Table of Contents

Filed Pursuant to Rule 424(b)(5)
Registration No. 333-219890

The information contained in this prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been declared effective by the Securities and Exchange Commission. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities, and we are not soliciting an offer to buy these securities, in any jurisdiction where the offer or sale is not permitted.

Subject to Completion, Dated February 7, 2018

Preliminary Prospectus Supplement **(To Prospectus Dated August 22, 2017)**

Shares

ADVERUM BIOTECHNOLOGIES

Common Stock

We are offering shares of our common stock. Our common stock is listed on The Nasdaq Global Market under the symbol "ADVM." On February 6, 2018, the last reported sale price of our common stock was $6.90 per share.

We are an "emerging growth company" under applicable Securities and Exchange Commission rules and are eligible for reduced public company disclosure requirements. See "Prospectus Supplement Summary—Corporate Information."

Our business and an investment in our common stock involve significant risks. These risks are described under the caption "Risk Factors" beginning on page S-9 of this prospectus supplement.

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

	Per Share	*Total*
Public offering price	**$**	**$**
Underwriting discounts and commissions(1)	**$**	**$**
Proceeds, before expenses, to Adverum Biotechnologies, Inc.	**$**	**$**

(1) We refer you to "Underwriting" beginning on page S-64 of this prospectus supplement for additional information regarding total underwriter compensation.

The underwriters may also purchase up to an additional shares from us at the public offering price, less the underwriting discount, within 30 days from the date of this prospectus supplement. See "Underwriting" for more information.

The underwriters expect to deliver the shares to purchasers against payment on or about , 2018, through the book-entry facilities of The Depository Trust Company.

Joint Book-Running Managers

Cowen **Piper Jaffray**

Lead Manager

Raymond James

Prospectus Supplement dated , 2018

TABLE OF CONTENTS

ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying prospectus are part of a "shelf" registration statement on Form S-3 (File No. 333-219890) that we initially filed with the Securities and Exchange Commission (SEC) on August 10, 2017, and that was amended on August 17, 2017 and declared effective by the SEC on August 22, 2017. This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this common stock offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference in the accompanying prospectus—the statement in the document having the later date modifies or supersedes the earlier statement.

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

We have not, and the underwriters have not, authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus supplement, the accompanying prospectus or in any free writing prospectus that we have authorized for use in connection with this offering. We and the underwriters take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus supplement and the accompanying prospectus do not constitute an offer to sell, or a solicitation of an offer to purchase, the securities offered by this prospectus supplement and the accompanying prospectus in any jurisdiction to or from any person to whom or from whom it is unlawful to make such offer or solicitation of an offer in such jurisdiction. The information contained in this prospectus supplement, the accompanying prospectus, any free writing prospectus that we have authorized for use in connection with this offering, including the documents incorporated by reference herein or therein is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of our common stock. It is important for you to read and consider all information contained in this prospectus supplement, the accompanying prospectus and any free writing prospectus that we have authorized for use in connection with this offering, including the documents incorporated by reference herein and therein, in making your investment decision. You should also read and consider the information in the documents to which we have referred you in the sections entitled "Where You Can Find Additional Information" and "Incorporation of Certain Information by Reference" in this prospectus supplement and "Incorporation by Reference" in the accompanying prospectus.

We and the underwriters are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of

this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

Except as otherwise indicated herein or as the context otherwise requires, references in this prospectus supplement to “Adverum,” “the company,” “we,” “us,” “our” and similar references refer to Adverum Biotechnologies, Inc., a corporation under the laws of the State of Delaware, and its wholly owned subsidiaries.

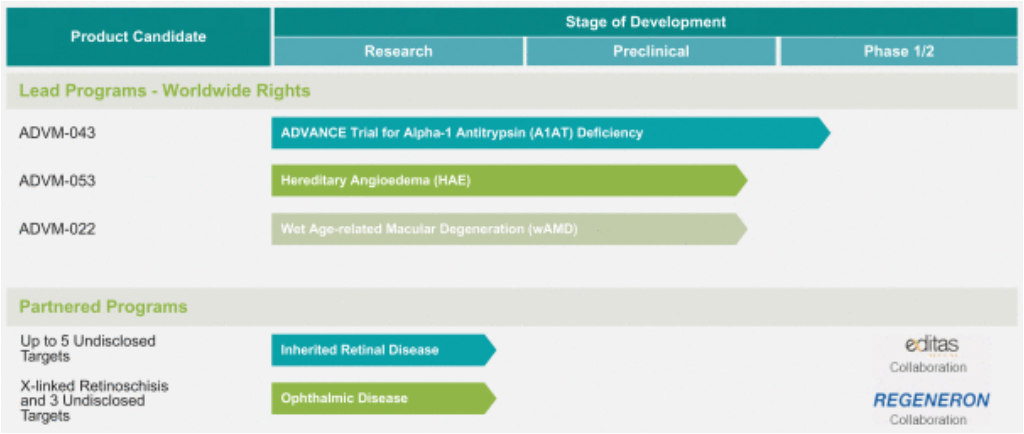
PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights certain information about us, this offering and selected information contained elsewhere in or incorporated by reference into this prospectus supplement. This summary is not complete and does not contain all of the information that you should consider before deciding whether to invest in our common stock. For a more complete understanding of our company and this offering, you should read and consider carefully the more detailed information included or incorporated by reference in this prospectus supplement, the accompanying prospectus and any free writing prospectus that we have authorized for use in connection with this offering, including the factors described under the heading "Risk Factors" beginning on page S-9 of this prospectus supplement, as well as the information included in any free writing prospectus that we have authorized for use in connection with this offering.

Company Overview

We are a clinical-stage gene therapy company targeting unmet medical needs in serious rare and ocular diseases. Leveraging our next-generation adeno-associated virus (AAV)-based directed evolution platform, we generate gene therapy product candidates designed to provide durable efficacy by inducing sustained expression of a therapeutic protein. Our core capabilities include clinical development and in-house manufacturing expertise, specifically in process development, assay development, and Good Manufacturing Practices quality control. Our leadership team has significant drug development and gene therapy expertise.

We are advancing our robust pipeline of gene therapy product candidates designed to treat rare diseases alpha-1 antitrypsin (A1AT) deficiency and hereditary angioedema (HAE), as well as wet age-related macular degeneration (wAMD). Our pipeline of lead and partnered gene therapy programs is shown below.

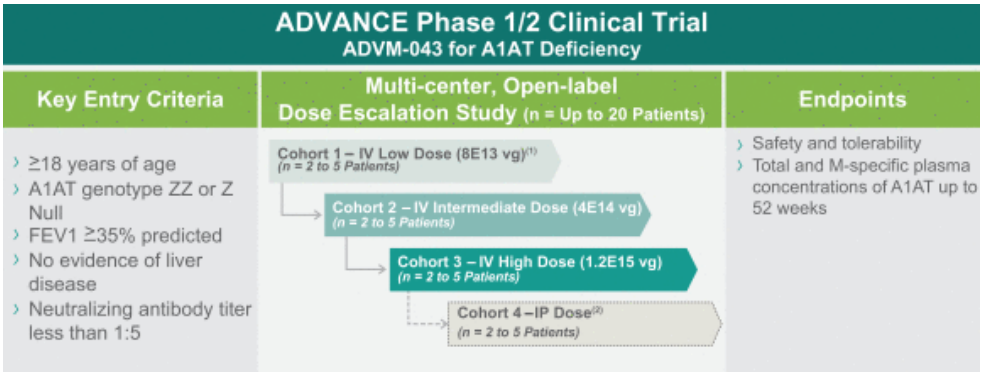


ADVM-043 for A1AT Deficiency

A1AT deficiency impacts approximately 100,000 individuals in the United States. The disease is caused by genetic mutations resulting in very low levels of A1AT. A1AT deficiency is associated with premature emphysema. We estimate the market for A1AT deficiency therapy in North America to have been approximately $704 million in 2016. The current standard of care for this disease includes weekly intravenous infusions of an alpha-1 proteinase inhibitor, which we estimate costs approximately $100,000 per year per patient.

For the treatment of A1AT deficiency, we are advancing our gene therapy product candidate ADVM-043. ADVM-043 is designed as a potential single-administration treatment to induce stable, long-term A1AT protein expression. In a preclinical proof-of-concept study, ADVM-043 demonstrated robust protein expression above therapeutic levels in mice following either intravenous (IV) or intrapleural (IP) administration. In another study in non-human primates, evidence of stable long-term expression of hA1AT mRNA was observed out to one year following IP administration of ADVM-043. We believe other published data supports our clinical plans for ADVM-043. A study conducted comparing placebo to protein augmentation demonstrated that augmentation of serum A1AT levels may slow the loss of lung function. Studies using an AAV1 gene therapy expressing A1AT administered intramuscularly demonstrated a linear relationship between dose of gene therapy given and protein expressed and also showed durability of protein expression out to five years post-administration.

We commenced a Phase 1/2 clinical trial of ADVM-043 in December 2017 (ADVANCE Phase 1/2 trial). The ADVANCE Phase 1/2 trial is a multi-center, open-label, dose-escalation study. The primary endpoint is safety and tolerability and secondary endpoints include changes in plasma concentrations of both total and M-specific A1AT levels. The study will include up to 20 patients across up to four dosing cohorts of up to five patients each. Patients are presently being enrolled in the first cohort. The first three cohorts of patients will receive a single intravenous (IV) administration of ADVM-043 and the fourth cohort of patients will receive a single intrapleural (IP) administration of ADVM-043. We expect to report preliminary data from this trial in the second half of 2018. The design of the ADVANCE trial is summarized below.



(1) Low dose of 8E13 total vg equivalent to approximately 1E12 vg/kg based on an 80-kg patient.

(2) Cohort 4 may open to evaluate IP administration of ADVM-043 at the dose that provided the best protein expression with IV administration.

ADVM-053 for HAE

HAE impacts approximately 8,000 individuals in the United States. The disease is caused by a genetic mutation that results in low levels of C1-esterase inhibitor (C1EI). Low levels of C1EI are associated with sudden swelling and edema of respiratory airways, gastrointestinal tract and extremities. The current standard of care prophylaxis treatment requires intravenous C1EI infusions 2-3 times per week, which can be burdensome for patients. A 2012 study demonstrated that daily infusions drop breakthrough swelling and edema attacks to near zero. However, we believe daily infusions are not clinically practical and other approaches are urgently needed. Preclinical studies demonstrated that a single intravenous administration of ADVM-053 showed robust C1EI expression and eliminated vascular permeability, a hallmark of the disease.

For the treatment of HAE, we are advancing our preclinical gene therapy product candidate ADVM-053. ADVM-053 is designed as a potential single-administration treatment to provide sustained expression of C1EI to eliminate protein level variability and prevent breakthrough attacks. In preclinical studies, a single intravenous administration of ADVM-053 increased C1EI protein expression above therapeutic levels and decreased vascular permeability. We plan to submit an investigational new drug application (IND) with the U.S. Food and Drug Administration (FDA) in the second half of 2018.

ADVM-022 for wAMD

Age-related macular degeneration is a progressive disease affecting the retinal cells in the macula, the region of the eye responsible for central vision. Disease progression results in the death of retinal calls and the gradual loss of vision. Approximately 10% of patients living with age-related macular degeneration have wAMD, an advanced form of the disease. A significant number of individuals are impacted by this disease, which has a prevalence of approximately 1.2 million individuals in the United States and 3.0 million on a worldwide basis. The incidence of new cases of wAMD in the United States is approximately 150,000 to 200,000 annually. The current standard of care therapies for wAMD include Lucentis® and EYLEA®, which together generated annual sales of $8.4 billion in 2016, as well as off-label use of Avastin®. These therapies generally require intravitreal injections every 4-8 weeks, which can be burdensome and can lead to compliance deficiencies and loss of vision from underdosing.

For wAMD, we are advancing our preclinical gene therapy product candidate ADVM-022. With a proprietary vector capsid (AAV.7m8) and a proprietary expression cassette, ADVM-022 is designed to be administered as a single intravitreal injection and minimize the treatment burden of frequent injections. In preclinical studies, a single intravitreal injection of ADVM-022 showed efficacy that was comparable to the anti-VEGF standard of care. We plan to submit an IND application with the FDA in the second half of 2018.

At scientific meetings, we have presented preclinical proof-of-concept data of ADVM-022's anti-angiogenic effect in the laser-induced choroidal neovascularization (CNV) model in non-human primates, the industry standard for testing new wAMD therapies. The data from a single injection of ADVM-022 showed efficacy that was comparable to the anti-VEGF standard of care, the positive control in the CNV model. At scientific meetings in September 2017, we presented additional long-term data, which continued to demonstrate sustained expression of anti-VEGF protein following a single intravitreal injection of ADVM-022. Pharmacokinetic data on one non-human primate demonstrated sustained expression for 52 weeks. In a separate ongoing study, sustained expression for at least seven months has been observed in several non-human primates. In this ongoing preclinical study, we continue to assess the durability of protein expression in non-human primates and expect to report 12-month efficacy data in the first half of 2018. Our other preclinical activities include a toxicology and biodistribution study of ADVM-022 and a pharmacokinetics study of EYLEA®, the current anti-VEGF

standard of care, to assess ADVM-022's level of expression of anti-VEGF protein relative to that standard of care.

Our earlier-stage research programs include gene therapy product candidates targeting cardiomyopathy associated with Friedreich's ataxia.

Our partnered programs include vectors we are developing under collaboration agreements. Under an agreement with Editas Medicine, we are leveraging our AAV-vectors for use with Editas' leading CRISPR-based genome editing technologies to treat up to five inherited retinal diseases. Our agreement with Regeneron provides for development of up to eight distinct ocular therapeutic targets, four of which are already identified, including AVA-311 for the treatment of juvenile X-Linked Retinoschisis (XLRS).

On May 11, 2016, we completed the acquisition of all of the outstanding shares of Annapurna Therapeutics SAS, a French simplified joint stock company (Annapurna), and, as a result, Annapurna is now our wholly-owned subsidiary. We changed our name to "Adverum Biotechnologies, Inc." upon completion of the Annapurna transaction.

Our Strengths

In 2016, the transaction between Avalanche and Annapurna brought together unique and complementary capabilities and assets to create Adverum. As a merged company, we believe we have the capabilities, resources, and expertise to enable Adverum to become a gene therapy leader. These strengths include:

- Industry-leading capabilities in AAV technology;
- Robust pipeline of gene therapy product candidates targeting the treatment of serious rare and ocular diseases;
- Robust patent portfolio;
- Proprietary vectors; and
- Experienced leadership team with expertise in developing gene therapies.

Adverum Strategy

Our goal is to transform the lives of patients through the discovery and development of novel medicines that potentially can offer life-changing therapeutic benefit to patients living with rare diseases or diseases of the eye who currently have limited or burdensome treatment options. The key elements of our strategy to achieve this goal are to:

- Target unmet needs in serious rare and ocular diseases;
- Accelerate the clinical development of our pipeline of gene therapies;
- Advance our earlier-stage research initiatives to leverage our industry-leading capabilities in novel vector development; and
- Collaborate with partners to leverage our industry-leading ophthalmic vector development and product delivery capabilities.

Preliminary Financial Data

As of December 31, 2017, we had approximately $190.5 million in cash, cash equivalents and short-term investments, and 49,015,339 shares of our common stock outstanding. The number of shares of our common stock outstanding as of December 31, 2017, does not include shares of

common stock underlying options or warrants or issuable upon vesting of restricted stock units outstanding as of such date, or shares available for future grant under our equity incentive plans as of such date. From January 1, 2018, through January 31, 2018, we sold an additional 1,419,893 shares of our common stock under our sales agreement with Cowen and Company, LLC (Cowen) for net proceeds of approximately $5.7 million, after payment of sales commissions to Cowen. We have not made any sales under the sales agreement subsequent to January 31, 2018. From January 1, 2018, to February 6, 2018, we issued 1,322,387 shares of common stock upon exercise of stock options and vesting of restricted stock units.

The preliminary financial data included in this prospectus supplement has been prepared by, and is the responsibility of, Adverum's management. There can be no assurance that our cash position as of December 31, 2017, will not differ from this estimate, including as a result of year-end closing and audit procedures or review adjustments. Any such changes could be material.

Deloitte & Touche LLP has not audited, reviewed, compiled, or performed any procedures with respect to the preliminary financial data. Accordingly, Deloitte & Touche LLP does not express an opinion or any other form of assurance with respect thereto.

Risks Associated with Our Business

Our business is subject to numerous risks. You should read these risks before you invest in our common stock. In particular, our risks include, but are not limited to, the following:

- We have incurred significant operating losses since inception, and we expect to incur significant losses for the foreseeable future. We may never become profitable or, if achieved, be able to sustain profitability;
- We will need to raise additional funding, which may not be available on acceptable terms, or at all. If we fail to obtain additional capital necessary to fund our operations, we will be unable to successfully develop and commercialize our product candidates;
- Our business will depend substantially on the success of one or more of our lead product candidates: ADVM-043, which is in early clinical development; and ADVM-053 and ADVM-022, which are still in preclinical development. If we are unable to obtain regulatory approval for, or successfully commercialize, any or all of our lead product candidates, our business will be materially harmed;
- Our gene therapy platform is based on a novel technology, which makes it difficult to predict the time and cost of product candidate development and subsequently obtaining regulatory approval;
- We may not be successful in our efforts to identify or discover additional product candidates;
- Except for our recently-initiated ADVANCE Phase 1/2 trial, we have not tested any of our internally-developed viral vectors or product candidates in clinical trials;
- Preliminary and interim data from our clinical trials that we may announce or publish from time-to-time may change as patient data becomes available;
- The results of preclinical studies and early clinical trials are not always predictive of future results. Any product candidate we or any of our future development partners advance into clinical trials may not have favorable results in later clinical trials, if any, and may not receive regulatory approval;
- Our product candidates are subject to extensive regulation, compliance with which is costly and time consuming, and such regulation may cause unanticipated delays or prevent the receipt of the required approvals to commercialize our product candidates; and
- We may not be successful in establishing and maintaining development or other strategic collaborations, which could adversely affect our ability to develop and commercialize product candidates and receive potential milestone payments.

Corporate Information

We were incorporated in Delaware in 2006 under the name “Avalanche Biotechnologies, Inc.” We completed the initial public offering of our common stock in August 2014. On May 11, 2016, upon the completion of our acquisition of Annapurna, we changed our name to “Adverum Biotechnologies, Inc.” Our common stock is currently listed on The Nasdaq Global Market under the symbol “ADVM.” We are an “emerging growth company” under the Jumpstart Our Business Startups Act of 2012 (JOBS Act), and therefore we are subject to reduced public company reporting requirements.

Our principal executive offices are located at 1035 O’Brien Drive, Menlo Park, CA 94025, and our telephone number is (650) 272-6269. Our internet address is www.adverum.com. The information on our website is not incorporated by reference into this prospectus and should not be considered to be a part of this prospectus. Our internet address is included in this prospectus as an inactive textual reference only.

All brand names or trademarks appearing in this prospectus supplement are the property of their respective holders. Use or display by us of other parties’ trademarks, trade dress, or products in this prospectus supplement and the accompanying prospectus is not intended to, and does not, imply a relationship with, or endorsements or sponsorship of, us by the trademark or trade dress owners.

The Offering

Common stock offered by us	shares, plus up to an additional shares if the underwriters exercise their option to purchase additional shares in full.
Common stock to be outstanding after the offering	shares, or shares if the underwriters exercise their option to purchase additional shares in full.
Option to purchase additional shares	The underwriters have an option to purchase up to additional shares of our common stock from us. The underwriters can exercise this option at any time within 30 days from the date of this prospectus supplement.
Use of proceeds	We currently intend to use the net proceeds from this offering to advance the clinical and preclinical development of our pipeline of gene therapy candidates for the treatment of rare and ocular diseases and for capital expenditures, working capital and general corporate purposes. We may also use a portion of the net proceeds to begin the initial stage of investing in a manufacturing facility to build on our internal process development capabilities. See “Use of Proceeds” on page S-56 of this prospectus supplement.
Risk Factors	You should read the “Risk Factors” section of this prospectus supplement beginning on page S-9 for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.
The Nasdaq Global Market Symbol	Our shares are listed on The Nasdaq Global Market under the symbol “ADVM.”

The number of shares of common stock to be outstanding after the offering is based on the number of shares outstanding as of September 30, 2017. As of that date, we had 43,517,412 shares of common stock outstanding, excluding:

- 7,370,289 shares of common stock underlying options outstanding as of September 30, 2017, at a weighted average exercise price of $4.52 per share;
- 90,000 shares of common stock underlying warrants outstanding as of September 30, 2017, at a weighted average exercise price of $6.77 per share;
- 2,468,176 shares of common stock issuable upon the vesting of restricted stock units outstanding as of September 30, 2017; and
- 2,632,691 shares of common stock available for future grant under our equity incentive plans as of September 30, 2017.

For information regarding shares outstanding at December 31, 2017 and issued in 2018 under our sales agreement with Cowen and pursuant to our equity plans, see "—Preliminary Financial Data" beginning on page S-4.

Unless we specifically state otherwise, the information in this prospectus supplement assumes that the underwriters in this offering do not exercise their option to purchase up to additional shares of our common stock within 30 days after the date of this prospectus supplement.

RISK FACTORS

Investing in our common stock involves risks. Before making an investment decision, you should carefully consider the risks described below, as well as the information and financial statements contained in the documents incorporated by reference herein. You should consider these risks in light of your particular investment objectives and financial circumstances. Our business, financial condition or results of operations could be materially adversely affected by any of these risks. The trading price of our common stock could decline due to any of these risks, and you may lose all or part of your investment.

Risks Related to Our Financial Position and Need for Capital

We have incurred significant operating losses since inception, and we expect to incur significant losses for the foreseeable future. We may never become profitable or, if achieved, be able to sustain profitability.

We have incurred significant operating losses since we were founded in 2006 and expect to incur significant losses for the foreseeable future as we continue development of our product candidates. As of September 30, 2017, we had an accumulated deficit of $239.3 million. Losses have resulted principally from costs incurred in our clinical trials for our prior wAMD product candidate, AVA-101, research and development programs and from our general and administrative expenses. In the future, we intend to continue to conduct research and development, clinical testing, regulatory compliance activities and, if any of our product candidates is approved, sales and marketing activities that, together with anticipated general and administrative expenses, will likely result in us incurring significant losses for the next several years.

We currently generate no revenue from sales, and we may never be able to commercialize any of our product candidates. We do not currently have the required approvals to market any of our product candidates, and we may never receive such approvals. We may not be profitable even if we or any of our future development partners succeed in commercializing any of our product candidates. Because of the numerous risks and uncertainties associated with developing and commercializing our product candidates, we are unable to predict the extent of any future losses or when we will become profitable, if at all.

We expect that our cash and cash equivalents will be sufficient to fund our lead gene therapy programs through the end of 2019. If this expectation proves to be wrong, we may be forced to delay, limit or terminate certain of our development efforts.

As of December 31, 2017, our cash, cash equivalents and short-term investments were approximately $190.5 million. We currently expect the net proceeds from this offering, together with our existing cash, cash equivalents and short-term investments, to fund our planned operations through the end of 2019. However, this estimate is based on a number of assumptions that may prove to be wrong, including our expectations about the timing of planned clinical trials, and changing circumstances beyond our control may cause capital to be consumed more rapidly than currently anticipated. As a result, our operating plan may change, and we may need to seek additional funds sooner than planned, through collaboration agreements and public or private financings. If we run low on capital before we are able to achieve meaningful clinical data for some or all of our lead product candidates, we may be unable to successfully raise additional funds, and, consequentially, may need to significantly curtail some or all of our development activities.

We will need to raise additional funding, which may not be available on acceptable terms, or at all. If we fail to obtain additional capital necessary to fund our operations, we will be unable to successfully develop and commercialize our product candidates.

We will require substantial future capital in order to complete the preclinical and clinical development for our product candidates and to potentially commercialize these product candidates. Any future clinical trials of our product candidates would cause an increase in our spending levels, as would other corporate activities. The amount and timing of any expenditure needed to implement our development and commercialization programs will depend on numerous factors, including:

- the type, number, scope, progress, expansion costs, results of and timing of any future preclinical studies and clinical trials of any of our product candidates which we are pursuing or may choose to pursue in the future;
- the need for, and the progress, costs and results of, any additional clinical trials or nonclinical studies of our product candidates we may initiate based on the results of any clinical trials that we may plan or discussions with the FDA, including any additional clinical trials or nonclinical studies the FDA or other regulatory agencies may require evaluating the safety of our product candidates;
- the costs of obtaining, maintaining and enforcing our patents and other intellectual property rights;
- the costs and timing of obtaining or maintaining manufacturing for our product candidates, including commercial manufacturing if any product candidate is approved;
- the costs and timing of establishing sales and marketing capabilities and enhanced internal controls over financial reporting;
- the terms and timing of establishing collaborations, license agreements and other partnerships;
- costs associated with any new product candidates that we may develop, in-license or acquire;
- the effect of competing technological and market developments;
- our ability to establish and maintain partnering arrangements for development; and
- the costs associated with being a public company.

Some of these factors are outside of our control. We do not expect our existing capital resources to be sufficient to enable us to fund the completion of our clinical trials and remaining development program through commercial introduction. We expect that we will need to raise additional funds in the future.

We have not sold any products, and we do not expect to sell or derive revenue from any product sales for the foreseeable future. We may seek additional funding through collaboration agreements and public or private financings. Additional funding may not be available to us on acceptable terms or at all and the terms of any financing may adversely affect the holdings or the rights of our stockholders. In addition, the issuance of additional shares by us, or the possibility of such issuance, may cause the market price of our shares to decline.

If we are unable to obtain funding on a timely basis, we will be unable to complete any future clinical trials for our product candidates and we may be required to significantly curtail some or all of our activities. We also could be required to seek funds through arrangements with collaborative partners or otherwise that may require us to relinquish rights to our product candidates or some of our technologies or otherwise agree to terms unfavorable to us.

Risks Related to the Discovery and Development of Our Product Candidates

Our business will depend substantially on the success of one or more of ADVM-043, ADVM-053, and ADVM-022, our lead product candidates. If we are unable to develop, obtain regulatory approval for, or successfully commercialize, any or all of our lead product candidates, our business will be materially harmed.

Our lead product candidates are in the early stages of development and will require substantial clinical development and testing, manufacturing bridging studies, process validation and regulatory approval prior to commercialization. We are conducting the ADVANCE trial in patients with A1AT deficiency and we are continuing pre-clinical development of our other lead product candidates to support planned INDs in the second half of 2018. It is critical to our business to successfully develop and ultimately obtain regulatory approval for one or more of these lead product candidates. Our ability to commercialize our product candidates effectively will depend on several factors, including the following:

- successful completion of preclinical studies and clinical trials, including the ability to demonstrate safety and efficacy of our lead product candidates;
- receipt of marketing approvals from the FDA and similar regulatory authorities outside the U.S.;
- establishing commercial manufacturing capabilities, for example, by making arrangements with third-party manufacturers;
- successfully launching commercial sales of the product, whether alone or in collaboration with others;
- acceptance of the product by patients, the medical community and third-party payers;
- establishing market share while competing with other therapies;
- a continued acceptable safety profile of our products following regulatory approval;
- maintaining compliance with post-approval regulation and other requirements; and
- qualifying for, identifying, registering, maintaining, enforcing and defending intellectual property rights and claims covering our product candidates.

If we, or our collaborators, 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 commercialize our product candidates, which would materially and adversely affect our business, financial condition and results of operations.

Moreover, of the large number of biologics and drugs in development in the pharmaceutical industry, only a small percentage result in the submission of a biologics license application (BLA) to the FDA and even fewer are approved for commercialization. Furthermore, even if we do receive regulatory approval to market any of our lead product candidates, any such approval may be subject to limitations on the indicated uses for which we may market the product, or limitations related to its distribution. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development programs, there can be no assurance that any of our product candidates will be successfully developed or commercialized. If we decide to invest in the continued development and potential commercialization of any or all of our lead product candidates and we or any of our future development partners are unable to develop, or obtain regulatory approval for, or, if approved, successfully commercialize, such product candidates, we may not be able to generate sufficient revenue to continue our business.

Our gene therapy platform is based on a novel technology, which makes it difficult to predict the time and cost of product candidate development and subsequently obtaining regulatory approval.

We have concentrated our research and development efforts on our gene therapy platform and our future success depends on the successful development of product candidates based on this platform. There can be no assurance that any development problems we experience in the future related to our platform will not cause significant delays or unanticipated costs, or that such development problems can be solved. We may also experience delays in developing a sustainable, reproducible and scalable manufacturing process or transferring that process to commercial partners, which may prevent us from completing our clinical trials or commercializing our products on a timely or profitable basis, if at all.

In addition, the clinical trial requirements of the FDA, the European Medicines Agency (EMA) and other regulatory agencies and the criteria these regulators may use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the potential products. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than for other, better known or extensively studied pharmaceutical or other product candidates. The FDA recently approved its first vector-based human gene therapy product, LUXTURNA™ (voretigene neparvovec-rzyl) for the treatment of biallelic RPE65 mutation-associated retinal dystrophy.

Regulatory requirements governing gene and cell therapy products may change in the future. Gene therapy clinical trials conducted at institutions that receive funding for recombinant DNA research from the National Institutes of Health (NIH) may also be subject to review by the NIH Office of Science Policy's Recombinant DNA Advisory Committee (RAC). Although the FDA decides whether individual gene therapy protocols may proceed, the RAC review process can impede the initiation of a clinical trial, even if the FDA has reviewed the study and approved its initiation. Clinical trial sites in the U.S. that receive NIH funding for research involving recombinant or synthetic nucleic acid molecules are required to follow RAC recommendations, or risk losing NIH funding for such research or needing NIH pre-approval before conducting such research.

Conversely, the FDA can put an IND on clinical hold even if the RAC has provided a favorable review of the gene transfer protocol. Also, before a clinical study can begin at an NIH-funded institution, that entity's institutional review board (IRB) and its Institutional Biosafety Committee will have to review the proposed clinical trial to assess the safety of the study. In addition, adverse developments in clinical trials of gene therapy products conducted by others may cause the FDA or other regulatory bodies to change the requirements for human research on or approval of any of our product candidates.

These regulatory review committees and advisory groups and the new guidelines they promulgate may lengthen the regulatory review process, require us to perform additional trials, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these treatment candidates or lead to significant post-approval limitations or restrictions. As we advance our product candidates, we may be required to consult with these regulatory and advisory groups, and comply with applicable guidelines or recommendations. If we fail to do so, we may be required to delay or discontinue development of our product candidates. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue to maintain our business.

We may not be successful in our efforts to identify or discover additional product candidates.

The success of our business depends primarily upon our ability to identify, develop and commercialize products based on our platform. Our research programs, including those subject to our collaborations with Regeneron and Editas, may fail to identify other potential product candidates for clinical development for a number of reasons. Our research methodology may be unsuccessful in identifying potential product candidates or our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval.

If any of these events occur, we may be forced to abandon our development efforts for a program or programs, which would have a material adverse effect on our business and could potentially cause us to cease operations. Research programs to identify new product candidates require substantial technical, financial and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful.

Except for our recently-initiated ADVANCE Phase 1/2 trial, we have not tested any of our internally-developed viral vectors or product candidates in clinical trials.

Drug development has inherent risk. Except for our ADVANCE Phase 1/2 trial, which was only initiated in December 2017, none of our current product candidates has been evaluated in human clinical trials, and we may experience unexpected results in the future. We or any of our future development partners will be required to demonstrate through adequate and well-controlled clinical trials that our product candidates containing our proprietary vectors are safe and effective, with a favorable benefit-risk profile, for use in their target indications before we can seek regulatory approvals for their commercial sale. Drug development is a long, expensive and uncertain process, and delay or failure can occur at any stage of development, including after commencement of any of our clinical trials.

The results of preclinical studies and early clinical trials are not always predictive of future results. Any product candidate we or any of our future development partners advance into clinical trials may not have favorable results in later clinical trials, if any, or receive regulatory approval.

If our proprietary vectors are not shown to be safe and effective, we may not realize the value of our investment in our technology. In addition, success in pre-clinical studies or in early clinical trials does not mean that later clinical trials will be successful, because product candidates in later-stage clinical trials may fail to demonstrate sufficient safety or efficacy despite having progressed through pre-clinical and initial clinical testing. Furthermore, any future trials will need to demonstrate sufficient safety and efficacy for approval by regulatory authorities in larger patient populations. Companies frequently suffer significant setbacks in advanced clinical trials, even after earlier clinical trials have shown promising results. In addition, only a small percentage of products under development result in the submission of a BLA to the FDA and even fewer are approved for commercialization.

We cannot be certain that any clinical trials that we plan will be successful, and any safety concerns observed in any one of our clinical trials in our targeted indications could limit the prospects for regulatory approval of our product candidates in those and other indications.

Preliminary and interim data from our clinical trials that we may announce or publish from time to time may change as more patient data become available.

From time to time, we may announce or publish preliminary or interim data from our clinical trials. Preliminary and interim results of a clinical trial are not necessarily predictive of final results.

Preliminary and interim data 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. As a result, preliminary and interim data should be viewed with caution until the final data are available. Material adverse changes in the final data compared to the interim data could significantly harm our business, prospects, financial condition and results of operations.

Our product candidates are subject to extensive regulation, compliance with which is costly and time consuming, and such regulation may cause unanticipated delays or prevent the receipt of the required approvals to commercialize our product candidates.

The clinical development, manufacturing, labeling, storage, record-keeping, advertising, promotion, import, export, marketing and distribution of our product candidates are subject to extensive regulation by the FDA in the U.S. and by comparable authorities in foreign markets. In the U.S., we are not permitted to market our product candidates until we receive regulatory approval from the FDA. The process of obtaining regulatory approval is expensive, often takes many years and can vary substantially based upon the type, complexity and novelty of the products involved, as well as the target indications and patient population. Approval policies or regulations may change, and the FDA has substantial discretion in the drug approval process, including the ability to delay, limit or deny approval of a product candidate for many reasons. Despite the time and expense invested in clinical development of product candidates, regulatory approval is never guaranteed.

The FDA or comparable foreign regulatory authorities can delay, limit or deny approval of a product candidate for many reasons, including:

- such authorities may disagree with the design or implementation of our or any of our future development partners' clinical trials;
- we or any of our future development partners may be unable to demonstrate to the satisfaction of the FDA or other regulatory authorities that a product candidate is safe and effective for any indication;
- such authorities may not accept clinical data from trials which are conducted at clinical facilities or in countries where the standard of care is potentially different from that of the U.S.;
- the results of clinical trials may not demonstrate the safety or efficacy required by such authorities for approval;
- we or any of our future development partners may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- such authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- approval may be granted only for indications that are significantly more limited than what we apply for and/or with other significant restrictions on distribution and use;
- such authorities may find deficiencies in the manufacturing processes or facilities of third-party manufacturers with which we or any of our future development partners contract for clinical and commercial supplies; or
- the approval policies or regulations of such authorities may significantly change in a manner rendering our or any of our future development partners' clinical data insufficient for approval.

With respect to foreign markets, approval procedures vary among countries and, in addition to the aforementioned risks, can involve additional product testing, administrative review periods and agreements with pricing authorities. In addition, events raising questions about the safety of certain marketed pharmaceuticals may result in increased cautiousness by the FDA and comparable foreign regulatory authorities in reviewing new drugs based on safety, efficacy or other regulatory considerations and may result in significant delays in obtaining regulatory approvals. Any delay in obtaining, or inability to obtain, applicable regulatory approvals would prevent us or any of our future development partners from commercializing our product candidates.

If we encounter difficulties enrolling subjects in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

We initiated the ADVANCE Phase 1/2 trial in patients with A1AT deficiency in December 2017. Identifying and qualifying subjects to participate in the ADVANCE trial and future planned clinical trials for ADVM-053 and ADVM-022 will be critical to our success. The timing of future clinical trials will depend on the speed at which we can recruit subjects to participate in future testing of these product candidates.

Subject enrollment, a significant factor in the timing of clinical trials, is affected by many factors including the size and nature of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the trial, the design of the clinical trial, competing clinical trials and clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating. We will be required to identify and enroll a sufficient number of subjects with the relevant disease we are targeting for any future clinical trials for our product candidates. Potential subjects may not be adequately diagnosed or identified with the diseases which we are targeting or may not meet the entry criteria for our trials. We also may encounter difficulties in identifying and enrolling subjects with a stage of disease appropriate for such future clinical trials. We may not be able to identify, recruit and enroll a sufficient number of subjects, or those with required or desired characteristics to achieve diversity in a study.

In particular, ADVM-043 and ADVM-053 are designed to treat rare genetic disorders with limited patient pools from which to draw for clinical trials. ADVM-043 is focused on the treatment of patients with A1AT deficiency. It is estimated that A1AT deficiency affects approximately 100,000 patients in the U.S.

ADVM-053 is focused on the treatment of patients with HAE. The prevalence of HAE is estimated to be 1 in 10,000 to 1 in 50,000, impacting approximately 8,000 individuals in the United States. Enrollment of eligible subjects with orphan diseases like A1AT and HAE may be limited or slower than we anticipate in light of the small subject populations involved. We plan to seek initial marketing approval of these product candidates in the U.S. and Europe and we may not be able to initiate clinical trials if we cannot enroll a sufficient number of eligible subjects to participate in the clinical trials required by the FDA or the EMA or other regulatory agencies. In addition, the process of finding and diagnosing subjects may prove costly.

Further, if patients are unwilling to participate in our gene therapy studies because of negative publicity from adverse events in the biotechnology or gene therapy industries or inadequate results in our preclinical studies or clinical trials or for other reasons, including competitive clinical trials for similar patient populations or available approved therapies, our recruitment of subjects, conduct of preclinical studies or clinical trials and ability to obtain regulatory approval of our product candidates may be hindered.

Trials using early versions of retroviral vectors, which integrate with, and thereby alter, the host cell's DNA, have led to several well-publicized adverse events. For example, generalized public backlash developed against gene therapy following the death in September 1999 of an 18-year-old who had volunteered for a gene therapy experiment at the University of Pennsylvania. Researchers at the university had infused the volunteer's liver with a gene aimed at reversing a rare metabolic disease of the liver. The procedure triggered an extreme immune-system reaction that caused multiple-organ failure in a very short time, leading to the first death to occur as a direct result of a gene therapy experiment. In addition, in 2003, 20 subjects treated for X-linked severe combined immunodeficiency in two gene therapy studies using a murine gamma-retroviral vector showed correction of the disease, but the trials were terminated after five subjects developed leukemia (four of whom were subsequently

cured). The cause of these adverse events was shown to be insertional oncogenesis, which is the process whereby the corrected gene inserts near a gene that is important in a critical cellular process like growth or division, and this insertion results in the development of a cancer (often leukemia). Using molecular diagnostic techniques, it was determined that clones from these subjects showed retrovirus insertion in proximity to the promoter of the LMO2 proto-oncogene. Earlier generation retroviruses like the one used in these two studies have been shown to preferentially integrate in regulatory regions of genes that control cell growth.

If we have difficulty enrolling a sufficient number of patients to conduct clinical trials on our product candidates as planned, we may need to delay, limit or terminate future clinical trials, any of which would have an adverse effect on our business.

We believe we have appropriately accounted for the above factors in our trials when determining expected clinical trial timelines, but we cannot assure you that our assumptions are correct or that we will not experience delays in enrollment, which would result in the delay of completion of such trials beyond our expected timelines.

The occurrence of serious complications or side effects in connection with use of our product candidates, either in preclinical studies or clinical trials or post-approval, could lead to discontinuation of our clinical development program, refusal of regulatory authorities to approve our product candidates or, post-approval, revocation of marketing authorizations or refusal to approve new indications, which could severely harm our business, prospects, financial condition and results of operations.

During the conduct of preclinical studies and clinical trials, subjects may experience changes in their health, including illnesses, injuries and discomforts. Often, it is not possible to determine whether or not the product candidate being studied caused these conditions. Various illnesses, injuries, and discomforts may be reported from time-to-time in clinical trials of our product candidates. It is possible that as we test our product candidates in larger, longer and more extensive clinical programs, or as use of these product candidates becomes more widespread if they receive regulatory approval, illnesses, injuries, discomforts and other adverse events that were observed in earlier trials, as well as conditions that did not occur or went undetected in previous trials, will be reported by patients. Many times, side effects are only detectable after investigational products are tested in large-scale, Phase 3 clinical trials or, in some cases, after they are made available to patients on a commercial scale after approval. If additional clinical experience indicates that any of our product candidates has side effects or causes serious or life-threatening side effects, the development of the product candidate may fail or be delayed, or, if the product candidate has received regulatory approval, such approval may be revoked, which would severely harm our business, prospects, financial condition and results of operations.

Our product candidates built on AAV vectors have similar risks to other gene therapy vectors, including inflammation, cytotoxic T-cell response, anti-AAV antibodies and immune response to the expressed transgene, such as T-cell responses and/or auto-antibodies against the expressed protein. Recent studies by third parties have also found that intravenous delivery of certain AAV vectors at very high doses may result in toxicity and that studies involving high doses of AAV vectors should be monitored carefully for such toxicity. In addition, patients given infusions of any protein may develop severe hypersensitivity reactions or infusion reactions. With respect to our product candidates that are being or may be studied in diseases of the eye, there are additional potential serious complications related to intravitreal injection to the eye. Serious complications or serious, unexpected side effects in connection with the use of our product candidates could materially harm our business, prospects, financial condition and results of operations.

Serious complications or serious, unexpected side effects in connection with the use of our product candidates could materially harm our business, prospects, financial condition and results of operations.

Risks Related to Our Reliance on Third Parties

We will rely on third parties to conduct our planned clinical trials. If these third parties do not meet our deadlines or otherwise conduct the trials as required, our clinical development programs could be delayed or unsuccessful and we may not be able to obtain regulatory approval for or commercialize our product candidates when expected or at all.

We do not have the ability to conduct all aspects of our preclinical testing or clinical trials ourselves. We are dependent on third parties to conduct preclinical studies and clinical trials for our product candidates, and, therefore, the timing of the initiation and completion of these studies or trials is controlled by such third parties and may occur at times substantially different from our estimates. Specifically, we use clinical research organizations (CROs) to conduct our clinical trials and we rely on medical institutions, clinical investigators, CROs and consultants to conduct our trials in accordance with our clinical protocols and regulatory requirements. Our CROs, investigators and other third parties play a significant role in the conduct of these trials and subsequent collection and analysis of data.

There is no guarantee that any CROs, investigators or other third parties on which we rely for administration and conduct of our clinical trials will devote adequate time and resources to such trials or perform as contractually required. If any of these third parties fails to meet expected deadlines, fails to adhere to our clinical protocols, fails to meet regulatory requirements, or otherwise performs in a substandard manner, our clinical trials may be extended, delayed or terminated. If any of our clinical trial sites terminates for any reason, we may experience the loss of follow-up information on subjects enrolled in our ongoing clinical trials unless we are able to transfer those subjects to another qualified clinical trial site. In addition, 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 the FDA concludes that the financial relationship may have affected the interpretation of the study, 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 any BLA we submit to the FDA. Any such delay or rejection could prevent us from commercializing our product candidates.

We have relied, and expect to continue to rely, on third parties to conduct some or all aspects of our vector production, product manufacturing, protocol development, research and preclinical and clinical testing, and these third parties may not perform satisfactorily.

We do not expect to independently conduct all aspects of our vector production, product manufacturing, protocol development, research and preclinical and clinical testing. We currently rely, and expect to continue to rely, on third parties with respect to these items.

Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it could delay our product development activities. Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations and study protocols. If any of these third parties on which we rely do not perform satisfactorily, we will remain responsible for ensuring that each of our IND-enabling studies and clinical trials are conducted in accordance with the study plan and protocols.

These third parties may not successfully carry out their contractual duties, meet expected deadlines or conduct our studies in accordance with regulatory requirements or our stated study plans and protocols. For example, on December 6, 2016, we delivered a notice to the appropriate persons at Cornell University of our intent to terminate our Amended and Restated Master Services Agreement for breach as a result of Cornell University's failure to deliver suitable materials for use in our clinical trials

of ADVM-043. If third parties breach their contractual obligations to us, we may not be able to complete, or may be delayed in completing, the preclinical studies and clinical trials required to support future IND submissions, development work, and approval of our product candidates.

Reliance on third-party manufacturers also entails risks to which we would not be subject to if we manufactured the product candidates ourselves, including:

- the inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- reduced control as a result of using third-party manufacturers for all aspects of manufacturing activities;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers or suppliers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier.

Any of these events could lead to clinical study delays or failure to obtain regulatory approval, or impact our ability to successfully commercialize future products.

We and our contract manufacturers are subject to significant regulation with respect to manufacturing our products. The manufacturing facilities on which we rely may not continue to meet regulatory requirements and may have limited capacity.

We currently have relationships with limited number of suppliers for the manufacturing of our viral vectors and product candidates. Our suppliers may require licenses to manufacture such components if such processes are not owned by the suppliers or in the public domain and we may be unable to transfer or sublicense the intellectual property rights we may have with respect to such activities. All entities involved in the preparation of therapeutics for clinical trials or commercial sale, including our existing contract manufacturer for our product candidates, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in late-stage clinical trials must be manufactured in accordance with the FDA's current Good Manufacturing Practices (cGMP). These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We or our contract manufacturers must supply all necessary documentation in support of a BLA on a timely basis and must adhere to the FDA's current Good Laboratory Practice regulations and cGMP regulations enforced by the FDA through its facilities inspection program. Our contract manufacturers have not produced a commercially-approved product and therefore have not obtained the requisite FDA approvals to do so. Our facilities and quality systems and the facilities and quality systems of some or all of our third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect our manufacturing facilities or those of our third-party contractors involved with the preparation of our product candidates or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If the facility does not pass a pre-approval plant inspection, FDA approval of the products will not be granted.

The regulatory authorities also may, at any time following approval of a product for sale, audit our manufacturing facilities or those of our third-party contractors. If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable

regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical study or commercial sales or the temporary or permanent closure of a facility. Such violations could also result in civil and/or criminal penalties. Any such remedial measures or other civil and/or criminal penalties imposed upon us or third parties with whom we contract could materially harm our business.

If we or our third-party manufacturers fail to maintain regulatory compliance, the FDA can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new drug product or biologic product, revocation of a pre-existing approval, other civil or criminal penalties or closing one or more manufacturing facilities. As a result, our business, financial condition and results of operations may be materially harmed.

Additionally, if supply from an approved manufacturer is interrupted, there could be a significant disruption in commercial supply. An alternative manufacturer would need to be qualified through a BLA supplement which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause the delay of clinical trials, regulatory submissions, required approvals or commercialization of our product candidates, cause us to incur higher costs and prevent us from commercializing our products successfully. Furthermore, if our suppliers fail to meet contractual requirements, and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical trials may be delayed or we could lose potential revenue.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties to research and develop and to manufacture our product candidates, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements with our advisors, employees, third-party contractors and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, including our trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's independent discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, these agreements typically restrict the ability of our advisors, employees, third-party contractors and consultants to publish data potentially relating to our trade secrets, although our agreements may contain certain limited publication rights. For example, any academic institution that we may collaborate with in the future will usually expect to be granted rights to publish data arising out of such collaboration, provided that we are notified in advance and given the opportunity to delay publication for a limited time period in order for us to secure patent protection of intellectual property rights arising from the collaboration, in addition to the opportunity to remove confidential or trade secret information from any such publication. In the future we may also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and

development or similar agreements. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of our agreements with third parties, independent development or publication of information by any of our third-party collaborators. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

Risks Related to Commercialization of Our Product Candidates

Any termination or suspension of, or delays in the commencement or completion of, clinical trials for our product candidates could result in increased costs to us, delay or limit our ability to generate revenue and adversely affect our commercial prospects.

Before we can initiate clinical trials in the U.S. for our product candidates, we need to submit the results of preclinical testing to the FDA, along with other information including information about product candidate chemistry, manufacturing and controls and our proposed clinical trial protocol, as part of an IND. We may rely in part on preclinical, clinical and quality data generated by CROs and other third parties for regulatory submissions for our product candidates. If these third parties do not make timely regulatory submissions for our product candidates, it will delay our plans for our clinical trials. If those third parties do not make this data available to us, we will likely have to develop all necessary preclinical and clinical data on our own, which will lead to significant delays and increase development costs of the product candidate. In addition, the FDA may require us to conduct additional preclinical testing for any product candidate before it allows us to initiate clinical testing under any IND, which may lead to additional delays and increase the costs of our preclinical development. Delays in the commencement or completion of any clinical trials that we plan for our product candidates could significantly affect our product development costs. We do not know whether any trials that we plan will begin on time or be completed on schedule, if at all. The commencement and completion of clinical trials can be delayed for a number of reasons, including delays related to:

- the FDA failing to grant permission to proceed or placing the clinical trial on hold;
- subjects failing to enroll or remain in our trial at the rate we expect;
- subjects choosing an alternative treatment for the indication for which we are developing our product candidates, or participating in competing clinical trials;
- lack of adequate funding to continue the clinical trial;
- subjects experiencing severe or unexpected drug-related adverse effects;
- a facility manufacturing any of our product candidates or any of their components being ordered by the FDA or other government or regulatory authorities to temporarily or permanently shut down due to violations of cGMP or other applicable requirements, or infections or cross-contaminations of product candidates in the manufacturing process;
- any changes to our manufacturing process that may be necessary or desired;
- third-party clinical investigators losing the licenses or permits necessary to perform our clinical trials, not performing our clinical trials on our anticipated schedule or consistent with the clinical trial protocol, Good Clinical Practice or regulatory requirements or other third parties not performing data collection or analysis in a timely or accurate manner;
- inspections of clinical trial sites by the FDA or the finding of regulatory violations by the FDA or an IRB that require us to undertake corrective action, result in suspension or termination of one or more sites or the imposition of a clinical hold on the entire trial or that prohibit us from using some or all of the data in support of our marketing applications;
- third-party contractors becoming debarred or suspended or otherwise penalized by the FDA or other government or regulatory authorities for violations of regulatory requirements, in which case we may need to find a substitute contractor, and we may not be able to use some or all of the data produced by such contractors in support of our marketing applications; or

- one or more IRBs refusing to approve, suspending or terminating the trial at an investigational site, precluding enrollment of additional subjects, or withdrawing its approval of the trial.

Product development costs will increase if we have delays in testing or approval of any of our product candidates, or if we need to perform more or larger clinical trials than planned. Additionally, changes in regulatory requirements and policies may occur, and we may need to amend clinical trial protocols to reflect these changes. Amendments may require us to resubmit our clinical trial protocols to IRBs for reexamination, which may impact the costs, timing or successful completion of a clinical trial. If we experience delays in completion of our clinical trials, or if we, the FDA or other regulatory authorities, the IRB, other reviewing entities, or any of our clinical trial sites suspend or terminate any of our clinical trials, the commercial prospects for a product candidate may be harmed and our ability to generate product revenue will be delayed. In addition, many of the factors that cause, or lead to, termination or suspension of, or a delay in the commencement or completion of, clinical trials may also ultimately lead to the denial of regulatory approval of a product candidate. If we make manufacturing or formulation changes to our product candidates, we may need to conduct additional studies to bridge our modified product candidates to earlier versions. Further, if one or more clinical trials are delayed, our competitors may be able to bring products to market before we do, and the commercial viability of our product candidates could be significantly reduced.

If we do not achieve our projected development goals in the time frames we announce and expect, the commercialization of our products may be delayed and, as a result, our stock price may decline.

From time to time, we estimate the timing of the accomplishment of various scientific, clinical, regulatory and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of, or the availability of data from, scientific studies and clinical trials and the submission of regulatory filings. From time to time, we may publicly announce the expected timing of some of these milestones. All of these milestones will be based on a variety of assumptions. The actual timing of these milestones can vary dramatically compared to our estimates, in some cases for reasons beyond our control. If we do not meet these milestones as publicly announced, the commercialization of our products may be delayed and, as a result, our stock price may decline.

Final marketing approval for our product candidates by the FDA or other regulatory authorities for commercial use may be delayed, limited or denied, any of which would adversely affect our ability to generate operating revenue.

After the completion of our clinical trials and, assuming the results of the trials are successful, the submission of a BLA, we cannot predict whether or when we will obtain regulatory approval to commercialize our product candidates, and we cannot, therefore, predict the timing of any future revenue. We cannot commercialize our product candidates until the appropriate regulatory authorities have reviewed and approved the applicable applications. We cannot assure you that the regulatory agencies will complete their review processes in a timely manner or that we will obtain regulatory approval for our product candidates. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action or changes in FDA policy during the period of product development, clinical trials and FDA regulatory review. If marketing approval for any product candidate is delayed, limited or denied, our ability to market the product candidate, and our ability to generate product sales, would be adversely affected.

Even if we obtain marketing approval for any of our product candidates, they could be subject to restrictions or withdrawal from the market, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our product candidates, when and if any of them are approved.

Even if U.S. regulatory approval is obtained, the FDA may still impose significant restrictions on a product's indicated uses, marketing or distribution or impose ongoing requirements for potentially costly and time consuming post-approval studies, post-market surveillance or clinical trials. Following approval, if at all, of any of our product candidates, such candidate will also be subject to ongoing FDA requirements governing the labeling, packaging, storage, distribution, safety surveillance, advertising, promotion, recordkeeping and reporting of safety and other post-market information. In addition, manufacturers of drug products and their facilities are subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP requirements relating to quality control, quality assurance and corresponding maintenance of records and documents. If we or a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions on that product, the manufacturing facility or us, including requesting recall or withdrawal of the product from the market or suspension of manufacturing.

If we or the manufacturing facilities for any product candidate that may receive regulatory approval fail to comply with applicable regulatory requirements, a regulatory agency may:

- issue warning letters or untitled letters;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve pending applications or supplements or applications filed by us;
- suspend or impose restrictions on operations, including costly new manufacturing requirements; or
- seize or detain products, refuse to permit the import or export of product or request us to initiate a product recall.

The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and generate revenue. The FDA has the authority to require a risk evaluation and mitigation strategy plan as part of a BLA or after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug, such as limiting prescribing to certain physicians or medical centers that have undergone specialized training, limiting treatment to patients who meet certain safe-use criteria and requiring treated patients to enroll in a registry.

In addition, if any of our product candidates is approved, our product labeling, advertising and promotion would be subject to regulatory requirements and continuing regulatory review. The FDA strictly regulates the promotional claims that may be made about prescription products. In particular, a product may not be promoted for uses that are not approved by the FDA as reflected in the product's approved labeling. If we receive marketing approval for a product candidate, physicians may nevertheless prescribe it to their patients in a manner that is inconsistent with the approved label. If we are found to have promoted such off-label uses, we may become subject to significant liability. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant sanctions. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

Even if we receive regulatory approval we still may not be able to successfully commercialize any of our product candidates, and the revenue that we generate from its sales, if any, could be limited.

Even if any of our product candidates receive regulatory approval, they may not gain market acceptance among physicians, patients, healthcare payers or the medical community. Coverage and reimbursement of our product candidates by third-party payers, including government payers, is also generally necessary for commercial success. The degree of market acceptance of our product candidates will depend on a number of factors, including:

- demonstration of clinical efficacy and safety compared to other more-established products;
- the limitation of our targeted patient population and other limitations or warnings contained in any FDA-approved labeling;
- acceptance of new therapeutic options by health care providers and their patients;
- the prevalence and severity of any adverse effects;
- new procedures or methods of treatment that may be more effective in treating or may reduce the incidences of wAMD, A1AT deficiency, HAE or other conditions for which our products are intended to treat;
- pricing and cost-effectiveness;
- the effectiveness of our or any future collaborators' sales and marketing strategies;
- our ability to obtain and maintain sufficient third-party coverage and reimbursement from government health care programs, including Medicare and Medicaid, private health insurers and other third-party payers;
- unfavorable publicity relating to the product candidate; and
- the willingness of patients to pay out-of-pocket in the absence of third-party coverage and reimbursement.

If any product candidate is approved but does not achieve an adequate level of acceptance by physicians, hospitals, healthcare payers or patients, we may not generate sufficient revenue from that product candidate and may not become or remain profitable. Our efforts to educate the medical community and third-party payers on the benefits of such a product candidate may require significant resources and may never be successful. In addition, our ability to successfully commercialize any of our product candidates will depend on our ability to manufacture our products, differentiate our products from competing products and defend and enforce our intellectual property rights relating to our products.

If the market for the treatment of wAMD is smaller than we believe it is, our future revenue may be adversely affected, and our business may suffer.

We are advancing the development of ADVM-022 for the treatment of wAMD, a disease we believe to be the most common cause of vision loss in adults over the age of 50 in developed countries. If the size of the market for wAMD is smaller than we anticipate, we may not be able to achieve profitability and growth. Our projections of the number of people who have wAMD, as well as the subset of people with these diseases who have the potential to benefit from treatment with wAMD, are based on estimates. These estimates have been derived from a variety of sources, including the scientific literature, surveys of clinics, patient foundations and market research and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower than expected. The effort to identify patients with diseases we seek to treat is in early stages, and we cannot accurately predict the number of patients for whom treatment might be possible. Additionally, the potentially addressable patient population may be limited or may not be amenable to treatment with our product candidates, and new patients may become increasingly difficult to identify or gain access to, which would adversely affect our results of operations and our business.

Because the target patient populations of ADVM-043 and ADVM-053 are relatively small, we must be able to successfully identify patients and achieve a significant market share to maintain profitability and growth. If the market opportunities for these product candidates are smaller than we believe they are, our future revenue may be adversely affected, and our business may suffer.

ADVM-043 and ADVM-053 are designed to treat rare genetic and orphan diseases. ADVM-043 is designed to treat A1AT deficiency, which impacts approximately 100,000 individuals in the U.S. ADVM-053 is designed to treat HAE, which impacts approximately 8,000 individuals in the U.S. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with these product candidates, are based on estimates. These estimates may prove to be incorrect and new studies may change the estimated incidence or prevalence of these diseases. The number of patients in the U.S., Europe and elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with these 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. Further, even if we obtain significant market share for our product candidates, because the potential target populations are very small, we may never achieve profitability despite obtaining such significant market share.

Additionally, because the target patient populations for these product candidates are relatively small, the pricing and reimbursement of these product candidates, if approved, must be adequate to support commercial infrastructure. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell these product candidates will be adversely affected. The manner and level at which reimbursement is provided for services related to these product candidates (e.g., for administration of such product to patients) is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell these products.

We may be unable to obtain orphan drug designation or exclusivity for ADVM-043, ADVM-053 or certain of our other product candidates. If our competitors are able to obtain orphan drug exclusivity for products that constitute the same drug and treat the same indications as our product candidates, we may not be able to have competing products approved by the applicable regulatory authority for a significant period of time.

Regulatory authorities in some jurisdictions, including the U.S. and the European Union, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is defined under the Food, Drug and Cosmetic Act as having a patient population of fewer than 200,000 individuals in the U.S., or a patient population greater than 200,000 in the U.S. where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the U.S. In the European Union, following the opinion of the EMA's Committee for Orphan Medicinal Products, the European Commission grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the European Union. Additionally, orphan designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biologic product.

Generally, if a product candidate with an orphan drug designation receives the first marketing 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 European Commission from approving another marketing application for a product that constitutes the same drug treating the same indication for that

marketing exclusivity period, except in limited circumstances. If another sponsor receives such approval before we do (regardless of our orphan drug designation), we will be precluded from receiving marketing approval for our product for the applicable exclusivity period. The applicable period is seven years in the U.S. and 10 years in the European Union. The exclusivity period in the U.S. can be extended by six months if the BLA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The exclusivity period in the European Union can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be revoked if any regulatory agency 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.

If we request orphan drug designation for ADVM-043, ADVM-053 or any of our other product candidates that we believe could qualify, there can be no assurances that the FDA or the European Commission will grant any of our product candidates such designation. Additionally, the designation of any of our product candidates as an orphan product does not guarantee that any regulatory agency will accelerate regulatory review of, or ultimately approve, that product candidate, nor does it limit the ability of any regulatory agency to grant orphan drug designation to product candidates of other companies that treat the same indications as our product candidates prior to our product candidates receiving exclusive marketing approval.

Even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs can be approved for the same condition. In the U.S., even after an orphan drug is approved, the FDA may subsequently approve another drug for the same condition if the FDA concludes that the latter drug is not the same drug as the first or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care as compared to the first. In the European Union, marketing authorization may be granted to a similar medicinal product for the same orphan indication if:

- the second applicant can establish in its application that its medicinal product, although similar to the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior;
- the holder of the marketing authorization for the original orphan medicinal product consents to a second orphan medicinal product application; or
- the holder of the marketing authorization for the original orphan medicinal product cannot supply sufficient quantities of orphan medicinal product.

Coverage and reimbursement may be limited or unavailable in certain market segments for our product candidates, which could make it difficult for us to sell our product candidates profitably.

Market acceptance and sales of our product candidates will depend significantly on the availability of adequate coverage and reimbursement from third-party payers for any of our product candidates and may be affected by existing and future health care reform measures. Government authorities and third-party payers, such as private health insurers and health maintenance organizations, decide which drugs they will pay for and establish reimbursement levels. Reimbursement by a third-party payer may depend upon a number of factors including the third-party payer's determination that use of a product candidate is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;

- cost-effective; and
- neither experimental nor investigational.

Obtaining coverage and reimbursement approval for a product candidate from a government or other third-party payer is a time-consuming and costly process that could require us to provide supporting scientific, clinical and cost effectiveness data for the use of the applicable product candidate to the payer. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. While there is no uniform coverage and reimbursement policy among payers in the United States, private payers often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. We cannot be sure that coverage or adequate reimbursement will be available for any of our product candidates. Further, reimbursement amounts may reduce the demand for, or the price of, our product candidates. If reimbursement is not available or is available only in limited levels, we may not be able to commercialize certain of our product candidates profitably, or at all, even if approved.

A number of gene therapy products have been approved over the past year by the FDA. Although the U.S. Center for Medicare & Medicaid Services (CMS) subsequently approved its first method of coverage and reimbursement for one such product, the methodology has been subject to challenge by members of Congress. CMS's decision as to coverage and reimbursement for one product does not mean that all similar products will be eligible for analogous coverage and reimbursement. As there is no uniform policy for coverage and reimbursement amongst third-party payors in the United States, even if CMS approves coverage and reimbursement for any of our product candidates, it is unclear what affect, if any, such a decision will have on our ability to obtain and maintain coverage and adequate reimbursement from other private payors.

As a result of legislative proposals and the trend toward managed health care in the U.S., third-party payers are increasingly attempting to contain health care costs by limiting both coverage and the level of reimbursement of new drugs. By way of example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively referred to as the Affordable Care Act, was enacted with a goal of reducing the cost of healthcare and substantially changing the way healthcare is financed by both government and private insurers. The Affordable Care Act, among other things, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program, extended the rebate program to individuals enrolled in Medicaid managed care organizations and established annual fees and taxes on manufacturers of certain prescription drugs.

Some of the provisions of the Affordable Care Act have yet to be implemented, and there have been judicial and Congressional challenges to certain aspects of the Affordable Care Act. Since January 2017, President Trump has signed two Executive Orders and other directives designed to delay, circumvent or loosen the implementation of certain provisions requirements mandated by the Affordable Care Act or otherwise circumvent some of the requirements for health insurance mandated by the Affordable Care Act. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the Affordable Care Act. While Congress has not passed repeal legislation, the Tax Cuts and Jobs Act of 2017 includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." Additionally, on January 23, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain Affordable Care Act-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers

based on market share, and the medical device excise tax on non-exempt medical devices. Congress may consider other legislation to repeal or replace elements of the Affordable Care Act.

Other legislative changes have also been proposed and adopted in the U.S. since the Affordable Care Act was enacted. On August 2, 2011, the Budget Control Act of 2011 created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This included aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013 and will stay in effect through 2024 unless additional Congressional action is taken.

These cost reduction initiatives could decrease the coverage and reimbursement that we receive for any approved products, and could seriously harm our business. We expect that additional healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal, state and foreign governments will pay for healthcare products and services, which could result in reduced demand for our products, if approved, or additional pricing pressures.

Recently there has been heightened governmental scrutiny over pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent Congressional inquiries and proposed and enacted federal legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. At the federal level, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

The continuing efforts of the government, insurance companies, managed care organizations and other payers of healthcare services to contain or reduce costs of health care may adversely affect:

- the demand for any product candidates for which we may obtain regulatory approval;
- our ability to set a price that we believe is fair for our product candidates;
- 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.

Due to the novel nature of our technology and the potential for our product candidates to offer therapeutic benefit in a single administration, we face uncertainty related to pricing and reimbursement for these product candidates.

Our product candidates are designed to provide potential therapeutic benefit after a single administration and, therefore, the pricing and reimbursement of our product candidates, if approved, must be adequate to support commercial infrastructure. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell our product candidates will be adversely affected. The manner and level at which reimbursement is provided for services related to our product candidates (e.g., for administration of our product to patients) is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell our products.

We are subject to many manufacturing risks, any of which could substantially increase our costs and limit supply of our products.

The process of manufacturing our products is complex, highly regulated and subject to several risks, including:

- The manufacturing of biologics is extremely susceptible to product loss due to contamination, equipment failure, improper installation or operation of equipment or vendor or operator error. Even minor deviations from normal manufacturing processes could result in reduced production yields, product defects and other supply disruptions. If microbial, viral or other contaminations are discovered in our products or in the manufacturing facility in which our products are made, such manufacturing facility may need to be closed for an extended period of time to investigate and remedy the contamination.
- The manufacturing facilities in which our products are made could be adversely affected by equipment failures, labor shortages, contaminants, raw materials shortages, natural disasters, power failures and numerous other factors.
- We and our contract manufacturers must comply with the FDA's cGMP regulations and guidelines. We and our contract manufacturers may encounter difficulties in achieving quality control and quality assurance and may experience shortages in qualified personnel. We and our contract manufacturers are subject to inspections by the FDA and comparable agencies in other jurisdictions to confirm compliance with applicable regulatory requirements. Any failure to follow cGMP or other regulatory requirements or any delay, interruption or other issues that arise in the manufacture, fill-finish, packaging or storage of our products as a result of a failure of our facilities or the facilities or operations of third parties to comply with regulatory requirements or pass any regulatory authority inspection could significantly impair our ability to develop and commercialize our products. This may lead to significant delays in the availability of products for our clinical trials or the termination or hold on a clinical trial, or the delay or prevention of a filing or approval of marketing applications for our product candidates. Significant noncompliance could also result in the imposition of sanctions, including fines, injunctions, civil penalties, failure of regulatory authorities to grant marketing approvals for our product candidates, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of products, operating restrictions and criminal prosecutions, any of which could be costly and damage our reputation. If we are not able to maintain regulatory compliance, we may not be permitted to market our products and/or may be subject to product recalls, seizures, injunctions or criminal prosecution.
- Our product candidates are biologics and require processing steps that are more complex than those required for most chemical pharmaceuticals. Moreover, unlike chemical pharmaceuticals, the physical and chemical properties of a biologic such as our product candidates generally cannot be adequately characterized prior to manufacturing the final product. As a result, an assay of the finished product is not sufficient to ensure that the product will perform in the intended manner. Accordingly, we expect to employ multiple steps to attempt to control our manufacturing process to assure that the process works and the product or product candidate is made strictly and consistently in compliance with the process.
- Problems with the manufacturing process, even minor deviations from the normal process, could result in product defects or manufacturing failures that result in lot failures, product recalls, product liability claims and insufficient inventory.
- Some of the raw materials required in our manufacturing process are derived from biological sources. Such raw materials are difficult to procure and may also be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our product candidates could adversely impact or disrupt commercialization.
- Any adverse developments affecting manufacturing operations for our products may result in shipment delays, inventory shortages, lot failures, product withdrawals or recalls, or other

interruptions in the supply of our products. We may also have to take inventory write-offs and incur other charges and expenses for products that fail to meet specifications, undertake costly remediation efforts or seek more costly manufacturing alternatives. We may encounter problems achieving adequate or clinical-grade materials that meet FDA, EMA or other applicable standards or specifications with consistent and acceptable production yields and costs.

We may not be successful in establishing and maintaining development or other strategic collaborations, which could adversely affect our ability to develop and commercialize product candidates and receive potential milestone payments.

We have entered into development or other strategic collaborations with major biotechnology or pharmaceutical companies. For example, our research collaboration and license agreement with Regeneron, which was announced in May 2014, covers up to eight distinct therapeutic targets, in which we could earn up to $80.0 million in development and regulatory milestones for product candidates directed toward each therapeutic target, for a combined total of up to $640.0 million in potential milestone payments for product candidates directed toward all eight therapeutic targets, and low- to mid-single digit royalties on worldwide net sales of collaboration product candidates. For any two therapeutic targets, we have an option to share up to 35% of the worldwide product candidate development costs and profits. Additionally, in August 2016, we entered into a collaboration, option and license agreement with Editas Medicine, pursuant to which we and Editas will collaborate on certain studies using AAV vectors in connection with Editas' genome editing technology and we will grant to Editas an exclusive option to obtain certain exclusive rights to use our proprietary vectors in up to five ophthalmic indications. If Editas elects to develop a product using certain of our proprietary vectors, we will be eligible to receive up to $5.5 million in development milestone payments and $10.0 million in commercialization milestone payments for such product, and tiered royalties between the mid-single digits and low teens on net sales of such product, subject to certain adjustments.

Research activities under our collaboration agreements are subject to mutually agreed-on research plans and budgets, and if we and our strategic partners are unable to agree on the research plan or research budget in a timely fashion or at all, performance of research activities will be delayed. In addition, some of our strategic partners may terminate any agreements they enter into with us or allow such agreements to expire by their terms. Furthermore, our strategic partners have negotiated for certain rights to control decisions regarding the development and commercialization of our product candidates, if approved, and may not conduct those activities in the same manner as we do.

Moreover, if we fail to maintain development or other strategic collaborations related to our product candidates that we may choose to enter into:

- the development of certain of our current or future product candidates may be terminated or delayed;
- our cash expenditures related to development of certain of our current or future product candidates would increase significantly, and we may need to seek additional financing;
- we may be required to hire additional employees or otherwise develop expertise, such as sales and marketing expertise, for which we have not budgeted; and
- we will bear all of the risk related to the development of any such product candidates.

We may form strategic alliances in the future, and we may not realize the benefits of such alliances.

We may form strategic alliances, create joint ventures or collaborations or enter into licensing arrangements with third parties that we believe will complement or augment our existing business, including for the continued development or commercialization of our product candidates. These relationships or those like them may require us to incur non-recurring and other charges, increase our

near- and long-term expenditures, issue securities that dilute our existing stockholders or disrupt our management and business. In addition, we face significant competition in seeking appropriate strategic partners and the negotiation process is time-consuming and complex. Moreover, we may not be successful in our efforts to establish a strategic partnership or other alternative arrangements for our product candidates because third parties may view the risk of failure in future clinical trials as too significant or the commercial opportunity for our product candidate as too limited. We cannot be certain that, following a strategic transaction or license, we will achieve the revenue or specific net income that justifies such transaction. Even if we are successful in our efforts to establish development partnerships, the terms that we agree upon may not be favorable to us, and we may not be able to maintain such development partnerships if, for example, development or approval of a product candidate is delayed or sales of an approved product candidate are disappointing. Any delay in entering into development partnership agreements related to our product candidates could delay the development and commercialization of our product candidates and reduce their competitiveness if they reach the market.

If our competitors develop treatments for the target indications of our product candidates that are approved more quickly than ours, marketed more successfully or demonstrated to be safer or more effective than our product candidates, our commercial opportunity will be reduced or eliminated.

We operate in highly competitive segments of the biopharmaceutical markets. We face competition from many different sources, including larger and better-funded pharmaceutical, specialty pharmaceutical and biotechnology companies, as well as from academic institutions, government agencies and private and public research institutions. Our product candidates, if successfully developed and approved, will compete with established therapies as well as with new treatments that may be introduced by our competitors. There are a variety of drug candidates in development or being commercialized by our competitors for the indications that we intend to test. Many of our competitors have significantly greater financial, product candidate development, manufacturing and marketing resources than we do. Large pharmaceutical and biotechnology companies have extensive experience in clinical testing and obtaining regulatory approval for drugs. In addition, universities and private and public research institutes may be active in our target disease areas, and some could be in direct competition with us. We also may compete with these organizations to recruit management, scientists and clinical development personnel. We will also face competition from these third parties in establishing clinical trial sites, registering subjects for clinical trials and in identifying and in-licensing new product candidates. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

New developments, including the development of other pharmaceutical technologies and methods of treating disease, occur in the pharmaceutical and life sciences industries at a rapid pace. Developments by competitors may render our product candidates obsolete or noncompetitive. Competition in drug development is intense. We anticipate that we will face intense and increasing competition as new treatments enter the market and advanced technologies become available.

Even if we obtain regulatory approval for our product candidates, the availability and price of our competitors' products could limit the demand, and the price we are able to charge, for our product candidates. For example, EYLEA is currently available in the U.S. for treatment of wAMD and macular edema following central retinal vein occlusion (CRVO), and in the United Kingdom, Germany, Switzerland, Australia, Japan and certain other countries for the treatment of wAMD. Additionally, marketing approval has been obtained in the EU for EYLEA for the treatment of visual impairment due to macular edema secondary to CRVO. We will not achieve our business plan if the acceptance of our product candidates is inhibited by price competition or the reluctance of physicians to switch from existing methods of treatment to our product candidates, or if physicians switch to other new drug products or choose to reserve our product candidates for use in limited circumstances. Our inability to

compete with existing or subsequently introduced drug products would have a material adverse impact on our business, prospects, financial condition and results of operations.

Our potential competitors in these diseases may be developing novel immune modulating therapies that may be safer or more effective than our product candidates, including ADVM-022. For example, if we continue clinical development of, and seek to commercialize, ADVM-022, it will compete with a variety of therapies currently marketed and in development for wAMD, using therapeutic modalities such as biologics, small molecules and gene therapy. Lucentis, EYLEA and Avastin are anti-VEGF therapies that are well established and widely accepted by physicians, patients and third-party payers as the standard of care for the treatment of wAMD. There are several other companies with marketed products or products in development for the treatment of wAMD, including Alcon, Allergan, Allegro Ophthalmics, LLC, Apellis Pharmaceuticals, Applied Genetic Technologies Corporation, Bayer, Hoffmann-La Roche Ltd., Iconic Therapeutics, Inc., Neurotech Pharmaceuticals, Inc., Novartis, Ocular Therapeutix, Inc., Ohr Pharmaceuticals, Inc., Ophthotech Corporation, Opthea Ltd., PanOptica Pharma, Genentech, SciFluor Life Science, LLC, Regeneron Pharmaceuticals, Inc., REGENXBIO Biosciences LLC, and Valeant Pharmaceuticals North America LLC.

For the treatment of A1AT deficiency and HAE, we know of a number of products currently in development that aim to reduce the frequency of injection, improve the route of administration, and deliver better efficacy compared to the standard-of-care treatments available today. There are several companies with products for A1AT deficiency in clinical development, including Applied Genetic Technologies Corporation and Kamada Ltd. For the treatment of HAE, there are several companies with products in clinical development, including CSL Behring, Biocryst Pharmaceuticals Inc., Ionis Pharmaceuticals, Inc., and Shire.

We have no sales, marketing or distribution capabilities, and we may have to invest significant resources to develop these capabilities.

We have no internal sales, marketing or distribution capabilities. If any of our product candidates ultimately receive regulatory approval, we may not be able to effectively market and distribute the product candidate. We may have to invest significant amounts of financial and management resources to develop internal sales, distribution and marketing capabilities, some of which will be committed prior to any confirmation that any of our product candidates will be approved, if at all. We may not be able to hire consultants or external service providers to assist us in sales, marketing and distribution functions on acceptable financial terms or at all. Even if we determine to perform sales, marketing and distribution functions ourselves, we could face a number of additional related risks, including:

- we may not be able to attract and build an effective marketing department or sales force;
- the cost of establishing a marketing department or sales force may exceed our available financial resources and the revenue generated by any product candidates that we may develop, in-license or acquire; and
- our direct sales and marketing efforts may not be successful.

Governments may impose price controls, which may adversely affect our future profitability.

We intend to seek approval to market our product candidates in both the U.S. and in foreign jurisdictions. If we obtain approval in one or more foreign jurisdictions, we will be subject to rules and regulations in those jurisdictions relating to our product candidates. In some foreign countries, particularly in the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product candidate. If reimbursement of our future products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, we may be unable to achieve or sustain profitability.

Risks Related to Our Business Operations

Negative public opinion and increased regulatory scrutiny of gene therapy and genetic research may damage public perception of our product candidates or adversely affect our ability to conduct our business or obtain marketing approvals for our product candidates.

Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. In particular, our success will depend upon physicians specializing in the treatment of those diseases that our product candidates target prescribing treatments that involve the use of our product candidates in lieu of, or in addition to, existing symptomatic treatments they are already familiar with and for which greater clinical data may be available.

More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop. For example, in 2003, trials using early versions of murine gamma-retroviral vectors, which integrate with, and thereby alter, the host cell's DNA, have led to several well-publicized adverse events, including reported cases of leukemia. Although none of our current product candidates utilize murine gamma-retroviral vectors, our product candidates use a viral delivery system. Adverse events in our clinical trials, even if not ultimately attributable to our product candidates, and the resulting publicity could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates. Although none of our current product candidates utilize the gamma-retroviruses used in the 2003 studies, our product candidates do use a viral vector delivery system. The risk of cancer remains a concern for gene therapy and we cannot assure that it will not occur in any of our future clinical trials. In addition, there is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biological activity of the genetic material or other components of products used to carry the genetic material.

Adverse events in our clinical trials or those conducted by other parties, even if not ultimately attributable to our product candidates, and the resulting publicity could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our potential product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates. If any such adverse events occur, development and commercialization of our product candidates or advancement of any potential clinical trials could be halted or delayed, which would have a material adverse effect on our business and operations.

We are dependent on the services of our key executives and scientific staff, and if we are not able to retain these members of our management or recruit additional management, clinical and scientific personnel, our business will suffer.

We are dependent on the principal members of our management and scientific staff. The loss of service of any of our management could harm our business. In addition, we are dependent on our continued ability to attract, retain and motivate highly qualified additional management, clinical and scientific personnel. If we are not able to retain our management, and to attract, on acceptable terms, additional qualified personnel necessary for the continued development of our business, we may not be able to sustain our operations or grow. Although we have executed employment agreements with each member of our current executive management team, these agreements are terminable at will with or without notice and, therefore, we may not be able to retain their services as expected.

We will need to expand and effectively manage our managerial, operational, financial, and other resources in order to successfully pursue our development and commercialization efforts. Our success

also depends on our continued ability to attract, retain and motivate highly qualified management and scientific personnel. We may not be able to attract or retain qualified management and scientific and clinical personnel in the future due to the intense competition for qualified personnel among biotechnology, pharmaceutical and other businesses, particularly in the San Francisco Bay Area. Our industry has experienced a high rate of turnover of management and scientific personnel in recent years. If we are not able to attract, retain and motivate necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our development objectives, our ability to raise additional capital and our ability to implement our business strategy.

Additionally, we do not currently maintain "key person" life insurance on the lives of our executives or any of our employees. This lack of insurance means that we may not have adequate compensation for the loss of the services of these individuals.

We may encounter difficulties in managing our growth and expanding our operations successfully.

We had 74 full-time employees as of January 31, 2018. We will need to grow our organization, or certain functions within our organization, substantially to continue development and pursue the potential commercialization of our product candidates, as well as function as a public company. As we seek to advance our product candidates, we may need to expand our financial, development, regulatory, manufacturing, marketing and sales capabilities or contract with third parties to provide these capabilities for us. As our operations expand, we expect that we will need to manage additional relationships with various strategic partners, suppliers and other third parties. Future growth will impose significant added responsibilities on members of management and require us to retain or otherwise manage additional internal capabilities. Our future financial performance and our ability to commercialize our product candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to manage our development efforts and clinical trials effectively and hire, train and integrate any additional management, clinical and regulatory, financial, administrative and sales and marketing personnel. We may not be able to accomplish these tasks, and our failure to so accomplish could prevent us from successfully growing our company.

If we fail to comply with applicable state and federal healthcare laws, we may be subject to civil or criminal penalties and/or exclusion from federal and/or healthcare programs.

In addition to FDA restrictions on the marketing of pharmaceutical products, several other types of state and federal healthcare fraud and abuse laws have been applied in recent years to restrict certain marketing practices in the pharmaceutical industry. These laws include anti-kickback, false claims, physician payment transparency and privacy and security laws and regulations. Because of the breadth of these laws and the narrowness of the safe harbors, it is possible that some of our business activities could be subject to challenge under one or more of these laws.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce, or in return for, purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. Remuneration has been broadly defined to include anything of value, including cash, improper discounts, and free or reduced price items and services. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formula managers on the other. Although there are several statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution, the exemptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchasing or recommending may

be subject to scrutiny if they do not qualify for an exemption or safe harbor. Many states have similar laws that apply to their state health care programs as well as private payers.

The federal Health Insurance Portability and Accountability Act of 1996 (HIPAA) created new federal criminal statutes that prohibit among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payers, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. The Affordable Care Act, among other things, amended the intent requirement of the federal Anti-Kickback Statute and certain criminal statute governing healthcare fraud statutes. A person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it. In addition, the Affordable Care Act provided that 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 False Claims Act.

Additionally, federal false claims laws and the civil monetary penalty law, including the False Claims Act, prohibits knowingly presenting or causing the presentation of a false, fictitious or fraudulent claim for payment to the U.S. government. Actions under the False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Violations of the False Claims Act can result in significant monetary penalties and treble damages. The federal government is using the False Claims Act, and the accompanying threat of significant liability, in its investigation and prosecution of pharmaceutical and biotechnology companies throughout the country, for example, in connection with the promotion of products for unapproved uses and other sales and marketing practices. The government has obtained multi-million and multi-billion dollar settlements under the False Claims Act in addition to individual criminal convictions under applicable criminal statutes. Given the significant size of actual and potential settlements, it is expected that the government will continue to devote substantial resources to investigating healthcare providers' and manufacturers' compliance with applicable fraud and abuse laws.

In addition, there has been a recent trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The Affordable Care Act, among other things, imposes new reporting requirements on drug manufacturers, under the federal Physician Payments Sunshine Act, for payments made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in civil monetary penalties of up to an aggregate of $0.2 million per year (or up to an aggregate of $1.0 million per year for "knowing failures"), for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. Certain states also mandate implementation of commercial compliance programs, impose restrictions on drug manufacturer marketing practices and/or require the tracking and reporting of gifts, compensation and other remuneration to physicians.

In the course of conducting our business, we may also obtain individually identifiable patient health information including retinal scans from subjects participating in our clinical trials. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 (HITECH), imposes, among other things, certain standards relating to the privacy, security, transmission and breach reporting of individually identifiable health information, upon certain health plans, healthcare clearinghouses and healthcare providers, and their respective business associates that perform services for them involving individually identifiable health information. In the event we are subject to HIPAA, and fail to properly maintain the privacy and security of certain individually identifiable health information, or we are responsible for an inadvertent disclosure or security breach of such individually

identifiable health information, we could be subject to enforcement measures, including civil and criminal penalties and fines for violations of state and federal privacy or security standards, such as HIPAA and HITECH, and their respective implementing regulations. Additionally, certain states have adopted comparable privacy and security laws and regulations, some of which may be more stringent than HIPAA. HIPAA, HITECH and comparable state 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. Any liability from failure to comply with the requirements of these laws, to the extent such requirements are deemed to apply to our operations, could adversely affect our financial condition. The costs of complying with privacy and security related legal and regulatory requirements are burdensome and could have a material adverse effect on our results of operations.

The need to build and maintain a robust compliance program with different compliance and/or reporting requirements increases the possibility that a healthcare company may violate one or more of the requirements. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs, imprisonment, and additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, any of which could adversely affect our ability to operate our business and our financial results.

We and our development partners, third-party manufacturer and suppliers use biological materials and may use hazardous materials, and any claims relating to improper handling, storage or disposal of these materials could be time consuming or costly.

We and our development partners, third-party manufacturer and suppliers may use hazardous materials, including chemicals and biological agents and compounds that could be dangerous to human health and safety or the environment. Our operations and the operations of our third-party manufacturers and suppliers also produce hazardous waste products. Federal, state and local laws and regulations govern the use, generation, manufacture, storage, handling and disposal of these materials and wastes. Compliance with applicable environmental laws and regulations may be expensive, and current or future environmental laws and regulations may impair our product development efforts. In addition, we cannot entirely eliminate the risk of accidental injury or contamination from these materials or wastes. We do not carry specific biological or hazardous waste insurance coverage, and our property, casualty and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or contamination. Accordingly, in the event of contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our other product candidates.

We face an inherent risk of product liability as a result of the clinical testing of our product candidates and will face an even greater risk if we commercialize our product candidates. For example, we may be sued if our product candidates allegedly caused or cause injury or are found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. 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 candidate, negligence, strict liability, and a breach of warranties. 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 or cease the commercialization of our product candidates.

Even a successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our product candidates;
- 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;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- the inability to commercialize our product candidates; and
- a decline in our stock price.

We currently hold $5 million in product liability insurance, which may not adequately cover all liabilities that we may incur. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of our product candidates. Although we plan to maintain such insurance, 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 will also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We may 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 capital to pay such amounts.

We and any of our future development partners will be required to report to regulatory authorities if any of our approved products cause or contribute to adverse medical events, and any failure to do so would result in sanctions that would materially harm our business.

If we and any of our future development partners or CROs are successful in commercializing our products, the FDA and foreign regulatory authorities would require that we and any of our future development partners report certain information about adverse medical events if those products may have caused or contributed to those adverse events. The timing of our obligation to report would be triggered by the date we become aware of the adverse event as well as the nature of the event. We and any of our future development partners may fail to report adverse events we become aware of within the prescribed timeframe. We and any of our future development partners may also fail to appreciate that we have become aware of a reportable adverse event, especially if it is not reported to us as an adverse event or if it is an adverse event that is unexpected or removed in time from the use of our products. If we and any of our future development partners fail to comply with our or their reporting obligations, the FDA or a foreign regulatory authority could take action, including criminal prosecution, the imposition of civil monetary penalties, and seizure of our products or delay in approval or clearance of future products.

Our internal computer systems, or those of our development partners, CROs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

In the ordinary course of our business, we, our CROs, and other third parties on which we rely collect and store sensitive data, including legally protected patient health information, personally identifiable information about our employees, intellectual property, and proprietary business

information. We manage and maintain our applications and data utilizing on-site systems. These applications and data encompass a wide variety of business critical information including research and development information and business and financial information.

The secure processing, storage, maintenance, and transmission of this critical information is vital to our operations and business strategy, and we devote significant resources to protecting such information. Despite the implementation of security measures to protect against unauthorized access or disclosure, our internal computer systems and those of our current and any future CROs and other contractors, consultants and collaborators are vulnerable to damage or attacks from computer viruses, unauthorized access, breaches, interruptions due to employee error, malfeasance or other disruptions, lapses in compliance with privacy and security mandates, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced any such material system failure, accident or security breach to date, any such event could compromise our networks and the information stored there could be accessed by unauthorized parties, publicly disclosed, lost or stolen. We have measures in place that are designed to detect and respond to such security incidents and breaches of privacy and security mandates. Any such access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, such as the HIPAA, government enforcement actions and regulatory penalties. Unauthorized access, loss or dissemination could also disrupt our operations, including our ability to conduct research and development activities, process and prepare company financial information, manage various general and administrative aspects of our business and damage our reputation, any of which could adversely affect our business. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Likewise, we rely on third parties to manufacture our product candidates and conduct clinical trials, and similar events relating to their computer systems could also have a material adverse effect on our business. In addition, there can be no assurance that we will promptly detect any such disruption or security breach, if at all. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development and commercialization of our product candidate could be delayed.

Business disruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or manmade disasters or business interruptions, for which we are predominantly self-insured. We rely on third-party manufacturers to produce our product candidates. Our ability to obtain clinical supplies of our product candidates could be disrupted if the operations of these suppliers are affected by a man-made or natural disaster or other business interruption. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses.

Our employees, independent contractors, principal investigators, CROs, consultants and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk that our employees, independent contractors, principal investigators, CROs, consultants and vendors may engage in fraudulent conduct or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violates: (1) FDA regulations, including those laws requiring the reporting of true, complete and accurate information to regulatory authorities, (2) manufacturing standards, (3) federal and state health care fraud and abuse laws and regulations or (4) laws that

require the reporting of financial information or data accurately. Specifically, sales, marketing, and business arrangements in the health care industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Activities subject to these laws also involve improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and 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. 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, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, 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.

Risks Relating to Our Intellectual Property

Our rights to develop and commercialize our product candidates are subject in part to the terms and conditions of licenses granted to us by other companies and universities.

We currently are heavily reliant upon licenses of certain patent rights and proprietary technology from third parties that are important or necessary to the development of our technology and products, including technology related to our manufacturing process and our gene therapy product candidates. These and other licenses may not provide adequate rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and products in the future. For example, the license granted to us by the Regents of the University of California (Regents) to make, develop and commercialize products covered by certain patent rights licensed to us under our agreement with the Regents is limited to the U.S. The license is also limited to the Regents' interest in the licensed patent rights which are co-owned by Chiron Corporation (Chiron), which was acquired by Novartis AG. As a result, we may not be able to prevent competitors from developing and commercializing competitive products in territories not included in our licenses to patents.

Licenses to additional third-party technology that may be required for our development programs may not be available in the future or may not be available on commercially reasonable terms, which could have a material adverse effect on our business and financial condition.

In some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties. In addition, we must obtain consent from the Regents before we can enforce patent rights licensed to us by the Regents. While such consent may not be unreasonably withheld, the Regents may withhold such consent or may not provide it on a timely basis. Therefore, we cannot be certain that these patents and applications will be prosecuted and enforced in a manner consistent with the best interests of our business. In addition, if third parties who license patents to us fail to maintain such patents, or lose rights to those patents, the rights we have licensed may be reduced or eliminated.

The patent rights subject to our exclusive license with the Regents are jointly owned by Chiron.

We currently have a license to the Regents' undivided interest in certain patent rights relating to the use of recombinant gene delivery vectors for treating or preventing diseases of the eye. The

licensed patent rights are jointly owned by the Regents and Chiron but our license extends only the Regents' interest in such patent rights. As a result, Chiron has a right to develop and commercialize products and technology using these patent rights, and to license to third parties the right to do so. This may lead to the development and commercialization of products and technology by others that are based on technology similar to our gene therapy platform, which may impair our competitive position in the marketplace and have an adverse impact on our business.

Joint ownership of these patent rights may also limit our ability to effectively enforce our rights in these patents against alleged infringers. First, Chiron may be required to participate in any potential suit against such third-party infringers but may not agree to do so. Additionally, Chiron may choose to license its interest in these patent rights to any such infringers without our consent in certain countries. Further, Chiron's joint ownership may limit the Regents' ability to prosecute related patent rights in foreign jurisdictions without the cooperation of Chiron. As a result, our business may be adversely impaired.

Our success depends on our ability to protect our intellectual property and our proprietary technologies.

Our commercial success depends in part on our ability to obtain and maintain patent protection and trade secret protection for our product candidates, proprietary technologies, and their uses as well as our ability to operate without infringing upon the proprietary rights of others. There can be no assurance that our patent applications or those of our licensors will result in additional patents being issued or that issued patents will afford sufficient protection against competitors with similar technology, nor is there any assurance that the patents issued will not be infringed, designed around or invalidated by third parties. Even issued patents may later be found unenforceable or may be modified or revoked in proceedings instituted by third parties before various patent offices or in courts. The degree of future protection for our proprietary rights is uncertain. Only limited protection may be available and may not adequately protect our rights or permit us to gain or keep any competitive advantage. This failure to properly protect the intellectual property rights relating to our product candidates could have a material adverse effect on our financial condition and results of operations.

Composition-of-matter patents on the biological or chemical active pharmaceutical ingredient are generally considered to be the strongest form of intellectual property protection for pharmaceutical products, as such patents provide protection without regard to any method of use. We cannot be certain that the claims in our patent applications covering composition-of-matter of any of our product candidates will be considered patentable by the U.S. Patent and Trademark Office (USPTO) and courts in the U.S. or by the patent offices and courts in foreign countries, nor can we be certain that the claims in our issued composition-of-matter patents will not be found invalid or unenforceable if challenged.

Method-of-use patents protect the use of a product for the specified method or for treatment of a particular indication. However, methods of treating human diseases are considered unpatentable in many jurisdictions, and even where available 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 or prosecute.

The patent application process is subject to numerous risks and uncertainties, and there can be no assurance that we or any of our future development partners will be successful in protecting our

product candidates by obtaining and defending patents. These risks and uncertainties include the following:

- the USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process. There are situations in which noncompliance can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case;
- patent applications may not result in any patents being issued;
- patents that may be issued or in-licensed may be challenged, invalidated, modified, revoked, circumvented, found to be unenforceable or otherwise may not provide any competitive advantage;
- our competitors, many of whom have substantially greater resources than we do and many of whom have made significant investments in competing technologies, may seek or may have already obtained patents that will limit, interfere with or eliminate our ability to make, use, and sell our potential product candidates;
- 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 U.S. for disease treatments that prove successful, as a matter of public policy regarding worldwide health concerns; and
- countries other than the U.S. may have patent laws less favorable to patentees than those upheld by the U.S. courts, allowing foreign competitors a better opportunity to create, develop and market competing product candidates.

In addition, we rely on the protection of our trade secrets and proprietary know-how. Although we have taken steps to protect our trade secrets and unpatented know-how, including entering into confidentiality agreements with third parties, and confidential information and inventions agreements with employees, consultants and advisors, we cannot provide any assurances that all such agreements have been duly executed, and third parties may still obtain this information or may come upon this or similar information independently.

Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating our trade secrets. If any of these events occurs or if we otherwise lose protection for our trade secrets or proprietary know-how, the value of this information may be greatly reduced.

Claims by third parties that we infringe their proprietary rights may result in liability for damages or prevent or delay our developmental and commercialization efforts.

The biotechnology industry has been characterized by frequent litigation regarding patent and other intellectual property rights. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are developing product candidates. As the biotechnology industry expands and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties. Because patent applications are maintained in secrecy until the application is published, we may be unaware of third party patents that may be infringed by commercialization of our product candidates. Moreover, because patent applications can take many years to issue, there may be currently-pending patent applications that may later result in issued patents that our product candidates may infringe. In addition, identification of third party patent rights that may be relevant to our technology is difficult because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty in assessing the meaning of patent claims. Any claims of patent infringement asserted by third parties would be time consuming and could:

- result in costly litigation;

- divert the time and attention of our technical personnel and management;
- cause development delays;
- prevent us from commercializing our product candidates until the asserted patent expires or is held finally invalid or not infringed in a court of law;
- require us to develop non-infringing technology, which may not be possible on a cost-effective basis; or
- require us to enter into royalty or licensing agreements, which may not be available on commercially reasonable terms, or at all.

Although no third party has asserted a claim of patent infringement against us as of the date of this prospectus supplement, others may hold proprietary rights that could prevent our product candidates from being marketed. Any patent-related legal action against us claiming damages and seeking to enjoin commercial activities relating to our product candidate or processes could subject us to potential liability for damages and require us to obtain a license to continue to manufacture or market our product candidates. We cannot predict whether we would prevail in any such actions or that any license required under any of these patents would be made available on commercially acceptable terms, if at all. In addition, we cannot be sure that we could redesign our product candidate or processes to avoid infringement, if necessary. Accordingly, an adverse determination in a judicial or administrative proceeding, or the failure to obtain necessary licenses, could prevent us from developing and commercializing our product candidates, which could harm our business, financial condition and operating results.

The patent protection and patent prosecution for some of our product candidates may be dependent on third parties.

While we normally seek to obtain the right to control the prosecution and maintenance of the patents relating to our product candidates, there may be times when the filing and prosecution activities for platform technology patents that relate to our product candidates are controlled by our licensors. For example, we do not have the right to prosecute and maintain the patent rights licensed to us under agreements with each of the Regents, Cornell University, and Virovek Corporation, and our ability to have input into such filing and prosecution activities is limited. If these licensors or any of our future licensors fail to appropriately prosecute and maintain patent protection for patents covering any of our product candidates or companion diagnostic, our ability to develop and commercialize those product candidates and companion diagnostic may be adversely affected and we may not be able to prevent competitors from making, using and selling competing products.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming, and unsuccessful. Further, our issued patents could be found invalid or unenforceable if challenged administratively or in court.

If we or any of our future development partners were to initiate legal proceedings against a third party to enforce a patent directed at one of our product candidates, or one of our future product candidates, the defendant could counterclaim that our patent is invalid and/or unenforceable in whole or in part. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge include an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could include an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO or made a misleading statement during prosecution. Third parties may also raise similar claims before the USPTO, even outside the context of litigation. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we

would lose at least part, and perhaps all, of the patent protection on such product candidate. Such a loss of patent protection would have a material adverse impact on our business.

Interference proceedings provoked by third parties or brought by us or declared by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our research and development programs, license necessary technology from third parties, or enter into development or manufacturing partnerships that would help us bring our product candidates to market.

Even if resolved in our favor, litigation or other legal proceedings relating to our intellectual property rights 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 conduct such litigation or proceedings adequately. 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. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could compromise our ability to compete in the marketplace.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions, or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

On September 16, 2011, the Leahy-Smith America Invents Act (Leahy-Smith Act), was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. In particular, under the Leahy-Smith Act, the U.S. transitioned in March 2013 to a “first to file” system in which the first inventor to file a patent application will be entitled to the patent. Third parties are allowed to submit prior art before the issuance of a patent by the USPTO, and we may become involved in post-grant proceedings including opposition, derivation, reexamination, *inter partes* review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope or enforceability of, or invalidate, our patent rights, which could adversely affect our competitive position.

We may not be successful in obtaining or maintaining necessary rights to our product candidates through acquisitions and in-licenses.

We currently have rights to intellectual property, through licenses from third parties and under patents that we own, to develop our product candidates. Because our programs may require the use of

proprietary rights held by third parties, the growth of our business will likely depend in part on our ability to acquire, in-license, or use these proprietary rights. For example, our product candidates may require specific formulations to work effectively and efficiently and the rights to these formulations may be held by others. We may be unable to acquire or in-license any compositions, methods of use, processes, or other third-party intellectual property rights from third parties that we identify as necessary for our product candidates. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources, and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment.

We sometimes collaborate with U.S. and foreign academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of that program and our business and financial condition could suffer.

We may fail to comply with any of our obligations under existing agreements pursuant to which we license or have otherwise acquired intellectual property rights or technology, which could result in the loss of rights or technology that are material to our business.

Licensing of intellectual property is of critical importance to our business and involves complex legal, business, and scientific issues. Disputes may arise regarding our rights to intellectual property licensed to us from a third party, including but not limited to:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the ownership of inventions and know-how resulting from the creation or use of intellectual property by us, alone or with our licensors and collaborators;
- the scope and duration of our payment obligations;
- our rights upon termination of such agreement; and
- the scope and duration of exclusivity obligations of each party to the agreement.

If disputes over intellectual property and other rights that we have licensed or acquired from third parties prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

We may be subject to claims that we have wrongfully hired an employee from a competitor or that we or our employees have wrongfully used or disclosed alleged confidential information or trade secrets of their former employers.

As is common in the biotechnology and pharmaceutical industry, in addition to our employees, we engage the services of consultants to assist us in the development of our product candidates. Many of our employees and consultants were previously employed at, or may have previously provided or may be currently providing consulting services to, other biotechnology or pharmaceutical companies including our competitors or potential competitors. We may become subject to claims that our company, our employees or a consultant inadvertently or otherwise used or disclosed trade secrets or other information proprietary to their former employers or their former or current clients. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could adversely impact our business. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to our management team.

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

We may also be subject to claims that former employees, collaborators or other third parties have an ownership interest in our patents or other intellectual property. We may be subject to ownership disputes in the future arising, for example, from conflicting obligations of consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

If we do not obtain patent term extension and data exclusivity for our product candidates, our business may be materially harmed.

Depending upon the timing, duration and specifics of FDA marketing approval of our product candidates, one or more of our U.S. patents may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act). The Hatch-Waxman Act permits a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, we may not be granted an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or restoration or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.

Our registered or unregistered trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over the long term, if we are

unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely impact our financial condition or results of operations.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involve a high degree of technological and legal complexity. Therefore, obtaining and enforcing biopharmaceutical patents is costly, time consuming and inherently uncertain. In addition, Congress may pass patent reform legislation that is unfavorable to us. The Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening 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 U.S. 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 we might obtain in the future.

We may not be able to protect our intellectual property rights throughout the world.

While we have issued patents directed at our lead products and pending patent applications directed at our product candidates in the U.S. and other countries, filing, prosecuting and defending patents on our other product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the U.S. can be less extensive than those in the U.S. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the U.S. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the U.S., or from selling or importing products made using our inventions in and into the U.S. or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection but enforcement is not as strong as that in the U.S. These products may compete with our product candidates, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to biopharmaceuticals, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. 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 patents at risk of being invalidated or interpreted narrowly and 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 or license.

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. For example:

- others may be able to make gene therapies that are similar to our product candidates but that are not covered by the claims of the patents that we own or have exclusively licensed;
- we or our licensors or future collaborators might not have been the first to make the inventions covered by the issued patent or pending patent application that we own or have exclusively licensed;
- we or our licensors or future collaborators might not have been the first to file patent applications covering certain of our inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- it is possible that our pending patent applications will not lead to issued patents;
- issued patents that we own or have exclusively licensed may be held invalid or unenforceable, 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, prospects, financial condition and results of operations.

Known third party patent rights could delay or otherwise adversely affect our planned development and sale of several of our lead programs.

We are aware of patent rights held by third parties that could be construed to cover certain aspects of our lead product candidates. A patent holder has the right to prevent others from making, using, or selling a drug that incorporates the patented compositions while the patent remains in force. While we believe that third party patent rights will not affect our planned development, regulatory clearance, and eventual marketing, commercial production, and sale of our product candidates, there can be no assurance that this will be the case. In each case, the relevant patent expires before we expect to commercially introduce such product candidate. In addition, the Hatch-Waxman exemption to U.S. patent law permits all uses of compounds in clinical trials and for other purposes reasonably related to obtaining FDA clearance of drugs that will be sold only after patent expiration, so our use of our product candidates in those FDA-related activities does not infringe any patent holder's rights. However, were a patent holder to assert its rights against us before expiration of such patent holder's patent for activities unrelated to FDA clearance, the development and ultimate sale of our lead product candidates could be significantly delayed, and we could incur the expense of defending a patent infringement suit and potential liability for damages for periods prior to the patent's expiration.

Risks Related to Our Common Stock

If we fail to maintain proper and effective internal control over financial reporting in the future, our ability to prepare accurate and timely consolidated financial statements being prepared in accordance with U.S. generally accepted accounting principles (U.S. GAAP) could be impaired, which could harm our operating results, investors' views of us and, as a result, the value of our common stock.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002 (Sarbanes-Oxley), our management is required to report upon the effectiveness of our internal control over financial reporting. When we lose our status as an "emerging growth company", unless we have become a smaller reporting company, our independent registered public accounting firm will also be required to attest to the effectiveness of our internal control over financial reporting, and the related report will also be required to be included in our annual reports filed with the SEC. However, for so long as we remain an emerging growth company, we intend to take advantage of an exemption available to companies meeting these criteria from these auditor attestation requirements. Sarbanes-Oxley Section 404 compliance requirements are complex and require significant documentation, testing, and possible remediation. If we (or our auditors if they are required to assess and attest to the effectiveness of our internal control over financial reporting) are unable to conclude that our internal control over financial reporting is effective, investors may lose confidence in our financial reporting, and the trading price of our common stock may decline.

Although we have determined that our internal control over financial reporting was effective as of December 31, 2016, we cannot assure you that there will not be material weaknesses in our internal control over financial reporting in the future. Any failure to maintain internal control over financial reporting could severely inhibit our ability to accurately report our financial condition, results of operations or cash flows. If we are unable to conclude that our internal control over financial reporting is effective, or if our independent registered public accounting firm determines we have a material weakness in our internal control over financial reporting, we could lose investor confidence in the accuracy and completeness of our financial reports, the market price of our common stock could decline, and we could be subject to sanctions or investigations by The Nasdaq Stock Market, the SEC or other regulatory authorities. Failure to implement and maintain effective internal control over financial reporting, including failure to remediate any material weaknesses we or our auditors identify, could also restrict our future access to the capital markets.

The trading price of the shares of our common stock has been and could continue to be highly volatile, and purchasers of our common stock could incur substantial losses.

Our stock price has been and is likely to continue to be volatile. The stock market in general and the market for biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. The market price for our common stock may be influenced by many factors, including those discussed above and others such as:

- our plans regarding further development of ADVM-043, ADVM-053, or ADVM-022;
- our ability to enroll patients in any clinical trials that we plan in the future;
- our ability to obtain regulatory approvals for our product candidates and delays or failure to obtain such approvals;
- results of any clinical trials, and the results of trials of our competitors or those of other companies in our market sector;
- regulatory developments in the U.S. and foreign countries;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems, especially in light of current reforms to the U.S. healthcare system;

- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures or capital commitments;
- failure to maintain our existing third party license and collaboration agreements;
- delays in manufacturing adequate supply of our product candidates;
- adverse publicity relating to the gene therapy market generally, including with respect to other products and potential products in such markets;
- market conditions in the pharmaceutical and biotechnology sectors and issuance of securities analysts' reports or recommendations;
- sales of our stock by insiders and stockholders;
- trading volume of our common stock;
- general economic, industry and market conditions other events or factors, many of which are beyond our control;
- additions or departures of key personnel; and
- intellectual property, product liability or other litigation against us.

In addition, in the past, stockholders have initiated class action lawsuits against biotechnology and pharmaceutical companies following periods of volatility in the market prices of these companies' stock, and similar litigation has been instituted against us. Such litigation could cause us to incur substantial costs and divert management's attention and resources, which could have a material adverse effect on our business, financial condition and results of operations.

We and certain of our former officers have been named defendants in purported securities class action lawsuits. These, and any additional securities litigation, could result in substantial losses and may divert management's time and attention from our business.

On June 15, 2015, we announced the top-line results of our Phase 2a clinical trial for AVA-101. In July 2015, three purported securities class action lawsuits were commenced in the U.S. District Court for the Northern District of California, naming as defendants us and certain of our former officers. These lawsuits assert that the defendants violated the Securities Exchange Act of 1934, as amended (Exchange Act), and the Securities Act of 1933, as amended (Securities Act), and allege that the defendants made materially false and misleading statements and omitted allegedly material information related to, among other things, the Phase 2a clinical trial for AVA-101 and the prospects of AVA-101. The plaintiffs seek unspecified damages, attorneys' fees and other costs, each on behalf of a purported class of persons and entities who purchased or otherwise acquired our publicly traded securities between July 31, 2014 and June 15, 2015. It is possible that additional suits will be filed with respect to these same matters and also naming us and/or our officers and directors as defendants.

In addition, in December 2015, a putative securities class action lawsuit was filed against us, our board of directors, underwriters of our January 13, 2015, follow-on public stock offering, and two of our institutional stockholders, in the Superior Court of the State of California for the County of San Mateo. The complaint alleges that, in connection with our follow-on stock offering, the defendants violated the Securities Act by allegedly making materially false and misleading statements and by allegedly omitting material information related to the Phase 2a clinical trial for AVA-101 and the prospects of AVA-101. The complaint seeks unspecified compensatory and rescissory damages, attorneys' fees and other costs.

In March 2017, we reached an agreement to settle the asserted actions. The proposed aggregate amount of the settlement is $13 million, of which $1 million would be contributed by us to cover our indemnification obligations to the underwriters, and the remainder would be contributed by our insurers. Notice of the settlement was provided to stockholders in the fall of 2017, and no stockholder objected to the settlement. In January 2018, the San Mateo Superior Court entered a judgment and

order finally approving the settlement and, in February 2018, the U.S. District Court dismissed the consolidated federal action with prejudice. If the settlement does not become effective and litigation resumes, following an appeal or otherwise, adverse outcomes in the actions could result in substantial damages. We and the defendants have denied and continue to deny each and all of the claims alleged in the actions, and the settlement does not assign or reflect any admission of fault, wrongdoing or liability as to any defendant. If final court approval is not obtained with respect to the settlement or the settlement otherwise does not become effective and litigation resumes, adverse outcomes in the actions could result in substantial damages.

The current securities litigation and any future litigation of this type could result in diversion of management's attention and resources, which could adversely impact our business. Monitoring and defending against legal actions is time-consuming for our management and detracts from our ability to focus fully on our business activities.

Our quarterly operating results may fluctuate significantly.

We expect our operating results to be subject to quarterly fluctuations. Our net loss and other operating results will be affected by numerous factors, including:

- variations in the level of expenses related to our clinical trial and development programs;
- addition or termination of clinical trials;
- any intellectual property infringement lawsuit in which we may become involved;
- regulatory developments affecting our product candidates;
- our execution of any collaborative, licensing or similar arrangements and the timing of payments we may make or receive under these arrangements;
- nature and terms of stock-based compensation grants; and
- derivative instruments recorded at fair value.

If our quarterly operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially.

If we sell shares of our common stock or securities convertible into or exercisable for shares of our common stock in future financings, licensing or collaboration arrangements, or acquisitions, or additional shares under our at-the-market sales agreement, stockholders may experience immediate dilution and, as a result, our stock price may decline.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, licensing, collaboration or similar arrangements, grants and debt financings. We do not have any committed external source of funds. As a result, we may from time to time issue additional shares of common stock or securities convertible into or exercisable for shares of our common stock. We filed a universal shelf registration statement on Form S-3 with the SEC, which was declared effective on August 22, 2017, pursuant to which we registered for sale up to $150 million of any combination of our common stock, preferred stock, debt securities, warrants, and/or units from time to time and at prices and on terms that we may determine, including up to $50 million of our common stock available for issuance pursuant to our sales agreement with Cowen. Pursuant to the sales agreement, we may offer and sell, from time to time at our discretion, shares of our common stock having an aggregate offering price of up to $50 million through Cowen as our sales agent. Under the sales agreement, Cowen may sell the shares by any method permitted by law deemed to be an "at the market" offering as defined in Rule 415 of the Securities Act. We may seek to raise additional capital at any time. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will

be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a holder of our common stock. Debt 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 or other distributions. Furthermore, we may issue common stock as consideration in acquisitions. For example, in May 2016, we issued 14,087,246 shares of our common stock to Annapurna's shareholders as consideration for all of the outstanding shares of Annapurna. If we issue common stock or securities convertible into common stock, our common stockholders would experience additional dilution and, as a result, our stock price may decline.

If we raise additional funds through licensing, collaboration or similar arrangements, we may have to relinquish valuable rights to our technologies, future revenue streams, research and development programs or product candidates or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or other arrangements 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 product candidates that we would otherwise prefer to develop and market ourselves.

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.

Provisions in our amended and restated certificate of incorporation and amended and restated bylaws may delay or prevent an acquisition of us or a change in our management. These provisions include:

- the authorization of the issuance of "blank check" preferred stock, the terms of which may be established and shares of which may be issued without stockholder approval;
- the limitation of the removal of directors by the stockholders;
- a staggered board of directors;
- the prohibition of stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders;
- the elimination of the ability of stockholders to call a special meeting of stockholders;
- the ability of our board of directors to accelerate the vesting of outstanding option grants, restricted stock units or other equity awards upon certain transactions that result in a change of control; and
- the establishment of advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted upon at stockholder meetings.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us. Although we believe these provisions collectively provide for an opportunity to obtain greater value for stockholders by requiring potential acquirers to negotiate with our board of directors, they would apply even if an offer rejected by our board were considered beneficial by some stockholders. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors, which is responsible for appointing the members of our management.

We do not intend to pay dividends on our common stock, and, consequently, your ability to achieve a return on your investment will depend on appreciation, if any, in the price of our common stock.

We have never declared or paid any cash dividend on our common stock and do not currently intend to do so for the foreseeable future. We currently anticipate that we will retain future earnings for

the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock. Therefore, the success of an investment in shares of our common stock will depend upon any future appreciation in their value. There is no guarantee that shares of our common stock will appreciate in value or even maintain the price at which our stockholders have purchased their shares.

We are an emerging growth company, and the reduced reporting requirements applicable to emerging growth companies may make our common stock less attractive to investors.

We are an emerging growth company, as defined in the JOBS Act. For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404 of Sarbanes-Oxley, reduced disclosure obligations regarding executive compensation and our periodic reports and proxy statements and exemptions from the requirements of holding nonbinding advisory votes on executive compensation and stockholder approval of any golden parachute payments not previously approved. We could be an emerging growth company until the last day of the fiscal year 2019, although circumstances could cause us to lose that status earlier, including if we become a large accelerated filer (in which case we will cease to be an emerging company as of the date we become a large accelerated filer, which, generally, would occur if, at the end of a fiscal year, among other things, the market value of our common stock that is held by non-affiliates exceeds $700 million as of the last business day of our most recently completed second fiscal quarter), if we have total annual gross revenue of $1.0 billion or more during any fiscal year (in which cases we would no longer be an emerging growth company as of December 31 of such fiscal year), or if we issue more than $1.0 billion in non-convertible debt during any three year period before that time (in which case we would cease to be an emerging growth company immediately). 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 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 Sarbanes-Oxley and reduced disclosure obligations regarding executive compensation and 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.

We have incurred and will continue to incur significant increased costs as a result of operating as a public company, and our management devotes substantial time to new compliance initiatives.

As a public company, we have incurred and will continue to incur significant legal, accounting and other expenses. We are subject to the reporting requirements of the Exchange Act, which require, among other things, that we file with the SEC annual, quarterly and current reports with respect to our business and financial condition. In addition, Sarbanes-Oxley, as well as rules adopted by the SEC and The Nasdaq Global Market that implement provisions of Sarbanes-Oxley, impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. Further, pursuant to the Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010, the SEC adopted additional rules and regulations in these areas, such as mandatory “say on pay” voting requirements that will apply to us when we cease to be an emerging growth company. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate.

The rules and regulations applicable to public companies have substantially increased our legal and financial compliance costs and make some activities more time-consuming and costly. To the extent these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition and results of operations. The increased costs will decrease our net income or increase our net loss, and may require us to reduce costs in other areas of our business or increase the prices of our products or services. For example, we expect these rules and regulations to make it more difficult and more expensive for us to obtain director and officer liability insurance, and we may be required to incur substantial costs to maintain the same or similar coverage. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers.

If securities or industry analysts do not publish research or reports or publish unfavorable research or reports about our business, our stock price and trading volume could decline.

The trading market for our common stock will depend in part on the research and reports that securities or industry analysts publish about us, our business, our market or our competitors. If one or more of the analysts who covers us downgrades our stock, our stock price would likely decline. If one or more of these analysts ceases to cover us or fails to regularly publish reports on us, interest in our stock could decrease, which could cause our stock price or trading volume to decline.

The recently passed comprehensive tax reform bill could adversely affect our business and financial condition.

On December 22, 2017, President Trump signed into law new legislation that significantly revises the Internal Revenue Code of 1986, as amended (the Code). The newly enacted federal income tax law, among other things, contains significant changes to corporate taxation, including adoption of a flat 21% corporate tax rate, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction of net operating losses generated in tax years beginning after December 31, 2017 to 80% of current year taxable income and elimination of carrybacks of such net operating losses, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, current inclusion in U.S. federal taxable income of certain earnings of controlled foreign corporations, immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits (including reducing the business tax credit for certain clinical testing expenses incurred in the testing of certain drugs for rare diseases or conditions generally referred to as “orphan drugs”). Notwithstanding the reduction in the corporate income tax rate, the overall impact of the new federal tax law is uncertain, and our business and financial condition could be adversely affected. In addition, it is uncertain if and to what extent various states will conform to the newly enacted federal tax law. The impact of this tax reform on holders of our common stock is also uncertain and could be adverse. Investors should consult with their legal and tax advisors with respect to this legislation and the potential tax consequences of investing in or holding our common stock.

Our ability to use net operating loss carryforwards and other tax attributes may be limited by the Code.

We have incurred substantial losses during our history and do not expect to become profitable in the near future and we may never achieve profitability. To the extent that we continue to generate taxable losses, unused losses will carry forward to offset future taxable income, if any, until such unused losses expire. As of December 31, 2016, we had U.S. federal net operating loss (NOL) carryforwards of approximately $22.0 million to offset future federal income. NOLs expire at various years beginning with 2036. As of December 31, 2016, we also had U.S. state NOL carryforwards of approximately $6.7 million to offset future state income. U.S. State NOLs expire at various years beginning with 2036. At December 31, 2016, we also had approximately $25.6 million of foreign net

operating loss carryforwards which may be available to offset future foreign income; these carryforwards do not expire.

Under the newly enacted federal income tax law, federal NOLs incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such federal net operating NOLs is limited. It is uncertain if and to what extent various states will conform to the newly enacted federal tax law. In addition, under Section 382 of the Code, our ability to utilize NOL carryforwards or other tax attributes, such as research tax credits, in any taxable year may be limited if we experience an "ownership change." Generally, a Section 382 ownership change occurs if there is a cumulative increase of more than 50 percentage points in the stock ownership of one or more stockholders or groups of stockholders who owns at least 5% of a corporation's stock within a specified testing period. Similar rules may apply under state tax laws. In connection with our acquisition of Annapurna in May 2016, we determined that certain NOLs for both federal and state purposes were severely limited and therefore we removed a significant amount of NOLs from our deferred tax assets. In addition, we may experience ownership changes as a result of this offering, future offerings or other changes in the ownership of our stock. As a result, the amount of the NOLs and research and credit carryforwards presented in our financial statements could be limited and may expire unutilized.

Risks Related to this Offering

Management will have broad discretion as to the use of the proceeds from this offering, and we may not use the proceeds effectively.

Our management will have broad discretion in the application of the net proceeds from this offering, and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. Our failure to apply these funds effectively could have a material adverse effect on our business and cause the price of our common stock to decline.

If you purchase shares of common stock in this offering, you will experience immediate dilution in your investment. You will experience further dilution if we issue additional equity securities in future fundraising transactions.

Purchasers of common stock in this offering will pay a price per share in this offering that exceeds the net tangible book value per share of our common stock. If you purchase shares of our common stock in this offering, you will experience immediate dilution of $ per share, representing the difference between the public offering price and our as adjusted net tangible book value per share as of September 30, 2017, after giving effect to this offering. See the section entitled "Dilution" below for a more detailed illustration of the dilution you would incur if you purchase common stock in this offering.

In addition, we have a significant number of stock options, warrants and restricted stock units outstanding. To the extent that stock options or warrants have been or may be exercised, restricted stock units vest, or other shares are issued, you may experience further dilution.

You may experience further dilution if we issue additional equity securities in future fundraising transactions.

To raise additional capital, we may in the future offer additional shares of our common stock or other securities convertible into or exchangeable for our common stock at prices that may not be the same as the price per share in this offering. We may sell shares or other securities in any other offering at a price per share that is less than the price per share paid by investors in this offering, and investors purchasing shares or other securities in the future could have rights superior to existing stockholders. The price per share at which we sell additional shares of our common stock, or securities convertible or exchangeable into common stock, in future transactions may be higher or lower than the price per share paid by investors in this offering. Further, the exercise of outstanding stock options and warrants and vesting of restricted stock units may result in further dilution of your investment.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

Some of the statements in this prospectus supplement, the accompanying prospectus, the documents incorporated by reference and any free writing prospectus that we have authorized for use in connection with this offering are forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. These statements are based on our current expectations, assumptions, estimates and projections about our business and our industry and involve known and unknown risks, uncertainties and other factors that may cause our company's or our industry's results, levels of activity, performance or achievements to be materially different from any future results, levels of activity, performance or achievements expressed or implied in, or contemplated by, the forward-looking statements. Forward-looking statements may include, but are not limited to, statements about:

- the initiation, progress, timing, costs and results of preclinical studies and any clinical trials for our product candidates;
- our ability to further improve our process development capabilities and viral vector technology;
- the timing or likelihood of regulatory filings and approvals;
- our plans to explore potential applications of our gene therapy platform in other indications in ophthalmology and rare diseases;
- our expectations regarding the clinical effectiveness and safety and tolerability of our product candidates;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the pricing and reimbursement of our product candidates, if approved;
- our expectation regarding the potential market sizes for our product candidates;
- our intellectual property position;
- the potential benefits of our strategic collaborations, our plans with respect to our strategic collaborations and our plans with respect to and our ability to enter into strategic arrangements;
- developments and projections relating to our competitors and our industry;
- our expectations regarding the time during which we will be an "emerging growth company" under the JOBS Act;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- the use of proceeds from this offering; and
- the safety, efficacy and projected development timeline and commercial potential of any product candidates.

In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "could," "would," "expects," "plans," "anticipates," "believes," "estimates," "projects," "predicts," "potential" and similar expressions intended to identify forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and are subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss in greater detail many of these risks under the heading "Risk Factors" contained in this prospectus supplement and in any free writing prospectuses we may authorize for use in connection with this offering. Also, these forward-looking statements represent our estimates and assumptions only as of the date of the document containing the applicable statement. Unless required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments. Thus, you should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements. You should read this prospectus supplement and accompanying prospectus

together with the documents we have filed with the SEC that are incorporated by reference and any free writing prospectus that we may authorize for use in connection with this offering completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in the foregoing documents by these cautionary statements.

In addition, statements that “we believe” and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this prospectus supplement, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and investors are cautioned not to unduly rely upon these statements.

USE OF PROCEEDS

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

We will retain broad discretion over the use of the net proceeds from this offering. We currently intend to use the net proceeds from this offering to advance the clinical and preclinical development of our pipeline of gene therapy candidates for the treatment of rare and ocular diseases and for capital expenditures, working capital and general corporate purposes. We may also use a portion of the net proceeds to begin the initial stage of investing in a manufacturing facility to build on our internal process development capabilities. We currently expect the net proceeds from this offering, together with our existing cash, cash equivalents and short-term investments, to fund our planned operations through the end of 2019 and to enable us to receive preliminary clinical data from at least two of our lead programs.

Our expected use of the net proceeds from this offering represents our current intentions based upon our present plans and business conditions. The amounts and timing of our actual use of net proceeds will vary depending on numerous factors. As a result, our management will have broad discretion in the application of the net proceeds, and investors will be relying on our judgment regarding the application of the net proceeds of this offering. In addition, we might decide to postpone or not pursue our planned development activities if the net proceeds of this offering and our other sources of cash are less than, or do not last as long as, expected.

Pending their use, we plan to invest the net proceeds from this offering in short- and intermediate-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government.

DILUTION

Our net tangible book value as of September 30, 2017, was approximately $176.0 million, or $4.04 per share. Net tangible book value per share is determined by dividing our total tangible assets, less total liabilities, by the number of shares of our common stock outstanding as of September 30, 2017. Dilution with respect to net tangible book value per share represents the difference between the amount per share paid by purchasers of shares of common stock in this offering, and the net tangible book value per share of our common stock immediately after this offering.

After giving effect to the sale of the shares of our common stock at the public offering price of $ per share and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our net tangible book value as of September 30, 2017, would have been $ million, or $ per share of common stock. This represents an immediate increase in the net tangible book value of $ per share to our existing stockholders and an immediate dilution in net tangible book value of $ per share to new investors. The following table illustrates this dilution on a per share basis:

Public offering price per share		$
Net tangible book value per share as of September 30, 2017	$4.04	
Increase in net tangible book value per share attributable to investors purchasing our common stock in this offering		
As adjusted net tangible book value per share after this offering		
Dilution per share to investors purchasing our common stock in this offering		$

The foregoing discussion and table do not take into account further dilution to new investors that could occur upon the exercise of the underwriters' option to purchase up to an additional shares within 30 days of the date of this prospectus supplement or the exercise of other outstanding options and warrants having a per share exercise price less than the public offering price per share in this offering. If the underwriters exercise in full their option to purchase additional shares, our net tangible book value on September 30, 2017, after giving effect to this offering, would have been approximately $ million, or approximately $ per share, representing an immediate dilution of $ per share to new investors purchasing shares of common stock in this offering.

The number of shares of common stock to be outstanding after the offering is based on the number of shares outstanding as of September 30, 2017. As of that date, we had 43,517,412 shares of common stock outstanding, excluding:

- 7,370,289 shares of common stock underlying options outstanding as of September 30, 2017, at a weighted average exercise price of $4.52 per share;
- 90,000 shares of common stock underlying warrants outstanding as of September 30, 2017, at a weighted average exercise price of $6.77 per share;
- 2,468,176 shares of common stock issuable upon the vesting of restricted stock units outstanding as of September 30, 2017; and
- 2,632,691 shares of common stock available for future grant under our equity incentive plans as of September 30, 2017.

For information regarding shares outstanding at December 31, 2017, and issued in 2018 under our sales agreement with Cowen and under our equity plans, see "Prospectus Supplement Summary—Preliminary Financial Data" beginning on page S-4.

In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe that we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

CAPITALIZATION

The following table sets forth our cash, cash equivalents and short-term investments and capitalization as of September 30, 2017:

- on an actual basis; and
- on an as adjusted basis to reflect the sale by us of shares of our common stock in this offering at $ per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

You should read the data set forth in the table below in conjunction with our financial statements, including the related notes, and "Management's Discussion and Analysis of Financial Condition and Results of Operations" from our Quarterly Report on Form 10-Q for the fiscal quarter ended September 30, 2017, which are incorporated by reference into this prospectus supplement.

	As of September 30, 2017	
	Actual	As Adjusted
	(unaudited) (in thousands, except share data)	
Cash, cash equivalents and short-term investments	$ 186,642	$
Stockholders' equity:		
Preferred stock, $0.0001 par value; 5,000,000 shares authorized, no shares issued and outstanding, actual and as adjusted	–	–
Common stock, $0.0001 par value; 300,000,000 shares authorized, 43,517,412 shares issued and outstanding, actual; shares issued and outstanding as adjusted	5	
Additional paid-in capital	420,811	
Accumulated other comprehensive loss	(551)	(551)
Accumulated deficit	(239,273)	(239,273)
Total stockholders' equity	180,992	
Total capitalization	$ 180,992	$

The number of shares of common stock to be outstanding after the offering is based on the number of shares outstanding as of September 30, 2017. As of that date, we had 43,517,412 shares of common stock outstanding, excluding:

- 7,370,289 shares of common stock underlying options outstanding as of September 30, 2017, at a weighted average exercise price of $4.52 per share;
- 90,000 shares of common stock underlying warrants outstanding as of September 30, 2017, at a weighted average exercise price of $6.77 per share;
- 2,468,176 shares of common stock issuable upon the vesting of restricted stock units outstanding as of September 30, 2017; and
- 2,632,691 shares of common stock available for future grant under our equity incentive plans as of September 30, 2017.

For information regarding shares outstanding at December 31, 2017, and issued in 2018 under our sales agreement with Cowen and under our equity plans, see "Prospectus Supplement Summary—Preliminary Financial Data" beginning on page S-4.

MATERIAL U.S. FEDERAL INCOME TAX CONSIDERATIONS FOR NON-U.S. HOLDERS

The following summary describes the material U.S. federal income tax consequences of the acquisition, ownership and disposition of our common stock acquired in this offering by Non-U.S. Holders (as defined below). This discussion is not a complete analysis of all potential U.S. federal income tax consequences relating thereto, and does not deal with foreign, state and local consequences that may be relevant to Non-U.S. Holders in light of their particular circumstances, nor does it address U.S. federal tax consequences (such as gift and estate taxes) other than income taxes. Special rules different from those described below may apply to certain Non-U.S. Holders that are subject to special treatment under the Internal Revenue Code of 1986, as amended (the Code), such as financial institutions, insurance companies, tax-exempt organizations, broker-dealers and traders in securities, U.S. expatriates, "controlled foreign corporations," "passive foreign investment companies," corporations that accumulate earnings to avoid U.S. federal income tax, corporations organized outside of the United States, any state thereof or the District of Columbia that are nonetheless treated as United States income taxpayers for United States federal tax purposes, persons that hold our common stock as part of a "straddle," "hedge," "conversion transaction," "synthetic security" or integrated investment or other risk reduction strategy, persons who acquire our common stock through the exercise of an option or otherwise as compensation, persons subject to the alternative minimum tax or federal Medicare contribution tax on net investment income, partnerships and other pass-through entities or arrangements, and investors in such pass-through entities or arrangements. Such Non-U.S. Holders are urged to consult their own tax advisors to determine the U.S. federal, state, local and other tax consequences that may be relevant to them. Furthermore, the discussion below is based upon the provisions of the Code, and Treasury regulations, rulings and judicial decisions thereunder as of the date hereof, and such authorities may be repealed, revoked or modified, perhaps retroactively, so as to result in U.S. federal income tax consequences different from those discussed below. We have not requested a ruling from the U.S. Internal Revenue Service (IRS) with respect to the statements made and the conclusions reached in the following summary, and there can be no assurance that the IRS will agree with such statements and conclusions. This discussion assumes that the Non-U.S. Holder holds our common stock as a "capital asset" within the meaning of Section 1221 of the Code (generally, property held for investment).

Persons considering the purchase of our common stock pursuant to this offering should consult their own tax advisors concerning the U.S. federal income, estate and other tax consequences of acquiring, owning and disposing of our common stock in light of their particular situations as well as any consequences arising under the laws of any other taxing jurisdiction, including any state, local or foreign tax consequences.

For the purposes of this discussion, a "Non-U.S. Holder" is, for U.S. federal income tax purposes, a beneficial owner of common stock that is neither a U.S. Holder, nor a partnership (or other entity treated as a partnership for U.S. federal income tax purposes regardless of its place of organization or formation). A "U.S. Holder" means a beneficial owner of our common stock that is for U.S. federal income tax purposes any of the following:

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

Distributions

Distributions, if any, made on our common stock to a Non-U.S. Holder to the extent treated as made out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles) generally will constitute dividends for U.S. tax purposes and will be subject to withholding tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty, subject to the discussion below regarding foreign accounts. To obtain a reduced rate of withholding under a treaty, a Non-U.S. Holder generally will be required to provide us with a properly executed IRS Form W-8BEN (in the case of individuals) or IRS Form W-8BEN-E (in the case of entities), or other appropriate form, including a U.S. taxpayer identification number, or in certain circumstances, a foreign tax identifying number, and certifying the Non-U.S. Holder's entitlement to benefits under that treaty. This certification must be provided to us or our paying agent prior to the payment of dividends and must be updated periodically. In the case of a Non-U.S. Holder that is an entity, Treasury Regulations and the relevant tax treaty provide rules to determine whether, for purposes of determining the applicability of a tax treaty, dividends will be treated as paid to the entity or to those holding an interest in that entity. If a Non-U.S. Holder holds stock through a financial institution or other agent acting on the holder's behalf, the holder will be required to provide appropriate documentation to such agent. The holder's agent will then be required to provide certification to us or our paying agent, either directly or through other intermediaries. If you are eligible for a reduced rate of U.S. federal withholding tax under an income tax treaty and you do not timely file the required certification, you may be able to obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim for a refund with the IRS.

We generally are not required to withhold tax on dividends paid to a Non-U.S. Holder that are effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, are attributable to a permanent establishment that such holder maintains in the United States) if a properly executed IRS Form W-8ECI, stating that the dividends are so connected, is furnished to us (or, if stock is held through a financial institution or other agent, to such agent) prior to the payment of such dividends. In general, such effectively connected dividends will be subject to U.S. federal income tax, on a net income basis at the regular graduated rates applicable to U.S. residents. A corporate Non-U.S. Holder receiving effectively connected dividends may also be subject to an additional "branch profits tax," which is imposed, under certain circumstances, at a rate of 30% (or such lower rate as may be specified by an applicable treaty) on the corporate Non-U.S. Holder's effectively connected earnings and profits, subject to certain adjustments. Non-U.S. Holders should consult their tax advisors regarding any applicable income tax treaties that may provide for different rules.

To the extent distributions on our common stock, if any, exceed our current and accumulated earnings and profits, they will first reduce the Non-U.S. Holder's adjusted basis in our common stock, but not below zero, and then will be treated as gain to the extent of any excess, and taxed in the same manner as gain realized from a sale or other disposition of common stock as described in the next section.

Gain on Disposition of Our Common Stock

Subject to the discussion below regarding backup withholding and foreign accounts, a Non-U.S. Holder generally will not be subject to U.S. federal income tax with respect to gain realized on a sale or other disposition of our common stock unless (a) the gain is effectively connected with a trade or business of such holder in the United States (and, if required by an applicable income tax treaty, is attributable to a permanent establishment that such holder maintains in the United States), (b) the Non-U.S. Holder is a nonresident alien individual and is present in the United States for 183 or more days in the taxable year of the disposition and certain other conditions are met or (c) we are or have been a "United States real property holding corporation" within the meaning of Code Section 897(c)(2) at any time within the shorter of the five-year period preceding such disposition or such holder's

holding period. In general, we would be a U.S. real property holding corporation if interests in U.S. real estate comprise (by fair market value) at least half of our business assets. We believe that we have not been and we are not, and do not anticipate becoming, a U.S. real property holding corporation. Even if we are treated as a U.S. real property holding corporation, gain realized by a Non-U.S. Holder on a disposition of our common stock will not be subject to U.S. federal income tax so long as (1) the Non-U.S. Holder owned, directly, indirectly and constructively, no more than five percent of our common stock at all times within the shorter of (i) the five-year period preceding the disposition or (ii) the holder's holding period and (2) our common stock is regularly traded on an established securities market. There can be no assurance that our common stock will continue to qualify as regularly traded on an established securities market. If any gain on your disposition is taxable because we are a United States real property holding corporation and your ownership of our common stock exceeds 5%, you will be taxed on such disposition generally in the manner applicable to U.S. persons.

If you are a Non-U.S. Holder described in (a) above, you will be required to pay tax on the net gain derived from the sale at regular graduated U.S. federal income tax rates, and corporate Non-U.S. Holders described in (a) above may be subject to the additional branch profits tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty. Gain described in (b) above will be subject to U.S. federal income tax at a flat 30% rate or such lower rate as may be specified by an applicable income tax treaty, which gain may be offset by certain U.S.-source capital losses (even though you are not considered a resident of the U.S.), provided that the Non-U.S. Holder has timely filed U.S. federal income tax returns with respect to such losses.

Information Reporting Requirements and Backup Withholding

Generally, we must report information to the IRS with respect to any distributions we pay on our common stock (even if the payments are exempt from withholding), including the amount of any such distributions, the name and address of the recipient, and the amount, if any, of tax withheld. A similar report is sent to the holder to whom any such distributions are paid. Pursuant to tax treaties or certain other agreements, the IRS may make its reports available to tax authorities in the recipient's country of residence.

Distributions to a Non-U.S. Holder that are classified as dividends paid by us (or our paying agents) may also be subject to U.S. backup withholding. U.S. backup withholding generally will not apply to a Non-U.S. Holder who provides a properly executed IRS Form W-8BEN, IRS Form W-8BEN-E, or IRS Form W-ECI, or otherwise establishes an exemption. Notwithstanding the foregoing, backup withholding may apply if the payor has actual knowledge, or reason to know, that the holder is a U.S. person who is not an exempt recipient.

U.S. information reporting and backup withholding requirements generally will apply to the proceeds of a disposition of our common stock effected by or through a U.S. office of any broker, U.S. or foreign, except that information reporting and such requirements may be avoided if the holder provides a properly executed IRS Form W-8BEN or IRS Form W-8BEN-E or otherwise meets documentary evidence requirements for establishing non-U.S. person status or otherwise establishes an exemption. Generally, U.S. information reporting and backup withholding requirements will not apply to a payment of disposition proceeds to a Non-U.S. Holder where the transaction is effected outside the U.S. through a non-U.S. office of a non-U.S. broker. Information reporting and backup withholding requirements may, however, apply to a payment of disposition proceeds if the broker has actual knowledge, or reason to know, that the holder is, in fact, a U.S. person. For information reporting purposes, certain brokers with substantial U.S. ownership or operations will generally be treated in a manner similar to U.S. brokers.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules may be credited against the tax liability of persons subject to backup withholding, provided that the required information is timely furnished to the IRS.

Foreign Accounts

Sections 1471 through 1474 of the Code (commonly referred to as FATCA) impose a U.S. federal withholding tax of 30% on certain payments, including dividends paid on and the gross proceeds of a disposition of our common stock paid to a foreign financial institution (as specifically defined by applicable rules) unless such institution enters into an agreement with the U.S. government to withhold on certain payments and to collect and provide to the U.S. tax authorities substantial information regarding U.S. account holders of such institution (which includes certain equity holders of such institution, as well as certain account holders that are foreign entities with U.S. owners). FATCA also generally imposes a federal withholding tax of 30% on certain payments, including dividends paid on and the gross proceeds of a disposition of our common stock to a non-financial foreign entity unless such entity provides the withholding agent with either a certification that it does not have any substantial direct or indirect U.S. owners or provides information regarding substantial direct and indirect U.S. owners of the entity. An intergovernmental agreement between the United States and an applicable foreign country may modify those requirements. The withholding tax described above will not apply if the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from the rules. Holders are encouraged to consult with their own tax advisors regarding the possible implications of FATCA on their investment in our common stock.

The withholding provisions described above currently apply to payments of dividends, and will apply to payments of gross proceeds from a sale or other disposition of common stock on or after January 1, 2019.

EACH PROSPECTIVE INVESTOR SHOULD CONSULT ITS OWN TAX ADVISOR REGARDING THE TAX CONSEQUENCES OF PURCHASING, HOLDING AND DISPOSING OF OUR COMMON STOCK, INCLUDING THE CONSEQUENCES OF ANY RECENT CHANGE IN APPLICABLE LAW.

UNDERWRITING

We and the underwriters for the offering named below have entered into an underwriting agreement with respect to the common stock being offered. Subject to the terms and conditions of the underwriting agreement, each underwriter has severally agreed to purchase from us the number of shares of our common stock set forth opposite its name below. Cowen and Company, LLC and Piper Jaffray & Co. are the representatives of the underwriters.

Underwriter	Number of Shares
Cowen and Company, LLC	
Piper Jaffray & Co.	
Raymond James & Associates, Inc.	
Total	

The underwriting agreement provides that the obligations of the underwriters are subject to certain conditions precedent and that the underwriters have agreed, severally and not jointly, to purchase all of the shares sold under the underwriting agreement if any of these shares are purchased, other than those shares covered by the option to purchase additional shares described below. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the non-defaulting underwriters may be increased or the underwriting agreement may be terminated.

We have agreed to indemnify the underwriters against specified liabilities, including liabilities under the Securities Act of 1933, and to contribute to payments the underwriters may be required to make in respect thereof.

The underwriters are offering the shares, subject to prior sale, when, as and if issued to and accepted by them, subject to approval of legal matters by their counsel and other conditions specified in the underwriting agreement. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

Option to Purchase Additional Shares. We have granted to the underwriters an option to purchase up to additional shares of common stock at the public offering price, less the underwriting discount. This option is exercisable for a period of 30 days. To the extent that the underwriters exercise this option, the underwriters will purchase additional shares from us in approximately the same proportion as shown in the table above.

Discounts and Commissions. The following table shows the public offering price, underwriting discount and proceeds, before expenses to us. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

We estimate that the total expenses of the offering, excluding underwriting discount, will be approximately $550,000 and are payable by us. We also have agreed to reimburse the underwriters for up to $25,000 for their FINRA counsel fee. In accordance with FINRA Rule 5110, this reimbursed fee is deemed underwriting compensation for this offering.

		Total	
	Per Share	Without Option	With Option
Public offering price			
Underwriting discount			
Proceeds, before expenses, to Company			

The underwriters propose to offer the shares of common stock to the public at the public offering price set forth on the cover of this prospectus. The underwriters may offer the shares of common stock to securities dealers at the public offering price less a concession not in excess of $ per share. If all of the shares are not sold at the public offering price, the underwriters may change the offering price and other selling terms.

Discretionary Accounts. The underwriters do not intend to confirm sales of the shares to any accounts over which they have discretionary authority.

Stabilization. In connection with this offering, the underwriters may engage in stabilizing transactions, overallotment transactions, syndicate covering transactions, penalty bids and purchases to cover positions created by short sales.

- Stabilizing transactions permit bids to purchase shares of common stock so long as the stabilizing bids do not exceed a specified maximum, and are engaged in for the purpose of preventing or retarding a decline in the market price of the common stock while the offering is in progress.
- Overallotment transactions involve sales by the underwriters of shares of common stock in excess of the number of shares the underwriters are obligated to purchase. This creates a syndicate short position which may be either a covered short position or a naked short position. In a covered short position, the number of shares over-allotted by the underwriters is not greater than the number of shares that they may purchase in the overallotment option. In a naked short position, the number of shares involved is greater than the number of shares in the overallotment option. The underwriters may close out any short position by exercising their overallotment option and/or purchasing shares in the open market.
- Syndicate covering transactions involve purchases of common stock in the open market after the distribution has been completed in order to cover syndicate short positions. In determining the source of shares to close out the short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared with the price at which they may purchase shares through exercise of the option to purchase additional shares. If the underwriters sell more shares than could be covered by exercise of the option to purchase additional shares and, therefore, have a naked short position, the position can be closed out only by buying shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that after pricing there could be downward pressure on the price of the shares in the open market that could adversely affect investors who purchase in the offering.
- Penalty bids permit the representative to reclaim a selling concession from a syndicate member when the common stock originally sold by that syndicate member is purchased in stabilizing or syndicate covering transactions to cover syndicate short positions.

These stabilizing transactions, syndicate covering transactions and penalty bids may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of our common stock. As a result, the price of our common stock in the open market may be higher than it would otherwise be in the absence of these transactions. Neither we nor the underwriters make any representation or prediction as to the effect that the transactions described above may have on the price of our common stock. These transactions may be effected on the Nasdaq Stock Market, in the over-the-counter market or otherwise and, if commenced, may be discontinued at any time.

Passive Market Making. In connection with this offering, underwriters and selling group members may engage in passive market making transactions in our common stock on the Nasdaq Stock Market in accordance with Rule 103 of Regulation M under the Securities Exchange Act of 1934, as amended, during a period before the commencement of offers or sales of common stock and extending through

the completion of the distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker's bid, such bid must then be lowered when specified purchase limits are exceeded.

Lock-Up Agreements. Pursuant to certain "lock-up" agreements, we and our executive officers, directors and certain of our other stockholders, have agreed, subject to certain exceptions, not to offer, sell, assign, transfer, pledge, contract to sell, or otherwise dispose of or announce the intention to otherwise dispose of, or enter into any swap, hedge or similar agreement or arrangement that transfers, in whole or in part, the economic consequence of ownership of, directly or indirectly, or make any demand or request or exercise any right with respect to the registration of, or file with the SEC a registration statement under the Securities Act relating to, any common stock or securities convertible into or exchangeable or exercisable for any common stock without the prior written consent of Cowen and Company, LLC and Piper Jaffray & Co., for a period of 90 days after the date of the underwriting agreement provided, that, after the 60th day following the date of the underwriting agreement, we may issue shares of our common stock pursuant to the at-the-market offering program sales agreement that we entered into with Cowen and Company, LLC in August 2017. Pursuant to the sales agreement, we may offer and sell, from time to time at our discretion, shares of our common stock having an aggregate offering price of up to $50 million through Cowen as our sales agent.

This lock-up provision applies to common stock and to securities convertible into or exchangeable or exercisable for common stock. The exceptions permit us, among other things and subject to restrictions, to: (a) issue common stock or options pursuant to employee benefit plans, (b) issue common stock upon exercise of outstanding options or warrants, or (c) file registration statements on Form S-8. The exceptions permit parties to the "lock-up" agreements, among other things and subject to restrictions, to: (a) make certain gifts, (b) if the party is a corporation, partnership, limited liability company or other business entity, make transfers to any stockholders, partners, members of, or owners of similar equity interests in, the party, or to an affiliate of the party, if such transfer is not for value, and (c) if the party is a corporation, partnership, limited liability company or other business entity, make transfers in connection with the sale or transfer of all of the party's capital stock, partnership interests, membership interests or other similar equity interests, as the case may be, or all or substantially all of the party's assets, in any such case not undertaken for the purpose of avoiding the restrictions imposed by the "lock-up" agreement. In addition, the lock-up provision will not restrict broker-dealers from engaging in market making and similar activities conducted in the ordinary course of their business.

Cowen and Company, LLC and Piper Jaffray & Co., in their sole discretion, may release our common stock and other securities subject to the lock-up agreements described above in whole or in part at any time. When determining whether or not to release our common stock and other securities from lock-up agreements, Cowen and Company, LLC and Piper Jaffray & Co. will consider, among other factors, the holder's reasons for requesting the release, the number of shares for which the release is being requested and market conditions at the time of the request.

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

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by

the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

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

United Kingdom. Each of the underwriters has represented and agreed that:

- it has not made or will not make an offer of the securities to the public in the United Kingdom within the meaning of section 102B of the Financial Services and Markets Act 2000 (as amended) (FSMA) except to legal entities which are authorized or regulated to operate in the financial markets or, if not so authorized or regulated, whose corporate purpose is solely to invest in securities or otherwise in circumstances which do not require the publication by us of a prospectus pursuant to the Prospectus Rules of the Financial Services Authority (FSA);
- it has only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of section 21 of FSMA) to persons who have professional experience in matters relating to investments falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 or in circumstances in which section 21 of FSMA does not apply to us; and
- it has complied with and will comply with all applicable provisions of FSMA with respect to anything done by it in relation to the securities in, from or otherwise involving the United Kingdom.

Switzerland. The securities will not be offered, directly or indirectly, to the public in Switzerland and this prospectus does not constitute a public offering prospectus as that term is understood pursuant to article 652a or 1156 of the Swiss Federal Code of Obligations.

European Economic Area. In relation to each Member State of the European Economic Area (the "EEA") which has implemented the European Prospectus Directive (each, a "Relevant Member State"), an offer of our shares may not be made to the public in a Relevant Member State other than:

- to any legal entity which is a qualified investor, as defined in the European Prospectus Directive;
- to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150 natural or legal persons (other than qualified investors as defined in the European Prospectus Directive), subject to obtaining the prior consent of the relevant dealer or dealers nominated by us for any such offer; or
- in any other circumstances falling within Article 3(2) of the European Prospectus Directive,

provided that no such offer of our shares shall require us or any underwriter to publish a prospectus pursuant to Article 3 of the European Prospectus Directive or supplement prospectus pursuant to Article 16 of the European Prospectus Directive.

For the purposes of this description, the expression an "offer to the public" in relation to the securities in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the securities to be offered so as to enable an investor to decide to purchase or subscribe for the securities, as the expression may be varied in that Relevant Member State by any measure implementing the European Prospectus Directive in that member state, and the expression "European Prospectus Directive'' means Directive 2003/71/EC (and amendments hereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member State) and includes any relevant implementing measure in each Relevant Member State. The expression 2010 PD Amending Directive means Directive 2010/73/EU.

Israel. In the State of Israel this prospectus shall not be regarded as an offer to the public to purchase shares of common stock under the Israeli Securities Law, 5728—1968, which requires a prospectus to be published and authorized by the Israel Securities Authority, if it complies with certain provisions of Section 15 of the Israeli Securities Law, 5728—1968, including, inter alia, if: (i) the offer is made, distributed or directed to not more than 35 investors, subject to certain conditions (the "Addressed Investors"); or (ii) the offer is made, distributed or directed to certain qualified investors defined in the First Addendum of the Israeli Securities Law, 5728—1968, subject to certain conditions (the "Qualified Investors"). The Qualified Investors shall not be taken into account in the count of the Addressed Investors and may be offered to purchase securities in addition to the 35 Addressed Investors. We have not and will not take any action that would require us to publish a prospectus in accordance with and subject to the Israeli Securities Law, 5728—1968. We have not and will not distribute this prospectus or make, distribute or direct an offer to subscribe for our common stock to any person within the State of Israel, other than to Qualified Investors and up to 35 Addressed Investors.

Qualified Investors may have to submit written evidence that they meet the definitions set out in of the First Addendum to the Israeli Securities Law, 5728—1968. In particular, we may request, as a condition to be offered common stock, that Qualified Investors will each represent, warrant and certify to us and/or to anyone acting on our behalf: (i) that it is an investor falling within one of the categories listed in the First Addendum to the Israeli Securities Law, 5728—1968; (ii) which of the categories listed in the First Addendum to the Israeli Securities Law, 5728—1968 regarding Qualified Investors is applicable to it; (iii) that it will abide by all provisions set forth in the Israeli Securities Law, 5728—1968 and the regulations promulgated thereunder in connection with the offered to be issued common stock; (iv) that the shares of common stock that it will be issued are, subject to exemptions available under the Israeli Securities Law, 5728—1968: (a) for its own account; (b) for investment purposes only; and (c) not issued with a view to resale within the State of Israel, other than in accordance with the provisions of the Israeli Securities Law, 5728—1968; and (v) that it is willing to provide further evidence of its Qualified Investor status. Addressed Investors may have to submit written evidence in respect of their identity and may have to sign and submit a declaration containing, inter alia, the Addressed Investor's name, address and passport number or Israeli identification number.

We have not authorized and do not authorize the making of any offer of securities through any financial intermediary on our behalf, other than offers made by the underwriters and their respective affiliates, with a view to the final placement of the securities as contemplated in this document. Accordingly, no purchaser of the shares, other than the underwriters, is authorized to make any further offer of shares on our behalf or on behalf of the underwriters.

Electronic Offer, Sale and Distribution of Shares. A prospectus in electronic format may be made available on the websites maintained by one or more of the underwriters or selling group members, if any, participating in this offering and one or more of the underwriters participating in this offering may distribute prospectuses electronically. The representatives may agree to allocate a number of shares to underwriters and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the underwriters and selling group members that will make internet distributions on the same basis as other allocations. Other than the prospectus in electronic format, the information on these websites is not part of this prospectus or the registration statement of which this prospectus forms a part, has not been approved or endorsed by us or any underwriter in its capacity as underwriter, and should not be relied upon by investors.

Other Relationships. Certain of the underwriters and their affiliates have provided, and may in the future provide, various investment banking, commercial banking and other financial services for us and our affiliates for which they have received, and may in the future receive, customary fees. In addition, we entered into an at-the-market offering program sales agreement with Cowen in August 2017. Pursuant to the sales agreement, we may offer and sell, from time to time at our discretion, shares of our common stock having an aggregate offering price of up to $50 million through Cowen as our sales agent.

LEGAL MATTERS

Cooley LLP will pass upon the validity of the common stock offered hereby. Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., will pass upon the validity of the common stock offered hereby for the underwriters.

EXPERTS

Our consolidated financial statements incorporated in this prospectus supplement and accompanying prospectus by reference from our Annual Report on Form 10-K for the year ended December 31, 2016, have been audited by Deloitte & Touche LLP, an independent registered public accounting firm, as stated in their report, which is incorporated herein by reference. Such consolidated financial statements have been so incorporated in reliance upon the report of such firm given upon their authority as experts in accounting and auditing.

WHERE YOU CAN FIND ADDITIONAL INFORMATION

This prospectus supplement is part of the registration statement on Form S-3 we filed with the SEC under the Securities Act and does not contain all the information set forth in the registration statement. Whenever a reference is made in this prospectus supplement or the accompanying prospectus to any of our contracts, agreements or other documents, the reference may not be complete and you should refer to the exhibits that are a part of the registration statement or the exhibits to the reports or other documents incorporated by reference into this prospectus supplement and the accompanying prospectus for a copy of such contract, agreement or other document. Because we are subject to the information and reporting requirements of the Exchange Act, we file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at http://www.sec.gov. You may also read and copy any document we file at the SEC's Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to "incorporate by reference" information from other documents that we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus supplement and the accompanying prospectus. Information in this prospectus supplement and the accompanying prospectus supersedes information incorporated by reference that we filed with the SEC prior to the date of this prospectus supplement and the accompanying prospectus, while information that we file later with the SEC will automatically update and supersede the information in this prospectus supplement and the accompanying prospectus. We incorporate by reference into this prospectus supplement, the accompanying prospectus and the registration statement of which this prospectus supplement and the accompanying prospectus are a part the information or documents listed below that we have filed with the SEC (Commission File No. 001-36579), excluding any portions of any Form 8-K that are not deemed "filed" pursuant to the General Instructions of Form 8-K:

- our Annual Report on Form 10-K for the year ended December 31, 2016, which was filed with the SEC on March 9, 2017;

- Our Quarterly Report on Form 10-Q for the quarter ended March 31, 2017, which was filed with the SEC on May 9, 2017;
- Our Quarterly Report on Form 10-Q for the quarter ended June 30, 2017, which was filed with the SEC on August 8, 2017;
- Our Quarterly Report on Form 10-Q for the quarter ended September 30, 2017, which was filed with the SEC on November 8, 2017;
- Our Quarterly Report on Form 10-Q/A for the quarter ended September 30, 2016, which was filed with the SEC on April 5, 2017;
- our Current Reports on Form 8-K filed with the SEC on February 3, 2017, February 10, 2017, February 14, 2017, March 1, 2017, March 14, 2017 (but not to the extent furnished and not filed), March 20, 2017, March 24, 2017, April 20, 2017 (but not to the extent furnished and not filed), April 21, 2017, April 27, 2017, June 9, 2017, June 20, 2017 (but not to the extent furnished and not filed), September 1, 2017, September 7, 2017, October 3, 2017, December 12, 2017, January 25, 2018, and January 26, 2018;
- the information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2016, referred to above from our definitive proxy statement filed with the SEC pursuant to Section 14 of the Exchange Act in connection with our 2017 Annual Meeting of Stockholders filed with the SEC on April 26, 2017; and
- the description of our common stock contained in our Registration Statement on Form 8-A filed with the SEC on July 28, 2014, including any amendments or reports filed for the purpose of updating such description.

We also incorporate by reference any future filings (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items unless such Form 8-K expressly provides to the contrary) made with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act. Information in such future filings updates and supplements the information provided in this prospectus supplement and the accompanying prospectus. Any statements in any such future filings will automatically be deemed to modify and supersede any information in any document we previously filed with the SEC that is incorporated or deemed to be incorporated herein by reference to the extent that statements in the later filed document modify or replace such earlier statements.

You can request a copy of these filings, at no cost, by writing or telephoning us at the following address or telephone number:

Adverum Biotechnologies, Inc.
1035 O'Brien Drive
Menlo Park, CA 94025
(650) 272-6269
Attn: Secretary

Table of Contents

$150,000,000

Common Stock

Preferred Stock

Debt Securities

Warrants

Units

We may offer and sell securities from time to time in one or more offerings of up to $150,000,000 in aggregate offering price. This prospectus describes the general terms of these securities and the general manner in which these securities will be offered. We will provide the specific terms of these securities in supplements to this prospectus. The prospectus supplements will also describe the specific manner in which these securities will be offered and may also supplement, update or amend information contained in this document. You should read this prospectus and any applicable prospectus supplement before you invest.

We may offer these securities in amounts, at prices and on terms determined at the time of offering. The securities may be sold directly to you, through agents, or through underwriters and dealers. If agents, underwriters or dealers are used to sell the securities, we will name them and describe their compensation in a prospectus supplement. For additional information on the methods of sale, you should refer to the section entitled "Plan of Distribution" in this prospectus.

Our common stock is traded on The NASDAQ Global Market under the symbol "ADVM." On August 15, 2017, the closing price for our common stock, as reported on The NASDAQ Global Market, was $2.55 per share. None of the other securities we may offer are currently traded on any securities exchange.

We are an "emerging growth company" as that term is used in the Jumpstart Our Business Startups Act of 2012 and, as such, have elected to avail ourselves of certain reduced public company reporting requirements for this prospectus and future filings.

Investing in these securities involves certain risks. See "Risk Factors" on page 2 of this prospectus and in any accompanying prospectus supplement and in the documents incorporated by reference in this prospectus for a discussion of the factors you should carefully consider before deciding to purchase these securities.

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

The date of this prospectus is August 22, 2017

TABLE OF CONTENTS

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, which we refer to as the "SEC," utilizing a "shelf" registration process. Under this shelf registration process, we may from time to time sell any combination of the securities described in this prospectus in one or more offerings for an aggregate initial offering price of up to $150,000,000.

This prospectus provides you with a general description of the securities we may offer. Each time we sell securities, we will provide one or more prospectus supplements that will contain specific information about the terms of the offering. The prospectus supplement may also add, update or change information contained in this prospectus. You should read both this prospectus and the accompanying prospectus supplement together with the additional information described under the heading "Where You Can Find More Information" beginning on page 31 of this prospectus.

THIS PROSPECTUS MAY NOT BE USED TO CONSUMMATE A SALE OF SECURITIES UNLESS IT IS ACCOMPANIED BY A PROSPECTUS SUPPLEMENT.

You should rely only on the information contained in or incorporated by reference in this prospectus, any accompanying prospectus supplement or in any related free writing prospectus filed by us with the SEC. We have not authorized anyone to provide you with different information. This prospectus and the accompanying prospectus supplement do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the securities described in the accompanying prospectus supplement or an offer to sell or the solicitation of an offer to buy such securities in any circumstances in which such offer or solicitation is unlawful. You should assume that the information appearing in this prospectus, any prospectus supplement, the documents incorporated by reference and any related free writing prospectus is accurate only as of their respective dates. Our business, financial condition, results of operations and prospects may have changed materially since those dates.

Unless the context otherwise indicates, references in this prospectus to "Adverum", "we", "our", "us" and "the Company" refer, collectively, to Adverum Biotechnologies, Inc., a Delaware corporation.

This prospectus incorporates by reference, and any prospectus supplement or free writing prospectus may contain and incorporate by reference, industry, statistical and market data from our own internal estimates and research as well as from industry and general publications and research, surveys and studies conducted by third parties. Industry publications, studies and surveys generally state that they have been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe that each of these studies and publications is reliable, we have not independently verified statistical, market and industry data from third-party sources. While we believe our internal company research is reliable and the market definitions are appropriate, neither such research nor these definitions have been verified by any independent source.

We own various U.S. federal trademark registrations and applications and unregistered trademarks, including our corporate logo. This prospectus and the information incorporated herein by reference contains references to trademarks, service marks and trade names referred to in this prospectus and the information incorporated herein, including logos, artwork, and other visual displays, may appear without the ® or ™ symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensor to these trademarks, service marks or trade names. We do not intend our use or display of other companies' trade names, service marks or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus, any applicable prospectus supplement or any related free writing prospectus are the property of their respective owners.

ADVERUM BIOTECHNOLOGIES, INC.

Overview

We are a gene therapy company advancing novel medicines that may offer life-changing benefits to patients living with serious rare and ocular diseases. We are leveraging our next-generation adeno-associated virus (AAV)-based directed evolution platform to generate gene therapy product candidates designed to provide durable efficacy by inducing sustained expression of a therapeutic protein. We have also acquired certain other gene therapy product candidates through our acquisition of Annapurna Therapeutics SAS, a privately-held French gene therapy company, on May 11, 2016. Our core capabilities include clinical development and in-house manufacturing expertise, specifically in process development, assay development, and novel vector development, and we are led by a team with significant drug development and gene therapy expertise.

We are focused on advancing our three lead gene therapy programs to address unmet needs in wet age-related macular degeneration and in rare diseases alpha-1 antitrypsin deficiency and hereditary angioedema.

Our earlier-stage research programs include gene therapies targeting cardiomyopathy associated with Friedreich's ataxia and severe allergy.

Corporate Information

We were incorporated in Delaware in 2006 under the name "Avalanche Biotechnologies, Inc." We completed the initial public offering of our common stock in August 2014. On May 11, 2016, upon the completion of our acquisition of Annapurna Therapeutics SAS, we changed our name to "Adverum Biotechnologies, Inc." Our common stock is currently listed on The NASDAQ Global Market under the symbol "ADVM." We are an "emerging growth company" under the Jumpstart Our Business Startups Act of 2012, and therefore we are subject to reduced public company reporting requirements.

Our principal executive offices are located at 1035 O'Brien Drive, Menlo Park, CA 94025, and our telephone number is (650) 272-6269. Our internet address is www.adverum.com. The information on our website is not incorporated by reference into this prospectus and should not be considered to be a part of this prospectus. Our internet address is included in this prospectus as an inactive textual reference only.

RISK FACTORS

An investment in our securities involves a high degree of risk. Before deciding whether to invest in our securities, you should consider carefully the risks and uncertainties described under the section captioned "Risk Factors" contained in the applicable prospectus supplement, our most recent Annual Report on Form 10-K and our most recent Quarterly Report on Form 10-Q, as may be updated by subsequent annual, quarterly and other reports that are incorporated by reference into this prospectus in their entirety. The risks described in these documents are not the only ones we face, but those that we consider to be material. There may be other unknown or unpredictable economic, business, competitive, regulatory or other factors that could have material adverse effects on our future results. Past financial performance may not be a reliable indicator of future performance, and historical trends should not be used to anticipate results or trends in future periods. If any of these risks actually occurs, our business, financial condition, results of operations or cash flow could suffer materially. In such event, the trading price of our securities could decline and you might lose all or part of your investment.

CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

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

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

- the initiation, progress, timing, costs and results of preclinical studies and any clinical trials for our product candidates;
- our ability to advance our viral vector manufacturing and delivery capabilities;
- the timing or likelihood of regulatory filings and approvals;
- our plans to explore potential applications of our gene therapy platform in other indications in ophthalmology and rare diseases;
- our expectations regarding the clinical effectiveness of our product candidates;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the pricing and reimbursement of our product candidates, if approved;
- our expectation regarding the potential market sizes for our product candidates;
- our intellectual property position;
- the potential benefits of our strategic collaborations, our plans with respect to our strategic collaborations and our plans with respect to and our ability to enter into strategic arrangements;
- developments and projections relating to our competitors and our industry;
- our expectations regarding the time during which we will be an "emerging growth company" under the Jumpstart Our Business Startups Act of 2012;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing; and
- the safety, efficacy and projected development timeline and commercial potential of any product candidates.

These statements relate to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these

forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed in the "Risk Factors" section in this prospectus, the section of any accompanying prospectus supplement entitled "Risk Factors" and the risk factors and cautionary statements described in other documents that we file from time to time with the SEC, specifically under "Item 1A. Risk Factors" and elsewhere in our most recent Annual Report on Form 10-K for the year ended December 31, 2016 and our most recent Quarterly Reports on Form 10-Q for the quarters ended March 31, 2017 and June 30, 2017, and our Current Reports on Form 8-K.

Any forward-looking statement in this prospectus reflects our current views with respect to future events and is subject to these and other risks, uncertainties and assumptions relating to our business, operations, results of operations, industry and future growth. Given these uncertainties, you should not place undue reliance on these forward-looking statements. These forward-looking statements speak only as of the date of this prospectus. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

RATIO OF EARNINGS TO FIXED CHARGES

The following table sets forth our ratio of earnings to fixed charges and the ratio of our combined fixed charges and preference dividends to earnings for each of the periods indicated. The following table is qualified by the more detailed information appearing in the computation table set forth in Exhibit 12.1 to the registration statement of which this prospectus is part and the historical financial statements, including the notes to those financial statements, incorporated by reference in this prospectus. We have paid no dividends on preferred shares during the periods indicated. Therefore, the ratios of earnings to combined fixed charges and preferred dividends are the same as the ratios of earnings to fixed charges.

	Year Ended December 31,			Six Months Ended
	2014	2015	2016	June 30, 2017
Ratio of earnings to fixed charges	N/A	N/A	N/A	N/A
Ratio of combined fixed charges and preference dividends to earnings	N/A	N/A	N/A	N/A

For purposes of computing the ratio of earnings to fixed charges and the ratio of our combined fixed charges and preference dividends to earnings, earnings consist of income (loss) from continuing operations before income taxes plus fixed charges. Fixed charges consist of interest expense on indebtedness and an estimate of the interest within rental expense.

We did not generate earnings for any of the years ended December 31, 2016, 2015 and 2014 and for the six month period ended June 30, 2017. Accordingly, our earnings were insufficient to cover fixed charges for such periods and we are unable to disclose a ratio of earnings to fixed charges for such periods. The dollar amount of the deficiency in earnings available for fixed charges for the years ended December 31, 2016, 2015 and 2014 and for the six month period ended June 30, 2017 was approximately $114.5 million, $47.5 million, $28.6 million, and $27.5 million, respectively.

USE OF PROCEEDS

Unless otherwise specified in connection with a particular offering of securities, the net proceeds from the sale of the securities offered by this prospectus will be used for general corporate purposes. General corporate purposes may include, without limitation, the research and development of our product pipeline and our AAV vector discovery platform, acquisitions or in-licenses of complimentary companies or businesses, repayment and refinancing of debt, working capital and capital expenditures. We may temporarily invest such net proceeds in investment-grade, interest-bearing securities until they are used for their stated purpose. We have not determined the amount of net proceeds to be used specifically for such purposes. As a result, management will retain broad discretion over the allocation of net proceeds.

DILUTION

If there is a material dilution of the purchasers' equity interests from the sale of common equity securities offered under this prospectus, we will set forth in any prospectus supplement the following information regarding any such material dilution of the equity interests of purchasers purchasing securities in an offering under this prospectus:

- the net tangible book value per share of our equity securities before and after the offering;
- the amount of the increase in such net tangible book value per share attributable to the cash payments made by purchasers in the offering; and
- the amount of the immediate dilution from the public offering price that will be absorbed by such purchasers.

THE SECURITIES WE MAY OFFER

This prospectus contains summary descriptions of the securities we may offer from time to time. These summary descriptions are not meant to be complete descriptions of each security. The particular terms of any security will be described in the applicable prospectus supplement.

DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock is intended as a summary only and therefore is not a complete description of our capital stock. This description is based upon, and is qualified by reference to, our amended and restated certificate of incorporation, our amended and restated bylaws and applicable provisions of Delaware corporate law. You should read our amended and restated certificate of incorporation and amended and restated bylaws, which have been publicly filed with the SEC, for the provisions that are important to you.

Authorized Capital Stock

The Company's authorized capital stock consists of 305,000,000 shares, of which 300,000,000 shares are common stock, par value $0.0001 per share and 5,000,000 shares are preferred stock, par value $0.0001 per share.

As of June 30, 2017, 43,201,786 shares of common stock were issued and outstanding, and no shares of preferred stock were issued or outstanding.

Common Stock

Each holder of our common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders, including the election of directors. In the election of directors, a plurality of the votes cast at a meeting of stockholders is sufficient to elect a director. Our stockholders do not have cumulative voting rights in the election of directors. Accordingly, holders of a majority of the voting shares are able to elect all of the directors. In all other matters, except as noted below under "—Amendment of our Amended and Restated Certificate of Incorporation or our Amended and Restated Bylaws" and "—Election and Removal of Directors" and except where a higher threshold is required by law, a majority of the votes cast affirmatively or negatively (excluding abstentions and broker non-votes) will decide such matters.

Subject to preferences that may be applicable to any then outstanding preferred stock, holders of our common stock are entitled to receive dividends, if any, as may be declared from time to time by our board of directors out of legally available funds.

In the event of our liquidation, dissolution or winding up, holders of our common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities and the satisfaction of any liquidation preference granted to the holders of any then outstanding shares of preferred stock.

Holders of our common stock have no preemptive, conversion, subscription or other rights, and there are no redemption or sinking fund provisions applicable to our common stock. The rights, preferences and privileges of the holders of our common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of preferred stock that we may designate in the future.

Preferred Stock

Our amended and restated certificate of incorporation authorizes our board of directors, without further action by our stockholders, to issue up to 5,000,000 shares of preferred stock in one or more series and to fix the

rights, preferences, privileges and restrictions thereof. These rights, preferences and privileges could include dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences, sinking fund terms and the number of shares constituting any series or the designation of such series, any or all of which may be greater than the rights of common stock. The issuance of our preferred stock could adversely affect the voting power of holders of common stock and the likelihood that such holders will receive dividend payments and payments upon liquidation. In addition, the issuance of preferred stock could have the effect of delaying, deferring or preventing a change of control of our company or other corporate action.

Anti-Takeover Effects of Provisions of our Amended and Restated Certificate of Incorporation, our Amended and Restated Bylaws and Delaware Law

Delaware law and our restated certificate of incorporation and our amended and restated bylaws contain provisions that could have the effect of delaying, deferring or discouraging another party from acquiring control of us. These provisions, which are summarized below, are expected to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors.

Undesignated Preferred Stock

The ability to authorize undesignated preferred stock makes it possible for our board of directors to issue preferred stock with voting or other rights or preferences that could impede the success of any attempt to change control of us. These and other provisions may have the effect of deterring hostile takeovers or delaying changes in control or management of our company.

Stockholder Meetings

Our charter documents provide that a special meeting of stockholders may be called only by our board of directors, the chairman of our board of directors, our Chief Executive Officer or, in the absence of a Chief Executive Officer, our President.

Requirements for Advance Notification of Stockholder Nominations and Proposals

Our amended and restated bylaws establish advance notice procedures with respect to stockholder proposals and the nomination of candidates for election as directors, other than nominations made by or at the direction of the board of directors or a committee of the board of directors.

Elimination of Stockholder Action by Written Consent

Our amended and restated certificate of incorporation eliminates the right of stockholders to act by written consent without a meeting.

Election and Removal of Directors

Our board of directors is divided into three classes. The directors in each class will serve for a three-year term, one class being elected each year by our stockholders. This system of electing and removing directors may tend to discourage a third party from making a tender offer or otherwise attempting to obtain control of us, because it generally makes it more difficult for stockholders to replace a majority of the directors. Our charter documents provide that directors may be removed only for cause with the vote of holders of 66 2/3% of the voting power of all the then-outstanding shares of our voting stock.

Delaware Anti-Takeover Statute

We are subject to Section 203 of the Delaware General Corporation Law. Section 203 provides that, subject to certain exceptions, a corporation shall not engage in any business combination with any “interested

stockholder" for a three-year period following the time that such stockholder becomes an interested stockholder unless:

- prior to such time, the board of directors of the corporation approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder; or
- upon consummation of the transaction which resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced (excluding certain shares); or
- at or subsequent to such time, the business combination is approved by the board of directors of the corporation and by the affirmative vote of at least 66 2/3% of the outstanding voting stock which is not owned by the interested stockholder.
- Except as specified in Section 203, an interested stockholder is generally defined as:
- any person that is the owner of 15% or more of the outstanding voting stock of the corporation, or is an affiliate or associate of the corporation and was the owner of 15% or more of the outstanding voting stock of the corporation, at any time within the three-year period immediately prior to the relevant date; and
- the affiliates and associates of any such person.

Section 203 may make it more difficult for a person who would be an "interested stockholder" to effect various business combinations with a corporation for a three-year period. We have not elected to be exempt from the restrictions imposed under Section 203. The provisions of Section 203 may encourage persons interested in acquiring us to negotiate in advance with the board of directors, since the stockholder approval requirement would be avoided if a majority of the directors then in office approves either the business combination or the transaction which results in any such person becoming an interested stockholder. Such provisions also may have the effect of preventing changes in our management. It is possible that such provisions could make it more difficult to accomplish transactions which our stockholders may otherwise deem to be in their best interests.

Amendment of our Amended and Restated Certificate of Incorporation or our Amended and Restated Bylaws

The amendment of any of the above provisions in our amended and restated certificate of incorporation, except for the provision making it possible for our board of directors to issue preferred stock, or the amendment of any provision in our amended and restated bylaws (other than by action of the board of directors), would require approval by holders of at least 66 2/3% of our then outstanding voting stock.

The provisions of the Delaware General Corporation Law, our amended and restated certificate of incorporation and our amended and restated bylaws could have the effect of discouraging others from attempting hostile takeovers and, as a consequence, they may also inhibit temporary fluctuations in the market price of our common stock that often result from actual or rumored hostile takeover attempts. These provisions may also have the effect of preventing changes in our management. It is possible that these provisions could make it more difficult to accomplish transactions that stockholders may otherwise deem to be in their best interests.

Delaware as Sole and Exclusive Forum

Our amended and restated certificate of incorporation provide, that unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware shall, to the fullest extent permitted by law, be the sole and exclusive forum for (i) any derivative action or proceeding brought on behalf of us, (ii) any action asserting a claim of breach of a fiduciary duty owed by, or otherwise wrongdoing by, any of our directors, officers or other employees to us or our stockholders, (iii) any action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law or our amended and restated certificate of

incorporation or amended and restated bylaws, (iv) any action to interpret, apply, enforce or determine the validity of our amended and restated certificate of incorporation or the bylaws, or (v) any action asserting a claim against us or any of our directors, officers or employees governed by the internal affairs doctrine.

Transfer Agent and Registrar

Wells Fargo Shareowner Services is the transfer agent and registrar for the Company's common stock. The transfer agent and registrar's address is Wells Fargo Shareowner Services, Attn: Manager of Account Administration, 1110 Centre Pointe Curve, Suite 101, Mendota Heights, MN 55120-4101.

Listing on the NASDAQ Global Market

Our common stock is listed on The NASDAQ Global Market under the symbol "ADVM."

DESCRIPTION OF DEBT SECURITIES

This section describes the general terms and provisions of our debt securities that we may issue from time to time. We may issue debt securities, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. While the terms we have summarized below will apply generally to any future debt securities we may offer under this prospectus, the applicable prospectus supplement or free writing prospectus will describe the specific terms of any debt securities offered through that prospectus supplement or free writing prospectus. The terms of any debt securities we offer under a prospectus supplement or free writing prospectus may differ from the terms we describe below. Unless the context requires otherwise, whenever we refer to the "indentures," we are also referring to any supplemental indentures that specify the terms of a particular series of debt securities.

We will issue any senior debt securities under the senior indenture that we will enter into with the trustee named in the senior indenture. We will issue any subordinated debt securities under the subordinated indenture that we will enter into with the trustee named in the subordinated indenture. We have filed forms of these documents as exhibits to the registration statement, of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

The indentures will be qualified under the Trust Indenture Act of 1939, as amended, or the Trust Indenture Act. We use the term "trustee" to refer to either the trustee under the senior indenture or the trustee under the subordinated indenture, as applicable.

The following summaries of material provisions of the senior debt securities, the subordinated debt securities and the indentures are subject to, and qualified in their entirety by reference to, all of the provisions of the indenture applicable to a particular series of debt securities. We urge you to read the applicable prospectus supplement or free writing prospectus and any related free writing prospectuses related to the debt securities that we may offer under this prospectus, as well as the complete applicable indenture that contains the terms of the debt securities. Except as we may otherwise indicate, the terms of the senior indenture and the subordinated indenture are identical.

General

We will describe in the applicable prospectus supplement or free writing prospectus the terms of the series of debt securities being offered, including:

- the title;
- the principal amount being offered, and if a series, the total amount authorized and the total amount outstanding;
- any limit on the amount that may be issued;
- whether or not we will issue the series of debt securities in global form, and, if so, the terms and who the depository will be;
- the maturity date;
- whether and under what circumstances, if any, we will pay additional amounts on any debt securities held by a person who is not a United States person for tax purposes, and whether we can redeem the debt securities if we have to pay such additional amounts;
- the annual interest rate, which may be fixed or variable, or the method for determining the rate and the date interest will begin to accrue, the dates interest will be payable and the regular record dates for interest payment dates or the method for determining such dates;

- whether or not the debt securities will be secured or unsecured, and the terms of any secured debt;
- the terms of the subordination of any series of subordinated debt;
- the place where payments will be payable;
- restrictions on transfer, sale or other assignment, if any;
- our right, if any, to defer payment of interest and the maximum length of any such deferral period;
- the date, if any, after which, the conditions upon which, and the price at which, we may, at our option, redeem the series of debt securities pursuant to any optional or provisional redemption provisions and the terms of those redemption provisions;
- the date, if any, on which, and the price at which we are obligated, pursuant to any mandatory sinking fund or analogous fund provisions or otherwise, to redeem, or at the holder's option, to purchase, the series of debt securities and the currency or currency unit in which the debt securities are payable;
- whether the indenture will restrict our ability or the ability of our subsidiaries, if any at such time, to:
    - incur additional indebtedness;
    - issue additional securities;
    - create liens;
    - pay dividends or make distributions in respect of our capital stock or the capital stock of our subsidiaries;
    - redeem capital stock;
    - place restrictions on our subsidiaries' ability to pay dividends, make distributions or transfer assets;
    - make investments or other restricted payments;
    - sell or otherwise dispose of assets;
    - enter into sale-leaseback transactions;
    - engage in transactions with stockholders or affiliates;
    - issue or sell stock of our subsidiaries; or
    - effect a consolidation or merger;
- whether the indenture will require us to maintain any interest coverage, fixed charge, cash flow-based, asset-based or other financial ratios;
- a discussion of certain material or special United States federal income tax considerations applicable to the debt securities;
- information describing any book-entry features;
- provisions for a sinking fund purchase or other analogous fund, if any;
- the applicability of the provisions in the indenture on discharge;
- whether the debt securities are to be offered at a price such that they will be deemed to be offered at an "original issue discount" as defined in paragraph (a) of Section 1273 of the Internal Revenue Code of 1986, as amended;
- the denominations in which we will issue the series of debt securities, if other than denominations of $1,000 and any integral multiple thereof;

- the currency of payment of debt securities if other than U.S. dollars and the manner of determining the equivalent amount in U.S. dollars; and
- any other specific terms, preferences, rights or limitations of, or restrictions on, the debt securities, including any additional events of default or covenants provided with respect to the debt securities, and any terms that may be required by us or advisable under applicable laws or regulations or advisable in connection with the marketing of the debt securities.

Conversion or Exchange Rights

We will set forth in the applicable prospectus supplement or free writing prospectus the terms on which a series of debt securities may be convertible into or exchangeable for our common stock, our preferred stock or other securities (including securities of a third-party). We will include provisions as to whether conversion or exchange is mandatory, at the option of the holder or at our option. We may include provisions pursuant to which the number of shares of our common stock, our preferred stock or other securities (including securities of a third-party) that the holders of the series of debt securities receive would be subject to adjustment.

Consolidation, Merger or Sale

Unless we provide otherwise in the prospectus supplement or free writing prospectus applicable to a particular series of debt securities, the indentures will not contain any covenant that restricts our ability to merge or consolidate, or sell, convey, transfer or otherwise dispose of all or substantially all of our assets. However, any successor to or acquirer of such assets must assume all of our obligations under the indentures or the debt securities, as appropriate. If the debt securities are convertible into or exchangeable for other securities of ours or securities of other entities, the person with whom we consolidate or merge or to whom we sell all of our property must make provisions for the conversion of the debt securities into securities that the holders of the debt securities would have received if they had converted the debt securities before the consolidation, merger or sale.

Events of Default Under the Indenture

Unless we provide otherwise in the prospectus supplement or free writing prospectus applicable to a particular series of debt securities, the following are events of default under the indentures with respect to any series of debt securities that we may issue:

- if we fail to pay interest when due and payable and our failure continues for 90 days and the time for payment has not been extended;
- if we fail to pay the principal, premium or sinking fund payment, if any, when due and payable at maturity, upon redemption or repurchase or otherwise, and the time for payment has not been extended;
- if we fail to observe or perform any other covenant contained in the debt securities or the indentures, other than a covenant specifically relating to another series of debt securities, and our failure continues for 90 days after we receive notice from the trustee or holders of at least 25% in aggregate principal amount of the outstanding debt securities of the applicable series; and
- if specified events of bankruptcy, insolvency or reorganization occur.

We will describe in each applicable prospectus supplement or free writing prospectus any additional events of default relating to the relevant series of debt securities.

If an event of default with respect to debt securities of any series occurs and is continuing, other than an event of default specified in the last bullet point above, the trustee or the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series, by notice to us in writing, and to the trustee if notice is given by such holders, may declare the unpaid principal, premium, if any, and accrued interest, if any,

due and payable immediately. If an event of default specified in the last bullet point above occurs with respect to us, the unpaid principal, premium, if any, and accrued interest, if any, of each issue of debt securities then outstanding shall be due and payable without any notice or other action on the part of the trustee or any holder.

The holders of a majority in principal amount of the outstanding debt securities of an affected series may waive any default or event of default with respect to the series and its consequences, except defaults or events of default regarding payment of principal, premium, if any, or interest, unless we have cured the default or event of default in accordance with the indenture. Any waiver shall cure the default or event of default.

Subject to the terms of the indentures, if an event of default under an indenture shall occur and be continuing, the trustee will be under no obligation to exercise any of its rights or powers under such indenture at the request or direction of any of the holders of the applicable series of debt securities, unless such holders have offered the trustee reasonable indemnity or security satisfactory to it against any loss, liability or expense. The holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee, or exercising any trust or power conferred on the trustee, with respect to the debt securities of that series, provided that:

- the direction so given by the holder is not in conflict with any law or the applicable indenture; and
- subject to its duties under the Trust Indenture Act, the trustee need not take any action that might involve it in personal liability or might be unduly prejudicial to the holders not involved in the proceeding.

A holder of the debt securities of any series will have the right to institute a proceeding under the indentures or to appoint a receiver or trustee, or to seek other remedies if:

- the holder has given written notice to the trustee of a continuing event of default with respect to that series;
- the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series have made written request, and such holders have offered reasonable indemnity to the trustee or security satisfactory to it against any loss, liability or expense or to be incurred in compliance with instituting the proceeding as trustee; and
- the trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series other conflicting directions within 90 days after the notice, request and offer.

These limitations do not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, the debt securities, or other defaults that may be specified in the applicable prospectus supplement or free writing prospectus.

We will periodically file statements with the trustee regarding our compliance with specified covenants in the indentures.

Modification of Indenture; Waiver

Subject to the terms of the indenture for any series of debt securities that we may issue, we and the trustee may change an indenture without the consent of any holders with respect to the following specific matters:

- to fix any ambiguity, defect or inconsistency in the indenture;
- to comply with the provisions described above under “Description of Our Debt Securities—Consolidation, Merger or Sale;”

- to comply with any requirements of the SEC in connection with the qualification of any indenture under the Trust Indenture Act;
- to add to, delete from or revise the conditions, limitations, and restrictions on the authorized amount, terms, or purposes of issue, authentication and delivery of debt securities, as set forth in the indenture;
- to provide for the issuance of and establish the form and terms and conditions of the debt securities of any series as provided under "—Description of Our Debt Securities—General," to establish the form of any certifications required to be furnished pursuant to the terms of the indenture or any series of debt securities, or to add to the rights of the holders of any series of debt securities;
- to evidence and provide for the acceptance of appointment hereunder by a successor trustee;
- to provide for uncertificated debt securities and to make all appropriate changes for such purpose;
- to add to our covenants such new covenants, restrictions, conditions or provisions for the benefit of the holders, to make the occurrence, or the occurrence and the continuance, of a default in any such additional covenants, restrictions, conditions or provisions an event of default or to surrender any right or power conferred to us in the indenture; or
- to change anything that does not materially adversely affect the interests of any holder of debt securities of any series.

In addition, under the indentures, the rights of holders of a series of debt securities may be changed by us and the trustee with the written consent of the holders of at least a majority in aggregate principal amount of the outstanding debt securities of each series that is affected. However, subject to the terms of the indenture for any series of debt securities that we may issue or as otherwise provided in the prospectus supplement or free writing prospectus applicable to a particular series of debt securities, we and the trustee may make the following changes only with the consent of each holder of any outstanding debt securities affected:

- extending the stated maturity of the series of debt securities;
- reducing the principal amount, reducing the rate of or extending the time of payment of interest, or reducing any premium payable upon the redemption or repurchase of any debt securities; or
- reducing the percentage of debt securities, the holders of which are required to consent to any amendment, supplement, modification or waiver.

Discharge

Each indenture provides that, subject to the terms of the indenture and any limitation otherwise provided in the prospectus supplement or free writing prospectus applicable to a particular series of debt securities, we can elect to be discharged from our obligations with respect to one or more series of debt securities, except for specified obligations, including obligations to:

- register the transfer or exchange of debt securities of the series;
- replace stolen, lost or mutilated debt securities of the series;
- maintain paying agencies;
- hold monies for payment in trust;
- recover excess money held by the trustee;
- compensate and indemnify the trustee; and
- appoint any successor trustee.

In order to exercise our rights to be discharged, we must deposit with the trustee money or government obligations sufficient to pay all the principal of, any premium and interest on, the debt securities of the series on the dates payments are due.

Form, Exchange and Transfer

We will issue the debt securities of each series only in fully registered form without coupons and, unless we otherwise specify in the applicable prospectus supplement or free writing prospectus, in denominations of $1,000 and any integral multiple thereof. The indentures provide that we may issue debt securities of a series in temporary or permanent global form and as book-entry securities that will be deposited with, or on behalf of, The Depository Trust Company or another depository named by us and identified in a prospectus supplement or free writing prospectus with respect to that series.

At the option of the holder, subject to the terms of the indentures and the limitations applicable to global securities described in the applicable prospectus supplement or free writing prospectus, the holder of the debt securities of any series can exchange the debt securities for other debt securities of the same series, in any authorized denomination and of like tenor and aggregate principal amount.

Subject to the terms of the indentures and the limitations applicable to global securities set forth in the applicable prospectus supplement or free writing prospectus, holders of the debt securities may present the debt securities for exchange or for registration of transfer, duly endorsed or with the form of transfer endorsed thereon duly executed if so required by us or the security registrar, at the office of the security registrar or at the office of any transfer agent designated by us for this purpose. Unless otherwise provided in the debt securities that the holder presents for transfer or exchange, we will make no service charge for any registration of transfer or exchange, but we may require payment of any taxes or other governmental charges.

We will name in the applicable prospectus supplement or free writing prospectus the security registrar, and any transfer agent in addition to the security registrar, that we initially designate for any debt securities. We may at any time designate additional transfer agents or rescind the designation of any transfer agent or approve a change in the office through which any transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for the debt securities of each series. If we elect to redeem the debt securities of any series, we will not be required to:

- issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or
- register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

Information Concerning the Trustee

The trustee, other than during the occurrence and continuance of an event of default under an indenture, undertakes to perform only those duties as are specifically set forth in the applicable indenture. Upon an event of default under an indenture, the trustee must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs.

Subject to this provision, the trustee is under no obligation to exercise any of the powers given it by the indentures at the request of any holder of debt securities unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur.

Payment and Paying Agents

Unless we otherwise indicate in the applicable prospectus supplement or free writing prospectus, we will make payment of the interest on any debt securities on any interest payment date to the person in whose name the debt securities, or one or more predecessor securities, are registered at the close of business on the regular record date for the interest.

We will pay principal of and any premium and interest on the debt securities of a particular series at the office of the paying agents designated by us, except that unless we otherwise indicate in the applicable prospectus supplement or free writing prospectus, we will make interest payments by check that we will mail to the holder or by wire transfer to certain holders. Unless we otherwise indicate in the applicable prospectus supplement or free writing prospectus, we will designate the corporate trust office of the trustee as our sole paying agent for payments with respect to debt securities of each series. We will name in the applicable prospectus supplement or free writing prospectus any other paying agents that we initially designate for the debt securities of a particular series. We will maintain a paying agent in each place of payment for the debt securities of a particular series.

All money we pay to a paying agent or the trustee for the payment of the principal of or any premium or interest on any debt securities that remains unclaimed at the end of two years after such principal, premium or interest has become due and payable will be repaid to us, and the holder of the debt security thereafter may look only to us for payment thereof.

Governing Law

The indentures and the debt securities will be governed by and construed in accordance with the laws of the State of New York, except to the extent that the Trust Indenture Act is applicable.

Ranking of Debt Securities

The subordinated debt securities will be subordinate and junior in priority of payment to certain of our other indebtedness to the extent described in a prospectus supplement or free writing prospectus. The subordinated indenture does not limit the amount of subordinated debt securities that we may issue. It also does not limit us from issuing any other secured or unsecured debt.

The senior debt securities will rank equally in right of payment to all our other senior unsecured debt. The senior indenture does not limit the amount of senior debt securities that we may issue. It also does not limit us from issuing any other secured or unsecured debt.

DESCRIPTION OF WARRANTS

The following description, together with the additional information we may include in any applicable prospectus supplements, summarizes the material terms and provisions of the warrants that we may offer under this prospectus and the related warrant agreements and warrant certificates. While the terms summarized below will apply generally to any warrants that we may offer, we will describe the particular terms of any series of warrants in more detail in the applicable prospectus supplement or free writing prospectus. If we indicate in the prospectus supplement or free writing prospectus, the terms of any warrants offered under that prospectus supplement may differ from the terms described below. Specific warrant agreements will contain additional important terms and provisions and will be incorporated by reference as an exhibit to the registration statement, which includes this prospectus.

General

We may issue warrants for the purchase of common stock, preferred stock and/or debt securities in one or more series. We may issue warrants independently or together with common stock, preferred stock and/or debt securities, and the warrants may be attached to or separate from these securities.

We will evidence each series of warrants by warrant certificates that we will issue under a separate warrant agreement. We will enter into the warrant agreement with a warrant agent. We will indicate the name and address of the warrant agent in the applicable prospectus supplement relating to a particular series of warrants.

We will describe in the applicable prospectus supplement or free writing prospectus the terms of the series of warrants, including:

- the title of such securities;
- the offering price and aggregate number of warrants offered;
- the currency for which the warrants may be purchased;
- if applicable, the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each such security or each principal amount of such security;
- if applicable, the date on and after which the warrants and the related securities will be separately transferable;
- if applicable, the minimum or maximum amount of such warrants which may be exercised at any one time;
- in the case of warrants to purchase debt securities, the principal amount of debt securities purchasable upon exercise of one warrant and the price at, and currency in which, this principal amount of debt securities may be purchased upon such exercise;
- in the case of warrants to purchase common stock or preferred stock, the number of shares of common stock or preferred stock, as the case may be, purchasable upon the exercise of one warrant and the price at which these shares may be purchased upon such exercise;
- the effect of any merger, consolidation, sale or other disposition of our business on the warrant agreement and the warrants;
- the terms of any rights to redeem or call the warrants;
- the terms of any rights to force the exercise of the warrants;
- any provisions for changes to or adjustments in the exercise price or number of securities issuable upon exercise of the warrants;
- the periods during which, and places at which, the warrants are exercisable;

- the manner of exercise;
- the dates on which the right to exercise the warrants will commence and expire;
- the manner in which the warrant agreement and warrants may be modified;
- federal income tax consequences of holding or exercising the warrants;
- the terms of the securities issuable upon exercise of the warrants; and
- any other specific terms, preferences, rights or limitations of or restrictions on the warrants.

Before exercising their warrants, holders of warrants will not have any of the rights of holders of the securities purchasable upon such exercise, including:

- in the case of warrants to purchase debt securities, the right to receive payments of principal of, or premium, if any, or interest on, the debt securities purchasable upon exercise or to enforce covenants in the applicable indenture; or
- in the case of warrants to purchase common stock or preferred stock, the right to receive dividends, if any, or, payments upon our liquidation, dissolution or winding up or to exercise voting rights, if any.

Governing Law

Unless we provide otherwise in any applicable prospectus supplement, the warrants and warrant agreements, and any claim, controversy or dispute arising under or related to the warrants or warrant agreements, will be governed by and construed in accordance with the laws of the State of Delaware.

DESCRIPTION OF UNITS

We may issue units comprised of shares of common stock, shares of preferred stock, debt securities and warrants in any combination. We may issue units in such amounts and in as many distinct series as we wish. This section outlines certain provisions of the units that we may issue. If we issue units, they will be issued under one or more unit agreements to be entered into between us and a bank or other financial institution, as unit agent. The information described in this section may not be complete in all respects and is qualified entirely by reference to the unit agreement with respect to the units of any particular series. The specific terms of any series of units offered will be described in the applicable prospectus supplement or free writing prospectus. If so described in a particular supplement or free writing prospectus, the specific terms of any series of units may differ from the general description of terms presented below. We urge you to read any prospectus supplement or free writing prospectus related to any series of units we may offer, as well as the complete unit agreement and unit certificate that contain the terms of the units. If we issue units, forms of unit agreements and unit certificates relating to such units will be incorporated by reference as exhibits to the registration statement, which includes this prospectus.

Each unit that we may issue will be issued so that the holder of the unit is also the holder of each security included in the unit. Thus, the holder of a unit will have the rights and obligations of a holder of each included security. The unit agreement under which a unit is issued may provide that the securities included in the unit may not be held or transferred separately, at any time or at any time before a specified date. The applicable prospectus supplement may describe:

- the designation and terms of the units and of the securities comprising the units, including whether and under what circumstances those securities may be held or transferred separately;
- any provisions of the governing unit agreement;
- the price or prices at which such units will be issued;
- the applicable United States federal income tax considerations relating to the units;
- any provisions for the issuance, payment, settlement, transfer or exchange of the units or of the securities comprising the units; and
- any other terms of the units and of the securities comprising the units.

The provisions described in this section, as well as those described under “Description of Capital Stock,” “Description of Debt Securities” and “Description of Warrants” will apply to the securities included in each unit, to the extent relevant and as may be updated in any prospectus supplements or free writing prospectuses.

Issuance in Series

We may issue units in such amounts and in as many distinct series as we wish. This section summarizes terms of the units that apply generally to all series. Most of the financial and other specific terms of a particular series of units will be described in the applicable prospectus supplement or free writing prospectus.

Unit Agreements

We will issue the units under one or more unit agreements to be entered into between us and a bank or other financial institution, as unit agent. We may add, replace or terminate unit agents from time to time. We will identify the unit agreement under which each series of units will be issued and the unit agent under that agreement in the applicable prospectus supplement or free writing prospectus.

The following provisions will generally apply to all unit agreements unless otherwise stated in the applicable prospectus supplement or free writing prospectus:

Modification without Consent

We and the applicable unit agent may amend any unit or unit agreement without the consent of any holder:

- to cure any ambiguity; any provisions of the governing unit agreement that differ from those described below;
- to correct or supplement any defective or inconsistent provision; or
- to make any other change that we believe is necessary or desirable and will not adversely affect the interests of the affected holders in any material respect.

We do not need any approval to make changes that affect only units to be issued after the changes take effect. We may also make changes that do not adversely affect a particular unit in any material respect, even if they adversely affect other units in a material respect. In those cases, we do not need to obtain the approval of the holder of the unaffected unit; we need only obtain any required approvals from the holders of the affected units.

Modification with Consent

We may not amend any particular unit or a unit agreement with respect to any particular unit unless we obtain the consent of the holder of that unit, if the amendment would:

- impair any right of the holder to exercise or enforce any right under a security included in the unit if the terms of that security require the consent of the holder to any changes that would impair the exercise or enforcement of that right; or
- reduce the percentage of outstanding units or any series or class the consent of whose holders is required to amend that series or class, or the applicable unit agreement with respect to that series or class, as described below.

Any other change to a particular unit agreement and the units issued under that agreement would require the following approval:

- If the change affects only the units of a particular series issued under that agreement, the change must be approved by the holders of a majority of the outstanding units of that series; or
- If the change affects the units of more than one series issued under that agreement, it must be approved by the holders of a majority of all outstanding units of all series affected by the change, with the units of all the affected series voting together as one class for this purpose.

These provisions regarding changes with majority approval also apply to changes affecting any securities issued under a unit agreement, as the governing document.

In each case, the required approval must be given by written consent.

Unit Agreements Will Not Be Qualified under Trust Indenture Act

No unit agreement will be qualified as an indenture, and no unit agent will be required to qualify as a trustee, under the Trust Indenture Act. Therefore, holders of units issued under unit agreements will not have the protections of the Trust Indenture Act with respect to their units.

Mergers and Similar Transactions Permitted; No Restrictive Covenants or Events of Default

The unit agreements will not restrict our ability to merge or consolidate with, or sell our assets to, another corporation or other entity or to engage in any other transactions. If at any time we merge or consolidate with, or

sell our assets substantially as an entirety to, another corporation or other entity, the successor entity will succeed to and assume our obligations under the unit agreements. We will then be relieved of any further obligation under these agreements.

The unit agreements will not include any restrictions on our ability to put liens on our assets, nor will they restrict our ability to sell our assets. The unit agreements also will not provide for any events of default or remedies upon the occurrence of any events of default.

Governing Law

The unit agreements and the units will be governed by Delaware law.

LEGAL OWNERSHIP OF SECURITIES

We can issue securities in registered form or in the form of one or more global securities. We describe global securities in greater detail below. We refer to those persons who have securities registered in their own names on the books that we or any applicable trustee, depositary or warrant agent maintain for this purpose as the "holders" of those securities. These persons are the legal holders of the securities. We refer to those persons who, indirectly through others, own beneficial interests in securities that are not registered in their own names, as "indirect holders" of those securities. As we discuss below, indirect holders are not legal holders, and investors in securities issued in book-entry form or in street name will be indirect holders.

Book-Entry Holders

We may issue securities in book-entry form only, as we will specify in any applicable prospectus supplement. This means securities may be represented by one or more global securities registered in the name of a financial institution that holds them as depositary on behalf of other financial institutions that participate in the depositary's book-entry system. These participating institutions, which are referred to as participants, in turn, hold beneficial interests in the securities on behalf of themselves or their customers.

Only the person in whose name a security is registered is recognized as the holder of that security. Securities issued in global form will be registered in the name of the depositary or its participants. Consequently, for securities issued in global form, we will recognize only the depositary as the holder of the securities, and we will make all payments on the securities to the depositary. The depositary passes along the payments it receives to its participants, which in turn pass the payments along to their customers who are the beneficial owners. The depositary and its participants do so under agreements they have made with one another or with their customers; they are not obligated to do so under the terms of the securities.

As a result, investors in a global security will not own securities directly. Instead, they will own beneficial interests in a global security, through a bank, broker or other financial institution that participates in the depositary's book-entry system or holds an interest through a participant. As long as the securities are issued in global form, investors will be indirect holders, and not legal holders, of the securities.

Street Name Holders

We may terminate a global security or issue securities in non-global form. In these cases, investors may choose to hold their securities in their own names or in "street name." Securities held by an investor in street name would be registered in the name of a bank, broker or other financial institution that the investor chooses, and the investor would hold only a beneficial interest in those securities through an account he or she maintains at that institution.

For securities held in street name, we or any applicable trustee or depositary will recognize only the intermediary banks, brokers and other financial institutions in whose names the securities are registered as the holders of those securities, and we or any applicable trustee or depositary will make all payments on those securities to them. These institutions pass along the payments they receive to their customers who are the beneficial owners, but only because they agree to do so in their customer agreements or because they are legally required to do so. Investors who hold securities in street name will be indirect holders, not holders, of those securities.

Legal Holders

Our obligations, as well as the obligations of any applicable trustee and of any third parties employed by us or a trustee, run only to the legal holders of the securities. We do not have obligations to investors who hold beneficial interests in global securities, in street name or by any other indirect means. This will be the case whether an investor chooses to be an indirect holder of a security or has no choice because we are issuing the securities only in global form.

For example, once we make a payment or give a notice to the legal holder, we have no further responsibility for the payment or notice even if that legal holder is required, under agreements with its participants or customers or by law, to pass it along to the indirect holders but does not do so. Similarly, we may want to obtain the approval of the legal holders to amend an indenture, to relieve us of the consequences of a default or of our obligation to comply with a particular provision of the indenture or for other purposes. In such an event, we would seek approval only from the holders, and not the indirect holders, of the securities. Whether and how the legal holders contact the indirect holders is up to the legal holders.

Special Considerations for Indirect Holders

If you hold securities through a bank, broker or other financial institution, either in book-entry form because the securities are represented by one or more global securities or in street name, you should check with your own institution to find out:

- how it handles securities payments and notices;
- whether it imposes fees or charges;
- how it would handle a request for the holders' consent, if ever required;
- whether and how you can instruct it to send you securities registered in your own name so you can be a holder, if that is permitted in the future;
- how it would exercise rights under the securities if there were a default or other event triggering the need for holders to act to protect their interests; and
- if the securities are in book-entry form, how the depositary's rules and procedures will affect these matters.

Global Securities

A global security is a security that represents one or any other number of individual securities held by a depositary. Generally, all securities represented by the same global securities will have the same terms.

Each security issued in book-entry form will be represented by a global security that we issue to, deposit with and register in the name of a financial institution or its nominee that we select. The financial institution that we select for this purpose is called the depositary. Unless we specify otherwise in any applicable prospectus supplement, DTC will be the depositary for all securities issued in book-entry form.

A global security may not be transferred to or registered in the name of anyone other than the depositary, its nominee or a successor depositary, unless special termination situations arise. We describe those situations below under " — Special Situations When a Global Security Will Be Terminated." As a result of these arrangements, the depositary, or its nominee, will be the sole registered owner and legal holder of all securities represented by a global security, and investors will be permitted to own only beneficial interests in a global security. Beneficial interests must be held by means of an account with a broker, bank or other financial institution that in turn has an account with the depositary or with another institution that does. Thus, an investor whose security is represented by a global security will not be a legal holder of the security, but only an indirect holder of a beneficial interest in the global security.

If the prospectus supplement for a particular security indicates that the security will be issued in global form only, then the security will be represented by a global security at all times unless and until the global security is terminated. If termination occurs, we may issue the securities through another book-entry clearing system or decide that the securities may no longer be held through any book-entry clearing system.

Special Consideration for Global Securities

The rights of an indirect holder relating to a global security will be governed by the account rules of the investor's financial institution and of the depositary, as well as general laws relating to securities transfers. We do not recognize an indirect holder as a holder of securities and instead deal only with the depositary that holds the global security.

If securities are issued only in the form of a global security, an investor should be aware of the following:

- an investor cannot cause the securities to be registered in his or her name, and cannot obtain non-global certificates for his or her interest in the securities, except in the special situations we describe below;
- an investor will be an indirect holder and must look to his or her own bank, broker or other financial institution for payments on the securities and protection of his or her legal rights relating to the securities, as we describe above;
- an investor may not be able to sell interests in the securities to some insurance companies and to other institutions that are required by law to own their securities in non-book-entry form;
- an investor may not be able to pledge his or her interest in a global security in circumstances where certificates representing the securities must be delivered to the lender or other beneficiary of the pledge in order for the pledge to be effective;
- the depositary's policies, which may change from time to time, will govern payments, transfers, exchanges and other matters relating to an investor's interest in a global security;
- we and any applicable trustee have no responsibility for any aspect of the depositary's actions or for its records of ownership interests in a global security, nor do we or any applicable trustee supervise the depositary in any way;
- the depositary may, and we understand that DTC will, require that those who purchase and sell interests in a global security within its book-entry system use immediately available funds, and your bank, broker or other financial institution may require you to do so as well; and
- financial institutions that participate in the depositary's book-entry system, and through which an investor holds its interest in a global security, may also have their own policies affecting payments, notices and other matters relating to the securities.

There may be more than one financial intermediary in the chain of ownership for an investor. We do not monitor and are not responsible for the actions of any of those intermediaries.

Special Situations When a Global Security Will Be Terminated

In a few special situations described below, the global security will terminate and interests in it will be exchanged for physical certificates representing those interests. After that exchange, the choice of whether to hold securities directly or in street name will be up to the investor. Investors must consult their own banks, brokers or other financial institutions to find out how to have their interests in securities transferred to their own name, so that they will be direct holders. We have described the rights of holders and street name investors above.

Unless we provide otherwise in any applicable prospectus supplement, the global security will terminate when the following special situations occur:

- if the depositary notifies us that it is unwilling, unable or no longer qualified to continue as depositary for that global security and we do not appoint another institution to act as depositary within 90 days;
- if we notify any applicable trustee that we wish to terminate that global security; or

- if an event of default has occurred with regard to securities represented by that global security and has not been cured or waived.

The prospectus supplement may also list additional situations for terminating a global security that would apply only to the particular series of securities covered by any applicable prospectus supplement. When a global security terminates, the depositary, and not we or any applicable trustee, is responsible for deciding the names of the institutions that will be the initial direct holders.

PLAN OF DISTRIBUTION

We may sell the common stock:

- through underwriters;
- through dealers;
- through agents;
- directly to purchasers; or
- through a combination of any of these methods or any other method permitted by law.

In addition, we may issue the securities as a dividend or distribution or in a subscription rights offering to our existing security holders.

We may directly solicit offers to purchase securities, or agents may be designated to solicit such offers. In the prospectus supplement relating to such offering, we will name any agent that could be viewed as an underwriter under the Securities Act and describe any commissions that we must pay to any such agent. Any such agent will be acting on a best efforts basis for the period of its appointment or, if indicated in the applicable prospectus supplement, on a firm commitment basis. This prospectus may be used in connection with any offering of our securities through any of these methods or other methods described in the applicable prospectus supplement.

The distribution of the securities may be effected from time to time in one or more transactions:

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

Each prospectus supplement will describe the method of distribution of the securities and any applicable restrictions.

The prospectus supplement with respect to the securities of a particular series will describe the terms of the offering of the securities, including the following:

- the name of the agent or any underwriters;
- the public offering or purchase price;
- any discounts and commissions to be allowed or paid to the agent or underwriters;
- all other items constituting underwriting compensation;
- any discounts and commissions to be allowed or paid to dealers; and
- any exchanges on which the securities will be listed.

If any underwriters or agents are used in the sale of the securities in respect of which this prospectus is delivered, we will enter into an underwriting agreement, sales agreement or other agreement with them at the time of sale to them, and we will set forth in the prospectus supplement relating to such offering the names of the underwriters or agents and the terms of the related agreement with them.

In connection with the offering of securities, we may grant to the underwriters an option to purchase additional securities with an additional underwriting commission, as may be set forth in the accompanying prospectus supplement. If we grant any such option, the terms of such option will be set forth in the prospectus supplement for such securities.

If a dealer is used in the sale of the securities in respect of which the prospectus is delivered, we will sell such securities to the dealer, as principal. The dealer, who may be deemed to be an "underwriter" as that term is defined in the Securities Act, may then resell such securities to the public at varying prices to be determined by such dealer at the time of resale.

If we offer securities in a subscription rights offering to our existing security holders, we may enter into a standby underwriting agreement with dealers, acting as standby underwriters. We may pay the standby underwriters a commitment fee for the securities they commit to purchase on a standby basis. If we do not enter into a standby underwriting arrangement, we may retain a dealer-manager to manage a subscription rights offering for us.

Agents, underwriters, dealers and other persons may be entitled under agreements which they may enter into with us to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, and may be customers of, engage in transactions with or perform services for us in the ordinary course of business.

If so indicated in the applicable prospectus supplement, we will authorize underwriters or other persons acting as our agents to solicit offers by certain institutions to purchase securities from us pursuant to delayed delivery contracts providing for payment and delivery on the date stated in the prospectus supplement. Each contract will be for an amount not less than, and the aggregate amount of securities sold pursuant to such contracts shall not be less nor more than, the respective amounts stated in the prospectus supplement. Institutions with whom the contracts, when authorized, may be made include commercial and savings banks, insurance companies, pension funds, investment companies, educational and charitable institutions and other institutions, but shall in all cases be subject to our approval. Delayed delivery contracts will not be subject to any conditions except that:

- the purchase by an institution of the securities covered under that contract shall not at the time of delivery be prohibited under the laws of the jurisdiction to which that institution is subject; and
- if the securities are also being sold to underwriters acting as principals for their own account, the underwriters shall have purchased such securities not sold for delayed delivery. The underwriters and other persons acting as our agents will not have any responsibility in respect of the validity or performance of delayed delivery contracts.

Offered securities may also be offered and sold, if so indicated in the prospectus supplement, in connection with a remarketing upon their purchase, in accordance with a redemption or repayment pursuant to their terms, or otherwise, by one or more remarketing firms, acting as principals for their own accounts or as agents for us. Any remarketing firm will be identified and the terms of its agreement, if any, with us and its compensation will be described in the applicable prospectus supplement. Remarketing firms may be deemed to be underwriters in connection with their remarketing of offered securities.

Certain agents, underwriters and dealers, and their associates and affiliates, may be customers of, have borrowing relationships with, engage in other transactions with, or perform services, including investment banking services, for us or one or more of our respective affiliates in the ordinary course of business.

In order to facilitate the offering of the securities, any underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the securities or any other securities the prices of which may be used to determine payments on such securities. Specifically, any underwriters may overallot in connection with the offering, creating a short position for their own accounts. In addition, to cover overallotments or to stabilize the price of the securities or of any such other securities, the underwriters may bid for, and purchase, the securities or any such other securities in the open market. Finally, in any offering of the securities through a syndicate of underwriters, the underwriting syndicate may reclaim selling concessions allowed to an underwriter or a dealer for distributing the securities in the offering if the syndicate repurchases previously distributed securities in transactions to cover syndicate short positions, in stabilization transactions or otherwise. Any of these activities

may stabilize or maintain the market price of the securities above independent market levels. Any such underwriters are not required to engage in these activities and may end any of these activities at any time.

Under Rule 15c6-1 of the Exchange Act, trades in the secondary market generally are required to settle in three business days, unless the parties to any such trade expressly agree otherwise. The applicable prospectus supplement may provide that the original issue date for your securities may be more than three scheduled business days after the trade date for your securities. Accordingly, in such a case, if you wish to trade securities on any date prior to the third business day before the original issue date for your securities, you will be required, by virtue of the fact that your securities initially are expected to settle in more than three scheduled business days after the trade date for your securities, to make alternative settlement arrangements to prevent a failed settlement.

The securities may be new issues of securities and may have no established trading market. The securities may or may not be listed on a national securities exchange. We can make no assurance as to the liquidity of or the existence of trading markets for any of the securities.

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

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

The anticipated date of delivery of offered securities will be set forth in the applicable prospectus supplement relating to each offer.

LEGAL MATTERS

Unless the applicable prospectus supplement indicates otherwise, the validity of the securities in respect of which this prospectus is being delivered will be passed upon by Munger, Tolles & Olson LLP. Additional legal matters may be passed upon for us or any underwriters, dealers or agents, by counsel that we will name in the applicable prospectus supplement.

EXPERTS

The consolidated financial statements of the Company incorporated in this Prospectus by reference from the Company's Annual Report on Form 10-K for the year ended December 31, 2016, have been audited by Deloitte & Touche LLP, an independent registered public accounting firm, as stated in their report, which is incorporated herein by reference. Such consolidated financial statements have been so incorporated in reliance upon the report of such firm given upon their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at http://www.sec.gov. Copies of certain information filed by us with the SEC are also available on our website at www.adverum.com. Our website is not a part of this prospectus and is not incorporated by reference in this prospectus. You may also read and copy any document we file at the SEC's Public Reference Room, 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room.

This prospectus is part of a registration statement we filed with the SEC. This prospectus omits some information contained in the registration statement in accordance with SEC rules and regulations. You should review the information and exhibits in the registration statement for further information about us and our consolidated subsidiary and the securities we are offering. Statements in this prospectus concerning any document we filed as an exhibit to the registration statement or that we otherwise filed with the SEC are not intended to be comprehensive and are qualified by reference to these filings. You should review the complete document to evaluate these statements.

INCORPORATION BY REFERENCE

The SEC allows us to incorporate by reference much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus is considered to be part of this prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus is continually updated and those future filings may modify or supersede some of the information included or incorporated in this prospectus. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus or in any document previously incorporated by reference have been modified or superseded. This prospectus incorporates by reference the documents listed below and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act (in each case, other than those documents or the portions of those documents not deemed to be filed) between the date of the initial registration statement and the effectiveness of the registration statement and following the effectiveness of the registration statement until the offering of the securities under the registration statement is terminated or completed:

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2016, filed with the SEC on March 9, 2017;
- the information specifically incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2016 from our definitive proxy statement on Schedule 14A, which was filed with the SEC on April 26, 2017;
- our Quarterly Reports on Form 10-Q for the quarterly periods ended March 31, 2017 and June 30, 2017, respectively, filed with the SEC on May 9, 2017 and August 8, 2017;
- our Current Reports on Form 8-K filed with the SEC on February 3, 2017, February 10, 2017, February 14, 2017, March 1, 2017, March 14, 2017 (but not to the extent furnished and not filed), March 20, 2017, March 24, 2017, April 20, 2017 (but not to the extent furnished and not filed), April 21, 2017, April 27, 2017, June 9, 2017, and June 20, 2017 (but not to the extent furnished and not filed); and
- the description of our common stock contained in our Registration Statement on Form 8-A filed with the SEC on July 28, 2014, including any amendments or reports filed for the purpose of updating such description.

You may request a copy of these filings, at no cost, by writing or telephoning us at the following address or telephone number:

Adverum Biotechnologies, Inc.
1035 O'Brien Drive
Menlo Park, CA 94025
Attn: Investor Relations
(650) 272-6269

Table of Contents

Shares

Common Stock

PROSPECTUS SUPPLEMENT

Joint Book-Running Managers

Cowen **Piper Jaffray**

Lead Manager

Raymond James

, 2018