UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 10-K

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

For the fiscal year ended December 31, 2016

or

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

For the transition period from _____ to _____

Commission File Number: 001-36579

Adverum Biotechnologies, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**20-5258327**
(State or other jurisdiction of incorporation or organization)	**(IRS Employer Identification No.)**

1035 O'Brien Drive
Menlo Park, California 94025
(650) 272-6269
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

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

Title of Each Class	**Name of Each Exchange on Which Registered**
Common Stock, par value $0.0001 per share	**Nasdaq Global Market**

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

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

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

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files): Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

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

Large accelerated filer	☐	Accelerated filer	☒
Non-accelerated filer	☐ (Do not check if a smaller reporting company)	Smaller reporting company	☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

As of June 30, 2016, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of the registrant's common stock held by non-affiliates of the registrant was approximately $99.8 million, based on the closing price of the registrant's common stock on the NASDAQ Global Market on June 30, 2016 of $3.16 per share. Shares of the registrant's common stock held by each officer and director and each person known to the registrant to own 10% or more of the outstanding common stock of the registrant have been excluded in that such persons may be deemed affiliates. This determination of affiliate status is not a determination for other purposes.

As of February 28, 2017, the registrant had 42,063,237 shares of common stock, par value $0.0001 par value, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the definitive proxy statement (the Proxy Statement) for the 2017 Annual Meeting of Stockholders of the registrant are incorporated by reference into Part III of this Annual Report on Form 10-K. The Proxy Statement will be filed with the Securities and Exchange Commission within 120 days of the registrant's fiscal year ended December 31, 2016.

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In this report, unless otherwise stated or the context otherwise indicates, references to "Adverum," "Adverum Biotechnologies," "the Company," "we," "us," "our" and similar references refer to Adverum Biotechnologies, Inc., a Delaware corporation.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements that involve risks and uncertainties. All statements other than statements of historical facts contained in this Annual Report on Form 10-K are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "may," "could," "will," "would," "should," "expect," "plan," "anticipate," "believe," "estimate," "intend," "predict," "seek," "contemplate," "potential" or "continue" or the negative of these terms or other comparable terminology. These 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 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 under "Risk Factors" and elsewhere in this Annual Report on Form 10-K.

Any forward-looking statement in this Annual Report on Form 10-K reflects our current views with respect to future events and is subject to these and other risks, uncertainties and assumptions relating to our 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 Annual Report on Form 10-K. 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.

This Annual Report on Form 10-K contains estimates, projections and other information concerning our industry, our business and the markets for certain drugs, including data regarding the estimated size of those markets, their projected growth rates and the incidence of certain medical conditions. Information that is based on estimates, forecasts, projections or similar methodologies is inherently subject to uncertainties, and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, studies and similar data prepared by third parties, industry, medical and general publications, government data and similar sources. In some cases, we do not expressly refer to the sources from which this data is derived. In that regard, when we refer to one or more sources of this type of data in any paragraph, you should assume that other data of this type appearing in the same paragraph is derived from the same sources, unless otherwise expressly stated or the context otherwise requires.

PART 1.

Item 1. Business

Overview

We are a gene therapy company committed to discovering and developing novel medicines that can offer potentially life-changing therapeutic benefit to patients living with rare diseases or diseases of the eye, who currently have limited or burdensome treatment options. We are leveraging our industry-leading adeno-associated virus (AAV)-based 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 on May 11, 2016, of Annapurna Therapeutics SAS (Annapurna), a privately-held French gene therapy company. 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 (wAMD) and in rare diseases alpha-1 antitrypsin (A1AT) deficiency and hereditary angioedema (HAE). Our pipeline of lead and partnered gene therapy programs is shown below.

For wAMD, we have two new anti-VEGF gene therapy candidates, ADVM-022 (AAV.7m8-aflibercept) and ADVM-032 (AAV.7m8-ranibizumab). These therapies utilize a proprietary vector and are administered intravitreally for this indication. Preclinical data demonstrate that ADVM-022 and ADVM-032 have the potential to minimize the treatment burden of frequent injections and maximize visual outcomes in patients living with this disease.

At recent scientific meetings we presented preclinical proof-of-concept data of ADVM-022 and ADVM-032's anti-angiogenic effect in a 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 and ADVM-032 showed efficacy that was comparable to the anti-VEGF standard of care, the positive control in the CNV model. We have selected ADVM-022 to advance in development first and we plan to initiate investigational new drug (IND)-enabling toxicology and biodistribution studies in the first half of 2017 to support a planned IND filing. We also continue to review data for our backup gene therapy for wAMD ADVM-032.

Before focusing on these two new therapies for wet AMD, we were developing AVA-101 in a Phase 2a clinical trial in 32 patients with wet AMD. In June 2015, we announced top-line results, and although we did not observe any serious safety issues, we also did not observe evidence of a complete and/or durable anti-VEGF response in the majority of subjects treated with AVA-101 as administered (via surgical sub-retinal delivery) in the Phase 2a study. As a result, in July 2016, we announced our decision to discontinue development of AVA-101.

With our pipeline of gene therapies for rare diseases, we are advancing ADVM-043 (formerly known as ANN-001) for the treatment of A1AT deficiency. ADVM-043 is a product candidate designed to be a single-administration treatment. This therapy has the potential to induce stable, long-term A1AT expression at therapeutic levels, as seen in preclinical proof-of-concept studies. ADVM-043 has an open IND with the U.S. Food and Drug Administration (FDA), and we plan to engage with the agency in the first half of

2017 to review our development plan. Concurrently, we are upgrading ADVM-043's manufacturing process to a commercial-grade baculovirus-based process and plan to transfer this process to a contract manufacturing organization to produce clinical materials for our trials. We plan to initiate a toxicology study using material produced from the new baculovirus-based process in the first half of 2017 and to begin patient enrollment in a Phase 1/2 trial in the fourth quarter of 2017.

We are also advancing ADVM-053 (formerly known as ANN-002) to treat HAE. In the first half of 2017, we plan to initiate IND-enabling studies for ADVM-053 and engage with the FDA to review our plans. We are working to transfer our manufacturing process to a contract manufacturing organization to produce clinical materials for our future ADVM-053 studies.

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

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 and, as a result, Annapurna is now our wholly-owned subsidiary. At the closing of the acquisition, we issued 14,087,246 shares of our common stock to the shareholders of Annapurna, and the outstanding options or other rights to purchase capital stock of Annapurna were exchanged for options relating to shares of our common stock.

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 complimentary 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 and diverse pipeline of gene therapies in ocular and rare diseases;
- Robust patent portfolio;
- Proprietary vectors;
- Experienced leadership team with expertise in developing gene therapies; and
- Strong cash and cash equivalents position of $222.2 million as of December 31, 2016, which is expected to fund our three lead gene therapy programs through the end of 2019.

Our 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:

- **Focus on advancing our three lead gene therapies into clinical development.** Our three lead gene therapy programs are ADVM-022 and ADVM-032 for our wAMD program, ADVM-043 for our A1AT deficiency program, and ADVM-053 for our HAE program. To advance these three gene therapies into clinical development, we plan to initiate toxicology studies and engage with the FDA to discuss our development plans. Enrollment for our first Phase 1/2 clinical trial is planned to begin in the fourth quarter of 2017 to evaluate ADVM-043 in patients with A1AT deficiency.
- **Establish a portfolio of gene therapies for ocular and rare diseases**. We have a robust and diverse pipeline of gene therapies and a leadership team with significant experience in the development of gene therapies. Our therapies are designed to deliver new, potentially single-administration treatments to patients living with ocular and rare diseases who currently have limited or burdensome treatment options. As an example, for the treatment of wAMD, the current standard-of-care treatment requires patients to receive intravitreal injections of anti-VEGF proteins every 4-8 weeks, which is difficult for patients to comply with and leads to loss of vision from underdosing. For the treatment of A1AT deficiency, the current standard-of-care treatment is weekly intravenous (IV) infusions of alpha-1 proteinase inhibitor, which leads to

worsening lung function from underdosing. For HAE, the current standard-of-care treatment is IV infusions of C1 Esterase Inhibitor (C1EI) 2-3 times a week, which only offer limited efficacy as patients can have breakthrough attacks, which can be deadly. Our goal is to build over time a portfolio of gene therapies to offer the potential for life-changing therapeutic benefit from a single-administration treatment.

- **Utilize our in-house manufacturing expertise to derisk process to support clinical and commercial product supply.** Our process development capabilities are designed to develop and deliver scalable, commercial-ready processes to contract manufacturing organizations for the manufacturing of our products for clinical and eventual commercial use. For ADVM-043, we currently are upgrading our manufacturing process to a baculovirus-based process and plan to transfer this process, as well as the process for manufacturing ADVM-053, to a contract manufacturing organization to produce clinical supply for our planned trials. We also have assay development capabilities and Good Manufacturing Product (GMP) quality control to optimize product release for human use and facilitate FDA regulatory compliance from an early clinical stage of the drug development process.
- **Advance our earlier-stage research initiatives to leverage our industry-leading capabilities in novel vector development.** We plan to continue to leverage our next-generation discovery platform and employ directed evolution to discover and manufacture novel vectors with the potential to enhance vector tropism for certain tissues and improve their antibody neutralization profile. We are also focused on discovering improved ubiquitous and cell-specific promoters and expression cassettes to offer optimal transgene expression target tissue and decrease off-target effects. Our research initiatives are also targeted at achieving production of a large amount of high-throughput libraries of novel vector variants, which are necessary for screening in large animals and/or in certain tissues. In addition, we are seeking vectors with a favorable neutralizing antibody profile. We plan to continue to use our internal expertise and relationships with thought leaders to identify additional target indications that we can develop in the future.
- **Collaborate with partners to leverage our industry-leading ophthalmic vector development and product delivery capabilities.** Under a collaboration 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 collaboration agreement with Regeneron provides for the development of up to eight distinct ocular therapeutic targets, four of which are already identified, including AVA-311 for the treatment of juvenile XLRS. We plan to continue to explore ways to work collaboratively with these and potential new partners who may benefit from our capabilities and expertise in AAV vector development and product delivery.

Gene Therapy Background

Gene therapy is a powerful treatment modality to address disease biology in a targeted and efficient way. Using gene therapy, physicians can introduce or re-introduce genes that encode a therapeutic protein. Instead of providing proteins or other therapies externally and dosing them over a long period, gene therapy offers the possibility of dosing once, or a very limited number of times, to achieve a long-term, durable benefit. Once a patient's cells have incorporated the therapeutic gene, the cells are able to continue to produce the therapeutic protein for years or, potentially, the rest of the patient's life.

Similar to existing classes of protein or biologic therapies such as monoclonal antibodies and drug-antibody conjugates, gene therapy has taken a number of years to evolve from a research tool into a viable and compelling treatment modality. There have been several recent advances in gene therapy, including the following:

- **Compelling clinical data.** Positive data from gene therapy have been reported in a variety of indications, including adrenoleukodystrophy, beta-thalassemia, chronic lymphoid leukemia, hemophilia, Spinal Muscular Atrophy, HIV and Parkinson's disease, as well as several ophthalmic diseases including LCA2, Choroideremia and Leber's Hereditary Optic Neuropathy.
- **Increased investment by biopharmaceutical companies.** The modality of gene therapy has been further validated by growing interest and investments by biopharmaceutical companies. Large, global biopharmaceutical companies, such as BioMarin Pharmaceutical Inc., Biogen Idec Inc., Celgene Corporation, GlaxoSmithKline plc, Novartis, Sanofi, Regeneron and Shire Pharmaceuticals Group Plc, have increased their investment in the gene therapy field. Additionally, pure-play gene therapy companies, such as Applied Genetic Technologies Corporation, Audentes Therapeutics, Inc., bluebird bio, Inc., Dimension Therapeutics, Editas Medicine, Inc., REGENXBIO Inc., Spark Therapeutics, Inc., uniQure N.V. and Voyager Therapeutics, have attracted recent investment in this growing field.
- **Regulatory clarity.** Although the FDA has not yet approved a human gene therapy product, it has provided guidance for the development of gene therapy products. For example, the FDA has established the Office of Cellular, Tissue and Gene Therapies within its Center for Biologics Evaluation and Research (CBER) to consolidate the review of gene therapy products, and the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its reviews.

Our Novel AAV Vector Discovery and Optimization System

Our next-generation discovery platform is based on vectors derived from adeno-associated virus (AAV), which is a small, non-pathogenic virus, with the DNA encoding the AAV viral genes removed and replaced with DNA encoding a therapeutic gene. The resulting vector is used to deliver a functional gene into a desired cell population, which when expressed, will result in continuous protein production. We believe AAV vectors offer numerous advantages over other viral and non-viral vector technologies used for gene therapy. These advantages, highlighted below, have the potential to allow AAVs to be safe, to be applicable for a variety of indications and to exhibit long-term efficacy.

- **Highly-efficient transfer of DNA.** AAV vectors offer highly-efficient transfer of DNA to the patient.
- **Long-term expression.** Once incorporated into the host cell, AAV vectors can continue to drive expression of a therapeutic protein for years.
- **Non-integrating.** AAV vectors do not readily integrate into the host cell's genome, mitigating the risk of potential safety concerns.
- **No introduction of exogenous proteins.** Therapeutic proteins are expressed by a patient's own cells, rather than through the introduction of an exogenous protein.
- **Non-pathogenic.** AAV vectors are not known to cause any disease in humans.
- **Low inflammatory potential.** AAV vectors elicit only a mild immune response, if any, in humans, particularly when used in the eye.
- **Non-replicating.** Once inside the host cell, AAV vectors do not replicate, thereby preventing the spread to unwanted tissues.
- **Ability to transduce non-dividing cells.** AAV vectors are able to transduce non-dividing cells and this is a significant advantage as many retinal cells cease to divide early in a person's life.
- **Tested in humans.** AAV vectors have been used safely in more than 130 gene therapy trials to date.

AAV is naturally occurring and has become a leading vector used in gene therapy. According to the *Journal of Gene Medicine*, AAV has been used in over 130 clinical trials as of August 2016 demonstrating the increasing acceptance of gene therapy as a safe and effective method for delivering therapeutic genes of interest. The most frequently studied variant of AAV is AAV2, which can preferentially infect a number of cell types, including those found in the retina.

As effective as existing AAV vectors are in gene therapy, we believe there is an opportunity to advance vector capabilities beyond those currently available. Naturally occurring AAV variants have evolved with particular characteristics, some of which pose limitations to their use in gene therapy.

In order to create next-generation vectors, we use a multi-step process known as directed evolution. Our directed evolution technology uses a library of genes coding for viral capsid proteins found in a number of naturally occurring AAVs. We modify these capsid genes in the laboratory to derive novel viral capsid exhibiting different properties and capabilities. Once we have created an initial pool of millions of different AAVs, each with distinct genetic and chemical composition, we screen the AAVs in the pool for novel properties, e.g., specific transduction of a particular cell type of interest or the capability to evade pre-existing neutralizing immune response. After identifying a smaller pool of optimized vectors from this screening process, we repeat the steps of diversity generation and screening until we have identified a select number of engineered AAVs with the characteristics we seek.

Our Product Candidates

We have a pipeline of lead and partnered gene therapy programs in ocular and rare diseases.

ADVM-022 and ADVM-032 for Treatment of Wet AMD

Market for Wet AMD

Age-related macular degeneration (AMD) 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 cells and the gradual loss of vision. As people age, the likelihood of disease progression increases and the resulting condition is referred to as AMD.

Approximately 10% of patients living with AMD have an advanced form of the disease called wet AMD (wAMD), in which blood vessels begin to invade the cellular space between layers of cells in the retina. These new blood vessels are often leaky, which results in fluid and blood in the retina and causes vision loss.

wAMD is a leading cause of vision loss. 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 million on a worldwide basis. The incidence of new cases of wAMD in the United States is approximately 150,000 to 200,000 annually, and this number is expected to grow significantly based on the country's aging population.

Although the underlying molecular causes of AMD are not completely known, VEGF is known to play a central role in the growth of new blood vessels in wet AMD. The standard-of-care therapies for wet AMD include Lucentis® and EYLEA®, which together generated annual sales of approximately $8.4 billion for 2016, as well as off-label use of Avastin®.

- Lucentis®, a recombinant humanized monoclonal antibody fragment that binds to and inhibits VEGF proteins in the eye, was approved in the United States in 2006 and in Europe in 2007. In 2016, Lucentis® achieved worldwide sales of approximately $3.2 billion.
- EYLEA®, a recombinant fusion protein containing portions of the human VEGF receptor that binds to VEGF, was approved in the United States in 2011. EYLEA® has exhibited strong adoption in the market due to its more convenient dosing regimen compared to Lucentis and in 2016, EYLEA® achieved worldwide sales of approximately $5.2 billion.
- Avastin® is a recombinant human monoclonal antibody that binds to VEGF and is approved as an anti-cancer agent. Avastin® is widely prescribed off-label in ophthalmic diseases such as wAMD and makes up approximately 60% of the wet AMD market by volume.

The current treatment regimen can be burdensome, as patients generally require intravitreal injections with anti-VEGF proteins every 4-8 weeks. Compliance with this regimen can be difficult for patients and their caregivers, leading to compliance deficiencies and loss of vision from underdosing.

Our Approach for Wet AMD

We have two new anti-VEGF gene therapy candidates for the treatment wAMD, ADVM-022 (AAV.7m8-aflibercept) and ADVM-032 (AAV.7m8-ranibizumab). These therapies utilize a proprietary vector and are administered intravitreally, avoiding a more invasive subretinal surgery.

Preclinical data demonstrate that ADVM-022 and ADVM-032 have the potential to minimize the treatment burden of frequent injections and maximize visual outcomes in patients living with this disease. At The Retina Society Meeting and the European Society of Gene and Cell Therapy (ESGCT) Conference held in October 2016, we first presented preclinical proof-of-concept data of these vectors' anti-angiogenic effect in a laser-induced choroidal neovascularization (CNV) model in non-human primates, the industry standard for testing new wAMD therapies. In this model, choroidal neovascularization is induced experimentally using a laser, then the lesions in each eye are graded for severity, grades I-IV. The efficacy is assessed by the reduction of the number of most severe, grade IV, lesions in the eye.

The data from this model showed that following a single injection of ADVM-022 and ADVM-032, efficacy was comparable to anti-VEGF standard of care, the positive control in the CNV model. Therapeutic protein levels are seen out to 20 weeks as measured in targeted vitreous and retinal tissue.

We have selected ADVM-022 to advance in development first. We plan to initiate IND-enabling toxicology and biodistribution studies in the first half of 2017 to support a planned IND filing. We also continue to review data for our backup gene therapy for wAMD ADVM-032.

ADVM-043 for Treatment of A1AT Deficiency

Market for A1AT Deficiency

A1AT deficiency is a fairly common orphan disease impacting approximately 100,000 individuals in the United States. The disease is caused by mutations in the SERPINA1 gene, resulting in very low levels of A1AT. A1AT deficiency is associated with premature emphysema.

The current standard-of-care treatment can be challenging for patients and their caregivers, with patients generally requiring weekly intravenous (IV) infusions of an alpha-1 anti-tripsin. The current treatment regimen can lead to worsening lung function which results primarily due to lack of patient compliance.

Our Approach for A1AT Deficiency

ADVM-043 is a product candidate designed to be a single administration treatment and has the potential to induce stable, long-term A1AT protein expression at therapeutic levels, as seen in preclinical proof-of-concept studies. In one study in mice, a single administration of ADVM-043 demonstrated robust A1AT protein expression above therapeutic levels seen from current standard-of-care treatments, with protein levels 2.5 times the therapeutic threshold. Additional data has shown hA1AT mRNA expressed in the lung following either intrapleural or intravenous administration.

In another study in non-human primates, evidence of stable long-term expression of hA1AT mRNA was observed out to one year following intrapleural administration of ADVM-043.

ADVM-043 has an open IND with the FDA, and we plan to engage with the agency in the first half of 2017 to review our development plan.

In October 2016, we decided to upgrade ADVM-043's manufacturing process to a commercial-grade baculovirus-based process. Following this upgrade, we plan to transfer this process to a contract manufacturing organization to produce clinical materials for our trials. We plan to initiate a toxicology study using material produced from the new baculovirus-based process in the first half of 2017 and plan to begin patient enrollment in a Phase 1/2 trial in the fourth quarter of 2017.

ADVM-053 for Treatment of HAE

Market for HAE

HAE is an orphan disease impacting approximately 8,000 individuals in the United States. This disease is caused by a genetic mutation that results in low levels of C1-esterase inhibitor (C1EI). Low C1EI levels are associated with sudden swelling and edema of respiratory airways, gastrointestinal tract, and extremities.

The current standard-of-care prophylaxis treatment can be burdensome for patients. The treatment regimen generally requires IV infusions of C1EI (Cinryze®) 2-3 times a week, which can be difficult for patients and their caregivers, and patients may still experience breakthrough attacks.

A prior study demonstrated that patients treated with more frequent infusions of C1-INH can significantly decrease and, in some patients, eliminate breakthrough attacks. However, we believe a more frequent daily infusion treatment regimen is not clinically practical and other approaches are urgently needed.

Our Approach for HAE

ADMV-053 is our gene therapy product candidate for the prophylaxis treatment of HAE. ADVM-053 is designed to be administered as a single intravenous injection to prevent HAE attacks.

In preclinical studies, a single intravenous administration of ADVM-053 showed robust C1EI expression. In a proof-of-concept study, ADVM-053 increased protein expression above anticipated therapeutic levels. An additional study, in a mice model of the disease, demonstrated that ADVM-053 decreased vascular permeability, the hallmark of this disease.

To advance the development of ADVM-053, we plan to initiate IND-enabling studies and engage with the FDA in the first half of 2017. We are working to transfer our manufacturing process to a contract manufacturing organization to produce clinical materials for our future studies. After these initiatives are completed, we plan to file an IND with the FDA.

Other Preclinical Product Candidates

In addition to our lead programs, we are developing a gene therapy product candidate for the treatment of Friedreich's ataxia, a debilitating neurodegenerative disease resulting in poor coordination of legs and arms, progressive loss of the ability to walk, generalized weakness, loss of sensation, scoliosis, diabetes and cardiomyopathy as well as impaired vision, hearing and speech. It affects approximately 5,000 people in the United States and approximately 5,000 to 10,000 people in Europe. Currently, we are conducting observational studies and are in the early stages of preclinical development.

We also have early-stage programs designed to treat, respectively, severe allergies and Juvenile X-linked Retinoschisis (XLRS), an inherited retinal disease that occurs almost exclusively in boys and young men and can lead to severe vision impairment or blindness that often manifests early in childhood.

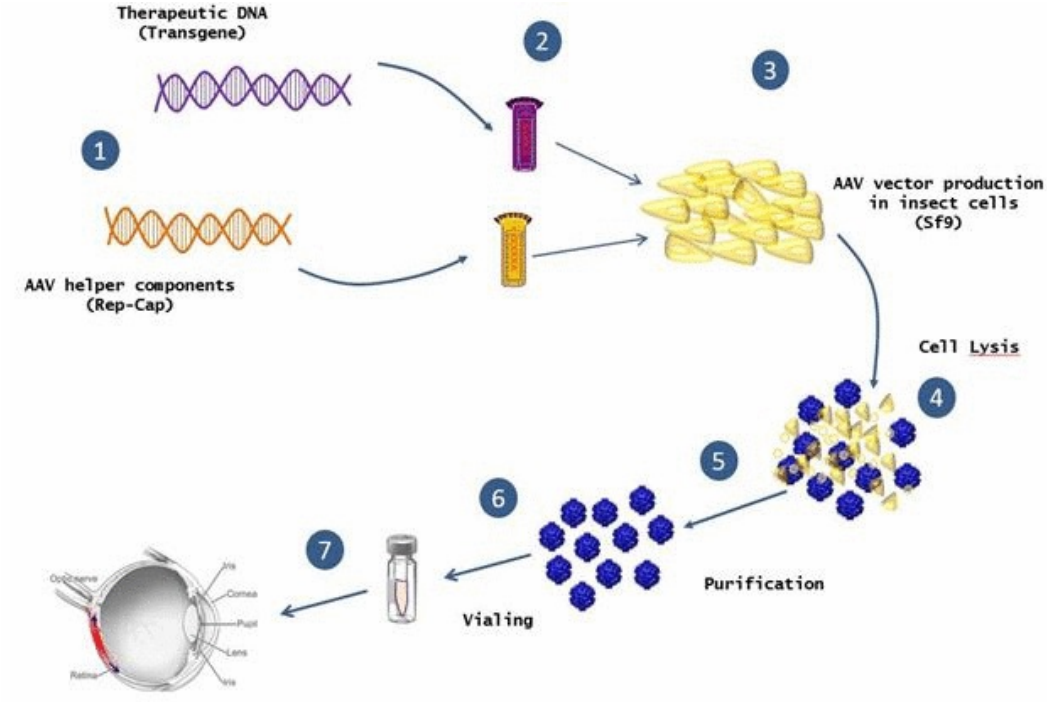
Manufacturing

We produce our AAVs using a proprietary manufacturing process based on insect cells and baculoviruses, a common family of viruses found in invertebrates. Our process is based on the Baculovirus Expression Vector System (BEVS), which has been used in a number of FDA- and EMA-approved products. This approach is well suited for the production of large quantities of AAVs, as it takes advantage of the efficiency of viral infection coupled with the high density and scalability of insect cells grown in serum-free suspension cultures. Compared to the mammalian cell-based approaches commonly used in the field, our manufacturing process is designed to produce higher yields of vectors in a cost-effective manner.

Our BEVS manufacturing process, using the eye as an example, is presented in the figure below.

1) The process begins with two DNA constructs, one encoding the therapeutic protein and the other encoding AAV helper components for the AAV capsid and replication of vectors.
2) Each DNA construct is inserted into the genome of a baculorvirus to create two types of recombinant baculoviruses.
3) The two baculoviruses are used to transduce Sf9 insect cells, which in turn produce large amounts of AAV vectors containing the therapeutic gene of interest.
4) The transduced Sf9 insect cells are then harvested and treated with a lysis buffer solution to burst the insect cells and release the AAV vectors.
5) Recovered AAV vectors are then purified to remove unwanted debris.
6) Following purification, the vectors are formulated in a physiological solution and placed in vials.
7) The resulting drug product is ready for use as a therapeutic treatment for the targeted disease (e.g., injection in the eye to treat wet AMD).

BEVS Manufacturing Process



Our AAV manufacturing method is industrialized, highly scalable and ready for adaptation for commercial stage. We believe our process provides the following advantages over competing systems:

- **Industrial-scale biologics production.** Our BEVS system can produce commercial quantities by incorporating scalable, well-established process steps used throughout the industry for biologic products.
- **Safety advantages.** Our BEVS system does not use mammalian cell cultures or tumorigenic cell lines, and the DNA sequences used to allow AAV vector production are inactive in mammalian cells, which lowers the risk of off-target expression from our products.
- **High yield and low cost.** Our BEVS system produces a high number of particles per cell, producing many thousand doses per manufacturing run. The yields are up to one hundred times greater than those obtained using conventional AAV production systems. This lowers the unit cost of goods, allowing us to meet global demand for large markets, such as wet AMD.
- **High purity.** Our BEVS system produces a highly pure drug substance, which reduces the presence of unwanted contaminants in the final product.
- **Precedent regulatory framework.** Our BEVS system is used for several FDA- and EMA-approved vaccines and gene therapy products including FluBlok®, Cervarix® and Glybera®.

We have entered into a manufacturing technology license agreement pursuant to which we and Lonza Houston, Inc. are assessing certain technology potentially useful for the manufacture of our products. The license agreement provides that the parties will conduct activities to evaluate such technology and that we may elect to engage Lonza to manufacture our products. We also granted to Lonza certain licenses to practice the manufacturing technology for products other than those being developed by us, our affiliates or sublicensees.

Competition

The biopharmaceutical industry is characterized by intense and dynamic competition to develop new technologies and proprietary therapies. Any product candidates that we successfully develop and commercialize will have to compete with existing therapies and new therapies that may become available in the future. While we believe that our AAV-based directed evolution platform, single-administration gene therapy candidates, and expertise in the field of gene therapy provide us with competitive advantages, we face potential competition from various sources, including larger and better-funded pharmaceutical, specialty pharmaceutical, and biotechnology companies, as well as from academic institutions, governmental agencies, and public and private research institutions.

Recently, many gene therapy companies have advanced their programs or have completed initial public offerings, which may enable these companies to compete with our platform and programs. These companies include 4D Molecular Therapeutics, Applied Genetic Technologies Corporation, Audentes Therapeutics, Inc., AveXis, Inc., REGENXBIO Biosciences, Dimension Therapeutics, Inc., Editas Medicine, Inc., MeiraGTx, Spark Therapeutics, Inc., uniQure N.V., and Voyager Therapeutics.

Our wAMD program candidates 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. Existing anti-VEGF therapies, Lucentis®, EYLEA® and Avastin®, are well-established therapies and are widely accepted by physicians, patients and third-party payers as the standard-of-care treatment of patients with wAMD. To date, we are not aware of any treatment that has demonstrated a better benefit to patients than regular anti-VEGF protein delivery.

We know of a significant number of product candidates in development for wAMD, and we group them into four main categories:

- Biosimilar anti-VEGFs
- Combination / add-on therapy for efficacy improvement (for example, anti-PDGF, Anti-angiopoietin-2, topical anti-VEGF)
- Next generation anti-VEGF with quarterly injection
- Implant / device to lower treatment frequency to 1-2 times per year

There are several other companies with marketed products or products in development for the treatment of wAMD. These companies include 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, PanOptica Pharma, Quark Pharmaceuticals, Roche (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, CSL, Ionis Pharmaceuticals, and Shire.

Many of our competitors, either alone or with their strategic partners, have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of treatments and commercializing those treatments. Accordingly, our competitors may be more successful than us in obtaining approval for treatments and achieving widespread market acceptance. Our competitors' treatments may be more effective, or more effectively marketed and sold, than any treatment we may commercialize and may render our treatments obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our treatments.

Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of our competitors. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical study sites and subject registration for clinical studies, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available. We expect any treatments that we develop and commercialize to compete on the basis of, among other things, efficacy, safety, convenience of administration and delivery, price, the level of generic competition and the availability of reimbursement from government and other third-party payers.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, we expect that our therapeutic products, if approved, will be priced at a significant premium over competitive generic products and our ability to compete may be affected in many cases by insurers or other third-party payers seeking to encourage the use of generic products.

License and Collaboration Agreements

Regeneron Research Collaboration and License Agreement

In May 2014, we entered into the Collaboration Agreement with Regeneron for an initial period of three years to research, develop and commercialize novel gene therapy products for the treatment of ophthalmologic diseases. These products are based on our proprietary viral vectors that express transgenes encoding molecules that modulate up to a total of eight specified targets, and encoding certain endogenous molecules known to bind to and modulate such targets. Such products, including AVA-311, are referred to collectively as "Products." On February 23, 2017, Regeneron notified us that, pursuant to Section 2.3 of the collaboration agreement, it is extending the research term of the Collaboration Agreement for an additional three years, through May 1, 2020.

Pursuant to the Collaboration Agreement, we and Regeneron have been conducting a research program to identify potential Products for a specified time period. Regeneron bears all costs of performing research under the Collaboration Agreement. Regeneron has a right to substitute a certain number of such targets and may, subject to a payment to us, expand the collaboration beyond the four initially designated targets to include up to four additional targets not currently being researched or developed by Adverum, and endogenous molecules known to bind to and modulate such additional targets, in the research program.

Regeneron has an option, exercisable with respect to all Products containing transgenes expressing molecules that modulate one of the specified targets, to obtain an exclusive, worldwide license to research, develop, use, import, export, make, manufacture and commercialize such Products for the treatment, prevention or diagnosis of human disease or other medical disorders. Regeneron may exercise this option prior to the expiration of the term of the research program, within a certain time period after the acceptance for filing with the FDA of the IND for such Products. Regeneron must pay us an option fee each time it exercises an option.

Regeneron has the right to file an IND with the FDA for Products prior to exercising its option. If Regeneron exercises its option for specified Products, Regeneron will be primarily responsible for developing, obtaining and maintaining regulatory approval for, and commercializing such Products.

We have a right to co-fund costs of developing, manufacturing and commercializing Products containing transgenes encoding molecules capable of modulating a target with respect to which Regeneron has exercised its option, subject to certain exceptions. We may exercise this co-funding right up to two times. If we exercise such right, we may elect to bear up to 35% of all development costs incurred for such Products. For any co-funded Products, Regeneron's payment obligations extend until the Product is no longer sold in the applicable territory. For those Products for which we exercise this option, either party may opt out of sharing development costs for all Products containing transgenes encoding molecules capable of modulating a protein target, in which case the other party may continue to develop and commercialize such Products, subject to the payment of a royalty to the other party ranging from low-single digit to low double digit royalties. While Regeneron will record all revenue from sales of the co-funded Products, Regeneron will share in the net profits and losses of sales of any Products for which we exercised our co-funding right, with each party receiving a share of profits and bearing its share of losses in accordance with the share of development costs borne by each party for such Product, provided that neither party exercises its opt-out right for such Products.

Under the Collaboration Agreement, Regeneron made an initial payment of $8.0 million dollars for collaboration research costs, a one-time option fee and a one-time license grant fee.

In addition to the initial payment, Regeneron may make the following payments to us:

- Reimbursement for additional collaboration research costs;
- Up to $80.0 million in development and regulatory milestones for product candidates directed toward each of the eight therapeutic candidates, for a combined total of up to $640.0 million in potential milestone payments for product candidates directed toward all eight therapeutic targets subject to the Collaboration Agreement; and
- Tiered, low- to mid-single digit royalties on annual net sales, subject to certain adjustments.

For each Product, Regeneron's payment obligations extend until the last to occur of the following: (i) the discontinuation of development of the Product or (ii) once a Product is approved by the FDA, the later of (x) the duration of patent coverage for the Product or (y) ten years after first commercial sale of the Product in a particular territory.

The Collaboration Agreement will expire with respect to each collaboration target upon the earlier of the (a) expiration of the research term if the option right has not been triggered by the end of the research term or (b) expiration of the option right if the option right has not been exercised by Regeneron. If the option right has been exercised, the agreement in connection with each collaboration target will expire upon expiration of all payment obligations by Regeneron. The Collaboration Agreement may also be terminated (i) by Regeneron at will, either in its entirety or on a target by target basis, upon 30 days' prior written notice to us, (ii) by either party, upon written notice in connection with a material breach remaining uncured 60 days after initial written notice, (iii) by us, if Regeneron challenges the patent rights licensed by us under the Collaboration Agreement or (iv) by either party, for insolvency of the other party.

Editas Medicine, Inc.

In August 2016, the Company entered into a collaboration, option, and license agreement with Editas Medicine, Inc. (Editas) pursuant to which the Company and Editas will collaborate on certain studies using AAV vectors in connection with Editas' genome editing technology and the Company will grant to Editas an exclusive option to obtain certain exclusive rights to use the Company's proprietary vectors in up to five ophthalmic indications (Indications). The Company received a $1.0 million non-refundable upfront payment, with $0.5 million of such payment to be credited against Editas' obligation to fund research and development costs. Under the terms of the agreement, both the Company and Editas will be subject to exclusivity obligations.

Editas may exercise the option, with respect to a designated initial Indication, until the first anniversary of the effective date of the agreement. With respect to the four other Indications, Editas may exercise the option until the third anniversary of the effective date, provided that the option will expire on the second anniversary of the effective date if Editas has not exercised the option with respect to the initial Indication or any other Indication by such date. Upon each exercise of the option, Editas will pay the Company a $1.0 million fee per Indication. If Editas elects to develop a product using certain of the Company's proprietary vectors, the Company 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.

Unless earlier terminated, the agreement will be in effect until the later of the expiration of the option exercise period or the expiration of the royalty term of the last product. At any time after the option is first exercised, Editas may terminate the Agreement for convenience in its entirety or on an indication-by-indication or country-by-country basis, upon prior written notice to the Company. The Company may also terminate the agreement if Editas challenges the Company's patents relating to its proprietary vectors and does not withdraw such challenge within a defined period of time. In addition, either party may terminate the agreement with written notice upon a bankruptcy of the other party or upon an uncured material breach by the other party.

University of California License Agreement

In May 2010, we entered into a license agreement with the Regents of University of California (Regents), as amended in September 2013. Under the license agreement, the Regents have granted to us an exclusive (even as to the Regents) license, with the right to grant sublicenses, under the Regents' undivided interest in patent rights covering a method of using recombinant gene delivery vectors for treating or preventing diseases of the eye, to develop, make, have made, use, offer for sale, import, export and sell products covered by such patent rights in all fields of use in the United States. The licensed patent rights are jointly owned by the Regents and Chiron Corporation, but our license extends only to the Regents' interest in such patent rights.

Under the license agreement, we are required to diligently proceed with the development, manufacture and sale of licensed products, which includes obligations to meet certain development-stage milestones within specified periods of time, and to market the resulting licensed products in sufficient quantity to meet market demand. We have the right and option to extend the date by which we must meet any milestone by six months up to two times by paying an extension fee for each such extension.

We have paid the Regents a license fee of $100,000. We are also obligated to make milestone payments totaling up to $900,000 upon reaching certain stages of development of the licensed products for one indication, and totaling up to $500,000 for each subsequent indication for which licensed products are developed, for up to a maximum of two additional indications. Through December 31, 2016, none of these goals had been achieved, and no milestones were payable. We must also pay the Regents a low single-digit royalty on net sales of the licensed products by us or our sublicensees, subject to a minimum annual royalty payment of $50,000 beginning in the calendar year after the first commercial sale of a licensed product, until the patent rights upon which such royalties are based expire or are held invalid, which is currently expected to occur in 2020, subject to any potential patent term extensions. We are obligated to reimburse the Regents for expenses associated with the prosecution and maintenance of the licensed patents. Finally, we are obligated to pay the Regents a mid-teen percentage of non-royalty licensing revenue we receive from sublicensees.

Our license agreement with the Regents continues in effect for the life of the last-to-expire patent. We may terminate this agreement without cause at any time upon 30 days' prior written notice to the Regents. The Regents may terminate this agreement for a breach by us that remains uncured for 60 days, if we become insolvent, if we directly or through a third party file a claim that a licensed patent right is invalid or unenforceable or if we fail to meet or extend the date for meeting certain diligence milestones.

Cornell University

In December 2015, Annapurna Therapeutics Limited, a subsidiary of Annapurna, entered into three licensing agreements with Cornell, pursuant to which we are advancing gene therapy programs ADVM-043 and ADVM-053, which originally were initiated at the Department of Genetic Medicine at Weill Cornell.

A1AT Deficiency License Agreement: Under this agreement, Annapurna Therapeutics Limited holds an exclusive license to certain technology related to A1AT deficiency and rights to an IND application to initiate clinical studies of gene therapy for A1AT.

HAE License Agreement: Under this agreement, Annapurna Therapeutics Limited holds an exclusive license to certain technology related to HAE and a non-exclusive license to certain other intellectual property related to the HAE program.

Allergy License Agreement: Under this agreement, Annapurna Therapeutics Limited holds an exclusive license to certain patents related to allergens and a non-exclusive license to certain other technology related to allergens.

Across these three license agreements, Cornell is entitled to receive aggregate annual maintenance fees ranging from $30,000 to $300,000 per year, up to $16.0 million in aggregate milestone payments and royalties on sales in the low single-digits, subject to adjustments and minimum thresholds.

Annapurna Therapeutics Limited may terminate any of these license agreements for convenience upon ninety days written notice. Cornell may terminate any of the license agreements for material breach if such breach is not cured within a specified number of days. Cornell may also terminate the HAE License Agreement and/or the Allergy License Agreement if Annapurna Therapeutics Limited commences any action and files a written claim asserting that any portion of the licensed patent rights is invalid or unenforceable.

In August 2014 and amended and restated in December 2015, Annapurna Therapeutics, SAS entered into a master services agreement (MSA) with Cornell. This MSA included research and development support for ADVM-043, ADVM-053, our program in Freidriech's ataxia and severe allergy and the production of clinical materials for ADVM-043 and ADVM-053. The MSA, as amended and restated, provided for Annapurna to pay Cornell $13.3 million ratably over 4 years for these services as services were performed.

In December 2016, we informed the appropriate persons at Cornell of breach and our intention to terminate the MSA. Our three licensing agreements with Cornell for these gene therapy programs remain unchanged.

The decision to terminate the MSA is a result of Cornell's failure to deliver clinical materials for ADVM-043 that would be suitable for use in human patients. As a result of this decision, we are in the final stages of contracting with a large-scale contract manufacturing organization that complies with current Good Manufacturing Practice industry standards and can produce product quantities for both our planned clinical trials and potential commercial supply. This is part of our planned upgrade of the manufacturing process for ADVM-043, implementing our proprietary, highly-scalable baculovirus-based production system, in advance of our plans to initiate a Phase 1/2 clinical trial for ADVM-043 in the fourth quarter of 2017.

REGENXBIO

A1AT Deficiency/Allergy License Agreement: In October 2015, Annapurna Therapeutics Limited entered into an exclusive worldwide license to certain intellectual property in order to make, have made, use, import, sell, and offer for sale certain licensed products for the treatment of A1AT deficiency. Under this agreement, Annapurna Therapeutics Limited also had an option to be granted an exclusive worldwide license to certain intellectual property related to the treatment of severe allergies, and this option expired in October 2016 and was not exercised. Under this license agreement, REGENXBIO, Inc. (REGENXBIO) is eligible to receive annual maintenance fees, up to approximately $20.0 million in combined milestone payments and royalties in the mid-to-high single digits.

Unless earlier terminated, this license agreement will be in effect on a country-by-country, licensed product-by-licensed product basis until the expiration, lapse, abandonment, or invalidation of the last claim of the licensed intellectual property to expire, lapse, or become abandoned or unenforceable for the applicable licensed product. Annapurna Therapeutics Limited may terminate this license agreement upon six months' prior written notice. REGENXBIO may terminate this license agreement if Annapurna Therapeutics Limited is a specified number of days late in paying money due under the license agreement, or if Annapurna Therapeutics Limited, its affiliates, or any sublicensees become insolvent or, effective immediately, if they commence any action against REGENEXBIO or its licensors to declare or render any claim of the licensed patent rights invalid or unenforceable. Either party may terminate this license agreement for material breach if such breach is not cured within a specified number of days.

Friedreich's Ataxia License Agreement: In April 2014, Annapurna entered into an exclusive worldwide license to certain intellectual property related to the Friedreich's Ataxia (FA) program to make, have made, use, import, sell, and offer for sale licensed products using AAVrh10 for FA where the vector is administered by any route except directly to the central nervous system (FA Systemic).

Under the terms of this license agreement, Annapurna also had an option to obtain a non-exclusive worldwide license to make, have made, use, import, sell and offer for sale licensed products using a single vector for each of FA where the vector is administered directly to the central nervous system (FA CNS) and FA Systemic. The option to obtain a non-exclusive license to FA Systemic expired in April 2015 and the option to obtain a non-exclusive license for FA CNS expired in April 2016.

Under this license agreement, REGENXBIO is eligible to receive annual maintenance fees, up to $13.9 million in combined milestone fees and royalties in the mid-to-high single digits. Annapurna is obligated to achieve certain development milestones with respect to each licensed disease indication, including the filing of an IND for each licensed disease indication within a specified time period, which Annapurna may extend for additional time for a specified number of extensions upon the payment of a fee.

Unless earlier terminated, this license agreement expires upon the expiration, lapse, abandonment, or invalidation of the last claim of the licensed intellectual property to expire, lapse, or become abandoned or unenforceable in all the countries of the world. Annapurna may terminate this license agreement upon six months' prior written notice. REGENXBIO may terminate this license agreement if Annapurna is a specified number of days late in paying money due under the license agreement, or if Annapurna, its affiliates, or any sublicensees become insolvent or, effective immediately, if they commence any action against REGENXBIO or its licensors to declare or render any claim of the licensed patent rights invalid or unenforceable. Either party may terminate this license agreement for material breach if such breach is not cured within a specified number of days.

Inserm Transfert

In July 2014, Annapurna entered into an agreement with Inserm Transfert (Inserm) whereby Annapurna holds an exclusive license to certain patents to develop, make, have made, use, import, offer for sale, and sell or otherwise distribute products for the treatment of Friedreich's ataxia and a non-exclusive license to certain other intellectual property related to the FA program. The agreement was amended in October 2015 to increase the scope of the intellectual property under the licenses. Under this agreement, Inserm is entitled to receive certain de minimis license payments, certain development milestone payments of up to approximately €2.0 million in the aggregate and royalties on sales in the low single-digits, subject to adjustments.

Unless earlier terminated, this agreement will be in effect on a country-by-country, licensed product-by-licensed product basis until the later of the expiration of the last claim of the licensed intellectual property which cover the manufacture, use or sale of such product in such country or 10 years after the first commercial sale of such product in such country in which such product is sold. Upon a country-by-country and product-by-product basis, Annapurna will have a fully paid up, perpetual, irrevocable license with respect to such product in such country under the licensed intellectual property following expiration of this agreement with respect to such product in the applicable country. Annapurna may terminate this agreement upon 60 days' prior written notice. Inserm may terminate this license agreement if Annapurna becomes the subject of a voluntary or involuntary petition in bankruptcy or fails to meet development milestones and such failure is not cured within a specified number of days. Inserm may also terminate the license granted to Annapurna in a given country if Annapurna (i) before regulatory approval of a product in any country, has ceased conducting any development of products in all countries for 12 consecutive months or (ii) after regulatory approval of a product in a given country, has ceased marketing such product in such country for 12 consecutive months.

Pursuant to Section 4.7 of the agreement with Inserm, our acquisition of Annapurna triggered a one-time payment to Inserm of €250,000.

Intellectual Property

Overview

We strive to protect and enhance the proprietary technology, inventions and improvements that are commercially important to the development of our business, including seeking, maintaining and defending patent rights, whether developed internally or licensed from third parties. We also rely on trade secrets relating to our proprietary technology platform and on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of gene therapy that may be important for the development of our business. We additionally may rely on regulatory protection afforded through orphan drug designations, data exclusivity, market exclusivity, and patent term extensions where available.

Our commercial success may depend in part on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce our patents; preserve the confidentiality of our trade secrets; and operate without infringing the valid enforceable patents and proprietary rights of third parties. Our ability to stop third parties from making, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable licenses, patents or trade secrets that cover these activities. In some cases, these rights may need to be enforced by third party licensors. With respect to both licensed and company-owned intellectual property, we cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our commercial products and methods of manufacturing the same.

We have more than 60 patent applications pending in the United States and foreign jurisdictions. At least 38 patent applications have been filed in the United States and foreign jurisdictions by or on behalf of universities which have granted us exclusive license rights to the technology. To date, 12 patents have been issued to us or to our licensors that are active. Our policy is to file patent applications to protect technology, inventions and improvements to inventions that are commercially important to the development of our business. We seek United States and international patent protection for a variety of technologies, including: research tools and methods, methods for transferring genetic material into cells, AAV-based biological products, methods for treating diseases of interest and methods for manufacturing our AAV-based products. We also intend to seek patent protection or rely upon trade secret rights to protect other technologies that may be used to discover and validate targets and that may be used to identify and develop novel biological products. We seek protection, in part, through confidentiality and proprietary information agreements. We are a party to various other license agreements that give us rights to use specific technologies in our research and development.

Company-owned Intellectual Property

We own a family of patent applications that are directed to AAV-based compositions and methods for treating or preventing eye diseases associated with neovascularization. The applications in this family relate to an AAV gene therapy for the treatment of wet AMD using an anti-VEGF composition, various unit dosages, dosing regimens and routes of administration. Four applications in this family are pending in the United States, and corresponding patent applications are pending in Australia, Brazil, Canada, China, Europe, Israel, India, Japan, South Korea, Mexico, New Zealand, Russia, Singapore, Thailand, Taiwan and South Africa. Patents that grant from this patent family are generally expected to expire in 2033, subject to possible patent term extensions.

We are also pursuing innovative ways to regulate the expression of transgenes in tissues. To that end, we have, in collaboration with Stanford University, filed a U.S. patent application that is directed to methods for regulating gene expression in a subject. Any patents that grant from this application are expected to expire in 2033, subject to possible patent term extensions.

Licensed Intellectual Property

We have obtained exclusive licenses to patents directed to both compositions of matter and methods of use.

For example, we have exclusively licensed the rights of the Regents to a U.S. patent directed to methods of treating ocular disease that relate to methods of using an AAV gene therapy approach. This patent is co-owned by the Regents and by Chiron Corporation, and will expire in 2020, unless a term extension is obtained for such patent. There are no foreign patents in this patent family.

We have exclusively licensed several families of patents and applications that relate to variant rAAV virions having desirable characteristics, such as increased infectivity, as well as novel methods to screen for such variants.

One patent family that we have exclusively licensed includes granted patents in Australia, Germany, France, the United Kingdom and Spain; three pending U.S. patent applications; and a pending patent application in Canada. The patents are projected to expire in 2024, subject to possible patent term extensions, as are any patents that granted from the pending applications.

Another patent family that we have exclusively licensed includes a granted U.S. patent that is projected to expire in 2031 and a pending U.S. patent application which, if granted, is also projected to expire in 2031, in both cases subject to possible patent term extensions.

A third patent family that we have exclusively licensed includes three pending U.S. patent applications and pending corresponding applications in Australia, Brazil, Canada, China, Europe, Hong Kong, Israel, India, Japan, South Korea, Mexico, Russia, Singapore and South Africa. Patents that grant from this patent family are generally expected to expire in 2032, subject to possible patent term extensions.

We have also nonexclusively licensed rights to a patent family that includes an issued European patent and related Chinese and U.S. patent applications directed to methods of manufacturing. The European patent is expected to expire in 2027, as are any patents that may grant from the related patent applications.

We have exclusively licensed intellectual property related to gene therapy for alpha-1 antitrypsin deficiency including Investigational New Drug Application No. 016008.

We have exclusively licensed a family of patent applications related to gene therapy treatments for hereditary angioedema (C1-esterase deficiency), which includes pending U.S. and foreign applications. Patents that grant from this patent family are generally expected to expire in 2036, subject to possible patent term extensions and adjustments.

We have exclusively licensed a family of patent applications related to gene therapy treatments for severe allergies, which includes pending U.S. and foreign applications. Patents that grant from this patent family are generally expected to expire in 2036, subject to patent term extensions and adjustments.

We have exclusively licensed a family of patents and applications related to the treatment of cardiomyopathy associated with Friedrich's ataxia. This family includes a granted US patent and pending applications in Australia, Brazil, Canada, Eurasia, Europe, Israel, India, Mexico, New Zealand, United States and South Africa. Patents that grant from this patent family are generally expected to expire in 2033, subject to possible patent term extensions and adjustments.

We have also exclusively licensed a patent family directed to the use of certain rAAVs for use in Friedrich's ataxia (systemic) including pending applications in Australia, Canada, China, Europe, Hungary, Israel, Japan, New Zealand and the United States. Patents that grant from this patent family are generally expected to expire in 2022, subject to possible patent term extensions and adjustments.

We have also exclusively licensed a patent family directed to the use of certain rAAVs for use in the treatment of alpha-1 antitrypsin deficiency, including pending applications in Australia, Canada, China, Europe, Hungary, Israel, Japan, New Zealand and the United States. Patents that grant from this patent family are generally expected to expire in 2022, subject to possible patent term extensions and adjustments.

Trademark Protection

We have registered trademarks in connection with our biological products. We may pursue additional registrations for future products in markets of interest. In addition to the above, we have established expertise and development capabilities focused in the areas of preclinical research and development, manufacturing and manufacturing process scale-up, quality control, quality assurance, regulatory affairs and clinical trial design and implementation. We believe that our focus and expertise will help us develop products based on our proprietary intellectual property.

Trade Secret Protection

Finally, we may rely, in some circumstances, on trade secrets to protect our technology. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

Government Regulation

The FDA and comparable regulatory authorities in state and local jurisdictions and in other countries impose substantial and burdensome requirements upon companies involved in the clinical development, manufacture, marketing and distribution of our product candidates. These agencies and other federal, state and local entities regulate research and development activities and the testing, manufacture, quality control, safety, effectiveness, labeling, storage, record keeping, approval, advertising and promotion, distribution, post-approval monitoring and reporting, sampling, and export and import of our product candidates.

In the United States, the FDA regulates drug and biologic products under the Federal Food, Drug, and Cosmetic Act (FFDCA), and the FDA implements regulations and other laws, including, in the case of biologics, the Public Health Service Act. If we fail to comply with applicable FDA or other requirements at any time during the product development process, clinical testing, the approval process, or after approval, we may become subject to administrative or judicial sanctions. These sanctions could include the FDA's refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution. Any FDA enforcement action could have a material adverse effect on us. Our product candidates may be subject to regulation by the FDA as biologics. Biologics require the submission of a Biologics License Application (BLA) and approval by the FDA before being marketed in the United States. Similarly, FDA approval is required before any new unapproved drug or dosage form, including a new use of a previously approved drug, can be marketed in the United States.

Within the FDA, CBER regulates gene therapy products. Within CBER, the review of gene therapy and related products is consolidated in the Office of Tissues and Advanced Therapies (formerly known as the Office of Cellular, Tissue and Gene Therapies), and FDA has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its reviews. CBER works closely with the U.S. National Institutes of Health (NIH) and the NIH Office of Biotechnology Activities' Recombinant DNA Advisory Committee (RAC), which makes recommendations to the NIH on gene therapy issues and engages in a public discussion of scientific, safety, ethical and societal issues related to proposed and ongoing gene therapy protocols. The FDA and the NIH have published guidance documents with respect to the development and submission of gene therapy protocols. The FDA also has published guidance documents related to, among other things, gene therapy products in general, their preclinical assessment, observing subjects involved in gene therapy studies for delayed adverse events, viral shedding, environmental assessments, potency testing, and chemistry, manufacturing and control information in gene therapy Investigational New Drug (IND) applications. FDA guidance documents provide the agency's current thinking about a particular subject, but are not legally binding. However, products in this area are novel and present highly complex scientific and medical issues, making the predictability of FDA's policies and practices in this area less certain.

The process required by the FDA before our product candidates may be marketed in the United States generally involves:

- Completion of extensive preclinical laboratory tests, preclinical animal studies and formulation studies all performed in accordance with the FDA's current Good Laboratory Practice, or GLP, regulations;
- Submission to the FDA of an IND, which must become effective before human clinical trials in the United States may begin;
- Approval by an independent institutional review board, or IRB, at each clinical trial site before each trial may be initiated;
- Performance of adequate and well-controlled human clinical trials according to the FDA's regulations commonly referred to as good clinical practice, and any additional requirements for the protection of human research subjects and their health information, to establish the purity, potency, safety and efficacy of the drug candidate for each proposed indication;
- Satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the drug or biologic is produced, prior to commercialization, to assess compliance with current Good Manufacturing Practice, or cGMP, regulations and any additional requirements pertaining to the manufacture and distribution of drug and biologic products;
- Submission to the FDA of a BLA for marketing approval that includes substantial evidence of safety, purity and potency from results of nonclinical testing and clinical trials;
- Successful completion of FDA audit(s) of the nonclinical and clinical trial sites that generated the data in support of the BLA;
- Successful completion of the advisory committee review, if FDA convenes an advisory committee; and
- Payment of user fees and FDA review and approval, or licensure, of the BLA prior to any commercial marketing, sale or shipment of the product.

The preclinical and clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

Before testing any biologic product candidate, including a gene therapy product, in humans, the product candidate enters the preclinical testing stage. Preclinical tests include laboratory evaluation of product chemistry, formulation, stability and toxicity, as well as animal studies to assess the characteristics and potential safety and efficacy of the product. The conduct of the preclinical tests must comply with federal regulations and requirements, including GLPs.

Where a gene therapy study is conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research, prior to the submission of an IND to the FDA, a protocol and related documentation are submitted to, and the study is registered with, the NIH Office of Biotechnology Activities, or OBA, pursuant to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines). Compliance with the NIH Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA. However, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. The NIH is responsible for convening the RAC, a federal advisory committee that discusses protocols that raise novel or particularly important scientific, safety or ethical considerations at one of its quarterly public meetings. The OBA will notify the FDA of the RAC's decision regarding the necessity for full public review of a gene therapy protocol. RAC proceedings and reports are posted to the OBA website and may be accessed by the public.

The results of preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical trial protocol, are submitted as part of an IND to the FDA. Some preclinical testing may continue even after the IND is submitted. The OBA notifies the FDA of the RAC's decision regarding the necessity for full public review of a gene therapy protocol. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions relating to the content(s) of the IND that could potentially expose human research subjects to health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the IND goes into effect and the clinical trial can begin. With gene therapy protocols, if the FDA allows the IND to proceed, but the RAC decides that full public review of the protocol is warranted, the FDA will request at the completion of its IND review that sponsors delay initiation of the protocol until after completion of the RAC review process. The FDA also may impose clinical holds on a biologic product candidate at any time before or during clinical trials due to safety concerns or non-compliance. If the FDA imposes a clinical hold on an IND, clinical trials may not commence or recommence without FDA authorization and then only under terms authorized by FDA.

Clinical trials involve the administration of the investigational product candidate to human subjects under the supervision of qualified investigators, generally physicians not employed by or under the study sponsor's control. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, the parameters to be used in monitoring subject safety, including stopping rules that assure a clinical trial will be stopped if certain adverse events should occur, and the effectiveness criteria to be used. Each protocol must be submitted to the FDA as part of the IND. An IRB for each medical center proposing to conduct a clinical trial must also review and approve a plan for any clinical trial before it can begin at that center and the IRB must monitor the clinical trial until it is completed. Clinical testing also must satisfy the Good Clinical Practice (GCP) requirements, including the requirements for informed consent from all subjects. FDA usually recommends that sponsors observe all surviving subjects who receive treatment using gene therapies in clinical trials for potential gene therapy-related delayed adverse events for a minimum 15-year period, including a minimum of five years of annual examinations followed by 10 years of annual queries, either in person or by questionnaire. FDA does not require the long-term tracking to be complete prior to its review of the BLA.

All clinical research performed in the United States in support of a BLA must be authorized in advance by the FDA under the IND regulations and procedures described above. However, a sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a foreign clinical trial is not conducted under an IND, under FDA regulations at 21 CFR 312.120, FDA will accept a well-designed, well-conducted, non-IND foreign study as support for an application for marketing approval if (i) the study was conducted in accordance with GCP as further detailed in the regulation, including review and approval by an independent ethics committee, and (ii) if FDA is able to validate the data from the study through an onsite inspection, if necessary. In addition, FDA requires that a sponsor or applicant who submits data from a foreign clinical study not conducted under an IND as support for a marketing application submit, in addition to other required information, a description of the actions the sponsor or applicant took to ensure that the research conformed to GCP. Further, where a sponsor intends for marketing approval of a new drug to be based solely on foreign clinical data, additional requirements apply that are described in FDA regulations.

Clinical Trials

For purposes of BLA submission and approval, clinical trials are typically conducted in three or four sequential phases, which may overlap or be combined.

- Phase 1: Clinical trials are initially conducted in a limited population of subjects to test the product candidate for safety, dose tolerance, absorption, metabolism, distribution and excretion in healthy humans or, on occasion, in patients with severe problems or life-threatening diseases to gain an early indication of its effectiveness.
- Phase 2: Clinical trials are typically well-controlled, closely monitored studies that are generally conducted in a limited subject population to evaluate dosage tolerance and appropriate dosage, identify possible adverse effects and safety risks, and evaluate preliminarily the efficacy of the product candidate for specific targeted indications in subjects with the disease or condition under study.

- Phase 3: Clinical trials are typically conducted when Phase 2 clinical trials demonstrate that a dose range of the product candidate is effective and has an acceptable safety profile. Phase 3 clinical trials are commonly referred to as "pivotal" studies, which typically denotes a study which presents the data that the FDA or other relevant regulatory agency will use to determine whether or not to approve a product candidate. Phase 3 clinical trials are generally undertaken with large numbers of subjects, such as groups of several hundred to several thousand, to further evaluate dosage, to provide substantial evidence of clinical efficacy and to further test for safety in an expanded and diverse subject population at multiple, geographically-dispersed clinical trial sites.
- Phase 4: In some cases, the FDA may condition approval of a BLA for a product candidate on the sponsor's agreement to conduct additional clinical trials after the product's approval. In other cases, a sponsor may voluntarily conduct additional clinical trials post approval to gain more information about the product. Such post approval trials are typically referred to as Phase 4 clinical trials or post-marketing or post approval studies.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical trial investigators. Annual progress reports detailing the results of the clinical trials must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA, the NIH and the investigators for serious and unexpected adverse events, any findings from other studies, tests in laboratory animals or in vitro testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, if at all. The FDA or the sponsor or its data safety monitoring board may suspend a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the biological product has been associated with unexpected serious harm to patients.

In addition to the regulations discussed above, there are a number of additional standards that apply to clinical trials involving the use of gene therapy. The FDA has issued various guidance documents regarding gene therapies, which outline additional factors that the FDA will consider at each of the above stages of development and relate to, among other things: the proper preclinical assessment of gene therapies; the chemistry, manufacturing and control information that should be included in an IND application; the proper design of tests to measure product potency in support of an IND or BLA application; and measures to observe delayed adverse effects in subjects who have been exposed to investigational gene therapies when the risk of such effects is high. Further, the FDA usually recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by 10 years of annual queries, either in person or by questionnaire. The NIH and the FDA have a publicly accessible database, the Genetic Modification Clinical Research Information System, which includes information on gene therapy trials and serves as an electronic tool to facilitate the reporting and analysis of adverse events on these trials.

Per the regulations, a sponsor of a sponsor (in industry or academia) of a clinical trial must register a clinical trial on the ClinicalTrial.gov website, the registry of new and on-going clinical trials of drugs, biologics, and device products. Sponsors are required to maintain the currency of the posting of the clinical trials posted on-line in the registry. This clinical trial registry and results data bank for clinical trials also contains summary results information on a clinical trial including adverse event information from the clinical trials and for pediatric post-market surveillance of a device product. The registry also provides information that helps patients find trials for which they might be eligible, enhance the design of clinical trials and prevent duplication of unsuccessful or unsafe trials, improve the evidence base that informs clinical care, increase the efficiency of drug and device development processes, improve clinical research practice, and build public trust in clinical research.

These phases of testing may not be completed successfully within any specified period, if at all. Concurrent with clinical trials, companies usually complete additional animal trials and must also develop additional information about the chemistry and physical characteristics of the product candidate and finalize a process for manufacturing the product candidate in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

Biologics License Applications (BLA)

The results of preclinical studies and of the clinical trials, together with other detailed information, including extensive manufacturing information and information on the composition of the product, are submitted to the FDA in the form of a BLA requesting approval to market the product for one or more specified indications. The submission of a BLA must be accompanied by a substantial user fee unless a waiver applies, and is subject to a sixty day review period to determine if the application is substantially complete to permit substantive review.

Under the Prescription Drug User Fee Act (PDUFA), the FDA has a performance goal to review applications within 6 months (for priority reviews) or 10 months (for standard reviews). The review timeline begins upon FDA's acceptance of the original application submission for filing, no later than 60 calendar days from the date FDA receives the application. In some instances, the review process and the PDUFA goal date may be extended depending on the information required in order the FDA reviewers to complete their review of the BLA.

The FDA may refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. The FDA may deny approval of a BLA if the applicable statutory and regulatory criteria are not satisfied, which may require additional clinical data or an additional Phase 3 clinical trial. Even if such data are submitted, the FDA may ultimately decide that the BLA does not satisfy the criteria for approval. Data from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret data. Moreover, even if a product receives approval, the approval may be significantly limited to specific disease and dosages or the indications for use may otherwise be limited or subject to Risk Evaluation and Mitigation Strategies, which could restrict the commercial value of the product. Once the FDA approves a BLA, or supplement thereto, the FDA may withdraw the approval if ongoing regulatory requirements are not met or if safety problems are identified after the product reaches the market. Where a withdrawal may not be appropriate, the FDA still may seize existing inventory of such product or require a recall of any biologic or drug already on the market. In addition, the FDA may require testing, including Phase 4 clinical trials and surveillance programs to monitor the effect of approved biologics which have been commercialized. The FDA has the authority to prevent or limit further marketing of a biologic or drug based on the results of these post-marketing programs.

Biologics may be marketed only for the FDA approved indications and in accordance with the provisions of the approved labeling. Further, if there are any modifications to the product, including changes in indications, labeling, or manufacturing processes or facilities, the applicant may be required to submit and obtain FDA approval of a new BLA or BLA supplement, which may require us to develop additional data or conduct additional preclinical studies and clinical trials.

Before approving a BLA, the FDA will inspect the facility or the facilities at which the finished biologic or drug product, and sometimes, for drug products, the active drug ingredient, is manufactured, and will not approve the product unless cGMP compliance is satisfactory. The FDA may also inspect the sites at which the clinical trials were conducted to assess their compliance, and will not approve the product unless compliance with IND study requirements and GCP requirements is satisfactory.

The testing and approval processes require substantial time, effort and financial resources, and each may take several years to complete. The FDA may not grant approval on a timely basis, or at all. Even if we believe a clinical trial has demonstrated safety and efficacy of one of our product candidates for the treatment of a disease, the results may not be satisfactory to the FDA. Preclinical and clinical data may be interpreted by the FDA in different ways, which could delay, limit or prevent regulatory approval. We may encounter difficulties or unanticipated costs in our efforts to secure necessary governmental approvals which could delay or preclude us from marketing drugs. The FDA may limit the indications for use or place other conditions on any approvals that could restrict the commercial application of the biologics or drugs. After approval, certain changes to the approved product, such as adding new indications, manufacturing changes, or additional labeling claims are subject to further FDA review and approval. Depending on the nature of the change proposed, a BLA supplement must be filed and approved before the change may be implemented. For many proposed post-approval changes to a BLA, the FDA has up to 180 days to review the application. As with new BLAs, the review process is often significantly extended by the FDA requests for additional information or clarification.

In addition, prior to submitting a BLA for a new biologic, a sponsor may be able to take advantage of one or more FDA programs that are intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life threatening condition (e.g., priority review, fast track designation) provided the product meets the criteria for those programs. While some of these programs have been in existence for a number of years, Congress established additional programs intended to expedite the development of drugs and biologics in the recently enacted 21st Century Cures Act (Cures Act), which was signed into law on December 13, 2016. Notably with respect to gene therapy products, section 3012 of the Cures Act clarifies the authority of FDA to facilitate the development, review, and approval of "genetically targeted drugs" and "variant protein targeted drugs" to address an unmet medical need in one or more patient subgroups, including subgroups of patients with different mutations of a gene, with respect to rare diseases or conditions that are serious or life-threatening. 21st Century Cures Act Section 3033 also

established a regenerative advanced therapy designation process intended to expedite the development of regenerative medicine therapies, defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, except for those regulated solely under Section 361 of the Public Health Service Act and part 1271 of Title 21, Code of Federal Regulations, that are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition, and for which preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition.

Other Regulatory Requirements

Any biologics manufactured or distributed by us or our collaborators pursuant to FDA approvals would be subject to continuing regulation by the FDA, including recordkeeping requirements and reporting of adverse experiences associated with the product. Biologic and drug manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMPs, which impose certain procedural and documentation requirements upon us and our third party manufacturers. Failure to comply with the statutory and regulatory requirements can subject a manufacturer to possible legal or regulatory action, such as warning letters, suspension of manufacturing, seizure of product, injunctive action or possible civil penalties. We cannot be certain that we or our present or future third-party manufacturers or suppliers will be able to comply with the cGMP regulations and other ongoing FDA regulatory requirements. If we or our present or future third-party manufacturers or suppliers are not able to comply with these requirements, the FDA may halt our clinical trials, require us to recall a product from distribution or withdraw approval of the BLA for that biologic.

The FDA closely regulates the post-approval marketing and promotion of biologics and drugs, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the internet. Under FDA's current interpretation of the relevant laws, in proactively promoting a drug, a company generally can make only those substantiated claims relating to safety and efficacy that are for indications approved by the FDA and that are otherwise consistent with the FDA-approved label for the drug or biologic. Failure to comply with these requirements can result in adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties. Physicians may prescribe legally available drugs for uses that are not described in the product's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical hold, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, impose stringent restrictions on manufacturers' communications regarding off-label use.

Other Healthcare Laws and Regulations

If we obtain regulatory approval for any of our product candidates, we may also be subject to healthcare regulation and enforcement by the federal government and the states and foreign governments in which we conduct our business. These laws may impact, among other things, our proposed sales, marketing, and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- The federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs;
- Federal false claims laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payers that are false or fraudulent;
- Federal criminal laws that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- The federal Physician Payment Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services information related to payments and other transfers of value to physicians, other healthcare providers, and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members;

- Health Insurance Portability and Accountability Act ("HIPAA"), as amended by Health Information Technology for Economic and Clinical Health Act ("HITECH"), which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information; and
- State and foreign law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payer, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

If our operations are found to be in violation of any of the laws described above or any other governmental laws and regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment, any of which could adversely affect our ability to operate our business and impact our financial results.

In addition, recent events in the pharmaceutical and biotechnology industry generally have resulted in increased public and governmental scrutiny of the cost of drugs. In particular, U.S. federal prosecutors have issued subpoenas to pharmaceutical companies seeking information about drug pricing practices and the U.S. Senate is investigating several pharmaceutical companies relating to drug price increases and pricing practices. If we obtain regulatory approval of any of our product candidates, our revenue and future profitability could be negatively affected if these inquiries were to result in legislative or regulatory proposals that limit our ability to increase the prices of our products.

Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any products for which we obtain regulatory approval. In the United States and markets in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend in part on the availability of coverage and reimbursement from third-party payers. Third-party payers include government authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payer will provide coverage for a drug product may be separate from the process for setting the reimbursement rate that the payer will pay for the drug product. Third-party payers may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drugs for a particular indication. Moreover, a payer's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

Third-party payers are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. In order to obtain coverage and reimbursement for any product that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain regulatory approvals. Our product candidates may not be considered medically necessary or cost-effective. If third-party payers do not consider a product to be cost-effective compared to other available therapies, they may not cover the product after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit. The United States government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. By way of example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively, the Affordable Care Act, contains provisions that may reduce the profitability of drug products, including, for example, increased the minimum rebates owed by manufacturers under the Medicaid Drug Rebate Program, extended the rebate program to individuals enrolled in Medicaid managed care plans, 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, and annual fees based on pharmaceutical companies' share of sales to federal health care programs. Adoption of government controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals. In addition, following the November 2016 Presidential election in the United States, significant uncertainty exists regarding the future of the Affordable Care Act. It is possible that there will be legislation in the future either to amend or replace the Affordable Care Act and that such new legislation will be generally unfavorable toward the pharmaceutical and biotechnology industries (including with regard to a possible reduction in the number of insured individuals with access to drug coverage or additional measures aimed at high cost drug and biologic products). At this time, it is unclear whether those changes will also have an impact on biologic product exclusivity or the biosimilar product licensure pathway established under the Biologics Price Competition and Innovation Act (BPCIA), which was enacted as part of the Affordable Care Act.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payers fail to provide adequate coverage and reimbursement. In addition, emphasis on cost containment measures in the United States and other countries has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

International Regulation

In addition to regulations in the United States, we or our collaborators will be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of our future drugs. Whether or not we obtain FDA approval for a drug, we or our collaborators must obtain approval of a drug by the comparable regulatory authorities of foreign countries before commencing clinical trials or marketing of the drug in those countries. The approval process varies from country to country, and the time may be longer or shorter than that required for FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from country to country.

Under European Union regulatory systems, marketing authorizations may be submitted either under a centralized, decentralized or mutual recognition procedure. The centralized procedure provides for the grant of a single marking authorization that is valid for all European Union member states. The decentralized procedure includes selecting one reference member state (RMS), and submitting to more than one member state at the same time. The RMS National Competing Authority conducts a detailed review and prepares an assessment report, to which concerned member states provide comment. The mutual recognition procedure provides for mutual recognition of national approval decisions. Under this procedure, the holder of a national marking authorization may submit an application to the remaining member states post-initial approval. Under the centralized procedure, within 120 days of receiving the applications and assessment report, each member state must decide whether to recognize approval.

In addition to regulations in Europe and the United States, we or our collaborators will be subject to a variety of foreign regulations governing clinical trials and commercial distribution of our future drugs.

Environmental Regulation

We are subject to numerous foreign, federal, state and local environmental, health and safety laws and regulations relating to, among other matters, safe working conditions, product stewardship and end-of-life handling or disposition of products, and environmental protection, including those governing the generation, storage, handling, use, transportation and disposal of hazardous or potentially hazardous materials. Some of these laws and regulations require us to obtain licenses or permits to conduct our operations. Environmental laws and regulations are complex, change frequently and have tended to become more stringent over time. Although the costs to comply with applicable laws and regulations, including requirements in the European Union relating to the restriction of use of hazardous substances in products, have not been material, we cannot predict the impact on our business of new or amended laws or regulations or any changes in the way existing and future laws and regulations are interpreted or enforced, nor can we ensure we will be able to obtain or maintain any required licenses or permits.

Employees

As of February 28, 2017, we had 61 full-time employees, including a total of 12 employees with M.D., DVM or Ph.D. degrees. Within our workforce, 42 employees are engaged in research and development and 19 in business development, finance, legal, human resources, facilities, information technology and general management and administration. None of our employees are represented by labor unions or covered by collective bargaining agreements.

Corporate and Available 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 website address is www.adverum.com. We make available on our website, free of charge, our Annual Report on Form 10-K, our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K and any amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission, or the SEC. Further, a copy of this Annual Report on Form 10-K is located at the SEC's Public Reference Room at 100 F Street, N.E., Washington, D. C. 20549. Information on the operation of the Public Reference Room can be obtained by calling the SEC at 1-800-SEC-0330. The SEC maintains a website that contains reports, proxy and information statements and other information regarding our filings at www.sec.gov. The information found on our website is not incorporated by reference into this Annual Report on Form 10-K or any other report we file with or furnish to the SEC.

Item 1A. Risk Factors

You should consider carefully the risks and uncertainties described below, together with all of the other information in this Annual Report on Form 10-K. If any of the following risks are realized, our business, financial condition, results of operations and prospects could be materially and adversely affected. The risks described below are not the only risks facing the Company. Risks and uncertainties not currently known to us or that we currently deem to be immaterial also may materially adversely affect our business, financial condition, results of operations, and/or prospects.

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. Annapurna has also incurred significant operating losses since inception. As of December 31, 2016, we had an accumulated deficit of $197.9 million. Losses have resulted principally from costs incurred in our clinical trials for AVA-101, research and development programs and from our general and administrative expenses as well as a $60.7 million write down of our goodwill and impairment of IPR&D in fiscal year 2016. 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 other 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, 2016, our cash and cash equivalents were $222.2 million. We expect that our cash and cash equivalents will be sufficient to fund our lead gene therapy programs through the end of 2019 and through achievement of meaningful clinical data for at least one of our lead programs. 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 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 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 trials 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

As a result of the transaction with Annapurna, we are transforming from a company developing product candidates for the treatment of eye diseases into a gene therapy company with a diverse pipeline of gene therapy product candidates. We may encounter challenges in implementing this transformation and the integration of Annapurna that could adversely impact our business and operations.

Prior to completion of the transaction with Annapurna in May 2016, all of our development efforts were focused on developing product candidates for the treatment of eye diseases. The pipeline acquired through the Annapurna transaction includes gene therapy product candidates designed to treat a range of diseases. The most advanced product candidate from the Annapurna pipeline is ADVM-043 (formerly ANN-001), which is designed to deliver alpha-1 antitrypsin protein, or A1AT, in patients with A1AT deficiency, a rare genetic disorder which may result in serious respiratory disease in adults and, less commonly, liver disease at any age. Our other lead product candidate from the Annapurna pipeline is ADVM-053 (formerly ANN-002), which is designed to treat patients with hereditary angioedema. Other product candidates from the Annapurna pipeline are designed to treat Friedreich's ataxia and severe allergies. Since the completion of the transaction, we have been advancing both our development programs for the treatment of eye diseases and Annapurna's development programs. As a result, we are transforming from a company focused solely on gene therapy treatments for eye diseases to a gene therapy company with a diverse pipeline of product candidates.

This transformation into a diversified gene therapy company poses risks relating to implementing a new business and operational strategy, including the following:

- the potential disruption of our ongoing development of product candidates for the treatment of eye diseases;
- demands on our management and our limited resources related to the increase in number and diversification of our product candidates;
- difficulties in coordinating research and development activities;
- the establishment of uniform standards, controls, procedures and policies; and
- uncertainties in the business relationships with our collaborators and suppliers due to the Annapurna transaction and our transformation into a diversified gene therapy company.

Additionally, there can be no guarantee that we and Annapurna will operate successfully as a combined company. Integration of Annapurna and consolidation of its operations into our organization has required and will continue to require considerable time and attention from management, which could result in the diversion of management resources from other important matters. Moreover, our chief executive officer, Dr. Amber Salzman resides in Philadelphia, and certain Annapurna operations will continue to be based in Paris.

If we are unable to successfully manage these or other risks and uncertainties relating to the integration of Annapurna's business into our organization, there will likely be adverse impacts on our business and operations.

Our business will depend substantially on the success of one or more of ADVM-022/ADVM-032, ADVM-043 and ADVM-053, our lead product candidates, 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 lead product candidates are in the early stage of development and will require additional preclinical studies, substantial clinical development and testing, manufacturing bridging studies and process validation and regulatory approval prior to commercialization. In the second quarter of 2016, we decided to discontinue development of our one product candidate that had been the focus of advanced development efforts, AVA-101 for the treatment of wAMD. We expect to initiate patient enrollment for a clinical study for our most advanced product candidate, ADVM-043, in the fourth quarter of 2017, and we are continuing pre-clinical development of our other lead product candidates. It is critical to our business to successfully develop and obtain ultimate 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 United States;
- 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. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development programs, we cannot assure you 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. At the moment, no gene therapy products have been approved in the United States and only one gene therapy product has been approved in Europe.

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 studies or commercializing our products on a timely or profitable basis, if at all.

In addition, the clinical study 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. As of the date of this Annual Report on Form 10-K the FDA has not approved any gene therapy products for sale and only one gene therapy product has been approved in the Western world, which makes it difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in either Europe or the United States. Approvals by the EMA may not be indicative of what the FDA may require for approval.

Regulatory requirements governing gene and cell therapy products may change in the future. For example, the FDA has established the Office of Cellular, Tissue and Gene Therapies within its Center for Biologics Evaluation and Research (CBER) to consolidate the review of gene therapy and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its review. Gene therapy clinical studies conducted at institutions that receive funding for recombinant DNA research from the U.S. National Institutes of Health (NIH) may also be subject to review by the NIH Office of Biotechnology Activities' 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 study, even if the FDA has reviewed the study and approved its initiation. Clinical trial sites in the United States 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 Investigational New Drug application (IND) on clinical hold even if the RAC has provided a favorable review. Also, before a clinical study can begin at an NIH-funded institution, that agency's institutional review board (IRB) and its Institutional Biosafety Committee will have to review the proposed clinical study 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 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 studies, 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. 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. Although our lead product candidates are currently in pre-clinical development, 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.

We have not tested any of our internally-developed viral vectors, or product candidates derived from these viral vectors, in clinical trials.

Drug development has inherent risk. None of our current product candidates have ever been evaluated in human clinical studies, 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. For example, following analysis of the data generated in our Phase 2a clinical trial of our prior wAMD product candidate AVA-101, we concluded that, overall, we did not observe evidence of a complete and/or durable anti-VEGF response in the majority of subjects treated with AVA-101 as administered in the Phase 2a study. 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.

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 United States and by comparable authorities in foreign markets. In the United States, 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 United States;
- 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 intend to initiate patient enrollment in a clinical trial for ADVM-043, in the fourth quarter of 2017. Identifying and qualifying subjects to participate in clinical studies of ADVM-043 and our other product candidates will be critical to our success. The timing of future clinical studies 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 studies. 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 studies. 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 United States.

ADVM-053 is focused on the treatment of patients with hereditary angioedema (HAE). The prevalence of HAE is estimated to be 1 in 10,000 to 1 in 50,000, with approximately 8,000 patients diagnosed across major markets. Enrollment of eligible subjects with orphan diseases 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 United States and Europe and we may not be able to initiate clinical studies if we cannot enroll a sufficient number of eligible subjects to participate in the clinical studies 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 or clinical studies or for other reasons, including competitive clinical trials for similar patient populations or available approved therapies, our recruitment of subjects, conduct of studies 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 studies 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 subjects to conduct clinical studies on our product candidates as planned, we may need to delay, limit or terminate future clinical studies, 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.

We have conducted, and may in the future conduct, clinical trials for product candidates in sites outside the United States and the FDA may not accept data from trials conducted in such locations.

We have conducted, and may in the future choose to conduct, one or more of our clinical trials outside the United States. For example, we conducted a Phase 1/2a trial for AVA-101 with the Lions Eye Institute in Australia.

Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of this data is subject to certain conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with ethical principles. The study population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. Generally, the patient population for any clinical studies conducted outside of the United States must be representative of the population for whom we intend to label the product in the United States. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will be dependent upon its determination that the studies also complied with all applicable U.S. laws and regulations. There can be no assurance the FDA will accept data from trials conducted outside of the United States. If the FDA does not accept the data from our clinical trials for our product candidates, it would likely result in the need for additional trials, which would be costly and time-consuming and delay or permanently halt our development of our product candidates.

The occurrence of serious complications or side effects in connection with use of our product candidates, either in preclinical 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, operating results and financial condition.

During the conduct of preclinical 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 have been reported from time-to-time during 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 subjects. 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, operating results and financial condition.

ADVM-022 and ADVM-032 may be studied in diseases of the eye in addition to AMD. There are many potential safety concerns associated with significant blockade of VEGF that may limit our ability to successfully develop and/or commercialize ADVM-022/ADVM-032. These serious and potentially life-threatening risks, based on clinical and preclinical experience of VEGF inhibitors, include bleeding, intestinal perforation, hypertension, proteinuria, congestive heart failure, heart attack, stroke and geographic atrophy. In addition, patients given infusions of any protein may develop severe hypersensitivity reactions or infusion reactions. Other VEGF inhibitors have reported side effects that became evident only after large-scale trials or after marketing approval when large numbers of patients were treated. ADVM-022/ADVM-032 are designed to be delivered by an intravitreal injection to the eye. Possible serious complications of intravitreal injection to the eye include but are not limited to eye-related adverse events such as retinal detachment, a serious infection (endophthalmitis), swelling within the eye (inflammation), cataract formation (clouding of the lens of the eye), glaucoma (increased pressure in the eye), hypotony (reduced pressure in the eye), damage to the retina or cornea (structures of the eye), and bleeding. There are risks in treating patients with gene therapy vectors, including adeno-associated virus (AAV), such as inflammation, cytotoxic T-cell response, anti-AAV antibodies and immune response to the expressed transgene, including T-cell responses and/or auto-antibodies against the expressed protein.

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

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 and clinical trials for our product candidates, and, therefore, the timing of the initiation and completion of these 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 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 by the FDA. Any such delay or rejection could prevent us from commercializing our product candidates.

We have relied, 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 the Company's clinical studies 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 and clinical studies required to support future IND submissions and approval of our product candidates.

Reliance on third-party manufacturers 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 studies 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 studies must be manufactured in accordance with current Good Manufacturing Practice (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 studies, 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 studies may be delayed or we could lose potential revenue.

If we have difficulties or experience delays in transferring our proprietary manufacturing processes to third party contract manufacturers, our planned clinical studies may be delayed, and our business may be materially harmed.

We produce our AAV vectors using a proprietary manufacturing process based on insect cells and baculoviruses. We recently decided to upgrade the ADVM-043 manufacturing process by implementing our proprietary baculovirus-based production system and transferring the third-party contract manufacturing for ADVM-043 to a large-scale contract manufacturer. In addition, we are working to transfer our proprietary manufacturing process to a contract manufacturing organization to produce clinical materials for our future ADVM-022 and ADVM-053 studies. If we have difficulties or experience delays in transferring manufacturing to such third-party contract manufacturers, the planned initiation of patient enrollment for our Phase 1/2 clinical trial for ADVM-043 in the fourth quarter of 2017 or future clinical studies of ADVM-022 and ADVM-053, as applicable, could be delayed. Any such delays could harm our ability to raise additional financing and commercialize our lead product candidates successfully, and our business may be materially harmed.

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 United States 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. For example, in connection with our decision in October 2016 to upgrade ADVM 043's manufacturing process to a commercial-grade baculovirus-based process, in the first half of 2017, we plan to conduct a toxicology study with a new baculovirus-based vector and engage with the FDA to review our development plan, and we now plan to initiate patient enrollment in a Phase 1/2 trial in the fourth quarter of 2017. 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 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 or marketing 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 our product candidate, 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 a new formulation 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 wet AMD, 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 our product candidate 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 wet AMD 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 wet AMD, 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 wet AMD is smaller than we anticipate, we may not be able to achieve profitability and growth. Our projections of the number of people who have wet AMD, as well as the subset of people with these diseases who have the potential to benefit from treatment with wet AMD, 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 United States. ADVM-053 is designed to treat HAE, which impacts approximately 8,000 individuals in the United States. 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 United States, 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 or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. 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. 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.

As a result of legislative proposals and the trend toward managed health care in the United States, 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, the Medicare Prescription Drug Improvement and Modernization Act of 2003 (MMA) changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for outpatient drug purchases by those covered by Medicare under a new Part D and introduced a new reimbursement methodology based on average sales prices for Medicare Part B physician-administered drugs, including anti-VEGF therapies currently on the market used by physicians and likely our anti-VEGF product candidate, if approved. As a result of this legislation and the expansion of federal coverage of drug products, there is additional pressure to contain and reduce costs. While the MMA applies only to drug benefits for Medicare beneficiaries, private payers often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates, and any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payers. These cost reduction initiatives and other provisions of the MMA could decrease the coverage and reimbursement that we receive for any approved products, and could seriously harm our business.

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.

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.

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.

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 studies or the termination or hold on a clinical study, 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 the Company will grant to Editas an exclusive option to obtain certain exclusive rights to use the Company's 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.

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 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 United States for treatment of wet AMD 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 wet AMD. 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/ADVM-032. For example, if we continue clinical development of, and seek to commercialize, ADVM-022/ADVM-032, 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 wet AMD. 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, Quark Pharmaceuticals, Roche (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., CSL, 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 United States 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 studies. 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.

Paul B. Cleveland was appointed Executive Chairman of the Board in October 2016 after joining as our President and Chief Executive Officer in December 2015. Amber Salzman, Ph.D. was appointed as our Chief Executive Officer in October 2016 after joining as our President and Chief Operating Officer, following the completion of the transaction with Annapurna in May 2016. In addition, Leone Patterson joined us as our Chief Financial Officer in June 2016. Our future performance will depend, in part, on our ability to successfully transition Mr. Cleveland and Dr. Salzman into their new roles, otherwise integrate newly hired executive officers, including Dr. Salzman and Ms. Patterson, into our management team and develop an effective working relationship among senior management. Our failure to transition and integrate these individuals and create effective working relationships among them and other members of management could result in inefficiencies in the development and commercialization of our product candidates, harming future regulatory approvals, sales of our product candidates and our results of operations. Moreover, Dr. Salzman resides in Philadelphia, and her location outside of our Menlo Park headquarters may make her integration into our organization more challenging.

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.

If we fail to effectively integrate our new executive officers into our organization, the future development and commercialization of our product candidates may suffer, harming future regulatory approvals, sales of our product candidates or our results of operations.

Our current management team has only been working together for a relatively short period of time and some of our current executive team, including Chief Executive Officer Amber Salzman, Ph.D. and Chief Financial Officer Leone Patterson, have been employed by us for less than a year. In addition, we may continue to expand our management team in the future. Our future performance will depend, in part, on our ability to successfully integrate recently and subsequently hired executive officers into our management team and their ability to develop and maintain an effective working relationship. Our failure to integrate these individuals with other members of management could result in inefficiencies in the development and commercialization of our product candidates, harming future regulatory approvals, sales of our product candidates and our results of operations. Moreover, Dr. Salzman resides in Philadelphia, and her location outside of our Menlo Park headquarters may make her integration into our organization more challenging. In addition to the competition for personnel, the San Francisco Bay Area in particular is characterized by a high cost of living. As such, we could have difficulty attracting experienced personnel to our company and may be required to expend significant financial resources in our employee recruitment and retention efforts.

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

We had 61 full-time employees as of February 28, 2017. We may 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, 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 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 $150,000 per year (or up to an aggregate of $1 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 certain confidential patient health information including retinal scans from subjects participating in our clinical trials. In the event of an inadvertent disclosure or security breach, 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, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 (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 and imprisonment, 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 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, third-party clinical research organizations or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Despite the implementation of security measures, our internal computer systems and those of our current and any future CROs and other contractors, consultants and collaborators are vulnerable to damage from computer viruses, unauthorized access, 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, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other similar disruptions. 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. 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 is 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 to make, have made, use, offer for sale, import, export and sell products covered by certain patent rights licensed to us under our agreement with the Regents is limited to the United States. The license is also limited to the Regents' interest in the licensed patent rights which are co-owned by Chiron Corporation (Chiron). 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 Corporation.

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 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 United States Patent and Trademark Office (USPTO) and courts in the United States 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, 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 United States for disease treatments that prove successful, as a matter of public policy regarding worldwide health concerns; and
- countries other than the United States may have patent laws less favorable to patentees than those upheld by United States 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 Annual Report on Form 10-K, 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 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 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 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 ordinary shares. 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 United States 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 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 the 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 these employees and consultants, and many of our employees, 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 United States patents may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments). The Hatch-Waxman Amendments permit 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 United States Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents 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 United States 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 United States can be less extensive than those in the United States. 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 United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we 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 United States. 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, results of operations and prospects.

Known third party patent rights could delay or otherwise adversely affect our planned development and sale of ADVM-022 or ADVM-032.

We are aware of patent rights held by third parties that may cover certain compositions within ADVM-022 (AAV.7m8-aflibercept) and ADVM-032 (AAV.7m8-ranibizumab). 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 ADVM-022 or ADVM-032, 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 anti-VEGF 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 ADVM-022 or ADVM-032, as the case may be, 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, 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" and if we reach an accelerated filer threshold, 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 and also not an accelerated filer, we intend to take advantage of an exemption available to companies meeting these criteria from these auditor attestation requirements. Section 404 of the Sarbanes-Oxley Act of 2002 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 Securities and Exchange Commission (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 in this "Risk Factors" section of this Annual Report on Form 10-K and others such as:

- our plans regarding further development of ADVM-022/ADVM-032, ADVM-043 or ADVM-053;
- our ability to enroll subjects 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 United States 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 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 United States District Court for the Northern District of California, naming as defendants us and certain of our officers. These lawsuits assert that the defendants violated the Exchange Act and 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 of 1933, as amended, 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.

We believe that we have meritorious defenses and intend to defend these lawsuits vigorously. However, the outcomes of these lawsuits are necessarily uncertain, and we may not prevail. In addition, while we have various insurance policies related to the risks associated with our business, including directors' and officers' liability insurance policies, there is no assurance that our insurance coverage, which contains a self-insured retention, will be sufficient or that our insurance carriers will cover all claims or litigation costs. Accordingly, we could be forced to expend significant resources in the defense of these suits. At this time, we are not able to estimate the possible costs to us from these matters, as these lawsuits are currently at an early stage and we cannot be certain how long it may take to resolve these matters or the possible amount of any damages that we may be required to pay. It is possible that we could, in the future, incur judgments or enter into settlements of claims for monetary damages. Decisions adverse to our interests in these actions could subject us to significant liabilities and could have a material adverse effect on our business, financial condition and results of operations. In addition, the uncertainty of the currently pending litigation could lead to more volatility in our stock price. If our stock price continues to experience volatility, we may be the subject of additional securities litigation in the future.

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.

Our failure to meet the continued listing requirements of The NASDAQ Global Market could result in a delisting of our common stock.

Due to the resignation of two of our independent directors in 2016, we are no longer in compliance with NASDAQ Listing Rule 5605(b)(1), which requires that the majority of the board be composed of independent directors, and NASDAQ Listing Rule 5605(c)(2)(A), which requires that the audit committee of the board be comprised of at least three directors who meet certain independence and other requirements. We have until March 27, 2017 to submit to NASDAQ a plan to regain compliance with these listing rules, and we intend to take all necessary steps to regain compliance. If we continue to fail to satisfy the continued listing requirements of The NASDAQ Global Market, NASDAQ may take steps to de-list our common stock. Such a delisting would likely have a negative effect on the price of our common stock and would impair your ability to sell or purchase our common stock when you wish to do so. In the event of a delisting, we would expect to take actions to restore our compliance with NASDAQ's listing requirements, but we can provide no assurance that any such action taken by us would allow our common stock to become listed again, stabilize the market price or improve the liquidity of our common stock, prevent our common stock from dropping below the NASDAQ minimum bid price requirement or prevent future non-compliance with NASDAQ's listing requirements.

If we sell shares of our common stock in future financings or acquisitions, stockholders may experience immediate dilution and, as a result, our stock price may decline.

We may from time to time issue additional shares of common stock at a discount from the current trading price of our common stock. As a result, our stockholders would experience immediate dilution upon the purchase of any shares of our common stock sold at such discount. In addition, as opportunities present themselves, we may enter into financing or similar arrangements in the future, including the issuance of debt securities, preferred stock or common stock. 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.

Our principal stockholders and management own a significant percentage of our stock and may be able to exert control over matters subject to stockholder approval.

As of February 28, 2017, our executive officers, directors and greater than 5% stockholders, in the aggregate, own approximately 47.5% of our outstanding common stock. As a result, such persons, acting together, may have the ability to control our management and affairs and substantially all matters submitted to our stockholders for approval, including the election and removal of directors and approval of any significant transaction. These persons also may have the ability to control our management and business affairs. This concentration of ownership may have the effect of delaying, deferring or preventing a change in control, impeding a merger, consolidation, takeover or other business combination involving us, or discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of our business, even if such a transaction would benefit other stockholders.

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 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 following the fifth anniversary of our IPO, 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 subsequently adopted by the SEC, and The NASDAQ Global Market to 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.

Our ability to use net operating loss carryforwards and other tax attributes may be limited by the Internal Revenue 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, the Company 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 Section 382 of the Internal Revenue Code of 1986, as amended (Code), the Company's ability to utilize NOL carryforwards or other tax attributes, such as research tax credits, in any taxable year may be limited if the Company experiences 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. The Company believes that it has experienced ownership changes under Section 382, which will result in limitations in the Company's ability to utilize net operating losses and credits. In addition, the Company may experience ownership changes as a result of the Company's initial public offering in August 2014, future offerings or other changes in the ownership of the Company's stock. As a result, the amount of the NOLs and research and credit carryforwards presented in the Company's financial statements could be limited and may expire unutilized. Due to a May 11, 2016 ownership change, we determined that certain NOLs for both federal and state purposes are severely limited and therefore we removed a significant amount NOL from our deferred tax assets.

Risks Related to Our Financial Results

We recognized impairment charges related to goodwill and in-process research and development (IPR&D) assets recorded in connection with the Annapurna transaction. Any impairment of our intangible assets in the future could negatively affect our operating results and financial condition.

We recorded goodwill and intangible assets, consisting of IPR&D assets related to Annapurna products in development, upon the acquisition of Annapurna. During the year, we noted a continuing decline in our stock price that resulted in our market capitalization being less than the carrying value of our net assets and less than our cash and cash equivalents balance as of June 30, 2016. As a result, we conducted a two-step impairment analysis and, based on the work performed, we recorded a goodwill impairment charge of $49.1 million in our consolidated statements of operations and comprehensive loss for the three month period ended June 30, 2016. We recorded additional goodwill impairment charge of $0.4 million in our consolidated statements of operations and comprehensive loss for the three month period ended September 30, 2016 for a total of $49.5 million.

In the fourth quarter of 2016, we performed our annual impairment assessment of IPR&D assets and determined that the fair value of $5.0 million was less than their carrying value of $16.2 million, which resulted in an $11.2 million IPR&D impairment charge. We will continue to conduct impairment analyses of the IPR&D assets on a regular basis, and we would be required to take impairment charges in the future if any assessments thereof reflect estimated fair values which are less than our recorded values, and such charges could be significant. Any impairment charges with respect to the IPR&D assets could negatively affect our operating results and financial condition.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

Our corporate headquarters are located in Menlo Park, California, where we lease and occupy approximately 36,000 square feet of office space. The current term of our lease expires on May 8, 2020, with an option to extend the term through May 8, 2024. We believe that our existing facilities are adequate for our current needs. When our lease expires, we may exercise our renewal option or look for additional or alternate space for our operations and we believe that suitable additional or alternative space will be available in the future on commercially reasonable terms.

Item 3. Legal Proceedings

In July 2015, three securities class action lawsuits were filed against us and certain of our officers in the United States District Court for the Northern District of California, 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. The lawsuits assert claims under the Exchange Act and 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 complaints seek unspecified damages, attorneys' fees and other costs. An amended consolidated complaint was filed in February 2016. On November 3, 2016, the Court granted the Company's motion to dismiss the consolidated complaint. The plaintiffs filed an amended consolidated complaint on December 2, 2016. The Company's motion to dismiss that amended complaint is pending. The Company also has filed a motion requesting that the Court order discovery in the related state court action (described below) stayed, and a motion requesting that the Court certify a class of investors who purchased the Company's securities between July 31, 2014 and June 15, 2015. Both motions are pending.

In December 2015, a 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 in essentially the same manner alleged by the consolidated federal action: 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. The plaintiff has dismissed the two institutional stockholder defendants. In August 2016, the Court denied the Company's motion to stay without prejudice, denied the Company's demurrer, and dismissed with leave to amend certain claims against the underwriter defendants. The plaintiff filed an amended complaint on November 2, 2016. The Company's demurrer to that amended complaint and renewed motion to stay the action is pending.

The Company believes that the claims in the asserted actions are without merit and intends to defend the lawsuits vigorously. Due to the inherent uncertainties of litigation, the Company cannot reasonably predict at this time the timing or outcomes of these matters. The Company expects to incur costs associated with defending the actions. While the Company has various insurance policies related to the risks associated with its business, including directors' and officers' liability insurance policies, there is no assurance that the Company will be successful in its defense of the actions, that its insurance coverage, which contains a self-insured retention, will be sufficient, or that its insurance carriers will cover all claims or litigation costs. Beginning in December 2016, the parties have been participating in private mediation, which to date has not progressed to a point where the Company is able to ascertain whether the mediation will be successful. Currently, there are no active mediation discussions between the parties. As a result of, among other things, the uncertain status of the mediation, the early stage of the proceedings, unresolved motions in the proceedings and the uncertainty of the potential outcomes of these and related issues, an estimate of a reasonably possible loss, or the range of losses, if any, or their effect, if any, on the Company's consolidated financial statements, is not reasonably possible to estimate at this time.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

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

Our common stock has been listed on The NASDAQ Global Market since July 31, 2014, and is currently listed under the symbol "ADVM". Prior to July 31, 2014, there was no public trading market for our common stock. The following table sets forth for the periods indicated the high and low sales prices per share of our common stock as reported on The NASDAQ Global Market:

Year Ended December 31, 2016	High	Low
First Quarter	$ 8.80	$ 4.15
Second Quarter	$ 6.24	$ 3.02
Third Quarter	$ 4.76	$ 3.04
Fourth Quarter	$ 4.35	$ 2.80

Year Ended December 31, 2015	High	Low
First Quarter	$ 62.48	$ 32.47
Second Quarter	$ 42.56	$ 15.03
Third Quarter	$ 17.01	$ 7.86
Fourth Quarter	$ 10.69	$ 7.40

As of February 28, 2017, we had approximately 29 holders of record of our common stock. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividend Policy

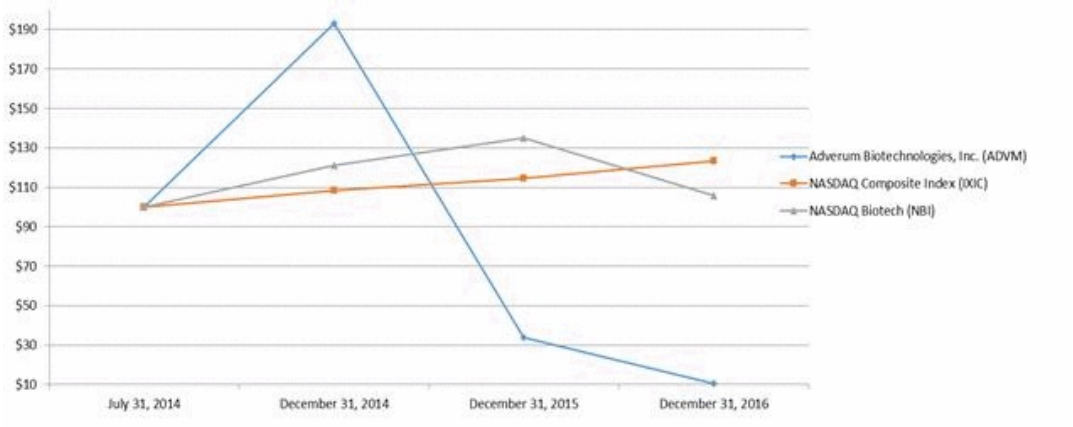
We have never declared or paid cash dividends on our capital stock. We intend to retain all available funds and any future earnings, if any, to fund the development and expansion of our business and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination related to dividend policy will be made at the discretion of our board of directors.

Equity Compensation Plans

For equity compensation plan information, please refer to Item 12 in Part III of this Annual Report on Form 10-K.

Stock Performance Graph

The following graph illustrates a comparison of the total cumulative stockholder return of an investment of $100 in cash on July 31, 2014, which is the date our common stock first began trading on the NASDAQ Global Market, through December 31, 2016 for (i) our common stock, (ii) the NASDAQ Composite Index and (iii) the NASDAQ Biotech Index. Pursuant to applicable SEC rules, all values assume reinvestment of the full amount of all dividends, however no dividends have been declared on our common stock to date. The stockholder return shown in the graph below is not necessarily indicative of future performance, and we do not make or endorse any predictions as to future stockholder returns. This graph shall not be deemed "soliciting material" or be deemed "filed" for purposes of Section 18 of the Exchange Act, or otherwise subject to the liabilities under that Section, and shall not be deemed to be incorporated by reference into any of our filings under the Securities Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.



$100 investment in stock or index	July 31, 2014	December 31, 2014	December 31, 2015	December 31, 2016
Adverum Biotechnologies, Inc. (ADVM)	$ 100.00	$ 192.93	$ 34.01	$ 10.36
NASDAQ Composite Index (IXIC)	$ 100.00	$ 108.38	$ 114.58	$ 123.19
NASDAQ Biotech (NBI)	$ 100.00	$ 121.12	$ 134.95	$ 105.69

Recent Sales of Unregistered Securities

In July 2016, the Company entered into a sponsored research agreement with The Alpha-1 Project, Inc. (TAP) in which TAP will fund the Company's A1AT research activities of up to $300,000. The Company issued common stock warrant for 10,000 shares exercisable anytime during five years from the issuance date at an exercise price of $4.33 per share. The warrant was issued to TAP pursuant to an exemption from registration provided under Section 4(a)(2) of the Securities Act of 1933, as amended (the Securities Act) since, among other things, the sale and issuance of the warrant did not involve a public offering and was acquired by TAP not with a view to the distribution thereof.

On May 11 2016, the Company issued 14,087,246 shares of common stock to the shareholders of Annapurna Therapeutics SAS (Annapurna) in exchange for all of the issued and outstanding capital stock of Annapurna. The sale and issuance of the shares of common stock were not registered under the Securities Act in reliance upon the exemption from registration provided by Section 4(a)(2) of the Securities Act, since, among other things, the sale and issuance of the shares of common stock did not involve a public offering and were acquired by the Annapurna shareholders not with a view to the distribution thereof. The Annapurna shareholders have certain demand and "piggyback" registration rights under the Securities Act with respect to these shares, subject to certain limitations, pursuant to our Amended and Restated Investor Rights Agreement.

Use of Proceeds

On August 5, 2014, we closed our IPO and issued 6,900,000 shares of our common stock at an initial offering price of $17.00 per share. The offer and sale of all of the shares in the IPO were registered under the Securities Act pursuant to a registration statement on Form S-1, as amended (File Nos. 333-197133 and 333-197739), which was declared effective by the SEC on July 30, 2014. The joint book-running managers for the IPO were Jefferies LLC, Cowen and Company, LLC and Piper Jaffray & Co. The aggregate offering price to the public for the shares sold in the IPO was $117.3 million. We received net proceeds from the IPO of approximately $106.5 million, after deducting underwriting discounts and commissions of approximately $8.2 million and expenses of approximately $2.6 million payable by us. None of the expenses associated with the IPO were paid to directors, officers, persons owning 10% or more of any class of equity securities, or to their associates, or to our affiliates.

We invested the funds received in short-term, interest-bearing investment-grade securities and government securities.

We have discontinued development of AVA-101, and so we will not use approximately $20 million of our net proceeds from the IPO to fund Phase 3 research and development startup activities for our AVA-101 study, as we had described in our final prospectus filed with the SEC on July 31, 2014 pursuant to Rule 424(b) of the Securities Act. Instead, we plan to reallocate such proceeds to fund research and development expenses for additional preclinical studies relating to our wet AMD gene therapies, ADVM-022 and ADVM-032 and for ADVM-043 for A1AT deficiency and for ADVM-053 for HAE.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

Item 6. Selected Financial Data

The following selected consolidated financial data should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations", the consolidated financial statements and related notes, and other financial information included in this Annual Report on Form 10-K.

We derived the consolidated financial data for the years ended December 31, 2016, 2015 and 2014 and as of December 31, 2016 and 2015 from our consolidated financial statements, which are included elsewhere in this Annual Report on Form 10-K. The consolidated financial data for the years ended December 31, 2013 and 2012 and as of December 31, 2013 and 2012 are derived from our audited financial statements which are not included in this Annual Report on Form 10-K. Historical results are not necessarily indicative of the results to be expected in future periods.

	Years ended December 31,				
(In thousands, except per share data)	2016	2015	2014	2013	2012
Consolidated Statements of Operations and Comprehensive Loss Data:					
Revenue					
Collaboration and license revenue	$ 1,455	$ 2,319	$ 572	$ —	$ —
Government grant revenue	—	—	—	480	30
Operating expenses:					
Research and development (2)	31,670	25,462	16,976	2,151	1,310
General and administrative (3)	24,355	22,107	7,998	1,783	536
Impairment of goodwill and intangible assets (5)	60,714	—	—	—	—
Restructuring charges (4)	—	2,573	—	—	—
Total operating expenses	116,739	50,142	24,974	3,934	1,846
Operating loss	(115,284)	(47,823)	(24,402)	(3,454)	(1,816)
Other income (expense)					
Interest expense	—	—	(18)	(73)	(8)
Other income (expense), net	762	370	(21)	(4)	(6)
Changes in fair value of embedded derivative	—	—	—	18	6
Changes in fair value of warrant liabilities	—	—	(759)	(92)	13
Loss on extinguishment of related-party convertible notes	—	—	(204)	(1,671)	—
Total other income (expense), net	762	370	(1,002)	(1,822)	5
Net loss before income tax benefit	(114,522)	(47,453)	(25,404)	(5,276)	(1,811)
Income tax benefit (6)	775	—	—	—	—
Net loss after income tax benefit	(113,747)	(47,453)	(25,404)	(5,276)	(1,811)
Deemed dividend (1)	—	—	(3,230)	—	—
Net loss attributable to common stockholders	$ (113,747)	$ (47,453)	$ (28,634)	$ (5,276)	$ (1,811)
Other comprehensive loss:					
Net unrealized loss on marketable securities	6	(6)	—	—	—
Foreign currency translation adjustment	(2)	(15)	(17)	19	8
Comprehensive loss	$ (113,743)	$ (47,474)	$ (25,421)	$ (5,257)	$ (1,803)
Net loss per share attributable to common stockholders-basic and diluted	$ (3.14)	$ (1.86)	$ (2.46)	$ (1.44)	$ (0.50)
Weighted-average common shares outstanding-basic and diluted	36,246	25,479	11,651	3,673	3,643

(1) In April 2014, we repurchased 531,208 shares of Series A convertible preferred stock for $4.0 million. The difference between the repurchase price of $7.53 per share and original issuance price of $1.45 per share was recorded as a deemed dividend of $3.2 million to a preferred stockholder and effected the calculation of net loss attributable to common stockholders and net loss per share for the year ended December 31, 2014.

(2) In 2016, the Company recorded approximately $1.4 million related to stock modifications in connection with separation agreements with executive officers.

(3) In July 2015, the Company's then Chief Executive officer resigned and some of his stock-based awards were forfeited and cancelled, which resulted in $2.4 million of additional stock-based compensation expense recorded in general and administrative expenses in our consolidated financial statements. In 2016, the Company recorded approximately $1.5 million related to stock modifications in connection with separation agreements with executive officers.

(4) The Company recorded estimated restructuring charges of approximately $2.6 million related to one-time termination severance payments and other employee-related benefits, including approximately $1.0 million of stock-based compensation expense related to the acceleration of RSUs in December 2015. During the fourth quarter of 2015, the Company paid out approximately $1.5 million in cash and stock. During the first quarter of 2016, the Company paid out approximately $1.0 million in cash related to the restructuring charges.

(5) The Company recorded a goodwill impairment charge of approximately $49.5 million related to its valuation analysis in the second and third quarter of 2016. Additionally, during the fourth quarter of 2016, the Company performed its annual impairment assessment of its in-process research and development (IPR&D) assets and recorded an $11.2 million impairment charge.

(6) During the fourth quarter of 2016, the Company recorded income tax benefit of $775,000 related to the change in the deferred tax liabilities balance due to intangible assets impairment recognized in the same quarter.

	As of December 31,				
	2016	2015	2014	2013	2012
(In thousands)					
Consolidated Balance Sheet Data:					
Cash and cash equivalent	$ 222,170	$ 221,348	$ 159,404	$ 564	$ 357
Marketable securities	—	37,732	—	—	—
Working capital	215,378	254,418	154,807	(340)	(457)
Total assets	234,583	264,319	161,906	1,085	386
Other non-current liabilities	(386)	—	—	—	—
Accumulated deficit	(197,915)	(84,168)	(36,715)	(8,869)	(3,593)
Total stockholders' equity	215,600	252,592	149,483	(8,210)	(3,468)

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

You should read the following discussion of our financial condition and results of operations in conjunction with the financial statements and the related notes included elsewhere in this Annual Report on Form 10-K. The following discussion contains forward-looking statements that reflect our plans, estimates and beliefs. Our actual results could differ materially from those discussed in the forward-looking statements. Factors that could cause or contribute to these differences include those discussed below and elsewhere in this Annual Report on Form 10-K, particularly in "Cautionary Note Regarding Forward-Looking Statements" and "Risk Factors."

Overview

We are a gene therapy company committed to discovering and developing novel medicines that can offer potentially life-changing therapeutic benefit to patients living with rare diseases or diseases of the eye, who currently have limited or burdensome treatment options. 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 on May 11, 2016, of Annapurna Therapeutics SAS (Annapurna), a privately-held French gene therapy company. 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 (wAMD) and in rare diseases alpha-1 antitrypsin (A1AT) deficiency and hereditary angioedema (HAE). For wAMD, we have two new anti-VEGF gene therapy candidates, ADVM-022 (AAV.7m8-aflibercept) and ADVM-032 (AAV.7m8-ranibizumab). These therapies utilize a proprietary vector and are administered intravitreally for this indication. Preclinical data demonstrate that ADVM-022 and ADVM-032 have the potential to minimize the treatment burden of frequent injections and maximize visual outcomes in patients living with this disease.

At recent scientific meetings we presented preclinical proof-of-concept data of ADVM-022 and ADVM-032's anti-angiogenic effect in a 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 and ADVM-032 showed efficacy that was comparable to the anti-VEGF standard of care, the positive control in the CNV model. We have selected ADVM-022 to advance in development first and we plan to initiate IND-enabling toxicology and biodistribution studies in the first half of 2017 to support a planned IND filing. We also continue to review data for our backup gene therapy for wAMD ADVM-032.

Before focusing on these two new therapies for wet AMD, we were developing AVA-101 in a Phase 2a clinical trial in 32 patients with wet AMD. In June 2015, we announced top-line results, and although we did not observe any serious safety issues, we also did not observe evidence of a complete and/or durable anti-VEGF response in the majority of subjects treated with AVA-101 as administered (via surgical sub-retinal delivery) in the Phase 2a study. As a result, in July 2016, we announced our decision to discontinue development of AVA-101.

With our pipeline of gene therapies for rare diseases, we are advancing ADVM-043 (formerly known as ANN-001) for the treatment of A1AT deficiency. ADVM-043 is a product candidate designed to be a single-administration treatment. This therapy has the potential to induce stable, long-term A1AT expression at therapeutic levels, as seen in preclinical proof-of-concept studies. ADVM-043 has an open IND with the U.S. Food and Drug Administration (FDA), and we plan to engage with the agency in the first half of 2017 to review our development plan. Concurrently, we are upgrading ADVM-043's manufacturing process to a commercial-grade baculovirus-based process and plan to transfer this process to a contract manufacturing organization to produce clinical materials for our trials. We plan to initiate a toxicology study with a new baculovirus-based vector in the first half of 2017 and to begin patient enrollment in a Phase 1/2 trial in the fourth quarter of 2017.

We are also advancing ADVM-053 (formerly known as ANN-002) to treat HAE. In the first half of 2017, we plan to initiate IND-enabling studies for ADVM-053 and engage with the FDA to review our plans. We are working to transfer our manufacturing process to a contract manufacturing organization to produce clinical materials for our future ADVM-053 studies.

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

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 and, as a result, Annapurna is now our wholly-owned subsidiary. At the closing of the acquisition, we issued 14,087,246 shares of our common stock to the shareholders of Annapurna, and the outstanding options or other rights to purchase capital stock of Annapurna were exchanged for options relating to shares of our common stock.

We changed our name to "Adverum Biotechnologies, Inc." upon completion of the Annapurna transaction.

Financial Overview

Summary

We have not generated positive cash flow or net income from operations since our inception and, at December 31, 2016, we had an accumulated deficit of $197.9 million, primarily as a result of research and development, general and administrative expenses, impairment of goodwill and intangible assets, and restructuring charges. We expect to incur substantial losses from operations in the foreseeable future as we continue our research and development efforts, advance our product candidates through preclinical and clinical development, manufacture clinical study materials, seek regulatory approval and prepare for, and if approved, proceed to commercialization. We are at an early stage of development and may never be successful in developing or commercializing our product candidates.

See "Risk Factors—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."

While we may in the future generate revenue from a variety of sources, including license fees, milestone and research and development payments in connection with strategic partnerships, and potentially revenue from approved product sales, we have not yet generated any revenue from approved therapeutic product candidates.

We entered into our first license and development revenue generating agreement with Regeneron in May 2014. We entered into the collaboration, option and license agreement with Editas in August 2016 that also is a revenue agreement as discussed in Note 7, *Significant Agreements*, in the consolidated financial statements included in this Form 10-K. We have no clinical or commercial manufacturing facilities, and all of our clinical manufacturing activities are contracted out to third parties. Additionally, we plan to use third-party clinical research organizations (CROs) to carry out our clinical development and we do not yet have a sales organization.

We expect to incur substantial expenditures in the foreseeable future for the development and potential commercialization of our product candidates. We will need substantial additional funding in the future to support our operating activities as we advance our product candidates through preclinical and clinical development, seek regulatory approval and prepare for and, if approved, proceed to commercialization. Adequate funding may not be available to us on acceptable terms, or at all. If we are unable to raise capital, or to do so on acceptable terms, when needed, or to form additional collaboration partnerships to support our efforts, we could be forced to delay, reduce or eliminate our research and development programs or potential commercialization efforts.

As of December 31, 2016, we had $222.2 million in cash and cash equivalents. We believe that we have sufficient funds to continue operations through the end of 2019.

Revenue

To date we have not generated any revenue from the sale of our products. In May 2014, we entered into a license and development agreement with Regeneron. Under the terms of the agreement, we received initial payments of $8.0 million that included payment for research license fees, prepaid collaboration research costs and the right of first negotiation for a potential license to develop and commercialize AVA-101. As the agreement provides for multiple deliverables, we account for this agreement as a multiple elements revenue arrangement. If deliverables do not appear to have a standalone fair value, they were combined with other deliverables into a unit of accounting with standalone fair value. We allocated the $8.0 million received to the fair values of the two units of accounting identified in the arrangement. We expect to recognize $6.5 million for research licenses and related research and development services ratably over the associated period of performance, which is the maximum research period of eight years. As there is no discernible pattern of performance and/or objectively measurable performance measures do not exist, we will recognize revenue on a straight-line basis over the eight-year performance period. The remaining $1.5 million allocated to the second unit of accounting for the time-limited right of first negotiation for AVA-101 was deferred. On November 2, 2015, Regeneron notified the management that it was not exercising this right of first negotiation and we recognized the entire $1.5 million as revenue in 2015.

The portion of the upfront payment that was applied to the original research budget was fully used in the fourth quarter of 2015, and the Company and Regeneron, through a joint review committee, agree annually on an updated research and development services budget through the research period. The Company invoices Regeneron quarterly for services performed in each prior quarters. These additional research fees are added to the research licenses and related research and development services unit of accounting, recorded as deferred revenue and recognized to revenue over the remaining maximum research term.

The Company recognized $1.3 million, $2.3 million and $0.6 million as revenue during the years ended December 31, 2016, 2015 and 2014, respectively.

On February 23, 2017, Regeneron notified the Company that pursuant to Section 2.3 of the license and development agreement, it is extending the research term of the license and development agreement for an additional three years, through May 1, 2020.

In August 2016, the Company entered into a collaboration, option and license agreement with Editas. Under the terms of the agreement, the Company received initial payments of $1.0 million that included $0.5 million for research services. As the agreement provides for multiple deliverables, the Company accounts for this agreement as a multiple elements revenue arrangement. At the inception of the agreement, identified deliverables include research services, manufacturing of viral vectors for research, participation in joint research committee and exclusivity during the option period. These deliverables did not appear to have a standalone value and were combined into one unit of accounting. Options for each indication to license the Company's AAV vector are considered substantive options and do not include significant incremental discounts. Therefore, they are not considered as deliverables under the agreement.

The Company allocated the $1.0 million received to a single unit of accounting identified in the arrangement. The Company expects to recognize $1.0 million ratably over the associated period of performance, which is the maximum research period of three years. As there is no discernible pattern of performance and/or objectively measurable performance measures do not exist, the Company will recognize revenue on a straight-line basis. The Company recognized $139,000 as revenue during the year ended December 31, 2016.

The Company recorded $8.9 million of deferred revenue, including $1.9 million as current deferred revenue, and $0.9 million as a receivable from collaborative partner as of December 31, 2016.

Our ability to generate product revenue and become profitable depends upon our ability to successfully develop and commercialize our product candidates. Because of the numerous risks and uncertainties associated with product development, we are unable to predict the amount or timing of product revenue. Even if we are able to generate revenue from the sale of our products, we may be unable to continue our operations at planned levels and be forced to reduce our operations.

Research and Development Expenses

Conducting a significant amount of research and development is central to our business model. Research and development expenses include certain payroll and personnel expenses, stock-based compensation expense, laboratory supplies, consulting costs, external contract research and development expenses, including expenses incurred under agreements with CROs, the cost of acquiring, developing and manufacturing clinical study materials and overhead expenses, including rent, equipment depreciation, insurance and utilities.

Research and development costs are expensed as incurred. Advance payments for goods or services for future research and development activities are deferred and expensed as the goods are delivered or the related services are performed.

We estimate preclinical study and clinical trial expenses based on the services performed pursuant to contracts with research institutions and CROs that conduct and manage preclinical studies and clinical trials on our behalf. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. We estimate the amounts incurred through communications with third party service providers and our estimates of accrued expenses as of each balance sheet date are based on information available at the time. If the actual timing of the performance of services or the level of effort varies from the estimate, we will adjust the accrual accordingly.

At this time, we cannot reasonably estimate the nature, timing or aggregate costs of the efforts that will be necessary to complete the development of any of our product candidates. The successful development and commercialization of a product candidate is highly uncertain, and clinical development timelines, the probability of success and development and commercialization costs can differ materially from expectations.

We received refundable tax credits from the Australian and French tax authorities in connection with certain research costs incurred by our subsidiary conducting research in Australia and France. These refunds do not depend on our taxable income or tax position and therefore we do not account for them under an income tax accounting model. We recognize such refunds as government grants in the period when qualified expenses are incurred as a reduction of research expenses. We have recorded the reimbursement from the Australian and French tax authorities as a reduction of research and development expense in the consolidated statements of operations and comprehensive loss for the applicable period. The Company recorded tax credits of $326,000 and $113,000 for the years ending December 31, 2016 and 2015, respectively.

General and Administrative Expenses

General and administrative expenses consist principally of personnel-related costs, stock-based compensation, professional fees for legal, consulting, audit and tax services, rent and other general operating expenses not otherwise included in research and development expenses. Our general and administrative expenses may increase in future periods if and to the extent we elect to increase our investment in infrastructure to support continued research and development activities and potential commercialization of our product candidates. We will continue to evaluate the need for such investment in conjunction with ongoing consideration of our pipeline of product candidates. We anticipate increased expenses related to audit, legal and regulatory functions, as well as director and officer insurance premiums and investor relations costs associated with being a public reporting company.

Impairment of Goodwill and Intangible Assets

We noted a continuing decrease in our stock price that resulted in our market capitalization being less than the carrying value of our net assets as of June 30, 2016 and the continuation of operating losses in subsequent years due to preclinical and expected clinical trials, we concluded that it is more likely than not that the fair value of our one reporting unit is less than its carrying value and concluded to perform a goodwill impairment analysis. We performed a two-step goodwill impairment analysis and recorded a $49.1 million and a $0.4 million goodwill impairment charge in the second and third quarter of 2016 in our consolidated statements of operations and comprehensive loss.

In the fourth quarter of 2016, we performed our annual assessment of our ADVM-043 and ADVM-053 IPR&D assets. Based on our decision in the fourth quarter to change our manufacturing process for ADVM-043 and ADVM-053 by implementing our proprietary baculovirus-based production system, we updated the related product development and manufacturing costs. In addition, we also reviewed and updated our expected timing of clinical trials, receipts of regulatory approvals and costs to complete. Based upon our analysis, we determined that the carrying value of $16.2 million for our ADVM-043 and ADVM-053 IPR&D assets was higher than their fair value of $5.0 million. Accordingly, we recorded an $11.2 million IPR&D impairment charge for the year ended December 31, 2016.

Other Income (Expense), Net

Other income (expense), net is comprised mainly of interest income on our cash equivalents and investment in marketable securities in 2016 and 2015, and changes in the fair value of common stock warrant liabilities and preferred stock warrant liabilities in 2014. In April 2014, we recorded a $0.2 million loss related to the conversion of all outstanding convertible notes into Series B convertible preferred stock. At the time of the IPO, all then outstanding warrants were exercised, and as a consequence, we do not expect to have any other income (expense), net related to changes in the fair value of warrant liabilities in future periods.

Income tax benefit

In the fourth quarter 2016, the Company recorded income tax benefit of $775,000 related to the change in the deferred tax liabilities balance due to intangible assets impairment recognized in the same quarter.

Critical Accounting Policies, Significant Judgments and Use of Estimates

This discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with U.S. GAAP. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the consolidated financial statements, as well as the reported expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates. We believe that the accounting policies discussed below are critical to understanding our historical and future performance, as these policies relate to the more significant areas involving management's judgments and estimates.

Revenue Recognition

We have primarily generated revenue through the license and research and collaboration arrangements with our strategic partners for the development and commercialization of product candidates.

The terms of these types of agreements may include (i) licenses to our technology, (ii) research and development services, and (iii) services or obligations in connection with participation in research or steering committees. Payments to us under these arrangements typically include one or more of the following: nonrefundable upfront and license fees, research funding, milestone and other contingent payments for the achievement of defined collaboration objectives and certain preclinical, clinical, and regulatory events, as well as royalties on sales of any commercialized products.

In arrangements involving the delivery of more than one element, each required deliverable is evaluated to determine whether it qualifies as a separate unit of accounting. The determination is based on whether the deliverable has "standalone value" to the customer. If a deliverable does not qualify as a separate unit of accounting, it is combined with the other applicable undelivered item(s) within the arrangement and these combined deliverables are treated as a single unit of accounting.

The arrangement's consideration that is fixed or determinable is allocated to each separate unit of accounting based on the relative selling price methodology in accordance with the selling price hierarchy, which includes vendor-specific objective evidence ("VSOE") of selling price, if available, or third-party evidence of selling price if VSOE is not available, or the best estimate of selling price, if neither VSOE nor third-party evidence is available.

Payments or reimbursements for our research and development efforts for the arrangements where such efforts are considered as deliverables are recognized as the services are performed and are presented on a gross basis. When upfront payments are received and if there is no discernible pattern of performance and/or objectively measurable performance measures do not exist, we recognize revenue ratably over the associated period of performance.

Our collaboration and license agreements may include contingent payments related to specified research, development and regulatory milestones. Such payments are typically payable under the collaborations when the collaboration partner claims or selects a target, or initiates or advances a covered product candidate in preclinical or clinical development, upon submission for marketing approval of a covered product with regulatory authorities, upon receipt of actual marketing approvals of a covered product or for additional indications, or upon the first commercial sale of a covered product. Each contingent and milestone payment is evaluated to determine whether it is substantive and at risk to both parties. We recognize any payment that is contingent upon the achievement of a substantive milestone entirely in the period in which the milestone is achieved. Any payments that are contingent upon achievement of a non-substantive milestone are recognized as revenue prospectively, when such payments become due and collectible, over the remaining expected performance period under the arrangement, which is generally the remaining period over which the research and development services are expected to be provided.

Accrued and Prepaid Research and Development Expense

We estimate our accrued and prepaid research and development expenses as of each balance sheet date. This process involves reviewing contracts and purchase orders, reviewing the terms of our license agreements, communicating with our applicable personnel to identify services that have been performed on our behalf, and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual cost. The majority of our service providers invoice us monthly in arrears for services performed. Expenses that are paid in advance of performance are deferred as a prepaid expense and expensed as the services are provided.

Examples of estimated accrued research and development expenses include fees to:

- contract manufacturers in connection with the production of clinical trial materials;
- CROs and other service providers in connection with clinical studies;
- investigative sites in connection with clinical studies;
- vendors in connection with preclinical development activities; and
- services providers for professional service fees such as consulting and related services.

Our understanding of the status and timing of services performed relative to the actual status and timing may vary and may result in our reporting changes in estimates in any particular period. To date, there have been no material differences from our estimates to the amount actually incurred. However, due to the nature of these estimates, we cannot assure you that we will not adjust our estimates in the future as we become aware of additional information about the status or conduct of our clinical studies or other research activities. For the years ended December 31, 2016 and 2015, there were no material changes from our estimates of accrued research and development expenses.

Stock-Based Compensation Expense

We recognize compensation costs related to stock-based awards granted to employees based on the estimated fair value of the awards on the date of grant, net of estimated forfeitures. We estimate the grant date fair value, and the resulting stock-based compensation expense, using the Black-Scholes valuation model for stock options, and using intrinsic value, which is our common stock price at the grant date for the restricted stock units (RSUs) awards. The grant date fair value of the stock-based awards is generally recognized on a straight-line basis over the requisite service period, which is generally the vesting period of the respective awards. Stock-based compensation expense related to awards to non-employees is recognized based on the then-current fair value at each measurement date over the associated service period of the award, which is generally the vesting term, using the accelerated attribution method. We have used the Black-Scholes valuation model to assist us in determining the fair value of stock-based awards. The Black-Scholes valuation model requires the use of following complex assumptions:

Expected volatility. We estimate expected volatility based on the average historical volatility of a peer group of comparable publicly traded life sciences and biotechnology companies with product candidates in similar stages of clinical development, as we do not have sufficient trading history for our common stock. We will continue to apply this process until a sufficient amount of historical information regarding the volatility of our own stock price becomes available.

Expected term. We derived the expected term using the "simplified" method (the expected term is determined as the average of the time-to-vesting and the contractual life of the options), as we have limited historical information to develop expectations about future exercise patterns and post vesting employment termination behavior. Expected term for non-employee awards is based on the remaining contractual term of an option on each measurement date. The expected term of the Employee Stock Purchase Plan (ESPP) rights equals to the six-month look-back period.

Risk-free interest rate. The risk-free interest rate is based on U.S. Treasury zero-coupon issues with remaining terms similar to the expected term on the options.

Expected dividend yield. We have never paid any dividends and do not plan to pay dividends in the foreseeable future, and, therefore, used an expected dividend yield of zero in the valuation model.

Forfeitures. We estimate forfeitures at the time of grant, and revise those estimates in subsequent periods if actual forfeitures differ from those estimates. We use historical data and expected terminations to estimate pre-vesting option forfeitures and record stock-based compensation expense only for those awards that are expected to vest. To the extent actual forfeitures differ from the estimates, the difference will be recorded as a cumulative adjustment in the period that the estimates are revised.

Valuation of Long-Lived Assets and Purchased Intangible Assets

We evaluate the carrying value of amortizable long-lived assets, whenever events, or changes in business circumstances or the planned use of long-lived assets indicate that their carrying amounts may not be fully recoverable or that their useful lives are no longer appropriate. If these facts and circumstances exist, we assess for recovery by comparing the carrying values of long-lived assets with their future undiscounted net cash flows. If the comparison indicates that impairment exists, long-lived assets are written down to their respective fair value based on discounted cash flows. Significant management judgment is required in the forecast of future operating results that is used in the preparation of expected undiscounted cash flows. If management's assumptions about future operating results were to change as a result of events or circumstances, we may be required to record an impairment loss on these assets. No impairment indicators were noted for the Company's amortizable long-lived assets, fixed assets, in the periods presented.

We also evaluate the carrying value of intangible assets (not subject to amortization) related to in-process research and development ("IPR&D") assets, which are considered to be indefinite-lived until the completion or abandonment of the associated research and development efforts. Accordingly, amortization of the IPR&D assets will not occur until the product reaches commercialization. During the period the assets are considered indefinite-lived, they will be tested for impairment on an annual basis, as well as between annual tests if we become aware of any events occurring or changes in circumstances that would indicate that the fair values of the IPR&D assets are less than their carrying amounts. Impairment loss is recorded when fair value of an IPR&D asset is less than its carrying value. If the related project is terminated or abandoned, we will also have an impairment related to the IPR&D assets.

If and when development is complete, which generally occurs when regulatory approval to market the product is obtained, the associated IPR&D assets would be deemed definite-lived and would then be amortized based on their estimated useful lives at that point in time based on respective patent terms and tested for impairment only when impairment indicators are present as discussed above under long-lived assets.

Income Tax

We recognize deferred income taxes for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. We periodically evaluate the positive and negative evidence bearing upon realizability of our deferred tax assets. Based upon the weight of available evidence, which includes our historical operating performance, reported cumulative net losses since inception and difficulty in accurately forecasting our future results, we maintained a full valuation allowance on the net deferred tax assets as of December 31, 2016 and 2015 of approximately $23.5 million and $28.9 million, respectively. We intend to maintain a full valuation allowance on the federal, state and foreign deferred tax assets until sufficient positive evidence exists to support reversal of the valuation allowance.

As of December 31, 2016, the Company 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, the Company 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, the Company 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 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 have experienced 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 own at least 5% of a corporation's stock within a specified testing period. Similar rules may apply under state tax laws. We believe that we have experienced ownership changes under Section 382 which will result in limitations in our ability to utilized net operating losses and credits. In addition, we may experience ownership changes as a result of our previous or future offerings or other changes in the ownership of our stock. As a result, the amount of the NOL carryforwards and research and credit carryforwards presented in our financial statements could be limited and may expire unutilized. Due to a May 11, 2016 ownership change, we determined that certain NOLs for both federal and state purposes are severely limited and therefore we removed a significant amount NOL from our deferred tax assets.

We record unrecognized tax benefits as liabilities and adjust these liabilities when our judgment changes as a result of the evaluation of new information not previously available. Because of the complexity of some of these uncertainties, the ultimate resolution may result in a payment that is materially different from our current estimate of the unrecognized tax benefit liabilities. These differences will be reflected as increases or decreases to income tax expense in the period in which new information is available. Our policy is to recognize interest and penalties related to income taxes as a component of income tax expense. No interest and penalties related to income taxes have been recognized in the statements of operations and comprehensive loss in 2016 and 2015.

Recent Accounting Standard Update Not Yet Effective—In August 2014, the Financial Accounting Standards Board (FASB) issued Accounting Standard Update (ASU) 2014-15, *Presentation of Financial Statements—Going Concern (Subtopic 205-40): Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern*, requiring management to evaluate whether events or conditions could impact an entity's ability to continue as a going concern and to provide disclosures if necessary. Management will be required to perform the evaluation within one year after the date that the financial statements are issued. Disclosures will be required if conditions give rise to substantial doubt and the type of disclosure will be determined based on whether management's plans will be able to alleviate the substantial doubt. The accounting standard update will be effective for the first annual period ending after December 15, 2016, and for annual periods and interim periods thereafter with early application permitted. This ASU will be effective for us in the first quarter of 2017. The adoption of this ASU is not expected to impact our consolidated financial statements and related disclosures.

In May 2014, the FASB issued ASU No. 2014-09, *Revenue from Contracts with Customers* (Topic 606), which supersedes the revenue recognition requirements in ASC 605*, Revenue Recognition*. This ASU is based on the principle that revenue is recognized to depict the transfer of goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. ASU 2014-09 defines a five step process to achieve this core principle and, in doing so, it is possible more judgment and estimates may be required within the revenue recognition process than required under existing GAAP including identifying performance obligations in the contract, estimating the amount of variable consideration to include in the transaction price and allocating the transaction price to each separate performance obligation. ASU 2014-09 is required to be adopted, using either of two methods: (i) retrospective to each prior reporting period presented with the option to elect certain practical expedients as defined within ASU 2014-09; or (ii) retrospective with the cumulative effect of initially applying ASU 2014-

09 recognized at the date of initial application and providing certain additional disclosures. In July 2015, the FASB voted to approve a one-year deferral of the effective date to December 15, 2017 for interim and annual reporting periods beginning after that date and permitted early adoption of the standard, but not before the original effective date of December 15, 2016. The FASB issued supplemental adoption guidance and clarification to ASU 2014-09 in March 2016, April 2016, May 2016 and December 2016 within ASU 2016-08 *Revenue From Contracts With Customers: Principal vs. Agent Considerations*, ASU 2016-10 *Revenue From Contracts with Customers: Identifying Performance Obligations and Licensing*, ASU 2016-12 *Revenue from Contracts with Customers: Narrow-Scope Improvements and Practical Expedients*, and ASU 2016-20 *Technical Corrections and Improvement to Topic 606 – Revenue from Contracts with* Customers, respectively. This ASU will be effective for us in the first quarter of 2018. Preliminarily, we intend to adopt the new standard in the first quarter of 2018 using the retrospective approach noted in (ii) above. We are currently evaluating the impact of the adoption of this standard on our consolidated financial statements and related disclosures.

In January 2016, the FASB issued ASU No. 2016-01, *Recognition and Measurement of Financial Assets and Financial Liabilities*, which amends the current guidance on the classification and measurement of financial instruments. Although this ASU retains many current requirements, it significantly revises an entity's accounting related to (1) the classification and measurement of investments in equity securities and (2) the presentation of certain fair value changes for financial liabilities measured at fair value. This ASU also amends certain disclosure requirements associated with the fair value of financial instruments. The new standard is effective for fiscal years and interim periods within those fiscal years beginning after December 15, 2017, with early adoption permitted for certain changes. This ASU will be effective for us in the first quarter of 2018, and must be adopted using a modified retrospective approach, with certain exceptions. Early adoption is permitted for certain provisions. The adoption of this standard is not expected to have a significant impact on our consolidated financial statements and related disclosures.

In February 2016, the FASB issued ASU No. 2016-2, *Leases*, which amends the current guidance on leasing activities to provide more transparency and comparability, and requires that all leases be recognized by lessees on their balance sheet as a right-of-use asset and corresponding lease liability, which are currently accounted for as operating leases. The new standard is effective for fiscal years and interim periods within those fiscal years beginning after December 15, 2018, with early adoption permitted. This ASU will be effective for us in the first quarter of 2019 and early adoption is permitted. This ASU requires adoption based upon a modified retrospective transition approach. We have not yet selected a transition method, have not yet determined whether we will elect early adoption and we are currently evaluating the impact of the adoption of this standard on our consolidated financial statements and related disclosures.

In March 2016, the FASB issued ASU No. 2016-9, *Compensation-Stock Compensation: Improvements to Employee Share-Based Payment Accounting,* which simplifies several aspects of the accounting for share-based payment award transactions, including: (1) the income tax consequences, (2) classification of awards as either equity or liabilities, and (3) classification in the consolidated statement of cash flows. The new standard is effective for fiscal years and interim periods within those fiscal years beginning after December 15, 2016 with early adoption permitted. This ASU will be effective for us in the first quarter of 2017. We are currently evaluating the impact of the adoption of this standard on our consolidated financial statements and related disclosures.

In June 2016, the FASB issued ASU No. 2016-13 *Measurement of Credit Losses on Financial Instruments* (ASU 2016-13). ASU 2016-13 requires measurement and recognition of expected credit losses for financial assets held. The new standard is effective for fiscal years beginning after December 15, 2020 and interim periods beginning after December 15, 2021 with early adoption permitted. This ASU will be effective for us in the first quarter of 2021 and must be adopted using a modified retrospective approach, with certain exceptions. Early adoption is permitted beginning in the first quarter of 2019. We have not yet determined whether we will elect early adoption and we are currently evaluating the impact of the adoption of this standard on our consolidated financial statements and related disclosures.

In August 2016, the FASB issued ASU No. 2016-15*, Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments (ASU 2016-15*), which clarifies the presentation and classification of certain cash receipts and cash payments in the statement of cash flows. This ASU is effective for public business entities for annual reporting periods beginning after December15, 2017, and interim periods within that reporting period. Early adoption is permitted. This ASU will be effective for us in the first quarter of 2018 and early adoption is permitted. We have not yet determined whether we will elect early adoption and are currently evaluating the impact of the adoption of this standard on our consolidated financial statements and related disclosures.

In November 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows (Topic 230): Restricted Cash (ASU 2016-18)*, which provides amendments to current guidance to address the classification and presentation of changes in restricted cash in the statement of cash flows. This ASU is effective for public business entities for annual reporting periods beginning after December15, 2017, and interim periods within that reporting period. Early adoption is permitted. This ASU will be effective for us in the first quarter of 2018 and early adoption is permitted. We have not yet determined whether we will elect early adoption and we are currently evaluating the impact of the adoption of this standard on our consolidated financial statements and related disclosures.

Emerging Growth Company Status

We are an "emerging growth company" as defined in the JOBS Act, and therefore we may take advantage of certain exemptions from various public company reporting requirements. As an "emerging growth company,"

- we will avail ourselves of the exemption from the requirement to obtain an attestation and report from our auditors on the assessment of our internal control over financial reporting pursuant to the Sarbanes-Oxley Act;
- we will provide less extensive disclosure about our executive compensation arrangements; and
- we will not require stockholder non-binding advisory votes on executive compensation or golden parachute arrangements.

However, we are choosing to irrevocably opt out of the extended transition periods available under the JOBS Act for complying with new or revised accounting standards. We will remain an "emerging growth company" for up to five years, although we will cease to be an "emerging growth company" upon the earliest of: (1) December 31, 2019; (2) the last day of the first fiscal year in which our annual gross revenues are $1 billion or more; (3) the date on which we have, during the previous rolling three-year period, issued more than $1 billion in non-convertible debt securities; and (4) the date on which we are deemed to be a "large accelerated filer" as defined in the Exchange Act.

Results of Operations

Comparison of the Years Ended December 31, 2016 and 2015

The following table summarizes our results of operations for the periods indicated (in thousands):

	Years ended December 31,		
	2016	2015	Increase/(Decrease)
Collaboration and license revenue	$ 1,455	$ 2,319	$ (864)
Operating expenses:			
Research and development	31,670	25,462	6,208
General and administrative	24,355	22,107	2,248
Impairment of goodwill and intangible assets	60,714	—	60,714
Restructuring charges	—	2,573	(2,573)
Total operating expenses	116,739	50,142	66,597
Operating loss	(115,284)	(47,823)	(67,461)
Other income, net	762	370	392
Net loss before income tax benefit	(114,522)	(47,453)	(67,069)
Income tax benefit	775	—	775
Net loss attributable to common stockholders	$ (113,747)	$ (47,453)	$ (66,294)

Revenue

Collaboration and license revenue decreased to $1.5 million for the year ended December 31, 2016, from $2.3 million for the year ended December 31, 2015. The decrease of $0.9 million was primarily due to the recognition of $1.5 million related to the Regeneron time-limited right of first negotiation to license AVA-101 future development and commercialization in fiscal year 2015 offset by $0.6 million related to license and research services that are deferred and recognized over maximum research terms under the Regeneron and Editas agreements.

Research and Development Expense

Research and development expense increased to $31.7 million for the year ended December 31, 2016, from $25.5 million for the year ended December 31, 2015. The increase in research and development expense was primarily due to a $2.6 million increase in stock-based compensation expenses, including $0.9 million relating to the accelerated vesting of Annapurna options and shares recorded after the acquisition closing and $1.4 million related to the accelerated vesting of executive stock options and RSUs, $2.8 million increase for outside services expense related to the Cornell MSA, $0.6 million increase in laboratory expense, $0.7 million increase in license fee expenses and $0.7 million increase in facilities allocation and depreciation charges, partially offset by $0.6 million decrease in materials expense, $0.4 million decrease in consulting and recruiting expenses, and $0.2 million decrease in compensation and benefits expenses.

For the periods presented, substantially all of our research and development expense related to Adverum development activities for its wet AMD program and our other potential product candidates in our development program. Upon completion of the Annapurna acquisition in May 2016, we began incurring expenses related to Annapurna's four development programs. We expect that research and development expenses will increase in future periods as we continue to invest in our pipeline products and preclinical studies relating to our gene therapies program.

General and Administrative Expense

General and administrative expense increased to $24.4 million for the year ended December 31, 2016, from $22.1 million for the year ended December 31, 2015. The increase in general and administrative expense was primarily due to increases of $2.5 million in Annapurna acquisition related expenses, $0.6 million increase in compensation and benefits, and $0.7 million in facilities allocation and depreciation expense, offset by $1.6 million decrease in stock-based compensation expense related to stock modifications for an executive officer's separation in 2015.

We expect general and administrative expenses may increase in future periods if and to the extent we elect to increase our investment in infrastructure to support continued research and development activities and potential commercialization of our product candidates. We will continue to assess such expenses in conjunction with ongoing consideration of our pipeline of product candidates.*Impairment of Goodwill and Intangible Assets*

We noted a continuing decrease in our stock price that resulted in our market capitalization being less than the carrying value of our net assets as of June 30, 2016 and the continuation of operating losses in subsequent years due to preclinical and expected clinical trials, we concluded that it is more likely than not that the fair value of our one reporting unit is less than its carrying value and concluded to perform a goodwill impairment analysis. We performed a two-step goodwill impairment analysis and recorded a $49.1 million and a $0.4 million goodwill impairment charge in the second and third quarter of 2016 in our consolidated statements of operations and comprehensive loss.

In the fourth quarter of 2016, we performed our annual assessment of our ADVM-043 and ADVM-053 IPR&D assets. Based on our decision to change our manufacturing process for ADVM-043 and ADVM-053 by implementing our proprietary baculovirus-based production system, we updated the related manufacturing costs. As a result, we revised our forecasts for the manufacturing and related costs. In addition, we also reviewed and updated our expected timing of clinical trials, receipts of regulatory approvals, and costs to complete. Based upon our analysis, we determined that the carrying value of $16.2 million for our ADVM-043 and ADVM-053 IPR&D assets was higher than their fair value of $5.0 million. Accordingly, we recorded an $11.2 million IPR&D impairment charge for the year ended December 31, 2016.

Restructuring Charges

In connection with the restructuring of the Company's workforce in the fourth quarter of 2015, the Company incurred aggregate restructuring charges of approximately $2.6 million related to one-time termination severance payments and other employee-related benefits, including approximately $1.0 million of stock-based compensation expense related to the acceleration of restricted stock units.

Other income, net

Other income, net is comprised primarily of interest income on our cash equivalents and investments in marketable securities in 2016 and 2015.

Income tax benefit

During the fourth quarter of 2016, the Company recorded income tax benefit of $775,000 related to the change in the deferred tax liabilities balance due to intangible assets impairment recognized in the same quarter.

Comparison of the Years Ended December 31, 2015 and 2014

The following table summarizes our results of operations for the periods indicated (in thousands):

	Years ended December 31,		
	2015	2014	Increase/(Decrease)
Collaboration and license revenue	$ 2,319	$ 572	$ 1,747
Operating expenses:			
Research and development	25,462	16,976	8,486
General and administrative	22,107	7,998	14,109
Restructuring charges	2,573	—	2,573
Total operating expenses	50,142	24,974	25,168
Operating loss	(47,823)	(24,402)	(23,421)
Other income (expense):			
Interest expense	—	(18)	18
Other income (expense), net	370	(21)	391
Change in fair value of embedded derivative	—	—	—
Change in fair value of warrant liabilities	—	(759)	759
Loss on extinguishment of related-party convertible notes	—	(204)	204
Net loss	(47,453)	(25,404)	(22,049)
Deemed dividend	—	(3,230)	3,230
Net loss attributable to common stockholders	$ (47,453)	$ (28,634)	$ (18,819)

Revenue

Collaboration and license revenue increased by $1.7 million to $2.3 million in 2015 from $0.6 million in 2014. In September 2015, we initiated, by notice and delivery of AVA-101 clinical data package to Regeneron, the time period for Regeneron to elect whether to exercise its right of first negotiation. In November 2015, Regeneron notified the Company that it was not exercising the right of first negotiation and the Company recognized $1.5 million related to the right of first negotiation as collaboration revenue in 2015. Collaboration revenue related to research licenses and related research and development services that we recognize ratably over the maximum research period of 8 years, was $0.8 million and $0.6 million in fiscal 2015 and 2014 years respectively.

Research and Development Expense

Research and development expense increased to $25.5 million for the year ended December 31, 2015, from $17.0 million for the year ended December 31, 2014. The increase in research and development expense was primarily due to increases of $5.7 million in salaries and related expenses due to increased employee headcount, $3.3 million in drug product process development expenses, clinical expenses, laboratory expenses and overhead and $2.4 million in external consulting expenses and research studies. The increase in research and development expenses was also due to a $0.2 million non-cash stock compensation charge related to the issuance of a common stock warrant. The increase was offset by $3.3 million decrease in stock-based compensation expenses, as most of the expense related to non-employee stock option awards that are remeasured based on the price of our common stock at December 31, 2015.

For the periods presented, substantially all of our research and development expense related to development activities for AVA-101, for the treatment of wet AMD, and our other potential product candidates in our development program.

General and Administrative Expense

General and administrative expense increased to $22.1 million for the year ended December 31, 2015 from $8.0 million for the year ended December 31, 2014. The increase in general and administrative expense was primarily due to increases of $3.6 million in salaries and expenses related to higher employee headcount, $5.2 million in stock-based compensation expenses, $1.9 million in public company-related expenses and overhead and $3.3 million in consulting and professional service expenses, as we expanded our operations and incurred additional costs as a public company.

Restructuring Charges

In connection with the restructuring of the Company's workforce in the fourth quarter of 2015, the Company incurred aggregate restructuring charges of approximately $2.6 million related to one-time termination severance payments and other employee-related benefits, including approximately $1.0 million of stock-based compensation expense related to the acceleration of restricted stock units.

Other income (expense), net

Other income (expense), net is comprised primarily of changes in the fair value of common stock warrant liabilities and preferred stock warrant liabilities in 2014 and interest income on our cash equivalents and investments in marketable securities in 2015. At the time of the IPO, all then outstanding warrants classified as liabilities were exercised, and as a consequence, the Company does not expect to have any other income (expense), net related to changes in the fair value of warrant liabilities in future periods.

Changes in Fair Value of Warrant Liabilities

We recorded changes in the fair value of warrant liabilities of ($0.8) million for the year ended December 31, 2014. In connection with the completion of the IPO in August 2014, all of the then outstanding warrants to purchase convertible preferred stock were exercised. As a result of the exercises, we recorded a $0.8 million loss related to the change in fair value in our consolidated statements of operations and comprehensive loss.

Loss on Extinguishment of Related Party Convertible Notes

In April 2014, we converted the outstanding balance under our related-party convertible notes of $2.0 million into 295,115 shares of Series B convertible preferred stock at 90% of the purchase price paid by other investors, in accordance with the terms of the agreement. As a result, we recorded a loss on the extinguishment of convertible notes of $0.2 million in 2014.

Deemed Dividend

In April 2014, we repurchased 531,208 shares of Series A convertible preferred stock for $4.0 million. The difference between the repurchase price of $7.53 per share and original issuance price of $1.45 per share was recorded as a deemed dividend of $3.2 million to a preferred stockholder and effected the calculation of net loss attributable to common stockholders and net loss per share for the year ended December 31, 2014.

Liquidity, Capital Resources and Plan of Operations

We have not generated positive cash flow or net income from operations since our inception and at December 31, 2016, we had an accumulated deficit of $197.9 million, primarily as a result of research and development and general and administration expenses. As of December 31, 2016, we had $222.2 million in cash and cash equivalents. We believe that our existing cash and cash equivalents as of December 31, 2016 will be sufficient to fund our operations through the end of 2019.

We expect to incur substantial expenditures in the foreseeable future for the development and potential commercialization of our product candidates and ongoing internal research and development programs. At this time, we cannot reasonably estimate the nature, timing or aggregate amount of such costs. However, in order to complete our planned preclinical trials and any future clinical trials, and to complete the process of obtaining regulatory approval for our product candidates, as well as to build the sales, marketing and distribution infrastructure that we believe will be necessary to commercialize our product candidates, if approved, we will require substantial additional funding in the future.

If and when we seek additional funding, we will do so through equity or debt financings, collaborative or other arrangements with corporate sources or through other sources of financing. Adequate additional funding may not be available to us on acceptable terms or at all. Our failure to raise capital in the future could have a negative impact on our financial condition and our ability to pursue our business strategies. In order to complete development and commercialization of any of our product candidates, we anticipate that we will need to raise substantial additional capital, the requirements of which will depend on many factors, including:

- the initiation, progress, timing, costs and results of preclinical studies and any clinical trials for our product candidates;
- the outcome, timing of and costs involved in, seeking and obtaining approvals from the Food and Drug Administration (FDA) and other regulatory authorities, including the potential for the FDA and other regulatory authorities to require that we perform more studies than those that we currently expect;

- the ability of our product candidates to progress through clinical development activities successfully;
- our need to expand our research and development activities;
- the rate of progress and cost of our commercialization of our products;
- the cost of preparing to manufacture our products on a larger scale;
- the costs of commercialization activities including product sales, marketing, manufacturing and distribution;
- the degree and rate of market acceptance of any products launched by us or future partners;
- the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights;
- our need to implement additional infrastructure and internal systems;
- our ability to hire additional personnel;
- our ability to enter into additional collaboration, licensing, commercialization or other arrangements and the terms and timing of such arrangements, and;
- the emergence of competing technologies or other adverse market developments.

If we are unable to raise additional funds when needed, we may be required to delay, reduce, or terminate some or all of our development programs and clinical trials. We may also be required to sell or license other technologies or clinical product candidates or programs that we would prefer to develop and commercialize ourselves.

Cash Flows

The following table sets forth the primary sources and uses of cash for each of the periods presented below (in thousands):

	Years ended December 31,		
	2016	2015	2014
Net cash (used in) provided by:			
Operating activities	$ (38,366)	$ (35,338)	$ (5,648)
Investing activities	38,775	(41,569)	(943)
Financing activities	556	138,860	165,442
Effect of exchange rate changes on cash and cash equivalents	(143)	(9)	(11)
Net increase in cash and cash equivalents	$ 822	$ 61,944	$ 158,840

Cash Used in Operating Activities

Net cash used in operating activities for the year ended December 31, 2016, was $38.4 million, primarily as a result of the net loss of $113.7 million offset by $60.7 million for non-cash charge related to goodwill and IPR&D assets impairment, $11.4 million for non-cash charge related to stock-based compensation expense, $1.6 million for depreciation and amortization expense, and $1.6 million for net increase in operating assets and liabilities.

Net cash used in operating activities for the year ended December 31, 2015, was $35.3 million, primarily as a result of the net loss of $47.5 million offset by $11.5 million for non-cash charge related to stock-based compensation, a $0.2 million non-cash stock compensation charge related to the issuance of warrant, $0.8 million for depreciation and amortization expense, $0.8 million for amortization of premium on marketable securities and $1.2 million for net decrease in operating assets and liabilities.

Net cash used in operating activities for the year ended December 31, 2014, was $5.6 million, primarily the result of the net loss of $25.4 million offset by the $7.5 million related to the upfront payments received from our research collaboration and license agreement with Regeneron, $9.5 million of non-cash charges related to stock-based compensation, loss on the extinguishment of related party convertible notes and warrant re-measurement and a $2.9 million increase in accounts payable and accrued expenses.

Cash Provided by (Used in) Investing Activities

Net cash provided by investing activities was $38.8 million for the year ended December 31, 2016, which primarily consisted of the maturities of marketable securities of $37.7 million and cash acquired through our Annapurna acquisition of $3.4 million, offset by purchases of property and equipment of $2.4 million.

Net cash used in investing activities was $41.6 million for the year ended December 31, 2015, which primarily consisted of the purchases of marketable securities of $88.4 million, offset by maturities of marketable securities of $49.9 million and by purchases of property and equipment of $3.0 million.

Net cash used in investing activities for the year ended December 31, 2014, consisted of purchases of property and equipment of $0.9 million.

Cash Provided by Financing Activities

Net cash provided by financing activities for the year ended December 31, 2016, of $0.6 million, which primarily consisted of $0.9 million from proceeds relating to the exercise of options for common shares and employee stock purchase plan purchases and $0.1 million relating to funds received from a financing arrangement offset by $0.5 million in taxes paid relating to net share settlement of restricted stock units.

Net cash provided by financing activities for the year ended December 31, 2015, of $138.9 million, which primarily consisted of $130.6 million net proceeds from our follow-on offering in January 2015 and $8.3 million from sale of common shares.

Net cash provided by financing activities for the year ended December 31, 2014, of $165.4 million, which primarily consisted of $116.5 million of net proceeds from our initial public offering and the concurrent private placement in July and August 2014, $0.6 million of proceeds from exercises of warrants, $50.4 million of proceeds from the sale of Series B convertible preferred stock, net of expenses, in April 2014, and $2.0 million of related-party convertible notes received in January and April 2014, offset by $4.0 million used to repurchase Series A convertible preferred stock in April 2014.

Contractual Obligations and Commitments

We have lease obligations consisting of an operating lease for our operating facility that expires in 2020. Additionally, we have contractual obligations to vendors.

The following table summarizes our contractual obligations as of December 31, 2016 (in thousands):

	Payment Due by Period				
	Less Than 1 Year	1 to 3 Years	4 to 5 Years	More Than 5 Years	Total
Operating lease obligations	$ 1,129	$ 2,762	$ —	$ —	$ 3,891
Contractual obligations	4,433	6,667	—	—	11,100
Total	$ 5,562	$ 9,429	$ —	$ —	$ 14,991

The lease agreement provides for an escalation of rent payments each year and will expire on May 8, 2020. We may extend the lease term for up to four years.

We have a contractual obligation at December 31, 2016 to pay $10.0 million over the next 3 year under a master services agreement with Cornell and $1.1 million for manufacturing with another vendor in 2017. The MSA was terminated as of January 6, 2017 and as such the $10.0 million will no longer exist commencing January 2017 but the commitment still exists at December 31, 2016.

We are obligated to make future payments to third parties under in-license agreements, including sublicense fees, royalties and payments that become due and payable on the achievement of certain development and commercialization milestones. As the amount and timing of sublicense fees and the achievement and timing of these milestones are not probable and estimable, such commitments have not been included on our balance sheet or in the contractual obligations tables above.

Off Balance Sheet Arrangements

Since our inception, we have not engaged in any off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

Foreign Currency Exchange Risk

A portion of our operating expenses are incurred outside the United States and are denominated in foreign currencies and are subject to fluctuations due to changes in foreign currency exchange rates, particularly changes in the Euro and Australian dollar. Additionally, fluctuations in foreign currency exchange rates may cause us to recognize transaction gains and losses in our statement of operations. To date, foreign currency transaction gains and losses have not been material to our consolidated financial statements, and we have not engaged in any foreign currency hedging transactions. As our international operations grow, we will continue to reassess our approach to managing the risks relating to fluctuations in currency rates.

Interest Rate Risk

We had cash and cash equivalents of $222.2 million as of December 31, 2016, consisting of money market funds and cash and cash equivalents and of $259.0 million as of December 31, 2015, consisting of money market funds, certificates of deposit, U.S. treasury securities and U.S. government agency securities. To date, fluctuations in interest income have not been significant.

We do not enter into investments for trading or speculative purposes and have not used any derivative financial instruments to manage our interest rate risk exposure. We have not been exposed to, nor do we anticipate being exposed to, material risks due to changes in interest rates. A hypothetical 10% change in interest rates during any of the periods presented would not have had a material impact on our consolidated financial statements.

Item 8. Financial Statements and Supplementary Data.

The financial statements required by this item are included as separate sections in this Annual Report on Form 10-K. See Item 15.

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

None.

ITEM 9A. CONTROLS AND PROCEDURES

Evaluation of disclosure controls and procedures

Management, including our Principal Executive Officer and Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, as of December 31, 2016. The evaluation of our disclosure controls and procedures included a review of our processes and implementation and the effect on the information generated for use in this Annual Report on Form 10-K. In the course of this evaluation, we sought to identify any material weaknesses in our disclosure controls and procedures to determine whether we had identified any acts of fraud involving personnel who have a significant role in our disclosure controls and procedures, and to confirm that necessary corrective action, including process improvements, was taken. This type of evaluation is done quarterly so that our conclusions concerning the effectiveness of these controls can be reported in our periodic reports filed with the SEC. The overall goals of these evaluation activities are to monitor our disclosure controls and procedures and to make modifications as necessary. We intend to maintain these disclosure controls and procedures, modifying them as circumstances warrant.

Based on that evaluation, the Principal Executive Officer and Chief Financial Officer concluded that as of December 31, 2016, the Company's disclosure controls and procedures were effective to provide reasonable assurance that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is (i) recorded, processed, summarized and reported as and when required and (ii) accumulated and communicated to our management, including the Principal Executive Officer and Chief Financial Officer, as appropriate to allow timely discussion regarding required disclosure.

Management's Annual Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting to provide reasonable assurance regarding the reliability of our financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles.

Management assessed our internal control over financial reporting as of December 31, 2016, the end of our fiscal year. Management based its assessment on criteria established in "Internal Control—Integrated Framework (2013)" issued by the Committee of Sponsoring Organizations of the Treadway Commission. Management's assessment included evaluation of such elements as the design and operating effectiveness of key financial reporting controls, process documentation, accounting policies, and our overall control environment. This assessment is supported by testing and monitoring performed by our internal accounting and finance organization.

Based on our assessment, management has concluded that our internal control over financial reporting was effective as of December 31, 2016. The results of management's assessment were reviewed with the Audit Committee.

Attestation Report of the Registered Public Accounting Firm

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

Changes in Internal Control over Financial Reporting

There have been no changes in our internal control over financial reporting during the year ended December 31, 2016 that have materially affected or are reasonably likely to materially affect, our internal control over financial reporting.

Inherent Limitations on Controls and Procedures

Our management, including the Principal Executive Officer and Chief Financial Officer, does not expect that our disclosure controls and procedures and our internal controls will prevent all error and all fraud. A control system, no matter how well designed and operated, can only provide reasonable assurances that the objectives of the control system are met. The design of a control system reflects resource constraints; the benefits of controls must be considered relative to their costs. Because there are inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within the Company have been or will be detected. As these inherent limitations are known features of the financial reporting process, it is possible to design into the process safeguards to reduce, though not eliminate, these risks. These inherent limitations include the realities that judgments in decision-making can be faulty and that breakdowns occur because of simple error or mistake. Controls can be circumvented by the individual acts of some persons, by collusion of two or more people, or by management override of the control. The design of any system of controls is based in part upon certain assumptions about the likelihood of future events. While our disclosure controls and procedures are designed to provide reasonable assurance of achieving their objectives, there can be no assurance that any design will succeed in achieving its stated goals under all future conditions. Over time, controls may become inadequate because of changes in conditions or deterioration in the degree of compliance with the policies or procedures. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

We intend to review and evaluate the design and effectiveness of our disclosure controls and procedures on an ongoing basis and to improve our controls and procedures over time and to correct any deficiencies that we may discover in the future. While our Principal Executive Officer and Chief Financial Officer have concluded that, as of December 31, 2016, the design of our disclosure controls and procedures, as defined in Rule 13a-15(e) under the Exchange Act, was effective, future events affecting our business may cause us to significantly modify our disclosure controls and procedures.

Item 9B. Other Information.

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this item will be contained in our definitive proxy statement to be filed with the Securities and Exchange Commission pursuant to Regulation 14A in connection with our 2017 Annual Meeting of Stockholders (the Proxy Statement), which is expected to be filed not later than 120 days after the end of our fiscal year ended December 31, 2016, under the headings "Executive Officers," "Election of Directors," "Corporate Governance," and " Section 16(a) Beneficial Ownership Reporting Compliance," and is incorporated herein by reference.

We have adopted a written code of business conduct and ethics that applies to our directors, officers and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. A current copy of the code is posted on the Corporate Governance section of our website, which is located at www.adverum.com. If we make any substantive amendments to, or grant any waivers from, the code of business conduct and ethics for our principal executive officer, principal financial officer, principal accounting officer, controller or persons performing similar functions, or any officer or director, we will disclose the nature of such amendment or waiver on our website or in a current report on Form 8-K.

Item 11. Executive Compensation.

The information required by this item will be contained in the Proxy Statement under the headings "Executive Compensation" and "Director Compensation," and is incorporated herein by reference.

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

The information required by this item will be contained in the Proxy Statement under the headings "Security Ownership of Certain Beneficial Owners and Management" and "Equity Compensation Plan Information," and is incorporated herein by reference.

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

The information required by this item will be contained in the Proxy Statement under the headings "Certain Relationships and Related Party Transactions" and "Corporate Governance," and is incorporated herein by reference.

Item 14. Principal Accountant Fees and Services.

The information required by this item will be contained in the Proxy Statement under the heading "Ratification of Independent Registered Public Accounting Firm—Principal Accounting Fees and Services" and is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

The financial statements schedules and exhibits filed as part of this Annual Report on Form 10-K are as follows:

(a)(1) Financial Statements

Consolidated Financial Statements and Report of Independent Registered Public Accounting Firm. See “Index to Consolidated Financial Statements”.

(a)(2) Financial Statement Schedules

All other schedules are omitted because they are not required or the required information is included in the financial statements or notes thereto.

(a)(3) Exhibits

Reference is made to the Exhibit Index accompanying this Annual Report on Form 10-K.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

Date: March 8, 2017

ADVERUM BIOTECHNOLOGIES, INC.

By: /s/ Paul B. Cleveland
Paul B. Cleveland
Executive Chairman of the Board and Principal Executive Officer

Power of Attorney

Each person whose individual signature appears below hereby authorizes and appoints Paul B. Cleveland and Leone Patterson, and each of them, with full power of substitution and resubstitution and full power to act without the other, as his or her true and lawful attorney-in-fact and agent to act in his or her name, place and stead and to execute in the name and on behalf of each person, individually and in each capacity stated below, and to file any and all amendments to this annual report on Form 10-K, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing, ratifying and confirming all that said attorneys-in-fact and agents or any of them or their or his substitute or substitutes may lawfully do or cause to be done by virtue thereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this annual report on Form 10-K has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

SIGNATURE	TITLE	DATE
/s/ Paul B. Cleveland Paul B. Cleveland	Executive Chairman of the Board and Principal Executive Officer *(Principal Executive Officer)*	March 8, 2017
/s/Leone Patterson Leone Patterson	Chief Financial Officer *(Principal Financial and Accounting Officer)*	March 8, 2017
/s/ Amber Salzman, Ph.D. Amber Salzman, Ph.D.	Director, President and Chief Executive Officer	March 8, 2017
/s/ Mitchell Finer, Ph.D. Mitchell Finer, Ph.D.	Director	March 8, 2017
/s/ Thomas F. Woiwode, Ph.D. Thomas F. Woiwode, Ph.D.	Director	March 8, 2017
/s/ Steven D. Schwartz, M.D. Steven D. Schwartz, M.D.	Director	March 8, 2017

ADVERUM BIOTECHNOLOGIES, INC.
CONSOLIDATED FINANCIAL STATEMENTS
YEARS ENDED DECEMBER 31, 2016, 2015 AND 2014

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REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders of
Adverum Biotechnologies, Inc.
Menlo Park, California

We have audited the accompanying consolidated balance sheets of Adverum Biotechnologies, Inc. and its subsidiaries (collectively the "Company") as of December 31, 2016 and 2015, and the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2016. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. The Company is not required to have, nor were we engaged to perform, an audit of their internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, such consolidated financial statements present fairly, in all material respects, the financial position of Adverum Biotechnologies, Inc. and its subsidiaries as of December 31, 2016 and 2015, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2016, in conformity with accounting principles generally accepted in the United States of America.

/s/ Deloitte & Touche LLP

San Jose, California
March 8, 2017

ADVERUM BIOTECHNOLOGIES, INC.
CONSOLIDATED BALANCE SHEETS
(In thousands, except share and per share data)

	December 31, 2016	December 31, 2015
Assets		
Current assets:		
Cash and cash equivalents	$ 222,170	$ 221,348
Marketable securities	—	37,732
Receivable from collaborative partner	886	449
Prepaid expenses and other current assets	2,218	1,463
Total current assets	225,274	260,992
Property and equipment, net	4,169	3,187
Deposit and other long-term assets	140	140
Intangible assets	5,000	—
Total assets	$ 234,583	$ 264,319
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 1,474	$ 605
Restructuring liabilities	25	1,013
Accrued expenses and other current liabilities	6,451	4,007
Deferred rent, current portion	96	66
Deferred revenue, current portion	1,850	883
Total current liabilities	9,896	6,574
Long-term liabilities:		
Deferred rent, net of current portion	352	447
Deferred revenue, net of current portion	7,099	4,706
Deferred tax liability, noncurrent	1,250	—
Other non-current liabilities	386	—
Total liabilities	18,983	11,727
Commitments and contingencies (Note 11)		
Stockholders' equity:		
Preferred stock, $0.0001 par value, 5,000,000 shares authorized; no shares issued and outstanding	—	—
Common stock, $0.0001 par value, 300,000,000 shares authorized at December 31, 2016 and 2015; 41,805,009 and 25,858,722 shares issued and outstanding at December 31, 2016 and 2015, respectively	4	3
Additional paid-in capital	413,518	336,768
Accumulated other comprehensive loss	(7)	(11)
Accumulated deficit	(197,915)	(84,168)
Total stockholders' equity	215,600	252,592
Total liabilities and stockholders' equity	$ 234,583	$ 264,319

See accompanying notes to consolidated financial statements.

ADVERUM BIOTECHNOLOGIES, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(In thousands, except per share data)

	Years ended December 31,		
	2016	2015	2014
Collaboration and license revenue	$ 1,455	$ 2,319	$ 572
Operating expenses:	—		
Research and development	31,670	25,462	16,976
General and administrative	24,355	22,107	7,998
Impairment of goodwill and intangible assets	60,714	—	$ —
Restructuring charges	—	2,573	—
Total operating expenses	116,739	50,142	24,974
Operating loss	(115,284)	(47,823)	(24,402)
Other income (expense)			
Interest expense	—	—	(18)
Other income (expense), net	762	370	(21)
Change in fair value of warrant liabilities	—	—	(759)
Loss on extinguishment of related-party convertible notes	—	—	(204)
Total other income (expense), net	762	370	(1,002)
Net loss before tax benefit	(114,522)	(47,453)	(25,404)
Income tax benefit	775	—	—
Net loss after tax benefit	(113,747)	(47,453)	(25,404)
Deemed dividend	—	—	(3,230)
Net loss attributable to common stockholders	$ (113,747)	$ (47,453)	$ (28,634)
Other comprehensive loss:			
Net unrealized gain (loss) on marketable securities	6	(6)	—
Foreign currency translation adjustment	(2)	(15)	(17)
Comprehensive loss	$ (113,743)	$ (47,474)	$ (25,421)
Net loss per share attributable to common stockholders-basic and diluted	$ (3.14)	$ (1.86)	$ (2.46)
Weighted-average common shares outstanding-basic and diluted	36,246	25,479	11,651

See accompanying notes to consolidated financial statements.

ADVERUM BIOTECHNOLOGIES, INC.
CONSOLIDATED STATEMENTS OF CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY
(In thousands except share and per share data)

	SERIES A CONVERTIBLE PREFERRED STOCK $0.0001 PAR VALUE		SERIES B CONVERTIBLE PREFERRED STOCK $0.0001 PAR VALUE		COMMON STOCK $0.0001 PAR VALUE		ADDITIONAL PAID-IN	ACCUMULATED OTHER COMPREHENSIVE	ACCUMULATED	TOTAL STOCKHOLDERS'
	Shares	Amount	Shares	Amount	Shares	Amount	CAPITAL	INCOME (LOSS)	DEFICIT	EQUITY
Balance at December 31, 2013	**3,899,232**	**7,992**	**—**	**—**	**3,672,885**	**—**	**632**	**27**	**(8,869)**	**(8,210)**
Beneficial Conversion feature in related-party convertible notes	—	—	—	—	—		2,000	—	—	2,000
Repurchase of beneficial conversion feature upon conversion of related-party convertible notes	—	—	—	—	—	—	(2,000)	—	—	(2,000)
Conversion of related-party convertible notes into Series B convertible preferred stock in April 2014	—	—	295,115	2,222	—	—	—	—	—	—
Issuance of Series B convertible preferred stock in April 2014 for cash, net of issuance costs of $2,806	—	—	7,025,888	50,099	—	—	—	—	—	—
Repurchase of Series A convertible preferred stock in April 2014	(531,208)	(770)	—	—	—	—	(788)	—	(2,442)	(3,230)
Issuance of common stock warrants in consideration for services	—	—	—	—	—	—	307	—	—	307
Issuance of Series A convertible preferred stock upon exercises of convertible preferred stock warrants in July 2014	54,716	79	—	—	—	—	851	—	—	851
Conversion of Series A preferred stock to common stock upon initial public offering	(3,422,740)	(7,301)	—	—	3,422,740	—	7,301	—	—	7,301
Conversion of Series B preferred stock to common stock upon initial public offering	—	—	(7,321,003)	(52,321)	7,321,003	1	52,320	—	—	52,321
Issuance of common stock upon exercise of warrants	—	—	—	—	352,415	—	526	—	—	526
Issuance of common stock upon initial public offering, net of issuance costs of $9,776 in July 2014	—	—	—	—	6,000,000	1	92,223	—	—	92,224
Issuance of common stock upon private placement in July 2014	—	—	—	—	588,235	—	10,000	—	—	10,000
Issuance of common stock upon exercise of option by underwriters, net of issuance costs of $1,071 in August 2014	—	—	—	—	900,000	—	14,229	—	—	14,229
Stock-based compensation expense	—	—	—	—	—	—	8,567	—	—	8,567
Common stock issued upon exercise of stock options	—	—	—	—	496,759	—	18	—	—	18
Foreign currency translation adjustments	—	—	—	—	—	—	—	(17)	—	(17)
Net loss	—	—	—	—	—	—	—	—	(25,404)	(25,404)
Balance at December 31, 2014	**—**	**—**	**—**	**—**	**22,754,037**	**2**	**186,186**	**10**	**(36,715)**	**149,483**
Issuance of common stock, net of issuance costs of $11,099	—	—	—	—	2,599,375	1	138,953	—	—	138,954
Issuance of common stock warrants in consideration for services	—	—	—	—	—	—	218	—	—	218
Stock-based compensation expense	—	—	—	—	—	—	11,505	—	—	11,505
Common stock issued upon exercise of stock options	—	—	—	—	399,434	—	188	—	—	188
Common stock issued under employee stock purchase plan	—	—	—	—	19,577	—	145	—	—	145
Common stock issued upon release of restricted stock units	—	—	—	—	132,397	—	—	—	—	—
Restricted stock surrendered for taxes	—	—	—	—	(46,098)	—	(427)	—	—	(427)
Net unrealized loss on marketable securities	—	—	—	—	—	—	—	(6)	—	(6)
Foreign currency translation adjustments	—	—	—	—	—	—	—	(15)	—	(15)
Net loss	—	—	—	—	—	—	—	—	(47,453)	(47,453)
Balance at December 31, 2015	**—**	**—**	**—**	**—**	**25,858,722**	**3**	**336,768**	**(11)**	**(84,168)**	**252,592**
Issuance of common stock in consideration of acquisition	—	—	—	—	14,087,246	1	64,844	—	—	64,845

ADVERUM BIOTECHNOLOGIES, INC.
CONSOLIDATED STATEMENTS OF CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY
(In thousands except share and per share data)

Remeasurement of contingent common stock warrant in consideration for services	—	—	—	—	—	—	8	—	—	8
Issuance of warrant in connection with financing arrangement							26			26
Stock-based compensation expense	—	—	—	—	—	—	11,416	—	—	11,416
Common stock issued upon exercise of stock options	—	—	—	—	1,525,687	—	763	—	—	763
Common stock issued under employee stock purchase plan	—	—	—	—	56,696	—	186	—	—	186
Common stock issued upon release of restricted stock units	—	—	—	—	385,524	—	—	—	—	—
Restricted stock surrendered for taxes	—	—	—	—	(108,866)	—	(493)	—	—	(493)
Net unrealized gain on marketable securities	—	—	—	—	—	—	—	6	—	6
Foreign currency translation adjustments	—	—	—	—	—	—	—	(2)	—	(2)
Net loss	—	—	—	—	—	—	—	—	(113,747)	(113,747)
Balance at December 31, 2016	**—**	**—**	**—**	**—**	**41,805,009**	**$ 4**	**$ 413,518**	**$ (7)**	**$ (197,915)**	**$ 215,600**

See accompanying notes to consolidated financial statements.

ADVERUM BIOTECHNOLOGIES, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

(In thousands)

	Years ended December 31,		
	2016	2015	2014
Cash flows from operating activities:			
Net loss	$ (113,747)	$ (47,453)	$ (25,404)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	1,603	812	162
Loss on disposal of property and equipment	—	21	—
Stock-based compensation expense	11,416	11,505	8,567
Non-cash research and development expense	8	218	—
Non-cash interest expense	—	—	18
Amortization of premium on marketable securities	—	780	—
Change in fair value of warrant liabilities	—	—	759
Loss on extinguishment of related-party convertible notes	—	—	204
Impairment of goodwill and intangible assets	60,714	—	—
Changes in operating assets and liabilities:			
Accounts receivable, net	(437)	(6)	8
Prepaid expenses and other current assets	71	(531)	(624)
Deposit and other long-term assets	—	(3)	7
Accounts payable	(111)	(312)	(6)
Accrued expenses and other current liabilities	(190)	724	2,904
Restructuring liabilities	(988)	1,013	—
Deferred revenue	3,360	(2,313)	7,459
Deferred rent	(65)	207	298
Net cash used in operating activities	(38,366)	(35,338)	(5,648)
Cash flows from investing activities:			
Purchases of marketable securities	—	(88,427)	—
Maturities of marketable securities	37,738	49,850	—
Purchases of property and equipment	(2,412)	(2,992)	(943)
Cash acquired in business acquisition	3,449	—	—
Net cash provided by (used in) investing activities	38,775	(41,569)	(943)
Cash flows from financing activities:			
Proceeds from public offering of common stock, net	—	138,954	106,453
Proceeds from sale of common stock to collaborative partner	—	—	10,000
Proceeds from issuance of Series B convertible preferred stock	—	—	52,905
Expenses related to issuance of Series B convertible preferred stock	—	—	(2,540)
Proceeds from issuance of related-party convertible notes	—	—	2,000
Repurchase of Series A convertible preferred stock	—	—	(4,000)
Proceeds from exercises of warrants	—	—	606
Proceeds from issuance of common stock pursuant to option exercises	763	188	18
Taxes paid related to net share settlement of restricted stock units	(493)	(427)	—
Proceeds from employee stock purchase plan	186	145	—
Proceeds from a financing arrangement	100	—	—
Net cash provided by financing activities	556	138,860	165,442
Effect of foreign currency exchange rate on cash and cash equivalents	(143)	(9)	(11)
Net increase in cash and cash equivalents	822	61,944	158,840
Cash and cash equivalents at beginning of period	221,348	159,404	564
Cash and cash equivalents at end of period	$ 222,170	$ 221,348	$ 159,404
Supplemental schedule of noncash investing and financing information			
Issuance of common stock and exchange of stock options for business acquisition	$ 64,845	$ —	$ —
Conversion of related-party convertible notes payable to convertible preferred stock	$ —	$ —	$ 2,000
Warrants issued in connection with issuance of Series B convertible preferred stock	$ —	$ —	$ 266
Warrants issued in connection with financing and license agreements	$ 26	$ 218	$ 42
Fixed assets in accounts payable and current liabilities	$ 180	$ 178	$ 235
Deferred stock issuance costs	$ —	$ —	$ 379

See accompanying notes to consolidated financial statements.

1. Description of the business

Nature of Business—Adverum Biotechnologies, Inc. (the "Company", "we" or "us") was incorporated in Delaware on July 17, 2006 as Avalanche Biotechnologies, Inc. and changed its name to Adverum Biotechnologies, Inc. on May 11, 2016. The Company is headquartered in Menlo Park, California. The Company is a gene therapy company committed to discovering and developing novel medicines that can offer potentially life-changing therapeutic benefit to patients living with rare diseases or diseases of the eye, who currently have limited or burdensome treatment options. We are leveraging our industry-leading adeno-associated virus (AAV)-based 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 on May 11, 2016, of Annapurna Therapeutics SAS (Annapurna), a privately-held French gene therapy company. 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. Since the Company's inception, it has devoted its efforts principally to performing research and development activities, including conducting preclinical studies, early clinical trials, filing patent applications, obtaining regulatory agreements, hiring personnel, and raising capital to support these activities.

The Company has not generated any revenue from the sale of products since its inception. The Company has experienced net losses since its inception and has an accumulated deficit of $197.9 million as of December 31, 2016. The Company expects to incur losses and have negative net cash flows from operating activities as it engages in further research and development activities. The Company believes that it has sufficient funds to continue operations through the end of 2019.

On May 11, 2016, the Company completed the acquisition of all the outstanding shares of Annapurna Therapeutics SAS, a French simplified joint stock company ("Annapurna"), in accordance with the terms of the acquisition agreement (the "Agreement") dated as of January 29, 2016, as amended on April 6, 2016. As a result, Annapurna is now a wholly owned subsidiary of the Company.

Pursuant to the terms of the Agreement, the Company issued 14,087,246 shares of the Company's common stock, par value $0.0001 per share, for all of the issued and outstanding capital stock of Annapurna. All outstanding options and other rights to purchase capital stock of Annapurna were exchanged into the Company's options for common stock. Refer to Note 3 for more details.

Upon completion of the acquisition, the Company changed its name to "Adverum Biotechnologies, Inc." The Company's shares of common stock listed on The NASDAQ Global Market, previously trading through the close of business on Wednesday, May 11, 2016 under the ticker symbol "AAVL," commenced trading on The NASDAQ Global Market under the ticker symbol "ADVM" on Thursday, May 12, 2016.

Initial Public and Follow-on Offerings—In August 2014 and January 2015, the Company completed its initial public offering (IPO) and concurrent private placement and a follow on offering and raised a total of net proceeds of $237.1 million. In March 2015, (i) the Company received net proceeds of approximately $8.3 million, after discounts and other issuance costs, which resulted from the sale of 230,000 common shares, and (ii) the Company issued 230,000 common shares to a stockholder that exercised warrants prior to the IPO.

2. Summary of significant accounting policies

Basis of Presentation and Principles of Consolidation— The Company's consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America (U.S. GAAP) and pursuant to the rules and regulations of the Securities and Exchange Commission (SEC). The consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries. All inter-company transactions and balances have been eliminated in consolidation.

Use of Estimates—The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets, liabilities, and the disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of income and expenses during the reporting period. The Company bases estimates and assumptions on historical experience when available and on various factors that it believes to be reasonable under the circumstances. On an ongoing basis, the Company evaluates its estimates and assumptions, including those related to research and development expense accruals, stock-based compensation expense, income taxes, and fair value of common stock warrants. The Company's actual results may differ from these estimates under different assumptions or conditions. There have been no significant changes from the Company's original estimates in any periods presented.

Foreign Currency Translation—The Company's consolidated financial statements are prepared in U.S. dollars. Its foreign subsidiaries use the Euro and Australian dollar as their functional currency and maintains their records in the local currency, except our Ireland subsidiary that uses U.S. dollars as its' functional currency. Assets and liabilities are re-measured at exchange rates in effect at the end of the reporting period at our France and Australia subsidiaries, and at historical exchange rates at our Irish subsidiary. Equity is measured at historical rates and income and expenses are re-measured at average exchange rates for the reporting period. The resulting foreign currency translation adjustment is recorded in accumulated other comprehensive loss in the consolidated balance sheets and in the consolidated statements of operations and comprehensive loss. Transactions denominated in foreign currency are translated at exchange rates at the date of transaction with foreign currency gains (losses) recorded in other income (expense), net in the consolidated statements of operations and other comprehensive loss.

Cash and Cash Equivalents—The Company considers all highly liquid investments purchased with original maturities of three months or less at the date of purchase to be cash equivalents. Cash and cash equivalents include cash held in banks and money market accounts. Cash equivalents are stated at fair value.

Marketable Securities—All marketable securities, which consist of debt securities and certificates of deposit, have been classified as "available for sale" and are carried at fair value. Unrealized gains and losses, net of any related tax effects, are excluded from earnings and are included in other comprehensive loss and reported as a separate component of stockholders' equity until realized. Realized gains and losses and declines in value judged to be other than temporary, if any, on available-for-sale securities are included in other income (expense), net. The cost of securities sold is based on the specific-identification method. The amortized cost of securities is adjusted for amortization of premiums and accretion of discounts to maturity. Interest on short-term investments is included in interest income. In accordance with the Company's investment policy, management invests to diversify credit risk and only invests in securities with high credit quality, including U.S. government securities.

The Company regularly evaluates whether declines in the fair value of its investments below their cost are other than temporary. The evaluation includes consideration of the cause of the impairment, including the creditworthiness of the security issuers, the number of securities in an unrealized loss position, the severity and duration of the unrealized losses, whether the Company has the intent to sell the securities, and whether it is more likely than not that the Company will be required to sell the securities before the recovery of their amortized cost basis. If the Company determines that the decline in fair value of an investment is below its accounting basis and this decline is other than temporary, the Company would reduce the carrying value of the security it holds and records a loss for the amount of such decline. The Company has not recorded any realized losses or declines in value judged to be other than temporary on its investments.

We did not have any marketable securities as of December 31, 2016.

Deposit—Deposit in the amount of $0.1 million as of December 31, 2016 and 2015 represents amounts paid in connection with the Company's facility lease agreement and recorded as a long-term asset.

Segment Reporting—The Company operates and manages its business as one reporting and operating segment, which is the business of developing and commercializing gene therapeutics. The Company's chief executive officer, who is the chief operating decision maker, reviews financial information on an aggregate basis for purposes of allocating resources and evaluating financial performance.

Concentrations of Credit Risk and Other Uncertainties—Financial instruments that potentially subject us to significant concentrations of credit risk consists primarily of cash and cash equivalents. As of December 31, 2016, substantially all of the Company's cash and cash equivalents was deposited in accounts at five financial institutions, and amounts may exceed federally insured limits. Management believes that the Company is not exposed to significant credit risk due to the financial strength of the depository institutions in which the financial instruments are held.

The Company is subject to certain risks and uncertainties, including, but not limited to changes in any of the following areas that the Company believes could have a material adverse effect on future financial position or results of operations: ability to obtain future financing; regulatory approval and market acceptance of, and reimbursement for, the Company's product candidates; performance of third-party clinical research organizations and manufacturers; development of sales channels; protection of the intellectual property; litigation or claims against the Company based on intellectual property, patent, product, regulatory or other factors; and the Company's ability to attract and retain employees necessary to support the growth.

Property and Equipment—Property and equipment are recorded at cost, net of accumulated depreciation and amortization. Depreciation is recorded using the straight-line method over the estimated useful lives of the assets, generally three to five years. Leasehold improvements are capitalized and amortized over the shorter period, expected life or lease term. Major replacements and improvements are capitalized, while general repairs and maintenance are expensed as incurred.

Valuation of Long-Lived Assets and Purchased Intangible Assets—The Company evaluates the carrying value of amortizable long-lived assets, whenever events, or changes in business circumstances or the planned use of long-lived assets indicate that their carrying amounts may not be fully recoverable or that their useful lives are no longer appropriate. If these facts and circumstances exist, the Company assesses for recovery by comparing the carrying values of long-lived assets with their future undiscounted net cash flows. If the comparison indicates that impairment exists, long-lived assets are written down to their respective fair value based on discounted cash flows. Significant management judgment is required in the forecasting of future operating results that is used in the preparation of expected undiscounted cash flows. If management's assumptions about future operating results were to change as a result of events or circumstances, the Company may be required to record an impairment loss on these assets. No impairment indicators were noted for the Company's amortizable long-lived assets, fixed assets, in the periods presented.

The Company also evaluates the carrying value of intangible assets (not subject to amortization) related to in-process research and development ("IPR&D") assets, which are considered to be indefinite-lived until the completion or abandonment of the associated research and development efforts. Accordingly, amortization of the IPR&D assets will not occur until the product reaches commercialization. During the period the assets are considered indefinite-lived, they will be tested for impairment on an annual basis, as well as between annual tests if the Company become aware of any events occurring or changes in circumstances that would indicate that the fair values of the IPR&D assets are less than their carrying amounts. If and when development is complete, which generally occurs when regulatory approval to market the product is obtained, the associated IPR&D assets would be deemed definite-lived and would then be amortized based on their estimated useful lives at that point in time based on respective patent terms. If the related project is terminated or abandoned, the Company will have an impairment related to the IPR&D assets, calculated as the excess of its carrying value over fair value. The Company estimated fair value of IPR&D assets acquired in Annapurna transaction at the acquisition closing date, May 11, 2016, to be $16.2 million. As a result of management's decision to change its manufacturing process for ADVM-043 and ADVM-053 by implementing its proprietary baculovirus-based production system during the fourth quarter of 2016 and based upon the Company's analysis of the fair value of the IPR&D assets as of December 31, 2016, the Company recorded an impairment charge of $11.2 million. Refer to Note 3 for further details.

Financial Liabilities—Prior to the Company's IPO, the Company had recorded convertible preferred stock warrants issued to investors and note holders as derivative liabilities. In connection with the completion of the Company's IPO in August 2014, all of the then outstanding warrants to purchase convertible preferred stock were exercised. As a result of the exercises, the Company recorded a $0.8 million loss related to the change in fair value in the Company's consolidated statements of operations and comprehensive loss and reclassified the fair value of $0.9 million to additional paid-in capital.

During 2016, the Company entered into a sponsored research agreement with The Alpha-1 project, Inc. (TAP) with an embedded derivative, the Company determined to account for this financial liability at fair value. Refer to Note 13 for further details.

Revenue Recognition—The Company has primarily generated revenue through license, research and collaboration arrangements with its strategic partners.

The terms of these types of agreements may include (i) licenses to our technology, (ii) research and development services, and (iii) services or obligations in connection with participation in research or steering committees. Payments to the Company under these arrangements typically include one or more of the following: nonrefundable upfront and license fees, research funding, milestone and other contingent payments for the achievement of defined collaboration objectives and certain preclinical, clinical, and regulatory events, as well as royalties on sales of any commercialized products.

In arrangements involving the delivery of more than one element, each required deliverable is evaluated to determine whether it qualifies as a separate unit of accounting. The determination is based on whether the deliverable has "standalone value" to the customer. If a deliverable does not qualify as a separate unit of accounting, it is combined with the other applicable undelivered item(s) within the arrangement and these combined deliverables are treated as a single unit of accounting.

The arrangement's consideration that is fixed or determinable is allocated to each separate unit of accounting based on the relative selling price methodology in accordance with the selling price hierarchy, which includes vendor-specific objective evidence ("VSOE") of selling price, if available, or third-party evidence of selling price if VSOE is not available, or the best estimate of selling price, if neither VSOE nor third-party evidence is available.

Payments or reimbursements for the Company's research and development efforts for the arrangements where such efforts are considered as deliverables are recognized as the services are performed and are presented on a gross basis. When upfront payments are received and if there is no discernible pattern of performance and/or objectively measurable performance measures do not exist, the Company recognizes revenue ratably over the associated period of performance.

The Company's collaboration and license agreements may include contingent payments related to specified research, development and regulatory milestones. Such payments are typically payable under the collaborations when the collaboration partner claims or selects a target, or initiates or advances a covered product candidate in preclinical or clinical development, upon submission for marketing approval of a covered product with regulatory authorities, upon receipt of actual marketing approvals of a covered product or for additional indications, or upon the first commercial sale of a covered product. Each contingent and milestone payment is evaluated to determine whether it is substantive and at risk to both parties. The Company recognizes any payment that is contingent upon the achievement of a substantive milestone entirely in the period in which the milestone is achieved. Any payments that are contingent upon achievement of a non-substantive milestone are recognized as revenue prospectively, when such payments become due and collectible, over the remaining expected performance period under the arrangement, which is generally the remaining period over which the research and development services are expected to be provided.

Collaboration and License Revenue

In August 2016, the Company entered into a collaboration, option and license agreement with Editas. Refer to Note 7 for details of the agreement. Under the terms of the agreement, the Company received initial payments of $1.0 million that included $0.5 million for research services. As the agreement provides for multiple deliverables, the Company accounts for this agreement as a multiple elements revenue arrangement. At the inception of the agreement, identified deliverables include research services, manufacturing of viral vectors for research, participation in joint research committee and exclusivity during the option period. These deliverables did not appear to have a standalone value and were combined into one unit of accounting. Options for each indication to license the Company's AAV vector are considered substantive options and do not include significant incremental discounts. Therefore, they are not considered as deliverables under the agreement.

The Company allocated the $1.0 million received to a single unit of accounting identified in the arrangement. The Company expects to recognize $1.0 million ratably over the associated period of performance, which is the maximum research period of three years. As there is no discernible pattern of performance and/or objectively measurable performance measures do not exist, the Company will recognize revenue on a straight-line basis. During the year ended December 31, 2016, the Company recognized $139,000 as collaboration and license revenue.

In May 2014, the Company entered into a research collaboration and license agreement with Regeneron to discover, develop and commercialize novel gene therapy products for the treatment of ophthalmologic diseases. Refer to Note 7 for details of the agreement. Under the terms of the agreement, the Company received initial upfront non-refundable cash payments of $8.0 million that included payment for research license fees, prepaid collaboration research costs and the time-limited right of first negotiation for license to develop and commercialize AVA-101. As the agreement provides for multiple deliverables, the Company accounts for this agreement as a multiple elements revenue arrangement. If deliverables did not appear to have a standalone value, they were combined with other deliverables into a unit of accounting with a standalone value. The Company allocated the $8.0 million to the relative fair value of the two units of accounting identified in the arrangement. The Company recognizes $6.5 million for the research licenses and related research and development services ratably over the associated period of performance, which is the maximum research period of eight years. As there is no discernible pattern of performance and/or objectively measurable performance measures do not exist, the Company recognizes revenue on a straight-line basis over the eight years performance period. The remaining $1.5 million allocated to the second unit of accounting for the time-limited right of first negotiation for license to develop and commercialize AVA-101. On November 2, 2015, Regeneron notified the Company that it is not exercising this right of first negotiation and the Company recognized the entire $1.5 million as revenue in 2015.

As original research budget was fully used in the fourth quarter of 2015, the Company and Regeneron will agree on the reimbursement of additional research expenses annually. The Company invoices for services performed quarterly. These additional research fees are added to the research licenses and related research and development services unit of accounting, recorded as deferred revenue and recognized to revenue over the remaining research term. The Company recognized $1.4 million and $0.8 million during the year ended December 31, 2016 and 2015, respectively, related to the research licenses and research and development services unit of accounting in the Regeneron agreement.

Research and Development Expenses—Research and development expenses are charged to expense as incurred. Research and development expenses include certain payroll, stock compensation and other personnel-related expenses, laboratory supplies, consulting costs, external contract research and development expenses, and allocated overhead, including rent, equipment depreciation and utilities. Advance payments for goods or services for future research and development activities are deferred and expensed as the goods are delivered or the related services are performed.

The Company estimates preclinical studies and clinical trial expenses based on the services performed pursuant to contracts with research institutions and clinical research organizations that conduct and manage preclinical studies and clinical trials on the Company's behalf. In accruing service fees, the Company estimates the time period over which services will be performed and the

level of effort to be expended in each period. These estimates are based on communications with the third party service providers and the Company's estimates of accrued expenses and on information available at each balance sheet date. If the actual timing of the performance of services or the level of effort varies from the estimate, the Company will adjust the accrual accordingly. There have been no significant changes from the Company's original estimates in any of the periods presented.

The Company received tax credits from the Australian and French governments in connection with certain research costs incurred in conducting research by the Company's Australian and French subsidiaries. These refunds do not depend on the taxable income or tax position of the Company and therefore the Company does not account for them under an income tax accounting model. The Company recognizes such tax credits in the period when qualified expenses are incurred as a reduction of research expenses. The Company has recorded the reimbursement of $0.3 million, $0.1 million and $0.1 million from the tax authorities as a reduction of research and development expense in the consolidated statements of operations and comprehensive loss in the years ended December 31, 2016, 2015 and 2014, respectively.

Fair Value Measurements—Fair value is defined as the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. As such, fair value is a market-based measurement that should be determined based on assumptions that market participants would use in pricing an asset or liability. The carrying amounts of the Company's financial instruments, including cash and cash equivalents, prepaid and other current assets, accounts payable, and accrued expenses approximate their fair values due to their short-term maturities. Refer to Note 6 for the methodologies and assumptions used in valuing financial instruments.

Stock-Based Compensation Expense—Stock-based compensation expense related to awards to employees is measured at the grant date based on the fair value of the award. The fair value of the award that is ultimately expected to vest is recognized as expense on a straight-line basis over the requisite service period, which is generally the vesting period. The expense recognized for the portion of the award that is expected to vest has been reduced by an estimated forfeiture rate. The forfeiture rate is determined at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates.

The Company uses the Black-Scholes valuation model as the method for determining the estimated fair value of stock-based awards.

Expected Term—The expected term assumption represents the period that the Company's stock-based awards are expected to be outstanding and is determined using the simplified method.

Expected Volatility—Expected volatility is estimated using comparable public companies volatility for similar terms.

Expected Dividend—The Black-Scholes valuation model calls for a single expected dividend yield as an input. The Company has never paid dividends and has no plans to pay dividends.

Risk-Free Interest Rate—The risk-free interest rate is based on the U.S. Treasury zero-coupon issues in effect at the time of grant for periods corresponding with the expected term of option.

Stock-based compensation expense related to awards granted to non-employees is recognized based on the then-current fair value at each measurement date over the associated service period of the award, which is generally the vesting term, using the accelerated attribution method. The fair value of non-employee stock options is estimated using the Black-Scholes valuation model with assumptions generally consistent with those used for employee stock options, with the exception of the expected term, which is the remaining contractual life at each measurement date. Refer to Note 14 for more information on assumptions used in estimated stock-based compensation expense.

Income Taxes—The Company accounts for income taxes using the asset and liability method. The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. Deferred tax assets and liabilities are determined based on the difference between the financial statement and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse.

In evaluating the ability to recover its deferred income tax assets, the Company considers all available positive and negative evidence, including its operating results, ongoing tax planning and forecasts of future taxable income on a jurisdiction-by-jurisdiction basis. In the event the Company determines that it would be able to realize its deferred income tax assets in the future in excess of their net recorded amount, it would make an adjustment to the valuation allowance that would reduce the provision for income taxes. Conversely, in the event that all or part of the net deferred tax assets are determined not to be realizable in the future, an adjustment to the valuation allowance would be charged to earnings in the period when such determination is made. As of December 31, 2016 and 2015, the Company has recorded a full valuation allowance on its deferred tax assets.

Tax benefits related to uncertain tax positions are recognized when it is more likely than not that a tax position will be sustained during an audit. Interest and penalties related to unrecognized tax benefits are included within the provision for income tax.

Comprehensive Loss—Comprehensive loss is comprised of net loss, deemed dividend to a preferred stockholder and other comprehensive income (loss). Other comprehensive income (loss) consists of foreign currency translation adjustments related to translation of the financial statements of the Company's Australia, and France subsidiaries and unrealized gain (loss) on marketable securities. The Company did not have reclassifications from other comprehensive income (loss) to the income (loss) during 2016 and 2015 fiscal years.

Basic and Diluted Net Loss Per Share—Basic net loss per common share is computed by dividing the net loss attributable to common stockholders by the weighted-average number of common shares outstanding during the period. Diluted net loss per common share is computed by dividing the net loss by the weighted-average number of common shares and dilutive common share equivalents outstanding during the period. Because the Company has reported a net loss attributable to common stockholders for all periods presented, diluted net loss per common share is the same as basic net loss attributable to common stockholders per common share for those periods. While shares of the convertible preferred stock were outstanding they were considered to be participating securities as they were entitled to participate in undistributed earnings with shares of common stock. Due to net losses in all periods presented, there is no impact on net loss per share calculation in applying the two-class method since the participating securities have no legal requirement to share in any losses.

Recent Accounting Standard Update Not Yet Effective—In August 2014, the Financial Accounting Standards Board (FASB) issued Accounting Standard Update (ASU) 2014-15, *Presentation of Financial Statements—Going Concern (Subtopic 205-40): Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern*, requiring management to evaluate whether events or conditions could impact an entity's ability to continue as a going concern and to provide disclosures if necessary. Management will be required to perform the evaluation within one year after the date that the financial statements are issued. Disclosures will be required if conditions give rise to substantial doubt and the type of disclosure will be determined based on whether management's plans will be able to alleviate the substantial doubt. The accounting standard update will be effective for the first annual period ending after December 15, 2016, and for annual periods and interim periods thereafter with early application permitted. This ASU will be effective for the Company in the first quarter of 2017. The adoption of this standard is not expected to impact the Company's consolidated financial statements and related disclosures.

In May 2014, the FASB issued ASU No. 2014-09, *Revenue from Contracts with Customers* (Topic 606), which supersedes the revenue recognition requirements in ASC 605*, Revenue Recognition*. This ASU is based on the principle that revenue is recognized to depict the transfer of goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. ASU 2014-09 defines a five step process to achieve this core principle and, in doing so, it is possible more judgment and estimates may be required within the revenue recognition process than required under existing GAAP including identifying performance obligations in the contract, estimating the amount of variable consideration to include in the transaction price and allocating the transaction price to each separate performance obligation. ASU 2014-09 is required to be adopted, using either of two methods: (i) retrospective to each prior reporting period presented with the option to elect certain practical expedients as defined within ASU 2014-09; or (ii) retrospective with the cumulative effect of initially applying ASU 2014-09 recognized at the date of initial application and providing certain additional disclosures. In July 2015, the FASB voted to approve a one-year deferral of the effective date to December 15, 2017 for interim and annual reporting periods beginning after that date and permitted early adoption of the standard, but not before the original effective date of December 15, 2016. The FASB issued supplemental adoption guidance and clarification to ASU 2014-09 in March 2016, April 2016, May 2016 and December 2016 within ASU 2016-08 *Revenue From Contracts With Customers: Principal vs. Agent Considerations*, ASU 2016-10 *Revenue From Contracts with Customers: Identifying Performance Obligations and Licensing*, ASU 2016-12 *Revenue from Contracts with Customers: Narrow-Scope Improvements and Practical Expedients* and ASU 2016-20 *Technical Corrections and Improvement to Topic 606 – Revenue from Contracts with* Customers, respectively. The ASU will be effective for the Company in the first quarter of 2018. Preliminarily, the Company intends to adopt the new standard in the first quarter of 2018 using the retrospective approach noted in (ii) above. The Company is currently evaluating the impact of the adoption of this standard on its consolidated financial statements and related disclosures.

In January 2016, the FASB issued ASU No. 2016-01, Recognition and Measurement of Financial Assets and Financial Liabilities, which amends the current guidance on the classification and measurement of financial instruments. Although this ASU retains many current requirements, it significantly revises an entity's accounting related to (i) the classification and measurement of investments in equity securities and (ii) the presentation of certain fair value changes for financial liabilities measured at fair value. This ASU also amends certain disclosure requirements associated with the fair value of financial instruments. The new standard is effective for fiscal years and interim periods within those fiscal years beginning after December 15, 2017, with early adoption permitted for certain changes. This ASU will be effective for the Company in the first quarter of 2018 and must be adopted using a modified retrospective approach, with certain exceptions. Early adoption is permitted for certain provisions. The adoption of this standard is not expected to have a significant impact on the Company's consolidated financial statements and related disclosures.

In February 2016, the FASB issued ASU No. 2016-2, *Leases*, which amends the current guidance on leasing activities to provide more transparency and comparability, and requires that all leases be recognized by lessees on their balance sheet as a right-of-use asset and corresponding lease liability, which are currently accounted for as operating leases. The new standard is effective for fiscal years and interim periods within those fiscal years beginning after December 15, 2018, with early adoption permitted. This ASU will be effective for the Company in the first quarter of 2019 and early adoption is permitted. The ASU requires adoption based upon a modified retrospective transition approach. The company has not yet selected a transition method, has not yet determined whether it will elect early adoption and is currently evaluating the impact of the adoption of this standard on its consolidated financial statements and related disclosures.

In March 2016, the FASB issued ASU No. 2016-9, *Compensation-Stock Compensation: Improvements to Employee Share-Based Payment Accounting,* which simplifies several aspects of the accounting for share-based payment award transactions, including: (1) the income tax consequences, (2) classification of awards as either equity or liabilities, and (3) classification in the consolidated statement of cash flows. The new standard is effective for fiscal years and interim periods within those fiscal years beginning after December 15, 2016, with early adoption permitted. This ASU will be effective for the Company in the first quarter of 2017. The Company is currently evaluating the impact of the adoption of this standard on its consolidated financial statements and related disclosures.

In June 2016, the FASB issued ASU No. 2016-13 *Measurement of Credit Losses on Financial Instruments* (ASU 2016-13). ASU 2016-13 requires measurement and recognition of expected credit losses for financial assets held. The new standard is effective for fiscal years beginning after December 15, 2020 and interim periods beginning after December 15, 2021 with early adoption permitted. This ASU will be effective for the Company in the first quarter of 2021 and must be adopted using a modified retrospective approach, with certain exceptions. Early adoption is permitted beginning in the first quarter of 2019. The Company has not yet determined whether it will elect early adoption and is currently evaluating the impact of the adoption of this standard on its consolidated financial statements and related disclosures.

In August 2016, the FASB issued ASU No. 2016-15, *Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments (ASU 2016-15)*, which clarifies the presentation and classification of certain cash receipts and cash payments in the statement of cash flows. This ASU is effective for public business entities for annual reporting periods beginning after December15, 2017, and interim periods within that reporting period. Early adoption is permitted. This ASU will be effective for the Company in the first quarter of 2018 and early adoption is permitted. The Company has not yet determined whether it will elect early adoption and is currently evaluating the impact of the adoption of this standard on its consolidated financial statements and related disclosures.

In November 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows (Topic 230): Restricted Cash (ASU 2016-18)*, which provides amendments to current guidance to address the classification and presentation of changes in restricted cash in the statement of cash flows. This ASU is effective for public business entities for annual reporting periods beginning after December 15, 2017, and interim periods within that reporting period. Early adoption is permitted. This ASU will be effective for the Company in the first quarter of 2018 and early adoption is permitted. The Company has not yet determined whether it will elect early adoption and is currently evaluating the impact of the adoption of these standards on its consolidated financial statements and related disclosures.

The Company has reviewed other recent accounting pronouncements and concluded they are either not applicable to the business or no material effect is expected on the consolidated financial statements as a result of future adoption.

Accounting Standard Update Recently Adopted—In April 2015, the FASB issued ASU No. 2015-05, *Customer's Accounting of Fees Paid in Cloud Computing Arrangement*, guidance on accounting for fees paid in cloud computing arrangements. If a cloud computing arrangement includes a software license, then the customer should account for the software license element of the arrangement consistent with the acquisition of other software licenses. If a cloud computing arrangement does not include a software license, the customer should account for the arrangement as a services contract. All software licenses recognized under this guidance will be accounted for consistent with other licenses of intangible assets. The Company elected to adopt this ASU in the first quarter of fiscal 2016. The adoption of this standard did not have any impact on the Company's consolidated financial statements.

3. Acquisition of Annapurna

(a) Purchase Price Allocation

On May 11, 2016, the Company completed the acquisition of all outstanding equity interests of Annapurna. Annapurna is a privately held French limited liability company and has two wholly-owned subsidiaries, Annapurna, Inc. in the U.S. and Annapurna Therapeutics Limited in Ireland. Annapurna is a biopharmaceutical company focused on discovering and developing novel gene therapy products for people living with severe rare diseases. The primary reasons for the acquisition were to expand the technology

platforms within the Company's research and development portfolio and to apply the Company's resources and expertise in gene vectors development to advance Annapurna's programs through development and clinical trials. Annapurna's results of operations and fair value of assets acquired and liabilities assumed are included in the Company's consolidated financial statements from the date of acquisition.

The purchase price consideration was estimated to be $64.8 million, which was based on the Company's common stock closing price on NASDAQ on the acquisition closing date of $4.14 per share. A total of 14,087,246 shares of the Company's common stock were issued to shareholders of Annapurna in exchange for all common and preferred stock outstanding at the closing date. Annapurna stockholders did not receive any fractional shares of the Company's common stock in connection with the acquisition. Instead of receiving any fractional shares, each Annapurna stockholder was paid an amount in cash (without interest) equal to such fraction amount multiplied by the average 10 business days sale price of the Company's common stock on NASDAQ from the acquisition date. Annapurna Series O preferred shares issued to founders were canceled prior to the acquisition date and were not included in the purchase price consideration. Vesting of certain of Annapurna's options and unvested common stock shares was accelerated at the closing date. The fair value of awards related to the accelerated vesting of options and shares of $0.9 million was excluded from the purchase price consideration and included in the Company's operating expenses post acquisition. A portion of the purchase price has been attributed to the exchange of Annapurna's options and other rights to purchase capital stock outstanding at the acquisition closing date for corresponding common stock options of the Company at an exchange ratio of 9.54655.

The Company reserved 3,673,940 shares for the future exercise of the Company's stock options. The total fair value of assumed Annapurna stock options and stock-based awards was estimated at $14.7 million on the acquisition date, using the Black-Scholes option pricing model, assuming no dividends, expected volatilities of 80% and 89%, risk-free interest rates of 1.4% and 1.1%, and expected lives of six and ten years for employees and non-employees awards, respectively. Of the total fair value, $7.4 million has been attributed as pre-combination service and included as part of the total purchase price consideration. The post-combination attribution amount of $7.2 million will be recognized as compensation expense over the remaining requisite service period. The Company has included $0.9 million in stock-based compensation expense related to the day-one post combination compensation expenses related to the accelerated vesting of options during the second quarter 2016.

Total purchase price consideration was estimated as follows (in thousands):

Fair value of common shares issued	$ 58,321
Fair value of the Company's common share options exchanged for Annapurna options and other awards attributable to pre-combination services	7,422
Less: value of common stock and options accelerated vesting at close date	(898)
Total purchase price consideration	$ 64,845

The transaction has been accounted for using the acquisition method based on ASC 805, *Business Combinations,* with Adverum identified as the acquirer, based on the existence of a controlling financial interest of the combined entities. Under the acquisition method, assets acquired and liabilities assumed were recorded at their estimated fair values as of May 11, 2016. Goodwill, as well as intangible assets that do not qualify for separate recognition, is measured as of the acquisition date as the excess of consideration transferred, which is also measured at fair value, and the net of the fair values of the assets acquired and the liabilities assumed as of the acquisition closing date. Goodwill represented expected synergies of two combined companies. Acquisition costs of $2.5 million were expensed as incurred and recorded as general and administrative expenses.

The allocation of total purchase price consideration is as follows (in thousands):

Cash	$ 3,449
Prepaid expenses and other assets	865
Property and equipment	185
Acquired intangible assets	16,200
Goodwill	49,514
Accounts payable	(1,118)
Accrued liabilities	(1,848)
Other noncurrent liabilities	(377)
Deferred tax liabilities	(2,025)
Total purchase price allocation	$ 64,845

The identifiable intangible assets acquired consist of IPR&D assets related to products in development, as summarized in the table below (in thousands):

IPR&D - Alpha-1 antitrypsin deficiency	$ 11,700
IPR&D - Hereditary angioedema	4,500
Total acquired intangible assets	$ 16,200

The fair value of each IPR&D asset is estimated using the income approach and calculated using cash flow projections adjusted for inherent risks regarding regulatory approval, promotion, and distribution, discounted at a rate of approximately 11.0%. The Company acquired two additional intangible assets relating to the Friedreich's Ataxia (FA) and severe allergy programs, but the fair value of each of these assets was determined to be nominal and is not included in the total acquired intangible assets. All IPR&D intangible assets acquired are currently classified as indefinite-lived and are not currently being amortized. Acquired IPR&D assets were impaired in the fourth quarter 2016, refer to the discussion below.

Goodwill, which represents the excess of the purchase price over the fair values assigned to the net assets acquired, was estimated in the amount of $49.5 million on the acquisition date. The full amount of the preliminary value of goodwill has been assigned to the entire Company, since management has determined that the Company has only one reporting unit. The goodwill is not deductible for tax purposes. During the second quarter of 2016, goodwill was impaired, refer to the discussion below.

The amount of net loss of Annapurna included in the consolidated statements of operations and comprehensive loss from the acquisition date through the period ended December 31, 2016 was $16.6 million, including the $11.2 million impairment to IPR&D assets. Annapurna did not generate any revenues prior or post acquisition.

The pro forma financial information combines the results of operations of Adverum and Annapurna as though the businesses had been combined as of the beginning of fiscal 2015. The pro forma financial information is presented for informational purposes only, and is not indicative of the results of operations that would have been achieved in the current or any future periods. The following table presents the unaudited pro forma results for the years ended December 31, 2016 and 2015 (in thousands, except per share data).

	Years ended December 31,	
	2016	2015
Pro forma information		
Collaboration and license revenue	$ 1,455	$ 2,319
Net loss	$ (117,551)	$ (61,774)
Basic and diluted loss per share	$ (2.85)	$ (1.56)
Weighted-average common shares outstanding - basic and diluted	41,288	39,566

Pro-forma adjustments included the following:

- Actual acquisition-related transaction costs of $2.5 million for year ended December 2016 were excluded from the 2016 pro forma results above. As these expenses were incurred prior to the closing of the acquisition, they were not included in the 2015 pro forma results.
- Stock-based compensation expense related to the accelerated vesting associated with the acquisition of $0.9 million was excluded from the 2016 pro forma results and was recorded in the year ended December 31, 2015.
- Stock-based compensation expense related to options granted to executives upon the acquisition closing of $0.2 million and $0.4 million was included in the 2016 and 2015 pro forma results above.
- Interest expense related to convertible notes and changes in fair value of preferred stock warrants of $0.5 million for the year ended December 31, 2015 and $1.0 million for the year ended December 31, 2016, were excluded from 2015 and 2016 pro-forma results above, as the convertible notes and warrants were settled prior to the acquisition closing.
- Bonuses paid in connection with closing of the acquisition in May 2016 of $0.4 million were excluded from the 2016 pro forma results and were recorded in the year ended December 31, 2015.

The unaudited condensed pro forma information does not include any anticipated synergies that may be achievable subsequent to the date of acquisition.

b) Impairment evaluation for goodwill and intangible assets

As the Company recorded goodwill and IPR&D intangible assets upon the acquisition of Annapurna, the Company is required to test goodwill and indefinite lived intangible assets for impairment on an annual basis or more frequently if indicators of impairment exist. The Company operates as one reporting unit and goodwill was recorded to this reporting unit.

During the second quarter of 2016, the Company noted a continuing decrease in its stock price that resulted in the market capitalization being less than the carrying value of the Company's net assets as of June 30, 2016. As the operating losses are expected to increase significantly in the following years due to continuing pre-clinical and expected clinical trials, the Company concluded that it is more likely than not that the fair value of the Company's one reporting unit is less than its carrying value and as a result performed a step one goodwill impairment analysis.

In performing the step one analysis, the Company determined the fair value of the reporting unit using a market-based approach. The Company multiplied the stock price of $3.16 on June 30, 2016 by the 41.3 million common shares outstanding and applied a control premium to estimate the common equity value on a controlling basis. As the fair value was less than the carrying value of the Company's net assets, the Company proceeded to step two of the impairment analysis.

The second step of the analysis includes allocating the calculated fair value (determined in the step one analysis) of the reporting unit to its assets and liabilities to determine an implied fair value of goodwill. The implied fair value of goodwill was determined in the same manner as the amount of goodwill recognized in an acquisition. That is, the estimated fair value of the reporting unit was allocated to all of the assets and liabilities as if the Company had been acquired and the estimated fair value was the purchase price paid. As part of this assessment the Company considered the preliminary valuation of Annapurna net assets acquired, excluding goodwill, as their fair value from May 11, 2016, the acquisition closing date, to June 30, 2016 did not change. The Company also noted that the fair value of current assets and liabilities approximates their carrying value due to their short-term nature, the Company's cash and cash equivalent balance is higher than the fair value estimated in the step one analysis, and the fair value of fixed assets approximates their recorded value as most of the Company's fixed assets are acquired in the last couple of years. Based on this analysis, the implied fair value of the goodwill was zero. Accordingly, the total goodwill impairment charge was $49.5 million, which is included in impairment of goodwill and intangible assets on the consolidated statements of operations and comprehensive loss for the year ended December 31, 2016.

In the fourth quarter of 2016, we performed our annual impairment assessment of our ADVM-043 and ADVM-053 IPR&D assets. Based on our decision in the fourth quarter to change our manufacturing process for ADVM-043 and ADVM-053 by implementing our proprietary baculovirus-based production system, we updated the related development and manufacturing costs. As a result, we revised our forecasts for manufacturing and related costs. In addition, we also reviewed and updated our expected timing of clinical trials, receipts of regulatory approvals and costs to complete. Based upon our analysis, we determined that the carrying value of $16.2 million for our ADVM-043 and ADVM-053 IPR&D assets was higher than their fair value of $5.0 million. Accordingly, we recorded an $11.2 million IPR&D impairment charge for the year ended December 31, 2016.

4. Restructuring Charges

On December 22, 2015, the Company implemented a restructuring plan to reduce operating costs and better align its workforce with the needs of its business following its decision to not initiate the Phase 2b clinical trial for AVA-101 in the second half of 2015. The plan resulted in a reduction of approximately 20% of the Company's workforce, or 15 employees. Affected employees are eligible to receive severance payments. The plan also triggered accelerated vesting of certain of the affected employees' restricted stock unit awards (RSUs).

In connection with the restructuring, the Company estimates aggregate restructuring charges of approximately $2.6 million in the fourth quarter of 2015 related to one-time termination severance payments and other employee-related benefits, including approximately $1.0 million of stock-based compensation expense related to the acceleration of RSUs. The Company recorded the $2.6 million as restructuring charges on the consolidated statements of operations and comprehensive loss for the year ended December 31, 2015.

The following table summarizes the restructuring activities for the years ended December 31, 2015 and 2016 (in thousands):

	One-Time Termination Benefits	Non-Cash Charge Related to Acceleration of RSUs	Total
Restructuring liability as of December 31, 2014	$ —	$ —	$ —
Costs incurred and recorded as restructuring charges	1,524	1,049	2,573
Cash payments	(511)	—	(511)
Non-cash settlements	—	(1,049)	(1,049)
Restructuring liability as of December 31, 2015	1,013	—	1,013
Cash payments	(988)	—	(988)
Restructuring liability as of December 31, 2016	$ 25	$ —	$ 25

5. Cash Equivalents and Marketable Securities

The following is a summary of the cash equivalents and marketable securities (in thousands):

December 31, 2016	Amortized Cost Basis	Unrealized Gains	Unrealized Loses	Estimated Fair Value
Money market funds - cash equivalent	$ 215,916	$ —	$ —	$ 215,916
Total cash equivalents	$ 215,916	$ —	$ —	$ 215,916
December 31, 2015				
Money market funds - cash equivalent	$ 208,588	$ —	$ —	$ 208,588
Certificates of deposit	1,680	—	—	1,680
U.S. treasury securities	15,046	—	(4)	15,042
U.S. government agency securities	21,012	—	(2)	21,010
	246,326	—	(6)	246,320
Less: Cash equivalents	(208,588)	—	—	(208,588)
Total marketable securities	$ 37,738	$ —	$ (6)	$ 37,732

During the year ended December 31, 2016, management sold the Company's marketable securities at maturity and did not recognize any gains or losses on liquidation.

6. Fair Value Measurements and Fair Value of Financial Instruments

The authoritative guidance on fair value measurements establishes a three-tier fair value hierarchy for disclosure of fair value measurements as follows:

Level 1: Quoted prices in active markets for identical assets or liabilities.

Level 2: Observable inputs other than Level 1 prices, such as quoted prices for similar assets or liabilities, quoted prices in markets that are not active, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

Level 3: Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

Assets and liabilities measured at fair value are classified in their entirety based on the lowest level of input that is significant to the fair value measurement. The Company's assessment of the significance of a particular input to the fair value measurement in its entirety requires management to make judgments and consider factors specific to the asset or liability.

The fair value of Level 1 securities are determined using quoted prices in active markets for identical assets. Level 1 securities consist of highly liquid money market funds. Financial assets and liabilities are considered Level 2 when their fair values are determined using inputs that are observable in the market or can be derived principally from or corroborated by observable market data such as pricing for similar securities, recently executed transactions, cash flow models with yield curves, and benchmark securities. In addition, Level 2 financial instruments are valued using comparisons to like-kind financial instruments and models that use readily observable market data as their basis. U.S. Treasury securities, U.S. government agency securities and certificate of deposit are valued primarily using market prices of comparable securities, bid/ask quotes, interest rate yields and prepayment spreads and are included in Level 2.

In certain cases where there is limited activity or less transparency around inputs to valuation, securities are classified as Level 3 within the valuation hierarchy. Level 3 liabilities that were measured at estimated fair value on a recurring basis consist of a financing arrangement entered in 2016.

During the periods presented, the Company has not changed the manner in which it values liabilities that are measured at estimated fair value using Level 3 inputs. There were no transfers within the hierarchy during the years ended December 31, 2016 and 2015.

The following table summarizes, for assets and liabilities recorded at fair value, the respective fair value and the classification by level of input within the fair value hierarchy as described above (in thousands):

	Total Carrying Value	Quoted Prices In Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
December 31, 2016				
Assets:				
Money market funds - cash equivalent	$ 215,916	$ 215,916	$ —	$ —
Total cash equivalents	$ 215,916	$ 215,916	$ —	$ —
Other noncurrent liability:				
Financing arrangement	$ 74	$ —	$ —	$ 74
December 31, 2015				
Assets:				
Money market funds - cash equivalent	$ 208,588	$ 208,588	$ —	$ —
Certificates of deposit	1,680	—	1,680	—
U.S. treasury securities	15,042	—	15,042	—
U.S. government agency securities	21,010	—	21,010	—
Total cash equivalents and marketable securities	$ 246,320	$ 208,588	$ 37,732	$ —

In August 2016, the Company entered into a financing arrangement with an independent third party for a total amount of $0.3 million. Under the terms of the financing arrangement, the Company may be required to repay up to $1.4 million, depending on the achievement of certain development and commercialization milestones. The Company elected the fair value option to account for this financing arrangement. The fair value of the financing arrangement was determined based on the expected value approach and is classified as Level 3 within the fair value hierarchy. The Company received approximately $0.1 million and the changes in the fair value were insignificant during the year ended December 31, 2016. The key unobservable inputs in the valuation model include timing of milestones, probability of achievement of development and commercial milestones, and a discount factor.

The following table presents quantitative information about the inputs and valuation methodologies used for the fair value measurements classified in Level 3 of the fair value hierarchy at December 31, 2016:

	Fair Value at December 31, 2016 (in thousands)	Valuation Methodology	Significant Unobservable Input	Weighted-Average (range - if applicable)
Financing arrangement	$ 74	Expected value approach	Milestone dates	2017 - 2023
			Discount rate	5.5%
			Percent probability of milestone achievements	18.2% to 80.0%

Non-financial assets such as intangible assets, property, plant, and equipment are evaluated for impairment and adjusted to their fair value using Level 3 inputs, only when impairment is recognized. Fair values are considered Level 3 when management makes significant assumptions in developing a discounted cash flow model based upon a number of considerations including projections of revenues, earnings and a discount rate. In addition, in evaluating the fair value of goodwill impairment, further corroboration is obtained using our market capitalization.

7. Significant Agreements

University of California— In May 2010, the Company entered into a license agreement with the Regents of University of California (Regents), as amended in September 2013. Under the license agreement, the Regents have granted to the Company an exclusive (even as to the Regents) license, with the right to grant sublicenses, under the Regents' undivided interest in patent rights covering a method of using recombinant gene delivery vectors for treating or preventing diseases of the eye, to develop, make, have made, use offer for sale, import, export and sell products covered by such patent rights in all fields of use in the United States. The licensed patent rights are jointly owned by the Regents and Chiron Corporation, but the Company's license extends only to the Regents' interest in such patent rights.

Under the license agreement, the Company is required to diligently proceed with the development, manufacture and sale of licensed products, which includes obligations to meet certain development-stage milestones within specified periods of time, and to market the resulting licensed products in sufficient quantity to meet market demand. The Company has the right and option to extend the date by which it must meet any milestone by six-months up to two times by paying an extension fee for each such extension.

The Company has paid the Regents a license fee of $100,000. The Company is also obligated to make milestone payments totaling up to $900,000 upon reaching certain stages of development of the licensed products for one indication, and totaling up to $500,000 for each subsequent indication for which licensed products are developed, for up to a maximum of two additional indications. Through December 31, 2016, none of these goals had been achieved, and no milestones were payable. The Company must pay the Regents a low single-digit royalty on net sales of the licensed products by the Company or its sublicensees, subject to a minimum annual royalty payment of $50,000 beginning in the calendar year after the first commercial sale of a licensed product, until the patent rights upon which such royalties are based expire or are held invalid, which is currently expected to occur in 2020, subject to any potential patent term extensions. The Company is obligated to reimburse the Regents for expenses associated with the prosecution and maintenance of the licensed patents. Finally, the Company is obligated to pay the Regents a mid-teen percentage of non-royalty licensing revenue that the Company receives from sublicensees.

The Company's license agreement with the Regents continues in effect for the life of the last-to-expire patent. The Company may terminate this agreement without cause at any time upon 30 days' prior written notice to the Regents. The Regents may terminate this agreement for a breach by the Company that remains uncured for 60 days, if the Company becomes insolvent, if the Company directly or through a third party files a claim that a licensed patent right is invalid or unenforceable or if the Company fails to meet or extend the date for meeting certain diligence milestones.

Regeneron—In May 2014, the Company entered into a research collaboration and license agreement with Regeneron to discover, develop and commercialize novel gene therapy products for the treatment of ophthalmologic diseases. The collaboration covers up to eight distinct therapeutic targets (collaboration targets). The Company and Regeneron will collaborate during the initial research period of three years that can be extended by Regeneron for up to an additional five years. During the research period, Regeneron has the option to obtain an exclusive worldwide license for a collaboration target's further development by giving written notice to the Company and paying $2.0 million per target. If Regeneron exercises its option, it will be responsible for all further development and commercialization of the target. The Company is then eligible to receive contingent payments of up to $80.0 million upon achievement of certain development and regulatory milestones for product candidates directed toward each collaboration target, for a combined total of up to $640.0 million in potential milestone payments for product candidates directed toward all eight collaboration targets, plus a royalty in the low- to mid-single-digits on worldwide net sales of collaboration products.

For any two collaboration targets, the Company has an option to share up to 35% of the worldwide product candidate development costs and profits. If the Company exercises this option, the Company will not be eligible for milestone and royalty payments discussed above but rather the Company will share development costs and profits with Regeneron.

The agreement will expire with respect to each collaboration target upon the earlier of the (a) expiration of the research term if the option right has not been triggered by the end of the research term or (b) expiration of the option right if the option right has not been exercised by Regeneron. If the option right has been exercised, the agreement in connection with each collaboration target will expire upon expiration of all payment obligations by Regeneron. In addition, the agreement, or Regeneron's rights to any target development under the agreement, may terminate early under the following situations:

- Regeneron may terminate the agreement for convenience at any time on a target by target basis or in totality upon a 30-day notice.
- Each party can terminate the agreement if another party commits a material breach or material default in performance of its obligations and such breach or default is not cured within 60 days.

- The agreement is automatically terminated upon initiation of any bankruptcy proceedings, reorganization or dissolution of either party.
- The Company can terminate the agreement upon 30-day notice if Regeneron challenges the validity, scope or enforceability of any Company patent.

Editas—In August 2016, the Company entered into a collaboration, option and license agreement with Editas Medicine, Inc. (Editas) pursuant to which the Company and Editas will collaborate on certain studies using adeno-associated viral (AAV) vectors in connection with Editas' genome editing technology and the Company will grant to Editas an exclusive option to obtain certain exclusive rights to use the Company's proprietary vectors in up to five ophthalmic indications (Indications). The Company received a $1.0 million non-refundable upfront payment, with $0.5 million of such payment to be credited against Editas' obligation to fund research and development costs. Under the terms of the agreement, both the Company and Editas will be subject to exclusivity obligations.

Editas may exercise the option, with respect to a designated initial Indication, until the first anniversary of the effective date of the agreement. With respect to the four other Indications, Editas may exercise the option until the third anniversary of the effective date, provided that the option will expire on the second anniversary of the effective date if Editas has not exercised the option with respect to the initial Indication or any other Indication by such date. Upon each exercise of the option, Editas will pay the Company a $1.0 million fee per Indication. If Editas elects to develop a product using certain of the Company's proprietary vectors, the Company will be eligible to receive up to a mid-teen million dollar amount in development and 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.

Unless earlier terminated, the agreement will be in effect until the later of the expiration of the option exercise period or the expiration of the royalty term of the last product. At any time after the option is first exercised, Editas may terminate the Agreement for convenience in its entirety or on an indication-by indication or country-by-country basis, upon prior written notice to the Company. The Company may also terminate the agreement if Editas challenges the Company's patents relating to its proprietary vectors and does not withdraw such challenge within a defined period of time. In addition, either party may terminate the agreement with written notice upon a bankruptcy of the other party or upon an uncured material breach by the other party.

Cornell University—In December 2016, the Company informed the appropriate persons at Cornell University (Cornell) that the Company decided to exercise its right to terminate the Company's master service agreement (MSA), originally established in August 2014 and amended in December 2015. This MSA included gene therapy programs ADVM-043, ADVM-053 and severe allergy. The Company's three licensing agreements with Cornell for these gene therapy programs remain unchanged.

The decision to terminate the MSA is a result of Cornell's failure to deliver therapeutic material of ADVM-043 suitable for use in human patients. As a result of this decision, the Company is in the final stages of contracting with a large-scale contract manufacturing organization that complies with current good manufacturing practice industry standards and can produce product quantities for both the Company's planned clinical trials and potential commercial supply. This is part of the Company's planned upgrade of the manufacturing process for ADVM-043, implementing its proprietary, highly-scalable baculovirus-based production system, in advance of the Company's plans to initiate a Phase 1/2 clinical trial for ADVM-043 in the fourth quarter of 2017.

Under the MSA, Cornell provided assistance in regulatory affairs, overall project management, and parameter development. The MSA, as amended, provided for Annapurna to pay Cornell $13.3 million ratably over 4 years for these services as services were performed.

In December 2015, Annapurna Therapeutics Limited entered into three licensing agreements with Cornell, pursuant to which Annapurna will advance its gene therapy programs ADVM-043, ADVM-053, and severe allergy, which originally were initiated at the Department of Genetic Medicine at Weill Cornell.

A1AT Deficiency License Agreement: Under this agreement, Annapurna Therapeutics Limited holds an exclusive license to certain technology related to alpha-1 antitrypsin (A1AT) deficiency and rights to an Investigational New Drug (IND) application to initiate clinical studies of gene therapy for A1AT.

HAE License Agreement: Under this agreement, Annapurna Therapeutics Limited holds an exclusive license to certain technology related to hereditary angioedema (HAE) and a non-exclusive license to certain other intellectual property related to the HAE program.

Allergy License Agreement: Under this agreement, Annapurna Therapeutics Limited holds an exclusive license to certain patents related to allergens and a non-exclusive license to certain other technology related to allergens.

Across these three license agreements, Cornell is entitled to receive aggregate annual maintenance fees ranging from $30,000 to $300,000 per year, up to $16.0 million in aggregate milestone payments and royalties on sales in the low single-digits, subject to adjustments and minimum thresholds. The Company accrued $0.8 million as of December 31, 2016 and recorded total research and development expenses of $1.8 million (post Annapurna's acquisition) for the period from May 11, 2016 through December 31, 2016, related to Cornell agreements. No milestone payments were probable to achieve and none were recorded as of December 31, 2016.

Annapurna Therapeutics Limited may terminate any of these license agreements for convenience upon ninety days written notice. Cornell may terminate any of the license agreements for material breach if such breach is not cured within a specified number of days. Cornell may also terminate the HAE License Agreement and/or the Allergy License Agreement if Annapurna Therapeutics Limited commences any action and files a written claim asserting that any portion of the licensed patent rights invalid or unenforceable.

Dr. Crystal, Chairman of Genetic Medicine, the Bruce Webster Professor of Internal Medicine and a Professor of Genetic Medicine and of Medicine at Weill Cornell, served as a consultant to Annapurna since inception and continues to provide services to the Company for the annual compensation of $0.3 million. Dr. Crystal also owns common shares of the Company and he does not have significant influence on the Company's operations.

REGENXBIO—*A1AT Deficiency/Allergy License Agreement*: In October 2015, Annapurna Therapeutics Limited entered into an exclusive worldwide license to certain intellectual property in order to make, have made, use, import, sell and offer for sale certain licensed products for the treatment of A1AT deficiency. Under this agreement, Annapurna Therapeutics Limited also has an option to be granted an exclusive worldwide license to certain intellectual property related to the treatment of severe allergies, which option expired in October 2016. Under this license agreement, REGENXBIO, Inc. (REGENXBIO) is eligible to receive annual maintenance fees, up to approximately $20.0 million in combined milestone payments and royalties in the mid-to-high single digits.

Unless earlier terminated, this license agreement will be in effect on a country-by-country, licensed product-by-licensed product basis until the expiration, lapse, abandonment, or invalidation of the last claim of the licensed intellectual property to expire, lapse, or become abandoned or unenforceable for the applicable licensed product. Annapurna Therapeutics Limited may terminate this license agreement upon six months' prior written notice. REGENXBIO may terminate this license agreement if Annapurna Therapeutics Limited is a specified number of days late in paying money due under the license agreement, or if Annapurna Therapeutics Limited, its affiliates, or any sublicensees become insolvent or, effective immediately, if they commence any action against REGENEXBIO or its licensors to declare or render any claim of the licensed patent rights invalid or unenforceable. Either party may terminate this license agreement for material breach if such breach is not cured within a specified number of days.

Friedreich's Ataxia License Agreement: In April 2014, Annapurna entered into an exclusive worldwide license to certain intellectual property related to the Friedreich's Ataxia (FA) program to make, have made, use, import, sell and offer for sale licensed products using AAVrh10 for FA where the vector is administered by any route except directly to the central nervous system (FA Systemic). Under the terms of this license agreement, Annapurna also had an option to obtain a non-exclusive worldwide license to make, have made, use, import, sell and offer for sale licensed products using a single vector for each of FA where the vector is administered directly to the central nervous system (FA CNS) and FA Systemic. Under this license agreement, REGENXBIO is eligible to receive annual maintenance fees, up to $13.85 million in combined milestone fees and royalties in the mid-to-high single digits. The option to obtain a non-exclusive license to FA Systemic expired in April 2015 and the option to obtain a non-exclusive license for FA CNS expired in April 2016. Annapurna is obligated to achieve certain development milestones with respect to each licensed disease indication, including the filing of an IND for each licensed disease indication within a specified time period, which Annapurna may extend for additional time for a specified number of extensions upon the payment of a fee.

The Company accrued $42,000 as of December 31, 2016 and recorded expenses of $62,000 (post Annapurna's acquisition) for the period May 11, 2016 through December 31, 2016, related to REGENXBIO agreements. No milestone payments were probable to achieve and none were recorded as of December 31, 2016.

Unless earlier terminated, this license agreement expires upon the expiration, lapse, abandonment, or invalidation of the last claim of the licensed intellectual property to expire, lapse, or become abandoned or unenforceable in all the countries of the world. Annapurna Therapeutics Limited may terminate this license agreement upon six months' prior written notice. REGENXBIO may terminate this license agreement if Annapurna Therapeutics Limited is a specified number of days late in paying money due under the license agreement, or if Annapurna Therapeutics Limited, its affiliates, or any sublicensees become insolvent or, effective immediately, if they commence any action against REGENXBIO or its licensors to declare or render any claim of the licensed patent rights invalid or unenforceable. Either party may terminate this license agreement for material breach if such breach is not cured within a specified number of days.

Inserm Transfert—In July 2014, Annapurna entered into an agreement with Inserm Transfert (Inserm) whereby Annapurna holds an exclusive license to certain patents to develop, make, have made, use, import, offer for sale and sell or otherwise distribute products for the treatment of Friedreich's ataxia and a non-exclusive license to certain other intellectual property related to the FA program. The agreement was amended in October 2015 to increase the scope of the intellectual property under the licenses. Under this agreement, Inserm is entitled to receive certain de minimis license payments, certain development milestone payments of up to approximately €2.0 million in the aggregate and royalties on sales in the low single-digits, subject to adjustments. No milestone payments were probable to achieve and none were recorded as of December 31, 2016.

Unless earlier terminated, this agreement will be in effect on a country-by-country, licensed product-by-licensed product basis until the later of the expiration of the last claim of the licensed intellectual property which cover the manufacture, use or sale of such product in such country or 10 years after the first commercial sale of such product in such country in which such product is sold. Upon a country-by-country and product-by-product basis, Annapurna will have a fully paid up, perpetual, irrevocable license with respect to such product in such country under the licensed intellectual property following expiration of this agreement with respect to such product in the applicable country. Annapurna may terminate this agreement upon 60 days' prior written notice. Inserm may terminate this license agreement if Annapurna becomes the subject of a voluntary or involuntary petition in bankruptcy or fails to meet development milestones and such failure is not cured within a specified number of days. Inserm may also terminate the license granted to Annapurna in a given country if Annapurna (i) before regulatory approval of a product in any country, has ceased conducting any development of products in all countries for 12 consecutive months or (ii) after regulatory approval of a product in a given country, has ceased marketing such product in such country for 12 consecutive months.

Pursuant to Section 4.7 of the agreement with Inserm, our acquisition of Annapurna triggered a one-time payment to Inserm of €250,000, which is recorded in accrued expenses and other current liabilities as of December 31, 2016.

8. Property and Equipment, Net

Property and equipment, net consists of the following (in thousands):

	December 31, 2016	December 31, 2015
Computer equipment and software	$ 300	$ 234
Laboratory equipment	4,285	3,041
Furniture and fixtures	552	552
Leasehold improvements	1,522	351
Construction in progress	104	—
Total property and equipment	6,763	4,178
Less accumulated depreciation and amortization	(2,594)	(991)
Property and equipment, net	$ 4,169	$ 3,187

Depreciation and amortization expense related to property and equipment was $1,603,000, $812,000 and $162,000 for the years ending December 31, 2016, 2015 and 2014, respectively.

9. Accrued Expenses and Other Current Liabilities

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

	December 31, 2016	December 31, 2015
Employees' compensation	$ 2,570	$ 2,047
Accrued preclinical costs	1,683	642
Accrued professional fees	894	1,177
Accrued clinical and process development costs	1,142	101
Other	162	40
Total accrued expenses and other current liabilities	$ 6,451	$ 4,007

10. Other non-current liabilities

Due to the innovative nature of Annapurna's product candidate development programs, Annapurna has benefited from certain sources of financial assistance from Banque Publique d'Investissement ("BPI France"). BPI France provides financial assistance and support

to emerging French enterprises to facilitate the development and commercialization of innovative technologies. The funds received by the Company are intended to finance its research and development efforts and the recruitment of specific personnel. The Company has received such funding in the form of conditional advances.

In August 2015, BPI France granted Annapurna a €750,000 interest free conditional advance, of which €500,000 was drawn down as of December 31, 2015. The remaining €250,000 advance was not and is not expected to be drawn down on. Payments are scheduled in equal quarterly amounts of €25,000 from September 30, 2017 to June 30, 2022. This payment schedule will be modified if the Company will receive revenue from license or product sales before advances are paid in full. The Company calculated 7% imputed interest expense on these advances that was recorded as a discount at the issuance date. The discount is amortized as an interest expense over the life of the advances. As of December 31, 2016 the carrying value, which approximates the fair value, of the conditional advance was $365,000 of which $312,000 is recorded in other non-current liabilities and $53,000 is recorded in accrued expenses and other current liabilities. In addition, the Company recorded $16,000 interest expense from the acquisition closing date to December 31, 2016.

In July 2016, the Company entered into a sponsored research agreement with The Alpha-1 Project, Inc. (TAP) in which TAP will fund the Company's A1AT research activities of up to $300,000. The Company may repay up to 4.5 times the received amount if and when certain product approval and sales milestones are achieved. During the third quarter, the Company received $100,000 and issued the common stock warrant for 10,000 shares exercisable anytime during five years from the issuance date at an exercise price of $4.33 per share. Warrants were valued at $26,000 at the issuance date and recorded as equity. Financing arrangement was recorded at estimated fair value of $74,000 in other noncurrent liabilities as of December 31, 2016. Refer to Note 6 for valuation details of this financing arrangement.

11. Commitments and Contingencies

Facility Lease Agreement

The Company leases its' office building under a non-cancelable lease agreement, which expires on May 8, 2020. The Company may extend this lease for up to four years. The lease agreement provides for an escalation of rent payments each year. The Company records rent expense on a straight-line basis over the term of the lease.

As of December 31, 2016, future minimum commitments under the Company's facility operating lease were as follows (in thousands):

Years ended December 31,	Future Commitments
2017	$ 1,129
2018	1,162
2019	1,197
2020	403
Total minimum lease payments	$ 3,891

Rent expense recognized under the operating lease, including additional rent charges for utilities, parking, maintenance, and real estate taxes was $1,745,000, $1,525,000 and $662,000 for the years ended December 31, 2016, 2015 and 2014, respectively.

Contractual Obligations

We have a contractual obligation at December 31, 2016 to pay $10.0 million over the next 3 year under a Cornell MSA and $1.1 million for manufacturing in 2017. The MSA was cancelled on January 6, 2017 and as such the $10.0 commitments do not exist in the first quarter of 2017 but the commitment still exists at December 31, 2016.

Collaborations and License Agreements

The Company is a party to various agreements, principally relating to licensed technology that requires future payments relating to milestones or royalties on future sales of specified products. Through December 31, 2016, none of the goals had been achieved under the license agreements and no milestones were accrued or payable. Because the achievement of these milestones is not fixed and determinable, such commitments have not been included on the Company's consolidated balance sheets. Aggregate annual maintenance fee's payments were approximately $0.6 and $0.1 million for each of the years ended December 31, 2016 and 2015.

Guarantees and Indemnifications

In the normal course of business, the Company enters into contracts and agreements that contain a variety of representations and warranties and provide for indemnification for certain liabilities. The exposure under these agreements is unknown because it involves

claims that may be made against the Company in the future but have not yet been made. To date, the Company has not paid any claims or been required to defend any action related to its indemnification obligations. However, the Company may record charges in the future as a result of these indemnification obligations. The Company also has indemnification obligations to its directors and executive officers for specified events or occurrences, subject to some limits, while they are serving at the Company's request in such capacities. There have been no claims to date and the Company believes the fair value of these indemnification agreements is minimal. Accordingly, the Company has not recorded any liabilities for these agreements as of December 31, 2016.

Legal Proceedings

From time to time, the Company may become involved in litigation and other legal actions. The Company estimates the range of liability related to any pending litigation where the amount and range of loss can be estimated. The Company records its best estimate of a loss when the loss is considered probable. Where a liability is probable and there is a range of estimated loss with no best estimate in the range, the Company records a charge equal to at least the minimum estimated liability for a loss contingency when both of the following conditions are met: (i) information available prior to issuance of the financial statements indicates that it is probable that a liability had been incurred at the date of the financial statements and (ii) the range of loss can be reasonably estimated.

In July 2015, three putative securities class action lawsuits were filed against the Company and certain of its officers in the United States District Court for the Northern District of California, each on behalf of a purported class of persons and entities who purchased or otherwise acquired the Company's publicly traded securities between July 31, 2014 and June 15, 2015. The lawsuits assert claims under the Exchange Act and 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 complaints seek unspecified damages, attorneys' fees and other costs. An amended consolidated complaint was filed in February 2016. On November 3, 2016, the Court granted the Company's motion to dismiss the consolidated complaint. The plaintiffs filed an amended consolidated complaint on December 2, 2016. The Company's motion to dismiss that amended complaint is pending. The Company also has filed a motion requesting that the Court order discovery in the related state court action (described below) stayed, and a motion requesting that the Court certify a class of investors who purchased the Company's securities between July 31, 2014 and June 15, 2015. Both motions are pending.

In December 2015, a putative securities class action lawsuit was filed against the Company, the Company's board of directors, underwriters of the Company's January 13, 2015, follow-on public stock offering, and two of the Company's institutional stockholders, in the Superior Court of the State of California for the County of San Mateo. The complaint alleges that, in connection with the Company's follow-on stock offering, the defendants violated the Securities Act of 1933, as amended, 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. The plaintiff has dismissed the two institutional stockholder defendants. In August 2016, the Court denied the Company's motion to stay without prejudice, denied the Company's demurrer, and dismissed with leave to amend certain claims against the underwriter defendants. The plaintiff filed an amended complaint on November 2, 2016. The Company's demurrer to that amended complaint and renewed motion to stay the action is pending.

The Company believes that the claims in the asserted actions are without merit and intends to defend the lawsuits vigorously. Due to the inherent uncertainties of litigation, the Company cannot reasonably predict at this time the timing or outcomes of these matters. The Company expects to incur costs associated with defending the actions. While the Company has various insurance policies related to the risks associated with its business, including directors' and officers' liability insurance policies, there is no assurance that the Company will be successful in its defense of the actions, that its insurance coverage, which contains a self-insured retention, will be sufficient, or that its insurance carriers will cover all claims or litigation costs. Beginning in December 2016, the parties have been participating in private mediation, which to date has not progressed to a point where the Company is able to ascertain whether the mediation will be successful. Currently, there are no active mediation discussions between the parties. As a result of, among other things, the uncertain status of the mediation, the early stage of the proceedings, unresolved motions in the proceedings and the uncertainty of the potential outcomes of these and related issues, an estimate of a reasonably possible loss, or the range of losses, if any, or their effect, if any, on the Company's consolidated financial statements, is not reasonably possible to estimate at this time.

12. Convertible Preferred Stock

In connection with the completion of the IPO in August 2014, all outstanding shares of Series A and Series B convertible preferred stock were converted into 10,689,027 shares of common stock on a one-for-one basis.

In April 2014, the Company completed a Series B convertible preferred stock financing, pursuant to which then outstanding convertible notes were converted into 295,115 shares of Series B convertible preferred stock at a conversion price of $6.78, which was equal to 90% of the original issuance price of $7.53 per share. At the time of the conversion, the Company recorded a $0.2 million loss on extinguishment of related-party convertible notes in the consolidated statements of operations and comprehensive loss and a repurchase of beneficial conversion feature of $2.0 million as credit to additional paid-in capital.

In April 2014, the Company repurchased 531,208 shares of Series A convertible preferred stock for $4.0 million. The difference between the repurchase price of $7.53 and original issuance price of $1.45 was recorded as a deemed dividend of $3.2 million to a preferred stockholder and effected the calculation of net loss attributable to common stockholders and net loss per share for the year ended December 31, 2014.

13. Warrants

In connection with an amendment to the Lions Eye Institute (LEI) research agreement in August 2012 the Company agreed to issue to LEI a warrant to purchase 25,000 shares of common stock. The Company estimated the fair value of the obligation to issue this warrant to be approximately $5,000, which was recorded as research and development expense and common stock warrant liability. Until the Company issued the warrant, it classified it as a common stock warrant liability and re-measured the fair value at the end of each reporting period. In March 2014, the Company issued the common stock warrant to LEI with an exercise price of $2.75 per share, at which time the issued common stock warrant was reclassified to additional paid-in capital.

In May 2014, the Company issued a warrant to purchase 63,415 shares of common stock with an exercise price of $6.83 to a financial services firm in connection with the Series B convertible preferred stock financing completed in April 2014. This warrant was exercisable immediately and expired on the earlier of the Company's IPO or May 15, 2019. The Company estimated the fair value of this warrant to be approximately $0.3 million which was recorded as expenses related to issuance of Series B convertible preferred stock. The fair value of the warrant was calculated using the Black-Scholes valuation model, and was based on the common stock fair value of $6.83 per share, contractual term of the warrant of 5 years, a risk-free interest rate of 1.55%, an expected volatility of 75% and a 0% expected dividend yield.

All of the above warrants to purchase common stock and preferred stock were exercised for cash of $0.6 million prior to the completion of the IPO in August 2014. As a result of the exercises of the warrants to purchase preferred stock, the Company recorded a $0.8 million loss related to the change in fair value in the Company's consolidated statements of operations and comprehensive loss and reclassified the fair value of $0.9 million to permanent equity. The fair value of the warrants to purchase preferred stock was calculated using the Black-Scholes valuation model, and was based on the common stock fair value of $17.00 per share, contractual term of the warrants of 1.1 years, a risk-free interest rate of 0.1%, an expected volatility of 70% and a 0% expected dividend yield.

On October 15, 2015, in connection with an amendment to the research agreement between the Company and the LEI, the Company issued to LEI a warrant to purchase 40,000 shares of common stock with an exercise price of $10.51 per share. This common stock warrant is exercisable immediately, and expires on October 15, 2020. The Company estimated the fair value of this warrant to be approximately $0.2 million which was recorded as debit to research and development expenses and credit to additional paid-in capital upon issuance. The fair value of the warrant was calculated using the Black-Scholes valuation model, and was based on the closing price of common stock on the issuance date of $8.35 per share, exercise price of $10.51, contractual term of the warrant of 5 years, a risk-free interest rate of 1.34%, an expected volatility of 75% and a 0% expected dividend yield.

The amendment also provides for the issuance of an additional warrant to LEI to purchase up to 40,000 shares of the Company's common stock upon completion of the 36 month follow-up on the Phase 2a AVA-101 clinical study (Contingent Warrant). As of December 31, 2015, none of the shares subject to the Contingent Warrant were vested and exercisable. The Company is accounting for this warrant as a stock-based award issued for service and estimated the fair value of the costs associated with the service performed to be approximately $8,000 which was recorded as debit to research and development expenses and credit to additional paid-in capital in 2016. The fair value of the Contingent Warrant was calculated using the Black-Scholes valuation model, and was based on the closing price of common stock on December 31, 2016 of $2.90 per share, expected term of the warrant of 5.6 years, a risk-free interest rate of 1.2%, an expected volatility of 72% and a 0% expected dividend yield.

In July 2016, in connection with the TAP financing agreement the Company issued the common stock warrant for 10,000 shares exercisable anytime during five years from the issuance date at an exercise price of $4.33 per share. The warrant was valued at $26,000 at the issuance date using the Black-Scholes valuation model with the following assumptions: exercise price of $4.33 per share, expected term of the warrants of 5 years, a risk-free interest rate of 1.07%, an expected volatility of 72% and a 0% expected dividend. Issued warrant was recorded to the additional paid-in-capital.

14. Stock Option Plans

On December 26, 2006, the Company adopted the 2006 Equity Incentive Plan, which was amended by the board of directors on November 15, 2012 (2006 Plan). The 2006 Plan allowed for the granting of ISOs and NSOs to the employees, members of the board of directors and consultants of the Company. ISOs were granted only to the Company's employees, including officers and directors who are also employees. NSOs were granted to the employees and consultants. In July 2014, the Company's board of directors and its

stockholders approved the establishment of the 2014 Equity Incentive Award Plan (2014 Plan), effective upon the date upon which the registration statement for the IPO was declared effective, which was July 30, 2014. As of the date of the IPO, the Company reserved for issuance under the 2014 Plan a total of 2,088,332 shares of its common stock, plus any additional shares that would otherwise return to the 2006 Plan as a result of forfeiture, termination or expiration of awards previously granted under the 2006 Plan. Options may no longer be issued under the 2006 Plan after July 30, 2014. In addition, the 2014 Plan provides for annual increases in the number of shares available for issuance thereunder on the first business day of each fiscal year, beginning with 2015, equal to four percent (4%) of the number of shares of the Company's common stock outstanding as of such date or a lesser number of shares as determined by the Company's board of directors.

As of December 31, 2016, a total of 13,162,656 shares of common stock were authorized for issuance and 3,079,676 shares were available for future grants under the 2014 Plan.

Options under the 2014 Plan may be granted for periods of up to 10 years and at prices no less than 100% of the estimated fair value of the shares on the date of grant as determined by the board of directors, provided, however, that the exercise price of an ISO and NSO granted to a 10% stockholder may not be less than 110% of the estimated fair value of the shares on the date of grant. Options granted to employees and non-employees generally vest ratably over four years.

In July 2014, the Company's board of directors and its stockholders approved the establishment of the 2014 Employee Stock Purchase Plan (2014 ESPP). The Company reserved for issuance 208,833 shares of its common stock and provided for annual increases in the number of shares available for issuance on the first business day of each fiscal year, beginning in 2015, equal to the lesser of one percent (1%) of the number of shares of the Company's common stock outstanding as of such date or a number of shares as determined by the Company's board of directors. During 2016, 56,696 shares were issued under the 2014 ESPP. A total of 618,687 shares of common stock have been reserved for issuance under the 2014 ESPP and were available for issuance under the 2014 ESPP as of December 31, 2016.

As of December 31, 2016, there was $0.1 million of unrecognized compensation cost related to the ESPP, which is expected to be recognized over a weighted-average period of 0.4 years.

The following table summarizes option activity under the Company's stock plans and related information:

(in thousands, except exercise prices and years)	Options Outstanding	Weighted-Average Exercise Price	Weighted-Average Remaining Contract Life (in years)	Aggregate Intrinsic Value [a]
Balance at December 31, 2015	5,494	$ 8.75	7.8	$ 28,618
Options granted	5,098	1.30		
Options exercised	(1,526)	0.52		
Options cancelled	(1,617)	12.82		
Balance at December 31, 2016	7,449	$ 4.46	8.4	$ 11,837
Vested and expected to vest as of December 31, 2016	7,337	$ 4.41	8.4	$ 11,836
Exercisable at December 31, 2016	3,995	$ 3.34	7.7	$ 8,674

(a) The aggregate intrinsic value is calculated as the difference between the options exercise price and the closing price of common stock of $2.90 per share as of December 31, 2016.

The options granted during 2016, includes the Company's stock options for 3,673,940 common stock shares issued in exchange for Annapurna stock options at $0.21 exercise price per share. In June 2016, the Company granted stock option to purchase 518,000 shares of common stock to its new Chief Executive Officer and Chief Financial Officer. In December 2015, the Company granted a stock option to purchase 910,000 shares of common stock shares to its new Principal Executive Officer. These options were granted outside of the 2014 Plan and not included in the table above.

The total intrinsic value of options exercised during the years ended December 31, 2016, 2015 and 2014 were $7.1 million, $11.2 million and $15.7 million, respectively.

The Company has recorded aggregate stock-based compensation expense related to the issuance of stock option awards to employees and nonemployees in the consolidated statement of operations and comprehensive loss as follows (in thousands):

	Years ended December 31,		
	2016	2015	2014
Research and development	$ 6,616	$ 4,009	$ 7,331
General and administrative	4,800	6,447	1,236
Restructuring charges	—	1,049	—
Total share-based compensation	$ 11,416	$ 11,505	$ 8,567

Departure of Key Executive Officers

Stock-based compensation expense included additional charges of $1.5 million, recorded in general and administrative expense, and $1.4 million, recorded in research and development expense, related to stock modifications in connection with separation agreements for four Company's executive officers for the year ended December 31, 2016.

Effective July 23, 2015, Thomas W. Chalberg, Jr., Ph.D., resigned as the Chief Executive Officer and President of the Company and as a member of the board of directors. In connection with Dr. Chalberg's resignation and his engagement as a consultant and Scientific Advisor, Dr. Chalberg and the Company entered into a Separation Agreement and General Release, dated July 23, 2015 (the Separation Agreement). Under the Separation Agreement, Dr. Chalberg is providing consulting services to the Company and serving as a member of the Company's Scientific Advisory Board until the first anniversary of July 23, 2015 (the consulting period). During the consulting period, subject to the terms and conditions of the Separation Agreement, Dr. Chalberg is paid a monthly fee at the same rate as his salary in effect prior to his resignation and is continuing to vest in outstanding equity awards held by him at the same rates in effect for such awards prior to his resignation. Shares of the Company's common stock subject to his outstanding equity awards that were otherwise scheduled to vest following the expiration of the consulting period will not vest under any circumstances and were forfeited and cancelled on July 23, 2015. As a result, the Company recorded a one-time share-based payment charge of $2.4 million related to the cancellation of unvested stock options in July 2015.

Restricted Stock Units (RSUs)

RSUs are share awards that entitle the holder to receive freely tradable shares of the Company's common stock upon vesting. The fair value of RSUs is based upon the closing sales price of the Company's common stock on the grant date. RSUs granted to employees generally vest over a two-to-four year period.

The following table summarizes the RSUs activity under the Company's stock plans and related information:

(in thousands, except grant date fair value and years)	Number of Units (in thousands)	Weighted-Average Grant Date Fair Value (in dollars)	Weighted-Average Remaining Contractual Term (in years)
Outstanding units at December 31, 2015	632	$ 13.07	1.1
Granted	1,303	4.40	
Vested and released	(386)	12.20	
Forfeited	(500)	7.10	
Outstanding units at December 31, 2016	1,049	$ 5.47	1.7

There were no RSUs granted prior to April 2015. The weighted-average grant date fair values of RSUs granted during fiscal years 2016 and 2015 were $4.40 and $13.85, respectively. The total fair value of RSUs that vested was $1.7 million and $1.4 million for the years ended December 31, 2016 and 2015, respectively. The number of restricted stock units vested includes shares of common stock that the Company withheld on behalf of employees to satisfy the minimum statutory tax withholding requirements. As of December 31, 2016, there was $3.8 million of unrecognized compensation cost related to unvested RSUs that the Company expects to recognize over a weighted-average period of 3.0 years.

Stock Options Granted to Employees

The fair value of each option issued to employees was estimated at the date of grant using the Black-Scholes valuation model with the following weighted-average assumptions:

	Options			Employee Stock Purchase Plan		
	Years ended December 31,			Years ended December 31,		
	2016	2015	2014	2016	2015	2014
Expected volatility	81%	79%	79%	70%	74%	—
Expected term (in years)	6.1	6.1	6.0	0.5	0.5	—
Expected dividend yield	—	—	—	—	—	—
Risk-free interest rate	1.8%	1.7%	1.9%	0.6%	0.1%	—

The weighted-average fair values of options granted during fiscal years 2016, 2015 and 2014 were $3.35, $15.91 and $9.56, respectively.

As of December 31, 2016, there was $11.3 million of unrecognized stock-based compensation expense related to employees' awards that is expected to be recognized over a weighted-average period of 2.7 years.

Stock Options Granted to Non-Employees

Stock-based compensation expense related to stock options granted to nonemployees is recognized as the stock options are earned. The Company believes that the estimated fair value of the stock options is more readily measurable than the fair value of the services rendered.

The following table presents the weighted-average assumptions used to estimate non-employees stock-based compensation expense:

	Years Ended December 31,		
	2016	2015	2014
Option grants:			
Expected volatility	82%	81%	79%
Expected term (in years)	9.1	3.3	7.5
Expected dividend yield	—	—	—
Risk-free interest rate	2.1%	1.0%	2.2%

As of December 31, 2016, there was $2.6 million of unrecognized stock-based compensation expense related to non-employees' awards that is expected to be recognized over a weighted-average period of 2.5 years.

15. 401(k) Savings Plan

The Company established a defined-contribution savings plan under Section 401(k) of the Code. The 401(k) Plan covers all employees who meet defined minimum age and service requirements, and allows participants to defer a portion of their annual compensation on a pretax basis. The amount of contributions that the Company made to the 401(k) Plan during the year ended December 31, 2016 and 2015 was $0.3 million and $0.1 million, respectively

16. Income Taxes

The Company recorded $0.8 million income tax benefit related to the change in the deferred tax liabilities balance due to intangible assets impairment recognized in the fourth quarter of 2016 and no income tax benefit or expense were recorded for the years ending December 31, 2015 and 2014.

The following table presents domestic and foreign components of loss before provision for income taxes (in thousands):

	Years ended December 31,		
	2016	2015	2014
U.S.	$ (96,498)	$ (47,235)	$ (25,006)
Foreign	(18,024)	(218)	(398)
Loss before income taxes	$ (114,522)	$ (47,453)	$ (25,404)

A reconciliation of income tax expense computed at the statutory federal income tax rate of 34% to income taxes as reflected in the financial statements is as follows (in thousands):

	Years ended December 31,		
	2016	2015	2014
Federal income tax expense at statutory rate	$ (38,938)	$ (16,134)	$ (8,637)
Loss on extinguishment of related-party convertible notes	—	—	69
Non-deductible foreign research expenses	21	45	85
Non-deductible stock compensation	1,356	1,418	161
Non-deductible expenses	985	295	285
Goodwill impairment	16,834		
Research and development tax credits	(326)	(910)	(304)
Change in valuation allowance	16,062	15,277	8,349
Foreign rate differential	3,231	9	(8)
Total tax expense (benefit)	$ (775)	$ —	$ —

Deferred income taxes reflect the net tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. The following table presents significant components of the Company's deferred tax assets (in thousands):

	As of December 31,		
	2016	2015	2014
Deferred tax assets:			
Net operating loss carryforwards	$ 15,785	$ 19,889	$ 8,526
Accruals, reserve and other	3,071	2,681	222
Stock-based compensation	3,848	4,328	3,032
Tax credit carryforwards	574	1,945	659
Property and equipment	54	—	—
Intangibles	68	45	24
Other	—	—	24
Total deferred tax assets before valuation allowance	23,400	28,888	12,487
Valuation allowance	(23,400)	(28,839)	(12,457)
Total deferred tax assets	—	49	30
Deferred tax liabilities:			
Property and equipment	—	(49)	(30)
IPR&D	(1,250)	—	—
Total deferred tax liabilities	$ (1,250)	$ (49)	$ (30)
Net deferred tax assets	$ —	$ —	$ —

The Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. Based on the Company's history of operating losses, the Company has concluded that it is more likely than not that the benefit of its deferred tax assets will not be realized. Accordingly, the Company has provided a full valuation allowance for deferred tax assets as of December 31, 2016, 2015 and 2014. The valuation allowance decreased approximately $5.4 million, and increased $16.4 million and $9.9 million during the years ended December 31, 2016, 2015 and 2014, respectively, due to net operating losses.

As of December 31, 2016, the Company had U.S. federal net operating losses (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, the Company 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, the Company 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.

As a result of certain realization requirements of Accounting Standard Codification Topic 718, *Compensation – Stock Compensation* (ASC 718), the table of deferred tax assets and liabilities does not include certain deferred tax assets as of December 31, 2016 that arose directly from tax deductions related to equity compensation that are greater than the compensation recognized for financial

reporting. Equity will be unaffected if and when such deferred tax assets are ultimately realized. The Company uses ASC 740 ordering when determining when excess tax benefits have been realized.

As of December 31, 2016, the Company had federal research and development tax credit carryforwards of approximately $0.3 million available to reduce future tax liabilities which expire at various years beginning with 2036. As of December 31, 2016, the Company had state credit carryforwards of approximately $0.4 million available to reduce future tax liabilities which do not expire.

Under Section 382 of the Internal Revenue Code of 1986, as amended (Code), the Company's ability to utilize NOL carryforwards or other tax attributes, such as research tax credits, in any taxable year may be limited if the Company experiences 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. The Company believes that it has experienced ownership changes under Section 382, which will result in limitations in the Company's ability to utilize net operating losses and credits. In addition, the Company may experience ownership changes as a result of the Company's initial public offering in August 2014, future offerings or other changes in the ownership of the Company's stock. As a result, the amount of the NOLs and research and credit carryforwards presented in the Company's financial statements could be limited and may expire unutilized. Due to a May 11, 2016 ownership change, we determined that certain NOLs for both federal and state purposes are severely limited and therefore we removed a significant amount of NOLs from our deferred tax assets.

The Company files income tax returns in the United States, and state and foreign jurisdictions. The federal, state and foreign income tax returns are open under the statute of limitations subject to tax examinations for the tax years ended December 31, 2012 through December 31, 2016. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the Internal Revenue Service, state or foreign tax authorities to the extent utilized in a future period.

The Company has total unrecognized tax benefits as of December 31, 2016, 2015 and 2014 of approximately $2.1 million, $1.6 million and $0.5 million, respectively. No amount of the unrecognized tax benefits, if recognized, would reduce the Company's annual effective tax rate because the benefits are in the form of deferred tax assets for which a full valuation allowance has been recorded. The Company does not anticipate a significant change to its unrecognized tax benefits over the next twelve months. A reconciliation of the unrecognized tax benefits is as follows (in thousands):

	Years ended December 31,		
	2016	2015	2014
Unrecognized tax benefits as of the beginning of the year	$ 1,568	$ 471	$ 43
Increase (decrease) related to prior year tax provisions	—	172	272
Increase related to current year tax provisions	589	925	156
Unrecognized tax benefits as of the end of the year	$ 2,157	$ 1,568	$ 471

The Company recognizes interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2016 and 2015, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's consolidated statements of operations and comprehensive loss. There are no ongoing examinations by taxing authorities at this time.

17. Net Loss per Share

The following table sets forth the computation of the basic and diluted net loss per share for the years ended December 31, 2016, 2015 and 2014 (in thousands, except per share data):

	Years ended December 31,		
	2016	2015	2014
Net loss	$ (113,747)	$ (47,453)	$ (25,404)
Deemed dividend	—	—	(3,230)
Net loss attributable to common stockholders	(113,747)	(47,453)	(28,634)
Weighted-average common shares outstanding used to calculate basic and diluted net loss per common share:			
Net shares outstanding	36,246	25,479	11,651
Basic and diluted net loss per share attributable to common stockholders	$ (3.14)	$ (1.86)	$ (2.46)

The following common stock equivalents outstanding at the end of the periods presented were excluded from the calculation of diluted net loss per share for the periods indicated because including them would have had an anti-dilutive effect (in thousands):

	As of December 31,		
	2016	2015	2014
Options to purchase common stock	7,449	5,494	4,932
Restricted stock units	1,049	632	—
Warrants to purchase common stock	50	40	—
	8,548	6,166	4,932

18. Selected Quarterly Financial Information (Unaudited)

The following amounts are in thousands, except per share amounts:

Quarterly Results of Operations	Quarters ended			
	March 31, 2016	June 30, 2016	September 30, 2016	December 31, 2016
Revenue	$ 265	$ 307	$ 395	$ 488
Total operating expenses (1)(2)(3)	$ (15,773)	$ (62,189)	$ (14,902)	$ (23,875)
Net loss	$ (15,392)	$ (61,660)	$ (14,301)	$ (22,394)
Basic and diluted net loss per share	$ (0.57)	$ (1.76)	$ (0.35)	$ (0.54)

Quarterly Results of Operations	Quarters ended			
	March 31, 2015	June 30, 2015	September 30, 2015	December 31, 2015
Revenue	$ 203	$ 203	$ 953	$ 960
Total operating expenses (4)(5)	$ (9,764)	$ (10,085)	$ (15,154)	$ (15,139)
Net loss	$ (9,509)	$ (9,766)	$ (14,084)	$ (14,094)
Basic and diluted net loss per share	$ (0.38)	$ (0.38)	$ (0.55)	$ (0.55)

(1) We performed a two-step goodwill impairment analysis and recorded a $49.1 million and a $0.4 million goodwill impairment charge in the second and third quarter of 2016, respectively, in our consolidated statements of operations and comprehensive loss.

(2) In the fourth quarter of 2016, we performed our annual assessment of our ADVM-043 and ADVM-053 IPR&D assets. We recorded a $11.2 million IPR&D impairment charge.

(3) In the first quarter of 2016, two officers of the company resigned and we recorded $2.2 million additional stock-based compensation expense related to acceleration of their stock-based awards due to modification of equity awards.

(4) In connection with the restructuring, the Company recorded estimated restructuring charges of approximately $2.6 million related to one-time termination severance payments and other employee-related benefits, including approximately $1.0 million of stock-based compensation expense related to the acceleration of RSUs in December 2015.

(5) In July 2015, the Company's then Chief Executive officer resigned and some of his stock-based awards were forfeited and cancelled, which that resulted in a $2.4 million of additional stock-based compensation expense recorded in general and administrative expenses in the Company's consolidated financial statements.

Basic and diluted net loss per share is computed independently for each of the quarters presented. Therefore, the sum of quarterly basic and diluted per share amounts may not equal annual basic and diluted net loss per share amounts.

19. Subsequent Event

On February 23, 2017, Regeneron notified us that, pursuant to Section 2.3 of the collaboration agreement, it is extending the research term of the Collaboration Agreement for an additional three years, through May 1, 2020.

EXHIBIT INDEX

EXHIBIT NUMBER	EXHIBIT DESCRIPTION	INCORPORATED BY REFERENCE			PROVIDED HEREWITH
		FORM	DATE	EXHIBIT NUMBER	
2.1	Acquisition Agreement, dated as of January 29, 2016, by and among Avalanche Biotechnologies, Inc., Annapurna Therapeutics SAS, the Contributors identified therein, and Shareholder Representative Services LLC as the Contributors' Representative.	8-K	February 1, 2016	2.1	
2.2	Amendment No. 1 to the Acquisition Agreement, dated as of April 6, 2016	8-K	April 7, 2016	2.1	
3.1	Amended and Restated Certificate of Incorporation.				X
3.2	Amended and Restated Bylaws.	8-K	May 12 2016	3.2	
4.1	Reference is made to Exhibits 3.1 through 3.2.				
4.2	Form of Common Stock Certificate.	S-1/A	July 25, 2014	4.1	
4.3	Amended and Restated Investor Rights Agreement, dated as of May 11, 2016, by and between Avalanche Biotechnologies, Inc. and certain of its stockholders.	8-K	May 12, 2016	4.1	
10.1†	Exclusive License for Use of Recombinant Gene Delivery Vectors for Treating or Preventing Diseases of the Eye, dated as of May 27, 2010, by and between Avalanche Biotechnologies, Inc. and The Regents of the University of California.	S-1/A	July 28, 2014	10.1	
10.2†	Amendment #1 to: Exclusive License for Use of Recombinant Gene Delivery Vectors for Treating or Preventing Diseases of the Eye, effective as of September 17, 2013, by and between Avalanche Biotechnologies, Inc. and The Regents of the University of California.	S-1	June 30, 2014	10.2	
10.3†	Research Collaboration and License Agreement, dated as of May 1, 2014, by and between Avalanche Biotechnologies, Inc. and Regeneron Pharmaceuticals, Inc.	S-1/A	July 28, 2014	10.3	
10.4†	Amended and Restated Master Service Agreement by and between Annapurna Therapeutics SAS and Cornell University, effective July 15, 2014.	10-Q	August 9, 2016	10.3	
10.5†	A1AT Deficiency License Agreement between Annapurna Therapeutics Limited and Cornell University, dated December 15, 2015.	10-Q	August 9, 2016	10.4	
10.6†	HAE License Agreement between Annapurna Therapeutics Limited and Cornell University, dated December 15, 2015.	10-Q	August 9, 2016	10.5	
10.7†	Allergy License Agreement between Annapurna Therapeutics Limited and Cornell University, dated December 15, 2015.	10-Q	August 9, 2016	10.6	
10.8†	License Agreement between Annapurna Therapeutics Limited and REGENXBIO Inc., dated October 20, 2015.	10-Q	August 9, 2016	10.7	
10.9†	License Agreement between AAVLife and REGENXBIO Inc., dated April 10, 2014.	10-Q	August 9, 2016	10.8	

EXHIBIT NUMBER	EXHIBIT DESCRIPTION	INCORPORATED BY REFERENCE			PROVIDED HEREWITH
		FORM	DATE	EXHIBIT NUMBER	
10.10†	License Agreement between AAVLife and Inserm Transfert, dated July 4, 2014.	10-Q	August 9, 2016	10.9	
10.11†	Amendment No. 1 to License Agreement between AAVLife and Inserm Transfert, dated October 5, 2015.	10-Q	August 9, 2016	10.10	
10.12†	Collaboration, Option and License Agreement with Editas Medicine, Inc., dated August 8, 2016.	10-Q	November 8, 2016	10.1	
10.13(#)	Avalanche Biotechnologies, Inc. Amended and Restated 2006 Equity Incentive Plan.	S-1	June 30, 2014	10.4	
10.14(#)	Form of Stock Option Grant Notice and Stock Option Agreement under the Amended and Restated 2006 Equity Incentive Plan.	S-1/A	July 25, 2014	10.16	
10.15(#)	Avalanche Biotechnologies, Inc. 2014 Equity Incentive Award Plan.	S-1/A	July 25, 2014	10.5	
10.16(#)	Form of Stock Option Grant Notice and Stock Option Agreement under the 2014 Equity Incentive Award Plan.	S-1/A	July 25, 2014	10.17	
10.17(#)	Form of Restricted Stock Award Grant Notice and Restricted Stock Award Agreement under the 2014 Equity Incentive Award Plan.	S-1/A	July 25, 2014	10.18	
10.18(#)	Form of Restricted Stock Unit Award Grant Notice and Restricted Stock Unit Award Agreement under the 2014 Equity Incentive Award Plan.	S-1/A	July 25, 2014	10.19	
10.19(#)	Avalanche Biotechnologies, Inc. 2014 Employee Stock Purchase Plan.	S-1/A	July 25, 2014	10.6	
10.20(#)	Letter Agreement, dated as of July 15, 2012, by and between Avalanche Biotechnologies, Inc. and Hans P. Hull.	S-1	June 30, 2014	10.9	
10.21(#)	Letter Agreement, dated as of June 3, 2013, by and between Avalanche Biotechnologies, Inc. and Mehdi Gasmi.	S-1	June 30, 2014	10.10	
10.22(#)	Letter Agreement, dated as of June 13, 2014, by and between Avalanche Biotechnologies, Inc. and Samuel Barone.	S-1	December 18, 2014	10.15	
10.23(#)	Letter Agreement, dated as of August 28, 2014, by and between Avalanche Biotechnologies, Inc. and Roman Rubio.	S-1	December 18, 2014	10.16	
10.24(#)	Separation Agreement and General Release, dated July 23, 2015, by and between Avalanche Biotechnologies, Inc. and Thomas W. Chalberg, Jr., Ph.D.	8-K	July 23, 2015	10.1	
10.25(#)	Special Bonus Letter, dated July 23, 2015, for Hans P. Hull.	8-K	July 23, 2015	10.2	
10.26(#)	Special Bonus Letter, dated July 23, 2015, for Mehdi Gasmi, Ph.D.	8-K	July 23, 2015	10.3	
10.27(#)	Form of Amendment to the Change in Control and Severance Agreement for Hans P. Hull.	10-Q	August 13, 2015	10.2	

EXHIBIT NUMBER	EXHIBIT DESCRIPTION	INCORPORATED BY REFERENCE			PROVIDED HEREWITH
		FORM	DATE	EXHIBIT NUMBER	
10.28(#)	Letter Agreement, dated as of August 11, 2015, by and between Avalanche Biotechnologies, Inc. and Hans P. Hull.	10-Q	August 13, 2015	10.3	
10.29(#)	Letter Agreement, dated as of August 11, 2015, by and between Avalanche Biotechnologies, Inc. and Mehdi Gasmi, Ph.D.	10-Q	August 13, 2015	10.5	
10.30(#)	Offer Letter, dated November 19, 2015, by and between Avalanche Biotechnologies, Inc. and Paul Cleveland.	8-K	November 20, 2015	10.1	
10.31(#)	Change in Control and Severance Agreement, dated November 19, 2015, by and between Avalanche Biotechnologies, Inc. and Paul Cleveland.	8-K	November 20, 2015	10.2	
10.32(#)	Offer Letter, dated January 29, 2016, by and between Avalanche Biotechnologies, Inc. and Amber Salzman.	8-K	February 1, 2016	10.2	
10.33(#)	Change in Control and Severance Agreement, dated January 29, 2016, by and between Amber Salzman and Avalanche Biotechnologies, Inc.	8-K	February 1, 2016	10.3	
10.34(#)	Offer Letter, dated January 29, 2016, by and between Avalanche Biotechnologies, Inc. and Carlo Russo.	8-K	May 12, 2016	10.1	
10.35(#)	Change in Control and Severance Agreement, dated January 29, 2016, by and between Carlo Russo and Avalanche Biotechnologies, Inc.	8-K	May 12, 2016	10.2	
10.36(#)	Form of Inducement Stock Option Agreement for Drs. Salzman and Russo	8-K	May 12, 2016	10.3	
10.37(#)	Offer Letter, dated June 10, 2016, by and between Adverum Biotechnologies, Inc. and Leone Patterson	8-K	June 13, 2016	10.1	
10.38(#)	Change in Control and Severance Agreement, dated June 10, 2016, by and between Adverum Biotechnologies, Inc. and Leone Patterson.	8-K	June 13, 2016	10.2	
10.39(#)	Amendment to Offer Letter, dated November 2, 2016, by and between Adverum Biotechnologies, Inc. and Amber Salzman.				X
10.40(#)	Amendment to Offer Letter, dated November 2, 2016, by and between Adverum Biotechnologies, Inc. and Paul Cleveland.				X
10.41	Lease Agreement, dated as of December 20, 2013, by and between Avalanche Biotechnologies, Inc. and O'Brien Drive Portfolio, LLC.	S-1	June 30, 2014	10.11	
10.42	First Amendment to Lease, dated August 1, 2014, by and between O'Brien Drive Portfolio, LLC and Avalanche Biotechnologies, Inc.	8-K	September 12, 2014	10.1	
10.43	Second Amendment to Lease, dated October 30, 2014, by and between O'Brien Drive Portfolio, LLC and Avalanche Biotechnologies, Inc.	8-K	November 4, 2014	10.1	
10.44(#)	Form of Indemnification Agreement for directors and executive officers.	S-1/A	July 18, 2014	10.12	
10.45(#)	2012 Change in Control Benefit Plan.	S-1/A	July 18, 2014	10.13	

EXHIBIT NUMBER	EXHIBIT DESCRIPTION	INCORPORATED BY REFERENCE			PROVIDED HEREWITH
		FORM	DATE	EXHIBIT NUMBER	
10.46(#)	Form of Change in Control Severance Agreement.	S-1/A	July 25, 2014	10.14	
10.47(#)	Form of Chief Executive Officer Change in Control Severance Agreement.	S-1/A	July 25, 2014	10.15	
10.48(#)	Form of Amendment to the Change in Control and Severance Agreement.	10-Q	August 13, 2015	10.1	
10.49(#)	Form of Inducement Stock Option Agreement.	8-K	November 20, 2015	10.3	
10.50	Form of Support and Voting Agreement.	8-K	February 1, 2016	10.1	
10.51	Separation Agreement and General Release, dated February 12, 2016, by and between Avalanche Biotechnologies, Inc. and Hans P. Hull	10-K	March 4, 2016		
10.52	Consulting Agreement, dated February 12, 2016, by and between Avalanche Biotechnologies, Inc. and Hans. P. Hull	10-K	March 4, 2016		
21.1	List of Subsidiaries.				X
23.1	Consent of Independent Registered Public Accounting Firm.				X
24.1	Power of Attorney (included on signature page hereto)				X
31.1	Certification of Principal Executive Officer, as required by Rule 13a-14(a) or Rule 15d-14(a).				X
31.2	Certification of Chief Financial Officer, as required by Rule 13a-14(a) or Rule 15d-14(a).				X
32.1*	Certification by the Principal Executive Officer and Chief Financial Officer, as required by Rule 13a-14(b) or Rule 15d-14(b) and Section 1350 of Chapter 36 of Title 18 of the United States Code (18 U.S.C. §1350).				X
101.INS	XBRL Instance Document.				X
101.SCH	XBRL Taxonomy Extension Schema Document.				X
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document.				X
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document.				X
101.LAB	XBRL Taxonomy Extension Label Linkbase Document.				X
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document.				X

† Portions of this exhibit (indicated by asterisks) have been omitted pursuant to a request for confidential treatment and this exhibit has been filed separately with the SEC.

# Indicates management contract or compensatory plan.

* The certification attached as Exhibit 32.1 that accompanies this Annual Report on Form 10-K is not deemed filed with the SEC and is not to be incorporated by reference into any filing of Adverum Biotechnologies, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date of this Form 10-K, irrespective of any general incorporation language contained in such filing.

Exhibit 3.1

AMENDED AND RESTATED

CERTIFICATE OF INCORPORATION

OF

ADVERUM BIOTECHNOLOGIES, INC.

ARTICLE I

The name of the corporation is Adverum Biotechnologies, Inc. (the "Corporation").

ARTICLE II

The address of the Corporation's registered office in the State of Delaware is 2711 Centerville Road, Suite 400, City of Wilmington, County of New Castle. The name of its registered agent at such address is Corporation Service Company.

ARTICLE III

The purpose of the Corporation is to engage in any lawful act or activity for which a corporation may be organized under the Delaware General Corporation Law.

ARTICLE IV

A. This Corporation is authorized to issue two classes of stock to be designated, respectively, "Common Stock" and "Preferred Stock." The total number of shares that the Corporation is authorized to issue is Three Hundred Five Million (305,000,000), divided into Three Hundred Million (300,000,000) shares of Common Stock and Five Million (5,000,000) shares of Preferred Stock. The Common Stock shall have a par value of $0.0001 per share and the Preferred Stock shall have a par value of $0.0001 per share.

B. The Preferred Stock may be issued from time to time in one or more series. The Board of Directors of the Corporation (the "Board of Directors") is hereby authorized, by filing a certificate (a "Certificate of Designation") pursuant to the Delaware General Corporation Law, to fix or alter from time to time the designation, powers, preferences and rights of the shares of each such series and the qualifications, limitations or restrictions of any wholly unissued series of Preferred Stock, and to establish from time to time the number of shares constituting any such series or any of them; and to increase or decrease the number of shares of any series subsequent to the issuance of shares of that series, but not below the number of shares of such series then outstanding. In case the number of shares of any series shall be decreased in accordance with the foregoing sentence, the shares constituting such decrease shall resume the status that they had prior to the adoption of the resolution originally fixing the number of shares of such series.

ARTICLE V

For the management of the business and for the conduct of the affairs of the Corporation, and in further definition, limitation and regulation of the powers of the Corporation, of its directors and of its stockholders or any class thereof, as the case may be, it is further provided that:

A. (1) The management of the business and the conduct of the affairs of the Corporation shall be vested in the Board of Directors. The number of directors which shall constitute the whole Board of Directors shall be fixed exclusively by one or more resolutions adopted from time to time by the Board of Directors.

(2) The directors shall be divided into three classes, designated as Class I, Class II and Class III, as nearly equal in number as possible. Directors shall be assigned to each class in accordance with a resolution or resolutions adopted by the Board of Directors. At the first annual meeting of stockholders following the effectiveness of this Amended and Restated Certificate of Incorporation (the "Qualifying Record Date"), the term of office of the Class I directors shall expire and Class I directors shall be elected for a full term of three years. At the second annual meeting of stockholders following the Qualifying Record Date, the term of office of the Class II directors shall expire and Class II directors shall be elected for a full term of three years. At the third annual meeting of stockholders following the Qualifying Record Date, the term of office of the Class III directors shall expire and Class III directors shall be elected for a full term of three years. At each succeeding annual meeting of stockholders, directors shall be elected for a full term of three years to succeed the directors of the class whose terms expire at such annual meeting.

Notwithstanding the foregoing provisions of this Article V(A), each director shall serve until his or her successor is duly elected and qualified or until his or her death, resignation or removal. No decrease in the number of directors constituting the Board of Directors shall shorten the term of any incumbent director.

(3) The Board of Directors or any individual director may be removed from office at any time (i) with cause by the affirmative vote of the holders of a majority of the voting power of all the then outstanding shares of voting stock of the Corporation entitled to vote at an election of directors (the "Voting Stock") or (ii) without cause by the affirmative vote of the holders of at least sixty-six and two-thirds percent (66-2/3%) of the voting power of all of the then-outstanding shares of Voting Stock.

(4) Any vacancies on the Board of Directors resulting from death, resignation, disqualification, removal or other causes and any newly created directorships resulting from any increase in the number of directors shall, unless the Board of Directors determines by resolution that any such vacancies or newly created directorships shall be filled by the stockholders, except as otherwise provided by law, be filled only by the affirmative vote of a majority of the directors then in office, even though less than a quorum of the Board of Directors, and not by the stockholders. Any director elected in accordance with the preceding sentence shall hold office for the remainder of the full term of the director for which the vacancy was created or occurred and until such director's successor shall have been elected and qualified.

B. (1) Subject to Article X of the Bylaws, in furtherance and not in limitation of the powers conferred by statute, the Board of Directors is expressly authorized to make, alter or repeal Bylaws of the Corporation. Notwithstanding the foregoing, the Bylaws of the Corporation may be rescinded, altered, amended or repealed in any respect by the affirmative vote of the holders of at least sixty-six and two-thirds percent (66-2/3%) of the voting power of all the then-outstanding shares of the Voting Stock.

(2) The directors of the Corporation need not be elected by written ballot unless the Bylaws so provide.

ARTICLE VI

A. Subject to the rights of the holders of any series of Preferred Stock or any other class of stock or series thereof having a preference over the Common Stock as to dividends or upon liquidation, any action required or permitted to be taken by the stockholders of the Corporation must be effected at a duly called annual or special meeting of the stockholders of the Corporation, and the taking of any action by written consent of the stockholders in lieu of a meeting of the stockholders is specifically denied.

B. Special meetings of the stockholders of the Corporation may be called, for any purpose or purposes, by the Secretary of the Corporation at the direction of the Board of Directors, pursuant to a resolution adopted by a majority of the entire Board of Directors, but such special meetings may not be called by any other person or persons.

C. Advance notice of stockholder nominations for the election of directors and of business to be brought by stockholders before any meeting of the stockholders of the Corporation shall be given in the manner provided in the Bylaws of the Corporation.

ARTICLE VII

A. To the maximum extent permitted by the Delaware General Corporation Law, as the same exists or as may hereafter be amended, a director of the Corporation shall not be personally liable to the Corporation or its stockholders for monetary damages for breach of fiduciary duty as a director. If the Delaware General Corporation Law is amended after approval by the stockholders of this Article VII to authorize corporate action further eliminating or limiting the personal liability of directors, then the liability of a director of the Corporation shall be eliminated or limited to the fullest extent permitted by the Delaware General Corporation Law as so amended.

B. The Corporation may indemnify to the fullest extent permitted by law any person made or threatened to be made a party to an action or proceeding, whether criminal, civil, administrative or investigative, by reason of the fact that he or she, or his or her testator or intestate is or was a director, officer, employee or agent of the Corporation or any predecessor of the Corporation, or serves or served at any other enterprise as a director, officer, employee or agent at the request of the Corporation or any predecessor to the Corporation.

C. Neither any amendment nor repeal of this Article VII, nor the adoption of any provision of the Corporation's certificate of incorporation inconsistent with this Article VII, shall eliminate or reduce the effect of this Article VII in respect of any matter occurring, or any action or proceeding accruing or arising or that, but for this Article VII, would accrue or arise, prior to such amendment, repeal or adoption of an inconsistent provision.

ARTICLE VIII

Unless the Corporation consents in writing to the selection of an alternative forum, the sole and exclusive forum for (i) any derivative action or proceeding brought on behalf of the Corporation, (ii) any action asserting a claim of breach of a fiduciary duty owed by any director, officer or other employee of the Corporation to the Corporation or the Corporation's stockholders, (iii) any action asserting a claim arising pursuant to any provision of the Delaware General Corporation Law, or (iv) any action asserting a claim governed by the internal affairs doctrine shall be the Court of Chancery of the State of Delaware, in all cases subject to the court's having personal jurisdiction over the indispensable parties named as defendants.

ARTICLE IX

Notwithstanding any other provisions of this Amended and Restated Certificate of Incorporation or any provision of law which might otherwise permit a lesser vote or no vote, but in addition to any affirmative vote of the holders of any particular class or series of the Voting Stock required by law, this Amended and Restated Certificate of Incorporation or any Certificate of Designation, the affirmative vote of the holders of at least sixty-six and two-thirds percent (66-2/3%) of the voting power of all of the then-outstanding shares of the Voting Stock, voting together as a single class, shall be required to alter, amend or repeal Articles V, VI, VII, VIII and IX.

34101462.1

Exhibit 10.39

Adverum Biotechnologies, Inc.
1035 O'Brien Drive,
Menlo Park, CA 94025
O: 650.272.6269

Amendment to January 29, 2016 Employment Offer Letter Agreement

This Amendment to Employment Agreement ("Amendment") is between Amber Salzman, Ph.D. and Adverum Biotechnologies, Inc. (formerly Avalanche Biotechnologies, Inc.) (the "Company," and together with Dr. Salzman, the "Parties"). Dr. Salzman will be assuming the position of Chief Executive Officer of the Company, and this Amendment sets forth the new terms of employment agreed upon by the Parties with respect to Dr. Salzman's new position. The Parties intend this Amendment to amend and, to the extent it is inconsistent with, supersede Dr. Salzman's prior Employment Offer Letter Agreement ("Employment Agreement"), dated January 29, 2016. To the extent it is not superseded, the Employment Agreement, including the attachments and agreements referenced in it, will remain in full force and effect.

Therefore, the Parties agree that effective October 14, 2016 (the "Effective Date"), the Employment Agreement is amended as follows:

I. Position and Responsibilities.

In the position of Chief Executive Officer and President, Dr. Salzman will serve in an executive capacity and will be required to perform the duties of Chief Executive Officer and President as commonly associated with this position, and other duties commensurate with such position as may be assigned to her by the Company's Board of Directors (the "Board") from time to time. Dr. Salzman will report directly to Executive Chairman of the Board, and will work primarily at the Company's offices located in Menlo Park, California. Dr. Salzman shall abide by the rules, regulations, and practices as adopted or modified from time to time in the Company's sole discretion.

II. Target Bonus.

A. Target Bonus (2017 and after). For each calendar year starting 2017, Dr. Salzman will be eligible to earn an annual performance bonus with a target bonus amount equal to fifty percent (50%) of her base salary during the bonus year, provided that she is actively employed through and including the date the bonus is paid. Dr. Salzman's annual bonus will be calculated based on attainment of individual goals (including corporate and personal objectives) to be determined by the Board each year. Bonus payments will be in the form of cash and will be granted entirely at the discretion of the Board. Any cash bonus payments will be less payroll deductions and all required withholdings.

B. Target Bonus (for 2016). For the calendar year 2016, Dr. Salzman will be eligible to earn a prorated annual performance bonus, with a target bonus amount equal to fifty percent (50%) of her base salary earned between May 11, 2016 (the closing date of the acquisition by the Company of all outstanding shares of Annapurna Therapeutics SAS) and the end of the calendar year 2016, provided that she is actively employed through and including the date the bonus is paid. As set forth in the Employment Agreement, Dr. Salzman's annual bonus will be calculated based on attainment of individual goals (including corporate and personal objectives) to be determined by the Board. Bonus payments will be in the form of cash and will be granted entirely at the discretion of the Board. Any cash bonus payments will be less payroll deductions and all required withholdings.

III. Entire Agreement

This Amendment, together with the Employment Agreement and any provisions specifically incorporated by reference in the Employment Agreement, is intended to be the final, complete, and exclusive statement of the terms of Dr. Salzman's employment by the Company and may not be contradicted by evidence of any prior or contemporaneous statements or agreements, except as specifically provided herein. To the extent that the practices, policies or procedures of the Company, now or in the future, apply to Dr. Salzman and are inconsistent with the terms the Employment Agreement (as amended by this Amendment), the provisions of the Employment Agreement (as amended) shall control. Any subsequent change in Dr. Salzman's duties, position, or compensation will not affect the validity or scope of the Employment Agreement (as amended).

Adverum Biotechnologies, Inc.
1035 O'Brien Drive,
Menlo Park, CA 94025
O: 650.272.6269

IV. Employee Acknowledgement

By her signature below, Dr. Salzman acknowledges that she has read this Amendment and fully understands its terms and legal effect. Dr. Salzman further acknowledges that she has had an opportunity to consult with her own legal counsel before signing this Amendment. She also acknowledges that the benefits provided under this Amendment exceed those provided under the Employment Agreement. Finally, Dr. Salzman acknowledges that she has entered into this Amendment freely based on her own judgment and not on any representations or promises other than those contained in this Amendment.

So Agreed:

/s/ Paul Cleveland
Adverum Biotechnologies, Inc.

Name: Paul Cleveland

Title: Executive Chairman of the Board of Directors

Date: November 2, 2016

/s/ Amber Salzman
Amber Salzman, Ph.D.

Date: November 2, 2016

Exhibit 10.40

Addendum to November 19, 2015 Offer Letter- Paul Cleveland

Effective as of October 14, 2016 (the "Effective Date"), Paul Cleveland and Adverum Biotechnologies, Inc. (formerly Avalanche Biotechnologies, Inc.) (the "Company") hereby amend the November 19, 2015 offer letter ("Offer Letter") between them as follows:

Rather than acting as Chief Executive Officer of the Company, as of the Effective Date, Mr. Cleveland will act as the Company's Executive Chair, with the following responsibilities: (a) Executive Chairman of the Board of Directors ("Board")- Mr. Cleveland will chair the meetings of the Board and of the Company's Executive Committee; and (b) with respect to the Executive Committee established by the Company on October 10, 2016 (the "Executive Committee")- Mr. Cleveland will share responsibility with the CEO of the Company for the following: (1) Development of the Company's overall strategy; (2) Communication of the Company's overall strategy to investors, analysts and others; (3) Recruiting executive officers (as needed);and (4) Cultivating relationships with key opinion leaders and serving as an outward-facing representative of the Company to the medical, scientific and financial community.

The Executive Chair role will continue until (A) the earlier of (1) Mr. Cleveland's resignation or termination and (2) the Company's next annual shareholders meeting, expected to take place in May, 2017 or (B) such later time as Mr. Cleveland and the Company mutually agree in writing (with (A) or (B), as applicable, the "Employment Period"). During the Employment Period, Mr. Cleveland will devote such time to his Executive Chair duties as he deems appropriate, based on a schedule that will be determined by him. During the Employment Period, Mr. Cleveland's annual base salary will be $324,000, less applicable deductions and withholdings. In addition, it is agreed that Mr. Cleveland will receive a 2016 bonus in the amount of $297,000, less applicable deductions and withholdings, to be paid at the same time as 2016 bonuses are paid to other Company executives, and will receive a 2017 bonus equal to $178,200 multiplied by the number of days Mr. Cleveland is employed in 2017 divided by 365, less applicable deductions and withholdings, to be paid in the next payroll period after the Employment Period. Mr. Cleveland will be entitled to continue his Company health benefits throughout the Employment Period and his December 9, 2015 stock option (910,000 shares) and May 11, 2016 stock option (381,000 shares) (collectively, the "Options") will continue to vest during the Employment Period as well as the further period, if any, in which Mr. Cleveland remains on the Board. Further, the deadline for Mr. Cleveland to exercise the vested but unexercised shares of his Options will be the earlier of (a) 3 years after the later of the Employment Period or his Board service; and (b) the expiration date for the Options, as provided in his stock option agreements.

In connection with Mr. Cleveland's employment as CEO, the Company and Mr. Cleveland entered into a November 19, 2015 Change in Control and Severance Agreement as Exhibit B to his Offer Letter (the "CIC Agreement"). As part of this Addendum, it is agreed that, if (1) Mr. Cleveland's employment as Executive Chair continues through the date of the Company's next annual shareholders meeting or (2) such earlier date as the Board or Executive Committee agree that he has satisfactorily completed his duties as Executive Chairman of the Board, then, in the event of (1) or (2) (as applicable, the "Severance Date"), Mr. Cleveland will receive the following severance benefits (the "Severance"): (x) a lump sum payment of $540,000, less applicable deductions and withholdings; and (y) if Mr. Cleveland elects COBRA coverage, payment by the Company of his COBRA premiums for the twelve (12) month period after the Employment Period ends, subject to applicable deductions and withholdings; *provided, however,* that as a pre-condition of receiving the Severance, Mr. Cleveland will be required to timely sign, date and return to the Company (or its successor), and to not subsequently revoke, a general release of all claims against the Company and its affiliates that becomes effective and irrevocable within sixty (60) days after the end of the Employment Period, with the cash portion of the Severance to be paid within three (3) business days after the effective date of the release.

Notwithstanding anything to the contrary herein, to the extent required by Section 409A of the Internal Revenue Code ("Section 409A"), a Severance Date shall not be deemed to have occurred for purposes of any provision of this Addendum providing for the payment of amounts or benefits upon or following a termination of employment unless such termination is also a "separation from service" within the meaning of Section 409A and the regulations thereunder.

Additionally, notwithstanding any provision to the contrary in this Addendum, if Mr. Cleveland is deemed at the time of his separation from service to be a "specified employee" for purposes of Section 409A(a)(2)(B)(i) of the Internal Revenue Code (the "Code"), to the extent delayed commencement of any portion of the benefits to which Mr. Cleveland is entitled under this Addendum is required in order to avoid a prohibited distribution under Section 409A(a)(2)(B)(i) of the Code, such portion of Mr. Cleveland's benefits shall not be provided to him prior to the earlier of (a) the expiration of the six (6) month period measured from the date of his separation from service or (b) the date of his death.

So Agreed:

/s/ Amber Salzman
Adverum Biotechnologies, Inc.

Name: Amber Salzman

Title: President and CEO

Date: November 2, 2016

/s/ Paul Cleveland
Paul Cleveland

Date: November 2, 2016

Exhibit 21.1

SUBSIDIARIES OF ADVERUM BIOTECHNOLOGIES, INC.

Name of Subsidiary	Country of Incorporation
Avalanche Australia PTY LTD	Australia
Annapurna Therapeutics, SAS	France
Annapurna, Inc.	Pennsylvania, USA
Annapurna Therapeutics, LTD	Ireland

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in Registration Statements No. 333-199296, No. 333-203398, and No. 333-211439 on Form S-8 of our report dated March 8, 2017, relating to the consolidated financial statements of Adverum Biotechnologies, Inc. and its subsidiaries appearing in this Annual Report on Form 10-K of Adverum Biotechnologies, Inc. for the year ended December 31, 2016.

/s/ DELOITTE & TOUCHE LLP

San Jose, California
March 8, 2017

EXHIBIT 31.1

CERTIFICATION OF THE PRINCIPAL EXECUTIVE OFFICER
PURSUANT TO SECTION 302 OF
THE SARBANES-OXLEY ACT OF 2002

I, Paul B. Cleveland, certify that:

1. I have reviewed this Annual Report on Form 10-K of Adverum Biotechnologies, Inc.;

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

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

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

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

   b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

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

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

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

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

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

Date: March 8, 2017

By: /s/ Paul B. Cleveland
Name: Paul B. Cleveland
Title: *Executive Chairman of the Board and Principal Executive Officer*

EXHIBIT 31.2

CERTIFICATION OF THE CHIEF FINANCIAL OFFICER
PURSUANT TO SECTION 302 OF
THE SARBANES-OXLEY ACT OF 2002

I, Leone Patterson, certify that:

1. I have reviewed this Annual Report on Form 10-K of Adverum Biotechnologies, Inc.;

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

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

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

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

   b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

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

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

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

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

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

Date: March 8, 2017

By: /s/ Leone Patterson
Name: Leone Patterson
Title: Chief Financial Officer
(Principal Financial and Accounting Officer)

EXHIBIT 32.1

CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER AND CHIEF FINANCIAL OFFICER
PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Adverum Biotechnologies, Inc. for the year ended December 31, 2016 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Paul B. Cleveland, as Principal Executive Officer of Adverum Biotechnologies, Inc., hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to the best of his knowledge, the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of Adverum Biotechnologies, Inc.

Date: March 8, 2017

By: /s/ Paul B. Cleveland
Paul B. Cleveland
Executive Chairman of the Board and Principal Executive Officer

In connection with the Annual Report on Form 10-K of Adverum Biotechnologies, Inc. for the year ended December 31, 2016 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Leone Patterson, as Chief Financial Officer of Adverum Biotechnologies, Inc., hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to the best of her knowledge, the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of Adverum Biotechnologies, Inc.

Date: March 8, 2017

By: /s/ Leone Patterson
Leone Patterson
Chief Financial Officer
(Principal Financial and Accounting Officer)