# 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, 2019**

**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.)** |

**800 Saginaw Drive**
**Redwood City, California 94063**
**(650) 656-9323**
**(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 | Trading Symbol | Name of Each Exchange on Which Registered |
|---|---|---|
| **Common Stock, par value $0.0001 per share** | **ADVM** | **Nasdaq Global Market** |

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

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

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

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

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

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

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

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

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

As of June 30, 2019, 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 $674.5 million, based on the closing price of the registrant's common stock on the Nasdaq Global Market on June 28, 2019 of $11.89 per share. Shares of the registrant's common stock held by each officer and director and each person known to the registrant to be affiliated with an officer or director 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, 2020, the registrant had 79,681,257 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 2020 Annual Meeting of Stockholders of the registrant are incorporated by reference into Part III of this Annual Report on Form 10-K. If the Proxy Statement is not filed by April 29, 2020, then the registrant will file an amendment to this Form 10-K on Form 10-K/A to include the Part III information in this Form 10-K.

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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.

Adverum, the Adverum logo and other trademarks or service marks of Adverum that may appear in this Annual Report on Form 10-K are the property of Adverum. This Annual Report on Form 10-K contains additional trade names, trademarks, and service marks of other companies.

Adverum does not intend its use or display of other companies' trade names, trademarks, or service marks to imply a relationship with, or endorsement or sponsorship of Adverum by, these other companies, and all such third-party trade names, trademarks, and service marks are the property of their respective owners.

## 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, designations and approvals;
- our plans to explore potential applications of our gene therapy platform in other indications in ocular 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 estimates regarding expenses, future revenue, our financial position, capital requirements, uses of cash and needs for additional financing and the period for which our cash resources will be sufficient to meet our operating requirements; 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 the heading “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. Moreover, we operate in a very competitive and rapidly changing environment. New risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this Annual Report on Form 10-K may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements. 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**

Adverum is a clinical-stage gene therapy company targeting unmet medical needs in ocular and rare diseases. We develop gene therapy product candidates designed to provide durable efficacy by inducing sustained expression of a therapeutic protein. Our core capabilities include novel vector discovery, preclinical and clinical development, and in-house manufacturing expertise, specifically in scalable process development, assay development, and current Good Manufacturing Practices ("cGMP") quality control.

Our lead product candidate ADVM-022 is a single intravitreal ("IVT") injection gene therapy targeting the treatment of wet age-related macular degeneration ("wet AMD") and diabetic retinopathy. ADVM-022 utilizes a proprietary vector capsid, AAV.7m8, carrying an aflibercept coding sequence under the control of a proprietary expression cassette. ADVM-022 is administered as a one-time IVT injection and is designed to deliver long-term efficacy and reduce the burden of frequent anti-vascular endothelial growth factor ("anti-VEGF") injections, optimize patient compliance, and improve vision outcomes for patients with wet AMD or diabetic retinopathy.

Wet AMD is a leading cause of vision loss in patients over 60 years of age, with a prevalence of approximately 1.2 million individuals in the U.S. and 3 million worldwide. In recognition of the need for new treatment options for wet AMD, the U.S. Food and Drug Administration ("FDA") granted Fast Track designation for ADVM-022 for the treatment of wet AMD. Diabetic retinopathy is the leading cause of vision impairment and blindness among working-age adults, with a prevalence of 8 million individuals in the U.S. and is growing with the prevalence of diabetes.

We are conducting the OPTIC trial, designed as a multi-center, open-label, Phase 1, dose-ranging safety trial of ADVM-022 in patients with wet AMD who have demonstrated responsiveness to anti-VEGF treatment. Patients in OPTIC are treatment-experienced, and previously required frequent anti-VEGF injections to control their wet AMD and to maintain functional vision.

Patients in cohort 1 (n=6) were treated with a higher dose of ADVM-022 (6 x 10^11 vg/eye). Patients in cohort 2 (n=6) were treated with a three-fold lower dose of ADVM-022 (2 x 10^11 vg/eye). In the first quarter of 2020, we completed patient dosing in cohort 3 (n=9, lower dose of 2 x 10^11 vg/eye) and began screening for cohort 4 (n=9, higher dose of 6 x 10^11 vg/eye). As we advance the OPTIC trial, we plan to present additional clinical data in the second quarter of 2020, and also longer-term data from cohorts 1-4 in the second half of 2020.

For diabetic retinopathy, we intend to file an investigational new drug ("IND") application in the first half of 2020. We plan to begin enrolling patients in a Phase 1/2 clinical trial in the second half of 2020 to expand our clinical development pipeline. In our preclinical pipeline, we are developing an investigational gene therapy candidate for the treatment of hereditary angioedema.

We have licensed the right to use AAV.7m8 to GenSight Biologics S.A. ("GenSight") to deliver certain therapeutic transgenes, including channelrhodopsin protein, which GenSight is using in their product candidate GS030 for retinitis pigmentosa, currently in clinical development.

In January 2020, we moved into our new facility in Redwood City, California. This new 81,000 square foot facility serves as our corporate headquarters and will include expanded laboratory space as well as space for expanded manufacturing process capabilities.

**Our Strengths**

We believe we have the capabilities, resources, and expertise to enable Adverum to become a leading gene therapy company. These strengths include:

- industry-leading development capabilities in adeno-associated virus ("AAV") technology;
- a pipeline of gene therapy product candidates targeting the treatment of ocular and rare diseases;
- in-house manufacturing expertise, specifically in scalable process development, assay development, and cGMP quality control;
- a growing portfolio of proprietary vectors;
- a robust patent portfolio; and
- an experienced leadership team with expertise in ophthalmology and drug development.

**Our Strategy**

Our goal is to discover, develop, and commercialize novel gene therapies with the potential to treat patients living with ocular and rare diseases. The key elements of our strategy to achieve this goal are to:

- **Target large patient populations impacted by wet AMD, diabetic retinopathy, and other chronic retinal conditions that respond to anti-VEGF therapy.** There are an estimated 1.2 million individuals in the U.S. and 3 million worldwide living with wet AMD, and the incidence of new cases is expected to continue to grow significantly as the population ages. There are an estimated 8 million individuals in the U.S. living with diabetic retinopathy and the incidence is expected to continue to grow significantly with the prevalence of diabetes. We estimate that the standard-of-care anti-VEGF therapies used to treat wet AMD and diabetic retinopathy generated in excess of $11 billion worldwide in sales in 2019.
- **Develop a one-time gene therapy treatment to relieve the burden of frequent, chronic treatment.** Our gene therapies are designed as single-administration treatments to address the unmet needs of patients with ocular and rare diseases. The current standard of care for wet AMD, diabetic retinopathy, and other chronic diseases requires frequent injections for the duration of the disease. As an example, for wet AMD, the current standard-of-care treatments require patients to receive IVT injections of anti-VEGF protein every 4-12 weeks. Similar regimens have been approved for diabetic retinopathy. Compliance with these regimens can be difficult for patients, caregivers, and healthcare systems, leading to undertreatment and resulting in loss of vision. A gene therapy administered as a single IVT injection has the potential to deliver long-term efficacy and reduce the burden of frequent anti-VEGF injections, optimize patient compliance and improve vision outcomes for patients.
- **Pursue indications with well-defined clinical and regulatory paths where possible, to mitigate the development risk.** We have selected indications that have prior clinical validation, including established endpoints, standard-of-care administration methods, and defined regulatory paths. For example, for wet AMD, aflibercept is an approved standard-of-care treatment, and ADVM-022 utilizes our proprietary vector AAV.7m8 designed to provide the same anti-VEGF protein through a single IVT injection.
- **Advance our earlier-stage research initiatives and leverage our industry-leading capabilities in novel vector development.** We leverage our next-generation AAV-based directed evolution platform to engineer AAV capsids with enhanced tropism for certain tissues and/or improved antibody neutralization profiles over existing AAV variants. Combining our vectorology and manufacturing expertise, we have the capability to generate high-quantity recombinant AAV capsid libraries that can be screened in large animals, rather than rodents, to maximize applicability of the screens to human subjects. We are also focused on discovering improved ubiquitous and cell-specific promoters and expression cassettes to offer optimal transgene expression target tissues. We plan to use this expertise to expand our pipeline and manage the life cycle of our novel gene therapies.
- **Collaborate with partners to leverage our industry-leading AAV vector expertise and ocular vector development and product delivery capabilities.** We explore opportunities to work collaboratively with potential new partners that may benefit from our capabilities and expertise in AAV vector development and product delivery.
- **Expand our process development capabilities to support late-stage clinical trials and commercialization.** Our new facility will allow us to expand our in-house process development capabilities. Our manufacturing process is based on the Baculovirus/Sf9 production system, which has been used for a number of vaccines and recombinant protein therapies approved by the FDA and European Medical Agency (“EMA”), and is capable of producing large quantities of AAVs. Our strategy is to develop scalable processes to transfer to our cGMP contract manufacturers, commensurate with our stage of development. Our new facility will allow us to expand our in-house process development capabilities to the 1,000-liter production scale to support larger, late-stage clinical trials and commercialization.

**Gene Therapy Background**

Gene therapy is a powerful treatment modality to address disease biology in a targeted and efficient way. With gene therapy, patients receive vectors encoding therapeutic genes, expressing a therapeutic protein or the functional version of a mutated protein. Instead of dosing patients with proteins or other therapies repeatedly 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 are transduced with a gene, the cells are potentially able to continue to produce the therapeutic protein for years.

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:

- **Substantial clinical data.** Positive data from gene therapy clinical trials have been reported in a variety of indications, including hemophilia, Spinal Muscular Atrophy, X-linked myotubular myopathy, Sanfilippo syndrome, ornithine

transcarbamylase deficiency, glycogen storage disease type 1a, and Duchenne muscular dystrophy, as well as several ocular diseases including biallelic RPE65 mutation-associated retinal dystrophy, choroideremia, and X-linked retinitis pigmentosa.

- **Significant investment by biopharmaceutical companies.** The modality of gene therapy has received significant interest and investments by biopharmaceutical companies. Large, global biopharmaceutical companies, such as Astellas Pharma Inc., BioMarin Pharmaceuticals Inc., Biogen Idec Inc., Bristol-Myers Squib, GlaxoSmithKline plc, Hoffmann-La Roche Ltd., Novartis, Regeneron, Sanofi, and Takeda Pharmaceuticals Company Ltd., have increased their investment in the gene therapy field. Additionally, pure-play gene therapy companies, such as Applied Genetic Technologies Corporation, REGENXBIO Inc., Ultragenyx Pharmaceutical Inc., uniQure N.V., Abeona Therapeutics, Sarepta Therapeutics, Solid Biosciences, and Voyager Therapeutics, have attracted recent investment in this growing field.
- **Approval of cell and gene therapy products by regulatory authorities.** The FDA and EMA have approved several cell and gene therapy products, including two AAV vector-based gene therapy products. In December 2017, the FDA approved its first AAV vector-based gene therapy product, LUXTURNA™ (voretigene neparvovec-rzyl) for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. In May 2019, the FDA approved ZOLGENSMA® (onasemnogene abeparvovec-xioi) for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with biallelic mutations in the survival motor neuron 1 (SMN1) gene.

***Our Novel AAV Vector Discovery and Optimization System***

Our next-generation discovery platform is based on vectors derived from AAV, which is a small, non-pathogenic virus, which carry a therapeutic DNA instead of the viral genes. The resulting vector is used to deliver a gene into a desired cell population, which when expressed, can provide sustained 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.

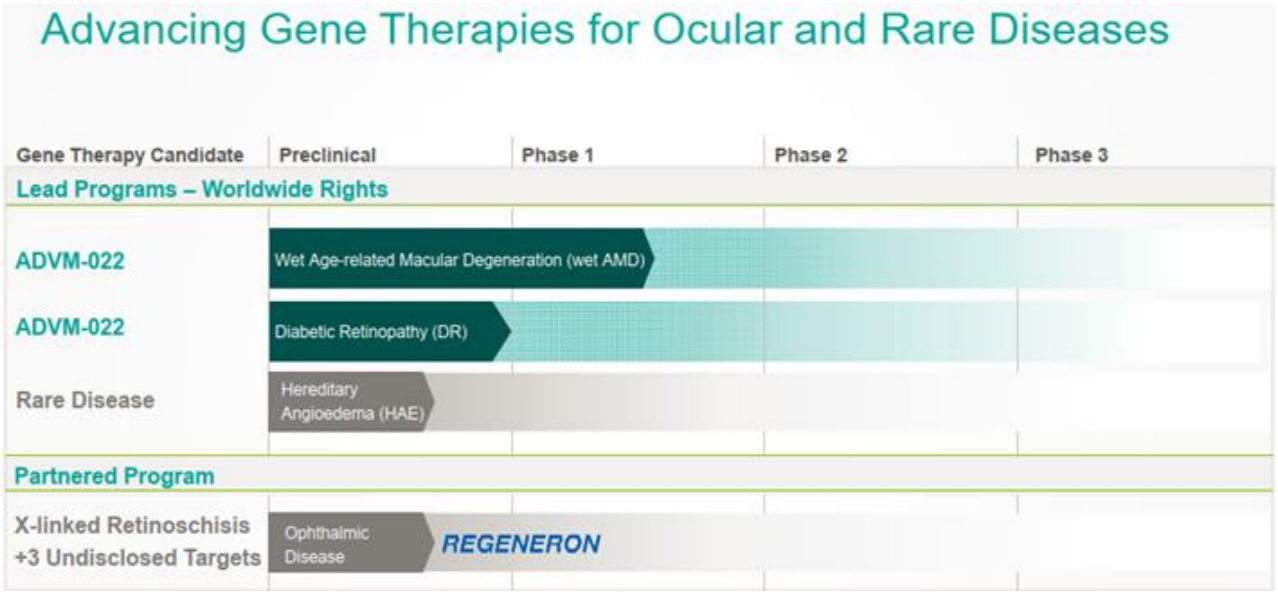
- **Highly-efficient transfer of DNA.** AAV vectors offer highly-efficient transfer of DNA to the patient.
- **Non-pathogenic.** Naturally occurring and recombinant AAV are not known to cause disease in humans.
- **Non-replicating.** Naturally occurring AAV is incapable of replication without co-infection of a helper virus such as adenovirus, herpes virus, or others. Recombinant AAV vectors used in our product candidates lack additional genes making them even less capable of replication.
- **Long-term expression.** Once incorporated into the host cell, AAV vectors can continue to drive expression of a therapeutic protein for years, making AAV-based gene therapy a compelling treatment modality for diseases requiring frequent chronic treatment regimens.
- **Low-integrating potential.** Recombinant AAV vector genomes remain mainly as a stable non-integrated episome in the host cell nucleus, mitigating safety concerns associated with genomic integration.
- **Low inflammatory potential.** Compared to other vectors used in direct gene therapy approaches, AAV vectors elicit relatively mild inflammatory reactions.
- **Ability to transduce non-dividing cells.** AAV vectors can efficiently transduce non-dividing cells or slow-dividing cells such as retinal cells and hepatocytes, which allow production of the therapeutic protein at the site of the disease (wet AMD) or its natural organ of production (C1-Esterase Inhibitor).
- **FDA approved.** In December 2017, the FDA approved its first AAV vector-based gene therapy product, LUXTURNA (voretigene neparvovec-rzyl) for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy, and in May 2019, the FDA approved ZOLGENSMA® (onasemnogene abeparvovec-xioi) for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with biallelic mutations in the survival motor neuron 1 (SMN1) gene.

AAV-derived vectors are a leading vector used in gene therapy. According to the *Journal of Gene Medicine*, AAV has been used in over 240 clinical trials as of September 2019. As effective as existing AAV vectors are in gene therapy, we believe there are opportunities for improvement. Naturally occurring AAV variants have evolved with particular characteristics, some of which remain and pose limitations to their use in gene therapy.

To create next-generation vectors, we use a multi-step process known as directed evolution. Our directed evolution technology uses a library of engineered AAV capsid genes, which exhibit different properties and capabilities than naturally occurring AAVs. Once we have created an initial pool of millions of different AAVs, we screen the AAVs in the pool for novel properties, e.g., specific transduction of a particular cell type, or the capability to evade pre-existing neutralizing immune response. Once capsids with desirable properties are identified, those capsids are screened to create a smaller pool of optimized vectors which are further screened until we have identified a select number of engineered AAVs with the characteristics we seek.

**Our Product Candidates**

We are advancing a pipeline of novel gene therapy product candidates designed to treat ocular and rare diseases. Our pipeline of internal programs and our partnered program is shown below.

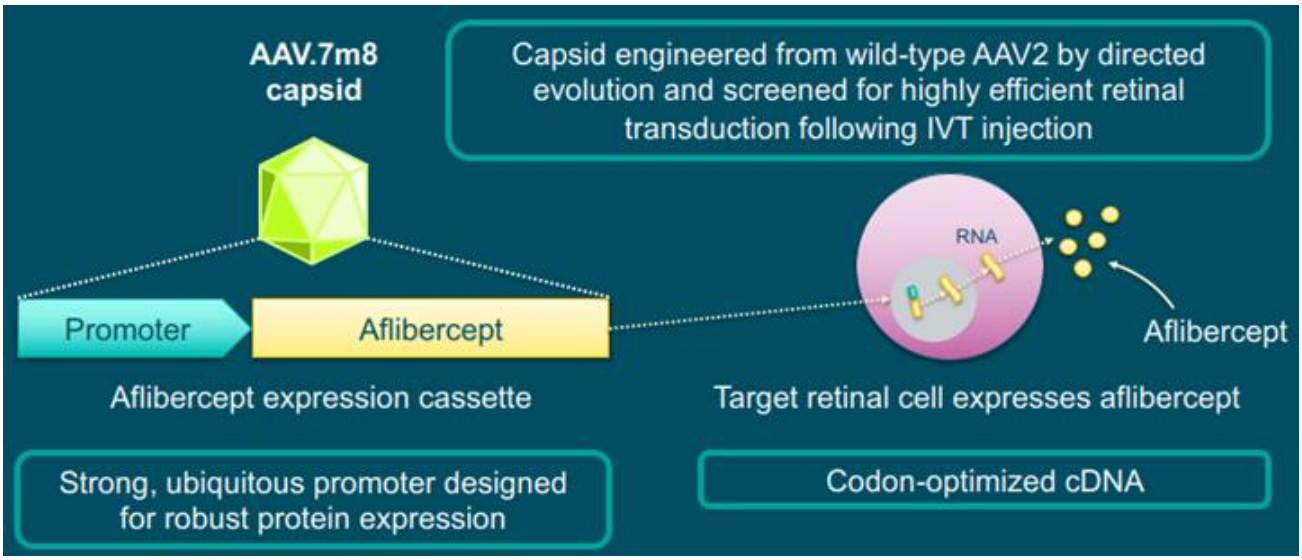



**Ocular Diseases**

***ADVM-022, Our Single Intravitreal Injection Gene Therapy Candidate for Treating Ocular Diseases***

ADVM-022 is our clinical-stage gene therapy product candidate being developed for the treatment of wet AMD and diabetic retinopathy. ADVM-022 utilizes a propriety vector capsid, AAV.7m8, carrying an aflibercept coding sequence under the control of a proprietary expression cassette. ADVM-022 is administered as a one-time IVT injection and is designed to deliver long-term efficacy and reduce the burden of frequent anti-VEGF injections, optimize patient compliance, and improve vision outcomes for patients with wet AMD or diabetic retinopathy.

The AAV.7m8 capsid was engineered from AAV2 by directed evolution to efficiently transduce retinal cells following intravitreal injection. The vector carries a vector genome ("vg") encoding a codon-optimized cDNA of the aflibercept protein, a current standard of care in wet AMD, under the control of a strong, ubiquitous expression cassette.



We believe IVT injection of gene therapy offers substantial benefits over subretinal injection, including:

- IVT injection is the current standard-of-care administration for therapies to treat patients with wet AMD and diabetic retinopathy;
- IVT injections are performed as a simple outpatient procedure during an office visit, instead of the surgical setting required for subretinal injections; and
- IVT injections offer the potential for wide distribution of vector, allowing it to transduce broader tissue area, where as transduction after subretinal injection is limited to the area near the site of injection.

***ADVM-022 for Treatment of Wet AMD***

**Market for Treating Patients with Wet AMD**

Age-related macular degeneration ("AMD") is a progressive disease affecting the retinal cells in the macula, the region of the retina at the back of the eye responsible for central vision. Disease progression results in the death of retinal cells and the gradual loss of vision.

Wet AMD, also known as neovascular AMD ("nAMD") is an advanced form of AMD, affecting approximately 10% of patients living with AMD. In patients with wet AMD, blood vessels begin to invade the 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.

Wet AMD is a leading cause of vision loss in patients over 60 years of age, with a prevalence of approximately 1.2 million individuals in the U.S. and 3 million worldwide. The incidence of new cases of wet AMD in the U.S. is approximately 150,000 to 200,000 annually, and this number is expected to grow significantly as the country's population ages.

The current standard-of-care therapy for wet AMD is chronic anti-VEGF IVT injections. These are effective but typically require eye injections every 4-12 weeks in order to maintain vision. Compliance with this regimen can be difficult for patients, caregivers, and healthcare systems, leading to undertreatment and resulting in loss of vision. We estimate that these standard-of-care therapies used for the treatment of wet AMD, diabetic retinopathy, retinal vein occlusion, and other ocular diseases generated in excess of $11 billion in sales worldwide in 2019.

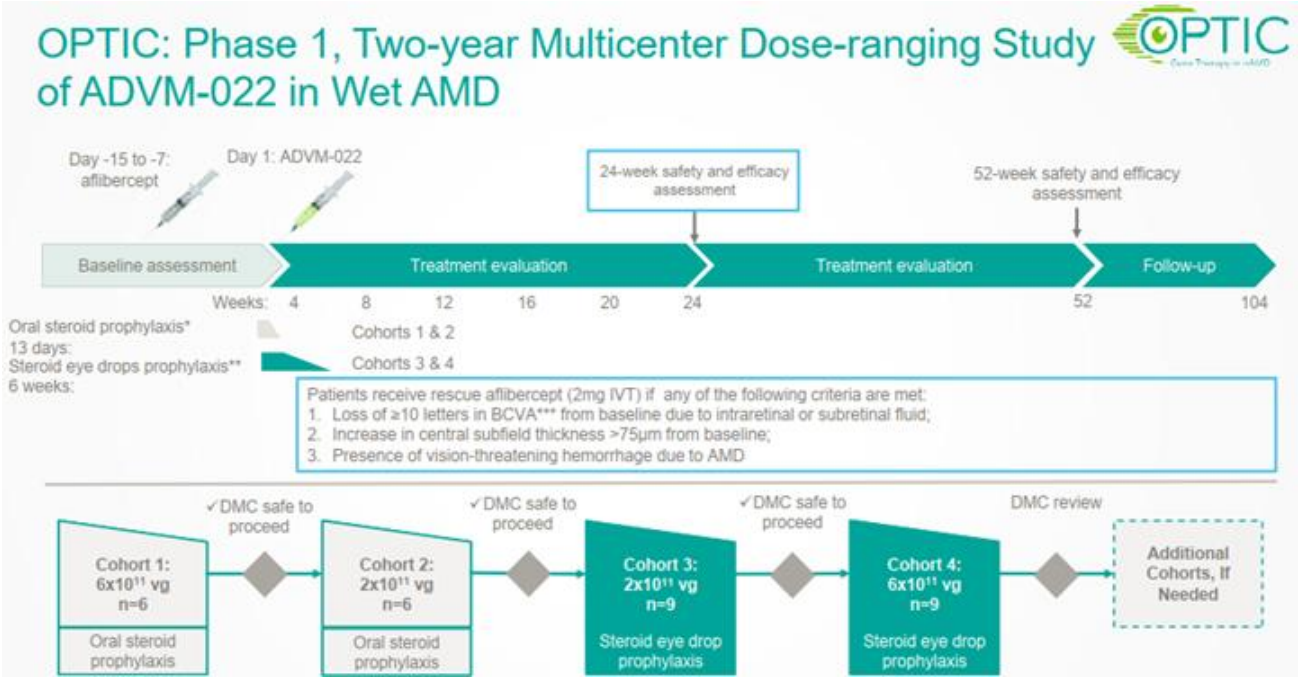
**Advancing the Clinical Development of ADVM-022 for Wet AMD**

We initiated the ADVM-022 phase 1 clinical trial entitled "An Open Label Phase 1 Study of ADVM 022 (AAV.7m8-aflibercept) in Neovascular (Wet) Age-Related Macular Degeneration – [OPTIC]" ("the OPTIC trial") with the first patient dosed in November 2018. We received Fast Track designation from the FDA for ADVM-022 for wet AMD in September 2018.

The OPTIC trial is designed as a multi-center, open-label, phase 1, dose-ranging safety trial of ADVM-022 in patients with wet AMD who have demonstrated responsiveness to anti-vascular endothelial growth factor ("anti-VEGF") treatment. Patients in OPTIC are treatment-experienced, and previously required frequent anti-VEGF injections to control their wet AMD and to maintain functional vision.

In OPTIC, patients are dosed with a single IVT injection of ADVM-022. Patients in cohort 1 (n=6) were treated with a higher dose of ADVM-022 (6 x 10^11 vg/eye). Patients in cohort 2 (n=6) were treated with a three-fold lower dose of ADVM-022 (2 x 10^11 vg/eye). Patients in cohorts 1 and 2 received a 14-day tapering course of prophylactic oral steroids following ADVM-022 administration. Patients in cohort 3 (n=9) were treated with the lower dose of ADVM-022 (2 x 10^11 vg/eye), and patients in cohort 4 (n=9) will be treated with the higher dose of ADVM-022 (6 x 10^11 vg/eye). Patients in cohorts 3 and 4 receive a 6-week tapering course of prophylactic topical steroids in place of the oral steroids.

The primary endpoint of the trial is the safety and tolerability of ADVM-022 after a single IVT administration. Secondary endpoints include changes in best-corrected visual acuity (BCVA), measurement of central subfield thickness ("CST", a measure of retinal thickness), as well as mean number of anti-VEGF rescue injections and percentage of patients needing anti-VEGF rescue injections. Each patient enrolled will be followed for a total of two years.




*Subjects received prophylaxis of 60 mg oral prednisone for 6 days starting at Day –3 followed by 7-day taper.
**Subjects receive prophylaxis of QID (4x/day) difluprednate eye drops for 3 weeks starting at Day 1 followed by a 3-week taper.
***BCVA, best-corrected visual acuity

Patients in cohorts 1 and 2 had both received a mean of 9.2 anti-VEGF injections in the 12 months prior to receiving ADVM-022, and patients in cohort 1 and 2 had received a mean of 35.3 injections (range 7-109) and 34.0 injections (range 4-69) respectively, since diagnosis of wet AMD.

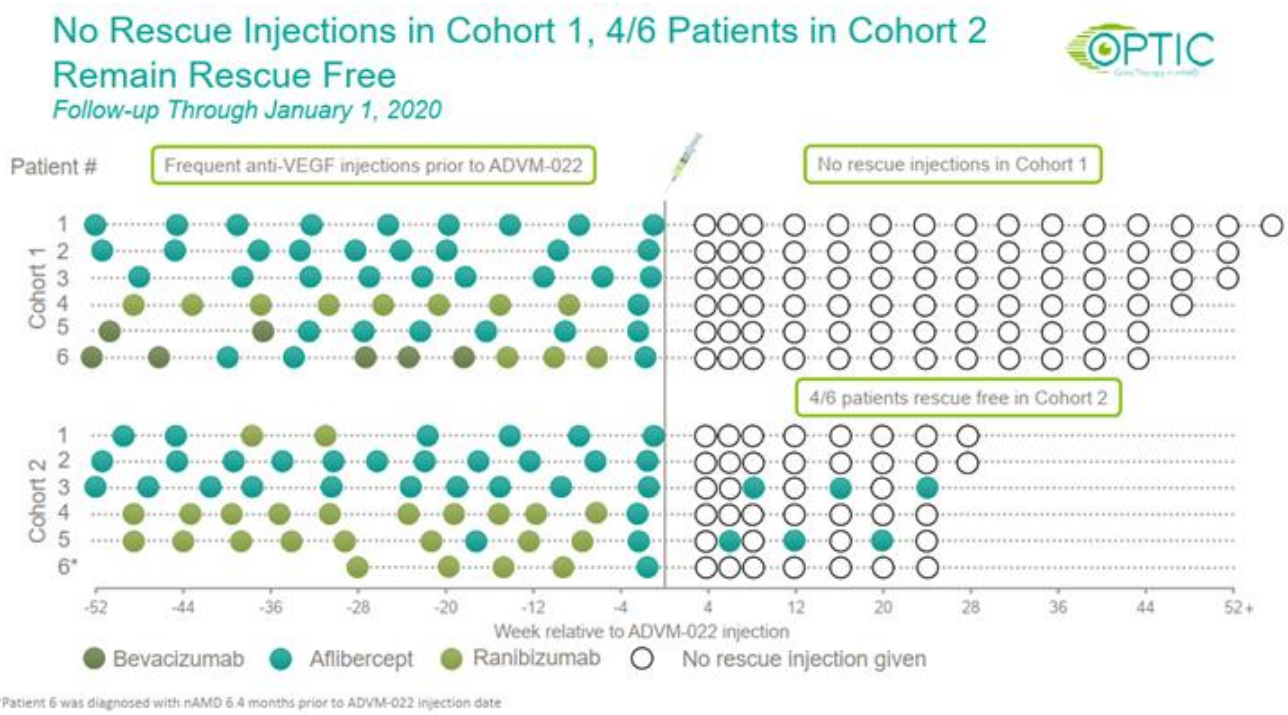
In February 2020, we presented data from cohorts 1 and 2, which included evidence that in treatment experienced patients previously requiring frequent anti VEGF injections to maintain vision, ADVM-022 has demonstrated a robust efficacy signal and evidence of a dose response (see figure and table below):

- Cohort 1 (6 x 10^11 vg/eye): 6 of 6 patients remain rescue injection free at a median follow up of 50 weeks with 3 patients at 52 weeks;
- Cohort 2 (three-fold lower dose 2 x 10^11 vg/eye): 4 of 6 patients remained rescue injection free at 24 weeks

In both cohorts 1 and 2 combined, 10 of 12 (83%) patients remain rescue injection free. For patients that remain injection free:

- Vision was generally maintained, as demonstrated by stable mean BCVA compared to baseline; and
- Retinal anatomy improvements were achieved and maintained, as observed by mean CST compared to baseline.

ADVM-022 continues to be well-tolerated with no drug-related or procedure-related serious adverse events (“SAEs”), no drug-related systemic adverse events and no adverse events meeting the criteria for dose-limiting toxicities (“DLTs”). ADVM-022-related adverse events (“AEs”) have been mild (71%) to moderate (29%).Low-grade ocular inflammation was commonly reported and was responsive to steroid eye drops. No vasculitis, retinitis, or choroiditis were observed. In cohorts 3 and 4, patients receive a tapering course of prophylactic topical steroid eye drops for a total of 6 weeks instead of the 13 day tapering course of prophylactic oral steroids used in cohorts 1 and 2.




*Patient 6 was diagnosed with nAMD 6.4 months prior to ADVM-022 injection date

| **Results Following a Single ADVM-022 Dose:** | **Cohort 1** | **Cohort 2** |
|---|---|---|
| Patients | 6 | 6 |
| Dose ADVM-022 | Higher Dose<br>6 x 10^11 vg/eye 50 weeks | Lower Dose<br>2 x 10^11 vg/eye 24 weeks |
| **Follow-up (median)** | | |
| **Rescue Injections:** | | |
| Number of patients requiring anti-VEGF rescue injections | 0/6 patients | 2/6 patients |
| Total anti-VEGF rescue injections | 0 injections | 6 injections |
| **Safety:** | | |
| Systemic adverse events | 0 | 0 |
| Dose-limiting toxicities (DLTs) | 0 | 0 |
| Serious adverse events (SAEs)[1] | 1 | 0 |
| Drug/procedure related SAEs | 0 | 0 |
| **Follow-up** | 44 weeks (median) | 24 weeks |
| **Change in BCVA[2]:** | | Full cohortRescue-free patients |
| Mean (ETDRS letters)[3] | -1.0 | -4.8-0.8 |
| Range (ETDRS letters) | -7 / +7 | -19 / +16-14 / +16 |
| **Change in CRT[3]:** | | |
| Mean (µm)[4] | -25.5 | -27.8-30.8 |
| Range (µm)[4] | -117 / +32 | -61 /-8-61 / -8 |

[1] This event (retinal detachment) was deemed unrelated to ADVM-022 or any study procedure.
[2] Best corrected visual acuity (BCVA) as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) (i.e., sight charts). Data through December 1, 2019 (Cohort 1).
[3] Central retinal thickness (CRT), also referred to as central subfield thickness (CST) assessed using Optical Coherence Tomography (OCT) imaging and measured by an independent Central Reading Center Data through December 1, 2019 (Cohort 1).
[4] BCVA and CST values for patient with retinal detachment (unrelated to study treatment) used last observations prior to detachment.

In the first quarter of 2020, we completed patient dosing in cohort 3 (n=9, lower dose of 2 x 10^11 vg/eye) and began screening for cohort 4 (n=9, higher dose of 6 x 10^11 vg/eye). As we advance the OPTIC trial, we plan to present additional clinical data in the second quarter of 2020, and also longer-term data from cohorts 1-4 in the second half of 2020.

***ADVM-022 for Treatment of Diabetic Retinopathy***

**Market for Treating Patients with Diabetic Retinopathy**

Diabetic retinopathy is caused by high blood sugar levels that cause damage to blood vessels in the retina. Blood vessels can swell, leak, or close to prevent blood flow. Diabetic retinopathy is the leading cause of vision impairment and blindness among working age adults. Of the estimated 8 million people with diabetic retinopathy in the U.S., only 2 million are diagnosed and only 1 million are being treated. As the prevalence of diabetes continues to grow, the prevalence of diabetic retinopathy is expected to increase.

Maintaining consistent levels of VEGF suppression with ADVM-022 could be particularly important for this rapidly-progressing disease. The current standard-of-care therapy for diabetic retinopathy is anti-VEGF intravitreal ("IVT") injections. These are effective but typically require eye injections every 4-12 weeks in order to maintain vision. Compliance with this regimen can be difficult for patients, caregivers, and healthcare systems, leading to undertreatment and resulting in loss of vision. We estimate that these standard-of-care branded anti-VEGF therapies used for the treatment of wet AMD, diabetic retinopathy, retinal vein occlusion, and other ocular diseases generated in excess of $11 billion in sales worldwide in 2019.

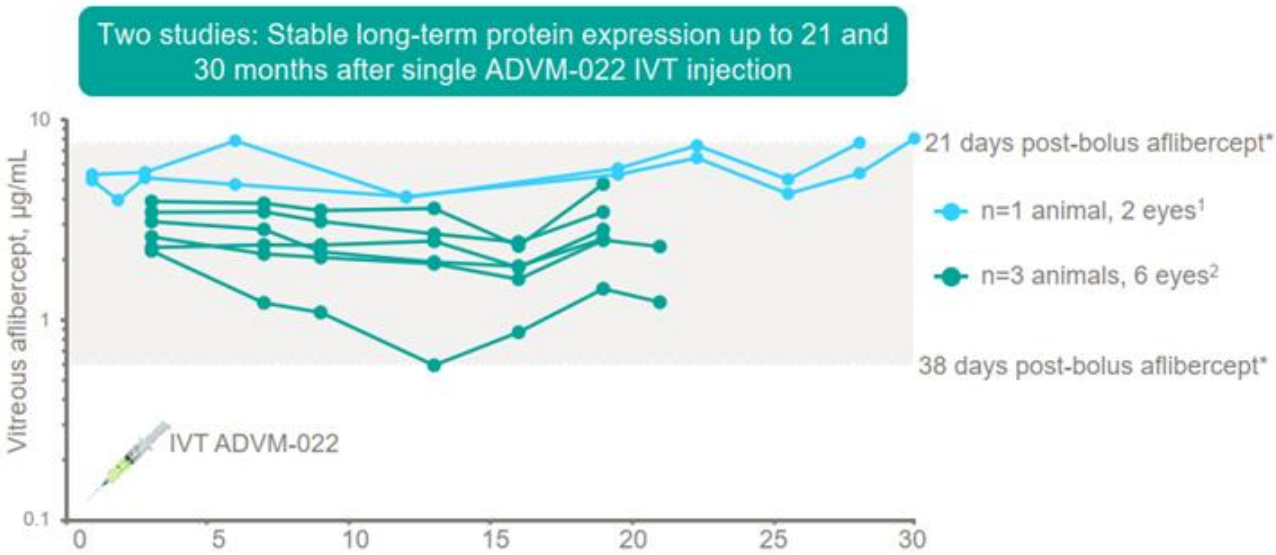
**Advancing the Clinical Development of ADVM-022 for Diabetic Retinopathy**

We are advancing ADVM-022 for the treatment of patients with diabetic retinopathy and intend to file an IND application in the second quarter of 2020. We plan to begin enrolling patients in a planned phase 1/2 clinical trial in the second half of 2020 to expand our clinical development pipeline.

***Preclinical Proof of Concept for ADVM-022***

ADVM-022 was designed to provide long-term aflibercept expression following intravitreal injection. To evaluate the potential of ADVM-022 to treat wet AMD, we assessed its efficacy non-human primates ("NHPs"). We observed that a single intravitreal administration of ADVM-022 provided sustained expression of aflibercept out to 30 months at levels comparable to those experienced three to four weeks post-injection of aflibercept protein.

**Preclinical NHP Data Demonstrate Long-Term Sustained Aflibercept Levels Comparable to Aflibercept Bolus Injection**

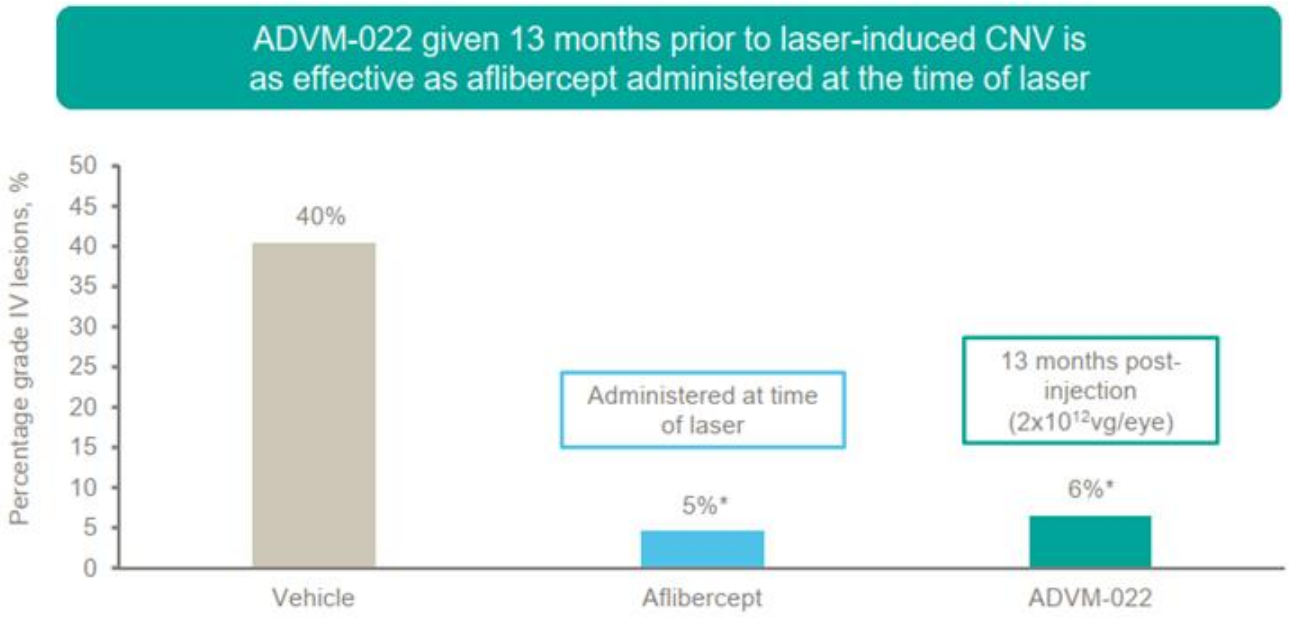



* Approximate aflibercept protein levels observed at 21 days and 38 days in NHPs following a bolus IVT injection of 1.2mg/eye of aflibercept (performed in a separate study)

1. Grishanin, R., Annual Congress European Society of Gene & Cell Therapy; 2018, Lausanne, Switzerland
2. Kiss, S., Annual Meeting of the American Society of Gene & Cell Therapy; 2019, Washington, DC

Further, in a laser-induced choroidal neovascularization model in NHPs, the industry standard model for testing new wet AMD therapies, we observed that a single intravitreal injection of ADVM-022 delivered 13 months before lasering provided the same level of protection from clinically-relevant lesions as an intravitreal bolus of aflibercept, the current standard of care, delivered at the time of lasering.

**ADVM-022 Aflibercept is Functionally Active and Suppresses Laser-induced CNV in Primates**




*p<0.0001

CNV, choroidal neovascularization
Source: Grishanin, R. et al. Molecular Therapy 2019;27:118–29

***ADVM-022 Partial Clinical Hold***

In April 2019, following completion of dosing of cohort 1, and prior to dosing of patients in cohort 2, the FDA placed our IND application for ADVM-022 for the treatment of wet AMD on clinical hold and requested certain information and requirements related to chemistry, manufacturing and controls ("CMC"). We subsequently responded to the FDA, and in May 2019, the FDA removed the clinical hold, allowing dose escalation up to 2 x 10^12 vg/eye in the OPTIC trial. However, our IND remains on partial clinical hold for dosing patients with a dose of 6 x 10^12 vg/eye. Given the preliminary robust anatomical response we observed from patients in the first cohort, we dosed patients in the second cohort with a three-fold lower dose of 2 x 10^11 vg/eye. We do not currently intend to dose patients at 6 x 10^12 vg/eye. We continue to work with the FDA to resolve the remaining CMC requirements. We anticipate the FDA will need to remove the remaining clinical hold in order for us to initiate a phase 3 clinical trial for ADVM-022.

**Rare Diseases**

***Treatment of Alpha-1 Antitrypsin Deficiency***

ADVM-043 was a gene therapy product candidate designed to provide stable, long-term alpha-1 antitrypsin ("A1AT") protein expression for the treatment of A1AT deficiency. Preclinical studies in mice and non-human primates showed that ADVM-043 provided stable, robust, long-term expression of A1AT protein. During a phase 1/2 clinical trial for ADVM-043, A1AT protein expression did not reach a clinically meaningful level, nor was a dose response observed with dose-escalation. In August 2019 we announced our decision to discontinue the development of a gene therapy candidate to treat A1AT deficiency. All six subjects from our trial have enrolled into a long-term follow-up study and will be monitored for an additional 2 years.

***Treatment of Hereditary Angioedema***

ADVM-053 is a preclinical gene therapy product candidate for the treatment of hereditary angioedema ("HAE"). ADVM-053 is designed to be administered as a single intravenous ("IV") injection to prevent HAE attacks. Like ADVM-043, ADVM-053 utilizes an

AAVrh.10-based vector, which has been shown to target the liver, the natural source of C1EI. In preclinical studies, a single IV administration of ADVM-053 showed robust C1EI protein expression. In a proof-of-concept study, ADVM-053 increased C1EI protein expression above anticipated therapeutic levels. An additional study, in a mouse model of the disease, demonstrated that ADVM-053 decreased vascular permeability. However, due to the lack of clinical efficacy that we observed in ADVM-043, we are evaluating potential paths forward for development of a product candidate for the treatment of HAE. In August 2019, we announced that we had moved our gene therapy program targeting HAE back into early development.

***Other Preclinical Product Candidates***

In addition to our lead programs, we are currently utilizing our industry-leading development capabilities for our AAV-based directed evolution platform and are conducting observational studies. We are in the early stages of preclinical development for additional product candidates that we may advance in the future.

***Partnered Program Product Candidates***

We have licensed to GenSight rights to use AAV.7m8 for GS030 gene therapy encoding channelrhodopsin protein. GenSight is conducting a phase 1/2 trial in retinitis pigmentosa in the U.S., France, and U.K., which began in October 2018.

**Manufacturing**

Our AAV vector manufacturing 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 per manufacturing campaign in a cost-effective manner.

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 quantities of product required at commercial stage 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 in humans.
- **High yield and low cost.** Because of its scalability, our BEVS system allows the production of large quantities of AAV vectors, up to the 2000-liter scale. Production at this scale lowers the unit cost of goods and may enable us to meet global demand for large markets, such as wet AMD.
- **High purity.** Our BEVS system coupled with our proprietary downstream purification process produces a highly pure drug substance.
- **Precedent regulatory framework.** Glybera, an AAV-based gene therapy, and several other vaccines and recombinant protein therapies have been approved by the FDA and/or EMA using a manufacturing process similar to our BEVS technology.

Our products are manufactured using proprietary cell banks and a scalable process developed internally that is transferred to approved Contract Manufacturing Organizations (“CMOs”). These CMOs produce investigational drugs under cGMP conditions to support our clinical trials. Raw materials of highest quality are purchased from various suppliers and are used throughout the manufacturing process.

We continue to evaluate new raw material suppliers, as well as CMOs with available manufacturing slots, in order to provide manufacturing flexibility. As we prepare for larger, late-stage clinical trials and potential commercialization, we plan to expand our in-house process development capabilities in stages, allowing us to develop larger-scale processes for transfer to our GMP contract manufacturers.

**Competition**

The biopharmaceutical industry is characterized by intense and dynamic competition to develop new proprietary technologies and therapies and a strong emphasis on intellectual property. We believe that our single administration, intravitreal approach for the treatment of wet AMD and diabetic retinopathy, our AAV-based directed evolution platform, and our expertise in the field of gene therapy provide us with competitive advantages. However, we face actual or 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.

Our gene therapy ADVM-022 for wet AMD and diabetic retinopathy utilizes a proprietary vector and is administered through a single intravitreal injection and will compete with a variety of therapies currently marketed and in development, including biologics, small

molecules and gene therapy. The key factors that contribute to success of any approved product include safety profile, efficacy, mode of administration and cost of goods. Existing anti-VEGF therapies are well-established therapies and are widely accepted by physicians, patients and third-party payers as the standard-of-care treatment of patients with wet AMD and diabetic retinopathy.

We know of a significant number of product candidates in development for chronic retinal conditions that respond to anti-VEGF therapy, including wet AMD and diabetic retinopathy, and we group them into four main categories:

- biosimilar anti-VEGFs (e.g. FYB201);
- combination / add-on therapy for efficacy or durability improvement (e.g. faricimab and OPT-302);
- next-generation anti-VEGF for durability improvement (e.g. abicipar pegol and KSI-301); and
- long-acting delivery device / gene therapy to lower treatment frequency (e.g. ranibizumab port delivery system, RGX-314).

There are several other companies with marketed products or products in development for the treatment of chronic retinal conditions that respond to anti-VEGF therapy, including wet AMD and diabetic retinopathy. These companies include Allergan, Bayer, Hoffmann-La Roche Ltd., Novartis, and Regeneron.

These companies, as well as competitors we may face, either alone or with their partners, for our other product candidates, 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.

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.

**License and Collaboration Agreements**

***Regeneron***

In May 2014, we entered into a collaboration agreement with Regeneron for an initial period of three years to research, develop and commercialize novel gene therapy products for the treatment of ocular 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. 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 February 2017, Regeneron exercised its option to extend the research term of the collaboration agreement for an additional three years, through May 1, 2020. Regeneron had the option to further extend the research term of the collaboration agreement for up to two additional years by providing notice of certain activities under the agreement by March 2, 2020, which Regeneron did not do. We anticipate that the agreement will expire by its terms on May 1, 2020.

***University of California***

*AAV.7m8 License Agreement*: In June 2013, we entered into an exclusive worldwide sublicensable license agreement with the Regents of University of California ("Regents") to certain intellectual property related to improved AAV vectors, including the AAV.7m8 capsid. Under this license agreement, we are obligated to make certain de minimis license payments, certain milestone payments totaling up to $1.0 million upon reaching certain stages of development of the licensed products for a first indication, and totaling up to $0.5 million for each subsequent indication for which licensed products are developed, for up to a maximum of two additional indications. In addition, we are obligated to pay Regents royalties on sales of licensed products in the low single-digits, subject to adjustments and minimum thresholds.

Unless earlier terminated, this agreement will be in effect on a country-by-country, licensed product-by-licensed product basis until the expiration of the last claim of the licensed intellectual property covering the manufacture, use, or sale of such product in such country. We may terminate this agreement in whole or in party by giving Regents 30 days' prior written notice. Regents may terminate this agreement for 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***

*Cornell License Agreements*

In December 2015, Annapurna Therapeutics SAS ("Annapurna") entered into three licensing agreements with Cornell University ("Cornell"), related to our 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, we held an exclusive license to certain know-how related to A1AT deficiency and rights to an IND application to initiate clinical studies of gene therapy for A1AT. Under our June 2019 settlement agreement with Cornell, our license to know-how was made non-exclusive.

*HAE License Agreement*: Under this agreement, we hold an exclusive license to certain technology related to HAE and a non-exclusive license to certain other intellectual property related to the HAE program.

Across these license agreements, Cornell is entitled to receive aggregate annual maintenance fees ranging from $30,000 to $0.3 million 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.

We 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 if we commence any action and file a written claim asserting that any portion of the licensed patent rights is invalid or unenforceable.

***Inserm Transfert***

In July 2014, we entered into an agreement with Inserm Transfert ("Inserm") whereby we hold an exclusive license to certain patents to develop and commercialize products for the treatment of Friedreich's ataxia ("FA") 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, we 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. We 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 us in a given country if we (i) before regulatory approval of a product in any country, have 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, have ceased marketing such product in such country for 12 consecutive months.

Pursuant to the agreement with Inserm, our acquisition of Annapurna triggered a one-time payment to Inserm of €0.3 million.

***GenSight***

In February 2014, we entered into an agreement with GenSight, in which we granted GenSight a non-exclusive license to our proprietary AAV.7m8 vector to develop gene therapy products to deliver certain therapeutic transgenes. Under the agreement, we are eligible to receive development, regulatory and commercial milestones. Also, we are eligible to receive low to mid-single digit royalties on sales of GenSight's licensed products.

GenSight is currently developing GS030, a gene therapy encoding channelrhodopsin protein which incorporates the AAV.7m8 capsid. GenSight is conducting a phase 1/2 trial with GS030 to treat retinitis pigmentosa in the U.S., France, and the U.K., which began in October 2018.

***Virovek***

On October 12, 2011, we entered into an agreement with Virovek, Inc. ("Virovek"), in which we received a non-exclusive license to certain Virovek technology and know-how related to methods and materials for manufacturing AAV. Under the agreement, Virovek is entitled to certain license payments and low-single digit royalty payments. This license with Virovek continues in effect until expiration of the last-to-expire patent.

In May 2019, we received from Virovek a notice of intent to terminate our license agreement. We do not believe that Virovek has the right to terminate the license, and are seeking a mutually agreeable solution to this dispute.

**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. Additionally, we 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; obtain regulatory exclusivity 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 own or license more than 40 issued patents which are still in force, and 150 patent applications pending in the U.S. and foreign jurisdictions. These numbers include more than 30 patents and 40 pending applications filed by or on behalf of universities which have granted us exclusive license rights to the technology. 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 patent protection in the U.S. and abroad for a variety of technologies, including research tools and methods, 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 four patent families that are directed to AAV-based compositions and methods for treating or preventing eye diseases associated with neovascularization. Patents and applications in the first of these families relate to compositions and methods for the AAV-based delivery of anti-VEGF proteins, for use in treating neovascular diseases of the eye, including wet AMD and diabetic retinopathy, in patients who respond to anti-VEGF protein therapy. Patents in this family have issued in the U.S. elsewhere in North America, and the Asia/Pacific region, and corresponding applications are pending in the U.S., elsewhere in North America, Europe, and Asia. Patents in this family are generally expected to expire in 2033, subject to possible patent term extensions. Applications in the second and third of these families relate to AAV gene therapy for the treatment of neovascular diseases of the eye, including wet AMD and diabetic retinopathy, using the AAV.7m8 vector to deliver ranibizumab or aflibercept. Each family has applications pending in the U.S. and corresponding applications pending abroad. Patents that may eventually issue from either of these patent families, if any, are generally expected to expire in 2037, subject to possible patent term extensions. The fourth family contains U.S. provisional applications and a PCT application, and is directed to methods of treating neovascular diseases of the eye, including wet AMD and diabetic retinopathy, with AAV.7m8-aflibercept. Patents that may eventually issue from this family, if any, are generally expected to expire in 2039.

We also own eleven patent families that are directed to various aspects of our proprietary technology platform. One of these families contains issued patents in the U.S. and Asia, and pending applications in the U.S., elsewhere in North America, Europe, and Asia. The remaining families contain pending U.S. provisional or PCT applications or national phase applications in the U.S., elsewhere in North America, Europe, and Asia. Patents that may eventually issue from these families, if any, are generally expected to expire between 2036 and 2040, subject to possible patent term extensions.

***Licensed Intellectual Property***

We have obtained both exclusive and non-exclusive licenses to patents directed to both compositions of matter and methods of use and to other intellectual property.

For example, we have exclusively licensed several families of patents and patent 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 directed to improved rAAV virions that we have exclusively licensed in the ocular field includes granted patents in the U.S., as well as elsewhere in North America and Europe, as well as pending patent applications in the U.S. The patents in this family are projected to expire in 2024, subject to possible patent term extensions.

Another patent family directed to improved rAAV virions that we have exclusively licensed includes granted U.S. patents and a pending U.S. patent application that are expected to expire in 2031, subject to possible patent term extensions.

A third patent family that we have exclusively licensed includes claims directed to the novel AAV.7m8 vector, which allows delivery of transgenes to the retina via intravitreal injection, and which we utilize in our product candidate ADVM-022. This family includes issued patents in the U.S. Corresponding applications are pending in the U.S. and elsewhere in North America, Asia and the Pacific. Patents that issue from this patent family, if any, are generally expected to expire in 2032, subject to possible patent term extensions.

We have also nonexclusively licensed rights to a patent family related to the Baculovirus/SF9 production system that includes issued patents in the U.S., Europe, and Asia. These patents are expected to expire in 2027, subject to possible patent term extensions.

We have licensed a family of patent applications related to gene therapy treatments for HAE, C1-esterase deficiency, which includes issued patents in the U.S. and Asia, and pending U.S. and foreign applications. Patents that grant from this patent family, if any, are generally expected to expire in 2036, subject to possible patent term extensions and adjustments.

We have exclusively licensed a family of patents and applications related to the treatment of cardiomyopathy associated with FA. This family includes a granted US patent and pending applications in the U.S. and elsewhere in North America, Europe, Asia, and the Pacific. Patents that grant from this patent family, if any, are generally expected to expire in 2033, subject to possible patent term extensions and adjustments.

We have exclusively licensed certain know-how related to gene therapy for A1AT deficiency and rights to an IND to perform clinical studies of gene therapy for A1AT.

***Trade Secret Protection***

In some circumstances we may rely on trade secrets to protect aspects of our technology and product candidates, including aspects for which we do not obtain patent protection. We seek to protect our trade secrets and confidential information, 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 confidential information 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***

In the U.S., biological products, including gene therapy products, are primarily regulated under the Federal Food, Drug, and Cosmetic Act (“FD&C Act”) and the Public Health Service Act (“PHSA”), as well as corresponding implementing regulations promulgated by the FDA. These laws and regulations govern, among other things, the testing, manufacturing, safety, purity, potency, efficacy, labeling, packaging, storage, distribution, record keeping, reporting, advertising and promotion, export and import of biologics products. Prior to conducting human clinical testing of our gene therapy products, we must submit an investigational new drug application (“IND”) to FDA, and the IND must become effective.

Within FDA, the Center for Biologics Evaluation and Research (“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 (“OTAT”). FDA has also established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER in its review.

FDA has published a growing body of guidance documents on topics relevant to the development of our product candidates, including, among other things, gene therapy products developed for retinal disorders, rare diseases; patient-focused drug development, preclinical testing of gene therapy products; CMC information requirements for gene therapy; and observation of subjects involved in gene therapy studies for delayed adverse events. All of these guidance documents are intended to facilitate the industry’s development of gene therapy products. Guidance documents provide the FDA’s current thinking about a particular subject, but are not legally binding on either FDA or the regulated industry.

The process required by FDA before our product candidates may be marketed in the U.S. generally involves the following:

- Completion of non-clinical laboratory tests, including evaluations of product chemistry, formulations, and toxicity and animal studies in accordance with current Good Laboratory Practice ("GLP"), regulations and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- Submission of an IND to the FDA, which must become effective before human clinical trials may begin;
- Approval by the independent institutional review board ("IRB") of each clinical protocol and each clinical trial site before the trial may be initiated at that site;
- Approval by the institutional biosafety committee ("IBC") of each clinical trial site, which assesses the safety of research involving, among other things, recombinant DNA, and identifies any potential risks to public health or the environment;
- Generation of substantial evidence from human clinical trials, conducted in accordance with Good Clinical Practice ("GCP") regulations, and any additional requirements for the protection of human research subjects and their health information, to establish the safety and potency of the biologic product for its proposed indication;
- Satisfactory completion of an FDA inspection of each manufacturing facility at which the biologic product is produced, to assure that the product is produced in compliance with cGMP, regulations, and any additional requirements made by the agency to assure that the methods and controls used during manufacturing are adequate to preserve the biological product's identity, strength, quality, and purity;
- Submission to FDA of a BLA for marketing approval that demonstrates purity, safety and potency of the biological product based on results of nonclinical testing and clinical trials, as well as information on the chemistry, manufacturing and controls to ensure product identity and quality, as well as proposed labeling;
- Successful completion of FDA audit(s) of the nonclinical and clinical trial sites and the clinical study sponsor that generated the data in support of the BLA;
- Successful completion of the advisory committee review, if the FDA convenes an advisory committee; and
- Payment of user fees and FDA review and licensure of the BLA prior to any commercial marketing, sale or shipment of the product; application fees for products designated as orphan drugs by FDA are generally waived.

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, and stability, 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.

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 IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions relating to the content of the IND during the review period or places the clinical study on a clinical hold. In that case, the IND sponsor and the FDA must resolve any outstanding concerns before the IND goes into effect and the clinical trial begins. The FDA can 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 proceed without FDA authorization, and then only under terms authorized by FDA. Accordingly, we cannot be sure that submission of an IND will result in FDA allowing the clinical study(ies) to begin, or that, once begun, issues will not arise that suspend or terminate the study(ies).

Clinical trials involve administering of the investigational biological product candidate to human subjects under the supervision of qualified investigators, who are 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 FDA as part of the IND. An independent IRB, and IBC, at each institution where the clinical trial will be conducted must also review and approve the plan for any clinical trial before it can begin at that institution, and the IRB must monitor the clinical trial until it is completed. For certain types of research, including research involving recombinant DNA, the IBC will also assess the safety of the research and identify any potential risk to public health or the environment, until the research is completed. Clinical testing also must satisfy GCP requirements, including the requirements for informed consent from all subjects.

All clinical research performed in the United States in support of a BLA must be authorized in advance by the FDA as described above. However, a sponsor who wishes to conduct a clinical trial outside the U.S. 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, the FDA will accept a well-designed, well-conducted, non-IND foreign clinical trial as support for a BLA if (i) the clinical trial 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 clinical trial through an onsite inspection, if necessary. In addition, when an applicant submits data from a foreign clinical trial not conducted under an IND to support a BLA, FDA requires a description of the actions the applicant took to

ensure that the research conformed to GCP. Further, additional requirements apply when a sponsor intends to base marketing approval of a new drug solely on foreign clinical data.

***Clinical Trials***

Clinical trials are typically conducted in three sequential phases, which may overlap or be combined.

- Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or healthy volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. In the case of some product candidates for severe or life-threatening diseases, the initial human testing is often conducted in patients. Phase 1 clinical trials of gene therapies are typically conducted in patients rather than healthy volunteers.
- Phase 2 clinical trials are typically conducted in a larger subject population than Phase 1 trials to evaluate dosage tolerance and appropriate dosage, identify possible adverse effects and safety risks, and to preliminarily evaluate the efficacy of the product candidate for specific targeted indications. For Phase 2 clinical trials in gene therapy, although the subject population may be larger than the Phase 1 trials, the subject population may still remain relatively limited.
- Phase 3 clinical trials are typically conducted when Phase 2 clinical trials demonstrate that a dose range of the biological product candidate is effective and has an acceptable safety profile. Phase 3 clinical trials are generally undertaken with large numbers of subjects, to provide substantial evidence of clinical efficacy, potency, and to further test for safety in an expanded and diverse subject population at multiple, geographically-dispersed clinical trial sites. 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.
- Post-approval clinical trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial approval. These clinical trials are used to gain additional data from treatment of patients in the intended therapeutic indication, particularly for long-term safety.

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 and the investigators for any serious and unexpected adverse event that occurs during the study, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the clinical protocol or Investigator’s Brochure, as well as any findings from other studies, tests in laboratory animals or in vitro testing that suggest a significant risk for human subjects from the product candidate. 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.

As human gene therapy products are a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the clinical trial period, the number of patients the FDA will require to be enrolled in the studies in order to establish the product’s safety, purity and potency, or that the data generated in these studies will be acceptable to FDA to support marketing approval. The FDA and the National Institutes of Health (NIH) developed a publicly accessible database, the Genetic Modification Clinical Research Information System, designed to facilitate safety reporting. The database includes information on gene transfer studies and serves as an electronic tool to facilitate the reporting and analysis of adverse events on these clinical trials.

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 CMC 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; 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, 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.

In accordance with 42 CFR Part 11, the responsible party for an applicable clinical trial must register the clinical trial on the ClinicalTrials.gov website, the registry of new, on-going, and completed clinical trials of drugs, biologics, and device products.

***Biologics License Applications***

The results of preclinical studies and clinical trial(s), together with detailed 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 filing review period to determine if the application is sufficiently complete to permit substantive review.

Under the Prescription Drug User Fee Act ("PDUFA"), 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 for 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 licensure of a BLA by issuing a complete response letter if the applicable statutory and regulatory criteria are not satisfied, and 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 licensure. Data from clinical trials are not always conclusive and the FDA may interpret the data differently than we interpret data. Moreover, even if a product receives licensure, the licensure may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited or subject to Risk Evaluation and Mitigation Strategies (REMS), which could restrict the commercial value of the product.

Once the FDA licenses a BLA, or supplement thereto, the FDA may withdraw the licensure if ongoing regulatory requirements are not met or if safety problems are identified after the product reaches the market. Even where a withdrawal is not required, the FDA still may seize existing inventory of such product or require a recall of product already on the market. In addition, the FDA may require testing, including Phase 4 clinical trials and surveillance programs to monitor the effect of licensed biologics that have been commercialized. The FDA has the authority to prevent or limit further marketing of a biologic 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 the sponsor to develop additional data or conduct additional preclinical studies and clinical trials.

Before licensing a BLA, the FDA will inspect the facilities at which the biologic is manufactured and will not license the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements. The FDA may also inspect the site(s) at which the clinical trials were conducted to assess their GCP compliance and will not approve the product unless compliance with the IND study requirements and GCP requirements is satisfactory.

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 that include new efficacy data, the FDA intends to review and act on the supplemental application within 10 months of receipt. As with new BLAs, the review process is often significantly extended by FDA requests for additional information or clarification.

A biological product approved under section 351(a) of the PHSA (a "reference product") can receive 12 years of data exclusivity, meaning that no biosimilar application that cites the reference product can be submitted to the FDA until four years after approval of the reference product, and no biosimilar application that cites the reference product can be approved during the full 12-year period. These exclusivity provisions only apply to biosimilars —companies that rely on their own data and file a full BLA may be approved earlier than 12 years.

***Expedited Development and Review Programs***

The FDA has provided guidance to sponsors developing regenerative medicine therapies for serious or life-threatening diseases or conditions, with recommendations on the expedited development and review of these therapies, as provided under the FD&C Act and the 21st Century Cures Act.

*Fast track designation.* To qualify for fast track designation, a product candidate must be intended to treat a serious condition and address an unmet medical need. Advantages of fast track designation include the possibility for a rolling review, eligibility for priority review, and the ability to have greater interactions with the FDA. In addition, under the Fast Track program and FDA's accelerated approval regulations, the FDA may approve a biologic product based on a surrogate endpoint. A surrogate endpoint is a measurement

of laboratory or clinical signs of a disease or conditions that substitutes for a direct measurement of how a patient feels, functions, or survives. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. A biologic product candidate approved using a surrogate endpoint is subject to rigorous post-marketing compliance requirements, including the completion of post-approval clinical trials to confirm the beneficial effect on a clinical endpoint. Failure to conduct or to confirm a clinical benefit during these required trials may result in FDA withdrawal of the approved biologic product from the market.

Any product submitted to the FDA for marketing approval, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as breakthrough therapy designation, regenerative medicine advanced therapy ("RMAT") designation, priority review designation, and accelerated approval.

*Breakthrough therapy designation.* To qualify for the breakthrough therapy program, a product candidate must be intended to treat a serious condition, and have preliminary clinical data indicating that it provides a substantial improvement on one or more clinically significant endpoints over existing therapies. The FDA will seek to ensure the sponsor of a breakthrough therapy product candidate receives intensive guidance on an efficient drug development program; intensive involvement of senior managers and experienced staff on a proactive, collaborative and cross-disciplinary review; and rolling review.

*Regenerative medicine advanced therapy ("RMAT") designation*. To qualify for the RMAT designation, a product candidate must be a regenerative medicine therapy intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition, and there must be preliminary clinical evidence that the candidate has the potential to address the unmet medical need. The FDA has indicated that gene therapies may qualify as regenerative medicine therapies. Advantages of RMAT designation include early interactions with FDA to discuss any potential surrogate or intermediate endpoints and address potential ways to support accelerated approval and satisfy post-approval requirements.

*Priority review.* A product, including those that receive fast track, breakthrough therapy, or RMAT designations, may be eligible for priority review, if the product meets the criteria for priority review at the time the BLA is submitted. If priority review is granted, FDA has a 6-month goal for reviewing the marketing application or efficacy supplement

*Accelerated approval.* Drug or biologic products with evidence showing that they provide meaningful therapeutic benefit over existing treatments for serious or life-threatening illnesses may receive accelerated approval. Accelerated approval means that a product candidate may be approved on the basis of clinical data establishing that the product candidate has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit. As a condition of approval, the FDA may require that a sponsor conduct post-marketing clinical trials.

***Orphan Drug Designation ("ODD")***

Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug or biological product intended to treat a rare disease or condition—generally a disease or condition that affects fewer than 200,000 individuals in the U.S., or if there is no reasonable expectation that the cost of developing and making the product available in the U.S. will be recovered from sales of the product.

ODD must be requested before submitting a BLA. ODD does not affect the regulatory review and approval process. However, if a product that has orphan designation subsequently receives the first BLA applicant to receive FDA approval for that product for the disease or condition for which it has such designation, that product is entitled to a seven-year exclusive marketing period in the U.S. for that product in the approved indication. During the seven-year marketing exclusivity period, the FDA may not approve any other applications to market the same drug or biological product for the same indication, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity. Among the other benefits of ODD are tax credits for certain research and a waiver of the user fee. In January 2020, FDA published a draft Guidance For Industry providing the current thinking on determining "sameness" for gene therapy products for purposes of orphan drug exclusivity.

***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 manufacturers and their subcontractors are required to register their establishments with FDA and certain state agencies, and are subject to periodic unannounced inspections by FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMP, 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, 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 biologic, 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 biologic. Claims must be truthful and non-misleading. Failure to comply with these requirements can result in fines, adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties.

Physicians may prescribe legally available biologics for uses that are not described in the product's labeling and that differ from those tested by the sponsor and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, impose stringent restrictions on manufacturers' communications regarding off-label use. If the FDA finds that we have promoted off-label use of any product that is eventually approved, sanctions could include refusal to approve pending applications, withdrawal of an approval, 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.

***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, including the False Claims Act and civil monetary penalty law, 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 ("CMS") 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, as amended by Health Information Technology for Economic and Clinical Health Act, which governs and protects the security and privacy of individually identifiable health information of certain health plans, healthcare clearinghouses and healthcare providers, and their respective business associates that perform services for them involving individually identifiable 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, imprisonment, and additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, any of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

In addition, the pharmaceutical and biotechnology industry have received increased public and governmental scrutiny for 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 gene therapy products. In the U.S. and other countries, sales of any products for which we receive marketing approval will depend in part on the availability of coverage and adequate 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. A number of gene or cell therapy products have been approved over the past several years by the FDA. Although the CMS subsequently approved its first method of coverage and reimbursement for Yescarta and Kymriah, the methodology has been subject to criticism by members of Congress. CMS's decision as to coverage and reimbursement for one product does not mean that all similar products will be eligible for analogous coverage and reimbursement. As there is no uniform policy for coverage and reimbursement amongst third-party payors in the United States, even if CMS approves coverage and reimbursement for any of our product candidates, it is unclear what affect, if any, such a decision will have on our ability to obtain and maintain coverage and adequate reimbursement from other private payors.

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 other measures, and tightening of restrictive policies in jurisdictions with existing controls and other 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). In addition, in December 2018, a federal district court judge in Texas found the ACA's individual mandate to be unconstitutional and therefore the entire law to be invalid. In December 2019, the Fifth Circuit affirmed the ruling regarding the individual mandate but remanded the case to the district court for additional analysis of the question of severability and whether portions of the law remain valid. It is likely that the case will ultimately be appealed to the Supreme Court. At this time, it is unclear whether those or future legislative changes and/or litigation 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 U.S. 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 U.S., 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 from the comparable regulatory authorities of foreign countries before commencing clinical trials or marketing of the drug in those countries. Many countries outside of the U.S. have a similar process that requires the submission of a clinical study application much like the IND prior to the commencement of human clinical studies. To obtain regulatory approval of a biological medicinal product under European Union (EU) regulatory systems, we must submit a marketing authorization application. 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 EU 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 EU member states. The decentralized procedure includes selecting one reference member state (RMS), and submitting to more than one EU member state at the same time. The RMS National Competent 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 marketing authorization may submit an application to the remaining member states post-initial approval. Under all three procedures, the Member States shall take measures to ensure the procedure granting a marketing authorization for medical products is completed within 210 days of submission.

In addition to regulations in the EU and the U.S., we or our collaborators will be subject to a variety of foreign regulations governing clinical trials and commercial distribution of our future products.

***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. Certain of our development and manufacturing activities involve use of hazardous materials, and we believe we are in compliance with the applicable environmental laws, regulations, permits, and licenses. However, we cannot ensure that environmental liabilities will not develop in the future. 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, 2020, we had 114 full-time employees, including a total of 18 employees with M.D. or Ph.D. degrees. Within our workforce, 84 employees are engaged in research and development and 30 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.”

Our principal executive offices are located at 800 Saginaw Drive, Redwood City, CA 94063, and our telephone number is (650) 656-9323. 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. 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 Adverum. 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 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. Losses have resulted principally from costs incurred in our research and development programs and from our general and administrative expenses. In the future, we intend to continue to conduct research and development, regulatory compliance activities and, if any of our product candidates is approved, sales and marketing activities that, together with anticipated general and administrative expenses, will likely result in us incurring significant losses for the next several years.

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

***We expect that our cash, cash equivalents, and short-term investments will be sufficient to fund our lead gene therapy programs into 2022. If this expectation proves to be wrong, we may be forced to delay, limit or terminate certain of our development efforts.***

We currently expect this cash, cash equivalents and short-term investments, including the funds received from our public offering of our common stock in February 2020, to fund our planned operations into 2022. 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 expected investments into our manufacturing capabilities, 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 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 potentially to commercialize these product candidates. Any future clinical trials or expansion of ongoing clinical trials of our product candidates would cause an increase in our spending levels, as would other corporate activities. The amount and timing of any expenditure needed to implement our development and commercialization programs will depend on numerous factors, including:

- the type, number, scope, progress, expansion costs, results of and timing of any future preclinical studies and clinical trials of any of our product candidates which we are pursuing or may choose to pursue in the future;
- the need for, and the progress, costs and results of, any additional clinical trials or nonclinical studies of our product candidates we may initiate based on the results of any clinical trials that we may plan or discussions with the FDA, including any additional clinical trials or nonclinical studies the FDA or other regulatory agencies may require evaluating the safety of our product candidates;
- the costs of obtaining, maintaining and enforcing our patents and other intellectual property rights;
- the costs and timing of obtaining or maintaining manufacturing for our product candidates, including commercial manufacturing;
- 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 programs through commercial introduction. We expect that we will need to raise additional funds in the future.

We have no product candidate approved by any regulatory authority, have not sold any products, and we do not expect to sell or derive revenue from any product sales for the foreseeable future. We may seek additional funding through collaboration agreements and public or private financings.

Additional funding may not be available to us on acceptable terms or at all and the terms of any financing may adversely affect the holdings or the rights of our stockholders. In addition, the issuance of additional shares by us, or the possibility of such issuance, may cause the market price of our shares to decline.

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

**Risks Related to the Discovery and Development of Our Product Candidates**

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

Our product candidates are in the early stages of development and will require substantial preclinical and/or clinical development and testing, manufacturing process improvement and validation, bridging studies and regulatory approval prior to commercialization. It is critical to our business to successfully develop and ultimately obtain regulatory approval for one or more of these 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 product candidates;
- receipt of marketing approvals for any future products for which we complete clinical trials, including securing regulatory exclusivity to the extent available;
- establishing commercial manufacturing capabilities, for example, by engaging third-party manufacturers that can provide products and services to support clinical development and the market demand for our product candidates, if approved;
- successful launch and commercial sales of the product, whether alone or in collaboration with potential partners;
- acceptance of the product as a viable treatment option 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 regulations 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, results of operations and prospects.

In April 2019, the FDA placed our IND application for ADVM-022 for the treatment of wet AMD on clinical hold and requested certain information and requirements related to chemistry, manufacturing and controls (“CMC”). We subsequently responded to the FDA, and in May 2019, the FDA lifted the clinical hold, allowing dose escalation up to 2 x 10^12 vg/eye in the OPTIC trial. However, our IND remains on partial clinical hold for dosing patients with a dose of 6 x 10^12 vg/eye. Given the preliminary robust anatomical response we observed from patients in the first cohort, we dosed patients in the second cohort with a lower dose of 2 x 10^11 vg/eye. We do not currently intend to dose patients at 6 x 10^12 vg/eye, but should we need to, there is no guarantee that the FDA will lift the partial clinical hold promptly, if at all. Further, the FDA imposed additional CMC requirements that we are working to resolve in order to advance the clinical development of ADVM-022 for the treatment of wet AMD. If we are unable to respond to these CMC requirements and the requirements related to the partial clinical hold to the FDA’s satisfaction and within the timeframe we expect, the FDA will not remove the clinical hold, which may prevent us from advancing our clinical program and our business may be harmed.

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 product candidates, any such approval may be subject to limitations on the indicated uses for which we may market the product, or limitations related to its distribution.

Accordingly, even if we are able to obtain the requisite financing to continue to fund our development programs, there can be no assurance that any of our product candidates will be successfully developed or commercialized. If we or any of our future development partners are unable to develop, or obtain regulatory approval for, or, if approved, successfully commercialize, any of our product candidates, we may not be able to generate sufficient revenue to continue our business.

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

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

In addition, the clinical trial requirements of the FDA, the European Medicines Agency ("EMA") and other regulatory agencies and the criteria these regulators may use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the potential products. The regulatory approval process for novel gene therapy products such as ours can be more expensive and take longer than for other product types, which are better known or more extensively studied to date. Regulatory approaches and requirements for gene therapy products continue to evolve, and any changes could create significant delay and unpredictability for product development and approval as compared to technologies with which regulatory agencies have more substantial experience. For example, the FDA issued a series of gene therapy draft guidance documents in January 2020 that we are evaluating and that may impact our future development efforts and clinical trial designs.

Also, before a clinical study can begin, that clinical site's institutional review board ("IRB") and its Institutional Biosafety Committee will have to review the proposed clinical trial to assess appropriateness to conduct the clinical study at that site. In addition, adverse developments in clinical trials of gene therapy products conducted by others may cause the FDA or other oversight bodies to change the requirements for human research on or for approval of any of our product candidates.

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

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

The success of our business depends primarily upon our ability to identify, develop and commercialize products based on our platform. Our research programs may fail to identify other potential product candidates for clinical development for a number of reasons. For example, our research methodology may be unsuccessful in identifying potential product candidates or our potential product candidates may be shown to lack efficacy, 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, financial condition, results of operations, and prospects 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 may ultimately prove to be unsuccessful.

***Few of our product candidates and proprietary viral vectors have been tested in clinical trials.***

Drug development has inherent risk. Few of our product candidates and proprietary viral vectors have been evaluated in clinical trials in patients. Our lead product candidate, ADVM-022 for the treatment of wet AMD and diabetic retinopathy, uses a proprietary vector, AAV.7m8, which has undergone limited human testing, and may experience unexpected results in clinical trials in the future. We, or any licensee or development partner, will be required to demonstrate through adequate and well-controlled clinical trials that our product candidate or another party's product candidate containing one of our proprietary viral vectors are safe and effective for use in their target indications before seeking regulatory approvals for 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 or any clinical trials using our proprietary viral vectors. Any such delay or failure could significantly harm our business prospects, financial condition and results of operations.

***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 product candidates are not shown to be safe and effective, we may not realize the value of our investment in our technology. Promising preclinical results generated with a product candidate in animal models do not guarantee similar results when the candidate is tested in humans. For example, the levels of protein expression achieved from a vector in a preclinical model, including non-human primate ("NHP") models, may be significantly higher than the level of protein expression achieved in humans. Similarly, human subjects administered our product candidates may develop side effects that were not observed in animal models and/or are more severe than those observed in animal models. In addition, even industry-accepted animal models may not accurately replicate human disease. For example, the laser-induced choroidal neovascularization model in NHP is the industry accepted animal model for wet AMD, where efficacy is assessed by reduction of the number of clinically relevant neovascular lesions. Even so, this model does not replicate all aspects of wet AMD in humans, some of which may be relevant to the success of ADVM-022. 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. Further, safety and/or efficacy issues with a product candidate may only become apparent when the candidate is tested in human patients suffering the relevant disease. For example, while pre-clinical testing of our product candidate ADVM-043, including in animal models, showed promise in the ADVANCE trial, A1AT protein did not reach a clinically meaningful level of expression in humans, and we subsequently decided to discontinue development of ADVM-043. In addition, in clinical trials, such as our OPTIC trial, each cohort of patients may be treated with a different dose of the tested drug or different prophylactic steroid regimen, potentially resulting in different safety profiles or efficacy levels in each of the cohorts. Furthermore, the initiation of future trials for a product candidate will be dependent upon demonstrating sufficient safety and efficacy to the relevant regulatory authorities in preceding or other ongoing trials using the same product candidate. Companies frequently suffer significant setbacks in advanced clinical trials, even after earlier clinical trials have shown promising results. In addition, only a small percentage of products under development result in the submission of a marketing application and even fewer are approved for commercialization. Even if our clinical trials successfully meet their endpoints for safety and efficacy, FDA and/or other regulatory agencies may still conclude that the product candidate has not demonstrated a beneficial risk/benefit profile or otherwise does not meet the relevant standard for approval.

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

***Preliminary and interim data from our clinical trials that we may announce or publish from time to time may change as each clinical trial progresses.***

From time to time, we may announce or publish preliminary or interim data from our clinical trials. Preliminary and interim results of a clinical trial are not necessarily predictive of final results. Preliminary and interim data are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues or further patient follow up occurs and more patient data become available. For example, although we have periodically announced interim data from the first and second cohorts of patients in our OPTIC trial, which showed no drug- or treatment-related series adverse events ("SAEs") or drug-limiting toxicities ("DLTs"), there is no guarantee that drug- or treatment-related SAEs or DLTs will not occur later in our OPTIC trial, either in these or other cohorts. In addition, in certain clinical trials, such as our OPTIC trial, individual cohorts of patients are enrolled with different dosages and other treatment conditions under our protocol. These different dosages and other treatment conditions may affect clinical outcomes, including safety profiles or efficacy, such as the number of rescue injections required, in each of the cohorts. As a result, preliminary and interim data should be viewed with caution and not relied upon until the final data from a locked database for the entire clinical trial are available. Material changes in the final data compared to preliminary or interim data could significantly harm our business prospects.

***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 preclinical and clinical development, manufacturing, analytical testing, labeling, storage, record-keeping, advertising, promotion, import, export, marketing and distribution of our product candidates are subject to extensive regulation by the FDA and by comparable regulatory authorities in foreign markets. In the U.S., we are not permitted to market our product candidates until we receive regulatory approval from the FDA. The process of obtaining regulatory approval is expensive, often takes many years and can vary substantially based upon the type, complexity and novelty of the products involved, as well as the target indications and patient population. Approval policies or regulations may change, and the regulatory authorities have 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;
- the FDA or other regulatory authorities may not accept clinical data from trials which are conducted at multinational clinical facilities or in countries where the standard of care is potentially different from that of the U.S.;
- the results of clinical trials may not demonstrate the safety or efficacy required by such authorities for approval;
- we or any of our future development partners may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- such authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- approval may be granted only for indications that are significantly more limited than what we apply for and/or with other significant restrictions on distribution and use;
- such authorities may find deficiencies in the manufacturing processes, analytical testing, or facilities of third-party manufacturers or testing laboratories 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 related products, including those already on the market, may result in increased cautiousness by the FDA and comparable foreign regulatory authorities in reviewing our product candidates 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 patients in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.***

Identifying and qualifying patients to participate in the OPTIC trial for ADVM-022 for the treatment of wet AMD, our planned Phase 1/2 trial for ADVM-022 for the treatment of diabetic retinopathy, and any future planned clinical trials will be critical to our success. The timing of current and future clinical trials will depend on the speed at which we can recruit patients to participate in future testing of these product candidates.

Patient 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 patients with wet AMD for the OPTIC trial for ADVM-022, and we will be required to identify and enroll a sufficient number of patients for our planned trials for ADVM-022 for the treatment of diabetic retinopathy and any future clinical trials for our product candidates. Potential patients may not be adequately diagnosed or identified with the diseases which we are targeting or may not meet the entry criteria for our trials. Additionally, some patients may have neutralizing antibodies at titer levels that would prevent them from being enrolled in a clinical trial for any of our product candidates, or may meet other exclusion criteria. The incidence of neutralizing antibodies in the population of patients, particularly for rare diseases, is unknown, and may be higher than we expect. As a consequence, enrollment in our clinical trials may be limited or slowed. We also may encounter difficulties in identifying and enrolling patients 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 patients, or those with required or desired characteristics to achieve diversity in a trial.

Rare diseases impact a small number of individuals in the U.S. (fewer than 200,000) and therefore there is a limited patient pool from which to draw for clinical trials. Enrollment of eligible patients with rare or orphan diseases may be limited or slower than we anticipate in light of the small patient populations involved.

We plan to seek initial marketing approval of these product candidates in the U.S. and/or Europe and we may not be able to successfully conduct clinical trials if we cannot enroll a sufficient number of eligible patients to participate in the clinical trials required by the FDA or the EMA or other regulatory agencies. In addition, the process of finding and diagnosing patients may prove costly.

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

Trials using early versions of retroviral vectors, which integrate into, and thereby alter, the host cell's DNA, have led to several well-publicized adverse events. Our product candidates use an adeno-associated viral vector delivery system. Nonetheless, if patients negatively associate our product candidates with the adverse events caused by previous gene therapy products, they may not choose to enroll in our clinical trials, which would have a material adverse effect on our business and operations.

If we have difficulty enrolling a sufficient number of patients to conduct clinical trials on our product candidates as planned, we may need to delay, limit or terminate future clinical trials, any of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

During the conduct of preclinical studies and clinical trials, animal models and patients 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 discomfort may be reported from time-to-time in clinical trials of our product candidates. It is possible that as we test our product candidates in larger, longer and more extensive clinical programs, or as use of these product candidates becomes more widespread if they receive regulatory approval, illnesses, injuries, discomfort and other adverse events that were observed in earlier trials, as well as conditions that did not occur or went undetected in previous trials, will be reported by patients. Many times, side effects are only detectable after investigational products are tested in large-scale, Phase 3 clinical trials or later stage 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 one or more of our product candidates has side effects or causes serious or life-threatening side effects, the development of one or more of our product candidates may fail or be delayed, or, if one or more of our product candidates has received regulatory approval, such approval may be revoked, which would severely harm our business prospects, financial condition and results of operations.

When a patient experiences a negative health event during a clinical trial, we must determine if it is related to our product candidate in order to understand the safety of our product candidates. The patients we enroll in our clinical trials for our current product candidates are less healthy than the general population, which increases the likelihood that a negative health event, unrelated to our product candidate, may occur. These health events may be misattributed to our product candidate, either by us, our investigators, or by regulators. Such misattribution could cause regulatory approval of our product candidates to be denied or delayed. For example, the patients enrolled in our OPTIC trial, and any future clinical trials for wet AMD, are often geriatric and have other health conditions unrelated to wet AMD. We cannot assure you that we will be able to accurately determine whether or not a negative health event was related to ADVM-022, nor can we assure you that the FDA or other regulatory authority responsible for reviewing the safety of ADVM-022 will agree with our determination. If a patient in OPTIC or another clinical trial experiences a negative health event, and that event is misattributed to ADVM-022, the trial may be placed on clinical hold, and regulatory approval of ADVM-022 may be delayed or denied.

In addition, if a patient enrolled in one of our clinical trials experiences a negative health event, they may be forced to withdraw from our trial, or may become temporarily unavailable for follow-up visits, which may impact the amount or quality of data we obtain from our trial, which in turn may delay or prevent regulatory approval of our product candidate. Because patients we enroll in our clinical trials for any of our product candidates are likely to be less healthy than the general population, and particularly in trials like OPTIC that enroll a small number of patients, this risk is increased.

Our product candidates built on AAV vectors have similar risks to other gene therapy vectors, including inflammation, cytotoxic T-cell responses, anti-AAV antibodies and immune response to the transgene product, such as T-cell responses and/or antibodies against the expressed protein. For example, based on our current clinical experience, ocular inflammation is a known side effect of ADVM-022 administration, but the duration of inflammation caused by ADVM-022, our ability to manage that inflammation using steroids or other anti-inflammatory treatments, and any potential clinical sequelae of that inflammation and treatments used to manage inflammation are not fully understood. If we are unable to manage this inflammation appropriately, the FDA or other regulatory authorities may not approve ADVM-022. Even if we achieve marketing approval, doctors may not prescribe, and patients may not use ADVM-022 or our other product candidates if they deem the levels or risk of inflammation to be unacceptable. Further, patients treated with ADVM-022 could develop antibodies against AAV.7m8 capsid and/or aflibercept protein. These antibodies could preclude these patients from receiving other AAV-based gene therapies and/or recombinant aflibercept protein in the future. Studies have also found that intravenous delivery of certain AAV vectors at very high doses may result in adverse events and have prompted the recommendation that studies involving high doses of AAV vectors should be monitored carefully for such adverse events. In addition, patients given infusions of any protein may develop severe hypersensitivity reactions, infusion reactions, or serious side

effects including transaminitis. With respect to our product candidates that are being or may be studied in diseases of the eye, there are additional potential serious complications related to intravitreal injection, such as retinal detachment, endophthalmitis, ocular inflammation, cataract formation, glaucoma, hypotony, damage to the retina or cornea, and bleeding in the eye. Serious complications or serious, unexpected side effects in connection with the use of our product candidates could materially harm our business prospects, financial condition and results of operations.

Additionally, our lead product candidate, ADVM-022 is designed for long-term, sustained expression of an exogenous protein, aflibercept. Even though Eylea® (aflibercept) has been approved by several regulatory authorities, including the FDA, for the treatment of wet AMD, there may be side effects associated with aflibercept being expressed as a gene therapy treatment modality. If such side effects are serious or life-threatening, the development of our product candidate and future product candidates may fail or be delayed, or, if such product candidate(s) have received regulatory approval, such approval may be revoked, which would severely harm our business prospects, financial condition and results of operation.

**Risks Related to Our Reliance on Third Parties**

***We will rely on third parties to conduct some preclinical testing and all of our planned clinical trials. If these third parties do not meet our deadlines or otherwise fail to 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, clinical testing, or clinical trials ourselves. We are dependent on third parties to conduct preclinical studies and clinical trials for our product candidates, and, therefore, the timing of the initiation and completion of these studies or trials is controlled in part by these third parties and may occur at times substantially different from our estimates. Specifically, we use and rely on medical institutions, clinical investigators, contract research organizations ("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 patients enrolled in our ongoing clinical trials unless we are able to transfer those patients 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, the utility of certain data from the clinical trial may be questioned and the utility of the clinical trial itself may be jeopardized, which could result in the delay or rejection of any IND or BLA we submit to the FDA, or equivalent submissions to other regulatory authorities. Any such delay or rejection could prevent us from commercializing our product candidates.

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

We do not expect to independently conduct all aspects of our vector production, product manufacturing, product testing, protocol development, protocol performance, and research. We currently rely, and expect to continue to rely, on third parties with respect to these items. We may not be able to enter into agreements with these third parties and if we do enter into agreements with these third parties, any of these third parties may not be successful at fulfilling their contractual obligations or may choose to 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 vector production, product manufacturing, product testing, protocol development, protocol performance, and research activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations. If any of these third parties on which we rely do not perform satisfactorily, we will remain responsible for ensuring that:

- each of our preclinical studies and clinical trials are conducted in accordance with the study plan and protocols and applicable GLP requirements;
- vector production, product manufacturing, and product testing are conducted in accordance with cGMP and other applicable regulatory requirements;
- other research is conducted in accordance with applicable industry and regulatory standards and norms;

any of which we may not be able to do.

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

Reliance on third-party manufacturers 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 some or 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 acquisition, change in control, or bankruptcy of the manufacturer or supplier.

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

***We and our contractors are subject to significant regulation with respect to manufacturing and testing our product candidates. We have a limited number of vendors on which we rely, including, in some cases, single source vendors, and the contract vendors on which we rely may not continue to meet regulatory requirements, may have limited capacity, or may have other factors limiting their ability to comply with their contracts with us.***

We currently have relationships with a limited number of suppliers for the manufacturing and testing of our vector product candidates. Our suppliers may require licenses to manufacture or test 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, and may be unable to acquire such rights, to the extent that we do not already have them.

All entities involved in the preparation of therapeutics for clinical trials or commercial sale, including our existing contract vendors for our product candidates, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in clinical trials must be manufactured and tested in accordance with cGMP regulations. 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 cGMP regulations enforced by the FDA through its facilities inspection program as well as other regulations enforced by other regulatory authorities. Our contract manufacturers have not produced a commercially-approved AAV product and therefore have not yet demonstrated compliance with cGMP regulations to the satisfaction of the FDA or other regulatory authority. 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. If the facility does not pass a pre-approval plant inspection, FDA or other regulatory approval of the products will not be granted. 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. Should the FDA or other regulatory authority determine that the facility is not in compliance with applicable regulations, the manufacture and release of our product candidates may not be possible, and our business could be harmed.

Changes in laws and governmental policies may have an effect on regulations. For example, we and our contract vendors currently rely on other contractors based in the United Kingdom (UK). If the implementation of new governmental policies associated with BREXIT occurs, these governmental policies may affect our UK-based contractors' ability to comply with applicable regulations, including existing EU regulations. If they are unable to return to compliance, or if an acceptable substitute vendor cannot be identified, it may negatively impact our business. Further, to the extent that our UK-based contractors have supply relationships with vendors in the EU, these contractors may experience difficulties, delay or increased costs in receiving materials from their vendors in the EU, which could have a material adverse effect on our UK-based contractors' ability to provide the services or materials to us.

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 we become aware of a violation of our product specifications or applicable regulations, independent of 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 which may include the temporary or permanent suspension of a clinical trial 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 contractors fail to maintain regulatory compliance, the FDA can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new biologic product, revocation of a pre-existing approval, injunction, seizure of product, or other civil or criminal penalties or closing one or more manufacturing or testing facilities. As a result, our business, financial condition and results of operations may be materially harmed.

Additionally, if the service provided by an approved manufacturing or testing contractor is interrupted, there could be a significant disruption in commercial supply. An alternative contractor would need to be qualified through a BLA supplement which could result in further delay. The regulatory agencies may also require additional studies showing comparability between approved product or testing, and product or testing provided after a contractor change, if a new manufacturing or testing contractor is relied upon for commercial production. Switching contractors may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

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

***Our reliance on third parties requires us to share our trade secrets and other confidential information, which increases the possibility that a competitor will discover them or that our confidential information, including 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 confidential information, including 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 containing confidentiality provisions 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 purposefully or inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Public disclosure of our confidential information also prevents us from seeking patent protection for that or related discoveries. Given that our proprietary position is based, in part, on our know-how and trade secrets, the unauthorized use or disclosure of our trade secrets would impair our competitive position and may have a material adverse effect on our business, financial conditions, results of operations and prospects.

In addition, these agreements typically restrict the ability of our advisors, employees, third-party contractors and consultants to publish data potentially relating to our confidential information and 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 information or trade secrets from any such publication. However, we may fail to recognize or identify to our collaborator such confidential information or trade secrets during the appropriate timeframe prior to publication, and they may be publicly disclosed without us filing for patent or other protection. 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, or publication of information by any of our third-party collaborators. A competitor’s discovery of our trade secrets could impair our competitive position and have an adverse impact on our business, financial condition, results of operations and prospects.

**Risks Related to Commercialization of Our Product Candidates**

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

Before we can initiate clinical trials in the U.S. for our product candidates, we need to submit the results of preclinical testing to the FDA, along with other information including information about product candidate chemistry, manufacturing and controls and our proposed clinical trial protocol, as part of an IND. We may rely in part on preclinical, clinical and quality data generated by CROs and other third parties for regulatory submissions for our product candidates. If these third parties do not provide timely data for our product candidates, it will delay our plans for our IND submissions and 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 with any regulatory authority or agency may significantly affect our product development timeline. 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 or terminated for a number of reasons, including delays or terminations related to:

- the FDA failing to grant permission to proceed or placing the clinical trial on hold;
- patients failing to enroll or remain in our trial at the rate we expect;
- patients 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;
- patients 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, lacking the ability or resources to appropriately handle our product candidates, 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 and 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 IND 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 patients, or withdrawing its approval of the trial.

In April 2019, the FDA placed our IND application for ADVM-022 for the treatment of wet AMD on clinical hold and requested certain information and requirements related to CMC as described in “Our business will depend substantially on the success of one or more of our product candidates. If we are unable to develop, obtain regulatory approval for, or successfully commercialize, any or all of our product candidates, our business will be materially harmed.” above. If we are unable to respond to these CMC requirements and the requirements related to the partial clinical hold to the FDA’s satisfaction and within the timeframe we expect, the FDA will not remove the clinical hold, which may prevent us from advancing our clinical program and our business may be harmed.

Product development costs will increase if we have delays in testing or approval of any of our product candidates, such as the partial clinical hold on our IND for ADVM-022 for the treatment of wet AMD, 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 review and approval, 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, such as the partial clinical hold on our IND for ADVM-022 for the treatment of wet AMD, may also ultimately lead to the denial of regulatory approval of a product candidate. If we make manufacturing or formulation changes to our product candidates, we may need to conduct additional studies to bridge our modified product candidates to earlier versions. Further, if one or more clinical trials are delayed, including as a result of the partial clinical hold on our IND for ADVM-022 for the treatment of wet AMD, or terminated, 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 product candidates, if approved, may be delayed and the credibility of our management team may be adversely affected and, as a result, our stock price may decline.***

From time to time, we estimate the timing of the accomplishment of various scientific, clinical, regulatory and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of,

or the availability of data from, scientific studies and clinical trials and the submission of regulatory filings. From time to time, we may publicly announce the expected timing of some of these milestones. All of these milestones will be based on a variety of assumptions. The actual timing of these milestones can vary dramatically compared to our estimates, in some cases for reasons beyond our control. If we do not meet these milestones as publicly announced, the commercialization of our products may be delayed and the credibility of our management team may be adversely affected 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.***

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

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

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

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

- issue warning letters or untitled letters;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve pending applications or supplements or applications filed by us;
- institute import holds;
- 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 ("REMS") 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 ongoing 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 be subject to permanent injunctions under which specified promotional conduct is changed or curtailed.

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

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

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

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

***If the market for our product candidate, if approved, in the treatment of wet AMD, or any other indication we seek to treat 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 or any other indication we seek to treat is smaller than we anticipate (including in our rare disease programs), we may not be able to achieve profitability and growth. Our projections of the number of people who have wet AMD and other indications, as well as the subset of people with the disease who have the potential to benefit from treatment with ADVM-022 or other future product candidates, 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 as we continue to enroll patients in the OPTIC trial of ADVM-022 for the treatment of wet AMD, and we cannot accurately predict the number of patients for whom treatment might be possible. For example, some patients with wet AMD have neutralizing antibodies at titer levels that may prevent them from benefiting from ADVM-022. If this patient population is larger than we estimate, the market for ADVM-022 may be smaller than we anticipate, and our future revenue may be adversely affected. In addition, we expect prophylactic steroid treatment will be required to manage inflammation associated with treatment with ADVM-022, and certain patients cannot be treated with prophylactic steroids. If this proportion of patient population is larger than we estimate, the market for ADVM-022 may be smaller than we anticipate. Additionally, the potentially addressable patient population may be limited or may not be amenable to treatment with our product candidates for other reasons, and new patients may become increasingly difficult to identify or gain access to, which would adversely affect our results of operations and our business.

Further, even if we obtain significant market share for any of our rare disease programs, because the potential target population is very small, we may never achieve profitability despite obtaining such significant market share.

Additionally, because the target patient population for any of our rare disease programs is 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 any of our product candidates targeting such rare disease will be adversely affected. The manner and level at which reimbursement is provided for services related to this product candidate (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 our product candidates targeting such rare disease.

***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; and
- cost-effective.

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

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

As a result of legislative proposals and the trend toward managed health care in the U.S., third-party payers are increasingly attempting to contain health care costs by limiting both coverage and the level of reimbursement of new drugs. By way of example, in March 2010, the 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.

There remain judicial and Congressional challenges to certain aspects of the Affordable Care Act. Since January 2017, President Trump has signed Executive Orders and other directives designed to eliminate, circumvent or loosen the implementation of certain provisions of the Affordable Care Act or otherwise circumvent some of the requirements for health insurance mandated by the Affordable Care Act. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the Affordable Care Act. While Congress has not passed repeal legislation, the Tax Cuts and Jobs Act of 2017 includes a provision that repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." Additionally, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the Affordable Care Act's mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminates the health insurer tax. Moreover, the Bipartisan Budget Act of 2018, or the BBA, among other things, amended the Affordable Care Act, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare Part D drug plans, commonly referred to as the "donut hole." Further, in December 2018, CMS published a final rule permitting further collections and payments to and from certain Affordable Care Act-qualified health plans and health insurance issuers under the Affordable Care Act adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. Congress may consider other legislation to repeal or replace elements of the Affordable Care Act. In December 2018, a federal district court judge in Texas found the ACA's individual mandate to be unconstitutional and therefore the entire law to be invalid. In December 2019, the Fifth Circuit affirmed the ruling regarding the individual mandate but remanded the case to the district court for additional analysis of the question of severability and whether other portions of the law remain valid. It is unclear

how this decision, future decisions, subsequent appeals, and other efforts to repeal and replace the ACA will impact the ACA and our business.

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 due to subsequent legislative changes to the statute, including the BBA, will stay in effect through 2029 unless additional Congressional action is taken.

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

Recently there has been heightened governmental scrutiny over pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. At the federal level, the Trump administration has proposed further drug price control measures that could be enacted by future regulatory action or in future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs, to set reimbursement under Medicare Part B according to an international pricing index, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. Further, the Trump administration released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. The U.S. Department of Health and Human Services solicited feedback on some of these measures and has implemented others under its existing authority. Although a number of these and other measures may require additional authorization to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

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 product candidates.

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

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

- The manufacturing and distribution 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 product candidates or in the manufacturing facility in which our product candidates 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 product candidates 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 product candidates 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 product candidates. This may lead to significant delays in the availability of sufficient supply of the product candidate substance for our clinical trials or the termination or hold on a clinical trial, or the delay or prevention of a filing or approval of marketing applications for our product candidates.
- Significant noncompliance could also result in the imposition of sanctions, including fines, injunctions, civil penalties, failure of regulatory authorities to grant marketing approvals for our product candidates, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of products, operating restrictions, and criminal prosecutions, any of which could be costly and damage our reputation. If we are not able to maintain regulatory compliance, we may not be permitted to market our product candidates, if approved, 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 and assure that the product or product candidate is made strictly and consistently in compliance with the process.
- We have to develop the manufacturing process for late stage clinical product, and our current process has not been fully characterized and therefore is open to potential variations that could lead to defective product substance that does not meet specification.
- Problems with the manufacturing, storage or distribution of our product candidates, including even minor deviations from our established parameters, 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 product candidates may result in shipment delays, inventory shortages, lot failures, product withdrawals or recalls, or other interruptions in the supply of our product candidates. We may also have to take inventory write-offs and incur other charges and expenses for product substance that fails to meet specifications, undertake costly remediation efforts, or seek more costly manufacturing alternatives. We may encounter problems manufacturing sufficient research-, clinical-, or commercial-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 milestone and/or royalty payments.***

We have entered into development or other strategic collaborations with major biotechnology or pharmaceutical companies. Research activities under our collaboration agreements are subject to mutually agreed-on research plans and budgets, and if we and our strategic partners are unable to agree on the research plan or research budget in a timely fashion or at all, performance of research activities will be delayed. In addition, some of our strategic partners may terminate any agreements they enter into with us or allow such agreements to expire by their terms. If we fail to maintain our current or future strategic collaborations, we may not realize milestone and royalty payments or other revenues under the collaboration agreements.

***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, marketed more successfully, or demonstrated to be safer or more effective or easier to administer 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, biotechnology, and gene therapy 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 and gene therapies in development or being commercialized by our competitors for the indications that we intend to test. Many of our competitors have significantly greater financial, product candidate development, manufacturing, and marketing resources than we do. Large pharmaceutical and biotechnology companies have extensive experience in clinical testing and obtaining regulatory approval for drugs. In addition, universities and private and public research institutes may be active in our target disease areas, and some could be in direct competition with us. We also may compete with these organizations to recruit management, scientists, and clinical development personnel. We will also face competition from these third parties in establishing clinical trial sites, registering patients for clinical trials, and in identifying and in-licensing new product candidates. For example, REGENXBIO is developing RGX-314, an AAV-based gene therapy delivering Lucentis (ranibizumab) for the treatment of wAMD, diabetic retinopathy, and diabetic macular edema, which competes for the same patients, study site resources, and personnel as ADVM-022. 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 biotechnology and vectorology technologies and methods of treating disease, occur in the pharmaceutical, biotechnology and gene therapy industries at a rapid pace. Developments by competitors may render our product candidates obsolete or noncompetitive. Competition in drug development is intense. In addition, we believe that duration of efficacy is an important consideration by physicians and patients when choosing a therapy. However, we do not know and may not know prior to any potential approval the duration of efficacy of our product candidates. 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, Lucentis® and EYLEA are currently available in the U.S. for treatment of wet AMD, diabetic macular edema, macular edema secondary to retinal vein occlusion and diabetic retinopathy. 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 or other therapies 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 therapies that may be safer or more effective or easier to administer than our product candidates. For example, if we continue clinical development of, and seek to commercialize, ADVM-022 for the treatment of wet AMD, it will compete with a variety of therapies currently marketed and in development for wet AMD, using therapeutic modalities such as biologics, small molecules, long acting delivery devices, and gene therapy. Lucentis and EYLEA 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 wet AMD, including Allergan, Bayer, Hoffmann-La Roche Ltd., Novartis, Regeneron and REGENXBIO.

***We have no sales, marketing or distribution capabilities, and we would 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 would have to invest significant amounts of financial and management resources to develop internal sales, distribution and marketing capabilities, some of which will be

committed prior to any confirmation that any of our product candidates will be approved, if at all. We may not be able to hire consultants or external service providers to assist us in sales, marketing and distribution functions on acceptable financial terms or at all. Even if we determine to perform sales, marketing and distribution functions ourselves, we could face a number of additional related risks, including:

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

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

We intend to seek approval to market our product candidates in both the U.S. and in foreign jurisdictions. If we obtain approval in one or more jurisdictions, we will be subject to rules and regulations in those jurisdictions relating to our product candidates. In some 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. Trials using early versions of retroviral vectors, which integrate into, and thereby alter, the host cell’s DNA, have led to several well-publicized adverse events. Although none of our current product candidates utilize retroviruses and we believe AAVs used in our product candidates have low-integrating potential and are not known to cause disease in humans, our product candidates do use a viral vector delivery system. The risk of serious adverse events remains a concern for gene therapy and we cannot assure that it will not occur in any of our current or future clinical trials. In addition, there is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biological activity of the genetic material or other components of products used to carry the genetic material.

Adverse events in trials or studies conducted by us or other parties, in particular involving the same or similar AAV serotypes to the ones we are using, even if not ultimately attributable to our product candidates or to an AAV serotype that we employ, and 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. Similarly, our lead product candidate, ADVM-022 expresses the aflibercept protein, which is also the active ingredient in Eylea. If safety or efficacy issues occur relating to Eylea, even if not ultimately attributable to aflibercept, this may negatively impact our product candidate. If any such adverse events or issues 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 clinical 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, clinical and scientific staff. The loss of service of any of our management or clinical or scientific staff 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 may not be able to attract or retain qualified management, scientific and clinical personnel in the future due to the intense competition for qualified personnel among biotechnology, pharmaceutical and other businesses, particularly in the San Francisco Bay

Area. Our industry has experienced a high rate of turnover of management and scientific personnel in recent years. If we are not able to attract, retain and motivate necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our development objectives, our ability to raise additional capital and our ability to implement our business strategy.

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

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

We had 107 full-time employees as of December 31, 2019. We will need to grow our organization, or certain functions within our organization, substantially to continue development and pursue the potential commercialization of our product candidates, as well as function as a public company. As we seek to advance our product candidates, we may need to expand our financial, development, regulatory, manufacturing, marketing and sales capabilities or contract with third parties to provide these capabilities for us. As our operations expand, we expect that we will need to manage additional relationships with various strategic partners, suppliers and other third parties. Future growth will impose significant added responsibilities on members of management and require us to retain or otherwise manage additional internal capabilities. Our future financial performance and our ability to commercialize our product candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to manage our development efforts and clinical trials effectively and hire, train and integrate any additional management, clinical and regulatory, financial, administrative and sales and marketing personnel. We may not be able to accomplish these tasks, and our failure to accomplish them 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 state 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 their exceptions and 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 exceptions and regulatory safe harbors protecting certain common activities from prosecution, the exceptions 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 exception 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 statutes governing healthcare fraud. A person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it. In addition, the Affordable Care Act provided that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

Additionally, federal false claims laws, including the False Claims Act, and the civil monetary penalty law prohibit knowingly presenting or causing the presentation of a false, fictitious, or fraudulent claim for payment to the U.S. government. Actions under the False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government.

Violations of the False Claims Act can result in significant monetary penalties and treble damages. The federal government is using the False Claims Act, and the accompanying threat of significant liability, in its investigation and prosecution of pharmaceutical and biotechnology companies throughout the country, for example, in connection with the promotion of products for unapproved uses and other sales and marketing practices. The government has obtained multi-million and multi-billion dollar settlements under the False Claims Act in addition to individual criminal convictions under applicable criminal statutes. Given the significant size of actual and

potential settlements, it is expected that the government will continue to devote substantial resources to investigating healthcare providers' and manufacturers' compliance with applicable fraud and abuse laws.

In addition, there has been a recent trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The Affordable Care Act, among other things, imposes new reporting requirements on drug manufacturers, under the federal Physician Payments Sunshine Act, for payments made by them to physicians, as defined by such law, 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 significant civil monetary penalties, 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.

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 significant penalties, including, without limitation, civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs, imprisonment, and additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, any of which could adversely affect our ability to operate our business and our financial results.

***We are subject to certain U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions, and other trade laws and regulations (collectively, "Trade Laws"). We can face serious consequences for violations.***

Among other matters, Trade Laws prohibit companies and their employees, agents, CROs, legal counsel, accountants, consultants, contractors, and other partners from authorizing, promising, offering, provide, soliciting, or receiving directly or indirectly, corrupt or improper payments or anything else or anything of value to or from recipients in the public or private sector. Violations of Trade laws can result in substantial criminal fines and civil penalties, imprisonment, the loss of trade privileges, debarment, tax assessments, breach of contract and fraud litigation, reputational harm, and other consequences. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. We also expect our non-U.S. activities to increase in time. We engage third parties for clinical trials and/or obtain necessary permits, licenses, registrations, and other regulatory approvals. We can be held liable for the corrupt or other illegal activities of our personnel, agents, or partners, even if we do not explicitly authorize or have prior knowledge of such activities.

***If we fail to comply with applicable U.S. and foreign privacy and data protection laws and regulation, we may be subject to liabilities that adversely affect our business, operations and financial performance.***

We are subject to or affected by numerous federal, state and foreign laws and regulations, as well as regulatory guidance, governing the collection, use, disclosure, retention, and security of personal data, such as information that we collect about patients and healthcare providers in connection with clinical trials in the U.S. and abroad. The global data protection landscape is rapidly evolving, and implementation standards and enforcement practices are likely to remain uncertain for the foreseeable future. This evolution may create uncertainty in our business, result in liability or impose additional costs on us. The cost of compliance with these laws, regulations and standards is high and is likely to increase in the future. Any failure or perceived failure by us to comply with federal, state, or foreign laws or self-regulatory standards could result in negative publicity, diversion of management time and effort and proceedings against us by governmental entities or others. In many jurisdictions, enforcement actions and consequences for noncompliance are rising.

For example, HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 ("HITECH"), imposes, among other things, certain standards relating to the privacy, security, transmission and breach reporting of individually identifiable health information, upon health plans, healthcare clearinghouses and certain healthcare providers, and their respective business associates that perform services for them involving individually identifiable health information. In the event we are subject to HIPAA, and fail to properly maintain the privacy and security of certain individually identifiable health information, or we are responsible for an inadvertent disclosure or security breach of such individually identifiable health information, we could be subject to enforcement measures, including civil and criminal penalties and fines for violations of state and federal privacy or security standards, such as HIPAA and HITECH, and their respective implementing regulations.

Additionally, certain states have adopted comparable privacy and security laws and regulations, some of which may be more stringent than HIPAA. HIPAA, HITECH and comparable state laws and regulations will be subject to interpretation by various courts and other governmental authorities, thus creating potentially complex compliance issues for us and our future customers and strategic partners. Any liability from failure to comply with the requirements of these laws, to the extent such requirements are deemed to apply to our operations, could adversely affect our financial condition. The costs of complying with privacy and security related legal and regulatory requirements are burdensome and could have a material adverse effect on our results of operations.

Our operations abroad may also be subject to increased scrutiny or attention from data protection authorities. Many countries in these regions have established or are in the process of establishing privacy and data security legal frameworks with which we, our customers, or our vendors must comply. For example, the EU has adopted the General Data Protection Regulation, or GDPR, which went into effect in May 2018 and introduced strict requirements for processing personal data. The GDPR is likely to increase compliance burden on us, including by mandating potentially burdensome documentation requirements, granting certain rights to individuals to control how we collect, use, disclose, retain and leverage information about them. The processing of sensitive personal data, such as physical health condition, may impose heightened compliance burdens under the GDPR and is a topic of active interest among foreign regulators. In addition, the GDPR provides for breach reporting requirements, more robust regulatory enforcement and fines of up to 20 million euros or up to 4% of the annual global revenue. In the United States, California recently enacted the California Consumer Privacy Act ("CCPA"), which took effect on January 1, 2020. The CCPA gives California residents expanded rights to access and delete their personal information, opt out of certain personal information sharing, and receive detailed information about how their personal information is used. The CCPA also requires covered businesses to provide detailed privacy notices to California residents and respond to requests from California residents to exercise their rights under the CCPA without discrimination. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. The CCPA may increase our compliance costs and potential liability. Some observers have noted that the CCPA could mark the beginning of a trend toward more stringent privacy legislation in the U.S. In addition to a new ballot measure already introduced in California which would amend the CCPA, the CCPA has prompted a number of proposals for new federal and state privacy legislation that, if passed, could increase our potential liability, increase our compliance costs and adversely affect our business. Further, as we continue to expand into other foreign countries and jurisdictions, we may be subject to additional laws and regulations that may affect how we conduct business.

***We and our development partners, third-party manufacturer and suppliers use biological materials and use or 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 use or 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 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 $5.0 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 product candidates. If we and any of our future development partners fail to comply with our or their reporting obligations, the FDA or a foreign regulatory authority could take action, including criminal prosecution, the imposition of civil monetary penalties, seizure of the product and delay in approval or clearance of other products.

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

In the ordinary course of our business, we, our CROs, and other third parties on which we rely, collect and store sensitive data, including legally protected patient health information, personally identifiable information about our employees, intellectual property, and proprietary business information. These applications and data encompass a wide variety of critical information including research and development information and business and financial information.

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

***We have entered into a lease for a new corporate, process development, and research headquarters, which may be more costly to continue building out than we anticipate and may not provide all of the functionality we expect, which could cause us to incur unanticipated costs.***

In June 2018, we entered into a lease for a building located in Redwood City, California, which we began occupying in January 2020. This facility serves as our new corporate headquarters and includes approximately 81,000 square feet of office, development, and research laboratory space. We believe this facility will enable us to increase our in-house process development capabilities to the

1000-liter scale. There can be no assurance that the continued cost of building out this space will not be significantly more than we expect, or that the functionality of this space will be as we expect.

Additionally, since we are not developing this space for clinical or commercial manufacturing production, we will continue to rely upon our limited number of suppliers to manufacture our gene therapy product candidates for clinical trials and if they are approved, for commercial sale.

***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, fires, disease epidemics such as the recent outbreak of the corona virus COVID-19, and other natural or manmade disasters or business interruptions, for which we are predominantly self-insured. For example, a disease epidemic, such as the corona virus COVID-19, that makes patients reluctant to make additional clinical trial visits to a healthcare provider, may make it more difficult to enroll patients in our clinical trials. In addition, we rely on third-party research facilities, manufacturers other service providers from other countries and from different parts of the U.S. to provide services and resources necessary to support our research and development plans, to produce our product candidates, and support our clinical trials. Our ability to obtain this necessary support or supplies could be disrupted if the operations of these suppliers or service providers, or national and international supply chains are affected by a man-made or natural disaster or other business interruption, including national or international health concerns such as the current COVID-19 epidemic. The occurrence of any of these business disruptions, including of our own operations, 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 our code of conduct or regulatory standards and requirements.***

We are exposed to the risk that our employees, independent contractors, principal investigators, CROs, consultants and vendors may engage in misconduct including code of conduct violations, fraudulent conduct or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct, or disclosure of unauthorized activities to us that violates: (1) FDA regulations, including those laws requiring the reporting of true, complete and accurate information to regulatory authorities, (2) manufacturing standards, (3) federal and state health care fraud and abuse laws and regulations or (4) laws that require the reporting of financial information or data accurately. Specifically, sales, marketing, and business arrangements in the health care industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Activities subject to these laws also involve improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

**Risks Relating to Our Intellectual Property**

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

We currently are heavily reliant upon licenses of certain patent rights and proprietary technology from third parties that are important or necessary to the development of our technology and products, including technology related to our manufacturing process and our gene therapy product candidates. These and other licenses may not provide adequate rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and products in the future, or may contain other limitations on our ability to use such intellectual property or technology. As a result, our ability to develop or commercialize our processes and product candidates may be limited by the terms of such agreements. Further, the third parties from whom we license certain patent rights and proprietary technology may attempt to terminate their agreements with us. For example, we have received from Virovek a notice of intent to terminate our non-exclusive license to certain Virovek technology and know-how related to methods and materials for manufacturing adeno-associated virus. While we do not believe Virovek has the right to terminate the agreement, if it were terminated, we may be unable to obtain a new license to Virovek technology on commercially reasonable terms, if at all. If we need to develop or acquire alternative manufacturing technology, our product development activities may be significantly delayed, and if we were unable to develop or acquire alternative manufacturing technology, it could have a material adverse effect on our business. In addition, we may not be able to prevent competitors from

developing and commercializing competitive products to the extent our licenses to patents are non-exclusive or limited with respect to fields of use or territories.

We anticipate that licenses to additional third-party technology will be required for our development programs, and these licenses may not be available in the future or may not be available on commercially reasonable terms, which could prevent us from commercializing our development programs and have a material adverse effect on our business and financial condition, results of operations and prospects.

***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 any of our product candidates will have patent protection, that our patent applications or those of our licensors will result in patents being issued or that issued patents, if any, will afford sufficient protection against competitors with similar technology, nor is there any assurance that the patents issued will not be infringed, designed around or invalidated by third parties. Even issued patents may later be found unenforceable or may be modified or revoked in proceedings instituted by third parties before various patent offices or in courts. The degree of future protection for our proprietary rights is uncertain. Only limited protection may be available and may not adequately protect our rights or permit us to gain or keep any competitive advantage. This failure to properly protect the intellectual property rights relating to our product candidates could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

We own and license certain method-of-use patents and applications covering methods of treating certain diseases with our product candidates. Method-of-use patents protect the use of a product for the specified method or for treatment of a particular indication. However, methods of treating human diseases are considered unpatentable in many jurisdictions, and even where available this type of patent does not prevent a competitor from making and marketing a product that is identical to our product candidate 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;
- patents may expire before or soon after the product they cover is commercialized;
- 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 product candidates;
- there may be significant pressure on the U.S. government and international governmental bodies to limit the scope of patent protection both inside and outside the U.S. for disease treatments that prove successful, as a matter of public policy regarding worldwide health concerns; and
- countries other than the U.S. may have patent laws less favorable to patentees than those upheld by the U.S. courts, allowing foreign competitors a better opportunity to create, develop and market competing product candidates.

In addition, we rely on the protection of our trade secrets and know-how. Although we have taken steps to protect our trade secrets and 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.

Trade secrets do not provide any protection against the independent development of the trade secret by a competitor or other third party. If a competitor independently obtains or develops our trade secret, either by reverse engineering our product or other legal means, we would be unable to prevent them from using the trade secret, and our competitive position would be harmed.

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, especially in the field of gene therapy, 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.

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, results of operations and prospects.

***The patent protection and patent prosecution for some of our product candidates are 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 Regents of the University of California, Cornell University, and Virovek, 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, our ability to develop and commercialize those product candidates may be adversely affected and we may not be able to prevent competitors from making, using and selling competing products.

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

If we or any of our future development partners were to initiate legal proceedings against a third party to enforce a patent directed at one of our product candidates, or one of our future product candidates, the defendant could counterclaim that our patent is invalid and/or unenforceable in whole or in part. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or

unenforceability are commonplace. Grounds for a validity challenge include an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement.

Grounds for an unenforceability assertion could include an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO or made a false or misleading statement during prosecution. Third parties may also raise similar claims before the USPTO, even outside the context of litigation. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on such product candidate. Such a loss of patent protection would have a material adverse impact on our business.

Interference proceedings provoked by third parties or brought by us or declared by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms.

Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our research and development programs, license necessary technology from third parties, or enter into development or manufacturing partnerships that would help us bring our product candidates to market.

Even if resolved in our favor, litigation or other legal proceedings relating to our intellectual property rights may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could compromise our ability to compete in the marketplace.

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

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

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

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

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

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

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

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

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

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

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

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

We may also be subject to claims that former employees, collaborators or other third parties have an ownership interest in our patents or other intellectual property. We require all employees to sign proprietary information and invention assignment agreements, but they may fail to do so, or our agreements may be found invalid or unenforceable. 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 extensions for patents covering our product candidates, our business may be materially harmed.***

If we are able to secure FDA marketing approval for one of our product candidates that is covered by an issued U.S. patent, that patent may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984 (“Hatch-Waxman Act”). The Hatch-Waxman Act permits a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, we may not be granted an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or restoration or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our business, financial conditions and results of operations may be materially and adversely affected.

***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 materially and adversely impact our business, financial condition, results of operations, or prospects.

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

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involve a high degree of technological and legal complexity. Therefore, obtaining and enforcing biopharmaceutical patents is costly, time consuming and inherently uncertain. In addition, Congress may pass patent reform legislation that is unfavorable to us. The Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents we might obtain in the future.

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

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

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to biopharmaceuticals, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful.

Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

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

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

- others may be able to make gene therapies that are similar to our product candidates but that are not covered by the claims of any 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;
- any patent applications that we have filed or may file in the future may not lead to issued patents;
- any of the issued patents that we own or have exclusively licensed may be held invalid or unenforceable, as a result of legal challenges by our competitors;
- any of the issued patents that we have filed or may file in the future may expire before or shortly after commercialization of the covered product;
- our competitors might conduct research and development activities in countries where, or for products for which, 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, financial condition, results of operations and prospects.

***Third party patent rights could delay or otherwise adversely affect our planned development and sale of product candidates of our programs.***

We are aware of patent rights held by third parties that could be construed to cover certain aspects of our product candidates. In addition, changes to our product candidates or their uses or manufacture may be covered by patents held by third parties, of which we are not yet aware. A patent holder has the right to prevent others from making, using, or selling a drug that incorporates the patented compositions while the patent remains in force. While we believe that third party patent rights will not affect our planned development, regulatory clearance, and eventual marketing, commercial production, and sale of our product candidates, there can be no assurance that this will be the case. In addition, the Hatch-Waxman exemption provided by U.S. patent law permits uses of compounds and biologics in clinical trials and for other purposes reasonably related to obtaining FDA approval of drugs and biologics 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 seeking FDA approval, the development and ultimate sale of our product candidates could be significantly delayed, and we could incur the expense of defending a patent infringement suit and potential liability for damages for periods prior to the patent's expiration.

**Risks Related to Our Common Stock**

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

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002 ("Sarbanes-Oxley"), our management is required to report upon the effectiveness of our internal control over financial reporting. Our independent registered public accounting firm is also required to attest to the effectiveness of our internal control over financial reporting, and the related report is required to be included in our annual reports filed with the SEC. Sarbanes-Oxley Section 404 compliance requirements are complex and require significant documentation, testing, and possible remediation. If we or our auditors 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, 2019, we cannot assure that there will not be material weaknesses in our internal control over financial reporting for this period, following completion of our independent registered public accounting firm's review of our internal control over financial reporting, or in the future. Any failure to maintain internal control over financial reporting could severely inhibit our ability to accurately report our financial condition, results of operations, or cash flows. If we are unable to conclude that our internal control over financial reporting is effective, or if our independent registered public accounting firm determines we have a material weakness in our internal control over financial reporting, we could lose investor confidence in the accuracy and completeness of our financial reports, the market price of our common stock could decline, and we could be subject to sanctions or investigations by The Nasdaq Stock Market, the SEC or other regulatory authorities. Failure to implement and maintain effective internal control over financial reporting, including failure to remediate any material weaknesses we or our auditors identify, could also restrict our future access to the capital markets.

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

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

- our ability to enroll and dose patients in any clinical trials that are on-going, or that we plan to conduct in the future;
- our ability to obtain regulatory approvals for our product candidates and delays or failure to obtain such approvals;
- our plans to conduct additional preclinical studies to determine the best gene therapy candidates to advance in development;
- results of any clinical trials, and the results of trials of our competitors or those of other companies in our market sector;
- investor perception and analysis of the results of our clinical trials, which may be different than our own;
- regulatory developments in the U.S. and foreign countries;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems, especially in light of current reforms to the U.S. healthcare system;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures or capital commitments;
- failure to maintain our existing third-party license and collaboration agreements;
- delays in manufacturing adequate supply of our product candidates;
- adverse publicity relating to the gene therapy market generally, including with respect to other products and potential products in such markets;
- market conditions in the pharmaceutical and biotechnology sectors and issuance of securities analysts' reports or recommendations;
- sales of our stock by insiders and stockholders;
- trading volume of our common stock;
- the outbreak of COVID-19;
- 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, results of operations and prospects.

***We have been subject to securities class action lawsuits in the past, and could be subject to additional such lawsuits in the future, which could result in substantial losses and may divert management's time and attention from our business.***

In the past, we and certain of our former officers were involved in purported securities class action lawsuits, which have since been settled. The purported securities class action lawsuits asserted that the defendants violated the Exchange Act and the Securities Act of 1933, as amended (the "Securities Act"), and alleged that the defendants who are no longer at Adverum made materially false and misleading statements and omitted allegedly material information related to, among other things, the Phase 2a clinical trial for AVA-101, a program which was discontinued in 2015, and the prospects of AVA-101. We settled these lawsuits for $13.0 million, of which $1.0 million we contributed to cover our indemnification obligations to the underwriters, and the remainder was contributed by our insurers. Any future litigation of this type could result in payment of damages or settlement fees and diversion of management's attention and resources, any of which could adversely impact our business. Monitoring and defending against legal actions are 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 or addition of cohorts to clinical trials;
- any intellectual property infringement lawsuit or other litigation in which we may become involved;
- regulatory developments affecting our product candidates;
- our execution of any collaborative, licensing or similar arrangements and the timing of payments we may make or receive under these arrangements;

- nature and terms of stock-based compensation grants; and
- derivative instruments recorded at fair value.

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

***If we sell shares of our common stock or securities convertible into or exercisable for shares of our common stock in future financings, licensing or collaboration arrangements, or acquisitions, stockholders may experience immediate dilution and, as a result, our stock price may decline.***

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, licensing, collaboration or similar arrangements, grants and debt financings. We do not have any committed external source of funds. As a result, we may from time to time issue additional shares of common stock or securities convertible into or exercisable for shares of our common stock. On August 8, 2019, we filed a universal shelf registration statement on Form S-3 with the SEC that automatically became effective, pursuant to which we registered for sale an undetermined amount of any combination of our common stock, preferred stock, debt securities, warrants, and/or units from time to time and at prices and on terms that we may determine, so long as we continue to satisfy the requirements of a "well-known seasoned issuer" under SEC rules. In February 2020 we sold an aggregate of 10,925,000 shares of our common stock for $140.8 million of net proceeds after deducting underwriting discounts and commissions and estimated offering expenses. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a holder of our common stock. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends or other distributions. Furthermore, we may issue common stock as consideration in acquisitions. If we issue common stock or securities convertible into common stock, our common stockholders would experience additional dilution and, as a result, our stock price may decline.

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

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

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

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

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

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

We have never declared or paid any cash dividend on our common stock and do not currently intend to do so for the foreseeable future. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock. Therefore, the success of an investment in shares of our common stock will depend upon any future appreciation in their value. There is no guarantee that shares of our common stock will appreciate in value or even maintain the price at which our stockholders have purchased their shares.

***We are a smaller reporting company, and the reduced reporting requirements applicable to smaller reporting companies may make our common stock less attractive to investors.***

We are a smaller reporting company. For as long as we continue to be a smaller reporting company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not smaller reporting companies, including reduced disclosure obligations regarding executive compensation. 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.

***Changes in tax laws or regulations that are applied adversely to us or our customers may have a material adverse effect on our business and financial condition.***

Legislation enacted on December 22, 2017, known as the Tax Cuts & Jobs Act (“TCJA”), significantly revises the Internal Revenue Code of 1986, as amended. The TCJA, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, creation of a base erosion and anti-abuse tax and modification or repeal of many business deductions and credits. Many aspects of the TCJA are unclear and may not be clarified for some time. Future guidance from the Internal Revenue Service and other tax authorities with respect to the TCJA may affect us, and certain aspects of the TCJA could be repealed or modified in future legislation. Notwithstanding the reduction in the corporate income tax rate, it is possible that the TCJA, or regulations or interpretations under it, or any other future changes in tax laws, could adversely affect our business and financial condition, and such effect could be material.

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

We have incurred substantial losses during our history and do not expect to become profitable in the near future and we may never achieve profitability. To the extent that we continue to generate taxable losses, unused losses will carry forward to offset future taxable income, if any, until such unused losses expire.

Under the TCJA, federal net operating losses (“NOLs”) incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such federal net operating NOLs is limited. In addition, under Section 382 of the Code, our ability to utilize NOL carryforwards or other tax attributes, such as research tax credits, in any taxable year may be limited if we experience an “ownership change.” Generally, a Section 382 ownership change occurs if there is a cumulative increase of more than 50 percentage points in the stock ownership of one or more stockholders or groups of stockholders who owns at least 5% of a corporation’s stock within a specified testing period. Similar rules may apply under state tax laws. In connection with our acquisition of Annapurna in May 2016, we determined that certain NOLs and research and developments tax credits for both federal and state purposes were severely limited and therefore we removed a significant amount of NOLs and research and development tax credits from our deferred tax assets. In addition, we may have experienced an ownership change as a result of the February 2018 underwritten public offering of our common stock, and may in the future experience ownership changes from future offerings or other changes in the ownership of our stock, including as a result of our February 2020 offering of our common stock. As a result, the amount of the NOLs and research and credit carryforwards presented in our financial statements could be limited and may expire unutilized.

**Item 1B. Unresolved Staff Comments**

Not applicable.

**Item 2. Properties**

Our corporate headquarters are located in Redwood City, California, where we lease and occupy approximately 81,000 square feet of office, laboratory, and process development space. In January 2020, we began occupying this new facility, which we believe is adequate for our current needs.

The term of the lease is ten years and also provides for two options to extend the lease term for a period of seven years each.

For our prior corporate headquarters in Menlo Park, California, the term of our lease expires on May 8, 2020. We do not intend to exercise the option to extend the term through May 8, 2024.

**Item 3. Legal Proceedings**

Not applicable.

**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 is listed on the Nasdaq Global Market under the symbol "ADVM".

### Holders of Record

As of February 28, 2020, we had approximately 15 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.

### Recent Sales of Unregistered Securities

On February 20, 2020, Adverum issued to The Alpha-1 Project, Inc. 7,250 shares of Adverum's common stock in connection with the full net exercise of a warrant to purchase 10,000 shares of Adverum's common stock. The shares were issued pursuant to Section 3(a)(9) of the Securities Act of 1933, as amended, in that no commission or other remunerations was paid in connection with the net exercise.

### Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

### Item 6. Selected Financial Data

Under SEC rules and regulations, as a smaller reporting company, we are not required to provide the information required by this item.

## 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

Adverum is a clinical-stage gene therapy company targeting unmet medical needs in ocular and rare diseases. We develop gene therapy product candidates designed to provide durable efficacy by inducing sustained expression of a therapeutic protein. Our core capabilities include novel vector discovery, preclinical and clinical development, and in-house manufacturing expertise, specifically in scalable process development, assay development, and current Good Manufacturing Practices ("cGMP") quality control.

Our lead product candidate ADVM-022 is a single intravitreal ("IVT") injection gene therapy targeting the treatment of wet age-related macular degeneration ("wet AMD") and diabetic retinopathy. ADVM-022 utilizes a proprietary vector capsid, AAV.7m8, carrying an aflibercept coding sequence under the control of a proprietary expression cassette. ADVM-022 is administered as a one-time IVT injection and is designed to deliver long-term efficacy and reduce the burden of frequent anti-vascular endothelial growth factor ("anti-VEGF") injections, optimize patient compliance, and improve vision outcomes for patients with wet AMD or diabetic retinopathy.

Wet AMD is a leading cause of vision loss in patients over 60 years of age, with a prevalence of approximately 1.2 million individuals in the U.S. and 3 million worldwide. In recognition of the need for new treatment options for wet AMD, the U.S. Food and Drug Administration ("FDA") granted Fast Track designation for ADVM-022 for the treatment of wet AMD. Diabetic retinopathy is the leading cause of vision impairment and blindness among working-age adults, with a prevalence of 8 million individuals in the U.S. and is growing with the prevalence of diabetes.

We are conducting the OPTIC trial, designed as a multi-center, open-label, Phase 1, dose-ranging safety trial of ADVM-022 in patients with wet AMD who have demonstrated responsiveness to anti-VEGF treatment. Patients in OPTIC are treatment-experienced, and previously required frequent anti-VEGF injections to control their wet AMD and to maintain functional vision.

Patients in cohort 1 (n=6) were treated with a higher dose of ADVM-022 (6 x 10^11 vg/eye). Patients in cohort 2 (n=6) were treated with a three-fold lower dose of ADVM-022 (2 x 10^11 vg/eye). In the first quarter of 2020, we completed patient dosing in cohort 3 (n=9, lower dose of 2 x 10^11 vg/eye) and began screening for cohort 4 (n=9, higher dose of 6 x 10^11 vg/eye). As we advance the OPTIC trial, we plan to present additional clinical data in the second quarter of 2020, and also longer-term data from cohorts 1-4 in the second half of 2020.

For diabetic retinopathy, we intend to file an investigational new drug ("IND") application in the first half of 2020. We plan to begin enrolling patients in a Phase 1/2 clinical trial in the second half of 2020 to expand our clinical development pipeline. In our preclinical pipeline, we are developing an investigational gene therapy candidate for the treatment of hereditary angioedema.

We have licensed the right to use AAV.7m8 to GenSight Biologics S.A. ("GenSight") to deliver certain therapeutic transgenes, including channelrhodopsin protein, which GenSight is using in their product candidate GS030 for retinitis pigmentosa, currently in clinical development.

In January 2020, we moved into our new facility in Redwood City, California. This new 81,000 square foot facility serves as our corporate headquarters and will include expanded laboratory space as well as space for expanded manufacturing process capabilities.

### Financial Overview

#### *Summary*

We have not generated positive cash flow or net income from operations since our inception and, as of December 31, 2019, we had an accumulated deficit of $385.0 million. We expect to incur substantial expenses and increasing 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.

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 product sales if any of our product candidates are approved, to date we have not generated any revenue from product sales.

We entered into our collaboration and license arrangements with Regeneron in May 2014 and Editas in August 2016. Both arrangements are revenue-generating arrangements. Refer to Note 2, *Summary of significant accounting policies—Revenue Recognition – Collaboration and License Revenue*, of the notes to consolidated financial statements included in this Form 10-K for details. We currently have no operational clinical or commercial manufacturing facilities, and all of our clinical manufacturing activities are currently contracted out to third parties. Additionally, we use third-party contract research organizations ("CROs") to carry out our clinical development and we do not have a sales organization.

We expect to incur substantial and increasing 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, 2019, we had $166.0 million in cash, cash equivalents and short-term investments. In February 2020 we sold an aggregate of 10,925,000 shares of our common stock for $140.8 million of net proceeds after deducting underwriting discounts and commissions and estimated offering expenses. We currently expect our cash, cash equivalents and short-term investments to fund our planned operations and capital expenditures into 2022.

***Revenue***

To date we have not generated any revenue from the sale of our products. We generate revenue through research, collaboration and license arrangements with our strategic partners. 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.

As of December 31, 2019, we had no deferred revenue related to collaboration arrangements with our strategic partners. We recognized $250,000 and $1.6 million of revenue associated with our collaboration arrangements during the years ended December 31, 2019 and 2018, respectively.

*Agreement with Editas*

In January 2018, we entered into an agreement to amend our collaboration, option and license agreement with Editas Medicine, Inc. ("Editas"). We originally entered into an agreement with Editas in August 2016 pursuant to which we and Editas collaborated on certain studies using AAV vectors in connection with Editas' genome editing technology and we granted to Editas an exclusive option to obtain certain exclusive rights to use our proprietary vectors in up to five ophthalmic indications.

Under the terms of the agreement, as amended, Editas had until November 2018 to exercise the option with respect to a designated initial indication, which Editas declined to do. With respect to the four other indications, Editas had until August 2019 to exercise the option, otherwise all options would expire. Editas did not exercise the option, and the agreement terminated on August 8, 2019.

Under Topic 606, the transaction price is $1.5 million, which includes the $1.0 million non-refundable upfront payment for license and research services at contract inception and the one-time, non-refundable cash payment of $0.5 million made by Editas in February 2018 in consideration for extending the agreement. We allocated the transaction price of $1.5 million to a single performance obligation for research and development services.

During the year ended December 31, 2018, we recognized revenue of $1.4 million associated with Editas. The remaining performance obligations for Editas were completed during 2018. During the year ended December 31, 2019, we recognized no revenue from the Editas collaboration agreement. As our collaboration agreement with Editas has terminated, we will no longer recognize any revenue from this agreement in future years.

*Agreement with Regeneron*

In May 2014, we entered into a research, collaboration and license 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, a prior AMD gene therapy that was discontinued in 2015. The $8.0 million was recognized fully by the end of 2015. In February 2017, Regeneron notified us that pursuant to the terms of the research, collaboration and license agreement, it extended the initial research term for an additional three years, through May 1, 2020. Regeneron had the option to further extend the research term of the collaboration agreement for up to two additional years, by providing notice of certain activities under the agreement by March 2, 2020, which Regeneron did not do. We anticipate that the agreement will expire by its terms on May 1, 2020.

Under our research, collaboration and license agreement with Regeneron, we are required to have a mutually agreed-on research plan with Regeneron in order to invoice Regeneron for services performed. For 2018 and 2019, we did not have a research plan in place, and, consequently, did not receive any reimbursements from Regeneron.

*Agreement with GenSight*

In February 2014, we entered into an agreement with GenSight, in which we granted GenSight a non-exclusive license to our proprietary AAV.7m8 vector to develop gene therapy products to deliver certain therapeutic transgenes. Under the agreement, we are eligible to receive development, regulatory and commercial milestones. Also, we are eligible to receive low to mid-single digit royalties on sales of GenSight's licensed products.

During the year ended December 31, 2019, GenSight achieved a clinical development milestone pursuant to the agreement. This milestone was previously constrained under Topic 606. We earned a $250,000 milestone payment, which we recognized as revenue in the consolidated statement of operations and comprehensive loss for the year ended December 31, 2019.

***Research and Development Expenses***

Conducting a significant amount of research and development is central to our business model. Research and development expenses include primarily personnel-related costs, 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 trial materials, and overhead expenses, such as 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.

***General and Administrative Expenses***

General and administrative expenses include primarily personnel-related costs, stock-based compensation, professional fees for legal, consulting, audit and tax services, overhead expenses, such as rent, equipment depreciation, insurance and utilities, 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 our ongoing consideration of our pipeline of product candidates. We anticipate increased expenses related to audit, legal, regulatory, and investor relations functions associated with being a public reporting company.

***Other Income (Expense), Net***

Other income (expense), net primarily comprises of interest income on our cash equivalents and investments in marketable securities.

**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. We base our estimates 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***

To date we have not generated any revenue from the sale of our products. We generate revenue through research, collaboration and license arrangements with our strategic partners.

*Collaboration Agreement with Editas*— Under Topic 606, the transaction price was $1.5 million related to the $1.0 million non-refundable upfront payment for license and research services at contract inception and the one-time, non-refundable cash payment of $0.5 million made by Editas in February 2018 in consideration for extending the agreement. We allocated the transaction price of $1.5 million to a single performance obligation to perform research and development services.

During the year ended December 31, 2019, we did not recognize revenue from the Editas collaboration agreement. During the year ended December 31, 2018, we recognized revenue of $1.4 million, associated with the Editas collaboration agreement. There was no outstanding deferred revenue associated with Editas as of December 31, 2019 and 2018.

*License Agreement with GenSight*— On February 2014, we entered into an agreement with GenSight, where we granted GenSight a non-exclusive license to our proprietary AAV.7m8 vector. Under the agreement, we are eligible to receive development, regulatory and commercial milestones. Also, we are eligible to receive low to mid-single digit royalties on sales of GenSight's licensed products.

During the years ended December 31, 2019 and 2018, GenSight achieved clinical development milestones pursuant to the agreement. Payments related to these milestones that were previously constrained under Topic 606 were recognized as revenue when achieved. For the years ended December 31, 2019 and 2018, we received milestone payments of $250,000 and $150,000, respectively, which we recognized as revenue in our consolidated statements of operations and comprehensive loss.

***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, 2019 and 2018, 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. 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 the closing price of our common stock on the grant date for the restricted stock units ("RSUs").

We recognize the grant-date fair value of the stock-based awards on a straight-line basis over the requisite service period, which is generally the vesting period of the respective awards. Prior to January 1, 2019, we recognized stock-based compensation expense related to awards for non-employees based on the then-current fair value at each measurement date over the associated service period of the award using the accelerated attribution method. As of January 1, 2019, we adopted Accounting Standards Update No. 2018-07 ("ASU 2018-07"), Improvements to Nonemployee Share-Based Payment Accounting ("Topic 718"), which subjects nonemployee awards to fixed measurement over a vesting period.

We use the Black-Scholes valuation model to assist us in determining the fair value of our stock options, which includes our employee stock purchase plan. The Black-Scholes valuation model requires the use of following assumptions:

*Expected volatility*. For 2019, we estimated 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, weighted with the historical volatility based on the trading history for our common stock.

*Expected term*. We derive the expected term using the "simplified" method that determines the expected term as the average of the time-to-vesting and the contractual life of the options. The expected term of the Employee Stock Purchase Plan ("ESPP") rights equals to the six-month look-back period.

*Risk-free interest rate*. We base the risk-free interest rate 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.

***Leases***

We adopted Accounting Standards Update (ASU) No. 2016-02, Leases (Topic 842) ("Topic 842") on January 1, 2019. For our long-term operating leases, we recognize a right-of-use asset and a lease liability on our consolidated balance sheets. We adopted the new standard using the modified retrospective approach and recorded a lease liability of $24.7 million, and a right-to-use asset of $23.1 million, and made no adjustment to the accumulated deficit. In connection with the adoption of the lease standard, we also derecognized deferred rent of $1.5 million. The adoption of Topic 842 did not have an impact on our consolidated statement of operations.

The lease liability is determined as the present value of future lease payments using an estimated rate of interest that we would pay to borrow equivalent funds on a collateralized basis at the lease commencement date. In order to estimate the incremental borrowing rate, management estimated its credit rating, adjusted the credit rating for the nature of the collateral, and benchmarked the borrowing rate against observable yields on comparable securities with a similar term. As of the adoption date, we estimated the incremental borrowing rate to be 8.5%. We based the right-of-use asset on the liability adjusted for any prepaid or deferred rent. We determined the lease term at the commencement date by considering whether renewal options and termination options are reasonably assured of exercise. Rent expense for the operating lease is recognized on a straight-line basis over the lease term and is included in operating expenses on the statements of operations and comprehensive loss. Variable lease payments include lease operating expenses.

We elected the practical expedients permitted under Topic 842, which among other things, allowed us to carry forward the historical lease classification of those leases in place as of January 1, 2019. We elected to exclude from our consolidated balance sheets recognition of leases having a term of 12 months or less (short-term leases) and elected to not separate lease components and non-lease components for our long-term real-estate leases.

**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, 2019 and 2018 of approximately $66.2 million and $47.3 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, 2019, we had U.S. federal net operating loss ("NOL") carryforwards of approximately $159.5 million to offset future federal income. Approximately $56.9 million of NOLs expire at various years beginning with 2036. As of December 31, 2019, we also had U.S. state NOL carryforwards of approximately $26.9 million to offset future state income. U.S. state NOLs expire at various years beginning with 2036. At December 31, 2019, we also had approximately $70.1 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. Due to a May 11, 2016 ownership change, we determined that certain NOLs and research and development tax credits for both federal and state purposes are severely limited and therefore we removed a significant amount NOL and research and development tax credits 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. We have not recognized any interest and penalties related to income taxes in the consolidated statements of operations and comprehensive loss during the years ended December 31, 2019 and 2018.

**Results of Operations**

***Comparison of the Years Ended December 31, 2019 and 2018***

| | Years ended December 31, | | |
|---|---|---|---|
| | 2019 | 2018 | Increase/(Decrease) |
| | (In thousands) | | |
| Collaboration and license revenue | $ 250 | $ 1,612 | $ (1,362) |
| Operating expenses: | | | |
| Research and development | 40,419 | 50,133 | (9,714) |
| General and administrative | 28,376 | 24,560 | 3,816 |
| Impairment of goodwill and intangible assets | — | 5,000 | (5,000) |
| Total operating expenses | 68,795 | 79,693 | (10,898) |
| Operating loss | (68,545) | (78,081) | 9,536 |
| Other income, net | 4,059 | 4,204 | (145) |
| Net loss before income tax benefit | (64,486) | (73,877) | 9,391 |
| Income tax benefit | — | 1,250 | (1,250) |
| Net loss | $ (64,486) | $ (72,627) | $ 8,141 |

*Revenue*

We recognized $250,000 of collaboration and license revenue for the year ended December 31, 2019 related to a milestone payment under our license agreement with GenSight compared to $1.6 million for the year ended December 31, 2018 related to research services under our collaboration agreement with Editas and milestone payment from GenSight.

*Research and Development Expense*

Research and development expense decreased $9.7 million to $40.4 million for the year ended December 31, 2019 from $50.1 million for the year ended December 31, 2018. This overall decrease was primarily due to $7.9 million decrease in production costs related to product candidates ADVM-022 and ADVM-053 due to a reduction in manufacturing activity, $2.5 million decrease in outside R&D services as our wAMD program transitioned to clinical trial, $1.0 million decrease in clinical trials cost, and $0.7 million decrease for personnel associated costs. These decreases were partially offset by a $1.8 million increase in facilities costs related to our new facility and a $0.5 million increase in laboratory expenses. We expect that research and development expenses will increase in future periods as we continue to invest in advancing our gene therapy product candidate ADVM-022 and earlier-stage research programs.

*General and Administrative Expense*

General and administrative expense increased $3.8 million to $28.4 million for the year ended December 31, 2019 from $24.6 million for the year ended December 31, 2018. This reflects increases of $2.0 million in G&A consulting and contractor costs, $1.8 million in professional expenses including higher audit, legal and investor relation services, $1.0 million in facilities cost related to our new facility, and $0.7 million in other business costs, partially offset by $1.6 million decrease in personnel associated costs primarily resulting from lower stock-based compensation expenses.

We expect that general and administrative expenses will increase in future periods as we continue to support advancing our gene therapy programs. We anticipate increased expenses related to audit, legal, regulatory, and investor relations functions to support our organizational growth.

*Goodwill and Intangible Assets Impairment Charge*

During the year ended December 31, 2018, we identified an impairment indicator related to the intangible asset for ADVM-043 and performed an impairment analysis. On October 30, 2018, we announced our decision to discontinue the development of ADVM-043. We recorded an impairment charge of $5.0 million on IPR&D assets related to our intangible asset for ADVM-043. There were no impairment charges during the year ended December 31, 2019.

*Other Income, Net*

The decrease of $145,000 in net other income for the year ended December 31, 2019 as compared to 2018 was primarily due to lower average invested balances.

*Income Tax Benefit*

There was no income tax benefit during the year ended December 31, 2019. In connection with our impairment charge, we derecognized a deferred tax liability of $1.3 million related to the intangible asset for ADVM-043 during the year ended December 31, 2018.

**Liquidity, Capital Resources and Plan of Operations**

We have not generated positive cash flow or net income from operations since our inception and as of December 31, 2019, we had an accumulated deficit of $385.0 million. As of December 31, 2019, we had $166.0 million in cash, cash equivalents and short-term investments. We believe that our existing cash, cash equivalents, and short-term investments as of December 31, 2019, together with the approximately $140.8 million of net proceeds after deducting underwriting discounts and commissions and estimated offering expenses from our February 2020 public offering of our common stock, will be sufficient to fund our planned operations and capital expenditures into 2022.

In February 2018, we completed an underwritten public offering for the sale of 10,222,235 shares of our common stock and raised total net proceeds of approximately $64.5 million, after discounts and other issuance costs.

In August 2017 we entered into an at-the-market offering program sales agreement with Cowen and Company, LLC, or Cowen, pursuant to which we sold $50 million of our common stock. In the three months ended December 31, 2019 we sold an aggregate of 2,436,065 shares of our common stock for net proceeds of $25.8 million. There is no capacity remaining on the at-the-market offering program.

In February 2020 we sold an aggregate of 10,925,000 shares of our common stock for $140.8 million of net proceeds after deducting underwriting discounts and commissions and estimated offering expenses.

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, and expenses to build out our new facility. At this time, we cannot reasonably estimate the nature, timing or aggregate amount of costs for our development, potential commercialization, and internal research and development programs. However, in order to complete our planned preclinical trials and current and 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. 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 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:

| | Years ended December 31, | |
|---|---|---|
| | 2019 | 2018 |
| | (In thousands) | |
| **Net cash (used in) provided by:** | | |
| Operating activities | $ (49,170) | $ (53,964) |
| Investing activities | (68,073) | 69,444 |
| Financing activities | 28,191 | 69,949 |
| Net increase (decrease) in cash and cash equivalents and restricted cash | $ (89,052) | $ 85,429 |

*Cash Used in Operating Activities*

Net cash used in operating activities for the year ended December 31, 2019 was $49.2 million, primarily as a result of the net loss of $64.5 million mainly driven by our continued research and development activities, partially offset by $10.3 million of non-cash charges mainly related to stock-based compensation expense, and $5.1 million of net change in operating assets and liabilities primarily caused by increases in our lease liability of $7.6 million primarily as a result of the receipt of tenant improvement allowance and $1.9 million in accrued expenses and other current liabilities, partially offset by $6.0 million change in prepaid expenses and other current assets and $2.2 million of amortization of our operating lease right-of-use assets.

Net cash used in operating activities for the year ended December 31, 2018 was $54.0 million, primarily as a result of the net loss of $72.6 million mainly driven by our continued research and development activities, partially offset by $20.3 million of non-cash charges mainly related to stock-based compensation expense, impairment of intangible asset and depreciation and amortization expense, and $1.6 million of net decrease in operating assets and liabilities.

*Cash (Used in) Provided by Investing Activities*

Net cash used in investing activities was $68.1 million for the year ended December 31, 2019, which consisted of $48.8 million of net purchases of marketable securities and $19.2 million of purchases of property and equipment. Purchases of property and equipment primarily consisted of the leasehold improvements related to the new facility.

Net cash provided by investing activities was $69.4 million for the year ended December 31, 2018 consisted of $70.3 million of net maturities of marketable securities, partially offset by $0.8 million of purchases of property and equipment. Purchases of property and equipment primarily consisted of the acquisition of laboratory equipment to support our research and development activities.

*Cash Provided by Financing Activities*

Net cash provided by financing activities for the year ended December 31, 2019 consisted of $25.9 million of the net proceeds from the sale of our common stock, primarily through our at-the-market offering program sales agreement with Cowen completed in December 2019, $3.9 million of the proceeds from the exercises of stock options and employee stock purchases, partially offset by $1.5 million in taxes paid relating to net share settlement of restricted stock units and $0.1 million repayment of our Banque Publique d'Investissement ("BPI France") loan.

Net cash provided by financing activities for year ended December 31, 2018 consisted of $70.2 million of the net proceeds from the sales of our common stock, primarily our underwritten public offering of our common stock in February in which we raised net proceeds of $64.5 million, $1.0 million of the proceeds from the exercises of stock options and employee stock purchases and $0.1 million of the proceeds from our financing arrangement with the Alpha-1 Project, Inc., partially offset by $1.0 million in taxes paid relating to net share settlement of restricted stock units and $0.2 million repayment of our BPI France loan.

**Off Balance Sheet Arrangements**

We do not have any off-balance sheet arrangements as defined in Regulation S-K, Item 303(a)(4)(ii).

**Item 7A. Quantitative and Qualitative Disclosures about Market Risk**

Under SEC rules and regulations, as a smaller reporting company, we are not required to provide the information required by this item.

**Item 8. Financial Statements and Supplementary Data.**

**ADVERUM BIOTECHNOLOGIES, INC.**
**CONSOLIDATED FINANCIAL STATEMENTS**
**AS OF AND FOR THE YEARS ENDED DECEMBER 31, 2019 AND 2018**

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## REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders
Adverum Biotechnologies, Inc.

### Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Adverum Biotechnologies, Inc. (the "Company") as of December 31, 2019 and 2018, the related consolidated statements of operations and comprehensive loss, stockholders' equity, and cash flows for the years then ended, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2019 and 2018, and the results of its operations and its cash flows for the years then ended, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2019, based on criteria established in Internal Control – Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated March 12, 2020 expressed an unqualified opinion thereon.

### Adoption of ASU No. 2016-02

As discussed in Note 2 to the consolidated financial statements, the Company changed its method for accounting for leases in 2019 due to the adoption of Accounting Standards Update (ASU) No. 2016-02, *Leases* (Topic 842), and the related amendments.

### Basis for Opinion

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

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2018.

San Jose, California
March 12, 2020

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

| | As of December 31, | |
|---|---|---|
| | 2019 | 2018 |
| **Assets** | | |
| Current assets: | | |
| Cash and cash equivalents | $ 65,897 | $ 154,949 |
| Short-term investments | 100,138 | 50,130 |
| Prepaid expenses and other current assets | 9,835 | 3,675 |
| Total current assets | 175,870 | 208,754 |
| Operating lease right-of-use assets | 20,963 | — |
| Property and equipment, net | 24,884 | 3,586 |
| Restricted cash | 999 | 999 |
| Deposit and other non-current assets | 11 | 156 |
| Total assets | $ 222,727 | $ 213,495 |
| **Liabilities and stockholders' equity** | | |
| Current liabilities: | | |
| Accounts payable | $ 4,103 | $ 1,707 |
| Accrued expenses and other current liabilities | 11,271 | 8,784 |
| Lease liability, current portion | 4,034 | — |
| Deferred rent, current portion | — | 228 |
| Total current liabilities | 19,408 | 10,719 |
| Long-term liabilities: | | |
| Deferred rent, net of current portion | — | 1,366 |
| Lease liability, net of current portion | 28,214 | — |
| Other non-current liabilities | 148 | 243 |
| Total liabilities | 47,770 | 12,328 |
| Commitments and contingencies (Note 8) | | |
| Stockholders' equity: | | |
| Preferred stock, $0.0001 par value, 5,000 shares authorized; no shares issued and outstanding | — | — |
| Common stock, $0.0001 par value, 300,000 shares authorized at December 31, 2019: 67,329 and 62,965 shares issued and outstanding at December 31, 2019 and 2018, respectively | 7 | 6 |
| Additional paid-in capital | 560,704 | 522,503 |
| Accumulated other comprehensive loss | (725) | (799) |
| Accumulated deficit | (385,029) | (320,543) |
| Total stockholders' equity | 174,957 | 201,167 |
| Total liabilities and stockholders' equity | $ 222,727 | $ 213,495 |

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, | |
|---|---|---|
| | 2019 | 2018 |
| Collaboration and license revenue | $ 250 | $ 1,612 |
| Operating expenses: | | |
| Research and development | 40,419 | 50,133 |
| General and administrative | 28,376 | 24,560 |
| Impairment of goodwill and intangible assets | — | 5,000 |
| Total operating expenses | 68,795 | 79,693 |
| Operating loss | (68,545) | (78,081) |
| Other income: | | |
| Other income, net | 4,059 | 4,204 |
| Net loss before income taxes | (64,486) | (73,877) |
| Income tax benefit | — | 1,250 |
| Net loss | $ (64,486) | $ (72,627) |
| Other comprehensive income: | | |
| Net unrealized gain on marketable securities | 33 | 168 |
| Foreign currency translation adjustment | 41 | (4) |
| Comprehensive loss | $ (64,412) | $ (72,463) |
| Net loss per share - basic and diluted | $ (1.01) | $ (1.18) |
| Weighted-average common shares outstanding-basic and diluted | 64,102 | 61,375 |

See accompanying notes to consolidated financial statements.

**ADVERUM BIOTECHNOLOGIES, INC.**
**CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY**
(In thousands)

| | COMMON STOCK | | ADDITIONAL PAID-IN CAPITAL | ACCUMULATED OTHER COMPREHENSIVE INCOME (LOSS) | ACCUMULATED DEFICIT | TOTAL STOCKHOLDERS' EQUITY |
|---|---|---|---|---|---|---|
| | Shares | Amount | | | | |
| **Balance at December 31, 2017** | **49,015** | **$ 5** | **$ 439,048** | **$ (963)** | **$ (254,062)** | **$ 184,028** |
| Issuance of common stock, net of issuance costs of $4,140 | 11,642 | 1 | 70,186 | — | — | 70,187 |
| Adoption of Topic 606 | — | — | — | — | 6,146 | 6,146 |
| Stock-based compensation expense | — | — | 13,432 | — | — | 13,432 |
| Common stock issued upon exercise of stock options | 1,606 | — | 688 | — | — | 688 |
| Common stock issued under employee stock purchase plan | 120 | — | 340 | — | — | 340 |
| Common stock issued upon release of restricted stock units | 774 | — | — | — | — | — |
| Restricted stock surrendered for taxes | (192) | — | (1,191) | — | — | (1,191) |
| Net unrealized gain on marketable securities | — | — | — | 168 | — | 168 |
| Foreign currency translation adjustments | — | — | — | (4) | — | (4) |
| Net loss | — | — | — | — | (72,627) | (72,627) |
| **Balance at December 31, 2018** | **62,965** | **6** | **522,503** | **(799)** | **(320,543)** | **201,167** |
| Issuance of common stock, net of issuance costs of $1,065 | 2,436 | 1 | 25,754 | — | — | 25,755 |
| Issuance of common stock, private placement | 20 | — | 134 | — | — | 134 |
| Stock-based compensation expense | — | — | 9,899 | — | — | 9,899 |
| Common stock issued upon exercise of stock options | 1,397 | — | 3,442 | — | — | 3,442 |
| Common stock issued under employee stock purchase plan | 86 | — | 442 | — | — | 442 |
| Common stock issued upon release of restricted stock units | 663 | — | — | — | — | — |
| Restricted stock surrendered for taxes | (238) | — | (1,470) | — | — | (1,470) |
| Net unrealized gain on marketable securities | — | — | — | 33 | — | 33 |
| Foreign currency translation adjustments | — | — | — | 41 | — | 41 |
| Net loss | — | — | — | — | (64,486) | (64,486) |
| **Balance at December 31, 2019** | **67,329** | **$ 7** | **$ 560,704** | **$ (725)** | **$ (385,029)** | **$ 174,957** |

See accompanying notes to consolidated financial statements.

**ADVERUM BIOTECHNOLOGIES, INC.**
**CONSOLIDATED STATEMENTS OF CASH FLOWS**
(In thousands)

| | Years ended December 31, | |
|---|---|---|
| | **2019** | **2018** |
| **Cash flows from operating activities:** | | |
| Net loss | $ (64,486) | $ (72,627) |
| Adjustments to reconcile net loss to net cash used in operating activities: | | |
| Depreciation and amortization | 1,573 | 1,750 |
| Stock-based compensation expense | 9,899 | 13,432 |
| Amortization of premium and discounts on marketable securities, net | (1,273) | 24 |
| Accreted interest on BPI | 22 | 95 |
| Impairment of goodwill and intangible assets | — | 5,000 |
| Other | 36 | (17) |
| Changes in operating assets and liabilities: | | |
| Prepaid expenses and other current assets | (5,954) | (793) |
| Deposit and other long-term assets | — | (16) |
| Operating lease right-of-use assets | 2,168 | — |
| Accounts payable | (650) | (67) |
| Accrued expenses and other current liabilities | 1,909 | 215 |
| Deferred revenue | — | (953) |
| Deferred rent | — | 1,243 |
| Lease liability | 7,586 | — |
| Deferred tax liability | — | (1,250) |
| Net cash used in operating activities | (49,170) | (53,964) |
| **Cash flows from investing activities:** | | |
| Purchases of marketable securities | (197,343) | (78,726) |
| Maturities of marketable securities | 148,517 | 148,979 |
| Purchases of property and equipment | (19,247) | (809) |
| Net cash provided by (used in) provided by investing activities | (68,073) | 69,444 |
| **Cash flows from financing activities:** | | |
| Proceeds from offering of common stock, net of issuance costs | 25,755 | 70,187 |
| Proceeds from issuance of common stock through private placement | 134 | — |
| Proceeds from issuance of common stock pursuant to option exercises | 3,442 | 688 |
| Taxes paid related to net share settlement of restricted stock units | (1,470) | (1,191) |
| Proceeds from employee stock purchase plan | 442 | 340 |
| Repayment of BPI loan | (112) | (175) |
| Proceeds from a financing arrangement | — | 100 |
| Net cash provided by financing activities | 28,191 | 69,949 |
| Net increase (decrease) in cash and cash equivalents and restricted cash | (89,052) | 85,429 |
| Cash and cash equivalents and restricted cash at beginning of period | 155,948 | 70,519 |
| Cash and cash equivalents and restricted cash at end of period | $ 66,896 | $ 155,948 |
| **Supplemental schedule of noncash investing information** | | |
| Fixed assets in accounts payable and current liabilities | $ 5,242 | $ 1,616 |

See accompanying notes to consolidated financial statements.

**ADVERUM BIOTECHNOLOGIES, INC.**

**Notes to Consolidated Financial Statements**

## 1. Description of the business

**Nature of Business**—Adverum Biotechnologies, Inc. (the "Company" or "Adverum") was incorporated in Delaware on July 17, 2006 and is headquartered in Redwood City, California. The Company is a clinical-stage gene therapy company targeting unmet medical needs in ocular and rare diseases. The Company develops gene therapy product candidates designed to provide durable efficacy by inducing sustained expression of a therapeutic protein. The Company's core capabilities include clinical development, novel vector discovery, and in house manufacturing expertise, specifically in scalable process development, assay development, and current Good Manufacturing Practices ("cGMP") quality control. Since the Company's inception, it has devoted its efforts to performing research and development activities, filing patent applications, 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 had an accumulated deficit of $385.0 million as of December 31, 2019. 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 into 2022.

## 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. The Company evaluates its estimates and assumptions, including those related to research and development expense accruals, stock-based compensation expense, income taxes, fair values of financial instruments, and incremental borrowing rate. 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. The Company's foreign subsidiaries use the Euro and Australian dollar as their functional currencies and maintain their records in their local currencies, except its Ireland subsidiary that uses the U.S. dollar as its functional currency. Assets and liabilities are re-measured at exchange rates in effect at the end of the reporting period for the Company's French and Australian subsidiaries, and at historical exchange rates for its 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 sheet. Transactions denominated in foreign currency are translated at exchange rates at the date of transaction with foreign currency gains (losses) recorded in other comprehensive income, net in the consolidated statements of operations and 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, money market accounts and highly liquid debt securities. Cash equivalents are stated at fair value.

**Restricted Cash**—Restricted cash primarily consists of cash collateral to letter of credit provided to the landlord in relation to a lease agreement (see Note 5).

**Short-Term Investments**—All short-term investments, 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 in the Company's consolidated statements of operations and comprehensive loss. 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 other income, net in the Company's consolidated statements of operations and comprehensive loss. 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 periodically 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.

**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 the Company to significant concentrations of credit risk consists primarily of cash, cash equivalents and short-term investments. Risks associated with cash, cash equivalents, short-term investments are mitigated by the Company's investment policy, which limits the Company's investing to only those marketable securities rated at least A-1/P-1 Short Term Rating and A/A2 Long Term Rating, as determined by independent credit rating agencies. Management believes that the Company is not exposed to significant credit risk.

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 of their expected lives or the 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 values 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. There were no impairment indicators noted for the Company's amortizable long-lived assets, fixed assets, in the year ended December 31, 2019.

The Company also evaluates the carrying value of intangible asset (not subject to amortization) related to in-process research and development ("IPR&D") asset, which is 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 intangible asset is considered indefinite-lived, it will be tested for impairment on an annual basis, as well as between annual tests if the Company becomes aware of any events occurring or changes in circumstances that would indicate that the fair value of the IPR&D asset is less than its carrying amount. If and when development is complete, which generally occurs when regulatory approval to market the product is obtained, the associated IPR&D asset would be deemed definite-lived and would then be amortized based on its estimated useful life at that point in time based on respective patent term. If a potential impairment exists, an impairment loss is measured as the excess of the asset's carrying value over its fair value. During the year ended December 31, 2018, the Company recorded an impairment charge of $5.0 million related to its intangible assets.

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

Under Topic 606, the Company recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the Company expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that the Company determines are within the scope of ASC 606, the Company performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the Company satisfies a performance obligation. At contract inception, once the contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within each contract and determines those that are performance obligations. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

The Company's license and collaboration arrangements with Editas Medicine, Inc. ("Editas") and GenSight Biologics ("GenSight") are within the scope of Topic 606.

*Collaboration Agreement with Editas*—Under Topic 606, the transaction price at contract inception was determined to be $1.0 million, which was related to the non-refundable upfront payment for license and research services. The transaction price of $1.0 million at contract inception was allocated to a single performance obligation.

During the year ended December 31, 2018, the Company recognized revenue of $1.5 million associated with the Editas collaboration agreement. The remaining performance obligations for Editas were completed during 2018. During the year ended December 31, 2019, the Company had no recognized revenue from the Editas collaboration agreement. There was no outstanding deferred revenue associated with Editas as of December 31, 2019 and 2018.

*License Agreement with GenSight*— On February 2014, the Company entered into an agreement with GenSight, where the Company granted GenSight a non-exclusive license to its proprietary AAV.7m8 vector. Under the agreement, the Company is eligible to receive development, regulatory and commercial milestones. Also, the Company is eligible to receive low to mid-single digit royalties on sales of GenSight's licensed products.

During the years ended December 31, 2019 and 2018, GenSight achieved clinical development milestones pursuant to the agreement. This milestone was previously constrained under Topic 606. The Company earned milestone payments of $250,000 and $150,000, which were recognized as revenue for the years ended December 31, 2019 and 2018, respectively.

**Research and Development Expenses**—Research and development expenses are charged to expense as incurred. Research and development expenses include primarily personnel-related costs, 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 trial materials, and overhead expenses, such as rent, equipment depreciation, insurance 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.

**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 equivalents, prepaid and other current assets, accounts payable, accrued expenses and other current liabilities approximate their fair values due to their short-term maturities. Refer to Note 3 for the methodologies and assumptions used in valuing financial instruments.

**Stock-based Compensation Expense**—Stock-based compensation expense related to stock awards to employees is measured at fair value of the award on the date of the grant. The Company estimates 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 the closing price of its common stock on the date of the grant, for the restricted stock units ("RSUs"). 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 Black-Scholes valuation model requires the use of following assumptions:

*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 a weighing of comparable public companies' volatility for similar terms and the Company's historical volatility.

*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.

**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, 2019 and 2018, 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 upon examination. Interest and penalties related to unrecognized tax liabilities are included within the provision for income tax.

**Comprehensive Loss**—Comprehensive loss comprises net loss and other comprehensive income. Other comprehensive income consists of foreign currency translation adjustments related to translation of the financial statements of the Company's Australia and France subsidiaries and unrealized gain on marketable securities. The Company did not record reclassifications from other comprehensive income (loss) to the income (loss) during the years ended December 31, 2019 and 2018.

**Basic and Diluted Net Loss Per Share**— Basic net loss per share is calculated by dividing the net loss by the weighted-average number of shares of common stock outstanding for the period. Diluted net loss per share is computed by giving effect to all potential dilutive common stock equivalents outstanding for the period using the treasury stock method. Outstanding stock options, restricted stock units ("RSUs"), employee stock purchase plan ("ESPP") and warrants are considered to be common stock equivalents and are only included in the calculation of diluted net loss per share when their effect is dilutive.

**Recently Adopted Accounting Pronouncements**

***Leases***

The Company adopted Accounting Standards Update (ASU) No. 2016-02, Leases (Topic 842) ("Topic 842") on January 1, 2019. For its long-term operating leases, the Company recognizes a right-of-use asset and a lease liability on its consolidated balance sheets. The Company adopted the new standard using the modified retrospective approach and, upon adoption, recorded a lease liability of $24.7 million, and a right-to-use asset of $23.1 million, and made no adjustment to the accumulated deficit. In connection with the adoption of the lease standard, the Company also derecognized deferred rent of $1.5 million. The adoption of Topic 842 did not have an impact on the consolidated statement of operations.

The lease liability is determined as the present value of future lease payments using an estimated rate of interest that the Company would pay to borrow equivalent funds on a collateralized basis at the lease commencement date. In order to estimate the incremental borrowing rate, management estimated its credit rating, adjusted the credit rating for the nature of the collateral, and benchmarked the borrowing rate against observable yields on comparable securities with a similar term. As of the adoption date, the Company estimated the incremental borrowing rate to be 8.5%. The Company based the right-of-use asset on the liability adjusted for any prepaid or deferred rent. The Company determined the lease term at the commencement date by considering whether renewal options and termination options are reasonably assured of exercise. Rent expense for the operating lease is recognized on a straight-line basis

over the lease term and is included in operating expenses on the statements of operations and comprehensive loss. Variable lease payments include lease operating expenses.

The Company elected the practical expedients permitted under Topic 842, which among other things, allowed the Company to carry forward the historical lease classification of those leases in place as of January 1, 2019. The Company elected to exclude from its consolidated balance sheets recognition of leases having a term of 12 months or less (short-term leases) and elected to not separate lease components and non-lease components for its long-term real-estate leases.

***Share-based payment to nonemployees***

In June 2018, the FASB issued ASU 2018-07, "Compensation – Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting" ("Topic 718") that expands the scope of Topic 718 to include share-based payment transactions for acquiring goods and services from nonemployees. The Company adopted ASU 2018–07 on January 1, 2019 and the impact of the adoption resulted in lower stock-based compensation of $1.4 million during the year ended December 31, 2019. Under the new standard, our share-based payment transactions with non-employees have a fixed measurement and are not remeasured over the vesting period.

**3. 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 is 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. government and agency securities, commercial paper, corporate bond and certificates 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.

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, 2019 and 2018.

The following is a summary of the Company's cash equivalents and short-term investments (in thousands):

| | December 31, 2019 | | | |
|---|---|---|---|---|
| | Amortized Cost Basis | Unrealized Gains | Unrealized Loses | Estimated Fair Value |
| **Level 1** | | | | |
| Money market funds | $ 15,056 | $ — | $ — | $ 15,056 |
| **Level 2** | | | | |
| U.S. government and agency securities | 37,974 | 14 | (2) | 37,986 |
| Commercial paper | 87,983 | 8 | (8) | 87,983 |
| Corporate bonds | 10,495 | 6 | — | 10,501 |
| Total cash equivalents and short-term investments | 151,508 | 28 | (10) | 151,526 |
| Less: Cash equivalents | (51,391) | — | 3 | (51,388) |
| Total short-term investments | $ 100,117 | $ 28 | $ (7) | $ 100,138 |

| | December 31, 2018 | | | |
|---|---|---|---|---|
| | Amortized Cost Basis | Unrealized Gains | Unrealized Loses | Estimated Fair Value |
| **Level 1** | | | | |
| Money market funds | $ 126 | $ — | $ — | $ 126 |
| **Level 2** | | | | |
| U.S. government and agency securities | 25,792 | 1 | (4) | 25,789 |
| Commercial paper | 147,606 | — | — | 147,606 |
| Corporate bonds | 27,778 | 5 | (17) | 27,766 |
| Certificates of deposit | 1,420 | — | — | 1,420 |
| Total cash equivalents and short-term investments | 202,722 | 6 | (21) | 202,707 |
| Less: Cash equivalents | (152,577) | — | — | (152,577) |
| Total short-term investments | $ 50,145 | $ 6 | $ (21) | $ 50,130 |

Management determined that the gross unrealized losses on the Company's marketable securities as of December 31, 2019 were temporary in nature. Therefore, none of the Company's marketable securities were other-than-temporarily impaired as of December 31, 2019.

All investments as of December 31, 2019 have a remaining maturity of one year or less.

There were no transfers within the hierarchy during the years ended December 31, 2019 and 2018.

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.

**4. Revenue**

***Editas*** — In January 2018, the Company entered into an agreement to amend its collaboration, option and license agreement with Editas Medicine, Inc. The Company originally entered into an agreement with Editas in August 2016 pursuant to which the Company and Editas collaborated on certain studies using AAV vectors in connection with Editas' genome editing technology and the Company granted to Editas an exclusive option to obtain certain exclusive rights to use the Company's proprietary vectors in up to five ophthalmic indications.

Under the terms of the agreement, as amended, Editas had until November 2018 to exercise the option with respect to a designated initial indication, which Editas declined to do. With respect to the four other indications, Editas had until August 2019 to exercise the option, otherwise all options would expire. Editas did not exercise the option, and the agreement terminated on August 8, 2019.

Under Topic 606, the transaction price is $1.5 million, which includes the $1.0 million non-refundable upfront payment for license and research services at contract inception and the one-time, non-refundable cash payment of $0.5 million made by Editas in February 2018 in consideration for extending the agreement. The transaction price of $1.5 million was allocated to a single performance obligation: research and development.

During the year ended December 31, 2018, the Company recognized revenue of $1.5 million associated with Editas. The remaining performance obligations for Editas were completed during 2018. During the year ended December 31, 2019, the Company had no recognized revenue from the Editas collaboration agreement. The Company had no deferred revenue balance as of December 31, 2019 and 2018.

***GenSight*** — In February 2014, the Company entered into an agreement with GenSight Biologics, S.A, in which the Company granted GenSight a non-exclusive license to its proprietary AAV.7m8 vector to develop gene therapy products to deliver certain therapeutic transgenes. Under the agreement, the Company is eligible to receive development, regulatory and commercial milestones. Also, the Company is eligible to receive low to mid-single digit royalties on sales of GenSight's licensed products. During the year ended December 31, 2019 and 2018, GenSight achieved clinical development milestones pursuant to the agreement. These milestones were previously constrained under Topic 606. The Company earned milestone payments of $250,000 and $150,000, which was recognized as revenue for the years ended December 31, 2019 and 2018, respectively.

## 5. Leases

In June 2018, the Company entered into an operating lease agreement for new office and laboratory space which consists of approximately 81,000 square feet located in Redwood City, California. The lease term is 10 years beginning September 2018 through February 2029 with two options to extend the lease term for a period of seven years each. The Company has the right to make tenant improvements, including the addition of laboratory space, with a lease incentive allowance of $8.1 million. The rent payments began on March 1, 2019. The lease agreement provides for an escalation of rent payments each year after an abatement period. In connection with the lease, the Company has provided the landlord with a letter of credit in the amount of $1.0 million. The security for the letter of credit of $1.0 million is classified as restricted cash under long term assets on the consolidated balance sheet. The Company also has an operating lease agreement for its Menlo Park office building which expires on May 8, 2020. The Company does not intend to exercise the option to extend the term.

The Company adopted Topic 842 (See Note 2) and recorded right-of-use assets of $23.1 million and a lease liability of $24.7 million as of January 1, 2019. The estimated incremental borrowing rate used to measure the lease liability is 8.5%.

Rent expense for the year ended December 31, 2019 and 2018 was $6.5 million, and $3.3 million, respectively, which includes variable lease costs for utilities, parking, maintenance, and real estate taxes. Variable lease expenses for the year ended December 31, 2019 was $1.6 million.

The undiscounted future non-cancellable lease payments under the Company's operating leases as of December 31, 2019 is as follows:

| Years ending December 31, | (In thousands) |
|---|---|
| 2020 | $ 4,221 |
| 2021 | 4,683 |
| 2022 | 4,846 |
| 2023 | 5,016 |
| 2024 | 5,191 |
| Thereafter | 23,646 |
| Total undiscounted lease payments | 47,603 |
| Less: Present value adjustments | (15,355) |
| Total | $ 32,248 |

## 6. Balance Sheet Components

### *Property and Equipment, Net*

Property and equipment, net consists of the following:

| | December 31, | |
|---|---|---|
| | 2019 | 2018 |
| | (In thousands) | |
| Computer equipment and software | $ 752 | $ 646 |
| Laboratory equipment | 6,291 | 5,470 |
| Furniture and fixtures | 678 | 678 |
| Leasehold improvements | 1,602 | 1,602 |
| Construction in progress | 23,553 | 1,612 |
| Total property and equipment | 32,876 | 10,008 |
| Less accumulated depreciation and amortization | (7,992) | (6,422) |
| Property and equipment, net | $ 24,884 | $ 3,586 |

Construction in progress was $23.6 million as of December 31, 2019 and $1.6 million as of December 31, 2018, representing the construction costs incurred for the Company's new facility in Redwood City, CA, which the Company began occupying in January 2020.

Depreciation and amortization expense related to property and equipment was $1.6 million and $1.8 million and for the years ended December 31, 2019 and 2018, respectively.

***Accrued Expenses and Other Current Liabilities***

Accrued expenses and other current liabilities consist of the following:

| | December 31, | |
|---|---|---|
| | 2019 | 2018 |
| | (In thousands) | |
| Compensation expense | $ 4,055 | $ 2,944 |
| Accrued professional fees | 2,607 | 2,291 |
| Accrued preclinical costs | 1,002 | 289 |
| Accrued clinical and process development costs | 971 | 1,561 |
| Other | 2,636 | 1,699 |
| Total accrued expenses and other current liabilities | $ 11,271 | $ 8,784 |

**7. Financing Arrangements**

***Banque Publique d'Investissement ("BPI France") Agreement***

In August 2015, BPI France granted Annapurna a €0.8 million interest-free conditional advance, of which €0.5 million was outstanding as of December 31, 2016. 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 interest expense over the life of the advances. As of December 31, 2019, the total carrying value, which approximates the fair value, of the conditional advance was $0.2 million, of which $0.1 million was recorded within other non-current liabilities and $0.1 million within accrued expenses and other current liabilities in the Company's consolidated balance sheets. As of December 31, 2018, the total carrying value, which approximates the fair value, of the conditional advance was $0.3 million, of which $0.2 million was recorded within other non-current liabilities and $0.1 million within accrued expenses and other current liabilities in the Company's consolidated balance sheets.

**8. Commitments and Contingencies**

***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, 2018, 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.

The Company was a party to a master services agreement ("MSA") with Cornell University ("Cornell") originally established in August 2014 and amended in December 2015. Under the MSA, Cornell provided assistance in regulatory affairs, overall project management, and parameter development. This MSA included services relating to gene therapy programs directed to A1AT deficiency, HAE and severe allergy. The MSA, as amended, provided for the Company to pay Cornell $13.3 million ratably over four years for these services as services were performed. In December 2016, the Company informed Cornell that the Company decided to terminate the MSA for material breach, effective January 6, 2017. Subsequently, Cornell informed the Company that it disputed the validity of the Company's termination of the MSA. In June 2019, Cornell and the Company entered into a settlement agreement, as a result of which the Company paid Cornell a $2.0 million settlement payment. There was no current period expense from the settlement, as the estimated costs associated with the termination of the MSA were previously accrued during the year ended December 31, 2017. The Company's license agreements with Cornell for A1AT deficiency and HAE remain in effect.

***Guarantees and Indemnifications***

In the normal course of business, the Company enters into contracts and agreements that contain a variety of representation 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, 2019 and 2018.

***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.

**9. Common Stock Warrants**

The table below represents the outstanding warrants to purchase common stock as of December 31, 2019 and 2018:

| Issue Date | Expiration Date | Number of Warrant Shares Outstanding and Exercisable | | Exercise Price Per Share |
|---|---|---|---|---|
| 12/31/2015 | 10/15/2020 | 40,000 | $ | 10.51 |
| 9/28/2017 | 9/29/2022 | 40,000 | $ | 3.65 |
| 8/4/2016 | 8/3/2021 | 10,000 | $ | 4.33 |
| | | 90,000 | | |

In February 2020, the warrants for the purchase of 10,000 shares of common stock issued in 2016 were net exercised for 7,250 shares of common stock.

**10. Stock 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 (the "2006 Plan"). The 2006 Plan allowed for the granting of incentive stock options ("ISOs") and non-qualified stock options ("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 (the "2014 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 the year ended December 31, 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.

In October 2017, the Company adopted the 2017 Inducement Plan (the "Inducement Plan"). The Company reserved 600,000 shares for issuance pursuant to stock options and RSUs under the Inducement Plan. The only persons eligible to receive grants of stock options and RSUs under Inducement Plan are individuals who satisfy the standards for inducement grants under Nasdaq guidance that is, generally, a person not previously an employee or director of Adverum, or following a bona fide period of non-employment, as an inducement material to the individual's entering into employment with Adverum.

The 2006 Plan, 2014 Plan and Inducement Plan are referred to collectively as the Plans. As of December 31, 2019, a total of 24,372,087 shares of common stock were reserved for issuance and 4,369,053 shares were available for future grants under the Plans.

***Stock Options***

Stock options under the 2014 Plan and the Inducement 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. Stock options granted to employees and non-employees generally vest ratably over four years.

The following table summarizes stock 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, 2017** | 6,695 | $ 4.51 | 7.4 | $ 9,539 |
| Granted | 2,049 | 5.94 | | |
| Exercised | (1,606) | 0.43 | | |
| Cancelled/forfeited | (691) | 5.90 | | |
| **Balance at December 31, 2018** | 6,447 | $ 5.83 | 7.6 | $ 3,594 |
| Granted | 4,978 | 7.16 | | |
| Exercised | (1,397) | 2.46 | | |
| Cancelled/forfeited | (1,033) | 4.93 | | |
| **Balance at December 31, 2019** | 8,995 | $ 7.19 | 7.6 | $ 48,073 |
| Vested and expected to vest as of December 31, 2019 | 8,995 | $ 7.19 | 7.6 | $ 48,073 |
| Exercisable at December 31, 2019 | 3,485 | $ 7.77 | 5.3 | $ 19,968 |

(a) The aggregate intrinsic value is calculated as the difference between the stock option exercise price and the closing price of the Company's common stock of $11.52 per share as of December 31, 2019.

The total intrinsic value of stock options exercised during the years ended December 31, 2019 and 2018 were $10.7 million and $8.2 million, respectively.

The fair value of each stock option issued 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, | |
| | 2019 | 2018 | 2019 | 2018 |
| Expected volatility | 81% | 80% | 105% | 78% |
| Expected term (in years) | 6.2 | 6.0 | 0.5 | 0.5 |
| Expected dividend yield | — | — | — | — |
| Risk-free interest rate | 2.1% | 2.8% | 1.9% | 2.3% |

The weighted-average fair values of options granted during the years ended December 31, 2019 and 2018, were $5.04 and $4.15, respectively.

As of December 31, 2019, there was $20.7 million of unrecognized stock-based compensation expense related to stock options that is expected to be recognized over a weighted-average period of 2.8 years.

***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 2–4 year period.

The following table summarizes the RSU 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) |
|---|---|---|---|
| **Balance at December 31, 2017** | 2,515 | $ 3.24 | 1.6 |
| Granted | 1,381 | 5.94 | |
| Vested and released | (774) | 3.46 | |
| Forfeited | (725) | 4.28 | |
| **Balance at December 31, 2018** | 2,397 | $ 9.23 | 4.8 |
| Granted | 250 | 3.95 | |
| Vested and released | (663) | 4.84 | |
| Forfeited | (863) | 4.86 | |
| **Balance at December 31, 2019** | 1,121 | $ 4.59 | 0.9 |

The weighted-average grant-date fair value of RSUs granted during the years ended December 31, 2019 and 2018, were $3.95 and $5.94, respectively. During the years ended December 31, 2019 and 2018, total fair value of RSUs vested was $3.4 million and $2.7 million, respectively. The number of RSUs 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, 2019, there was $3.0 million of unrecognized compensation cost related to unvested RSUs that is expected to be recognized over a weighted-average period of 1.5 years.

***ESPP***

In July 2014, the Company approved the establishment of the 2014 Employee Stock Purchase Plan (the "ESPP"). The Company reserved 208,833 shares of its common stock for issuance 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 the Company's common stock shares outstanding as of such date or a number of shares as determined by the Company's board of directors. During the year ended December 31, 2019, 86,405 shares were issued under the ESPP. As of December 31, 2019, a total of 1,875,022 shares of common stock were available for future issuance under the ESPP. As of December 31, 2019, there was $222,000 of unrecognized compensation cost related to the ESPP.

***Stock-Based Compensation Recognized in the Consolidated Statement of Operations and Comprehensive Loss***

The following table presents, by operating expense, the Company's stock-based compensation expense:

| | Years ended December 31, | |
|---|---|---|
| | 2019 | 2018 |
| | (In thousands) | |
| Research and development | $ 3,536 | $ 4,820 |
| General and administrative | 6,363 | 8,612 |
| Total share-based compensation expense | $ 9,899 | $ 13,432 |

During the years ended December 31, 2019 and 2018, the Company recorded approximately $1.2 million and $4.1 million, respectively of stock-based compensation expense as a result of the modification of the vesting and exercisability of stock awards associated with the departure of its executives, and directors.

**11. 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, 2019 and 2018 was $0.4 million and $0.4 million, respectively.

**12. Income Taxes**

Due to the full valuation allowance, no income tax benefit or expense was recorded for the year ended December 31, 2019. The Company recorded $1.3 million income tax benefit related to the change in the deferred tax liabilities balance due to intangible assets impairment recognized in the third quarter of 2018.

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

| | Years ended December 31, | |
|---|---|---|
| | 2019 | 2018 |
| | (In thousands) | |
| U.S. | $ (59,426) | $ (45,024) |
| Foreign | (5,060) | (28,853) |
| Loss before income taxes | $ (64,486) | $ (73,877) |

A reconciliation of income tax expense computed at the statutory federal income tax rate of 21% during the years ended December 31, 2019 and 2018 to income taxes as reflected in the financial statements is as follows:

| | Years ended December 31, | |
|---|---|---|
| | 2019 | 2018 |
| | (In thousands) | |
| Federal income tax expense at statutory rate | $ (13,542) | $ (15,514) |
| Stock compensation | (1,212) | (1,512) |
| Non-deductible expenses | 307 | 75 |
| Other | 298 | 41 |
| Research and development tax credits | (948) | (1,215) |
| Change in valuation allowance | 18,312 | 11,219 |
| Foreign rate differential | (212) | (586) |
| State deferred tax adjustment | 3,239 | — |
| Change in state uncertain tax positions | (6,242) | 6,242 |
| Total tax benefit | $ — | $ (1,250) |

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:

| | As of December 31, | |
|---|---|---|
| | 2019 | 2018 |
| | (In thousands) | |
| Deferred tax assets: | | |
| Net operating loss carryforwards | $ 53,309 | $ 37,247 |
| Accruals, reserve and other | 834 | 827 |
| Stock-based compensation | 4,767 | 4,549 |
| Tax credit carryforwards | 6,008 | 4,161 |
| Property and equipment | — | 310 |
| Intangibles | 24 | 38 |
| Lease obligation | 6,896 | — |
| Other | 151 | 122 |
| Total deferred tax assets before valuation allowance | 71,989 | 47,254 |
| Valuation allowance | (66,201) | (47,254) |
| Total deferred tax assets | 5,788 | — |
| Deferred tax liabilities: | | |
| Property and equipment | (1,305) | — |
| Right-of-use assets | (4,483) | — |
| Total deferred tax liabilities | $ (5,788) | $ — |
| 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, 2019 and 2018. The valuation allowance increased approximately $18.9 million and $11.8 million during the years ended December 31, 2019 and 2018, respectively.

As of December 31, 2019, the Company had U.S. federal net operating losses ("NOLs") carryforwards of approximately $159.5 million to offset any future federal income. Approximately $56.9 million of NOLs expire at various years beginning with 2036. As of December 31, 2019, the Company also had U.S. state NOL carryforwards of approximately $26.9 million to offset any future state income. U.S. state NOLs expire at various years beginning with 2036. At December 31, 2019, the Company also had approximately $70.1 million of foreign net operating loss carryforwards which may be available to offset future foreign income; these carryforwards do not expire.

As of December 31, 2019 , the Company had federal research and development tax credit carryforwards of approximately $4.6 million available to reduce future tax liabilities which expire at various years beginning with 2036. As of December 31, 2019, the Company had state credit carryforwards of approximately $4.6 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 NOLs and credits. As a result, the amount of the NOLs and research and development credit carryforwards presented in the Company's consolidated financial statements are permanently limited and will expire unutilized. Therefore, the Company removed a significant amount of NOLs and credits from its deferred taxe assets.

The Company files income tax returns in the U.S. federal, 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, 2016 through December 31, 2018. 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, 2019 and 2018 of approximately $3.6 million and $8.8 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:

| | Years ended December 31, | |
|---|---|---|
| | 2019 | 2018 |
| | (In thousands) | |
| Unrecognized tax benefits as of the beginning of the year | $ 8,805 | $ 2,745 |
| Increase (decrease) related to prior year tax provisions | (6,242) | 1,941 |
| Increase related to current year tax provisions | 995 | 4,119 |
| Unrecognized tax benefits as of the end of the year | $ 3,558 | $ 8,805 |

The Company recognizes interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2019, and 2018, 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.

**13. Net Loss per Share**

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:

| | As of December 31, | |
|---|---|---|
| | 2019 | 2018 |
| | (In thousands) | |
| Stock options | 8,995 | 6,447 |
| Restricted stock units | 1,121 | 2,397 |
| ESPP | 15 | 62 |
| Warrants to purchase common stock | 90 | 90 |
| | 10,221 | 8,996 |

**14. Related Party Transactions**

In May 2019, the Company entered into a common stock purchase agreement with James Scopa, a member of the Board, and Anne Kenner, as Trustees for the James P. Scopa and Anne E. Kenner Family Trust (the "Trust"), pursuant to which the Trust purchased an aggregate of 20,000 shares of the Company's common stock at a price of $6.71 per share, for an aggregate cash purchase price of $0.1 million.

**15. Subsequent Events**

In February 2020, the Company sold an aggregate of 10,925,000 shares of its common stock for $140.8 million of net proceeds after deducting underwriting discounts and commissions and estimated offering expenses.

**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 Ms. Patterson, our President and Chief Executive Officer and Mr. Leung, our 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, 2019. 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 Chief Executive Officer and Chief Financial Officer concluded that as of December 31, 2019, our 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 Chief 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, 2019, 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, 2019. The results of management's assessment were reviewed with the Audit Committee.

Our independent registered public accounting firm, Ernst & Young LLP, has audited the financial statements included in this Annual Report and has issued a report on the effectiveness of our internal control over financial reporting. The report of Ernst & Young LLP is included below.

*Attestation Report of the Registered Public Accounting Firm*

**REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM**

The Board of Directors and Stockholders
Adverum Biotechnologies, Inc.

**Opinion on Internal Control Over Financial Reporting**

We have audited Adverum Biotechnologies, Inc. internal control over financial reporting as of December 31, 2019, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework), (the COSO criteria). In our opinion, Adverum Biotechnologies, Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2019, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2019 and 2018, the related consolidated statements of operations and comprehensive loss, stockholders' equity, and cash flows for the years then ended, and the related notes and our report dated March 12, 2020 expressed an unqualified opinion thereon.

**Basis for Opinion**

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Annual Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

**Definition and Limitations of Internal Control Over Financial Reporting**

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

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

/s/ Ernst & Young LLP

San Jose, California

March 12, 2020

***Changes in Internal Control over Financial Reporting***

There were no changes in our internal control over financial reporting during the quarter ended December 31, 2019 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 Chief 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 Chief Executive Officer and Chief Financial Officer concluded that, as of December 31, 2019, 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.**

***2020 Annual Meeting of Stockholders***

The 2020 annual meeting of stockholders is scheduled to be held on June 23, 2020 (the “2020 Annual Meeting of Stockholders”). As a result, stockholders wishing to present a proposal for inclusion in our proxy materials for such meeting pursuant to Rule 14a-8 of the Securities Exchange Act of 1934, as amended, must submit their proposals so that they are received by us at our principal executive offices no later than the close of business on April 10, 2020 and must otherwise comply with the requirements of Rule 14a-8 in order to be considered for inclusion in our proxy materials for the 2020 Annual Meeting of Stockholders.

In addition, stockholders wishing to nominate a candidate for election to our board of directors or propose other business at an annual meeting other than pursuant to Rule 14a-8 of the Exchange Act must submit a written notice so that it is received by us at our principal executive offices no earlier than the close of business on March 25, 2020.
Nominations or proposals should be sent in writing to our Corporate Secretary at Adverum Biotechnologies, Inc., 800 Saginaw Drive, Redwood City, CA 94063. While our board will consider stockholder proposals, we reserve the right to omit from the proxy statement stockholder proposals that we are not required to include under the Exchange Act, including Rule 14a-8.

## 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 2019 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, 2019 , under the headings "Executive Officers," "Election of Directors," "Corporate Governance," and "Delinquent Section 16(a) Reports," 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 "Non-employee 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 Selection of Independent Registered Public Accounting Firm" and is incorporated herein by reference.

## PART IV

**Item 15. Exhibits, Financial Statement Schedules.**

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

See Index to Consolidated Financial Statements in Item 8 of this Annual Report on Form 10-K. No financial statement schedules are provided because the information called for is not required or is shown in the consolidated financial statements or related notes.

(b) The following exhibits are included herein or incorporated by reference:

### EXHIBIT INDEX

| EXHIBIT NUMBER | EXHIBIT DESCRIPTION | INCORPORATED BY REFERENCE | | | | PROVIDED HEREWITH |
|---|---|---|---|---|---|---|
| | | FILE NUMBER | FORM | DATE | EXHIBIT NUMBER | |
| 3.1 | Amended and Restated Certificate of Incorporation. | 001-36579 | 10-K | March 9, 2017 | 3.1 | |
| 3.2 | Amended and Restated Bylaws. | 001-36579 | 8-K | December 16, 2019 | 3.1 | |
| 4.1 | Reference is made to Exhibits 3.1 through 3.2. | | | | | |
| 4.2 | Form of Common Stock Certificate. | 333-197133 | S-1/A | July 25, 2014 | 4.1 | |
| 4.3 | Description of Common Stock | | | | | X |
| 10.1† | Research Collaboration and License Agreement, dated as of May 1, 2014, by and between Avalanche Biotechnologies, Inc. and Regeneron Pharmaceuticals, Inc. | 333-197133 | S-1/A | July 29, 2014 | 10.3 | |
| 10.2† | License Agreement between AAVLife and Inserm Transfert, dated July 4, 2014. | 001-36579 | 10-Q | August 9, 2016 | 10.9 | |
| 10.3† | Amendment No. 1 to License Agreement between AAVLife and Inserm Transfert, dated October 5, 2015. | 001-36579 | 10-Q | August 9, 2016 | 10.10 | |
| 10.4(#) | Avalanche Biotechnologies, Inc. Amended and Restated 2006 Equity Incentive Plan. | 333-197133 | S-1 | June 30, 2014 | 10.4 | |
| 10.5(#) | Form of Stock Option Grant Notice and Stock Option Agreement under the Amended and Restated 2006 Equity Incentive Plan. | 333-197133 | S-1/A | July 25, 2014 | 10.16 | |
| 10.6(#) | Adverum Biotechnologies, Inc. 2014 Equity Incentive Award Plan, as amended and restated. | 001-36579 | 10-K | March 6, 2019 | 10.12 | |
| 10.7(#) | Form of Stock Option Grant Notice and Stock Option Agreement under the 2014 Equity Incentive Award Plan. | 333-197133 | 10-K | March 6, 2018 | 10.14 | |
| 10.8(#) | Form of Restricted Stock Award Grant Notice and Restricted Stock Award Agreement under the 2014 Equity Incentive Award Plan. | 333-197133 | S-1/A | July 25, 2014 | 10.18 | |
| 10.9(#) | Form of Restricted Stock Unit Award Grant Notice and Restricted Stock Unit Award Agreement under the 2014 Equity Incentive Award Plan. | 001-36579 | 10-K | March 6, 2018 | 10.16 | |
| 10.10(#) | Adverum Biotechnologies, Inc. 2014 Employee Stock Purchase Plan, as amended and restated. | 001-36579 | 10-K | March 6, 2019 | 10.16 | |
| 10.11(#) | Letter Agreement, dated as of June 3, 2013, by and between Avalanche Biotechnologies, Inc. and Mehdi Gasmi. | 333-197133 | S-1 | June 30, 2014 | 10.10 | |
| 10.12(#) | Offer Letter, dated June 10, 2016, by and between Adverum Biotechnologies, Inc. and Leone Patterson | 001-36579 | 8-K | June 13, 2016 | 10.1 | |

| EXHIBIT NUMBER | EXHIBIT DESCRIPTION | INCORPORATED BY REFERENCE | | | | PROVIDED HEREWITH |
|---|---|---|---|---|---|---|
| | | FILE NUMBER | FORM | DATE | EXHIBIT NUMBER | |
| 10.13(#) | Offer Letter, dated May 4, 2015, by and between Avalanche Biotechnologies, Inc. and Jennifer Cheng, Ph.D. | 001-36579 | 10-K | March 6, 2018 | 10.30 | |
| 10.14 | 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 | |
| 10.15 | First Amendment to Lease, dated August 1, 2014, by and between O'Brien Drive Portfolio, LLC and Avalanche Biotechnologies, Inc. | 001-36579 | 8-K | September 12, 2014 | 10.1 | |
| 10.16 | Second Amendment to Lease, dated October 30, 2014, by and between O'Brien Drive Portfolio, LLC and Avalanche Biotechnologies, Inc. | 001-36579 | 8-K | November 4, 2014 | 10.1 | |
| 10.17(#) | Form of Indemnification Agreement for directors and executive officers. | 333-197133 | S-1/A | July 18, 2014 | 10.12 | |
| 10.18(#) | 2012 Change in Control Benefit Plan. | 333-197133 | S-1/A | July 18, 2014 | 10.13 | |
| 10.19(#) | Form of Change in Control Severance Agreement for executive officers other than the chief executive officer. | 001-36579 | 10-K | March 6, 2018 | 10.36 | |
| 10.20(#) | Amendment to the Change in Control and Severance Agreement for Mehdi Gasmi. | 001-36579 | 10-K | March 6, 2019 | 10.32 | |
| 10.21(#) | Form of Inducement Stock Option Agreement outside of plan. | 001-36579 | 8-K | November 20, 2015 | 10.3 | |
| 10.22(#) | Form of Inducement Restricted Stock Unit Agreement outside of plan | 333-218465 | S-8 | June 2, 2017 | 99.6 | |
| 10.23(#) | Form of Stock Option Grant Notice and Option Agreement under the 2017 Inducement Plan. | 333-220894 | S-8 | October 11, 2017 | 99.2 | |
| 10.24(#) | Form of Restricted Stock Award Grant Notice and Restricted Stock Award Agreement under the 2017 Inducement Plan. | 333-220894 | S-8 | October 11, 2017 | 99.3 | |
| 10.25 | Lease dated as of June 28, 2018, between Adverum Biotechnologies, Inc. and HCP LS Redwood City, LLC | 001-36579 | 10-Q | August 8, 2018 | 10.2 | |
| 10.26† | Exclusive License Agreement, between the Company and the Regents of the University of California ("UC"), dated June 17, 2013 (the "UC License") | 001-36579 | 10-K | March 6, 2019 | 10.46 | |
| 10.27† | License Agreement, between the Company and Virovek, Inc. ("Virovek"), dated October 12, 2011 (the "Virovek License") | 001-36579 | 10-K | March 6, 2019 | 10.47 | |
| 10.28(#) | Amended and Restated Offer Letter with Leone Patterson, dated October 24, 2018 | 001-36579 | 10-K | March 6, 2019 | 10.48 | |
| 10.29(#) | Change in Control and Severance Agreement with Leone Patterson, dated October 24, 2018 | 001-36579 | 10-K | March 6, 2019 | 10.49 | |
| 10.30(#) | Employment Agreement, dated February 27, 2019, with Thomas Leung | 001-36579 | 10-Q | May 8, 2019 | 10.1 | |
| 10.31(#) | Separation Letter, dated May 1, 2019, between Adverum Biotechnologies, Inc. and Paul Cleveland | 001-36579 | 10-Q | August 8, 2019 | 10.2 | |
| 10.32(#) | Employment Agreement, dated February 28, 2019, among Adverum Biotechnologies, Inc. and Aaron Osborne. | 001-36579 | 10-Q | November 7, 2019 | 10.1 | |
| 10.33(#) | Employment Agreement, dated October 11, 2019, among Adverum Biotechnologies, Inc. and Peter Soparkar. | 001-36579 | 10-Q | November 7, 2019 | 10.2 | |

| EXHIBIT NUMBER | EXHIBIT DESCRIPTION | INCORPORATED BY REFERENCE | | | | PROVIDED HEREWITH |
|---|---|---|---|---|---|---|
| | | FILE NUMBER | FORM | DATE | EXHIBIT NUMBER | |
| 10.34(#) | Separation and Consulting Agreement, dated July 31, 2019, between Adverum Biotechnologies, Inc. and Mehdi Gasmi. | 001-36579 | 10-Q | November 7, 2019 | 10.3 | |
| 10.35(#) | Separation Letter and Consulting Agreement, dated September 3, 2019 and September 6, 2019, respectively, between Adverum Biotechnologies, Inc. and Jennifer Cheng. | 001-36579 | 10-Q | November 7, 2019 | 10.4 | |
| 10.36(#) | Non-Employee Director Compensation Policy, effective December 13, 2019 | | | | | X |
| 10.37(#) | 2017 Inducement Plan, as amended and restated. | 333-233135 | S-8 | August 8, 2019 | 99.1 | |
| 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 of Principal Executive Officer pursuant to 18 U.S.C. section 1350, as adopted pursuant to section 906 of the Sarbanes-Oxley Act of 2002. | | | | | X |
| 32.2 | Certification of Principal Financial and Accounting Officer pursuant to 18 U.S.C. section 1350, as adopted pursuant to section 906 of the Sarbanes-Oxley Act of 2002. | | | | | 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.

**Item 16. Form 10-K Summary**

None.

## 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 12, 2020

ADVERUM BIOTECHNOLOGIES, INC.

By: /s/ Leone Patterson
**Leone Patterson**
President and Chief Executive Officer
*(Principal Executive Officer)*

By: /s/ Thomas Leung
**Thomas Leung**
Chief Financial Officer
*(Principal Financial and Accounting Officer)*

**Power of Attorney**

Each person whose individual signature appears below hereby authorizes and appoints Leone Patterson and Thomas Leung, 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/ Leone Patterson<br>Leone Patterson | President and Chief Executive Officer and Director<br>*(Principal Executive Officer)* | March 12, 2020 |
| /s/ Thomas Leung<br>Thomas Leung | Chief Financial Officer<br>*(Principal Financial and Accounting Officer)* | March 12, 2020 |
| /s/ Patrick Machado, J.D.<br>Patrick Machado, J.D. | Chairman of the Board | March 12, 2020 |
| /s/ Eric G. Carter<br>Eric G. Carter, M.D., Ph.D. | Director | March 12, 2020 |
| /s/ Mehdi Gasmi, Ph.D.<br>Mehdi Gasmi | Director | March 12, 2020 |
| /s/ Rekha Hemrajani, M.B.A.<br>Rekha Hemrajani, M.B.A. | Director | March 12, 2020 |
| /s/ Mark Lupher, Ph.D.<br>Mark Lupher, Ph.D. | Director | March 12, 2020 |
| /s/ James Scopa, J.D., M.B.A.<br>James Scopa, J.D., M.B.A. | Director | March 12, 2020 |
| /s/ Richard N. Spivey, Pharm.D.<br>Richard N. Spivey, Pharm.D. | Director | March 12, 2020 |
| /s/ Thomas F. Woiwode, Ph.D.<br>Thomas F. Woiwode, Ph.D. | Director | March 12, 2020 |

**Exhibit 4.3**

**ADVERUM BIOTECHNOLOGIES, INC.**
**DESCRIPTION OF CAPITAL STOCK**

Our authorized capital stock consists of 300,000,000 shares of common stock, $0.0001 par value per share, and 5,000,000 shares of preferred stock, $0.0001 par value per share. A description of material terms and provisions of our certificate of incorporation and bylaws affecting the rights of holders of our common stock is set forth below. The description is intended as a summary, and is qualified in its entirety by reference to our certificate of incorporation and the bylaws.

**Common Stock**

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

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

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

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

**Anti-takeover Effects of Provisions of our Certificate of Incorporation and Bylaws and Delaware Law**

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

***Undesignated Preferred Stock***

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

***Stockholder Meetings***

Our charter documents provide that a special meeting of stockholders may be called only by the secretary of our company at the direction of the board of directors.

***Requirements for Advance Notification of Stockholder Nominations and Proposals***

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

***Elimination of Stockholder Action by Written Consent***

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

***Election and Removal of Directors***

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

***Delaware Anti-Takeover Statute***

We are subject to Section 203 of the DGCL, which prohibits a Delaware corporation from engaging in a business combination with any interested stockholder for a period of three years following the date the person became an interested stockholder, with the following exceptions:

- before such date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested holder;

- upon completion of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the

  time the transaction began, excluding for purposes of determining the voting stock outstanding (but not the outstanding voting stock owned by the interested stockholder) those shares owned (a) by persons who are directors and also officers and (b) pursuant to employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; and

- on or after such date, the business combination is approved by the board of directors and authorized at an annual or special meeting of the stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock that is not owned by the interested stockholder.

In general, Section 203 of the DGCL defines business combination to include the following:

- any merger or consolidation involving the corporation and the interested stockholder;

- any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;

- subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;

- any transaction involving the corporation that has the effect of increasing the proportionate share of the stock or any class or series of the corporation beneficially owned by the interested stockholder; and

- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits by or through the corporation.

Section 203 of the DGCL defines an “interested stockholder” as an entity or person who, together with the entity’s or person’s affiliates and associates, beneficially owns, or is an affiliate of the corporation and within three years prior to the time of determination of interested stockholder status did own, 15% or more of the outstanding voting stock of the corporation. A Delaware corporation may “opt out” of these provisions with an express provision in its certificate of incorporation. We have not opted out of these provisions, which may as a result, discourage or prevent mergers or other takeover or change of control attempts of us.

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

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

of our then outstanding voting stock

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

***Delaware as Sole and Exclusive Forum***

Our amended and restated certificate of incorporation provides that, unless we consent 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 Adverum, (ii) any action asserting a claim of breach of a fiduciary duty owed by any director, officer or other employee of Adverum to us or our 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. This provision does not apply to actions arising under the Securities Act or the Exchange Act, or any claim for which the federal courts have exclusive jurisdiction.

**Exhibit 10.36**

**ADVERUM BIOTECHNOLOGIES, INC.**

**NON-EMPLOYEE DIRECTOR COMPENSATION POLICY**

**ADOPTED BY THE BOARD: DECEMBER 13, 2019**

Each member of the board of directors (the "***Board***") of Adverum Biotechnologies, Inc. (the "***Company***") who is a Non-Employee Director (as defined in the Adverum Biotechnologies, Inc. 2014 Equity Incentive Award Plan (the "***Plan***")) will be eligible to receive cash and equity compensation as set forth in this Adverum Biotechnologies, Inc. Non-Employee Director Compensation Policy (this "***Policy***"). The cash and equity compensation described in this Policy will be paid or granted, as applicable, automatically and without further action of the Board to each Non-Employee Director who is eligible to receive such cash or equity compensation, unless such Non-Employee Director declines the receipt of such cash or equity compensation by written notice to the Company prior to the time period for which compensation is paid. This Policy, as adopted on December 13, 2019, will become effective immediately and will remain in effect until it is revised or rescinded by further action of the Board or the Compensation Committee of the Board. Capitalized terms not explicitly defined in this Policy but defined in the Plan will have the same definitions as in the Plan.

**1. CASH COMPENSATION.**

**(a) Annual Retainers.** Each Non-Employee Director will be eligible to receive the following annual retainers for service as (i) a member and/or chair of the Board and (ii) a member or chair/co-chair of a committee of the Board ("***Committee***") set forth below, as applicable.

| Board or Committee | Type of Retainer* | Amount (Per Year) |
|---|---|---|
| **Board** | Chair | $35,000 |
| | Member | $40,000 |
| **Audit Committee** | Chair | $20,000 |
| | Member (Non-Chair) | $10,000 |
| **Compensation Committee** | Chair | $15,000 |
| | Member (Non-Chair) | $7,500 |
| **Nominating and Corporate Governance Committee** | Chair | $10,000 |
| | Member (Non-Chair) | $5,000 |
| **Research and Development Committee** | Chair/Co-Chair | $15,000 |
| | Member (Non-Chair/Co-Chair) | $7,500 |

* The chair of the Board is eligible to receive a retainer for service as the chair and an additional retainer for service as a member of the Board. The chair/co-chair of each Committee is eligible to receive a retainer for service as the chair/co-chair, but not an additional retainer for service as a member of the Committee.

The annual retainers will be paid on the last day of the quarter and partial service for that quarter will receive *pro rata* treatment.

**(b) Expenses.** Each Non-Employee Director will be eligible for reimbursement from the Company for all reasonable out-of-pocket expenses incurred by the Non-Employee Director in connection with his or her attendance at Board and Committee meetings.

To the extent that any taxable reimbursements are provided to a Non-Employee Director, they will be provided in accordance with Section 409A of the Internal Revenue Code of 1986, as amended, and the Treasury Regulations and other guidance thereunder and any state law of similar effect, including, but not limited to, the following provisions: (i) the amount of any such expenses eligible for reimbursement during the Non-Employee Director's taxable year may not affect the expenses eligible for reimbursement in any other taxable year; (ii) the reimbursement of an eligible expense must be made no later than the last day of the Non-Employee Director's taxable year that immediately follows the taxable year in which the expense was incurred; and (iii) the right to any reimbursement may not be subject to liquidation or exchange for another benefit.

**2. EQUITY COMPENSATION.** The options described in this Policy will be granted under the Plan and will be subject to the terms and conditions of (i) this Policy, (ii) the Plan and (iii) the form of Option Agreement approved by the Board for the grant of options to Non-Employee Directors under the Plan.

**(a) Initial Grants.** Each person who first becomes a Non-Employee Director, whether through election by the stockholders of the Company or appointment by the Board to fill a vacancy, automatically will be granted a Nonstatutory Stock Option to purchase 70,000 shares of Common Stock (an "***Initial Option***") on the date of his or her initial election or appointment to be a Non-Employee Director.

**(b) Annual Grants.** On the date of each annual meeting of the Company's stockholders: (i) each person who is then a Non-Employee Director and will be continuing as a Non-Employee Director following the date of such annual meeting (other than any Non-Employee Director receiving an Initial Option on the date of such annual meeting) automatically will be granted a Nonstatutory Stock Option to purchase 45,000 shares of Common Stock; and (ii) the Chair of the Board automatically will be granted an additional Nonstatutory Stock Option to purchase 10,000 shares of Common Stock. Each of the options granted pursuant to (i) and (ii), is referred to as an "***Annual Option***". The foregoing notwithstanding, the first Annual Option to be granted pursuant to (ii) above (the "***First Chair Grant***") shall be granted on January 1, 2020, and shall be for 15,000 shares rather than 10,000 shares, and no grant pursuant to (ii) above shall be made at the 2020 annual meeting of the Company's stockholders.

**(c) Terms of Options.**

**(i)** Exercise Price. The exercise price of each Initial Option and Annual Option will be equal to 100% of the Fair Market Value of the Common Stock subject to such option (as determined in accordance with the Plan) on the date such option is granted.

**(ii)** Vesting. Each Initial Option and Annual Option will vest and become exercisable as follows:

**(A)** Each Initial Option will vest and become exercisable in equal annual installments on each of the first three anniversaries of the date of grant of such option, provided that the Non-Employee Director has not had a Termination of Service prior to each such date; *provided*, *however*, that the vesting shall accelerate, and the Initial Option shall become fully vested and exercisable, upon the consummation of a Change in Control.

**(B)** Each Annual Option will vest and become exercisable on the earlier of (i) the date of the next annual meeting of the Company's stockholders (the 2021 annual meeting of the Company's stockholders in the case of the First Chair Grant), or (ii) the first anniversary of the date of grant of such option (18 months following the grant date in the case of the First Chair Grant), provided that the Non-Employee Director has not had a Termination of Service prior to such date; *provided*, *however*, that

the vesting shall accelerate, and each Annual Option shall become fully vested and exercisable, upon the consummation of a Change in Control.

**Exhibit 21.1**

## SUBSIDIARIES OF ADVERUM BIOTECHNOLOGIES, INC.

| Name of Subsidiary | Country of Incorporation |
|---|---|
| Avalanche Australia PTY LTD | Australia |
| Adverum Biotechnologies, SAS | France |
| Annapurna Therapeutics, LTD | Ireland |

**Exhibit 23.1**

**CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM**

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statements on Form S-8 Nos. 333-223894, 333-218465, 333-211439, 333-203398, 333-199296, 333-230138, 333-233135, and 333-220894
(2) Registration Statements on Form S-3 Nos. 333-219890 and 333-233134

of our reports dated March 12, 2020, with respect to the consolidated financial statements of Adverum Biotechnologies Inc. and the effectiveness of internal control over financial reporting of Adverum Biotechnologies, Inc. included in this Annual Report (Form 10-K) of Adverum Biotechnologies Inc. for the year ended December 31, 2019.

/s/ Ernst & Young LLP

San Jose, California
March 12, 2020

**Exhibit 31.1**

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

I, Leone Patterson, certify that:

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

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

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

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) 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 report based on such evaluation; and

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

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

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

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

Date: March 12, 2020

By: /s/ Leone Patterson
Name: Leone Patterson
Title: Chief Executive Officer
*(Principal Executive Officer)*

**Exhibit 31.2**

**CERTIFICATION OF THE PRINCIPAL FINANCIAL AND ACCOUNTING OFFICER**
**PURSUANT TO SECTION 302 OF**
**THE SARBANES-OXLEY ACT OF 2002**

I, Thomas Leung, certify that:

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

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

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

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

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

   b. 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 report based on such evaluation; and

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

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

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

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

Date: March 12, 2020

By: /s/ Thomas Leung
Name: Thomas Leung
Title: Chief Financial Officer
*(Principal Financial and Accounting Officer)*

**Exhibit 32.1**

**CERTIFICATION 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, 2019 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Leone Patterson, as Chief 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 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 12, 2020

By: /s/ Leone Patterson

Leone Patterson

Chief Executive Officer
(Principal Executive Officer)

**Exhibit 32.2**

**CERTIFICATION 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, 2019 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Thomas Leung, 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 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 12, 2020

By: /s/ Thomas Leung

Thomas Leung

Chief Financial Officer
(Principal Financial and Accounting Officer)