	1,631	$ 12.26
Vested	–	–
Forfeited	–	–
Unvested restricted stock units as of June 30, 2022	1,631	$ 12.26

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. Restricted stock units awarded by the Company vest in equal amounts annually over two years.

As of June 30, 2022, the Company had unrecognized stock-based compensation expense related to its unvested restricted stock units of $20,000, which is expected to be recognized over the remaining weighted-average vesting period of 2.0 years.

Item 2. 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 unaudited condensed consolidated financial statements and related notes appearing elsewhere in this Quarterly Report on Form 10-Q and with the audited consolidated financial statements and related notes included in our Annual Report on Form 10-K for the fiscal year ended December 31, 2021, filed with the Securities and Exchange Commission on March 30, 2022. 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 Quarterly Report. See "Special Note Regarding Forward-Looking Statements" in this Quarterly 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 was 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 study in healthy volunteers and AV-101 was generally well-tolerated with no serious adverse events reported. We announced the initiation of Inhaled iMatinib Pulmonary Arterial Hypertension Clinical Trial (IMPAHCT), our Phase 2b/Phase 3 trial of AV-101 in PAH patients in December 2021, and 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.

COVID-19 Pandemic

The global coronavirus disease 2019, or COVID-19, pandemic continues to evolve, and we will continue to monitor the COVID-19 situation. The extent of the impact of the ongoing COVID-19 pandemic and its variants on our business, operations and clinical development timelines, supply chain and plans remains uncertain, and will depend on certain developments, including the duration and spread of the outbreak, including the identification of new variants of the virus, and its impact on our clinical trial enrollment and trial sites, both of which could impact the timing of our release of trial data, contract research organizations, or CROs, third-party manufacturers, and other third parties with whom we do business, as well as its impact on regulatory authorities and our key scientific and management personnel. The ultimate impact of the ongoing COVID-19 pandemic or a similar health epidemic is highly uncertain and subject to change. To the extent possible, we are conducting business as usual, with only necessary or advisable modifications to employee travel.

We will continue to actively monitor the rapidly evolving situation related to COVID-19 and may take further actions that alter our operations, including those that may be required by federal, state or local authorities, or that we determine are in the best interests of our employees and other third parties with whom we do business. At this point, the extent to which the ongoing COVID-19 pandemic may affect our business, operations and clinical development timelines and plans, including the resulting impact on our expenditures and capital needs, remains uncertain and is subject to change.

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 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.

Interest Income

Interest income consists of interest earned on our cash and cash equivalents and short-term investments.

Results of Operations

Comparison of the Three Months Ended June 30, 2022 and 2021 (Unaudited)

The following table summarizes our results of operations for the three months ended June 30, 2022 and 2021 (in thousands):

	Three Months Ended June 30,		
	2022	2021	Change
	(unaudited)		
Operating expenses:			
Research and development	$ 8,363	$ 4,327	$ 4,036
General and administrative	3,852	1,447	2,405
Total operating expenses	12,215	5,774	6,441
Loss from operations	(12,215)	(5,774)	(6,441)
Other income (expense):			
Interest income	230	2	228
Other expense	(6)	(3)	(3)
Total other income (expense)	224	(1)	225
Net loss	$ (11,991)	$ (5,775)	$ (6,216)

Research and Development Expenses

Research and development expenses for the three months ended June 30, 2022 were $8.4 million compared to $4.3 million for the three months ended June 30, 2021. The increase of $4.0 million was primarily due to our ongoing Phase 2b/Phase 3 trial causing increases of $3.3 million in clinical costs, $1.0 million in payroll costs, $0.3 million in stock-based compensation and $0.2 million in other miscellaneous costs, partially offset by lower contract manufacturing costs of $0.6 million and preclinical costs of $0.2 million.

General and Administrative Expenses

General and administrative expenses for the three months ended June 30, 2022 were $3.9 million compared to $1.4 million for the three months ended June 30, 2021. The increase of $2.4 million was primarily due to becoming a public company and hiring additional employees causing increases of $0.9 million in professional services related to other consulting expenses, corporate legal fees, audit and accounting services and $0.7 million in insurance expenses, in addition to $0.2 million in payroll costs and stock-based compensation of $0.6 million.

Total Other Income (Expense)

Other income for the three months ended June 30, 2022 was $0.2 million compared to other expense of $1,000 for the three months ended June 30, 2021. The change of $0.2 million was due to interest earned on our cash and cash equivalents and short-term investments for the three months ended June 30, 2022.

Comparison of the Six Months Ended June 30, 2022 and 2021 (Unaudited)

The following table summarizes our results of operations for the six months ended June 30, 2022 and 2021 (in thousands):

	Six Months Ended June 30,		
	2022	2021	Change
	(unaudited)		
Operating expenses:			
Research and development	$ 15,618	$ 6,523	$ 9,095
General and administrative	7,615	2,031	5,584
Total operating expenses	23,233	8,554	14,679
Loss from operations	(23,233)	(8,554)	(14,679)
Other income (expense):			
Interest income	338	2	336
Other expense	(6)	(4)	(2)
Total other income (expense)	332	(2)	334
Net loss	$ (22,901)	$ (8,556)	$ (14,345)

Research and Development Expenses

Research and development expenses for the six months ended June 30, 2022 were $15.6 million compared to $6.5 million for the six months ended June 30, 2021. The increase of $9.1 million was primarily due to initiating our Phase 2b/Phase 3 trial causing increases of $5.4 million in clinical costs, $1.8 million in contract manufacturing costs, $1.6 million in payroll costs, $0.6 million in stock-based compensation and $0.3 million in other miscellaneous costs, partially offset by lower preclinical costs of $0.6 million.

General and Administrative Expenses

General and administrative expenses for the six months ended June 30, 2022 were $7.6 million compared to $2.0 million for the six months ended June 30, 2021. The increase of $5.6 million was primarily due to becoming a public company causing increases of $1.3 million in insurance expenses and $2.3 million in professional services related to other consulting expenses, corporate legal fees, audit and accounting services, as well as increases of $0.7 million in payroll costs and $1.3 million in stock-based compensation.

Total Other Income (Expense)

Other income for the six months ended June 30, 2022, was $0.3 million compared to other expense of $2,000 for the six months ended June 30, 2021. The change of $0.3 million was due to interest earned on our cash and cash equivalents and short-term investments for the six months ended June 30, 2022.

Liquidity and Capital Resources

From our inception through June 30, 2022, we have received aggregate net proceeds of $79.4 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, commissions and offering costs.

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 as of June 30, 2022 of $152.0 million will be sufficient to fund our planned operations into the second half of 2025. 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.

Lease Obligations

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 base rent under the Waltham Lease is $43.00 per rentable square foot, or approximately $18,000 per month and is subject to scheduled annual increases of $1.00 per rentable square foot during the lease term. The term of the Waltham Lease is thirty-nine months, unless extended or earlier terminated pursuant to the terms of the Waltham Lease. We 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 June 30, 2022, 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 Six Months Ended June 30, 2022 and 2021 (Unaudited)

The following table sets forth a summary of the net cash flow activity for the six months ended June 30, 2022 and 2021 (in thousands):

	Six Months Ended June 30,	
	2022	**2021**
Net cash used in operating activities	$ (14,537)	$ (7,780)
Net cash used in investing activities	(12,205)	(40)
Net cash provided by financing activities	2	62,397
Net (decrease) increase in cash and cash equivalents	$ (26,740)	$ 54,577

Operating Activities

Net cash used in operating activities for the six months ended June 30, 2022 was $14.5 million, consisting primarily of our net loss incurred during the period of $22.9 million adjusted for non-cash charges of $2.2 million for stock-based compensation expense and $6.2 million for net changes in operating assets and liabilities. The net change in operating assets and liabilities primarily related to a $5.5 million increase in prepaid expenses and other current assets, a $1.1 million increase in accounts payable and accrued and other current liabilities, partially offset by a $0.4 million decrease in other long-term assets.

Net cash used in operating activities for the six months ended June 30, 2021 was $7.8 million, consisting primarily of our net loss incurred during the period of $8.6 million adjusted for $0.4 million for net changes in operating assets and liabilities. The net change in operating assets and liabilities primarily related to a $0.5 million increase in accounts payable and accrued and other current liabilities, partially offset by a $0.1 increase in other long-term assets. Non-cash charges include stock-based compensation expense of $0.4 million.

Investing Activities

Net cash used in investing activities for the six months ended June 30, 2022 of $12.2 million was comprised of purchases of short-term investments of $71.8 million, partially offset by sales and maturities of short-term investments of $59.7 million and purchases of property and equipment of $0.2 million.

Net cash used in investing activities for the six months ended June 30, 2021 was $40,000 for purchases of property and equipment to support our research activities.

Financing Activities

Net cash provided by financing activities for the six months ended June 30, 2021 was $62.4 million due to $63.5 million in net proceeds received from the Second Milestone Closing and Third Milestone Closing of Series A redeemable convertible preferred stock on June 4, 2021, net of issuance of costs, partially offset by $1.1 million of deferred offering costs for the IPO.

Critical Accounting 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.

There have been no significant changes in our critical accounting policies and estimates during the six months ended June 30, 2022, as compared to the critical accounting policies and estimates disclosed in “Management’s Discussion and Analysis of Financial Condition and Results of Operations” included in our Annual Report on Form 10-K.

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

We have reviewed all recently issued accounting pronouncements by the Financial Accounting Standards Board and other standard-setting bodies and have determined that such standards that do not require adoption until a future date are not expected to have a material impact on our consolidated financial statements, if adopted, or do not otherwise apply to our operations.

Item 3. Quantitative and Qualitative Disclosures About Market Risk.

Interest Rate Fluctuation Risk

We hold certain financial instruments for which a change in prevailing interest rates may cause the principal amount of the cash equivalents to fluctuate. Financial instruments that potentially subject us to significant concentrations of credit risk consist primarily of cash and cash equivalents. We invest our excess cash primarily in money market funds. The primary objectives of our investment activities are to ensure liquidity and to preserve principal while at the same time maximizing the income we receive without significantly increasing risk. We do not believe interest rate fluctuations have had a material effect on our results of operations during the six months ended June 30, 2022 and 2021.

Foreign Currency Fluctuation Risk

We are exposed to market risk related to changes in foreign currency exchange rates. We contract with vendors that are located outside the United States and certain invoices are denominated in foreign currencies. We are subject to fluctuations in foreign currency rates in connection with such arrangements. We do not currently hedge our foreign currency exchange risk. We do not believe exchange rate fluctuations have had a material effect on our results of operations during the six ended June 30, 2022 and 2021.

Inflation Fluctuation Risk

Inflation generally affects us by increasing our cost of labor and research and development contract costs. We do not believe inflation has had a material effect on our results of operations during the six months ended June 30, 2022 and 2021.

Item 4. Controls and Procedures.

Disclosure Controls and Procedures

Our management, with the participation of our chief executive officer and chief financial officer, evaluated the effectiveness of our disclosures controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, as of June 30, 2022. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, as appropriate, to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of June 30, 2022, our chief executive officer and chief financial officer concluded that, as of such date, our disclosure controls and procedures were effective at a reasonable assurance level.

Changes in Internal Control over Financial Reporting

Management determined that, as of June 30, 2022, there were no changes in our internal control over financial reporting that occurred during the fiscal quarter then ended that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II - OTHER INFORMATION

Item 1. Legal Proceedings.

From time to time, we may be involved in lawsuits, claims, investigations and proceedings, consisting of intellectual property, commercial, employment and other matters which arise in the ordinary course of business. While the outcome of any such proceedings cannot be predicted with certainty, as of June 30, 2022, we were not party to any legal proceedings that we would expect to have a material adverse impact on our financial position, results of operations or cash flow.

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 Quarterly Report on Form 10-Q 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.

The risk factors denoted with a "", if any, are newly added or have been materially updated from our Annual Report on Form 10-K for the year ended December 31, 2021.*

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 the initiation of our Inhaled iMatinib Pulmonary Arterial Hypertension Clinical Trial (IMPAHCT) Phase 2b/Phase 3 clinical trial for AV-101 in PAH patients in December 2021. 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 $22.9 million and $8.6 million for the six months ended June 30, 2022 and 2021, respectively. As of June 30, 2022, we had an accumulated deficit of $59.3 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 environments, including as a result of the ongoing coronavirus disease 2019, or COVID-19, pandemic;
- 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 COVID-19 or any of its variants 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. 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 June 30, 2022, we had cash and cash equivalents and short-term investments of $152.0 million. We expect our existing cash and cash equivalents and short-term investments will be sufficient to fund our planned operations into the second half of 2025 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) to the ongoing COVID-19 pandemic; 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 more recently due to the ongoing COVID-19 pandemic, 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.

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.

The ongoing COVID-19 pandemic, or a similar pandemic, epidemic, or outbreak of an infectious disease, may materially and adversely affect our business and our financial results and could cause a disruption to the development of AV-101. As a result of medical complications associated with PAH, the patient populations that AV-101 targets may be particularly susceptible to COVID-19, 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.

Public health crises such as pandemics or similar outbreaks could adversely impact our business. In December 2019, a novel strain of a virus named SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), or coronavirus, which causes COVID-19, spread to most countries across the world, including all 50 states within the United States. The COVID-19 pandemic is evolving, with new variants of the SARS-CoV-2 virus identified, and has led to the implementation of various responses, including government-imposed quarantines, travel restrictions, vaccine mandates and other public health safety measures. The extent to which the coronavirus impacts our operations or those of our third party partners, including our preclinical studies or clinical trial operations, will depend on future developments, which are highly uncertain and cannot be predicted with confidence, including the duration of the outbreak, developments or perceptions regarding the safety of vaccines, new information concerning the severity of the coronavirus and any additional preventative and protective actions taken to contain the coronavirus or treat its impact, among others. The continued spread of COVID-19 globally, including the identification of new variants of COVID-19, could adversely impact our clinical trial operations, including our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19 if an outbreak occurs in their geography. Similar to other biopharmaceutical companies, we may experience protocol deviations or delays in activating clinical trial sites, enrolling patients and completing our ongoing Phase 2b/Phase 3 clinical trial of AV-101. We have experienced delays in activating new trial sites due to staff shortages and short-term interruptions at clinical trial sites due to COVID-19 related issues, and general supply chain delays. These delays may also impact our ability to release data within our anticipated timeframe.

In addition, as a result of medical complications associated with PAH, the patient populations that AV-101 targets may be particularly susceptible to COVID-19, 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 the ongoing COVID-19 pandemic has to patient enrollment or treatment or the execution of our AV-101 clinical trials could cause costly delays to clinical trial activities, 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 is dependent upon clinical trial sites which could be and have been adversely affected by global health matters, such as pandemics. We are conducting our Phase 2b/Phase 3 clinical trial for AV-101 in geographies which are currently affected by the COVID-19 pandemic. Some factors from the ongoing COVID-19 pandemic that have the potential to delay or otherwise adversely affect site initiation and patient enrollment in the clinical trials of AV-101, as well as our business generally, include:

- the diversion of healthcare resources away from the conduct of clinical trials to focus on pandemic concerns, including the attention of physicians serving as our clinical trial investigators, hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;

- limitations on travel that could interrupt key trial and business activities, such as clinical trial site initiations and monitoring, domestic and international travel by employees, contractors or patients to clinical trial sites, including any government-imposed travel restrictions or quarantines that will impact the ability or willingness of patients, employees or contractors to travel to our clinical trial sites or secure visas or entry permissions, a loss of face-to-face meetings and other interactions with potential partners, any of which could delay or adversely impact the conduct or progress of our prospective clinical trials;

- the potential negative affect on the operations of our third-party manufacturers;

- ongoing interruptions in global shipping affecting the transport of clinical trial materials, such as investigational drug product, our DPIs and other supplies used in our clinical trials;

- business disruptions caused by workplace, laboratory and office closures and an increased reliance on employees working from home, disruptions to or delays in ongoing laboratory experiments;

- operations, staffing shortages, travel limitations or mass transit disruptions, any of which could adversely impact our business operations or delay necessary interactions with local regulators, ethics committees and other important agencies and contractors;

- changes in local regulations as part of a response to the ongoing COVID-19 pandemic, which may require us to change the ways in which our clinical trials are conducted, which may result in unexpected costs, or to discontinue such clinical trials altogether; and

- interruption or delays in the operations of the FDA or other regulatory authorities, which may impact review and approval timelines.

We may be required to develop and implement additional clinical trial policies and procedures designed to help protect subjects from the COVID-19 virus. For example, in March 2020, the FDA issued a guidance, which the FDA has continued to periodically revise, on conducting clinical trials during the pandemic, which describes a number of considerations for sponsors of clinical trials impacted by the pandemic. We cannot presently predict the scope and severity of the planned and potential shutdowns or disruptions of businesses and government agencies, such as the SEC, or FDA.

These and other factors arising from the ongoing COVID-19 pandemic could worsen in countries that are already afflicted with COVID-19, particularly as new variants of the virus continue to be identified, or could continue to spread to additional countries. Any of these factors, and other factors related to any such disruptions that are unforeseen, could have a material adverse effect on our business and our results of operations and financial condition. Further, uncertainty around these and related issues could lead to adverse effects on the economy of the United States and other economies, which could impact our ability to raise the necessary capital needed to develop and commercialize AV-101. We will continue to monitor the latest developments, disruptions and uncertainties relating to the COVID-19 pandemic, including the pace of vaccinations and the emergence of new and more contagious strains of the virus, and any resulting impact on our business, financial condition, results of operations and prospects. Any resulting financial impact cannot be reasonably estimated at this time and may have a material adverse impact on our business, financial condition and results of operations.

**** 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 December 2021, we announced the initiation of our Phase 2b/Phase 3 trial of AV-101 with a target enrollment of 200 patients in the Phase 2b portion. We are in the process of site activation and patient enrollment. At this time, we expect to complete patient enrollment of the Phase 2b portion of the trial in the middle of 2023 and report topline data from the Phase 2b portion of the trial in the fourth quarter of 2023 or first quarter of 2024. However, it is difficult to predict the timing of topline data availability with certainty due to the ongoing impacts of COVID-19 that continue to cause site activation delays for the Phase 2b portion of our trial. 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 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.

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.

**** If we encounter difficulties with site initiation 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 may experience difficulties in patient enrollment in our clinical trials for a variety of reasons and have experienced site initiation delays as a result of COVID-19, including as a result of staff shortages and short-term interruptions at clinical trial sites, and the prioritization of COVID-19 research and treatment matters by hospitals and academic institutions. In December 2021, we announced initiation of our Phase 2b/Phase 3 clinical trial of AV-101 with a target enrollment of 200 patients in the Phase 2b portion. We are in the process of site activation and patient enrollment. At this time, we expect to complete patient enrollment of the Phase 2b portion of the trial in the middle of 2023 and report topline data from the Phase 2b portion of the trial in the fourth quarter of 2023 or first quarter of 2024. However, it is difficult to predict the timing of topline data availability with certainty due to the ongoing impacts of COVID-19 that continue to cause site activation delays for the Phase 2b 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 impact of the ongoing COVID-19 pandemic on our ability to identify patients able to enroll in our clinical trials and the ability of enrolled patients to complete our clinical trials;
- 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;
- the clinical site's ability to obtain and maintain patient consents;
- delays in or temporary suspension of the enrollment of patients in our ongoing clinical trial due to the ongoing COVID-19 pandemic; and
- the risk that patients enrolled in clinical trials will drop out of the trials before completion, including as a result of contracting COVID-19, its variants or other health conditions or being forced to quarantine.

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.

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 trial of AV-101 in healthy volunteers and announced initiation of our Phase 2b/Phase 3 dose-ranging clinical trial in PAH patients in December 2021. 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 begin on time, 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 PAH patients 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. In particular, we expect that AV-101 will face competition from prostanoids available in oral form as Orenitram (United Therapeutics Corporation, or United Therapeutics) and Uptravi (Janssen Pharmaceuticals, Inc., or Janssen), by inhalation as Tyvaso (United Therapeutics), and by infusion as Remodulin (United Therapeutics), which are existing drug products indicated for the treatment of PAH, potential new entrants such as sotatercept (Acceleron Pharma, Inc.), a wholly-owned subsidiary of Merck & Co., Inc., or Merck, rodatristat ethyl (Altavant Sciences, Inc.) and/or, seralutinib (Gossamer Bio, Inc.), as well as generic equivalents of Tyvaso following the expiry of Tyvaso's patent in 2018. On October 15, 2018, United Therapeutics Corporation, or United Therapeutics, and MannKind closed their worldwide exclusive licensing and collaboration agreement for the development and commercialization of a dry powder formulation of treprostinil. Under the agreement, United Therapeutics will be responsible for global development, regulatory and commercial activities. MannKind will manufacture clinical supplies and initial commercial supplies of the product while long-term commercial supplies will be manufactured by United Therapeutics. On May 24, 2022, United Therapeutics announced the approval of Tyvaso DPI for the treatment of PAH (WHO Group 1) and pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3). On November 8, 2021, Liquidia Corporation announced that they received tentative approval for the treatment of PAH to improve exercise ability in adult patients with New York Heart Association (NYHA) Functional Class II-III symptoms from the FDA for Yutrepia, a dry powdered formulation of Treprostinil which may receive final approval in October 2022 or earlier upon resolution of on-going litigation with United Therapeutics. Additionally, we are aware that Arena Pharmaceuticals, Inc., or Arena, has commenced a Phase 3 trial evaluating ralinepag, an oral prostanoid product for the treatment of patients suffering from PAH. On January 24, 2019, Arena and United Therapeutics closed on a global license agreement for ralinepag. Under the agreement, United Therapeutics is now responsible for the development, manufacture and commercialization of ralinepag. These collaborations may accelerate competition for AV-101. Finally, we are aware that Tenax Therapeutics, Inc. and Aerami Therapeutics, Inc. have announced they intend to develop imatinib for PAH. 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). 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), rodatristat ethyl (Altavant Sciences, Inc.) and/or, seralutinib (Gossamer Bio, Inc.). 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, 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 anti-proliferative 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.

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. Factors payors consider in determining reimbursement are based on whether the product is: (i) a covered benefit under its health plan; (ii) safe, effective and medically necessary; (iii) appropriate for the specific patient; (iv) cost-effective; and (v) neither experimental nor investigational.

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.

In June 2021, we hired a Senior Vice President of Commercial but we currently 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. For example, since the beginning of the pandemic, several vaccines for COVID-19 have received Emergency Use Authorization by the FDA and a number of those later received marketing approval. Additional vaccines may be authorized or approved in the future. The resultant demand for vaccines and potential for manufacturing facilities and materials to be commandeered under the Defense Production Act of 1950, or equivalent foreign legislation, has placed strain on manufacturing supply chains and may make it more difficult to obtain materials or manufacturing slots for the products needed for our clinical trials, which could lead to delays in these trials. In particular, 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, including the COVID-19 pandemic and its continued spread. 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 will be managed by one CRO and carried out in over 20 countries and numerous 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 two issued U.S. patents and many pending patent applications with respect to AV-101 (of which two have recently received a notice of allowance). 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 two 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 preissuance 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 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 plan to 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 PAH patients. 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; and (ii) the trials were performed by clinical investigators of recognized competence and pursuant to GCP regulations. 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, grants orphan drug designation to promote the development of drugs 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 or (ii) without incentives, it is unlikely that the marketing of the drug in the European Union would be sufficient 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 drug 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 Europe. The European 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.

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 can subsequently approve the same product for the same condition if the FDA 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 drug designation from the EMA, there is no guarantee that we will enjoy the benefits of such designation.

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 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. 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. 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. 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 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 health care professionals beginning in 2022 (physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists & anesthesiologist assistants, and certified nurse-midwives), 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;

- 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.

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. See the section of our Annual Report on Form 10-K entitled “Business – Healthcare Reform and Legislation”.

We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our current or future product candidates or additional pricing pressures. In particular any policy changes through CMS as well as local state Medicaid programs could have a significant impact on our business.

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.

Separately, since March 2020 when foreign and domestic inspections were largely placed on hold due to the COVID-19 pandemic, the FDA has been working to resume routine surveillance, bioresearch monitoring and pre-approval inspections on a prioritized basis. Since April 2021, the FDA has conducted limited inspections and employed remote interactive evaluations, using risk management methods, to meet user fee commitments and goal dates. Ongoing travel restrictions and other uncertainties continue to impact oversight operations both domestic and abroad and it is unclear when standard operational levels will resume. The FDA is continuing to complete mission-critical work, prioritize other higher-tiered inspectional needs (e.g., for-cause inspections), and carry out surveillance inspections using risk-based approaches for evaluating public health. Should the FDA determine that an inspection is necessary for approval and an inspection cannot be completed during the review cycle due to restrictions on travel, and the FDA does not determine a remote interactive evaluation to be adequate, the agency has stated that it generally intends to issue, depending on the circumstances, a complete response letter or defer action on the application until an inspection can be completed. During the COVID-19 public health emergency, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. Regulatory authorities outside the United States may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic and may experience delays in their regulatory activities. If a prolonged government shutdown or other disruption 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. Future shutdowns or other disruptions could also affect other government agencies such as the SEC, which may also impact our business by delaying review of our public filings, to the extent such review is necessary, and our ability to access the public markets.

Risks Relating to Employee Matters and Managing Growth

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

As of August 12, 2022, we had 25 full-time employees. 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 from cyberattacks, which could result in the disclosure 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 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. Cyberattacks 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, 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 security breaches 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 cyberattacks are a threat, and there can be no assurance that our efforts will prevent information security breaches 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. Any failure to prevent or mitigate security breaches or improper access to, use of, or disclosure 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 attacks 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 security breaches or improper access to or disclosure of such information could have similarly adverse consequences for us. If we are unable to prevent or mitigate the impact of such security breaches, 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, or CCPA, which went into effect on January 1, 2020, creates a private right of action for data breaches impacting California residents that is expected to increase data breach litigation.

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, 2021, the Company had federal net operating loss (NOL) carryforwards of approximately $7.5 million and is accruing additional net operating losses in calendar year 2022, 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 in taxable years beginning after December 31, 2020.

Comprehensive tax reform legislation could adversely affect our business and financial condition.

The rules dealing with United States 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 United States 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 such changes have been made and changes are likely to continue to occur in the future. For example, the TCJA was enacted in 2017 and made significant changes to corporate taxation, including the reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, the limitation of the tax deduction for net interest expense to 30% of adjusted taxable income (except for certain small businesses), the limitation of the deduction for net operating losses from taxable years beginning after December 31, 2017 to 80% of current year taxable income and the elimination of net operating loss carrybacks generated in taxable years ending after December 31, 2017 (though any such net operating losses may be carried forward indefinitely), and the modification or repeal of many business deductions and credits.

Additionally, on March 27, 2020, former President Trump signed into law the Coronavirus Aid, Relief, and Economic Security Act, which, among other things, suspends the 80% limitation on the deduction for net operating losses in taxable years beginning before January 1, 2021, permits a 5-year carryback of net operating losses arising in taxable years beginning after December 31, 2017 and before January 1, 2021, and generally caps the limitation on the deduction for net interest expense at 50% of adjusted taxable income for taxable years beginning in 2019 and 2020.

The recent presidential and congressional elections in the United States could also result in significant changes in, and uncertainty with respect to, tax legislation, regulation and government policy directly affecting us and our business. For example, the United States government may enact significant changes to the taxation of business entities including, among others, a permanent increase in the corporate income tax rate, an increase in the tax rate applicable to the global intangible low-taxed income and elimination of certain exemptions, and the imposition of minimum taxes or surtaxes on certain types of income. The likelihood of these changes being enacted or implemented is unclear.

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 promulgated or issued under existing or new tax laws, which could result in an increase in our or our stockholders' 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 ongoing COVID-19 pandemic has 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 an escalation in conflict between Russia and Ukraine, including any resulting sanctions, export controls or other restrictive actions, also could lead to disruption, instability, and volatility in the global markets. 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.

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 regulation, 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, which went into effect on January 1, 2020, 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 that is expected to increase data breach litigation. The CCPA may increase our compliance costs and potential liability. Some observers have noted that the CCPA could mark the beginning of a trend toward more stringent privacy legislation in the United States, which could increase our potential liability and adversely affect our business. Further, on November 3, 2020, the CPRA was voted into law by California residents. The CPRA significantly amends the CCPA, and imposes additional data protection obligations on companies doing business in California, including additional consumer rights processes and opt outs for certain uses of sensitive data. It also creates a new California data protection agency specifically tasked to implement and enforce the CCPA and the CPRA, which would likely result in increased regulatory scrutiny of California businesses in the areas of data protection and security. The substantive requirements for businesses subject to the CPRA will go into effect on January 1, 2023, and become enforceable on July 1, 2023. The effects of the CCPA and 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 expect that more federal and state-level privacy legislation may be enacted. For example, on March 2, 2021, Virginia enacted the Consumer Data Protection Act, or the CDPA. The CDPA will become effective January 1, 2023. The CDPA will regulate how businesses (which the CDPA refers to as "controllers") collect and process personal sensitive data, conduct data protection assessments, transfer personal data to affiliates and respond to consumer rights requests. Such 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, or the GDPR, went into effect in May 2018 and imposes strict requirements for processing the personal information of individuals within the European Economic Area, or the EEA, including clinical trial data. The GDPR has and will continue to increase compliance burdens on us, including by mandating potentially burdensome documentation requirements and granting certain rights to individuals to control how we collect, use, disclose, retain and process information about them. The processing of sensitive personal data, such as physical health condition, may impose heightened compliance burdens under the GDPR and is a topic of active interest among foreign regulators. The GDPR also increases the scrutiny of transfers of personal data from the EEA to the United States and other jurisdictions that the European Commission does not recognize as having "adequate" data protection laws; in July 2020, the Court of Justice of the European Union limited how organizations could lawfully transfer personal data from the EEA to the United States by invalidating the EU-U.S. Privacy Shield and imposing further restrictions on use of the standard contractual clauses, which could increase our costs and our ability to efficiently process personal data from the EEA. In addition, the GDPR provides for more robust regulatory enforcement and fines of up to €20 million or 4% of the annual global revenue of the noncompliant company, whichever is greater.

Relatedly, following the United Kingdom's withdrawal from the EEA and the EU, the GDPR ceased to apply in the United Kingdom at the end of the transition period on December 31, 2020. However, as of January 1, 2021, the United Kingdom's European Union (Withdrawal) Act 2018 incorporated the GDPR (as it existed on December 31, 2020 but subject to certain United Kingdom specific amendments) into United Kingdom law, referred to as the UK GDPR. The UK GDPR and the United Kingdom Data Protection Act 2018 set out the United Kingdom's data protection regime, which is independent from but aligned to the EU's data protection regime. Non-compliance with the UK GDPR may result in monetary penalties of up to the greater of £17.5 million or 4% of global turnover. Although the United Kingdom is regarded as a third country under the EU's GDPR, the European Commission, or EC, has now issued a decision recognizing the United Kingdom as providing adequate protection under the GDPR and, therefore, transfers of personal data originating in the EU to the United Kingdom remain unrestricted. Like the GDPR, the UK GDPR restricts personal data transfers outside the United Kingdom to countries not regarded by the United Kingdom as providing adequate protection. The United Kingdom government has confirmed that personal data transfers from the United Kingdom to the EEA remain free flowing. 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 $7.7M 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 $1.07 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 Quarterly Report on form 10-Q. 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 or significant deficiencies 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 will incur increased costs as a result of operating as a public company, and our management will be 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 have begun and 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 will be required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. 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 will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we 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. We have begun 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 2. Unregistered Sales of Equity Securities and Use of Proceeds.

None.

Use of Proceeds from our Public Offering of Common Stock

On July 2, 2021, we closed our initial public offering, or IPO, in which we issued and sold 8,682,142 shares of common stock, including the exercise in full by the underwriters of their option to purchase up to 1,302,231 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, or the Prospectus. Jefferies LLC, Cowen and Company, LLC and Evercore Group L.L.C. acted as joint book-running managers for the IPO. The aggregate gross proceeds to us from our IPO, inclusive of the over-allotment exercise, were $139.8 million.

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 of 1933, as amended, on June 30, 2021.

Item 3. Defaults Upon Senior Securities.

None.

Item 4. Mine Safety Disclosures.

Not applicable.

Item 5. Other Information.

None.

Item 6. Exhibits.

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).
10.1	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) .
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+	Certifications 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+	Certifications 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.
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 Data File (the cover page XBRL tags are embedded within the iXBRL document).

* Filed herewith.

\+ The certifications furnished in Exhibits 32.1 and 32.2 hereto are deemed to be furnished with this Quarterly Report on Form 10-Q and will not be deemed to be "filed" for purposes of Section 18 of 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 the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

AEROVATE THERAPEUTICS, INC

Date: August 15, 2022

By: */s/ Timothy P. Noyes*
Timothy P. Noyes
Chief Executive Officer
(Principal Executive Officer)

Date: August 15, 2022

By: */s/ George Eldridge*
George Eldridge
Chief Financial Officer
(Principal Financial and Accounting Officer)

Exhibit 31.1

CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER PURSUANT TO RULE 13a-14(a) / RULE 15d-14(a) OF THE SECURITIES EXCHANGE ACT OF 1934, AS AMENDED

I, Timothy P. Noyes, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Aerovate Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) (Paragraph omitted pursuant to SEC Release Nos. 33-8238/34-47986 and 33-8392/34-49313);

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

/s/ Timothy P. Noyes

Timothy P. Noyes
Chief Executive Officer
(Principal Executive Officer)

Dated: August 15, 2022

Exhibit 31.2

CERTIFICATION OF PRINCIPAL FINANCIAL OFFICER PURSUANT TO RULE 13a-14(a) / RULE 15d-14(a) OF THE SECURITIES EXCHANGE ACT OF 1934, AS AMENDED

I, George A. Eldridge, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Aerovate Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) (Paragraph omitted pursuant to SEC Release Nos. 33-8238/34-47986 and 33-8392/34-49313);

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

/s/ George A. Eldridge

George A. Eldridge
Chief Financial Officer
(Principal Financial and Accounting Officer)

Dated: August 15, 2022

Exhibit 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

In connection with the Quarterly Report on Form 10-Q of Aerovate Therapeutics, Inc. (the "Company") for the quarter ended June 30, 2022 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I hereby certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, to the best of my knowledge, that:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ Timothy P. Noyes
Timothy P. Noyes
Chief Executive Officer
(Principal Executive Officer)

Dated: August 15, 2022

Exhibit 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

In connection with the Quarterly Report on Form 10-Q of Aerovate Therapeutics, Inc. (the "Company") for the quarter ended June 30, 2022 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I hereby certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, to the best of my knowledge, that:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ George A. Eldridge
George A. Eldridge
Chief Financial Officer
(Principal Financial and Accounting Officer)

Dated: August 15, 2022