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, 2022

or

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

For the transition period from _____ to _____

Commission File Number: 001-36579

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.)**

100 Cardinal Way
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. ☐

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

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

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report Yes ☐ No ☒

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, 2022, 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 $114.9 million, based on the closing price of the registrant's common stock on the Nasdaq Global Market on June 30, 2022 of $1.20 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 March 17, 2023, the registrant had 100,559,291 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 2023 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 May 1, 2023, 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 nonclinical studies and any clinical trials for our product candidates;
- our ability to advance our viral vector manufacturing and delivery capabilities;
- our research and development expenses could fluctuate and may increase;
- the timing or likelihood of regulatory submissions, designations and approvals;
- our plans to explore potential applications of our gene therapy platform in other indications in highly prevalent 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 in "Risk Factors Summary" below and 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. In addition, statements that "we believe" and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this Annual Report on Form 10-K, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and investors are cautioned not to unduly rely upon these statements.

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.

RISK FACTORS SUMMARY

Investing in common stock involves numerous risks, including the risks described in "Item 1A. Risk Factors" of this Annual Report on Form 10-K. Below are some of these risks, any one of which could materially adversely affect our business, financial condition, results of operations, and prospects.

- 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 expect that our cash, cash equivalents, and short-term investments will be sufficient to fund our lead gene therapy programs into 2025. If this expectation proves to be wrong, we may be forced to delay, limit or terminate certain of our development efforts before then.
- 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 are not currently in compliance with Nasdaq's continued listing standards, and if we are not able to regain compliance with Nasdaq's continued listing standards our common stock may be delisted.
- 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.
- 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.
- The occurrence of serious complications or side effects that outweigh the therapeutic benefit in connection with or during use of our product candidates, whether in nonclinical 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.
- The results of nonclinical 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 we are unable to successfully develop and maintain robust and reliable manufacturing processes for our product candidates, we may be unable to advance clinical trials or licensure applications and may be forced to delay or terminate a program.
- If we are unable to produce sufficient quantities of our product candidates at acceptable costs, we may be unable to meet clinical or potential commercial demand, lose potential revenue, have reduced margins, or be forced to terminate a program.
- 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 are subject to many manufacturing and distribution risks, any of which could substantially increase our costs and limit supply of our product candidates.
- We have relied, and expect to continue to rely, on third parties under contracts and partnerships to conduct some or all aspects of our research and development, including vector production, process development, assay development, product candidates and product manufacturing and testing, protocol development, clinical trials, product distribution, commercialization, nonclinical studies, research and related activities, and these third parties may not perform satisfactorily.
- We will rely on third parties to conduct some nonclinical 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.
- Our success depends on our ability to protect our intellectual property and our proprietary technologies.
- 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.
- We may not be successful in obtaining or maintaining necessary rights to our product candidates through acquisitions and in-licenses.
- 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.

- The patent protection and patent prosecution for some of our product candidates are dependent on third parties.
- We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.
- Third party patent rights could delay or otherwise adversely affect our planned development and sale of product candidates of our programs.
- We may not be able to obtain intellectual property rights or protect our intellectual property rights throughout the world.
- Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.
- If we do not obtain patent term extensions for patents covering our product candidates, our business may be materially harmed.
- 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.
- Final marketing approval for our product candidates by the FDA or other regulatory authorities outside the U.S. for commercial use may be delayed, limited or denied, any of which would adversely affect our ability to generate operating revenue.
- 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.
- 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.
- 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.
- 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.
- Healthcare and other reform legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and, if approved, may affect the prices we may obtain.
- 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.
- 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 may encounter difficulties in managing our growth and expanding our operations successfully.
- The coronavirus (“COVID-19”) pandemic has impacted our business practices and the effects of its continued impact on our business, results of operations, and financial condition will depend on future developments, which cannot be predicted.
- 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.
- If we sell shares of our common stock or securities convertible into or exercisable for shares of our common stock in future financings, pursuant to licensing, collaboration or other arrangements, stockholders may experience immediate dilution and, as a result, our stock price may decline.

PART 1.

Item 1. Business

Overview

Adverum is a clinical-stage company that aims to establish gene therapy as a new standard of care for highly prevalent ocular diseases. We discover and develop gene therapy product candidates intended to provide durable efficacy by inducing sustained expression of a therapeutic protein. Our core capabilities include novel vector evaluation, cassette engineering, and ocular IND-enabling nonclinical and clinical development. In addition, we have in-house manufacturing expertise, specifically in scalable process development, assay development, and current Good Manufacturing Practices ("GMP") quality control.

Ixo-vec (ADVM-022)

Our lead product candidate, ixoberogene soroparvovec ("Ixo-vec"), formerly referred to as ADVM-022, is a single, in-office intravitreal ("IVT") injection gene therapy product designed to deliver long-term durable therapeutic levels of aflibercept associated with a robust, sustained treatment response, reducing the treatment burden and fluctuations in macular fluid associated with bolus anti-vascular endothelial growth factor ("VEGF") IVT injections. Ixo-vec utilizes an engineered, proprietary vector capsid, AAV.7m8, carrying an aflibercept coding sequence under the control of a proprietary expression cassette capable of transducing retinal cells after a single in-office IVT injection. This product is intended to improve both real-world vision and quality of life outcomes for patients. Ixo-vec is currently being developed for the treatment of patients with wet age-related macular degeneration ("wet AMD") who are responsive to anti-VEGF therapy.

Wet AMD is a leading cause of blindness in patients over 65 years of age, with a prevalence of approximately 20 million individuals worldwide living with wet AMD. Age-related macular degeneration ("AMD") is expected to impact 288 million people worldwide by 2040, with wet AMD accounting for approximately ten percent of those cases. 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 Ixo-vec for the treatment of wet AMD.

In November 2018, we initiated the OPTIC trial, designed as a multi-center, open-label, dose-ranging, safety and efficacy trial of Ixo-vec in subjects with wet AMD who have demonstrated responsiveness to anti-VEGF treatment. Subjects in OPTIC are treatment experienced, and previously required frequent anti-VEGF injections to manage their wet AMD and to maintain functional vision. We completed enrollment for OPTIC in July 2020 and will continue to present updated efficacy, aflibercept protein levels and safety data from the trial through two years and into the extension study as we continue to follow our subjects for an additional three years for a total of five years. To date, we have seen strong signals of therapeutic efficacy in OPTIC in both the 6 x 10^11 vg/eye ("6E11") and 2 x 10^11 vg/eye ("2E11") doses, including continuous stable aflibercept protein levels from 10 weeks to three years, maintenance to improvement in best-corrected visual acuity and central subfield thickness ("CST"), a measure of fluid in and beneath the retina, as well as a reduction in CST fluctuations. Ixo-vec has been generally well tolerated, with the most common adverse events being dose-dependent adeno-associated virus ("AAV") associated ocular inflammation that has been responsive to topical corticosteroid therapy.

Nonclinical studies have indicated that a 6 x 10^10 vg/eye ("6E10") dose has the potential to achieve therapeutic levels of aflibercept. In April 2022, we announced we received feedback from the FDA via a Type C meeting written response related to our planned Phase 2 trial of Ixo-vec in wet AMD. We requested the FDA's feedback to ensure alignment with the regulatory agency ahead of filing the Investigational New Drug ("IND") amendment for our Phase 2 trial, which IND amendment was submitted on May 26, 2022.

In September 2022, we dosed the first subject in our Phase 2 LUNA ("LUNA") trial of Ixo-vec. The LUNA trial is a multicenter, double-masked, randomized, parallel-group Phase 2 trial evaluating two doses of Ixo-vec - 2E11, the lower dose used in the OPTIC trial, and a new, lower 6E10 dose - in up to 72 subjects with wet AMD. The LUNA trial will assess four new enhanced prophylactic corticosteroid regimens, including local corticosteroids and combinations of local and systemic corticosteroids to test the relative contribution of local versus systemic AAV exposure on ocular inflammation. Specific regimens include topical difluprednate ("Durezol®"), dexamethasone intravitreal implant ("Ozurdex®"), and a combination of either topical Durezol® or IVT Ozurdex® with oral prednisone.

The trial will randomize the participants equally between the 2E11 and 6E10 Ixo-vec doses and will be conducted at approximately 40 sites in the U.S. and Europe. Four prophylactic corticosteroid regimens will be studied. The primary endpoints will be similar to the OPTIC trial and focus on mean change in best-corrected visual acuity and CST from baseline to one year, and incidence and severity of adverse events. Other endpoints will include aflibercept protein levels starting at 14 weeks, an interim efficacy and safety analysis at 26 weeks and will include a reduction in fluctuations in CST and in treatment burden. The study will also evaluate the effectiveness and tolerability of the prophylactic corticosteroid regimens.

In June 2022, we announced that the European Medicines Agency ("EMA") has granted Ixo-vec Priority Medicines ("PRIME") designation. PRIME is a program launched by the EMA to enhance support for research on and development of medicines that have demonstrated preliminary safety and efficacy and thus the potential to target a significant unmet medical need and bring a major therapeutic advantage to patients. This regulatory program offers developers of promising medicines enhanced interaction and early dialogue and is designed to optimize development plans and speed evaluation ensuring these medicines reach patients as early as possible. In November 2022, a PRIME kickoff meeting was held to initiate interaction with the EMA experts and to familiarize EMA with the product, development program, and planned regulatory strategy.

Immunogenicity to AAV therapy has been broadly reported to be associated both with systemic and ocular gene therapies, regardless of route of administration, and is generally understood to be dose-related. Based on an extensive evaluation of data from all of our subjects treated with Ixo-vec and all of our nonclinical data by internal and external experts, we believe that utilizing the 2E11 and 6E10 doses, along with the new enhanced prophylactic corticosteroid regimens, which include local corticosteroids and a combination of local and systemic corticosteroids, will allow us to minimize post-prophylaxis inflammation in our trial subjects going forward.

In May 2020, we initiated the INFINITY trial, a multi-center, Phase 2, randomized, double-masked, active comparator-controlled study evaluating a single IVT injection of Ixo-vec in subjects with diabetic macular edema ("DME"). A dose limiting toxicity at the 6E11 dose in this population with poorly controlled diabetes and micro vascular complications was identified in April of 2021. Consequently, we are no longer pursuing Ixo-vec for DME, nor are we evaluating the 6E11 dose in wet AMD. We have not seen similar subject safety concerns in any of our subjects at either the 2E11 dose in the INFINITY or OPTIC trials or the 6E11 dose in the OPTIC trial.

As we advance Ixo-vec for wet AMD, we are continuing to develop our manufacturing expertise for ongoing supply. We maintain control of key aspects of the manufacturing process, specifically in scalable process development, assay development, and GMP quality controls.

ADVM-062

Our second product candidate, ADVM-062 (AAV.7m8-L-opsin), is a novel gene therapy product candidate being developed to deliver a functional copy of the OPN1LW gene to the foveal cones of patients suffering from blue cone monochromacy ("BCM") via a single IVT injection. ADVM-062 utilizes Adverum's propriety vector capsid, AAV.7m8. In January 2022, we announced that the FDA granted Orphan Drug Designation to ADVM-062.

BCM affects approximately 1 to 9 in 100,000 males, worldwide. This X-linked recessive hereditary condition is caused by the absence of function in the L and the M opsin gene(s) and can manifest in loss of visual acuity, photosensitivity, myopia and infantile nystagmus that can persist into adulthood. Consequently, individuals with BCM have visual impairments to important aspects of daily living such as facial recognition, learning, reading, and daylight vision. Currently, there is no cure for BCM and to our knowledge, no other therapies to treat BCM are in development. We are collaborating with the families of patients affected with BCM (BCM Families Foundation) to help advance our therapies. In an effort to prioritize Ixo-vec clinical development and focus on establishing gene therapy as a new standard of care for highly prevalent ocular diseases, we are in the process of identifying a suitable partner to further develop this product candidate.

Recent Restructuring

In July 2022, we announced we had taken measures to restructure our operations, including reductions in both headcount and expenses to prioritize Ixo-vec's clinical development, and focus our pipeline strategy on certain highly prevalent ocular diseases. The restructuring was completed in the fourth quarter of 2022. We expect these restructuring measures will be sufficient to extend our cash runway into 2025. See, however, Item 1A. Risk Factors – "We expect that our cash, cash equivalents, and short-term investments will be sufficient to fund our lead gene therapy program into 2025. If this expectation proves to be wrong, we may be forced to delay, limit or terminate certain of our development efforts before then."

Impact of COVID-19

Our results of operations and financial condition for the year ended December 31, 2022 were not significantly impacted by the COVID-19 pandemic. We are actively monitoring and managing our response to the COVID-19 pandemic and assessing actual and potential impacts to these areas. Please refer to the "Risk Factors" section for further discussion of the risks we face as a result of the COVID-19 pandemic.

Impact on Operations

We are continuously evaluating and addressing potential impacts of the COVID-19 pandemic on our operations, and are committed to the health and safety of our employees and their families. We have reopened our offices to allow our employees more flexibility to mix virtual and in-person work and to advance our culture and corporate goals. We believe this will also enable greater balance and well-being of our employees. We continue to update our policies and implement new practices to align with the current guidance from state and federal governments and health authorities. We believe these measures and others have allowed us to mitigate, but not eliminate, the effects and risks on our on-site operations posed by the COVID-19 pandemic.

Impact on Clinical Trials

The ultimate impact of the COVID-19 pandemic on our ongoing and planned clinical trials is uncertain and subject to change. To date, we believe we have experienced limited impact due to COVID-19 on our ongoing clinical programs, including the OPTIC and LUNA clinical trials. We are working closely with our clinical trial sites to monitor and attempt to address or limit the potential negative impacts of the evolving COVID-19 outbreak and the emergence of COVID-19 variants on subject safety, trial enrollment, continued participation and follow-up of subjects already enrolled in our clinical studies, protocol compliance, data quality, and overall study integrity. Despite these efforts, we are unsure as to whether the COVID-19 pandemic will significantly impact future trial enrollment or completion of our current or planned clinical studies.

Impact on Supply Chain and Manufacturing

While we have not yet experienced significant disruptions to our supply chain and manufacturing as a result of the COVID-19 pandemic, we cannot be certain that this trend will continue. Based on current information, we believe that our partners in our supply chain have been and will continue to serve us continuously. The COVID-19 pandemic and other factors have adversely impacted the global supply chain for other supplies and materials which could impact our future operations. To mitigate against future potential delays in supplies and materials we use in our operations, including product supply, we are continuously implementing additional measures to address potential risks as we identify them, including securing additional supplies and manufacturing capacity reserve, which have resulted in additional expenses and may result in other additional expenses in the future. Given the uncertainty regarding the impact delays and disruption in the global supply chain may have on our operations, we are unable to quantify the ultimate impact on our future results at this time.

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 AAV ocular gene therapy and AAV product optimization, including cassette engineering and vectorizing therapeutic biologics;
- deep understanding of how immunogenicity impacts ocular gene therapy;
- a pipeline of gene therapy product candidates targeting the treatment of highly prevalent ocular diseases;
- deep expertise developing and administering clinical trials with a focus on regulatory compliance in the U.S and Europe;
- in-house gene therapy manufacturing expertise, specifically in scalable process development, assay development, and GMP quality control;
- maturing a portfolio of proprietary vectors with specific ocular cell tropism;
- a robust patent portfolio; and
- an experienced leadership team with expertise in ophthalmology, gene therapy, drug development, regulatory approval and commercialization.

Our Strategy

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

- **Target large patient populations impacted by wet AMD and other chronic retinal conditions that respond to anti-VEGF therapy**. There are approximately 20 million individuals worldwide living with wet AMD, and the incidence of new cases is expected to continue to grow significantly worldwide as populations age. AMD is expected to impact 288 million people worldwide by 2040, with wet AMD accounting for approximately ten percent of those cases. We estimate that the standard-of-care anti-VEGF therapies used to treat wet AMD and other chronic retinal conditions that respond to anti-VEGF therapy generated in excess of $13 billion worldwide in sales in 2021.

- **Develop a single intravitreal injection gene therapy treatment to relieve the burden of frequent, chronic injections and improve real-world vision and quality of life outcomes.** Our gene therapies are designed as a single, in-office IVT injection therapy to address the unmet needs of patients with highly prevalent ocular diseases. The current standards of care for wet AMD and other VEGF-mediated chronic retinal diseases require frequent injections for the duration of the disease. As an example, for wet AMD, a current standard-of-care treatment requires patients to receive IVT injections of anti-VEGF protein every 4-16 weeks. We believe that durable treatment to reduce injection frequency and improve long term visual outcomes is the largest unmet need for wet AMD patients and their caregivers. Lifetime need for frequent injections burdens patients, caregivers, healthcare providers and healthcare systems. Real world evidence shows reduction in patients' vision over time associated with insufficient treatment, and the persistence of macular fluid between anti-VEGF injections, including as a result of poor adherence to the frequent injection regimen. Furthermore, bolus anti-VEGF injections may result in fluctuations in macular fluid that have been shown to have negative impacts on visual outcomes over time. A gene therapy administered as a single, in-office IVT injection has the potential to deliver long-term efficacy, reduce the burden of frequent anti-VEGF injections, minimize macular fluid and macular fluid fluctuation and improve vision outcomes for patients.
- **Pursue indications with well-defined clinical and regulatory paths where possible, to mitigate the development risk.** In wet AMD, we have selected an indication that has prior clinical validation, including established endpoints, standard-of-care administration methods, and defined regulatory paths. In wet AMD, aflibercept is an approved standard-of-care IVT injection treatment, and ADVM-022 utilizes our proprietary vector, AAV.7m8, designed to provide a codon optimized cassette of aflibercept through a single IVT injection.
- **Advance our pipeline by moving our early-stage research assets into our development pipeline and leverage our industry-leading capabilities in AAV vector and cassette optimization.** Integrating our AAV engineering, cassette optimization and innovation together with our manufacturing expertise, we have the capability to generate high-quality recombinant AAV products. By expanding our understanding of AAV-induced inflammation and the intersection of ocular and systemic inflammatory responses, we are better able to generate optimal prophylaxis strategies and best in class IVT products. We believe that this knowledge, together with ongoing discovery of improved ubiquitous and cell-specific promoters will improve our ability to create optimized AAV cassettes for ocular gene therapy. 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 or may be interested in licensing our rare disease programs.
- **Expand our process development capabilities to support late-stage clinical trials and commercialization.** 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 EMA, and is capable of producing large quantities of AAVs. Our strategy is to develop scalable processes to transfer to our global GMP contract manufacturers, providing a flexible manufacturing strategy to support a potential global supply.

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 to achieve long-term, durable benefits. 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, Sanfilippo syndrome, ornithine transcarbamylase deficiency, glycogen storage disease type 1a, sickle cell disease, Parkinson's disease, and Duchenne muscular dystrophy, as well as several ocular diseases including biallelic RPE65 mutation-associated retinal dystrophy, choroideremia, Leber's hereditary optic neuropathy, 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., Biogen Idec Inc., Bristol-Myers Squib, CSL Behring, Daiichi Sankyo, Hoffmann-La Roche Ltd., Johnson & Johnson, Novartis, and Regeneron have increased their investment in the gene therapy field. Additionally, pure-play gene therapy companies, such as 4D Molecular Therapeutics, Passage Bio, REGENXBIO Inc., Rocket Pharmaceuticals, Sangamo Therapeutics, Sarepta Therapeutics, Sio Gene Therapies, Solid Biosciences, and uniQure N.V. have attracted recent investment in this growing field.
- **Approval of cell and gene therapy products by regulatory authorities.** The FDA and EC have approved several cell and gene therapy products, including AAV vector-based gene therapy products, several of which are currently being marketed.

Our Novel AAV Vector 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 stable non-integrating episomes, 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 that may be mitigated with adequate corticosteroid prophylaxis.
- **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 (e.g., wet AMD).
- **Approval of cell and gene therapy products by regulatory authorities.** The FDA and EC have approved several cell and gene therapy products, including AAV vector-based gene therapy products, several of which are currently being marketed.

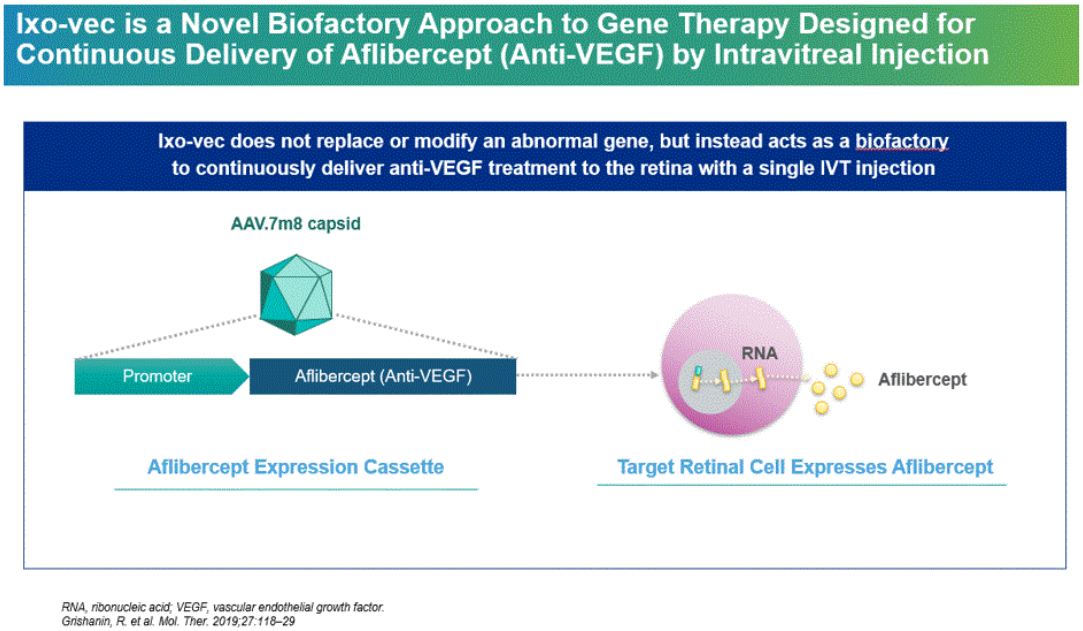
AAV-derived vectors are a leading vector used in gene therapy. According to the *Journal of Gene Medicine*, AAV has been used in over 260 clinical trials as of January 2021. As effective as existing AAV vectors are in gene therapy, we believe there are opportunities for improvement. Naturally occurring 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. 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.

Ixo-vec, Our Single Intravitreal Injection Gene Therapy Candidate for Treating "Wet AMD"

Ixo-vec, formerly referred to as ADVM-022, is our lead gene therapy product candidate being developed for the treatment of patients with wet AMD who are responsive to anti-vascular endothelial growth factor ("VEGF") therapy of wet AMD. Ixo-vec is designed to deliver long-term, durable therapeutic levels of aflibercept associated with a robust, sustained treatment response, reducing the treatment burden and fluctuations in macular fluid associated with bolus anti-VEGF IVT injections. Ixo-vec utilizes an engineered, proprietary vector capsid, AAV.7m8, carrying an aflibercept coding sequence under the control of a proprietary expression cassette capable of transducing retinal cells after a single in-office IVT injection. This product is intended to improve both real-world vision and quality of life outcomes for patients. Unlike other ophthalmic gene therapies that require a surgery to administer the gene therapy under the retina (sub-retinal approach), or a medical device to deliver the gene therapy (supra-choroidal approach), Ixo-vec has the advantage of being administered as a one-time IVT injection in the office 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.

The AAV.7m8 capsid was engineered from AAV2 by directed evolution to efficiently transduce retinal cells following a routine 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.



RNA, ribonucleic acid; VEGF, vascular endothelial growth factor.
Grishanin, R. et al. Mol. Ther. 2019;27:118–29

We believe IVT injection of gene therapy offers substantial advantages compared to subretinal surgical administration of gene therapy, for the treatment of wet AMD:

- IVT injection is a simple procedure performed during an office visit, and is the mode of administration for current standard-of-care therapies to treat patients with wet AMD; and
- In comparison, a surgical setting is required for subretinal injections, with the attendant risks associated with intraocular surgery and vitrectomy.

Market for Treating Patients with Wet AMD

Age-related macular degeneration 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 or nAMD, is an advanced form of AMD, affecting approximately 10% of patients living with AMD. In patients with wet AMD, the growth of abnormal 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 blindness in patients over 65 years of age, with a prevalence of approximately 20 million individuals worldwide living with wet AMD. The incidence of new cases of wet AMD is expected to grow significantly

worldwide as populations age. AMD is expected to impact 288 million people worldwide by 2040, with wet AMD accounting for approximately ten percent of those cases.

The current standard of care therapy for wet AMD is chronic and requires frequent anti-VEGF injections for the duration of the disease. These are effective, but typically require eye injections every 4-16 weeks in order to maintain vision. Real-world evidence shows that this regimen can be difficult to adhere to for patients, caregivers, and healthcare systems, leading to undertreatment associated with persistent macular fluid as well as fluctuations of macular fluid, all resulting in loss of vision over time. We estimate that the standard-of-care anti-VEGF therapies used to treat wet AMD and other chronic retinal conditions that respond to anti-VEGF therapy generated in excess of $13 billion worldwide in sales in 2021.

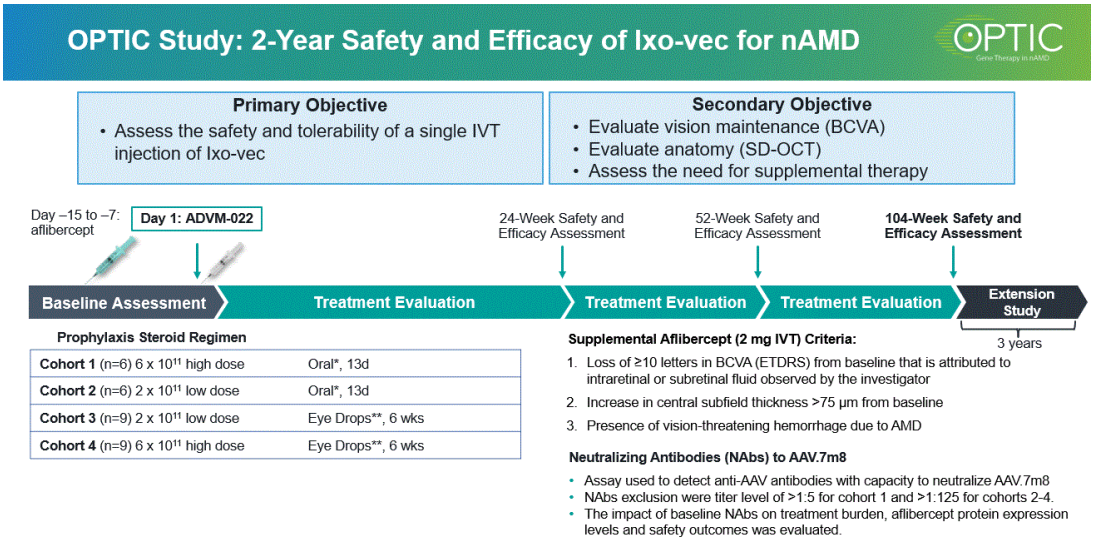
Advancing the Clinical Development of Ixo-vec for Wet AMD

We initiated the Ixo-vec phase 1 clinical trial entitled “An Open Label Phase 1 Study of Ixo-vec (AAV.7m8-aflibercept) in Neovascular (Wet) Age-Related Macular Degeneration" (“OPTIC”) with the first subject dosed in November 2018. We received Fast Track designation from the FDA for Ixo-vec for wet AMD in September 2018. The last subject completed the two-year OPTIC trial in June 2022. Most of the subjects have enrolled in a three-year extension study to continue to monitor safety and efficacy out to a total of five years.

The OPTIC trial was designed as a multi-center, open-label, Phase 1, dose-ranging safety trial of Ixo-vec in subjects with wet AMD who have demonstrated responsiveness to anti-VEGF treatment. Subjects in OPTIC are treatment-experienced, and previously required frequent anti-VEGF injections to manage their wet AMD and to maintain functional vision.

In OPTIC, subjects were dosed with a single IVT injection of Ixo-vec. Subjects in cohort 1 (n=6) were treated with a 6E11 dose of Ixo-vec. Subjects in cohort 2 (n=6) were treated with a three-fold 2E11 dose of Ixo-vec. Subjects in cohorts 1 and 2 received a 13-day tapering course of prophylactic oral corticosteroids following Ixo-vec administration. Subjects in cohort 3 (n=9) were treated with a 2E11 dose of Ixo-vec, and subjects in cohort 4 (n=9) were treated with a 6E11 dose of Ixo-vec. Subjects in cohorts 3 and 4 received a 6-week tapering course of prophylactic topical corticosteroids in place of the oral corticosteroids.

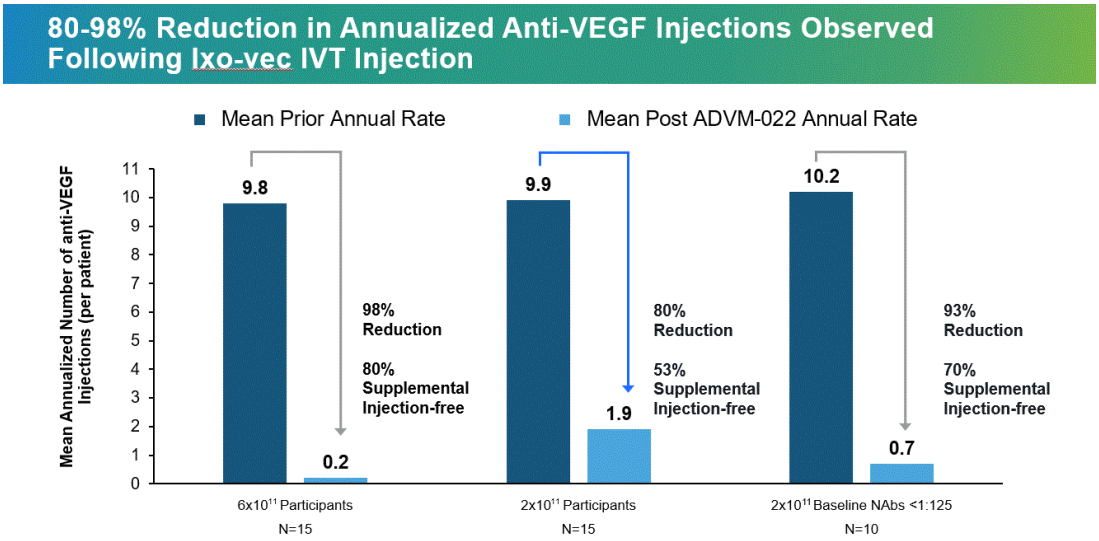
The primary endpoint of the trial was the safety and tolerability of Ixo-vec after a single IVT administration. Secondary endpoints include changes in best-corrected visual acuity (BCVA), measurement of central subfield thickness (“CST”, a measure of retinal thickness), as well as mean number of anti-VEGF supplemental injections and percentage of subjects needing anti-VEGF supplemental injections. Each subject enrolled was followed for a total of two years in OPTIC.



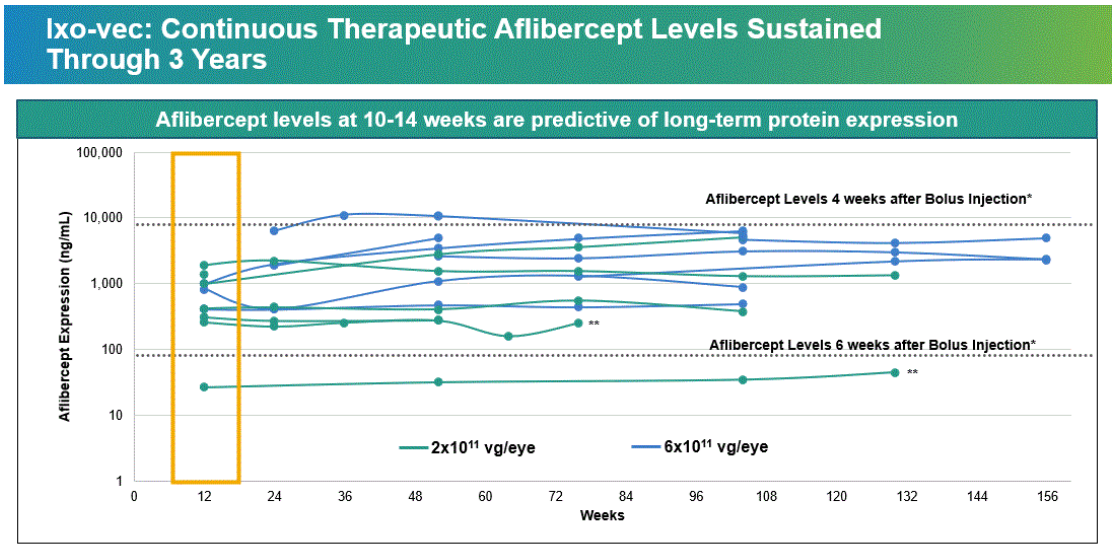
*Final 2-Year Analysis. *Subjects received prophylaxis of 60 mg oral prednisone for 6 days starting at Day –3 followed by 7-day taper. **Subjects received prophylaxis of QID difluprednate eye drops for 3 weeks starting at Day 1 followed by a 3-week taper. Final analysis includes all participants regardless of baseline neutralizing antibody titer. AAV, adeno-associated virus; AMD, age-related macular degeneration; BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; IVT, intravitreal therapy; QID, four times daily; SD-OCT, spectral domain optical coherence tomography; NCT03748784.*

In OPTIC, Ixo-vec showed a robust treatment response from both doses through 104 weeks. Subjects who received 6E11 of Ixo-vec, Cohorts 1 and 4, experienced a 98% reduction in annualized anti-VEGF injections and 80% remained supplemental anti-VEGF injection free. Subjects who received 2E11 of Ixo-vec, Cohorts 2 and 3, experienced an 80% reduction in annualized anti-VEGF injections and 53% remained supplemental anti-VEGF injection free. The last subject completed the OPTIC study in June 2022. We have initiated an extension study to continue to follow our subjects for an additional three years for a total of five years. Ixo-vec continues to be well tolerated with a favorable safety profile at both doses. We will continue to present updated efficacy, aflibercept protein levels and safety data as the subjects progress through the extension study.

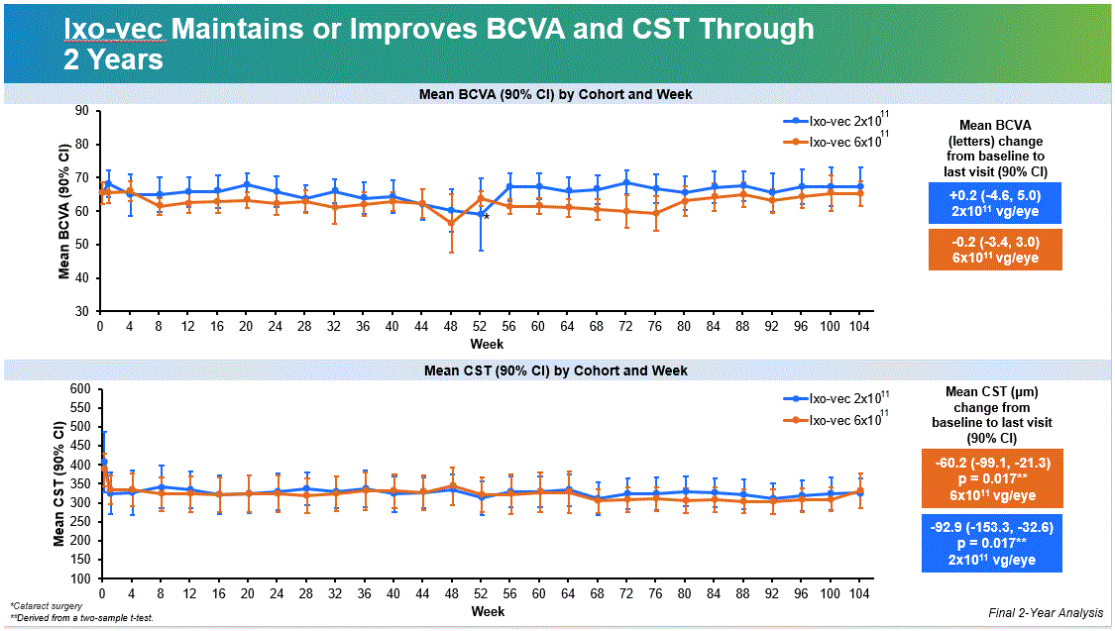
The graphics below show selected data from OPTIC and the OPTIC long-term extension trial, including the 80% to 98% reduction in annualized anti-VEGF injections observed following Ixo-vec IVT injection; maintenance of continued aflibercept protein levels through three years post Ixo-vec injection; and maintenance of BCVA and CST through two years post Ixo-vec injection. We also present a case study showing that in a subject who had experienced high or fluctuating fluid and CST prior to receiving Ixo-vec, a single Ixo-vec IVT injection reduced absolute levels and fluctuations in fluid and CST through two years post injection.

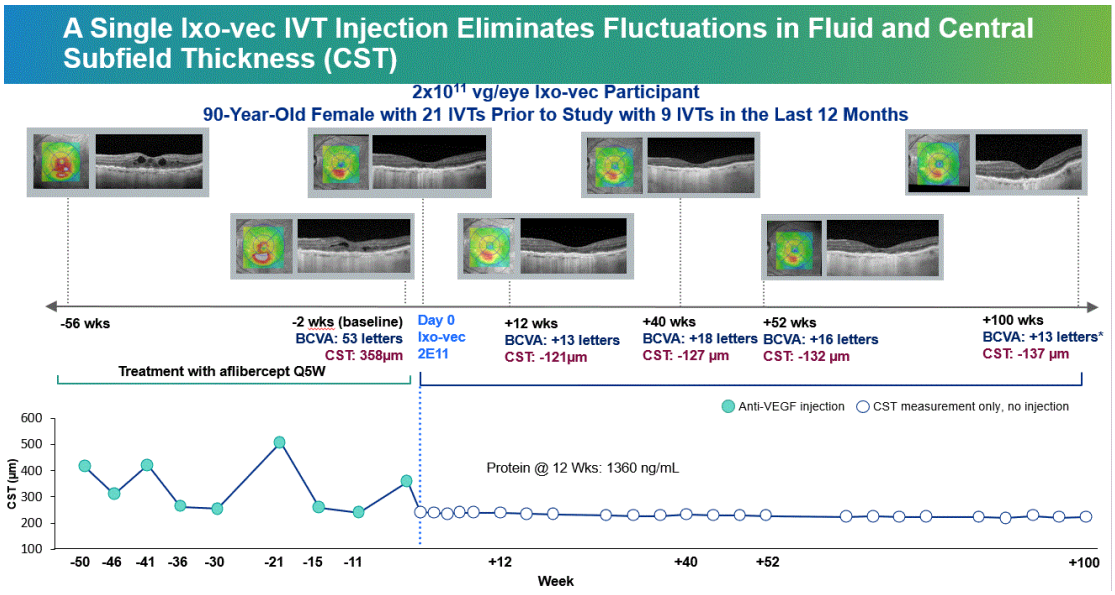


Final 2-Year Analysis 2022.
Annualized rate (Prior) = (number of IVTs in 12 months prior to Ixo-vec) / (days from the first IVT in the past 12 months to Ixo-vec / 365.25).
Annualized rate (Post) = (numbers of aflibercept IVTs since Ixo-vec) / (days from Ixo-vec to the last study follow-up / 365.25).
NAb, neutralizing antibody; VEGF, vascular endothelial growth factor.



*Final 2-Year Analysis 2022. *Modeled based on Do et al. Retina 2020; 40:643-647. ** Participant received supplemental aflibercept injections. Protocol amendment for aqueous sample collection for participants that consented. To isolate the effect of ADVM-022, samples that were collected within 2 months of supplemental aflibercept are not shown.*





*Data Cut: Feb 24, 2022. *No CST reading available at week 104. BCVA at week 104 was 58 letters.*

In September 2022, we dosed the first subject in our Phase 2 LUNA trial of Ixo-vec. The LUNA trial is a multicenter, double-masked, randomized, parallel-group Phase 2 trial evaluating two doses of Ixo-vec - 2E11, the lower dose used in the OPTIC trial, and a new, lower 6E10 dose - in up to 72 subjects with wet AMD. The LUNA trial will assess four new enhanced prophylactic corticosteroid regimens, including local corticosteroids and combinations of local and systemic corticosteroids to test the relative contribution of local versus systemic AAV exposure on ocular inflammation. Specific regimens include topical difluprednate ("Durezol®"), dexamethasone intravitreal implant ("Ozurdex®"), and a combination of either topical Durezol® or IVT Ozurdex® with oral prednisone.

The trial will randomize the participants equally between the 2E11 and 6E10 Ixo-vec doses and will be conducted at approximately 40 sites in the U.S. and Europe. Four prophylactic corticosteroid regimens will be studied. The primary endpoints will be similar to the OPTIC trial and focus on mean change in best-corrected visual acuity and CST from baseline to one year, and incidence and severity of adverse events. Other endpoints will include aflibercept protein levels starting at 14 weeks, an interim efficacy and safety analysis at 26 weeks and will include a reduction in fluctuations in CST and in treatment burden. The study will also evaluate the effectiveness and tolerability of the prophylactic corticosteroid regimens.

Additional Programs

Nonclinical Product Candidates

ADVM-062 (AAV.7m8-L-opsin) is a novel gene therapy product candidate being developed to deliver a functional copy of the OPN1LW gene to the foveal cones of patients suffering from blue cone monochromacy ("BCM") via a single IVT injection. ADVM-062 utilizes Adverum's propriety vector capsid, AAV.7m8. In January 2022, we announced the FDA granted Orphan Drug Designation to ADVM-062.

BCM affects approximately 1 to 9 in 100,000 males, worldwide. This X-linked recessive hereditary condition is caused by the absence of function in the L and the M opsin gene(s) and can manifest in loss of visual acuity, photosensitivity, myopia and infantile nystagmus that can persist into adulthood. Consequently, individuals with BCM have visual impairments to important aspects of daily living such as facial recognition, learning, reading, and daylight vision. Currently, there is no cure for BCM.

In addition to Ixo-vec and ADMV-062, we are currently conducting nonclinical studies on 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 I/II trial in retinitis pigmentosa in the U.S., France, and U.K., which began in October 2018. In October 2021, GenSight announced it had been granted Fast Track Designation by the FDA for GS030 and in February 2023, announced one-year safety data and efficacy signals from its PIONEER Phase I/II clinical trial for retinitis pigmentosa.

Manufacturing

As we advance Ixo-vec for wet AMD, we are continuing to develop our manufacturing expertise for ongoing supply. We maintain control of key aspects of the manufacturing process, specifically in scalable process development, assay development, and GMP quality controls.

Our AAV vector manufacturing process is based on the Baculovirus Expression Vector System ("BEVS"), which has been used in a number of FDA- and EC-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 may allow the production of large quantities of AAV vectors, up to the 2000-liter scale.
- **High purity.** Our BEVS system coupled with our proprietary downstream purification process produces a highly pure drug substance.
- **Precedent regulatory framework.** Several other vaccines and recombinant protein therapies have been approved using a manufacturing process similar to our BEVS technology.

Our products are manufactured using cell banks and a scalable process developed internally and externally that are transferred to approved Contract Manufacturing Organizations ("CMOs"). These CMOs produce investigational drugs under GMP conditions to support our clinical trials. High quality raw materials are purchased from various suppliers and are used throughout the manufacturing process.

We continue to evaluate new raw material suppliers, as well as additional CMOs, in order to provide manufacturing flexibility. As we prepare for larger, late-stage clinical trials and potential commercialization, we have in-house process development capabilities, allowing us to develop larger-scale processes for transfer to our global GMP contract manufacturers. We leverage GMP contract manufacturer partnerships for flexible clinical and future commercial supply. This strategy capitalizes on our internal AAV manufacturing expertise while providing both security, expandability and flexibility as we prepare to potentially deliver one of the first gene therapies for large indications.

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, our AAV-based directed evolution platform, our nonclinical and clinical development experience, our gene therapy manufacturing experience 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 Ixo-vec for wet AMD 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, long-acting delivery devices and gene therapy. The key factors that contribute to success of any approved product include safety profile, efficacy, durability, 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.

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

- biosimilar anti-VEGFs (e.g., FYB201);
- bispecific / combination / add-on therapy for efficacy or durability improvement (e.g., Vabysmo® (faricimab) and OPT-302);
- next-generation anti-VEGF for durability improvement;
- long-acting delivery device / gene therapy to lower treatment frequency (e.g., RGX-314); and
- other molecules that inhibit neovascularization in wet AMD (e.g., tyrosine kinase inhibitors).

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. These companies include 4D Molecular Therapeutics, Bayer, Clearside Biomedical, EyePoint Pharmaceuticals, Hoffmann-La Roche Ltd., Novartis, Ocular Therapeutix, Regeneron and REGENXBIO.

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

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.

GenSight Biologics

In February 2014, we entered into an agreement with GenSight Biologics ("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 I/II trial with GS030 to treat retinitis pigmentosa in the U.S., France, and the U.K., which began in October 2018. In October 2021, GenSight announced it had been granted Fast Track Designation by the FDA for GS030 and in February 2023, announced one-year safety data and efficacy signals from its PIONEER Phase I/II clinical trial for retinitis pigmentosa.

Lexeo Therapeutics

In January 2021, we entered into an agreement with Lexeo Therapeutics ("Lexeo"), pursuant to which we granted Lexeo an exclusive license to the intellectual property rights, pre-clinical data and know how associated with our Friedrich's Ataxia program. Under the agreement, we are eligible to receive development and commercial milestones and royalties related to sales of a product containing our licensed rights. Lexeo is currently developing LX2006, an adeno-associated virus mediated treatment.

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.

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.

As of March 1, 2023, we own or license more than 365 issued patents that are still in force, including more than 35 issued U.S. patents and 11 European patents validated cumulatively in more than 245 countries, as well as more than 210 patent applications pending in the U.S. and foreign jurisdictions, three of which have been allowed. These numbers include more than 50 patents and 35 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 at least 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. Nineteen patents in this family have issued in the U.S., elsewhere in North America, Europe and the Asia/Pacific region, and nine corresponding applications are pending in the U.S., elsewhere in North America, Europe, and the Asia/Pacific region. Patents in this family are generally expected to expire in 2033, subject to possible patent term adjustments and patent term extensions. Patents and applications in the second 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 aflibercept. One issued European patent is validated in thirty-seven countries, seven patents are issued in North America, the Asia/Pacific region, Israel and South Africa, and at least thirteen corresponding applications are pending in the U.S., elsewhere in North America, Europe, and Asia/Pacific region. Patents in this family are generally expected to expire in 2037, subject to possible patent term adjustment and patent term extensions. The third of these families contains granted applications in Europe (validated in 37 countries), Japan, and pending U.S. and corresponding foreign applications directed 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. Patents that may eventually issue from this patent family, if any, are generally expected to expire in 2037, subject to possible patent term adjustments and patent term extensions. The fourth family contains 27 pending applications, 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 to 2041 subject to possible patent term adjustments and patent term extensions.

We also own eleven patent families that are directed to various aspects of our proprietary technology platform. Fourteen patents in these families have issued patents in the U.S., Europe, and the Asia/Pacific region, including one issued European patent validated in six countries, as well as at least forty-nine pending applications, including PCT applications or national phase applications in the U.S., elsewhere in North America, Europe, and the Asia/Pacific region. Patents that may eventually issue from these families, if any, are generally expected to expire between 2035 and 2041, 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 ten granted patents in the U.S., elsewhere in North America and Europe, including one European patent validated in three countries, as well as two pending patent applications in the U.S. The patents in this family are projected to expire between 2024 and 2029 in the U.S. and in 2024 elsewhere, subject to possible patent term extensions.

Another patent family directed to improved rAAV virions that we have exclusively licensed includes three granted U.S. patents 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 at least fifty issued patents in the U.S., elsewhere in North America, Europe, Asia, and the Pacific, including a European patent validated in thirty-seven countries. Seventeen corresponding applications are pending in the U.S. and elsewhere in North America, Europe, Asia and the Pacific. Patents that issue from this patent family are generally expected to expire in 2032, subject to possible patent term extensions.

We have also non-exclusively licensed rights to a patent family related to the Baculovirus/SF9 production system that includes eight issued patents in the U.S., Europe, and Asia, including a European patent validated in three countries. These patents are expected to expire in 2027.

We have exclusively licensed a family of patents and applications related to the treatment of cardiomyopathy associated with Friedreich's Ataxia. This family includes two patents granted in the U.S., one in New Zealand and fourteen pending applications in the U.S. and elsewhere in North America, Europe, Asia, and the Pacific. Patents that grant from this patent family are generally expected to expire in 2033, subject to possible patent term extensions and adjustments. In January 2021, we granted an exclusive (even as to us) sublicense to this patent family, which does not relate to ADVM-022, to Lexeo Therapeutics.

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. However, trade secrets can be difficult to protect. For more information regarding the risks related to our intellectual property, see "Risk Factors—Risks Relating to Our Intellectual Property." of this Annual Report on Form 10-K.

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 the FDA, and the IND must be cleared by the FDA.

Within the 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"). The FDA has also established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER in its review.

The 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 and rare diseases; patient-focused drug development and nonclinical 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 the FDA or the regulated industry.

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

- Completion of nonclinical 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 be cleared 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;
- Submission to the FDA of a BLA for marketing approval that demonstrates adequate efficacy and acceptable safety profile of the biological product based on results of nonclinical testing and clinical trials, as well as providing information on the chemistry, manufacturing and controls to ensure product identity, purity, potency and quality, as well as proposed labeling;
- 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 GMP, 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 safety, identity, strength, quality, purity, and potency;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.

Before testing any biological product candidate, including a gene therapy product, in humans, the product candidate enters the nonclinical testing stage. Nonclinical tests include animal studies to assess the characteristics and potential safety and efficacy of the product. The conduct of the nonclinical tests must comply with federal regulations and requirements, including GLPs.

The results of nonclinical tests, together with manufacturing information, such as laboratory evaluation of product chemistry, formulation, and stability, as well as any available clinical data or literature and a proposed clinical trial protocol, are submitted as part of an IND to the FDA. Some nonclinical 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 the FDA.

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 the 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 ("U.S.") 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 the 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, the 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, 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 the 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. Similar rules govern the conduct of clinical trials in the European Economic Area ("EEA").

Similar to the U.S., the various phases of nonclinical and clinical research in the European Union ("EU") are subject to significant regulatory controls. Previously, in the EU, pursuant to the EU Clinical Trials Directive 2001/20/EC, a clinical trial application had to be submitted to each country's national regulatory authority in which the clinical trial was to take place, together with an independent ethics committee, much like the FDA and IRB, respectively. Although the Directive sought to harmonize the EU clinical trials regulatory framework, setting out common rules for the control and authorization of clinical trials in the EU, the EU Member States have transposed and applied the provisions of the Directive in a manner that is often not uniform. This led to variations in the rules governing the conduct of clinical trials in the individual EU Member States. In 2014, a new Clinical Trials Regulation 536/2014, replacing the current Directive, was adopted. The new Regulation is directly applicable in all EU Member States (without national implementation) and entered into application on 31 January 2022. The new Regulation seeks to simplify and streamline the approval of clinical trials in the EU. Pursuant to the Regulation, the sponsor shall submit a single application for approval of a clinical trial via the EMA's Clinical Trials Information System, or CTIS, which will cover all regulatory and ethics assessments from the member states concerned. Any submissions made from January 31, 2023 onwards must be made through CTIS and all trials authorized pursuant to the Directive that are still ongoing on January 31, 2025 must be made through CTIS. Once the CTA is approved in accordance with a member state's requirements, clinical trial development may proceed. Approval and monitoring of clinical trials in the EU is, as it was under the Directive, the responsibility of individual member states, but compared to the position prior to the applicability of the Clinical Trials Regulation there is likely to be more collaboration, information-sharing, and decision-making between member states. The new Regulation also aims to streamline and simplify the rules on safety reporting and introduces enhanced transparency requirements, such as mandatory submission of a summary of the clinical trial results to a new EU database.

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 nonclinical 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, the FDA usually recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for up to 5-years for nonintegrating vectors such as AAV vectors.

The responsible party for an applicable clinical trial must register the clinical trial in Phase 2 or later on the ClinicalTrials.gov website, including the registry of new, on-going, and completed clinical trials of drugs, biologics, and device products.

Biologics License Applications

The results of nonclinical studies and clinical trial(s), together with detailed information on the quality 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"), the FDA has a performance goal to review applications within 6 months from successful filing of the application for priority reviews or 10 months for standard reviews. The review timeline begins upon the FDA's acceptance of the original application submission for filing, no later than 60 calendar days from the date the 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 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 nonclinical 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 GMP 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. The FDA may also inspect the facilities of the sponsor to ensure that processes and procedures are in compliance with GMP/GCP requirements.

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 marketing exclusivity, four years of which constitute data exclusivity. In other words, 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.

In the EEA (which is comprised of 27 Member States of the EU plus Norway, Iceland, and Liechtenstein), medicinal products can only be commercialized after a related Marketing Authorization, or MA, has been granted. Marketing authorization for medicinal products can be obtained through several different procedures. These are through a centralized, mutual recognition procedure, decentralized procedure, or national procedure (if marketing authorization is sought for a single EU Member State). The centralized procedure allows a company to submit a single application to the EMA. If a related positive opinion is provided by the EMA, the EC will grant a centralized marketing authorization that is valid in all 27 EU Member States and three of the four European Free Trade Associations, or EFTA, countries (Norway, Iceland, and Liechtenstein) all of whom make up the EEA.

The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, advance therapy medicinal products such as gene therapy, orphan medicinal products, regenerative medicinal products, and medicinal

products containing a new active substance indicated for the treatment of HIV, AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and other immune dysfunctions and viral diseases. The Centralized Procedure is optional for products containing a new active substance that is not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or for which grant of centralized marketing authorization is in the interest of patients at EU level in the EU.

The decentralized authorization procedure permits companies to file identical applications for authorization to several EU Member States simultaneously for a medicinal product that has not yet been authorized in any EU Member State. The competent authority of a single EU Member State, the reference member state, is appointed to review the application and provide an assessment report. The competent authorities of the other EU Member States, the concerned member states, are subsequently required to grant marketing authorization for their territories on the basis of this assessment. The only exception to this is where an EU Member State considers that there are concerns of potential serious risk to public health related to authorization of the product. In these circumstances, the matter is submitted to the Heads of Medicines Agencies, or Co-ordination Group for Mutual Recognition and Decentralised procedures - Human, for review. The mutual recognition procedure allows companies that have a medicinal product already authorized in one EU Member State to apply for this authorization to be recognized by the competent authorities in other EU Member States.

In the EU, biological products authorized according to the centralized authorization procedure are entitled to eight years' data exclusivity and 10 years' market exclusivity.

The procedure for approval of biosimilars following expiry of exclusivity differs from that for generic medicinal products. Developers of biosimilars must demonstrate through comprehensive comparability studies with the "reference" biological medicine that their biosimilar product is highly similar to the reference medicine, notwithstanding natural variability inherent to all biological medicines and that there are no clinically meaningful differences between the biosimilar and the reference medicine in terms of safety, quality and efficacy.

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.

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 the 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 the 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, the 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 September 2021, the FDA finalized Guidance For Industry on determining "sameness" for gene therapy products for purposes of orphan drug exclusivity.

In the EU, orphan drug designation may be granted to products that can be used to treat life-threatening diseases or chronically debilitating conditions with an incidence of no more than five in 10,000 people or that, for economic reasons, would be unlikely to be developed without incentives. Medicinal products for which orphan designation has been granted are entitled to a range of benefits during the development and regulatory review process and to ten years of exclusivity in all EU member states upon approval. As in the U.S., a similar medicinal product with the same orphan indication may be approved, notwithstanding orphan product exclusivity, if the exclusivity holder gives consent or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if the similar product is deemed safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity granted in relation to the original orphan medicinal product may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity.

Other Regulatory Requirements

Any biologics manufactured or distributed by us or our collaborators pursuant to FDA or EU and other governmental authorities' approvals would be subject to continuing regulation by the FDA, the EMA and other governmental authorities, including recordkeeping requirements and reporting of adverse experiences associated with the product. Biologic manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies, or equivalent EU and other governmental authorities and are subject to periodic unannounced inspections by the FDA, certain state agencies and EU and other governmental authorities for compliance with ongoing regulatory requirements, including GMP, 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 GMP regulations and other ongoing FDA, EU or other governmental authorities' regulatory requirements. If we or our present or future third-party manufacturers or suppliers are not able to comply with these requirements, the FDA, EMA, EU Member State or other governmental authorities 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. For example, under the 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.

In the EU, the advertising and promotion of pharmaceutical products are subject to laws governing promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. For example, applicable laws require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities in connection with a marketing authorization approval. The SmPC is the document that provides information to physicians concerning the safe and effective use of the product. Promotional activity that does not comply with the SmPC is considered off-label and is prohibited in the EU. Other relevant laws at EU level and in the individual EU member states also apply to the advertising and promotion of medicinal products, including laws that prohibit the direct-to-consumer advertising of prescription-only medicinal products and further limit or restrict the advertising and promotion of our products to the general public and to health care professionals. Violations of the rules governing the promotion of medicinal products in the EU could be penalized by administrative measures, fines and imprisonment.

Privacy Laws

In the ordinary course of our business, we may process confidential, sensitive, and proprietary information, including personal information. Accordingly, we are, or may become, subject to numerous data privacy and security obligations, including federal, state, local, and foreign laws, regulations, guidance, and industry standards governing data privacy and security. Such obligations may include, without limitation, the Federal Trade Commission Act, the California Consumer Privacy Act of 2018, as amended by the California Privacy Rights Act of 2020, or CPRA, (collectively, "CCPA"), the EU General Data Protection Regulation ("EU GDPR"), the EU GDPR as it forms part of United Kingdom ("UK"), law by virtue of section 3 of the European Union (Withdrawal) Act 2018 ("UK GDPR"), and The Health Insurance Portability and Accountability Act, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and their implementing regulations (collectively, "HIPAA"). In addition to the CCPA, several other states within the U.S., such as Virginia and Colorado, passed comprehensive privacy laws and similar laws are being considered in several other states, as well as at the federal and local levels.

The EU GDPR and CCPA are examples of the increasingly stringent and evolving regulatory frameworks related to personal information processing that may increase our compliance obligations and exposure for any actual or perceived noncompliance.

For example, European data privacy and security laws (including the EU GDPR, and UK GDPR) impose significant and complex compliance obligations on entities that are subject to those laws. These obligations may include limiting personal information processing to only what is necessary for specified, explicit, and legitimate purposes; requiring a legal basis for personal information processing; requiring the appointment of a data protection officer in certain circumstances; increasing transparency obligations to data subjects; requiring data protection impact assessments in certain circumstances; limiting the collection and retention of personal information; increasing rights for data subjects; formalizing a heightened and codified standard of data subject consents; requiring the implementation and maintenance of technical and organizational safeguards for personal information; mandating notice of certain personal information breaches to the relevant supervisory authority(ies) and affected individuals; and mandating the appointment of representatives in the UK and/or the EU in certain circumstances.

The CCPA imposes obligations on covered businesses to provide specific disclosures related to a business's collecting, using, and disclosing personal information and to respond to certain requests from California residents related to their personal information (for example, requests to know of the business's personal information processing activities, to correct or delete the individual's personal information, and to opt out of certain personal information disclosures). Also, the CCPA provides for administrative fines and a private right of action for certain data breaches which may include an award of statutory damages. In addition, the California Privacy Rights Act of 2020 ("CPRA"), effective January 1, 2023, expanded the CCPA. The CPRA's recent amendments to the CCPA established a new regulatory agency to implement and enforce the law.

The Health Insurance Portability and Accountability Act, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and their implementing regulations (collectively, "HIPAA") imposes requirements on "covered entities," including certain healthcare providers, health plans, and healthcare clearinghouses, as well as their respective "business associates" that create, receive, maintain and transmit individually identifiable health information for or on behalf of a covered entity relating to the privacy, security and transmission of individually identifiable health information. We may obtain health information from third parties, such as research institutions, that are subject to privacy and security requirements under HIPAA. Although we are not directly subject to HIPAA other than with respect to providing certain employee benefits, we could potentially be subject to penalties if we, our affiliates, or our agents obtain, use, or disclose individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA.

For more information regarding the risks to our business related to laws and regulations to which we are or may become subject, see "Risk Factors—Risks Related to Our Business Operations."

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 research activities, as well as our proposed sales, marketing, and education programs. 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 cash or in kind, to induce or reward the purchasing, leasing, ordering, or arranging for or recommending the purchase, lease, or order of any health care item or service for which payment may be made, in whole or in part, by federal healthcare programs such as the Medicare and Medicaid programs. This statute has been interpreted to apply to arrangements between pharmaceutical companies on one hand and prescribers, purchasers and formulary managers on the other. Liability may be established under the federal Anti-Kickback Statute without proving actual knowledge of the statute or specific intent to violate it. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Law constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. Although there are a number of statutory exemptions and regulatory safe harbors to the federal Anti-Kickback Statute protecting certain common business arrangements and activities from prosecution or regulatory sanctions, the exemptions and safe harbors are drawn narrowly, and practices that do not fit squarely within an exemption or safe harbor, or for which no exception or safe harbor is available, may be subject to scrutiny;
- The federal civil False Claims Act, which prohibits, among other things, individuals or entities from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment of government funds, or knowingly making, using or causing to be made or used, a false record or statement material to an obligation to pay money to the government or knowingly concealing or knowingly and improperly avoiding, decreasing or concealing an obligation to pay money to the federal government. Actions under the False Claims Act may be brought by the U.S. Attorney General or as a qui tam action by a private individual (a whistleblower) in the name of the government and the individual, and the whistleblower may share in any monetary recovery. Many pharmaceutical and other healthcare companies have been investigated and have reached substantial financial settlements with the federal government under the civil False Claims Act for a variety of alleged improper marketing activities, including: providing free product to customers with the expectation that the customers would bill federal programs for the product; providing sham consulting fees, grants, free travel and other benefits to physicians to induce them to prescribe the company's products; and inflating prices reported to private price publication services, which are used to set drug payment rates under government healthcare programs. In addition, the government has pursued civil False Claims Act cases against a number of pharmaceutical companies for causing false claims to be submitted as a result of the marketing of their products for unapproved, and thus non-reimbursable, uses. Because of the threat of treble damages and mandatory penalties per false or fraudulent claim or statement, healthcare and pharmaceutical companies often resolve allegations without admissions of liability for significant and material amounts. Pharmaceutical and other healthcare companies also are subject to other federal false claim laws, including, among others, federal criminal healthcare fraud and false statement statutes that extend to non-government health benefit programs;
- Federal criminal laws that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, which also, prohibits, among other things, executing, or attempting to execute, a scheme to defraud any healthcare benefit program or making false, fictitious, or fraudulent statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- The 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 direct and indirect payments and other transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), other healthcare professionals (such as physicians assistants and nurse practitioners), and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members;
- Outside the U.S., interactions between pharmaceutical companies and physicians are also governed by strict laws, regulations, industry self-regulation codes of conduct and physicians' codes of professional conduct. The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products, which is prohibited in the EU, is governed by the national anti-bribery laws of the EU member states. Violation of these laws could result in substantial fines and imprisonment. Certain EU member states, or industry codes of conduct, require that payments made to physicians be publicly disclosed. Moreover, agreements with physicians must often be the subject of prior notification and approval by the physician's employer, his/her competent professional organization, and/or the competent authorities of the individual EU member states. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment; 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 sales or marketing arrangements and claims involving healthcare 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; state laws that restrict the ability of manufacturers to offer co-pay support to patients for certain prescription drugs; 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 significant penalties, including civil, criminal, and administrative penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs (such as Medicare and Medicaid), 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. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Moreover, achieving and sustaining compliance with applicable federal and state privacy, security, and fraud laws may prove costly.

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 and Healthcare Reform Legislation

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. For example, although CMS has approved coverage for Chimeric Antigen Receptor T-cell therapies, such as Yescarta and Kymriah, and has established reimbursement methods for these therapies, these policies could be changed in the future. 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 payers in the U.S., 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 payers.

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 U.S. 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 of 2010, collectively, the Affordable Care Act, contains provisions that may reduce the profitability of drug products, including, for example, by increasing the minimum rebates owed by manufacturers under the Medicaid Drug Rebate Program, extending the rebate program to individuals enrolled in Medicaid managed care plans, addressing 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 imposing 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 coverage of or payments for pharmaceuticals, or affect rebates or other price concessions owed on such products. Certain provisions of the Affordable Care Act have been subject to judicial challenges as well as efforts to repeal, replace, or otherwise modify them or to alter their interpretation and implementation. For example, the Tax Cuts and Jobs Act, enacted on December 22, 2017, eliminated the tax-based payment for individuals who fail to maintain minimum essential coverage under section 5000A of the Internal Revenue Code of 1986, commonly referred to as the individual mandate, effective January 1, 2019. For example, on June 17, 2021, the U.S. Supreme Court dismissed a challenge on procedural grounds that argue the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. On January 28, 2021, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the Affordable Care Act marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including, among others, policies that undermine protections for people with pre-existing conditions, demonstrations and waivers under Medicaid and the Affordable Care Act that may reduce coverage or undermine the programs thereunder, including work requirements, and policies that make it more difficult to access health benefits through Medicaid or the Affordable Care Act. In addition, on August 16, 2022, President Biden signed the Inflation Reduction Act of 2022 "Inflation Reduction Act" into law, which among other things, extends enhanced subsidies for individuals purchasing health insurance coverage in Affordable Care Act marketplaces through plan year 2025. The Inflation Reduction Act also eliminates the "donut hole" under the Medicare Part D program beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket cost and creating a new manufacturer discount program.

Additional legislative changes, regulatory changes, and judicial challenges related to the Affordable Care Act remain possible. Any such changes could affect the number of individuals with health coverage. It is possible that the Affordable Care Act, as currently enacted or as it may be amended in the future, and other healthcare reform measures that may be adopted in the future could have a material adverse effect on our industry generally and on our ability to successfully commercialize our product candidates, if approved.

At this time, it is unclear whether such legislative changes, regulatory changes, or judicial challenges related to the Affordable Care Act, or other health care reform measures 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.

Other legislative changes have also been proposed and adopted in the U.S. since the Affordable Care Act was enacted. For example, 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, on average, 2% per fiscal year, which went into effect on April 1, 2013 and due to subsequent legislative changes to the statute, will stay in effect through 2031 unless additional congressional action is taken. Under current legislation, the actual reduction in Medicare payments will vary from 1% in 2022 to up to 3% in the final fiscal year of this sequester. Further, Congress is considering additional health reform measures.

In addition, there has been increasing legislative, regulatory, and enforcement interest in the U.S. with respect to drug pricing practices. For example, in July 2021, the Biden administration released an executive order, "Promoting Competition in the American Economy," with multiple provisions aimed at prescription drugs. In response to Biden's executive order, on September 9, 2021, Health and Human Services ("HHS") released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue to advance these principles. The Inflation Reduction Act also, among other things, (1) directs HHS to negotiate the price of certain single-source drugs and biologics covered under Medicare and (2) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. These provisions will take effect progressively starting in fiscal year 2023, although they may be subject to legal challenges. It is currently unclear how the Inflation Reduction Act will be implemented but is likely to have a significant impact on the pharmaceutical industry. Further, the Biden administration released an additional executive order on October 14, 2022 directing HHS to submit a report on how the Center for Medicare and Medicaid Innovation can be further leveraged to test new models for lowering drug costs for Medicare and Medicaid beneficiaries. It is unclear whether this executive order or similar policy initiatives will be implemented in the future. It is possible that the Affordable Care Act, as currently enacted or may be amended in the future, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare financing, more rigorous coverage criteria, and new payment methodologies and in additional downward pressure on coverage and payment and the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from commercial payers. Coverage policies and 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.

Similar to what is occurring in the U.S., political, economic and regulatory developments outside of the U.S. are also subjecting the healthcare industry to fundamental changes and challenges. Pressure by governments and other stakeholders on prices and reimbursement levels continue to exist. In various EU member states, we expect to be subject to continuous cost-cutting measures, such as lower maximum prices, lower or lack of reimbursement coverage and incentives to use cheaper, usually generic, products as an alternative. Health technology assessment ("HTA") of medicinal products is becoming an increasingly common part of the pricing and reimbursement procedures in some EU member states, including countries representing major markets. The HTA process, which is governed by the national laws of these countries, is the procedure according to which the assessment of the public health impact, therapeutic impact and the economic and societal impact of use of a given medicinal product in the national healthcare systems of the individual country is conducted. HTA generally compares attributes of individual medicinal products, as compared with other treatment options available on the market. The outcome of HTA regarding specific medicinal products will often influence the pricing and reimbursement status granted to these medicinal products by the competent authorities of individual EU member states. On January 31, 2018, the EC adopted a proposal for an HTA regulation intended to boost cooperation among EU member states in assessing health technologies, including new medicinal products. The HTA regulation, which aims to harmonize the clinical benefit assessment of HTA across the EEA, will apply from January 12, 2025. The HTA regulation provides that EU member states will be able to use common HTA tools, methodologies, and procedures across the EU. Individual EU member states will continue to be responsible for assessing nonclinical (e.g., economic, social and ethical) aspects of health technologies, and making decisions on pricing and reimbursement.

The making available or placing on the EU market of unauthorized medicinal products is generally prohibited. However, the competent authorities of the EU member states may exceptionally and temporarily allow and reimburse the supply of such unauthorized products, either on a named patient basis or through a compassionate use process, to individual patients or a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorized medicinal product. Such reimbursement may no longer be available if authorization for named patient or compassionate use programs expire or is terminated or if marketing authorization is granted for the product. In some EU member states, authorization and reimbursement policies may also delay commercialization of our products, or may adversely affect our ability to sell our products on a profitable basis. After initial price and reimbursement approvals, reductions in prices and changes in reimbursement levels can be triggered by multiple factors, including reference pricing systems and publication of discounts by third party payers or authorities in other countries. In the EU, prices can be reduced further by parallel distribution and parallel trade, or arbitrage between low-priced and high-priced EU member states.

The availability of adequate government reimbursement for our products may also be subject to regulatory changes and controls.

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 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.

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.

Testing and Approval of Pharmaceutical Products in the EU. The EU and many individual countries have regulatory structures similar to the U.S. for conducting nonclinical and clinical testing and applying for marketing approval or authorization, although specifics may vary widely from country to country. Clinical trials in the EU must be conducted in accordance with the requirements of the EU Clinical Trials Directive, as implemented in national law by individual EU member states, or in accordance with the EU Clinical Trials Regulation which became applicable on January 13, 2022, and applicable good clinical practice standards. In the EU, there are several procedures for requesting marketing authorization which can be more efficient than applying for authorization on a country-by-country basis. There is a "centralized" procedure allowing submission of a single marketing authorization application to the European Medicines Agency, or EMA. If the EMA issues a positive opinion, the EC will grant a centralized marketing authorization that is valid in all EU member states and three of the four European Free Trade Association countries (Iceland, Liechtenstein and Norway). The centralized procedure is mandatory for certain medicinal products, including orphan medicinal products and biotechnology-derived medicinal products, and optional for others. There is also a "decentralized" procedure allowing companies to file identical applications to several EU member states simultaneously for product candidates that have not yet been authorized in any EU member state and a "mutual recognition" procedure allowing companies that have a product already authorized in one EU member state to apply for that authorization to be recognized by the competent authorities in other EU member states.

The maximum timeframe for the evaluation of an application in the EU under the centralized procedure is 210 days, subject to certain exceptions and clock stops. An initial marketing authorization granted in the EU is valid for five years, with renewal subject to reevaluation of the risk-benefit profile of the product. Once renewed, the authorization is usually valid for an unlimited period unless the national competent authority or the EC decides on justified grounds to proceed with one additional five-year renewal.

In the EU, if an applicant can demonstrate that comprehensive data on the efficacy and safety of the product under normal conditions of use cannot be provided due to certain specified objective and verifiable reasons, products may be granted marketing authorization "under exceptional circumstances." A marketing authorization granted under exceptional circumstances is valid for five years, subject to an annual reassessment of conditions imposed by the EC.

The UK's withdrawal from the EU on January 31, 2020, commonly referred to as Brexit, has led to diversion between the UK and EU regulatory environments, and there is significant uncertainty concerning the extent to which the UK and the EU regulatory environments may diverge further in the future. Any further divergence may lead to increased costs and administrative burden. On December 24, 2020, the EU and UK reached an agreement in principle on the framework for their future relationship, the EU-UK Trade and Cooperation Agreement. The Agreement formally entered into force on May 1, 2021. The Agreement primarily focuses on ensuring free trade between the EU and the UK in relation to goods, including medicinal products. Although the body of the Agreement includes general terms which apply to medicinal products, greater detail on sector-specific issues is provided in an Annex to the Agreement. The Annex provides a framework for the recognition of GMP inspections and for the exchange and acceptance of official GMP documents. The regime does not, however, extend to procedures such as batch release certification and Great Britain (England, Scotland and Wales) is treated as a third country. Northern Ireland, with regard to EU regulations, continues to follow the EU regulatory rules. As part of the Agreement, the EU and the UK will recognize GMP inspections carried out by the other Party and the acceptance of official GMP documents issued by the other Party. The Agreement also encourages, although it does not oblige, the parties to consult one another on proposals to introduce significant changes to technical regulations or inspection procedures. Among the areas of absence of mutual recognition are batch testing and batch release. The UK continues to accept EU batch testing and batch release, but has recently conducted a consultation as to the future strategy for batch testing policy; two years notice will be provided of any changes to such a policy. However, the EU continues to apply EU laws that require batch testing and batch release to take place in the EU territory. This means that medicinal products that are tested and released in the UK must be retested and re-released when entering the EU market for commercial use. As regards marketing authorizations, Great Britain has a separate regulatory submission process, approval process and a separate national marketing authorization. Northern Ireland is, however, covered by centralized marketing authorizations granted by the EC. The UK Medicines and Healthcare products Regulatory Agency is the UK competent authority for the regulation and authorizations or medicinal products in the UK. Some diversion has already taken place, most notably the EU's regulatory environment for clinical trials has been harmonized as part of the Clinical Trials Regulation. It is currently unclear as to what extent the UK will seek to align its regulations with the EU. Failure of the UK to closely align its regulations with the EU may have an effect on the cost of conducting clinical trials in the UK as opposed to other countries and/or make it harder to seek a marketing authorization for our product candidates on the basis of clinical trials conducted in the UK.

Manufacture of Medicinal Products in the EU. In the EU, a manufacturing authorization from the national regulatory authority of the member state in which the manufacturing of medicinal products is carried out is required to manufacture medicinal products. The manufacturing authorization holder must comply with various requirements set out in applicable EU laws, regulations and guidance. These requirements include compliance with EU GMP standards when manufacturing products and their APIs, including APIs manufactured outside of the EU with the intention of importing them into the EU. In addition to inspection reports, manufacturers and marketing authorization holders may be subject to civil, criminal or administrative sanctions, including suspension of manufacturing authorization, in cases of non-compliance with the EU or EU member states' requirements applicable to manufacturing.

Data and Marketing Exclusivity. In the EU, innovative medicinal products that are subject to marketing authorization on the basis of a full dossier qualify for eight years' data exclusivity upon marketing authorization and an additional two years' market exclusivity. Data exclusivity prevents regulatory authorities in the EU from referencing the innovator's data to assess a generic application or biosimilar application for eight years from the date of authorization of the innovative product, after which a generic or biosimilar marketing authorization application can be submitted, and the innovator's data may be referenced. However, the generic product or biosimilar products cannot be marketed in the EU for a further two years thereafter. The overall ten-year period may be extended for a further year to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Data exclusivity periods are currently the same in Great Britain as in the EU. However, following Brexit, the UK could change the duration of data exclusivity periods under its national legislation.

Environmental, Health and Safety Regulation

We are subject to numerous foreign, federal, state and local environmental, health and safety ("EHS") laws and regulations relating to, among other matters, safe working conditions, product stewardship, environmental protection, and handling or disposition of products, including those governing the generation, storage, handling, use, transportation, release, and disposal of hazardous or potentially hazardous materials, medical waste, and infectious materials. Some of these laws and regulations also require us to obtain licenses or permits to conduct our operations. If we fail to comply with such laws or obtain and comply with the applicable permits, we could face substantial fines or possible revocation of our permits or limitations on our ability 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 EHS liabilities will not develop in the future. EHS 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 EU 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.

Human Capital Management

As of December 31, 2022, we had approximately 123 full-time employees. Of these employees, 25 hold Ph.D. or M.D. degrees, 89 are engaged in research and development, and 34 are engaged in business development, finance, legal, human resources, facilities, information technology, and general management and administration. We also engage temporary employees and consultants. Our employees are not represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good. Our employee engagement is highly favorable, which we attribute to our shared mission of transforming the lives of those affected by highly prevalent ocular diseases and has led to our being named a Top Workplace for each of 2021 and 2022 by Bay Area News Group.

Our employees are one of our most valuable assets and are essential to our success. We have been purposeful in our efforts to hire, develop and retain diverse talent as well as create an inclusive culture. We are investing in the creation of a work environment that values the health, safety and wellness of our team, and where our employees are inspired to deliver their best every day. All employees are responsible for upholding the Adverum Code of Business Conduct and Ethics, as well as complying with our Employee Handbook, which together form the foundation of our policies and practices. We continue to expand our systems to track key human capital metrics such as demographics, diversity, compensation and benefits, and engagement.

Diversity, Equity and Inclusion

We are committed to diversity, equity and inclusion ("DEI") across all aspects of our company, including hiring, promotion and development practices. As of December 31, 2022, racial and ethnic minorities represented 65.9% of our employee base. 52% of our workforce were women and 50% of our positions at director-level and above were held by women. Our employees bring diversity to our workplace across many critical categories, and we believe our company is stronger as a result of our diverse experiences and backgrounds. We are committed to creating and maintaining a diverse, inclusive and safe work environment where our employees can bring their best selves to work each day. We continue to implement employee-led resource groups ("ERGs") and to assemble DEI-related resources for our employees. We currently have two ERGs that represent and support two diverse communities in our workforce: SOAR (Supporting Women of All Ranks ERG), providing support and mentorship for our female workforce, including guidance on career advancement and the LGBTQ+ (Pride ERG), working to foster an inclusive workplace culture that supports our LGBTQ+ workforce. These ERGs mentor, foster, encourage and inspire employees in all stages of their careers by providing access to senior leadership, peer groups, mentoring and other valuable resources to help them pursue their career ambitions.

Compensation and Benefits

Our commitment to our employees starts with benefit and compensation programs that value their contributions and offer physical, financial and personal health programs to them and their families. We strive to provide pay, benefits and services that are competitive to market and create incentives to attract and retain employees. Our compensation package includes market-competitive pay, broad-based stock grants and bonuses, healthcare and retirement benefits, and paid time off. We also offer an Employee Stock Purchase Program through which employees can purchase company stock at a discounted price and offer stipends to cover expenses associated with working from home and the use of personal devices for work purposes. Additionally, we continue to advance transparency in our pay and representation data by complying with all applicable statutory filing requirements.

Communication and Engagement

We strongly believe that Adverum's success depends on our employees understanding how their work contributes to the company's overall strategy. We strive to foster open and direct communication and seek to empower our employees to be our greatest ambassadors. We use a variety of channels to facilitate this exchange of information, including quarterly business updates from the senior management team; regular all hands meetings, open forums and company-wide written communications; postings on our company intranet; and employee engagement surveys.

Health, Wellness and Safety

Employee safety and well-being is of paramount importance to us, particularly in light of COVID-19. In response to the pandemic, we have taken extra precautions to reduce the risk of virus exposure for our employees. We provide protective equipment for our employees working on site, have implemented new safety protocols and procedures, and provide access to COVID-19 rapid testing. We have also established a governance structure to ensure timely communication and decision making. For our remote employees, we provide productivity and collaboration tools and resources, allow flexible schedules and support their information technology needs. We also regularly promote employee assistance programs to support our employees' physical, financial and mental well-being.

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 100 Cardinal Way, 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 us. 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. Further, the current coronavirus ("COVID-19") pandemic and actions taken to address the pandemic may exacerbate the risks described below.

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, marketing and other activities that, together with anticipated general and administrative expenses, will likely result in us incurring significant losses for the next several years or longer.

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 2025. If this expectation proves to be wrong, we may be forced to delay, limit or terminate certain of our development efforts before then.

We currently expect our cash, cash equivalents and short-term investments to fund our planned operations into 2025. 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, investments into our manufacturing capabilities, the scope of our research and development activities, continued compliance with and receipt of rent under our sublease, and changing circumstances beyond our control, that 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 and are unable to successfully raise additional funds on terms acceptable to us, we 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 nonclinical and clinical development for our product candidates and potentially to commercialize these product candidates. Any future clinical trials or ongoing clinical trials of our product candidates could cause an increase in our spending levels, as would other corporate activities, such as expenses related to manufacturing supply of our product candidates. 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, costs, results of and timing of any future nonclinical studies and clinical trials of any of our product candidates that 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 United States Food and Drug Administration (“FDA”) or other regulatory authorities outside the United States (“U.S.”), including any additional clinical trials or nonclinical studies the FDA or other regulatory authorities outside the U.S. 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 internal and external commercial manufacturing;
- The availability and cost of acquiring and shipping of supplies necessary for manufacturing and clinical trials;
- the costs and timing of establishing sales, marketing, distribution and other commercial capabilities;
- 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;
- the cost and timing of establishing enhanced internal controls over financial reporting; 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. General market conditions resulting from rising interest rates, inflation, global supply chain issues, Russia’s invasion of Ukraine, the COVID-19 pandemic, as well as other market conditions, as well as our ability to maintain our Nasdaq listing, may make it difficult for us to obtain adequate additional financing when needed or on attractive terms, or at all. 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 may be unable to complete any current or 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.

We are not currently in compliance with Nasdaq's continued listing standards, and if we are not able to regain compliance with Nasdaq's continued listing standards our common stock may be delisted.

Our common stock trades on The Nasdaq Global Select Market ("Nasdaq") under the symbol "ADVM." On November 18, 2022, we received a letter from the Nasdaq Listing Qualifications Staff of The Nasdaq Stock Market notifying us that we were out of compliance with the Nasdaq $1.00 per share minimum closing bid price rule. We have until May 17, 2023, to regain compliance with the minimum bid price rule. If we do not achieve compliance by May 17, 2023, we may be eligible for an additional 180-day period to regain compliance if we meet the continued listing requirement for market value of publicly held shares and all other initial listing standards, with the exception of the bid price requirement, and provide written notice to Nasdaq of our intention to cure the deficiency during the second compliance period by effecting a reverse stock split, if necessary. However, if it appears to the Nasdaq staff that we will not be able to cure the deficiency, or if we do not meet the other listing standards, Nasdaq could provide notice that our common stock will become subject to delisting. In the event Adverum receives notice that its common stock is being delisted, Nasdaq rules permit Adverum to appeal any delisting determination by the Nasdaq staff to a Hearings Panel. Accordingly, our common stock is subject to the risk of being delisted.

Adverse developments affecting the financial services industry, such as actual events or concerns involving liquidity, defaults or non-performance by financial institutions could adversely affect our current financial condition and projected business operations.

Actual events involving limited liquidity, defaults, non-performance or other adverse developments that affect financial institutions, transactional counterparties or other companies in the financial services industry or the financial services industry generally, or concerns or rumors about any events of these kinds or other similar risks, have in the past and may in the future lead to market-wide liquidity problems. For example, on March 10, 2023, Silicon Valley Bank ("SVB"), where we hold a small portion of our cash and cash equivalents, was closed by the California Department of Financial Protection and Innovation, which appointed the Federal Deposit Insurance Corporation ("FDIC"), as receiver. On March 12, 2023, the Department of the Treasury, the Federal Reserve, and the FDIC jointly released a statement that depositors at SVB would have access to their funds, even those funds in excess of the standard FDIC insurance limits, under a systemic risk exception. As of March 13, 2023, we had access to our cash and cash equivalents at SVB; however, there is uncertainty in the markets regarding the stability of regional banks and the safety of deposits in excess of the FDIC insured deposit limits. The ultimate outcome of these events cannot be predicted, but these events could have a material adverse effect on our business operations if our ability to access funds at SVB or any other banks we use is compromised.

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.

We currently have one product candidate in clinical trials, and if that product candidate is not successful our business could be materially impacted. Our other product candidates are in the early stages of development and will require substantial nonclinical and/or clinical development and testing, manufacturing process improvement and validation, clinical 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 nonclinical 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, partnering with a pharmaceutical licensee with manufacturing capabilities, or developing our own manufacturing capabilities 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.

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 or marketing authorization application ("MAA") to the European Medicines Agency ("EMA"), 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, or be conditional on future development activities and clinical results. 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, or, if approved, successfully commercialize, any of our product candidates, we may not be able to generate sufficient revenue to continue our business.

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.

Drug development has inherent risk. Our lead product candidate, ixoberogene soroparvovec ("Ixo-vec"), formerly referred to as ADVM-022, for the treatment of wet age-related macular degeneration ("wet AMD"), uses a proprietary vector, AAV.7m8, which has undergone limited human testing, and may generate unexpected results in clinical trials in the future, such as the dose-limiting toxicity at the 6 x 10^11 vg/eye ("6E11") dose tested in the INFINITY trial in diabetic macular edema ("DME") subjects. Although we will be bound by the generally applicable laws governing approval, the fact that our product is a gene therapy and the broad patient population that it is intended to treat means that the safety and efficacy of our product and the related clinical data will be under increased scrutiny by competent authorities. There have been several significant adverse side effects in gene therapy treatments in the past, including reported cases of leukemia and death seen in other trials using other genomic therapies. Gene therapy is still a relatively new approach to disease treatment and additional adverse side effects could develop. There also is the potential risk of significantly delayed adverse events following exposure to gene therapy products due to persistent biologic activity of the genetic material or other components of products used to carry the genetic material. Possible adverse side effects that could occur with treatment with gene therapy products include an immunologic reaction early after administration that, while not necessarily adverse to the patient's health, could substantially limit the effectiveness of the treatment.

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 is safe and effective for use in its 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 occurrence of serious complications or side effects that outweigh the therapeutic benefit in connection with or during use of our product candidates, whether in nonclinical 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 nonclinical studies and clinical trials, animal models and human subjects may experience changes in their health, including illnesses, injuries and discomforts. Often, it is not possible to determine whether or not the product candidate being studied caused these conditions. In addition, subjects may not comply with the requirements of the study, such as missing physician visits or not taking eye drops as prescribed, which may result in changes to their health or vision that are then attributed to the product candidate. Various illnesses, injuries, and discomfort may be reported from time-to-time in clinical trials of our product candidates. For example, a dose-limiting toxicity at the 6E11 dose tested in our INFINITY trial in DME

subjects resulted in our announcement on July 22, 2021 that we were discontinuing development of Ixo-vec for the DME indication. It is possible that as we test Ixo-vec and other product candidates, in current and future 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, including the dose-limiting toxicity at the 6E11 dose tested in the INFINITY trial, as well as conditions that did not occur or went undetected in previous trials, will be reported by subjects. In some cases, 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 causes serious or life-threatening side effects, or side effects that outweigh the therapeutic benefit of the product candidate, 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.

In order to understand the safety of our product candidates, when a subject experiences a negative health event during a clinical trial, we must determine if it is related to our product candidate. The subjects we enroll in our clinical trials for our current product candidates are generally 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 subjects enrolled in our wet AMD trials 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 experienced by a subject in any of these or subsequent trials was related to Ixo-vec, nor can we assure you that the FDA or other regulatory authorities outside the U.S. responsible for reviewing the safety of Ixo-vec will agree with our determination. If a subject in one of our clinical trials experiences a negative health event, and that event is misattributed to Ixo-vec, the trial and other trials of Ixo-vec may be placed on clinical hold, and regulatory approval of Ixo-vec may be delayed or denied.

In addition, if a subject enrolled in one of our clinical trials experiences a negative health event, the subject 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 subjects 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 subjects, this risk is increased.

Our product candidates built on adeno-associated viral vector ("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, dose-related ocular inflammation is a known side effect of Ixo-vec administration, but the duration of inflammation caused by Ixo-vec, our ability to prevent or manage that inflammation using corticosteroids or other anti-inflammatory or immunomodulatory treatments, and any potential clinical sequelae of that inflammation and treatments used to manage inflammation are not fully understood. The primary purpose of our LUNA trial is to identify the best combination of a prophylactic corticosteroid regimen and dose of Ixo-vec that minimizes post-prophylactic inflammation while at the same time providing efficacy. If we are unable to manage this inflammation appropriately, we may not be able to further develop Ixo-vec and the FDA or other regulatory authorities outside the U.S. may not approve Ixo-vec. Even if we achieve marketing approval, doctors may not prescribe, and patients may not use, Ixo-vec or our other product candidates if they deem the levels or risk of inflammation to be unacceptable or if they are unwilling or unable to use the required prophylactic corticosteroid regimen. Further, patients treated with Ixo-vec could develop antibodies against AAV.7m8 capsid and/or aflibercept protein. These antibodies could preclude these patients from receiving other AAV-based gene therapies in the future. In addition, patients previously treated with or exposed to other AAV-based gene therapies could develop antibodies against AAV.7m8 and/or the aflibercept protein, which could reduce or eliminate the effectiveness of Ixo-vec or could cause unanticipated adverse reactions to Ixo-vec. Studies have also found that intravenous delivery of certain AAV vectors at 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 therapeutic protein or injection of gene therapies that express a therapeutic 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, 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, Ixo-vec, 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 via 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.

The results of nonclinical 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 or product candidates. Promising nonclinical 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 nonclinical model, including non-human primate 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. Success in nonclinical 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 nonclinical and initial clinical testing. Further, safety and/or efficacy issues with a product candidate may become apparent only when the product candidate is tested in human subjects suffering from the relevant disease. 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. We will still need to conduct Phase 3 pivotal trials in which we anticipate Ixo-vec will be compared to available therapies and utilize longer term endpoints in order to support submission and approval of a BLA or equivalent outside of the U.S. 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, the FDA and/or other regulatory authorities outside the U.S. 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.

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 the time, cost and probability of subsequently obtaining regulatory approval.

We have concentrated our research and development efforts on our gene therapy platform and in product candidates based on this platform, and our future success depends on the successful development of such product candidates. 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 external commercial manufacturing sites, 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, EMA and other regulatory authorities outside the U.S. and the criteria these regulators may use to determine the quality, 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 treatment modalities, which are better known or more extensively studied to date. In 2017 and 2019, the FDA approved the first two products in vivo gene therapy. To date, approvals for gene therapy products by the FDA have been generally for rare diseases with limited treatment options. Because we are targeting a broad population of patients with wet AMD, for which there is an approved and widely adopted standard of care, the benefit-risk profile of Ixo-vec may be subject to greater scrutiny by regulatory authorities. 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 authorities have more substantial experience, including, for example, reevaluating whether to require a companion diagnostic for gene therapy products.

Before a clinical trial can begin to enroll at a clinical site, the site's Institutional Review Board (“IRB”) and its Institutional Biosafety Committee must review the proposed clinical trial to assess appropriateness to conduct the clinical trial at that site. In addition, adverse events in clinical trials of gene therapy products conducted by others may cause the FDA or other regulatory authorities outside the U.S. to change the requirements for human research on or for approval of any of our product candidates.

These regulatory agencies, 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 chemistry, manufacturing, and controls 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 or the consultations take longer than we expect, 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.

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 our 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, 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 and patient's safety concerns over participating in a clinical trial, including during a pandemic. We will be required to identify and enroll a sufficient number of patients for any clinical trial 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. 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.

We plan to seek initial marketing approval of our 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, the EMA or other regulatory authorities outside the U.S. In addition, the process of finding and diagnosing patients may prove costly.

Further, if patients and investigators are unwilling to participate in our gene therapy studies because of the dose-limiting toxicity at the 6E11 dose tested in the INFINITY trial, or because of negative publicity from other adverse events in the biotechnology or gene therapy sector or inadequate results in our nonclinical studies or clinical trials or for other reasons, including competitive clinical trials for similar patient populations or available approved therapies, our recruitment of patients, or conduct of 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 AAV delivery system, with which host integration has been less of a concern. Nonetheless, if patients negatively associate our product candidates with the adverse events caused by previous gene therapy products, they may choose not 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.

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 nonclinical 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 outside the U.S. 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 regulatory authorities outside the U.S. 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 outside the U.S. that a product candidate is safe and effective for any indication;
- the FDA or other regulatory authorities outside the U.S. 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. or the other regulatory authorities outside 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 nonclinical 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 our manufacturing processes, analytical testing, or facilities or 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 regulatory authorities outside the U.S. 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.

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 subject enrollment continues or further subject follow up occurs and more subject data become available. For example, although we have periodically announced interim data from subjects in our OPTIC trial, which showed all Ixo-vec related adverse events as mild to moderate in severity, there is no guarantee that in the future, we will not have more severe drug- or treatment-related adverse events in subjects treated with Ixo-vec, such as the dose-limiting toxicity at the 6E11 dose tested in our INFINITY trial. In addition, in certain clinical trials, such as our OPTIC trial, individual cohorts of subjects were enrolled with different dosages and other treatment conditions under our protocol. These different doses, populations, and other treatment conditions may affect clinical outcomes, including safety profiles or efficacy, such as the number of supplemental 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.

Fast Track designation by the FDA and PRIME designation by the EMA for Ixo-vec may not lead to a faster development, regulatory review or approval, and it does not increase the likelihood that Ixo-vec will receive marketing approval in the U.S.

We received Fast Track designation for Ixo-vec in September 2018 for the treatment of wet AMD. The FDA may grant Fast Track designation to a drug that is intended to treat a serious condition and nonclinical or clinical data demonstrate the potential to address unmet medical needs. The FDA provides opportunities for frequent interactions with the review team for a Fast Track product, including pre-investigational new drug application ("IND") meetings, end-of-phase 1 meetings, and end-of-phase 2 meetings with the FDA to discuss study design, extent of safety data required to support approval, dose-response concerns, and use of biomarkers. A Fast Track product may also be eligible for rolling review, where the FDA reviews portions of a marketing application before the sponsor submits the complete application.

The European Medicines Agency EMA granted Ixo-vec Priority Medicines ("PRIME") designation in June 2022 for the treatment of wet AMD. PRIME is a program launched by the EMA to enhance support for research on and development of medicines that have demonstrated preliminary safety and efficacy and thus the potential to target a significant unmet medical need and bring a major therapeutic advantage to patients. This regulatory program offers developers of promising medicines enhanced interaction and early dialogue with the EMA and is designed to optimize development plans and speed evaluation ensuring these medicines reach patients as early as possible.

However, Fast Track and PRIME designations for Ixo-vec may not result in a faster development process, review or approval compared to products considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA or the EMA. In addition, the FDA may rescind the Fast Track designation for Ixo-vec if FDA later determines that Ixo-vec no longer meets the qualifying criteria for Fast Track designation.

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 technology. 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 could have a material adverse effect on our business, financial condition, results of operations, and prospects. 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.

Risks Related to Manufacturing

If we are unable to successfully develop and maintain robust and reliable manufacturing processes for our product candidates, we may be unable to advance clinical trials or licensure applications and may be forced to delay or terminate a program.

The development of commercially viable manufacturing processes typically is very difficult to achieve, is often very expensive and may require extended periods of time. As we develop, seek to optimize, and operate the Ixo-vec manufacturing process, internally or through third parties, we will likely face technical and scientific challenges, considerable capital costs, and potential difficulty in recruiting and hiring experienced, qualified personnel. There may also be unexpected technical or operational issues during clinical manufacturing campaigns or process validation campaigns. For example, all Good Manufacturing Practices ("GMP") activities at our Redwood City facility, and external manufacturing, testing, and distribution partners are subject to significant health authority regulation with respect to manufacturing and testing our product candidates. If we are unable to satisfy these regulatory requirements, or if we are unable to solve the technical, scientific, and other challenges described above, we may be unable to manufacture a sufficient supply of our product candidates for our clinical trials and may be forced to delay or terminate our development programs. Additionally, changes in manufacturing processes (including cell lines), equipment or facilities (including moving manufacturing or testing from one of our facilities to another one of our facilities or a third-party facility, or from a third-party facility to one of our facilities) may require us to conduct additional studies to demonstrate comparability in order to receive regulatory approval of any manufacturing modifications. As a result, we could experience manufacturing delays that prevent us from completing our clinical studies in a timely manner, if at all.

We may revise the process that we use to manufacture Ixo-vec for clinical trials. Before we use a revised process in clinical trials, we must submit analytical comparability data to the FDA and comparable regulatory authorities outside the U.S. to demonstrate that the process changes have not altered Ixo-vec in a manner that undermines the applicability of the clinical data from our clinical trials. If the FDA and comparable regulatory authorities outside the U.S. do not find our analytical comparability data sufficient, the FDA and comparable regulatory authorities outside the U.S. could place our IND or equivalent on clinical hold until we conduct additional nonclinical or clinical comparability studies demonstrating that the Ixo-vec manufactured by our revised process and our previous process are materially equivalent, which could substantially delay the development process. If we make further changes to the manufacturing process, equipment or facilities of Ixo-vec in the future, the FDA and comparable regulatory authorities outside the U.S. may require us to demonstrate comparability between Ixo-vec manufactured before and after the change. For example, the FDA and comparable regulatory authorities outside the U.S. could require comparability studies to demonstrate that Ixo-vec manufactured in its current facilities is comparable to Ixo-vec manufactured at future commercial supply sites.

We do not know whether any required comparability studies will begin as planned, will need to be restructured or will be completed on schedule, or at all. If the results of these comparability studies are not positive or are only modestly positive or if there are safety concerns, we may be delayed in obtaining marketing approval for Ixo-vec or not obtain marketing approval at all. Our product development costs also will increase if we experience delays in testing or regulatory approvals.

If we are unable to produce sufficient quantities of our products and product candidates at acceptable costs, we may be unable to meet clinical or potential commercial demand, lose potential revenue, have reduced margins, or be forced to terminate a program.

Due to the complexity of manufacturing our products, we may not be able to manufacture sufficient quantities to meet clinical or potential commercial demand. Our inability to produce enough of a product meeting all release acceptance criteria at acceptable costs may cause us to be unable to meet clinical or potential commercial demand, to lose potential revenue, to have reduced margins, or to be forced to discontinue such product.

As we develop, seek to optimize and operate the Ixo-vec manufacturing process internally or through third parties, we will likely face technical and scientific challenges, considerable costs, and potential difficulty in recruiting and hiring experienced, qualified personnel. There may also be unexpected technical or operational issues during clinical or commercial manufacturing campaigns. As a result, we could experience manufacturing delays that prevent us from commercializing Ixo-vec, if approved, on a profitable basis, if at all.

In addition, our manufacturing processes will subject us to a variety of U.S. federal, state and local laws and regulations governing the use, generation, manufacture, storage, handling and disposal of hazardous materials and wastes resulting from their use, as well as comparable legislation and regulations outside of the U.S. We will incur significant costs in complying with these laws and regulations.

Gene therapy products are novel and complex and have only in limited cases been manufactured at scales sufficient for pivotal trials and commercialization. Few pharmaceutical contract manufacturers specialize in gene therapy products and those that do are still developing appropriate processes and facilities for large-scale production. If we are unable to secure adequate manufacturing capacity from our contract manufacturing partners, or if our contracted slots are cancelled or delayed in order to prioritize other projects, we may be unable to produce sufficient quantities of our product candidates for our development programs.

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 used in clinical trials or approved for commercial sale must be manufactured and tested in accordance with GMP 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 GMP regulations enforced by the FDA through its facilities inspection program as well as other regulations enforced by other regulatory authorities outside the U.S. Our contract manufacturers have not produced a commercially-approved AAV product and therefore have not yet demonstrated compliance with GMP regulations to the satisfaction of the FDA or other regulatory authorities outside the U.S. 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. If the facility does not pass a pre-approval plant inspection, the FDA or other regulatory approval of the products will not be granted. In addition, the regulatory authorities may, at any time, audit or inspect any manufacturing facility we may have or those of our third-party contractors involved with the preparation of our product candidates or the associated quality systems for compliance with the regulations applicable to the activities being conducted. Should the FDA or other regulatory authorities outside the U.S. 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, on January 31, 2020, the United Kingdom ("UK") withdrew from the European Union ("EU"), commonly referred to as Brexit. Pursuant to the formal withdrawal arrangements agreed between the UK and the EU, the UK was subject to a transition period until December 31, 2020, or the Transition Period, during which EU rules continued to apply. The UK-EU Trade and Cooperation Agreement, which has applied since the end of the Transition Period, provides for tariff-free trade of goods, but not services, between the UK and the EU, but there may however be additional non-tariff costs which did not exist prior to the end of the Transition Period. Further, should the UK further diverge from the EU from a regulatory perspective in relation to medical products, tariffs could be put into place in the future.

Although the body of the UK-EU Trade and Cooperation Agreement includes general terms which apply to medicinal products, greater detail on sector-specific issues is provided in an Annex to the Agreement. The Annex provides a framework for the recognition of GMP inspections and for the exchange and acceptance of official GMP documents. The regime does not, however, extend to procedures such as batch release certification, and Great Britain (England, Scotland and Wales) is treated as a third country. Northern Ireland, with regard to EU regulations, continues to follow the EU regulatory rules. As part of the UK-EU Trade and Cooperation Agreement, the EU and the UK will recognize GMP inspections carried out by the other Party and the acceptance of official GMP documents issued by the other Party. The UK-EU Trade and Cooperation Agreement also encourages, although it does not oblige, the parties to consult one another on proposals to introduce significant changes to technical regulations or inspection procedures. Among the areas of absence of mutual recognition are batch testing and batch release. The UK continues to accept EU batch testing and batch release, but has recently conducted a consultation as to the future strategy for batch testing policy; two years notice will be provided of any change to such a policy. However, the EU continues to apply EU laws that require batch testing and batch release to take place in the EU territory. This means that medicinal products that are tested and released in the UK must be retested and re-released when entering the EU market for commercial use. As regards marketing authorizations, Great Britain has a separate regulatory submission process, approval process and a separate national marketing authorization. Northern Ireland is, however, covered by centralized marketing authorizations granted by the European Commission ("EC").

There are currently delays on cross-border trade between the UK and the EU as businesses and governmental bodies adapt to the arrangements. We and our contract vendors currently rely on other contractors based in the UK. The implementation of new governmental policies associated with Brexit 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, inspect any manufacturing facility we may have 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 or other regulatory authorities outside the U.S. 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. Alternative contractors could need to be qualified through a BLA supplement which could result in further delay. The regulatory authorities 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. Changing 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.

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:

- Due to the complexity of manufacturing our product candidates, we may not be able to manufacture sufficient quantities to support our clinical trials. Delays in manufacture and supply by our contract manufacturing partners may also cause delays in their ability to supply the amount of our product that we have ordered and on which we have based our expected development timelines. Our inability to produce enough of a product candidate at acceptable costs may result in the delay or termination of development programs.
- The manufacturing and distribution of biologics is extremely susceptible to product loss due to contamination, equipment failure, improper installation or operation of equipment, vendor or operator error, or transportation or storage conditions of the product. Even minor deviations from prescribed 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 GMP 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 regulatory authorities in other jurisdictions to confirm compliance with applicable regulatory requirements. Any failure to follow GMP or other regulatory requirements or any delay, interruption, or other issues that arise in the manufacture, fill-finish, packaging, storage, or distribution 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 continue 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 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.

Risks Related to Our Reliance on Third Parties

We have relied, and expect to continue to rely, on third parties under contracts and partnerships to conduct some or all aspects of our research and development, including vector production, process development, assay development, product candidates and product manufacturing and testing, protocol development, clinical trials, product distribution, commercialization, nonclinical studies, research and related activities, and these third parties may not perform satisfactorily.

We do not expect to independently conduct all aspects of our vector production, product and product candidate manufacturing and testing, protocol development, clinical trials, product distribution, commercialization, nonclinical studies, research and related activities. 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 or partnerships with these third parties and if we do enter into agreements with these third parties, we cannot be assured these agreements will be on favorable economic terms or that any of these third parties will be successful at fulfilling their contractual obligations, and it is possible they may choose to terminate their engagements with us. If we need to enter into alternative arrangements, it could delay or jeopardize our product development activities or be more costly. Our reliance on these third parties for vector production, process development, assay development, product and product candidate manufacturing and testing, protocol development, clinical trials, product distribution, commercialization, nonclinical studies, research and related 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 nonclinical studies and clinical trials are conducted in accordance with the study plan and protocols and applicable regulatory requirements;
- vector production, product and product candidate manufacturing and testing are conducted in accordance with applicable GMP requirements and other applicable regulatory requirements; and
- other research, process development, and assay development are conducted in accordance with applicable industry and regulatory standards and norms;

any of which we may not be able to do.

We will continue to rely on third-party manufacturers and suppliers, and may enter into partnerships and other business development arrangements, which entails risks, including:

- the inability to negotiate manufacturing, supplier agreements, partnerships or other agreements with third parties under commercially reasonable terms;
- reduced control as a result of using third-party manufacturers or partners for some or all aspects of manufacturing activities;
- termination or nonrenewal of manufacturing agreements, partnerships, or supplier 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, supplier or partner, or their commitments to other vaccine and therapeutics production projects that may reduce available manufacturing capacity.

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

We will rely on third parties to conduct some nonclinical 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 nonclinical testing, clinical testing, or clinical trials ourselves. We are dependent on third parties to conduct nonclinical 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 subjects enrolled in our ongoing clinical trials unless we are able to transfer those subjects to another qualified clinical trial site.

In addition, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and may receive 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 outside the U.S. Any such delay or rejection could prevent us from commercializing our product candidates.

Risks Relating to Our Intellectual Property

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. 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.

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 conduct research and to develop and 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 they 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, academic institutions that we collaborate with often require 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, including through breach of our agreements with third parties, failure of our security measures or publication of information by any of our third-party collaborators, 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. 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.

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 to defend against 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.

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 may 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 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 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.

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, in 2019 we 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. Although no further action has been taken in that matter, it illustrates that if one of our licenses were to be terminated, we may be unable to obtain a new license to that 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 to advance our current development programs, as well as additional development programs we may initiate in the future. If these licenses are not available on commercially reasonable terms or at all, we may not be able to commercialize our current and future development programs, which will have a material adverse effect on our business and 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 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 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.

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 cause them to infringe patents held by third parties. 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.

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. Further, following Russia's invasion of Ukraine in February 2022, the U.S. government has levied sanctions against Russia and Belarus, Russia has issued a decree that removes protections for some patent holders who are registered in unfriendly countries, including the U.S., and the USPTO has terminated its engagement with officials from intellectual property agencies in Russia, Belarus and Eurasia, so we are not currently maintaining certain intellectual property filings in these jurisdictions. 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 as patents 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 to us, if any, may not be commercially meaningful.

For example, the complexity and uncertainty of European patent laws have also increased in recent years. In Europe, a new unitary patent system will likely be introduced by the end of 2023, which would significantly impact European patents, including those granted before the introduction of such a system. Under the unitary patent system, European applications will soon have the option, upon grant of a patent, of becoming a Unitary Patent which will be subject to the jurisdiction of the Unitary Patent Court (UPC). As the UPC is a new court system, there is no precedent for the court, increasing the uncertainty of any litigation. Patents granted before the implementation of the UPC will have the option of opting out of the jurisdiction of the UPC and remaining as national patents in the UPC countries. Patents that remain under the jurisdiction of the UPC will be potentially vulnerable to a single UPC-based revocation challenge that, if successful, could invalidate the patent in all countries who are signatories to the UPC. We cannot predict with certainty the long-term effects of any potential changes

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.

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.

If we do not obtain patent term extensions for patents covering our product candidates, our business may be materially harmed.

Patent terms may not be able to protect our competitive position for an adequate period of time with respect to our current or future technologies or product candidates. Patents have a limited lifespan. In the U.S., if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. As a result, our owned and in-licensed patent portfolio provides us with limited rights that may not last for a sufficient period of time to exclude others from commercializing product candidates similar or identical to ours. Even if patents covering our product candidates are obtained, once the patent life has expired, we may be open to competition from competitive products, including generics or biosimilars. For example, given the large amount of time required for the research, development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

Extensions of patent term may be available, but there is no guarantee that we would have patents eligible for extension, or that we would succeed in obtaining any particular extension—and no guarantee any such extension would confer a patent term for a sufficient period of time to exclude others from commercializing product candidates similar or identical to ours. 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”). Depending upon the timing, duration and specifics of FDA marketing approval of product candidates, the Hatch-Waxman Act permits a patent restoration term of up to five years beyond the normal expiration of the patent, which is limited to the approved product or approved indication. In the U.S., patent term extension cannot extend the remaining term of a patent beyond 14 years from the date of product approval; only one patent may be extended; and extension is available for only those claims covering the approved drug, a method for using it, or a method for manufacturing it. Similar extensions of patent term are available in Europe and other jurisdictions. 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.

The interpretation by the regulatory authorities in the EU of applicable EU regulations governing data and market exclusivity may impact our entitlement to data and market exclusivity. The revisions to the orphan drug legislation in the EU and the EU rules governing Supplementary Protection Certificates that are currently being discussed may also impact our entitlement to this exclusivity.

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 or threaten 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 accused infringer could claim that our patent is invalid and/or unenforceable in whole or in part. In patent litigation in the U.S., defendant counterclaims alleging invalidity and/or unenforceability are commonplace, as are claims seeking declaratory judgment of invalidity. 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 patent office 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 or patent office 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.

Some intellectual property that we have in-licensed or may in-license may have been discovered through government funded programs and thus may be subject to federal regulations such as "march-in" rights, certain reporting requirements and a preference for U.S.-based companies. Compliance with such regulations may limit our exclusive rights and limit our ability to contract with non-U.S. manufacturers.

Intellectual property rights we have licensed, including certain rights related to our proprietary AAV.7m8 capsid, were generated through the use of U.S. government funding and are therefore subject to certain federal regulations. As a result, the U.S. government may have certain rights to intellectual property embodied in our current or future product candidates pursuant to the Bayh-Dole Act of 1980, or Bayh-Dole Act, and implementing regulations. These U.S. government rights in certain inventions developed under a government-funded program include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right to require us or our licensors to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations (also referred to as "march-in rights"). The U.S. government also has the right to take title to these inventions if we, or the applicable licensor, fail to disclose the invention to the government and fail to file an application to register the intellectual property within specified time limits. These time limits have recently been changed by regulation, and may change in the future. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us or the applicable licensor to expend substantial resources. In addition, the U.S. government requires that any products embodying the subject invention or produced through the use of the subject invention be manufactured substantially in the U.S. The manufacturing preference requirement can be waived if the owner of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the U.S. or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. manufacturers may limit our ability, or that of our sublicensees, to contract with non-U.S. product manufacturers for products covered by such intellectual property. To the extent

any of our current or future intellectual property is generated through the use of U.S. government funding, the provisions of the Bayh-Dole Act may similarly apply.

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, what activities satisfy those diligence obligations, and to what extent those obligations are relieved or delayed by external factors beyond our control, such as the COVID-19 pandemic;
- 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.

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.

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.

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.

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.

We currently have one product candidate in clinical trials. Before we can initiate clinical trials for other product candidates in the U.S., we need to submit the results of nonclinical 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 nonclinical, 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 nonclinical and clinical data on our own, which will lead to significant delays and increase development costs of the product candidate. In addition, the FDA or other regulatory authorities may require us to conduct additional nonclinical testing for any of our product candidates before they allow us to initiate clinical testing under any IND or equivalent, or at any stage of clinical development of Ixo-vec or other new product candidates based on concerns that arise as the clinical program progresses or if significant manufacturing process changes are made to the program, which may lead to additional delays and increase the costs of our nonclinical 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 clinical 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 or other regulatory authorities outside the U.S. 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 outside the U.S. to temporarily or permanently shut down due to violations of

GMP or other applicable requirements, or infections or cross-contaminations of product candidates in the manufacturing process, or in the manufacturing facilities in which our product candidates are made;
- availability of non-investigational materials or supplies required for the clinical trials;
- any changes to our manufacturing process that may be necessary or desired;
- availability of non-investigational materials or supplies required for manufacturing;
- third-party clinical investigators losing the licenses, permits or resources 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, sample testing or analysis in a timely and accurate manner;
- inspections of clinical trial sites by the FDA or other regulatory authorities outside the U.S., or the finding of regulatory violations by the FDA or other regulatory authorities outside the U.S., or an IRB that requires us to undertake corrective action resulting in suspension or termination of one or more clinical sites or the imposition of a clinical hold on the IND or that prohibits 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 outside the U.S. 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 a clinical site, precluding enrollment of additional patients, or withdrawing its approval of the trial.

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

We have amended our protocol and from time to time may further amend our protocol based on a variety of factors, and these changes may have unanticipated consequences on our clinical trial outcomes.

Final marketing approval for our product candidates by the FDA or other regulatory authorities outside the U.S. 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, and/or an MAA, 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 authorities 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 policies from the FDA or other regulatory authorities outside the U.S. 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 receive regulatory approval, we still may not be able to successfully commercialize any of our product candidates, and the revenue that we generate from product sales, if any, could be limited.

Even if one or more 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 labeling approved for our products by the FDA or other applicable regulatory authorities outside the U.S., including the possible inclusion of a "black box warning" from the FDA or other applicable regulatory authorities outside the U.S. alerting health care providers to potential serious side effects associated with using a product or the imposition of a Risk Evaluation and Mitigation Strategy ("REMS");
- 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 incidence of wet AMD, 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 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 a gene encoding a therapeutic antibody fragment similar to ranibizumab (LUCENTIS®) for the treatment of wet AMD and diabetic retinopathy, which competes for the same patients, study site resources, and personnel as Ixo-vec. 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 gene therapy 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. 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, Ixo-vec 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 4D Molecular Therapeutics, Bayer, Hoffmann-La Roche Ltd., Novartis, Regeneron and REGENXBIO.

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 outside the U.S. for compliance with GMP requirements relating to manufacturing, 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 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 and other regulatory authorities outside the U.S. strictly regulate 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 competent regulatory authority 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 regulatory and enforcement authorities outside the U.S. 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 U.S. 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.

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 U.S., 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 gene therapy products, 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 payers in the U.S., 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 payers.

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 the company to sell its products at a profit. The U.S. 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, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act (collectively, 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.

Certain provisions of the Affordable Care Act have been subject to executive, Congressional, and judicial challenges as well as efforts to repeal, replace, or otherwise modify them or alter their interpretation and implementation. For example, the Tax Cuts and Jobs Act of 2017 included 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, on June 17, 2021 the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Further, prior to the U.S. Supreme Court ruling, on January 28, 2021, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the Affordable Care Act marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including, among others, policies that undermine protections for people with pre-existing conditions, demonstrations and waivers under Medicaid and the Affordable Care Act that may reduce coverage or undermine the programs thereunder, including work requirements, and policies that make it more difficult to access health benefits through Medicaid or the Affordable Care Act. On August 16, 2022, President Biden signed the Inflation Reduction Act of 2022 (the "Inflation Reduction Act") into law, which among other things, extends enhanced subsidies for individuals purchasing health insurance coverage in Affordable Care Act marketplaces through plan year 2025. The Inflation Reduction Act also eliminates the "donut hole" under the Medicare Part D program beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket cost and through a newly established manufacturer discount program. Additional legislative changes, regulatory changes, and judicial challenges related to the Affordable Care Act remain possible. Any such changes could affect the number of individuals with health coverage. It is possible that the Affordable Care Act, as currently enacted or as it may be amended in the future, and other healthcare reform measures that may be adopted in the future could have a material adverse effect on our industry generally and on our ability to successfully commercialize our product candidates, if approved.

Healthcare and other reform legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and, if approved, may affect the prices we may obtain.

Legislative changes have also been proposed and adopted in the U.S. since the Affordable Care Act was enacted. For example, 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, on average, 2% per fiscal year, which went into effect on April 1, 2013 and due to subsequent legislative changes to the statute, will stay in effect until 2031 unless additional congressional action is taken. Under current legislation, the actual reduction in Medicare payments will vary from 1% in 2022 to up to 4% in the final fiscal year of this sequester. Further, Congress is considering additional health reform measures.

These cost reduction initiatives could decrease the coverage and reimbursement that we receive for any approved products and could seriously harm our business. The Biden administration expressed its intent to pursue certain policy initiatives to reduce drug prices. For example, in July 2021, the Biden administration released an executive order, "Promoting Competition in the American Economy," with multiple provisions aimed at prescription drugs. In response to Biden's executive order, on September 9, 2021, Health and Human Services ("HHS") released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue to advance these principles. Further, the Inflation Reduction Act, among other things, (1) directs HHS to negotiate the price of certain single-source drugs and biologics covered under Medicare and (2) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. These provisions will take effect progressively starting in fiscal year 2023, although they may be subject to legal challenges. It is currently unclear how the Inflation Reduction Act will be implemented but is likely to have a significant impact on the pharmaceutical industry. Further, the Biden administration released an additional executive order on October 14, 2022 directing HHS to submit a report on how the Center for Medicare and Medicaid Innovation can be further leveraged to test new models for lowering drug costs for Medicare and Medicaid beneficiaries. It is unclear whether this executive order or similar policy initiatives will be implemented in the future.

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.

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.

It is possible that additional governmental action could be taken in response to the COVID-19 pandemic, and that such action could affect our business.

If the market for Ixo-vec, if approved, in the treatment of wet AMD or any other indication we seek to treat is smaller than we believe it is, or if our product candidate is approved with limitations that reduce the market size, or if this occurs for any of our other product candidates, our future revenue may be adversely affected, and our business may suffer.

We are advancing the development of Ixo-vec 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, 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 Ixo-vec 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. We cannot accurately predict the number of patients for whom treatment for wet AMD using Ixo-vec or any of our other product candidates might be possible or whether the FDA or other regulatory authorities may approve indications for Ixo-vec or any of our other product candidates that are more limited than we expect due to efficacy or safety concerns. For example, some patients have neutralizing antibodies at titer levels that may prevent them from benefiting from Ixo-vec. If this patient population is larger than we estimate, the market for Ixo-vec may be smaller than we anticipate, and our future revenue may be adversely affected. In addition, we expect prophylactic corticosteroid treatment will be required to manage inflammation associated with treatment with Ixo-vec, and certain patients cannot be treated with prophylactic corticosteroids. If this proportion of the patient population is larger than we estimate, the market for Ixo-vec 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.

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.

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 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 biotechnology and pharmaceutical companies in the past and may do so again in the future. 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.

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, including Member States of the European Economic Area ("EEA"), the pricing of prescription pharmaceuticals is subject to governmental control. Additional countries may adopt similar approaches to the pricing of prescription drugs. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product candidate. There can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after coverage and reimbursement have been obtained. Reference pricing used by various countries and parallel distribution, or arbitrage between low-priced and high-priced countries, can further reduce prices. Publication of discounts by third-party payers or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. 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.

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.

We have no sales, marketing, distribution, or market access and reimbursement capabilities, and we would have to invest significant resources to develop these capabilities.

We have no internal sales, marketing, distribution, or market access and reimbursement 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, marketing, distribution, or market access and reimbursement 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, distribution, or market access and reimbursement functions on acceptable financial terms or at all. Even if we determine to perform sales, marketing, distribution, or market access and reimbursement 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, sales force, or distribution capabilities;
- 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.

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, such as the dose-limiting toxicity at the 6E11 dose tested in our INFINITY trial, 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, Ixo-vec, expresses the aflibercept protein, which is also the active component 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 or consulting 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.

Our restructuring and the associated headcount reduction may not result in anticipated savings, could result in total costs and expenses that are greater than expected and could disrupt our business.

In July 2022, we implemented a restructuring of operations, including reductions in both headcount and expenses. We may not realize, in full or in part, the anticipated benefits, savings and improvements in our cost structure from our restructuring efforts due to unforeseen difficulties, delays or unexpected costs. If we are unable to realize expected operational efficiencies and the cost savings from the restructuring, our operating results and financial condition would be adversely affected. Due to our restructuring, we may not be able to effectively manage our operations or retain qualified personnel, which may result in weaknesses to our infrastructure and operations, increased risk that we may be unable to comply with legal and regulatory requirements, increased risks to our internal controls and disclosure controls, and loss of employees and reduced productivity among remaining employees.

The restructuring resulted in the loss of institutional knowledge and expertise and the reallocation of and combination of certain roles and responsibilities across the organization, all of which could adversely affect our operations. Further, the restructuring and possible additional cost-containment measures may yield unintended consequences, such as attrition beyond our intended workforce reduction and reduced employee morale. We may be required to rely more heavily on temporary or part-time employees, third party contractors and consultants to assist with managing our operations. These consultants are not our employees and may have commitments to, or consulting or advisory contracts with, other entities that may limit their availability to us. We will have only limited control over the activities of these consultants and in many instances can expect these individuals to devote only limited time to our activities. Failure of any of these persons to devote sufficient time and resources to our business could harm our business. Employee litigation related to the headcount reduction could be costly and prevent management from fully concentrating on the business.

If our management is unable to successfully manage this transition and these restructuring activities, our expenses may be more than expected and we may be unable to fund our Ixo-vec development plan or implement our business strategy. As a result, our business, prospects, financial condition and results of operations could be negatively affected.

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

In the future, 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.

Russia's invasion of Ukraine and current adverse economic conditions could adversely affect our revenue, financial condition, or results of operations.

The global disruption to, and potential impacts on, the health of the global economy arising from, related to, or resulting from Russia's invasion of Ukraine in February 2022 could affect our business and operations. For example, the credit and financial markets have been adversely affected by the war and measures taken in response thereto, potentially impacting our ability to raise adequate additional capital when needed or on favorable terms. In addition, current economic conditions, such as recent global supply chain disruptions, labor shortages, rising interest rates and inflation, may adversely impact our operations, for example by increasing our costs, disrupting our suppliers' ability to provide us with materials and supplies needed for both our manufacturing and clinical trials, or causing delays to our clinical trial and manufacturing timelines, which may negatively impact our business. These economic conditions make it more difficult for us to accurately forecast and plan our future business activities.

The coronavirus ("COVID-19") pandemic has impacted our business practices and the effects of its continued impact on our business, results of operations, and financial condition will depend on future developments, which cannot be predicted.

The COVID-19 pandemic and the emergence of new variants have caused us to modify our business practices, including the adoption of a hybrid mix of virtual and in-person work, updating our policies and implementing new practices to align with guidance from state and federal governments and health authorities. We may take further actions that may be required by government authorities or that we determine are in the best interests of our employees, customers, and business partners. We are uncertain that such measures will be sufficient to mitigate future risks posed by the virus and its variants or otherwise be satisfactory to government authorities and how long we will be required to continue these measures.

Separately, an increased reliance by us and the companies with which we do business on information technology systems to support a hybrid workforce may increase cyber security risk, create data accessibility issues, increase the risk for communication disruptions, or otherwise disrupt or delay normal business operations.

The COVID-19 pandemic may also affect our current and planned trials, development programs and our timelines for commercialization. We and our CROs, clinical sites and contract manufacturing organizations ("CMOs") may face disruptions that may affect our ability to conduct and timely complete ongoing clinical trials, nonclinical studies, obtain clinical supplies, and conduct other research and development activities. The response to the COVID-19 pandemic also could redirect resources with respect to regulatory and intellectual property matters in a way that could adversely impact our ability to progress regulatory approvals and protect our intellectual property.

In addition, if our relationships with our manufacturers, service providers, suppliers, or other vendors are terminated, materially altered, or scaled back as a result of the COVID-19 pandemic or other health epidemics, we may not be able to enter into arrangements with alternative manufacturers, service providers, suppliers, or other vendors or do so on commercially reasonable terms or in a timely or cost-effective manner. Further, delays could occur which could adversely impact our ability to meet our desired clinical development and any future commercialization timelines. The COVID-19 pandemic may also affect the operations of the FDA or other health regulatory authorities outside the U.S., which could result in delays of meetings, reviews and approvals, including with respect to our product candidates.

While the potential economic impact brought by, and the duration of, COVID-19 may be difficult to assess or predict, the widespread pandemic could result in significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity. In addition, the recent recession or market correction, which has been attributed in part to the COVID-19 pandemic, could materially affect our business and the value of our common stock.

Although we are taking steps to mitigate all of these effects, the occurrence of any of these disruptions, including of our own operations, could delay our clinical trials and development programs, and otherwise harm our operations and financial condition and increase our costs and expenses.

The extent to which the COVID-19 pandemic continues to impact our business, results of operations, and financial condition will depend on future developments, which are uncertain and cannot be predicted, including, but not limited to, the duration and spread or any future resurgence of the outbreak, its severity, the actions to contain the virus or treat its impact, and how quickly and to what extent normal economic and operating conditions can resume. Even after the COVID-19 outbreak has subsided, we may experience materially adverse impacts to our business as a result of its global human and economic impact, or as a result of our actions taken and not taken as mitigation measures during the COVID-19 pandemic.

If our information technology systems or data, or those of third parties upon which we rely, are or were compromised, we could experience adverse consequences resulting from such compromise, including but not limited to regulatory investigations or actions; litigation; fines and penalties; disruptions of our business operations; reputational harm; loss of revenue or profits; material disruption of our product development programs; and other adverse consequences.

In the ordinary course of our business, we and other third parties on which we rely collect, receive, use, process, generate, transfer, make accessible, protect, secure, dispose of, transmit, share, and store sensitive, confidential, and proprietary information, including personal information (such as health-related information and medical information), intellectual property, trade secrets, research and development information, financial information, and other business information. As a result, we and the third parties upon which we rely face a variety of evolving threats, including but not limited to ransomware attacks, which could cause security incidents.

Cyberattacks, malicious internet-based activity, online and offline fraud, and other similar activities threaten the confidentiality, integrity, and availability of our confidential, sensitive, and proprietary data and information technology systems, and those of the third parties upon which we rely. Such threats are prevalent, continue to rise, are becoming increasingly difficult to detect, and come from a variety of sources, including traditional computer "hackers," threat actors, "hacktivist," organized criminal threat actors, personnel (such as through theft or misuse), sophisticated nation-states, and nation-state-supported actors.

Some actors now engage and are expected to continue to engage in cyber-attacks, including without limitation nation-state actors for geopolitical reasons and in conjunction with military conflicts and defense activities. During times of war and other major conflicts, we and the third parties upon which we rely may be vulnerable to a heightened risk of these attacks, including retaliatory cyber-attacks, that could materially disrupt our systems and operations, supply chain, and ability to produce, sell and distribute our products and services.

Despite the implementation of security measures, our internal computer systems and data and those of third parties upon which we rely are subject to a variety of evolving threats, including but not limited to social-engineering attacks (including through phishing attacks), malicious code (such as viruses and worms), malware (including as a result of advanced persistent threat intrusions), denial-of-service attacks (such as credential stuffing), credential harvesting, personnel misconduct or error, ransomware attacks, supply-chain attacks, software bugs, server malfunctions, software or hardware failures, loss of data or other information technology assets, adware, telecommunications failures, and other similar threats.

In particular, ransomware attacks, including by organized criminal threat actors, nation-states, and nation-state supported actors, are becoming increasingly prevalent and severe and can lead to significant interruptions in our operations, disruptions of clinical trials, loss of confidential, sensitive, or proprietary data and income, reputational harm, and diversion of funds. Extortion payments may alleviate the negative impact of a ransomware attack, but we may be unwilling or unable to make such payments due to, for example, applicable laws or regulations prohibiting payments.

Remote work has become more common and has increased risks to our information technology systems and data, as more of our employees utilize network connections, computers, and devices outside our premises or network, including working at home, while in transit and in public locations. Additionally, future or past business transactions (such as acquisitions or integrations) could expose us to additional cybersecurity risks and vulnerabilities, as our systems could be negatively affected by vulnerabilities present in acquired or integrated entities' systems and technologies. Furthermore, we may discover security issues that were not found during due diligence of such acquired or integrated entities, and it may be difficult to integrate companies into our information technology environment and security program.

In addition, our reliance on third-party service providers could introduce new cybersecurity risks and vulnerabilities, including supply-chain attacks, and other threats to our business operations. We rely on third-party service providers and technologies to operate critical business systems to process confidential, sensitive, or proprietary data in a variety of contexts, including, without limitation, CROs, CMOs, collaborators, cloud-based infrastructure, data center facilities, encryption and authentication technology, employee email, content delivery to customers, and other functions. We also rely on third-party service providers to provide other products, services, parts, or otherwise to operate our business. Our ability to monitor these third parties' information security practices is limited, and these third parties may not have adequate information security measures in place. If our third-party service providers experience a security incident or other interruption, we could experience adverse consequences. While we may be entitled to damages if our third-party service providers fail to satisfy their privacy or security-related obligations to us, any award may be insufficient to cover our damages, or we may be unable to recover such award. In addition, supply-chain attacks have increased in frequency and severity, and we cannot guarantee that third parties' infrastructure in our supply chain or our third-party partners' supply chains have not been compromised.

Any of the previously identified or similar threats could cause a security incident or other interruption that could result in unauthorized, unlawful, or accidental acquisition, modification, destruction, loss, alteration, encryption, disclosure of, or access to our confidential, sensitive, or proprietary information or our information technology systems, or those of third parties upon which we rely. A security incident or other interruption could result in delays to the development and commercialization of our product candidates, disruption of our programs, negative publicity and financial loss. We may expend significant resources or modify our business activities (including our clinical trial activities) to try to protect against security incidents. Certain data privacy and security obligations may require us to implement and maintain specific security measures, industry-standard or reasonable security measures to protect our information technology systems and confidential, sensitive, or proprietary information. For example, the loss of clinical trial information 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 information.

While we have implemented security measures designed to protect against security incidents, there can be no assurance that these measures will be effective. Furthermore, because such threats and techniques change frequently, are often sophisticated in nature, and may not be detected until after a security incident has occurred, we may be unable to anticipate these techniques or implement adequate preventative measures. We may also experience security incidents that may remain undetected for an extended period. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations. Further, we may experience delays in developing and deploying remedial measures designed to address any such identified vulnerabilities.

Applicable data privacy and security obligations may require us to notify relevant stakeholders, such as governmental authorities, partners, and affected individuals, of security incidents. Such disclosures may involve inconsistent requirements and are costly, and the disclosures or the failure to comply with such requirements could lead to adverse consequences. If we (or a third party upon whom we rely) experience a security incident or are perceived to have experienced a security incident, we may experience adverse consequences. These consequences may include: government enforcement actions (for example, investigations, fines, penalties, audits, and inspections); additional reporting requirements and/or oversight; restrictions on processing confidential, sensitive, or proprietary information (including personal information); litigation (including class-action claims); indemnification obligations; negative publicity; reputational harm; monetary fund diversions; interruptions in our operations (including availability of data); financial loss; and other similar harms.

A security incident 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, delay or impede the development of our products, 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. To the extent that any disruption or security incident 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 candidates could be delayed. In addition, there can be no assurance that we will promptly detect any such disruption or security incident, if at all.

Our contracts may not contain limitations of liability, and even where they do, there can be no assurance that limitations of liability in our contracts are sufficient to protect us from liabilities, damages, or claims related to our data privacy and security obligations. We cannot be sure that our insurance coverage will be adequate or sufficient to protect us from or to mitigate liabilities arising out of our data privacy and security practices, that such coverage will continue to be available on commercially reasonable terms or at all, or that such coverage will pay future claims.

In addition to experiencing a security incident, third parties may gather, collect, or infer confidential, sensitive, or proprietary information about us from public sources, data brokers, or other means that reveals competitively sensitive details about our organization and could be used to undermine our competitive advantage or market position.

If we fail to comply with applicable state and federal healthcare laws and regulations, 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 restrict certain practices, including research and marketing, in the pharmaceutical industry. These laws include anti-kickback, false claims, and healthcare professional payment transparency 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, directly or indirectly, in cash or in kind, to induce or reward the purchasing, leasing, ordering, arranging for, or recommending the purchase, lease or order of any healthcare item or service for which payment may be made, in whole or in part, 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 may be subject to scrutiny if they do not qualify for an exception or safe harbor. Liability may be established under the federal Anti-Kickback Statute without proving actual knowledge of the statute or specific intent to violate it. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act. 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”) imposes criminal liability for 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 federal civil False Claims Act, which prohibits, among other things, individuals or entities from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment of government funds, or knowingly making, using or causing to be made or used, a false record or statement material to an obligation to pay money to the government or knowingly concealing or knowingly and improperly avoiding, decreasing or concealing an obligation to pay money to the federal 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. Pharmaceutical and other healthcare companies have faced enforcement actions under the federal civil False Claims Act for, among other things, allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product and for allegedly causing false claims to be submitted because of the companies' marketing of the product for unapproved, and thus non-reimbursable, uses. In addition, a claim can be deemed to be false due to failure to comply with legal or regulatory requirements material to the government's payment decision. False Claims Act liability is potentially significant in the healthcare industry because the statute provides for treble damages and significant mandatory penalties per false claim or statement. Pharmaceutical and other healthcare companies also are subject to other federal false claims laws, including, among others, federal criminal healthcare fraud and false statement statutes.

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, imposed new reporting requirements on drug manufacturers, under the federal Physician Payments Sunshine Act, for payments and other transfers of value made by them to physicians (defined to include doctors, dentists, optometrists, podiatrists, and chiropractors), certain other healthcare professionals (such as a physician assistants and nurse practitioners), 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 and localities also mandate implementation of commercial compliance programs, restrict the ability of manufacturers to offer co-pay support to patients for certain prescription drugs, impose restrictions on drug manufacturer marketing practices, require the tracking and reporting of gifts, compensation and other remuneration to physicians and/or require the registration of pharmaceutical sales representatives.

We will need to build and maintain a robust compliance program with different compliance and/or reporting requirements. We cannot ensure that our compliance controls, policies, and procedures will be sufficient to protect against acts of our employees, vendors, or other third parties that may violate such laws. 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, administrative, 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.

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 products or 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 $10 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 are subject to stringent and changing U.S. and foreign laws, regulations, rules, contractual obligations, policies, and other obligations related to data privacy and security. Our actual or perceived failure to comply with such obligations could lead to regulatory investigations or actions; litigation; fines and penalties; disruptions of our business operations; reputational harm; loss of revenue or profits; interruption of our clinical trials; and other adverse business consequences.

In the ordinary course of business, we collect, receive, store, process, generate, use, transfer, disclose, make accessible, protect, secure, dispose of, transmit, and share sensitive, proprietary, and confidential information, including personal information, business data, trade secrets, intellectual property, and data we collect about trial participants in connection with clinical trials. Our processing activities may subject us to numerous data privacy and security obligations, such as laws, regulations, guidance, industry standards, external and internal policies, contractual requirements, and other obligations relating to data privacy and security and that govern processing of confidential, sensitive, or proprietary data (including personal information) by us or on our behalf, including information that we collect or will collect about subjects and healthcare providers in connection with clinical trials.

In the U.S., federal, state, and local governments have enacted numerous data privacy and security laws and regulations, including those relating to data breach notification, personal information privacy, consumer protection (e.g., Section 5 of the Federal Trade Commission Act), and other similar laws (e.g., wiretapping laws). 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, as well as their covered subcontractors. We may obtain health information from third parties, such as research institutions, that are subject to privacy and security requirements under HIPAA. Although we are not directly subject to HIPAA other than with respect to providing certain employee benefits, we could potentially be subject to penalties if we, our affiliates, or our agents obtain, use, or disclose individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA.

In addition, the California Consumer Privacy Act of 2018, as amended by the California Privacy Rights Act of 2020, or the CPRA (collectively, "CCPA") applies to personal information of consumers, business representatives, and employees, and requires businesses to provide specific disclosures in privacy notices and honor requests of California residents to exercise certain rights related to their personal information. The CCPA provides for administrative fines for noncompliance (up to $7,500 per violation) and allows private litigants affected by certain data breaches to recover significant statutory damages. Although the CCPA exempts some data processed in the context of clinical trials, the CCPA may increase compliance costs and potential liability with respect to other personal information we maintain about California residents. Additionally, the CPRA’s recent amendments expand the CCPA’s requirements, including by adding a new right for individuals to correct their personal information and establishing a new regulatory agency to implement and enforce the law. Other states, such as Virginia and Colorado, have also passed comprehensive data privacy and security laws, and similar laws are being considered in several other states, as well as at the federal and local levels. These developments may further complicate compliance efforts, and increase legal risk and compliance costs for us and the third parties upon whom we rely.

Outside the U.S., an increasing number of laws, regulations, and industry standards apply to data privacy and security. For example, the EU GDPR, the United Kingdom's GDPR ("UK GDPR"), Brazil's General Data Protection Law (Lei Geral de Proteção de Dados Pessoais, or "LGPD") (Law No. 13,709/2018), and China's Personal Information Protection Law ("PIPL") impose strict requirements for processing personal information, including health-related information. For example, under the EU GDPR, companies may face temporary or definitive bans on data processing; other corrective actions; private litigation related to processing of personal information brought by classes of data subjects or consumer protection organizations authorized by law to represent their interests; and/or fines up to the greater of €20 million or 4% of annual global revenue, and separately £17.5 million or 4% of annual global revenue under the UK GDPR. EU member states are also able to legislate separately on health and genetic information, and we must comply with these local laws where we operate.

In addition, we may be unable to transfer personal information from Europe and other jurisdictions to the U.S. or other countries due to data localization requirements or limitations on cross-border data flows. Europe and other jurisdictions have enacted laws requiring data to be localized or limiting the transfer of personal information to other countries. In particular, the European Economic Area ("EEA") and the United Kingdom ("UK") have significantly restricted the transfer of personal information to the U.S. and other countries whose data privacy and security laws they believe are inadequate. Other jurisdictions may adopt similarly stringent interpretations of their data localization and cross-border data transfer laws. Although there are currently various mechanisms that may be used to transfer personal information from the EEA and UK to the U.S. in compliance with law, such as the EEA and UK's standard contractual clauses, these mechanisms are subject to legal challenges, and there is no assurance that we can satisfy or rely on these measures to lawfully transfer personal information to the U.S. If there is no lawful manner for us to transfer personal information from the EEA and the UK, or other jurisdictions to the U.S., or if the requirements for a legally-compliant transfer are too onerous, we could face significant adverse consequences, including the interruption or degradation of our operations, the need to relocate part of or all of our business or data processing activities to other jurisdictions at significant expense, increased exposure to regulatory actions, substantial fines and penalties, the inability to transfer data and work with partners, vendors and other third parties, and injunctions against our processing or transferring of personal information necessary to operate our business. Additionally, companies that transfer personal information out of the EEA and UK to other jurisdictions, particularly to the U.S., are subject to increased scrutiny from regulators, individual litigants, and activities groups. Some European regulators have ordered certain companies to suspend or permanently cease certain transfers of personal information out of Europe for allegedly violating the GDPR's cross-border data transfer limitations.

Our obligations related to data privacy and security are quickly changing, becoming increasingly stringent, and creating regulatory uncertainty. Additionally, these obligations may be subject to differing applications and interpretations, which may be inconsistent or conflict among jurisdictions. Preparing for and complying with these obligations requires significant resources and may necessitate changes to our information technologies, systems, and practices and to those of any third parties that process confidential, sensitive, or proprietary information on our behalf.

We may at times fail (or be perceived to have failed) to in our efforts to comply with our data privacy and security obligations. Moreover, despite our efforts, our personnel or third parties upon whom we rely may fail to comply with such obligations, which could negatively impact our business operations. If we or the third parties on which we rely fail, or are perceived to have failed, to address or comply with applicable data privacy and security obligations, we could face significant consequences. These consequences may include, but are not limited to, government enforcement actions (e.g., investigations, fines, penalties, audits, inspections, and similar); litigation (including class-action claims); additional reporting requirements and/or oversight; bans on processing personal information; orders to destroy or not use personal information; and imprisonment of company officials (for example, under HIPAA). Any of these events could have a material adverse effect on our reputation, business, or financial condition, including but not limited to: loss of customers; interruptions or stoppages in our business operations (including, clinical trials); inability to process personal information or to operate in certain jurisdictions; limited ability to develop or commercialize our products; expenditure of time and resources to defend any claim or inquiry; adverse publicity; or revision or restructuring of our operations.

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.

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.

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 employees, independent contractors, principal investigators, CROs, CMOs, 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, CMOs, 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 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 significant 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.

Changes in tax laws or regulations that are applied adversely to us or our customers may have a material adverse effect on our business, cash flow, financial condition, or results of operations.

Legislation enacted on December 22, 2017, known as the Tax Cuts & Jobs Act ("TCJA") enacted many significant changes to the U.S. tax laws. 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. In addition, in response to the COVID-19 pandemic, the Coronavirus Aid, Relief, and Economic Security Act ("CARES Act") was signed into law in March 2020. The CARES Act modifies certain of the changes made by the TCJA. Changes in corporate tax rates, the realization of net deferred tax assets relating to our U.S. operations, and the deductibility of expenses under the TCJA, as amended by the CARES Act, or future tax reform legislation could have a material impact on the value of our deferred tax assets, could result in significant one-time charges in the current or future taxable years, and could increase our future U.S. tax expense. The foregoing items, as well as any other future changes in tax laws, could have a material adverse effect on our business, cash flow, financial condition, or results of operations. For example, the recently enacted Inflation Reduction Act of 2022 includes provisions that will impact the U.S. federal income taxation of corporations, including imposing a minimum tax on the book income of certain large corporations and an excise tax on certain corporate stock repurchases that would be imposed on the corporation repurchasing such stock. In addition, it is uncertain if and to what extent various states will conform to the TCJA, as amended by the CARES Act, the Inflation Reduction Act, or other newly enacted federal tax legislation.

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, except as described below.

Under the TCJA, federal NOLs incurred in taxable years beginning after 2017 and in future years may be carried forward indefinitely, but the deductibility of such federal NOLs for taxable years beginning after 2022 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. 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.

As a result, the amount of the NOLs and research credit carryforwards presented in our financial statements could be limited and may expire unutilized. In addition, state suspensions of the ability to use NOLs, and research credits, may limit our ability to use our NOLs and research credits to offset state taxable income and taxes.

Risks Related to Our Common Stock

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 subjects 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 nonclinical studies to determine the best gene therapy candidates to advance in development;
- results of any clinical trials of our product candidates and the results of trials of competing product candidates or 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;
- our financial results, variations in our financial results and the adequacy of our cash runway to achieve key milestones, 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 gene therapy and to biotechnology 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;
- our ability to maintain our Nasdaq listing;
- sales of our stock by insiders and stockholders;
- trading volume of our common stock;
- the continuing effects of the COVID-19 pandemic;
- 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.

If we sell shares of our common stock or securities convertible into or exercisable for shares of our common stock in future financings, pursuant to licensing, collaboration or other arrangements, 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, debt and other 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. 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 have identified a material weakness in our internal control over financial reporting. If we fail to remediate this material weakness or if we discover or develop additional material weaknesses or otherwise fail to establish and maintain effective control over financial reporting, our ability to accurately and timely report our financial results could be adversely affected and our financial statements may need to be restated.

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. During the year ended December 31, 2022, we identified a deficiency in the operating effectiveness of controls in our financial statement close process that we considered to be a material weakness. An immaterial non-cash lease accounting error was identified in previously issued financial statements. While the identified error was not material, we considered the magnitude of the potential errors that could arise from the operating deficiency as potentially material. As a result, we are unable to assert that our internal control over financial reporting is effective as of December 31, 2022. For so long as we are unable to assert that our internal control over financial reporting is effective, or when required in the future, if our independent registered public accounting firm is unable to express an unqualified opinion as to the effectiveness of our internal control over financial reporting, investors may lose confidence in the accuracy and completeness of our financial reports, the market price of our common stock could be adversely affected and we could become subject to litigation or investigations by the stock exchange on which our securities are listed, the SEC or other regulatory authorities, which could require additional financial and management resources.

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 we contributed $1.0 million 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 detract 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, which may include:

- variations in the level of expenses related to our clinical trial and development programs;
- addition, termination or modification of 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;
- the nature and terms of stock-based compensation grants; and
- derivative instruments recorded at fair value.

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

Our certificate of incorporation and bylaws provide that the Court of Chancery of the State of Delaware and the federal district courts of the United States of America. will be the exclusive forums for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers, or employees.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for the following types of actions or proceedings under Delaware statutory or common law:

- any derivative action or proceeding brought on our behalf;
- any action asserting a breach of fiduciary duty;
- any action asserting a claim against us arising under the Delaware General Corporation Law; and
- any action asserting a claim against us that is governed by the internal-affairs doctrine.

This provision would not apply to suits brought to enforce a duty or liability created by the Securities Exchange Act of 1934, as amended. Furthermore, Section 22 of the Securities Act creates concurrent jurisdiction for federal and state courts over all such Securities Act actions. Accordingly, both state and federal courts have jurisdiction to entertain such claims.

To prevent having to litigate claims in multiple jurisdictions and the threat of inconsistent or contrary rulings by different courts, among other considerations, our amended and restated bylaws provide that the federal district courts of the United States of America will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act. While the Delaware courts have determined that such choice of forum provisions are facially valid, a stockholder may nevertheless seek to bring a claim in a venue other than those designated in the exclusive forum provisions. In such instance, we would expect to vigorously assert the validity and enforceability of the exclusive forum provisions of our certificate of incorporation and bylaws. This may require significant additional costs associated with resolving such action in other jurisdictions and there can be no assurance that the provisions will be enforced by a court in those other jurisdictions.

These exclusive forum provisions may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers, or other employees, which may discourage lawsuits against us and our directors, officers and other employees. If a court were to find either exclusive-forum provision in our certificate of incorporation or bylaws to be inapplicable or unenforceable in an action, we may incur further significant additional costs associated with resolving the dispute in other jurisdictions, all of which could seriously harm our business.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

Our corporate headquarters are located in Redwood City, California, consisting of approximately 120,000 square feet of office, laboratory, and process development space under a lease that will expire in December 2031, which space is currently not fully utilized. Accordingly, on March 24, 2023, we entered into an amendment to the lease pursuant to which we are relinquishing approximately one third of the space back to the landlord effective on September 30, 2023.

In addition, we lease a manufacturing facility in North Carolina, consisting of approximately 173,820 square feet, which facility is subleased through the lease term of October 2037.

We believe that our properties are adequate and suitable for our current needs; however, we are continuing to evaluate our real estate strategy in response to the changing needs of our in-office, hybrid and remote workforce.

Item 3. Legal Proceedings

On November 22, 2022, Lyudmila Pazyuk ("Plaintiff") filed a derivative complaint (Pazyuk v. Machado et al. C.A. No. 2022-1062-MTZ) in the Delaware Court of Chancery (the "Complaint") on behalf of Adverum against Adverum's nine current directors and four former directors (the "Individual Defendants"). The Complaint asserts five counts (breach of fiduciary duty, unjust enrichment, aiding and abetting breaches of fiduciary duty, waste of corporate assets and breach of fiduciary duty of disclosure) against each of the Individual Defendants related to Adverum's non-employee director compensation. Plaintiff seeks unspecified damages, restitution and that Adverum make changes to its corporate governance practices surrounding non-employee director compensation. Adverum and the Individual Defendants filed a motion to dismiss the Complaint on February 24, 2023. The motion is pending.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

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

Holders of Record

As of March 17, 2023, we had approximately 17 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

None

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

Item 6. [Reserved]

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."

Financial Overview

Summary

We have not generated positive cash flow or net income from operations since our inception and, as of December 31, 2022, we had an accumulated deficit of $802.6 million. We expect to incur substantial expenses and continuing losses from operations in the foreseeable future as we conduct our research and development efforts, advance our product candidates through nonclinical 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 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 will need substantial additional funding in the future to support our operating activities as we advance our product candidates through nonclinical 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, 2022, we had $185.6 million in cash, cash equivalents and short-term investments. We believe that our cash, cash equivalents and short-term investments are sufficient to fund operations into 2025. However, we may need to raise additional funds sooner as a result of a number of risks and uncertainties, including those set forth in Item 1A. Risk Factors – "We expect that our cash, cash equivalents, and short-term investments will be sufficient to fund our lead gene therapy programs into 2025. If this expectation proves to be wrong, we may be forced to delay, limit or terminate certain of our development efforts before then."

Revenue

To date we have not generated any revenue from the sale of our products. We have generated revenue through research, collaboration and license arrangements with 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, our sales may not be sufficient to generate cash from operations, in which case we may be unable to continue our operations at planned levels and be forced to reduce our operations.

Research and Development Expenses

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

We expense research and development costs as incurred. We defer and expense advance payments for goods or services for future research and development activities as the goods are delivered or the related services are performed.

We estimate nonclinical study and clinical trial expenses based on the services performed pursuant to contracts with research institutions and CROs that conduct and manage nonclinical 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 need to 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 primarily include 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 may require increased expenses related to audit, legal and regulatory functions, as well as director and officer insurance premiums and investor relations costs.

In July 2022, we implemented a restructuring of operations, including reductions in both headcount and expenses, to prioritize our clinical development of Ixo-vec and focus our pipeline strategy on certain highly prevalent ocular diseases, which included a reduction in our workforce by approximately 37%. The restructuring was completed in the fourth quarter of 2022.

Other Income (Expense), Net

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

Critical Accounting Judgments and 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.

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 nonclinical 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, 2022 and 2021, there were no material changes from our estimates of accrued research and development expenses.

Leases

We account for leases under Accounting Standards Update ("ASU") No. 2016-02, Leases (Topic 842) effective 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. The lease liability is determined as the present value of future lease payments reduced by lease incentives, if any, 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 determine the incremental borrowing rate, we estimate our credit rating, adjust the credit rating for the nature of the collateral, and benchmark the borrowing rate against observable yields on comparable securities with a similar term. We base the right-of-use lease asset on the lease liability adjusted for any prepaid or deferred rent. We determine the lease term at the commencement date by considering whether renewal options and termination options are reasonably assured of exercise.

Rent expense for operating leases 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.

Sublease income for operating leases is classified as a reduction of rent expense in operating expenses. The difference between sublease income recorded and cash received from the subtenant accrues as a deferred rent receivable. During the year ended December 31, 2022, management reassessed the probability of collection of the deferred rent receivable from the subtenant over the remaining term of a sublease. Management assessed the collectability to be less than probable and we recognized an adjustment to eliminate the deferred rent receivable as a current period adjustment to sublease income, resulting in an increase in general and administrative expenses during the year ended December 31, 2022. The deferred rent receivable as of December 31, 2022 and 2021 was zero and $0.8 million, respectively.

Impairment of Long-Lived Assets

We evaluate the carrying value of amortizable long-lived assets, whenever events, or changes in business circumstances or the planned use of long-lived assets indicate that their carrying amounts may not be fully recoverable or that their useful lives are no longer appropriate. If these facts and circumstances exist, we assess for recovery by comparing the carrying values of long-lived assets with their future undiscounted net cash flows. If the comparison indicates that impairment exists, long-lived assets are written down to their respective fair values. For example, in 2022 we identified impairment indicators in certain laboratory equipment and tested the recoverability of the carrying amount of the asset group. The carrying amount of the asset group exceeded our anticipated undiscounted cash flows. As a result of our evaluation, we recorded an impairment charge of $2.1 million for the year ended December 31, 2022. The assets indicated as impaired were written down to the estimated fair value, which was determined using a market approach.

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") and performance stock units ("PSU"). Expense recognition of PSU and performance-based options commences when the associated performance-based criteria are determined to be probable.

We recognize the grant-date fair value of stock-based awards on a straight-line basis over the requisite service period, which is generally the vesting period of the respective awards.

The Black-Scholes valuation model requires the use of following assumptions:

Expected volatility. We base the expected volatility on our historical stock price volatility.

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.

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, 2022 and 2021 of approximately $188.1 million and $148.4 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, 2022, we had U.S. federal net operating loss ("NOL") carryforwards of approximately $418.9 million to offset future federal income. Approximately $57.3 million of NOLs expire at various years beginning with 2036. As of December 31, 2022, we also had U.S. state NOL carryforwards of approximately $239.9 million to offset future state income. U.S. state NOLs expire in various years beginning with 2037. At December 31, 2022, we also had approximately $49.0 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 June 30, 2020 ownership change, we determined that certain NOLs and research and development tax credits for both federal and state purposes are subject to the 382 limitation; however, it was determined that there should be no material impact to our ability to utilize before expiration.

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. As of December 31, 2022, the total amount of unrecognized tax benefits that would affect our effective tax rate, if recognized, is $1.0 million.

Our policy is to recognize interest and penalties related to income taxes and to uncertain tax positions as a component of income tax expense. As of December 31, 2022 and 2021, we accrued $0.3 million interest and penalties related to uncertain tax positions. There are no ongoing examinations by tax authorities at this time.

Results of Operations

Comparison of Results of Operations for the Years Ended December 31, 2022 and 2021

The following table summarizes our results of operations for the periods indicated:

	Years ended December 31,		
	2022	2021	Increase/(Decrease)
	(In thousands)		
Collaboration and license revenue	$ —	$ 7,500	$ (7,500)
Operating expenses:			
Research and development	99,277	89,181	10,096
General and administrative	57,858	64,441	(6,583)
Total operating expenses	157,135	153,622	3,513
Operating loss	(157,135)	(146,122)	(11,013)
Other income, net	2,673	582	2,091
Net loss before income taxes	(154,462)	(145,540)	(8,922)
Income tax provision	(74)	—	(74)
Net loss	$ (154,536)	$ (145,540)	$ (8,996)

Revenue

We recognized no revenue for the year ended December 31, 2022. The $7.5 million license revenue for the year ended December 31, 2021 was related to an upfront payment received in January 2021 upon execution of a license agreement with Lexeo Therapeutics, Inc.

Research and Development Expense

Research and development expense increased $10.1 million to $99.3 million for the year ended December 31, 2022 from $89.2 million for the year ended December 31, 2021. This overall increase was primarily related to a $7.7 million increase in clinical trials-related expenses primarily related to the initiation of the LUNA trial, $3.7 million in restructuring costs incurred, a $2.5 million increase in license fees, and $2.1 million in impairment of laboratory equipment, partially offset by a decrease of $2.4 million in spending on outside research and development services, a $2.4 million decrease in spending on consultants and contractors, and a $1.8 million decrease in material production and bioanalytics. Stock-based compensation expense included in research and development expenses was $7.1 million for the year ended December 31, 2022, compared to $8.9 million for the year ended December 31, 2021.

For the periods presented, our research and development activities were attributable to our wet AMD, diabetic macular edema, and earlier-stage research programs. We expect that research and development expenses will fluctuate in future periods as we focus on advancing Ixo-vec for the treatment of wet AMD.

General and Administrative Expense

General and administrative expense decreased $6.6 million to $57.9 million for the year ended December 31, 2022 from $64.4 million for the year ended December 31, 2021, primarily related to a decrease of $6.1 million in personnel-associated costs including lower salary and wage expenses and stock-based compensation expense as a result of lower headcount during 2022, and a $5.3 million decrease in professional services mainly for investor relations and legal fees in connection with our proxy contest which ended in May 2021, partially offset by a $6.0 million increase in facilities costs as we recognized a full year expense for lease that we entered into in 2021, and $1.0 million in restructuring costs incurred in the July 2022 restructuring. Stock-based compensation expense included in general and administrative expenses was $13.0 million for the year ended December 31, 2022, compared to $16.3 million for the year ended December 31, 2021.

We expect that general and administrative expenses will decrease in future periods as we streamline our operations. We anticipate decreased expenses related to the human resources, legal, and finance functions brought about by the restructuring measures.

Other Income, Net

The increase of $2.1 million in net other income for the year ended December 31, 2022 as compared to 2021 was primarily due higher average yields in investments and unrealized foreign currency gains.

Income Tax Provision

We recognized an income tax provision of $0.1 million for the year ended December 31, 2022 related to foreign operations. We recognized no income tax provision for the year ended December 31, 2021.

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, 2022, we had an accumulated deficit of $802.6 million. As of December 31, 2022, we had $185.6 million in cash, cash equivalents and short-term investments. compared to $305.2 million as of December 31, 2021. We believe that our existing cash and cash equivalents and short-term investments as of December 31, 2022 will be sufficient to fund our operations and meet our existing contractual obligations and other cash requirements into 2025. However, we may need to raise additional funds sooner as a result of a number of risks and uncertainties, including those set forth in Item 1A. Risk Factors – “We expect that our cash, cash equivalents, and short-term investments will be sufficient to fund our lead gene therapy programs into 2025. If this expectation proves to be wrong, we may be forced to delay, limit or terminate certain of our development efforts before then.”

We expect to incur substantial expenditures in the foreseeable future for the development and potential commercialization of our product candidates and ongoing internal research and development programs. At this time, we cannot reasonably estimate the nature, timing or aggregate amount of costs for our development, potential commercialization, and internal research and development programs. However, in order to complete our planned nonclinical 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 nonclinical 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;
- the emergence of competing technologies or other adverse market developments; and
- the effects of the COVID-19 pandemic on our business, results of operations, and financial condition.

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,	
	2022	**2021**
	(In thousands)	
Net cash (used in) provided by:		
Operating activities	$ (108,091)	$ (107,831)
Investing activities	141,720	78,709
Financing activities	607	2,397
Net increase (decrease) in cash, cash equivalents and restricted cash	$ 34,236	$ (26,725)

Cash Used in Operating Activities

During the year ended December 31, 2022, net cash used in operating activities was $108.1 million, primarily as a result of net loss of $154.5 million due to the continued activities developing our product candidates, partially offset by $26.6 million of non-cash charges mainly related to $20.1 million of stock-based compensation expense, $6.5 million of depreciation and amortization expenses, and a $2.1 million of impairment of long-lived assets, and $19.9 million of net increase in cash from changes in operating assets and liabilities, resulting primarily from $17.6 million in changes of lease liabilities and right-of-use and $2.2 million due to timing of expenses and payments.

During the year ended December 31, 2021, net cash used in operating activities was $107.8 million, primarily as a result of net loss of $145.5 million due to the continued activities developing our product candidates, partially offset by $33.6 million of non-cash charges mainly related to $25.2 million of stock-based compensation expense, $4.6 million of depreciation and amortization expenses, $2.8 million of amortization of premium on marketable securities, and $1.1 million of impairment of long-lived assets, and $4.1 million of net increase in cash from changes in operating assets and liabilities, which fluctuate due to timing of expenses and payments.

Cash Provided by Investing Activities

Net cash provided by investing activities for the year ended December 31, 2022 consisted of $153.5 million of net maturities of marketable securities, partially offset by $11.8 million of purchases of property and equipment primarily related to the new facilities.

Net cash provided by investing activities for the year ended December 31, 2021 consisted of $93.8 million of net maturities and sales of marketable securities, partially offset by $15.1 million of purchases of property and equipment primarily related to the new facilities.

Cash Provided by Financing Activities

Net cash provided by financing activities for the year ended December 31, 2022 consisted of $0.6 million in proceeds from employee stock purchase plan.

Net cash provided by financing activities for the year ended December 31, 2021 consisted of $1.7 million of net proceeds from the sale of our common stock, and $0.9 million in proceeds from employee stock purchase plan, partially offset by $0.2 million repayment of loans.

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, 2022 AND 2021

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REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Stockholders and Board of Directors of 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, 2022 and 2021, 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, 2022 and 2021, and the results of its operations and its cash flows for the years then ended, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

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

Our audits included performing procedures to assess the risks of material misstatement of the 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.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Accrued research and development expenses – clinical and manufacturing costs

Description of the Matter

The Company recorded research and development expenses of $99.3 million for the year ended December 31, 2022. As described in Note 2, research and development costs are expensed as incurred. Research and development costs include fees paid to contract research organizations that conduct certain research and development activities on the Company's behalf and contract manufacturing organizations in connection with the production of materials for clinical trials.

Auditing the Company's research and development expenses for contract research organizations and contract manufacturing organizations and related accruals was challenging due to the complex nature of evaluating the completeness and accuracy of the expenses and accruals. Research and development expenses are recognized as the services are being performed by the vendors, which requires management to accurately monitor the activity at the vendors to determine the extent of unbilled services performed during the reporting period.

How We Addressed the Matter in Our Audit	To test the completeness and accuracy of the contract research organization and contract manufacturing organization expenses and related accruals, our audit procedures included, among others, confirming with a sample of vendors the progress of activities under research and development contracts at period end, testing a sample of cash disbursements after period end to assess the completeness of the expense recognition, and testing a sample of research and development expenses recorded during the period and evaluating the timing, amount and project coding of the expense recognition.

/s/ Ernst & Young LLP

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

San Jose, California
March 30, 2023

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

	As of December 31,	
	2022	2021
Assets		
Current assets:		
Cash and cash equivalents	$ 68,431	$ 34,195
Short-term investments	117,158	270,993
Lease incentive receivable	—	5,709
Prepaid expenses and other current assets	5,006	6,248
Total current assets	190,595	317,145
Operating lease right-of-use assets	78,934	86,000
Property and equipment, net	34,927	33,060
Restricted cash	2,503	2,503
Deferred rent receivable	—	769
Deposit and other non-current assets	1,413	250
Total assets	$ 308,372	$ 439,727
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 2,238	$ 1,387
Accrued expenses and other current liabilities	16,767	18,047
Lease liability, current portion	13,241	1,886
Total current liabilities	32,246	21,320
Long-term liabilities:		
Lease liability, net of current portion	93,561	101,108
Other non-current liabilities	1,047	1,114
Total liabilities	126,854	123,542
Commitments and contingencies (Note 7)		
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, 2022: 100,117 and 98,381 shares issued and outstanding at December 31, 2022 and 2021, respectively	10	10
Additional paid-in capital	985,651	964,965
Accumulated other comprehensive loss	(1,531)	(714)
Accumulated deficit	(802,612)	(648,076)
Total stockholders' equity	181,518	316,185
Total liabilities and stockholders' equity	$ 308,372	$ 439,727

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,	
	2022	2021
Collaboration and license revenue	$ —	$ 7,500
Operating expenses:		
Research and development	99,277	89,181
General and administrative	57,858	64,441
Total operating expenses	157,135	153,622
Operating loss	(157,135)	(146,122)
Other income, net	2,673	582
Net loss before income taxes	(154,462)	(145,540)
Income tax provision	(74)	—
Net loss	$ (154,536)	$ (145,540)
Other comprehensive loss:		
Net unrealized loss on marketable securities	(788)	(428)
Foreign currency translation adjustment	(29)	(25)
Comprehensive loss	$ (155,353)	$ (145,993)
Net loss per share - basic and diluted	$ (1.56)	$ (1.48)
Weighted-average common shares outstanding - basic and diluted	99,251	98,039

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 Loss	Accumulated Deficit	Total Stockholders Equity
	Shares	Amount				
Balance at December 31, 2020	**97,549**	**$ 10**	**$ 937,134**	**$ (261)**	**$ (502,536)**	**$ 434,347**
Issuance of common stock, net of issuance costs of $9	121	—	1,685	—	—	1,685
Stock-based compensation expense	—	—	25,194	—	—	25,194
Common stock issued upon exercise of stock options	9	—	51	—	—	51
Common stock issued under employee stock purchase plan	397	—	901	—	—	901
Common stock issued upon release of restricted stock units	305	—	—	—	—	—
Net unrealized loss on marketable securities	—	—	—	(428)	—	(428)
Foreign currency translation adjustments	—	—	—	(25)	—	(25)
Net loss	—	—	—	—	(145,540)	(145,540)
Balance at December 31, 2021	**98,381**	**10**	**964,965**	**(714)**	**(648,076)**	**316,185**
Stock-based compensation expense	—	—	20,079	—	—	20,079
Common stock issued upon exercise of stock options	15	—	3	—	—	3
Common stock issued under employee stock purchase plan	886	—	604	—	—	604
Common stock issued upon release of restricted stock units	835	—	—	—	—	—
Net unrealized loss on marketable securities	—	—	—	(788)	—	(788)
Foreign currency translation adjustments	—	—	—	(29)	—	(29)
Net loss	—	—	—	—	(154,536)	(154,536)
Balance at December 31, 2022	**100,117**	**$ 10**	**$ 985,651**	**$ (1,531)**	**$ (802,612)**	**$ 181,518**

See accompanying notes to consolidated financial statements.

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

	Years ended December 31,	
	2022	2021
Cash flows from operating activities:		
Net loss	$ (154,536)	$ (145,540)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	6,528	4,645
Stock-based compensation expense	20,079	25,194
Net (accretion) amortization of (discount) premium on marketable securities, net	(880)	2,770
Loss on disposal of property and equipment	122	—
Impairment of long-lived assets	2,124	1,063
Other	(1,417)	(25)
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	1,653	(2,257)
Deposit and other long-term assets and deferred rent receivable	(394)	(990)
Operating lease right-of-use assets	4,040	2,719
Accounts payable	845	(1,612)
Accrued expenses, other current and non-current liabilities	64	3,274
Other non-current liabilities	74	—
Lease liability	13,607	2,928
Net cash used in operating activities	(108,091)	(107,831)
Cash flows from investing activities:		
Purchases of marketable securities	(104,363)	(407,514)
Maturities of marketable securities	257,899	492,356
Sales of marketable securities	—	8,990
Purchases of property and equipment	(11,816)	(15,123)
Net cash provided by investing activities	141,720	78,709
Cash flows from financing activities:		
Proceeds from offering of common stock, net of issuance costs	—	1,685
Proceeds from issuance of common stock pursuant to option exercises	3	51
Proceeds from employee stock purchase plan	604	901
Repayment of BPI loan	—	(240)
Net cash provided by financing activities	607	2,397
Net increase (decrease) in cash, cash equivalents and restricted cash	34,236	(26,725)
Cash, cash equivalents and restricted cash at beginning of period	36,698	63,423
Cash, cash equivalents and restricted cash at end of period	$ 70,934	$ 36,698
Cash and cash equivalents	$ 68,431	$ 34,195
Restricted cash	2,503	2,503
Cash, cash equivalents and restricted cash at end of period	$ 70,934	$ 36,698
Supplemental schedule of noncash investing information		
Right-of-use assets obtained in exchange for lease liability	$ —	$ 84,005
Decrease in right-of-use asset and lease liability due to termination	$ —	$ 15,768
Remeasurement of right-of-use asset on lease modification	$ 2,842	$ 2,052
Fixed assets in accounts payable and current liabilities	$ 64	$ 1,402

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 aims to establish gene therapy as a new standard of care for highly prevalent ocular diseases. The Company develops gene therapy product candidates intended to provide durable efficacy by inducing sustained expression of a therapeutic protein.

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 $802.6 million as of December 31, 2022. The Company expects to incur losses and have negative net cash flows from operating activities as it engages in further research and development activities. As of December 31, 2022, the Company had cash, cash equivalents and short-term investments of $185.6 million, which the Company believes will be sufficient to fund its operations into 2025.

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 intercompany 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—Assets and liabilities of non-U.S. subsidiaries that operate in a local currency environment, where the local currency is the functional currency, are translated to U.S. dollars at exchange rates in effect at the balance sheet date, with the resulting translation adjustments directly recorded to a separate component of accumulated other comprehensive loss. Upon sale or upon complete or substantially complete liquidation of an investment in a foreign entity, the amount attributable to that entity and accumulated in the translation adjustment component of equity is removed from the separate component of equity and reported as part of the gain or loss on sale or liquidation of the investment for the period during which the sale or liquidation occurs. Income and expense accounts are translated at average exchange rates for the period. Transactions which are not in the functional currency of the entity are remeasured into the functional currency and gains or losses resulting from the remeasurement recorded in other income (expense).

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 in debt securities 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 consist 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 securities having specified credit ratings. 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: the 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 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 growth.

As of December 31, 2022, the Company held cash deposits at Silicon Valley Bank ("SVB") in excess of government insured limits. On March 10, 2023, SVB was closed by the California Department of Financial Protection and Innovation, and the Federal Deposit Insurance Corporation ("FDIC") was appointed as receiver. On March 12, 2023, the U.S. Treasury Department, the Federal Reserve and the FDIC jointly announced enabling actions that fully protect all SVB depositors' insured and uninsured deposits, and that such depositors would have access to all of their funds starting March 13, 2023. On March 13, 2023, the Company was able to access its deposits with SVB. As such, no losses have been incurred by the Company on deposits that were held at SVB. Management believes that the Company is not currently exposed to significant credit risk as the Company's investments are held in custody at a third-party financial institution. Subsequent to March 13, 2023, the Company transferred most of the cash in SVB to a third-party financial institution. As of March 24, 2023, the Company has a remaining $2.5 million deposit with SVB, which secures a letter of credit on a lease.

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. The Company recorded within research and development expense in the consolidated statements of operations and comprehensive loss an impairment charge of $2.1 million as result of an impairment analysis (see Note 6) for the year ended December 31, 2022.

Leases — For long-term operating leases, the Company recognizes a right-of-use asset and a lease liability on the Company's consolidated balance sheets. The lease liability is determined as the present value of future lease payments reduced by lease incentives, if any, using an estimated rate of interest that it would pay to borrow equivalent funds on a collateralized basis at the lease commencement date. In order to determine the incremental borrowing rate, the Company estimates its credit rating, adjusts the credit rating for the nature of the collateral, and benchmarks the borrowing rate against observable yields on comparable securities with a similar term. It bases the right-of-use lease asset on the lease liability adjusted for any prepaid or deferred rent. The Company determines the lease term at the commencement date by considering whether renewal options and termination options are reasonably assured of exercise.

Rent expense for operating leases 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. The variable lease payments primarily consist of common area maintenance and other operating costs.

Sublease income for operating leases is classified as a reduction of rent expense in operating expenses. The difference between sublease income recorded and cash received from the subtenant accrues as a deferred rent receivable. During the year ended December 31, 2022, the Company reassessed the probability of collection of the deferred rent receivable from the subtenant over the remaining term of a sublease. The Company assessed the collectability to be less than probable and recognized an adjustment to eliminate the deferred rent receivable as a current period adjustment to sublease income, resulting in an increase in general and administrative expenses during the year ended December 31, 2022. As a result of the adjustment to eliminate the deferred rent receivable, sublease income for the year ended December 31, 2022 was a negative $0.3 million. The deferred rent receivable as of December 31, 2022 and 2021 was zero and $0.8 million, respectively.

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.

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 research and clinical trial expenses based on the services performed pursuant to contracts with research institutions and clinical research organizations that conduct and manage nonclinical 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 adjusts the accrual accordingly.

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 employee stock purchase and using intrinsic value, which is the closing price of its common stock on the date of the grant, for restricted stock units ("RSUs") and performance stock units ("PSUs"). Expense recognition of PSU and performance-based options commences when the associated performance-based criteria are determined to be probable.

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 based on the Company's historical stock price 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, 2022 and 2021, 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 loss. Other comprehensive loss consists of foreign currency translation adjustments and unrealized loss on marketable securities.

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, RSUs, and employee stock purchase plan ("ESPP") 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.

Recent Accounting Pronouncements

In June 2016, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") 2016-13, Financial Instruments – Credit Losses: Measurement of Credit Losses on Financial Instruments ("Topic 326") and also issued subsequent amendments to the initial guidance: ASU 2018-19, ASU 2019-04, ASU 2019-05, and ASU 2019-11. The standard requires that financial assets measured at amortized cost be presented at the net amount expected to be collected. The measurement of expected credit losses is based on historical experience, current conditions, and reasonable and supportable forecasts that affect collectability. Topic 326 also eliminates the concept of "other-than-temporary" impairment when evaluating available-for-sale debt securities and instead focuses on determining whether any impairment is a result of a credit loss or other factors. An entity will recognize an allowance for credit losses on available-for-sale debt securities rather than an other-than-temporary impairment that reduces the cost basis of the investment. The Company adopted Topic 326 on January 1, 2023, which had no material impact on the Company's financial statements and related disclosures.

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 bonds 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.

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

	December 31, 2022			
	Amortized Cost Basis	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Level 1				
Money market funds	$ 10,235	$ —	$ —	$ 10,235
Level 2				
U.S. government and agency securities	59,487	—	(824)	58,663
Commercial paper	102,722	—	(246)	102,476
Corporate bonds	2,059	—	(35)	2,024
Total cash equivalents and short-term investments	174,503	—	(1,105)	173,398
Less: Cash equivalents	(56,256)	—	16	(56,240)
Total short-term investments	$ 118,247	$ —	$ (1,089)	$ 117,158

	December 31, 2021			
	Amortized Cost Basis	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Level 1				
Money market funds	$ 10,311	$ —	$ —	$ 10,311
Level 2				
U.S. government and agency securities	62,268	—	(218)	62,050
Commercial paper	177,215	1	(61)	177,155
Corporate bonds	47,323	—	(39)	47,284
Total cash equivalents and short-term investments	297,117	1	(318)	296,800
Less: Cash equivalents	(25,808)	—	1	(25,807)
Total short-term investments	$ 271,309	$ 1	$ (317)	$ 270,993

As the Company may sell these securities at any time for use in current operations even if the securities have not yet reached maturity, all marketable securities are classified as current assets in the Company's consolidated balance sheet. Management regularly reviews all of the Company's investments for other-than-temporary declines in estimated fair value. The aggregate fair value of the marketable securities in an unrealized loss position as of December 31, 2022 was $155.5 million, which are highly liquid securities with high credit ratings that have final maturity of less than two years from date of purchase. Management determined that the gross unrealized losses on the Company's marketable securities as of December 31, 2022 were temporary in nature and none were in continuous loss position for 12 months or more. Management concluded that none of the Company's marketable securities were other-than-temporarily impaired as of December 31, 2022.

As of December 31, 2022, $5.0 million of marketable securities had remaining maturities between one and two years. The remainder of the marketable securities have a remaining maturity of one year or less.

During the year ended December 31, 2022, the Company performed an impairment test to measure certain laboratory equipment at fair value. The assets are measured at fair value using Level 3 inputs on a non-recurring basis as a result of the occurrence of certain triggering events indicating the carrying value of the assets may not be recoverable. See Note 6, Balance Sheet Components for additional information.

4. Revenue

Lexeo — On January 25, 2021, the Company and Lexeo Therapeutics, Inc ("Lexeo") entered into a License Agreement pursuant to which the Company granted Lexeo an exclusive, worldwide, royalty-bearing license to certain of the Company's intellectual property to develop, manufacture, and commercialize a gene therapy product to treat cardiomyopathy due to Friedreich's Ataxia. Upon execution of the agreement, Lexeo paid the Company a one-time, non-creditable and non-refundable upfront payment of $7.5 million.

Under the terms of the agreement, the Company is eligible to receive additional payments upon the achievement of certain milestones. Additionally, the Company will receive royalty payments on net sales subject to a cap and reductions based on patent expiry, anti-stacking, and a defined royalty floor percentage.

Under Topic 606, the initial transaction price is the $7.5 million the Company received for the license granted. As described above, the arrangement provides for additional payments to the Company when certain development and commercial milestones are achieved. Because these milestone payments are not within the control of the Company and are not considered probable of being achieved until the events occur, the Company did not include them in the transaction price. The Company recognized $7.5 million of license revenue during the year ended December 31, 2021.

5. Leases

Redwood City

As of December 31, 2022, the Company has a lease for facilities in Redwood City, which provided a total of tenant improvement allowances of $6.8 million. Related to the Redwood City lease, the Company provided the landlord with a letter of credit in the amount of $2.5 million, which is classified as restricted cash under long term assets on the Company's consolidated balance sheets. The Redwood City lease expires in December 2031, with an option to extend for a period of eight years.

On November 1, 2021, the Company entered into an amendment to terminate the lease of one of its Redwood City premises under the existing lease and paid a termination fee of $0.4 million. Concurrently, the Company entered into an agreement to sublease a portion of such premises at $0.1 million monthly base rent through June 30, 2022. For short-term leases the Company does not recognize a right-of-use asset and lease liability and recognizes the lease expense over the term of the lease on a straight-line basis.

North Carolina

On January 8, 2021, the Company entered into an operating lease agreement for a building in North Carolina ("NC Premises"). The lease commenced in April 2021 when the Company obtained control of the NC Premises, and the lease term expires in October 2037 with two options to extend the lease term for a period of five years each.

On October 26, 2021, the Company entered into a sublease agreement with a subtenant for the North Carolina property through October 2037, the remainder of the lease term. The remainder of the tenant improvement allowance under the original lease of approximately $22.7 million was transferred to the subtenant. This change in the Company's payment terms with the landlord at the time of the sublease was considered to be a lease modification and the Company remeasured the lease liability on the modification date. The base annual rental rates, payment schedules and amounts under the sublease agreement are substantially the same as the original payment terms by Adverum to the landlord.

Sublease income for operating leases is classified as a reduction of rent expense in operating expenses. The difference between sublease income recorded and cash received from the subtenant accrues as a deferred rent receivable. During the year ended December 31, 2022, management reassessed the probability of collection of the deferred rent receivable from the subtenant over the remaining term of a sublease. Management assessed the collectability to be less than probable and the Company recognized an adjustment to eliminate the deferred rent receivable as a current period adjustment to sublease income, resulting in an increase in general and administrative expenses during the year ended December 31, 2022. The deferred rent receivable as of December 31, 2022 and 2021 was zero and $0.8 million, respectively.

As of December 31, 2022, the weighted-average remaining lease term was 10.2 years for the Company's leases and the weighted-average Incremental Borrowing Rate ("IBR") was 9.9%. IBR is an estimated rate of interest used to determine present value of future lease payments in order to measure lease liability, which rate is what the Company would pay to borrow equivalent funds on a collateralized basis at the lease commencement date. In order to determine the IBR, the Company estimates its credit rating, adjusts the credit rating for the nature of the collateral, and benchmarks the borrowing rate against observable yields on comparable securities with a similar term.

On March 24, 2023, the Company entered into an agreement to terminate the lease of one of its Redwood City premises, which will be effective September 30, 2023. As of December 31, 2022, including the effect of this subsequent event, the undiscounted future non-cancellable lease payments under the lease agreements are as follows (in thousands):

December 31,	Operating Leases	Sublease Payment Receivable
2023	$ 11,484	$ 5,844
2024	11,857	6,019
2025	12,242	6,200
2026	12,639	6,385
2027	13,050	6,577
Thereafter	104,410	76,174
Total undiscounted lease payments	165,682	107,199
Less: Present value adjustments	(74,766)	
Total	$ 90,916	

Rent expense for the years ended December 31, 2022, and 2021 was $17.2 million and $12.8 million, respectively, which includes variable lease costs for utilities, parking, maintenance, and real estate taxes. Variable lease expenses for the years ended December 31, 2022 and 2021 were $2.3 million and $1.8 million, respectively. Cash paid for amounts included in the measurement of lease liabilities for the twelve months ended December 31, 2022 and 2021 was $6.0 million and $5.2 million, respectively. Sublease income was $(0.3) million and $1.2 million for the years ended December 31, 2022 and 2021, respectively, which was classified as a general and administrative expense or reduction in general and administrative expense, respectively.

6. Balance Sheet Components

Property and Equipment, Net

Property and equipment, net consists of the following:

	December 31,	
	2022	2021
	(In thousands)	
Computer equipment and software	$ 1,325	$ 1,224
Laboratory equipment	14,382	12,778
Furniture and fixtures	868	1,136
Leasehold improvements	34,336	26,701
Construction in progress	1,010	4,395
Total property and equipment	51,921	46,234
Less accumulated depreciation and amortization	(16,994)	(13,174)
Property and equipment, net	$ 34,927	$ 33,060

The Company performed an impairment analysis for certain laboratory equipment assets based on the identification of impairment indicators during the year ended December 31, 2022. The analysis determined that the fair value of the assets, which was determined using a market approach, was lower than the carrying value. As a result of the evaluation, an impairment charge of $2.1 million was recognized for the year ended December 31, 2022. The assets indicated as impaired were written down to their estimated fair value.

Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consist of the following:

	December 31,	
	2022	2021
	(In thousands)	
Compensation expense	$ 8,710	$ 9,209
Accrued professional fees	532	550
Accrued nonclinical costs	1,162	2,895
Accrued clinical and process development costs	5,692	2,058
State taxes payable	254	1,318
Other	417	2,017
Total accrued expenses and other current liabilities	$ 16,767	$ 18,047

7. Commitments and Contingencies

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, 2022, 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.

8. 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 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, 2022, a total of 37,900,792 shares of common stock were reserved for issuance and 3,202,937 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, 2020	10,432	$ 7.19	8.2	$ 31,626
Granted	8,231	7.04		
Exercised	(9)	5.86		
Cancelled/forfeited	(5,366)	10.32		
Balance at December 31, 2021	13,288	$ 5.83	6.9	$ 145
Granted	10,933	1.24		
Exercised	(15)	0.19		
Cancelled/forfeited	(4,886)	5.29		
Balance at December 31, 2022	19,320	$ 3.38	8.0	$ 29
Vested and expected to vest as of December 31, 2022	19,320	$ 5.79	8.0	$ 29
Exercisable at December 31, 2022	6,102	$ 11.03	6.4	$ 29

(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 as quoted on a national exchange.

The total intrinsic value of stock options exercised during the years ended December 31, 2022 and 2021 was $18,000 and $0.1 million, respectively.

Options granted during the year ended December 31, 2022 include 2.5 million shares of performance-based stock options with both performance and service vesting conditions.

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,	
	2022	2021	2022	2021
Expected volatility	89%	91%	77%	122%
Expected term (in years)	6.0	6.0	1.2	1.2
Expected dividend yield	—	—	—	—
Risk-free interest rate	2.6%	1.0%	3.0%	0.1%

The weighted-average fair values of options granted during the years ended December 31, 2022 and 2021 were $0.93 and $5.18, respectively.

As of December 31, 2022, there was $30.4 million of unrecognized stock-based compensation expense related to stock options that is expected to be recognized over a weighted-average period of 2.6 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	Weighted-Average Grant Date Fair Value	Weighted-Average Remaining Contractual Term (in years)
Balance at December 31, 2020	540	$ 6.41	0.8
Granted	2,585	3.90	
Vested and released	(305)	5.26	
Forfeited	(694)	5.68	
Balance at December 31, 2021	2,126	3.76	1.4
Granted	857	1.43	
Vested and released	(835)	3.41	
Forfeited	(455)	3.21	
Balance at December 31, 2022	1,693	$ 2.90	1.2

RSUs granted during the year ended December 31, 2022 include 0.4 million shares of performance stock units with both performance and service vesting conditions.

During the years ended December 31, 2022 and 2021, total fair value of RSUs vested was $2.8 million and $1.6 million, respectively. The number of RSUs vested includes shares of common stock that the Company withheld on behalf of employees or sold to cover to satisfy the minimum statutory tax withholding requirements. As of December 31, 2022, there was $1.6 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, 2022, 887,061 shares were issued under the ESPP. As of December 31, 2022, a total of 7,043,481 shares of common stock were available for future issuance under the ESPP. As of December 31, 2022, there was $0.6 million 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 the Company's stock-based compensation expense:

	Years ended December 31,	
	2022	2021
	(In thousands)	
Research and development	$ 7,108	$ 8,875
General and administrative	12,971	16,319
Total share-based compensation expense	$ 20,079	$ 25,194

During the year ended December 31, 2021, the Company recorded approximately $1.6 million of stock-based compensation expense as a result of the modification of the vesting and exercisability of stock awards associated with the departure of certain of its executives and directors.

9. 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 years ended December 31, 2022 and 2021 was $1.1 million and $1.0 million, respectively.

10. Restructuring

In July 2022, the Company implemented a restructuring of operations, including reductions in both headcount and expenses, to prioritize its clinical development of ixoberogene soroparvovec ("Ixo-vec"), formerly referred to as ADVM-022, and focus its pipeline strategy on certain highly prevalent ocular diseases.

Under the restructuring plan, the Company reduced its workforce by 75 employees (approximately 37%) as of July 6, 2022. Below is a summary of restructuring costs during the year ended December 31, 2022:

	Severance and Benefits Costs	Stock-Based Compensation	Total
		(In thousands)	
Charges	$ 4,632	$ 53	$ 4,685
Cash payments made	(4,632)	—	(4,632)
Non-cash	—	(53)	(53)
Balance at December 31, 2022	$ —	$ —	$ —

In the year ended December 31, 2022, the Company recorded $4.7 million of restructuring costs, of which $3.7 million was classified as research and development expenses and $1.0 million was classified as general and administrative expenses. The Company completed the restructuring in the fourth quarter of 2022.

11. Income Taxes

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

	Years ended December 31,	
	2022	2021
	(In thousands)	
U.S.	$ (154,002)	$ (145,375)
Foreign	(460)	(165)
Loss before income taxes	$ (154,462)	$ (145,540)

The components of the Company's income tax provision were as follows:

	Years ended December 31,	
	2022	2021
	(In thousands)	
Current:		
Foreign	$ 74	$ —
Total current tax provision	74	—
Deferred		
Foreign	—	—
Total deferred tax provision	—	—
Total income tax provision	$ 74	$ —

Income tax provision for the years ended December 31, 2022 and 2021 differed from the amounts computed by applying the statutory federal income tax rate of 21% to pretax loss as a result of the following:

	Years ended December 31,	
	2022	2021
	(In thousands)	
Federal income tax expense at statutory rate	$ (32,437)	$ (30,563)
Stock compensation	3,414	1,662
Non-deductible expenses	52	28
Research and development tax credits	(2,529)	(2,672)
Change in valuation allowance	31,542	41,324
Foreign rate differential	(46)	(9)
Impact of internal reorganization	103	(9,763)
Other	(25)	(7)
Total tax provision	$ 74	$ —

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 and liabilities:

	As of December 31,	
	2022	2021
	(In thousands)	
Deferred tax assets:		
Net operating loss carryforwards	$ 111,709	$ 105,509
Accruals, reserve and other	2,053	2,272
Tax credit carryforwards	21,439	16,838
Stock-based compensation	10,705	9,741
Property and equipment	279	—
Intangibles	1,562	1,613
Lease obligation	26,241	24,224
Capital losses	9,850	9,850
Capitalized costs	23,697	—
Total deferred tax assets before valuation allowance	207,535	170,047
Valuation allowance	(188,141)	(148,440)
Total deferred tax assets	19,394	21,607
Deferred tax liabilities:		
Right-of-use assets	(19,394)	(20,227)
Property and equipment	—	(1,380)
Total deferred tax liabilities	$ (19,394)	$ (21,607)
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, 2022 and 2021. The valuation allowance increased approximately $39.7 million and $53.8 million during the years ended December 31, 2022 and 2021, respectively.

As of December 31, 2022, the Company had U.S. federal net operating losses ("NOLs") carryforwards of approximately $418.9 million to offset any future federal income. Approximately $57.3 million of NOLs expire at various years beginning with 2036. As of December 31, 2022, the Company also had U.S. state NOL carryforwards of approximately $239.9 million to offset any future state income. U.S. state NOLs expire at various years beginning with 2037. At December 31, 2022, the Company also had approximately $49.0 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, 2022, the Company had federal research and development tax credit carryforwards of approximately $17.5 million available to reduce future tax liabilities which expire at various years beginning with 2036. As of December 31, 2022, the Company had state credit carryforwards of approximately $15.5 million available to reduce future tax liabilities which do not expire.

Effective January 1, 2022, the Tax Cuts and Jobs Act ("TCJA") eliminated the option to deduct research and development expenditures in the current year and requires taxpayers to capitalize such expenses pursuant to Internal Revenue Code Section 174. The capitalized expenses are amortized over a 5-year period for domestic expenses and a 15-year period for foreign expenses. As a result of this provision of the TCJA, deferred tax assets related to capitalized research expenses increased by $23.7 million, net of amortization on research expenses capitalized in current year.

Under Section 382 and 383 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 June 30, 2020 ownership change, we determined that certain NOLs and research and development tax credits for both federal and state purposes are subject to the 382 limitation; however, it was determined that there should be no material impact to the ability of the utilization before expiration.

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, 2017 through December 31, 2021. 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, 2022 and 2021 of approximately $24.7 million and $21.9 million, respectively. As of December 31, 2022, the total amount of unrecognized tax benefits that would affect the Company's effective tax rate, if recognized, is $1.0 million. 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,	
	2022	2021
	(In thousands)	
Unrecognized tax benefits as of the beginning of the year	$ 21,944	$ 8,677
Increase related to prior year tax provisions	274	10,656
Increase related to current year tax provisions	2,527	2,611
Unrecognized tax benefits as of the end of the year	$ 24,745	$ 21,944

The Company recognizes interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2022 and 2021, the Company accrued interest and penalties related to uncertain tax positions of $0.3 million. There are no ongoing examinations by taxing authorities at this time.

12. 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,	
	2022	2021
	(In thousands)	
Stock options	19,320	13,288
Restricted stock units	1,693	2,126
ESPP	307	148
	21,320	15,562

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 Laurent Fisher, our Chief Executive Officer and Linda Rubinstein, 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, 2022. 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. We conduct this type of evaluation 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.

During the year ended December 31, 2022, we identified a deficiency in the operating effectiveness of controls in our financial statement close process that we considered to be a material weakness. An immaterial non-cash lease accounting error was identified in previously issued financial statements. While the identified error was not material, we considered the potential magnitude of the error(s) that could arise from the operating deficiency as potentially material.

We discussed these matters with our independent registered public accounting firm and our Audit Committee. Our remediation activities are not complete and we continue to seek ways to strengthen the operation of our controls over our financial statement close process, and we may need to continue effective operation of these controls for one or more quarters before we can conclude that the material weakness has been corrected.

As a result of the existence of the material weakness, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were not effective as of December 31, 2022.

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, 2022, 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 not effective as of December 31, 2022 as a result of the material weakness described above. The results of management's assessment were reviewed with the Audit Committee.

Remediation Plan

To address our material weaknesses, we have implemented and continue to implement increased rigor to ensure controls operate with regard to material non-routine transactions. Consistent with past practice, preparation of technical accounting memos should operate for all material non-routine transactions, including modifications of existing agreements. Management will consider whether it is appropriate to engage additional outside financial reporting and technical accounting expertise to assist in the determination and analysis of potential accounting and statutory reporting impacts taking into consideration complexity of transactions and to ensure we bridge and improve the knowledge and expertise within Finance on such specific non-routine transactions.

While we believe that these efforts will improve our internal control over financial reporting, the implementation of our remediation is ongoing and will require validation and testing of the design and operating effectiveness of our internal controls over a sustained period of financial reporting cycles. The actions that we are taking are subject to ongoing senior management review, as well as audit committee oversight. We will not be able to conclude whether the steps we are taking will fully remediate the material weaknesses in our internal control over financial reporting until we have completed our remediation efforts and subsequent evaluation of their effectiveness.

Changes in Internal Control over Financial Reporting

As described under the Remediation Plan above, we have implemented increased rigor to ensure controls operated over material non-routine transactions during the quarter ended December 31, 2022. Such remediation actions were changes in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the quarter ended December 31, 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

Our corporate headquarters are located in Redwood City, California, consisting of approximately 120,000 square feet of office, laboratory, and process development space under a lease that will expire in December 2031, which space is currently not fully utilized. Accordingly, on March 24, 2023, we entered into a Third Amendment to Lease (Partial Lease Termination) (the "Third Amendment"), between us and HCP LS Redwood City, LLC (the "Landlord"), pursuant to which we are relinquishing approximately one third of the space back to the landlord effective on September 30, 2023.

In addition, on March 24, 2023, we entered into a Fourth Amendment to Lease (the "Fourth Amendment"), between us and the Landlord, pursuant to which the Landlord is providing to us additional tenant improvement allowance funds in connection with our potential construction of tenant improvements at the portion of our corporate headquarters located in Redwood City, California, that we are not relinquishing back to the landlord.

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

Not applicable

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this item 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 2023 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, 2022, under the headings "Executive Officers," "Election of Directors," "Corporate Governance," and, if applicable, "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 proposal titled, "Ratification of Selection of Independent Registered Public Accounting Firm" and is incorporated herein by reference.

PART IV

Item 15. Exhibit and 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	June 29, 2020	3.1	
4.1	Reference is made to Exhibits 3.1 through 3.2.					
4.2	Description of Common Stock	001-36579	10-K	March 1, 2021	4.2	
10.1A†	License Agreement between AAVLife and Inserm Transfert, dated as of July 4, 2014.	001-36579	10-Q	August 9, 2016	10.9	
10.1B†	Amendment No. 1 to License Agreement between AAVLife and Inserm Transfert, dated as of October 5, 2015.	001-36579	10-Q	August 9, 2016	10.10	
10.2†	Exclusive License Agreement between Avalanche Biotechnologies, Inc. and the Regents of the University of California, dated as of June 17, 2013.	001-36579	10-K	March 6, 2019	10.46	
10.3†	License Agreement between Avalanche Biotechnologies, Inc. and Virovek, Inc., dated as of October 12, 2011.	001-36579	10-K	March 6, 2019	10.47	
10.4A	Lease Agreement between Adverum Biotechnologies, Inc. and HCP LS Redwood City, LLC, dated as of June 28, 2018.	001-36579	10-Q	August 8, 2018	10.2	
10.4B	First Lease Amendment between Adverum Biotechnologies, Inc. and HCP LS Redwood City, LLC, dated as of April 19, 2021.	001-36579	10-Q	August 5, 2021	10.1	
10.4C	Second Amendment to Lease (Partial Lease Termination) between Adverum Biotechnologies, Inc. and HCP LS Redwood City, LLC, dated as of November 1, 2021.	001-36579	10-K	March 29, 2022	10.4C	
10.4D	Third Amendment to Lease (Partial Lease Termination) between Adverum Biotechnologies, Inc. and HCP LS Redwood City, LLC, dated as of March 24, 2023.					X
10.4E	Fourth Amendment to Lease between Adverum Biotechnologies, Inc. and HCP LS Redwood City, LLC, dated as of March 24, 2023.					X
10.5A	Lease Agreement between Adverum NC, LLC (a wholly owned subsidiary of the Company) and ARE-NC REGION NO. 21, LLC, dated as of January 8, 2021.	001-36579	10-Q	May 6, 2021	10.5	
10.5B	Sublease Agreement between Adverum NC, LLC and Jaguar Gene Therapy, LLC, dated as of October 26, 2021.	001-36579	10-K	March 29, 2022	10.5B	

EXHIBIT NUMBER	EXHIBIT DESCRIPTION	INCORPORATED BY REFERENCE				PROVIDED HEREWITH
		FILE NUMBER	FORM	DATE	EXHIBIT NUMBER	
10.6A(#)	2017 Inducement Plan, as amended and restated	333-253727	S-8	March 1, 2021	99.3	
10.6B(#)	Form of Stock Option Grant Notice and Option Agreement under the 2017 Inducement Plan.	333-220894	S-8	October 11, 2017	99.2	
10.6C(#)	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	
10.7(#)	Adverum Biotechnologies, Inc. 2014 Employee Stock Purchase Plan, as amended and restated.	001-36579	10-Q	August 11, 2022	10.4	
10.8A(#)	Adverum Biotechnologies, Inc. 2014 Equity Incentive Award Plan, as amended and restated.	001-36579	10-Q	August 10, 2020	10.8	
10.8B(#)	Form of Stock Option Grant Notice and Stock Option Agreement under the 2014 Equity Incentive Award Plan.	001-36579	10-K	March 6, 2018	10.14	
10.8C(#)	Form of Restricted Stock Unit Award Grant Notice and Restricted Stock Unit Award Agreement under the 2014 Equity Incentive	001-36579	10-K	March 6, 2018	10.16	
10.8D(#)	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	
10.8E(#)	Form of Performance Stock Unit Award Grant Notice and Performance Stock Unit Award Agreement under the 2014 Equity Incentive Award Plan.	001-36579	10-K	March 29, 2022	10.8E	
10.9(#)	Form of Change in Control and Severance Agreement for executive officers other than the chief executive officer.	001-36579	10-K	March 29, 2022	10.9	
10.10(#)	Form of Indemnification Agreement for directors and executive officers.	001-36579	10-Q	May 28, 2020	10.1	
10.11(#)	Non-Employee Director Compensation Policy.	001-36579	10-Q	May 6, 2021	10.7	
10.12A(#)	Employment Agreement between Adverum Biotechnologies, Inc. and Laurent Fischer, dated as of June 11, 2020.	001-36579	10-Q	August 10, 2020	10.1	
10.12B(#)	Change in Control and Severance Agreement between Adverum Biotechnologies, Inc. and Laurent Fischer, dated as of June 11, 2020.	001-36579	10-Q	August 10, 2020	10.2	
10.13(#)	Employment Agreement between Adverum Biotechnologies, Inc. and Peter Soparkar, dated as of October 11, 2019.	001-36579	10-Q	November 7, 2019	10.2	
10.14(#)	Employment Agreement between Adverum Biotechnologies, Inc. and Brigit Riley, dated as of May 21, 2021.	001-36579	10-K	March 29, 2022	10.19	
10.15(#)	Employment Agreement between Adverum Biotechnologies, Inc. and Setareh Seyedkazemi, dated as of December 3, 2021.	001-36579	10-K	March 29, 2022	10.21	
10.16(#)	Employment Agreement between Adverum Biotechnologies, Inc. and Richard Beckman, dated as of December 30, 2021.	001-36579	10-K	March 29, 2022	10.22	

EXHIBIT NUMBER	EXHIBIT DESCRIPTION	INCORPORATED BY REFERENCE				PROVIDED HEREWITH
		FILE NUMBER	FORM	DATE	EXHIBIT NUMBER	
10.17A(#)	Employment Agreement between Adverum Biotechnologies, Inc. and John Rakow, dated as of January 20, 2020.	001-36579	10-Q	August 11, 2022	10.1A	
10.17B(#)	Promotion Letter between Adverum Biotechnologies, Inc. and John Rakow, dated as of July 15, 2021.	001-36579	10-Q	August 11, 2022	10.1B	
10.17C(#)	Promotion Letter between Adverum Biotechnologies, Inc. and John Rakow, dated as of June 4, 2022.	001-36579	10-Q	August 11, 2022	10.1C	
10.18(#)	Consulting Agreement between Adverum Biotechnologies, Inc. and Nancy E. Pecota, dated as of June 29, 2022.	001-36579	10-Q	August 11, 2022	10.3	
10.19A(#)	Employment Agreement between Adverum Biotechnologies, Inc. and Rupert D'Souza, dated as of November 12, 2021.	001-36579	10-K	March 29, 2022	10.20	
10.19B(#)	Separation Agreement and General Release of Claims between Adverum Biotechnologies, Inc. and Rupert D'Souza, dated as of June 7, 2022.	001-36579	10-Q	August 11, 2022	10.2	
10.20(#)	Confidential Consulting Agreement between Adverum Biotechnologies, Inc. and FLG Partners, LLC, dated as of November 22, 2022.					X
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	Inline XBRL Instance Document.					
101.SCH	Inline XBRL Taxonomy Extension Schema Document.					
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document.					
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document.					
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document.					
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document.					

EXHIBIT NUMBER	EXHIBIT DESCRIPTION	INCORPORATED BY REFERENCE				PROVIDED HEREWITH
		FILE NUMBER	FORM	DATE	EXHIBIT NUMBER	
104	The cover page of the Company's Annual Report on Form 10-K has been formatted in Inline XBRL.					

† 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.

* This certification attached to 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 30, 2023

ADVERUM BIOTECHNOLOGIES, INC.

By: /s/ Laurent Fischer

Laurent Fischer, M.D.
President and Chief Executive Officer
(Principal Executive Officer)

By: /s/ Linda Rubinstein

Linda Rubinstein
Chief Financial Officer
(Principal Financial Officer and Principal Accounting Officer)

Power of Attorney

Each person whose individual signature appears below hereby authorizes and appoints Laurent Fischer and Linda Rubinstein, 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/ Laurent Fischer Laurent Fischer, M.D.	President and Chief Executive Officer and Director *(Principal Executive Officer)*	March 30, 2023
/s/ Linda Rubinstein Linda Rubinstein	Chief Financial Officer *(Principal Financial Officer and Principal Accounting Officer)*	March 30, 2023
/s/ Patrick Machado Patrick Machado	Chairman of the Board	March 30, 2023
/s/ Soo Hong Soo Hong	Director	March 30, 2023
/s/ Mark Lupher Mark Lupher, Ph.D.	Director	March 30, 2023
/s/ Rabia Gurses Ozden Rabia Gurses Ozden, M.D.	Director	March 30, 2023
/s/ James Scopa James Scopa	Director	March 30, 2023
/s/ Dawn Svoronos Dawn Svoronos	Director	March 30, 2023
/s/ Reed Tuckson Reed Tuckson, M.D.	Director	March 30, 2023
/s/ Scott Whitcup Scott Whitcup, M.D.	Director	March 30, 2023

Exhibit 10.4D

THIRD AMENDMENT TO LEASE
(PARTIAL LEASE TERMINATION)

This Third Amendment to Lease (Partial Lease Termination) (this "**Third Amendment**") is entered into as of the 24th day of March, 2023, by and between **HCP LS REDWOOD CITY, LLC,** a Delaware limited liability company ("**Landlord**"), and **ADVERUM BIOTECHNOLOGIES, INC.**, a Delaware corporation ("**Tenant**").

R E C I T A L S :

A. Landlord and Tenant are parties to that certain Lease dated June 28, 2018 (the "**Original Lease**"), as amended by that certain First Amendment to Lease dated April 19, 2021 (the "**First Amendment**",) and that certain Second Amendment to Lease (Partial Lease Termination) dated November 1, 2021 (the "**Second Amendment**" and together with the Original Lease and the First Amendment, the "**Lease**"), whereby Tenant leases approximately 119,642 rentable square feet of space ("**RSF**"), consisting of (i) all of the rentable area (containing 39,967 RSF) (the "**900 Premises**") in the building located at 900 Saginaw Drive, Redwood City, California (the "**900 Building**"), and (ii) all of the rentable area (containing 79,675 RSF RSF) (the "**100 Premises**") in the building located at 100 Cardinal Way, Redwood City, California (the "**100 Building**") (collectively, the "**Premises**").

B. Tenant and Landlord desire to enter into this Third Amendment in order to terminate the Lease with respect to the 900 Premises only and to release one another from their respective obligations thereunder, except as otherwise provided herein.

A G R E E M E N T :

NOW, THEREFORE, in consideration of the foregoing recitals and the conditions and the covenants hereinafter contained, and for other consideration hereinafter set forth, the receipt and sufficiency of which are hereby acknowledged, Landlord and Tenant hereby agree as follows.

1. **Capitalized Terms**. All capitalized terms when used herein shall have the same meaning as is given such terms in the Lease unless expressly superseded by the terms of this Third Amendment.

2. **Termination of the Lease of 900 Premises**. Landlord and Tenant hereby agree that conditioned upon the performance by the parties of the provisions of this Third Amendment, the Lease, with respect to the 900 Premises only, shall terminate and be of no further force or effect as of 11:59 P.M. on September 30, 2023 (the "**900 Termination Date**"). Accordingly, effective as of 11:59 P.M. Pacific Daylight Time on the 900 Termination Date, (i) the 900 Premises shall no longer be considered a part of the Premises, and Landlord and Tenant shall be

relieved of their respective obligations under the Lease with respect to the 900 Premises, except those obligations under the Lease which relate to the term of Tenant's lease of the 900 Premises prior to the 900 Termination Date and which specifically survive the expiration of the Lease (unless otherwise set forth elsewhere in this Third Amendment) (including, without limitation, Tenant's payment of reconciliation of Direct Expenses) and Landlord shall have all the rights and remedies with respect to such obligations as set forth in the Lease, and (ii) the "Premises" shall consist only of the 100 Premises, and the "Building" shall mean only the 100 Building. Nothing contained herein shall relieve Landlord or Tenant of their respective obligations with respect to the 100 Premises. In the event that Tenant retains possession of the 900 Premises or any part thereof after the 900 Termination Date, then the provisions of Article 16 of the Original Lease shall apply.

3. **Surrender of 900 Premises**. Tenant hereby agrees to vacate the 900 Premises and surrender and deliver exclusive possession of the 900 Premises to Landlord on or before the 900 Termination Date and Landlord hereby agrees to accept the 900 Premises, in its condition as of the date hereof as full satisfaction of Tenant's repair, maintenance and surrender obligations under the Lease except that the 900 Premises shall be in vacant broom clean condition, and holes patched and painted to match nearby areas. Landlord hereby acknowledges that Tenant shall not be required to remove or restore any of the alterations and improvements existing in or serving the 900 Premises as of the date of this Third Amendment (including the Pad, Pad Equipment, Rooftop Equipment, or Lines serving the 900 Premises).

4. **Letter of Credit**. Landlord and Tenant hereby acknowledge that, in accordance with the Lease, Tenant has previously delivered to Landlord an L-C in the amount of $2,502,813.54. Provided that Tenant is not in default of this Lease as of the 900 Termination Date, then in connection with the termination of the Lease with respect to the 900 Premises, the L-C shall be subject to reduction following the 900 Termination Date to a new total of $1,881,586.10. Such reduction shall be accomplished by means of an amendment to the L-C issued following the 900 Termination Date (which amendment shall be in form and content reasonably acceptable to Landlord) or a new L-C in such reduced amount (which amendment shall be in form and content reasonably acceptable to Landlord and in compliance with the terms of the Lease).

5. **Representations of Tenant**. Tenant represents and warrants to Landlord that (a) Tenant has not heretofore assigned or sublet all or any portion of its interest in the 900 Premises; (b) no other person, firm or entity has any right, title or interest in the 900 Premises through Tenant; (c) Tenant has the full right, legal power and actual authority to enter into this Third Amendment and to terminate the Lease with respect to the 900 Premises without the consent of any person, firm or entity; and (d) Tenant has the full right, legal power and actual authority to bind Tenant to the terms and conditions hereof. Tenant further represents and warrants to Landlord that as of the date hereof there are no, and as of the 900 Termination Date there shall not be any, mechanic's liens or other liens encumbering all or any portion of the 900 Premises, by virtue of any act or omission on the part of Tenant, its predecessors, contractors, agents, employees, successors or assigns. Notwithstanding the termination of the Lease with respect to the 900 Premises and the release of liability provided for herein, the representations and

warranties set forth in this Section 5 shall survive the 900 Termination Date and Tenant shall be liable to Landlord for any inaccuracy or any breach thereof.

6. **Authority**. Each of Landlord and Tenant represents and warrants to the other that it has (a) the full right, legal power and actual authority to enter into this Third Amendment and to terminate the Lease with respect to the 900 Premises without the consent of any person, firm or entity; and (b) the full right, legal power and actual authority to bind itself to the terms and conditions hereof. Landlord represents and warrants that there is no mortgage or deed of trust encumbering the 900 Premises and Landlord has the full right, legal power and actual authority to enter into this Third Amendment and to terminate the Lease with respect to the 900 Premises without the consent of any person, firm or entity.

7. **Remainder of Premises; Notice Address**. Notwithstanding anything to the contrary herein, and for the avoidance of doubt, all terms of the Lease with respect to the 100 Premises shall (i) not be affected by this Third Amendment or the termination of the Lease with respect to the 900 Premises, and (ii) shall remain in full force and effect, including but not limited to Tenant's extension rights set forth in Section 2.2. of the Original Lease and Section 3.2 of the First Amendment with respect to the 100 Premises and Tenant's right to use of any EV Spaces serving the 100 Premises pursuant to the terms of the Lease. Effective as of the 900 Termination Date, Tenant's address for Notices shall be amended to:

Adverum Biotechnologies, Inc.
100 Cardinal Way
Redwood City, California 94063
Attention: Chief Financial Officer

8. **Disposition of Personal Property**. Except for any Personal Property (defined below) that Tenant and Landlord and/or Landlord's successor tenant may agree can remain in the 900 Premises, in the event that Tenant does not remove any of its personal property, equipment and signage ("**Personal Property**") from the 900 Premises prior to the 900 Termination Date, Tenant acknowledges that Landlord shall be entitled, but shall not be obligated, to dispose of said Personal Property in any manner it deems fit, and charge the cost of such disposal to Tenant. Tenant hereby waives any rights it may have to notice under California Civil Code sections 1980 et seq. with respect to such Personal Property.

9. **Attorneys' Fees**. Should any dispute arise between the parties hereto or their legal representatives, successors and assigns concerning any provision of this Third Amendment or the rights and duties of any person in relation thereto, the party prevailing in such dispute shall be entitled, in addition to such other relief that may be granted, to recover reasonable attorneys' fees and legal costs in connection with such dispute.

10. **Governing Law**. This Third Amendment shall be governed and construed under the laws of the State of California.

11. **Counterparts; Signatures**. This Third Amendment may be executed in counterparts, each of which shall be deemed an original, but such counterparts, when taken together, shall constitute one agreement. The parties hereto consent and agree that this Third Amendment may be signed and/or transmitted by facsimile, e-mail of a .pdf document or using electronic signature technology (e.g., via DocuSign or similar electronic signature technology), and that such signed electronic record shall be valid and as effective to bind the party so signing as a paper copy bearing such party's handwritten signature. The parties further consent and agree that (1) to the extent a party signs this Third Amendment using electronic signature technology, by clicking "SIGN", such party is signing this Third Amendment electronically, and (2) the electronic signatures appearing on this Third Amendment shall be treated, for purposes of validity, enforceability and admissibility, the same as handwritten signatures.

12. **Binding Effect**. This Third Amendment shall inure to the benefit of, and shall be binding upon, the parties hereto and their respective legal representatives, successors and assigns.

13. **Time of the Essence**. Time is of the essence of this Third Amendment and the provisions contained herein.

14. **Further Assurances**. Landlord and Tenant hereby agree to execute such further documents or instruments as may be necessary or appropriate to carry out the intention of this Third Amendment.

15. **Voluntary Agreement**. The parties have read this Third Amendment and mutual release as contained herein, and on the advice of counsel they have freely and voluntarily entered into this Third Amendment.

[SIGNATURES APPEAR ON THE FOLLOWING PAGE]

IN WITNESS WHEREOF, Landlord and Tenant have executed this Third Amendment as of the day and year first above written.

"**LANDLORD**"		"**TENANT**"	
HCP LS REDWOOD CITY, LLC, a Delaware limited liability company		**ADVERUM BIOTECHNOLOGIES, INC.**, a Delaware corporation	
By:	/s/ Scott Bohn	By:	/s/ Peter Soparkar
Name:	Scott Bohn	Name:	Peter Soparkar
Its:	Chief Development Officer	Its:	Chief Operating Officer
		Reviewed by ADVM Legal: JR	

Exhibit 10.4E

FOURTH AMENDMENT TO LEASE

This Fourth Amendment to Lease (this "**Fourth Amendment**") is entered into as of the 24th day of March, 2023, by and between **HCP LS REDWOOD CITY, LLC,** a Delaware limited liability company ("**Landlord**"), and **ADVERUM BIOTECHNOLOGIES, INC.**, a Delaware corporation ("**Tenant**").

R E C I T A L S :

A. Landlord and Tenant are parties to that certain Lease dated June 28, 2018 (the "**Original Lease**"), as amended by that certain First Amendment to Lease dated April 19, 2021 (the "**First Amendment**",) and that certain Second Amendment to Lease (Partial Lease Termination) dated November 1, 2021 (the "**Second Amendment**") and that certain Third Amendment to Lease (Partial Lease Termination) dated March 24, 2023 (the "**Third Amendment**" and together with the Original Lease, the First Amendment and the Second Amendment, the "**Lease**"), whereby Tenant leases (subject to Recital B below) approximately 119,642 rentable square feet of space ("**RSF**"), consisting of (i) all of the rentable area (containing 39,967 RSF) (the "**900 Premises**") in the building located at 900 Saginaw Drive, Redwood City, California (the "**900 Building**"), and (ii) all of the rentable area (containing 79,675 RSF RSF) (the "**100 Premises**" or the "**Expansion Premises**") in the building located at 100 Cardinal Way, Redwood City, California (the "**100 Building**") (collectively, the "**Premises**").

B. Landlord and Tenant are concurrently entering into the Third Amendment in order to provide for the termination of the Lease with respect to the 900 Premises pursuant to the terms thereof.

C. Tenant and Landlord desire to enter into this Fourth Amendment in order to provide for additional tenant improvement allowance funds in connection with Tenant's ongoing construction of Tenant Improvements in the 100 Premises pursuant to the terms of the Tenant Work Letter attached to the First Amendment as **Exhibit B** (the "**First Amendment Tenant Work Letter**"), and otherwise amend the Lease pursuant to the terms hereof.

A G R E E M E N T :

NOW, THEREFORE, in consideration of the foregoing recitals and the conditions and the covenants hereinafter contained, and for other consideration hereinafter set forth, the receipt and sufficiency of which are hereby acknowledged, Landlord and Tenant hereby agree as follows.

1. **Capitalized Terms**. All capitalized terms when used herein shall have the same meaning as is given such terms in the Lease unless expressly superseded by the terms of this Fourth Amendment.

2. **Second Additional Tenant Improvement Allowance**. Pursuant to the terms of the First Amendment Tenant Work Letter, Tenant received an Expansion Premises Tenant Improvement Allowance and an Additional TI Allowance in connection with Tenant's construction of Expansion Tenant Improvements in the 100 Premises (referred to therein as the Expansion Premises). In addition to the foregoing allowances, from and after the date of this Fourth Amendment, Tenant shall have the right, by written notice to Landlord given on or before the Second Additional TI Allowance Outside Date, to cause Landlord to provide up to $2,000,000.00 (the "**Second Additional TI Allowance**") towards the payment of the costs of the Tenant Improvement Allowance Items for the 100 Premises only (referred to in the First Amendment Tenant Work Letter as the Expansion Premises) as additional Expansion Tenant Improvements, and accordingly the construction of such Expansion Tenant Improvements and corresponding disbursement of the Second Additional TI Allowance shall be pursuant to the terms of the First Amendment Tenant Work Letter, and accordingly the terms of such First Amendment Tenant Work Letter are incorporated herein by reference. In the event Tenant timely exercises its right to use all or any portion of the Second Additional TI Allowance, Tenant shall be required to pay Landlord, commencing on the first day of the calendar month following the month during which Landlord makes the first disbursement of the Second Additional TI Allowance that Tenant has elected to use (the "**Second Additional Payment Commencement Date**"), the "Second Additional TI Allowance Payment," as that term is defined below, in consideration of Landlord's provision of the Second Additional TI Allowance. The "**Second Additional TI Allowance Payment**" shall be determined as the missing component of an annuity, which annuity shall have (i) the amount of the Second Additional TI Allowance utilized by Tenant (the "**Utilized Amount**") as the present value amount, (ii) a number equal to the number of full calendar months then remaining in the Lease Term as the number of payments, (iii) a monthly interest factor equal to seventy-five one-hundredths percent (0.75%), which is equal to nine percent (9%) divided by twelve (12) months per year, and (iv) the Second Additional TI Allowance Payment as the missing component of the annuity. For the avoidance of doubt, such amounts shall not be subject to annual increase. Following the calculation of the Second Additional TI Allowance Payment, Landlord and Tenant will enter into a lease amendment to confirm the amount thereof. Provided that Tenant has timely elected to cause Landlord to provide all or any portion of the Second Additional TI Allowance, any portion of the Second Additional TI Allowance as to which Tenant has not properly requested disbursement by September 30, 2026 (as such date may be extended by one (1) day for each day of delay by Tenant in completing the Expansion Tenant Improvements due to an event that qualifies as a Landlord Caused Delay or Coronavirus Delay (as such terms are defined in the First Amendment Tenant Work Letter)) (the **"Second Additional TI Allowance Outside Date"**), shall revert to Landlord and Tenant shall have no further rights with respect thereto. For the avoidance of doubt, Tenant is not required to expend the Second Additional TI Allowance equally across the 100 Premises (or Expansion Premises). The terms of Section 2.3 of the First Amendment Tenant Work Letter shall also apply to the Second Additional TI Allowance. Landlord hereby approves DGA or CAS as the Architect and Landmark Builders, XL, Hathaway Dinwiddie, Novo Construction or Dome Construction as the Contractor. A fee payable to PMA in the amount of $1.83 per RSF of the portion of the 100 Premises (or Expansion Premises) that are subject to the construction of the Expansion Tenant Improvements paid for with the Second Additional TI Allowance (rather than the amount set forth in Section 4.1.1 of the First Amendment Tenant

Work Letter), shall be payable to Landlord from the Second Additional TI Allowance. Landlord generally approves the construction of laboratory space on the second (2nd) floor of the 100 Premises, provided that the implementation of the same remains subject to Landlord's review and approval pursuant to the terms of the Lease and the First Amendment Tenant Work Letter. In connection with the foregoing, Landlord may require removal and restoration of the Expansion Tenant Improvements that utilize the Second Additional TI Allowance only if Landlord has not agreed in Sections 2.1 or 3.2 of **Exhibit B** to the First Amendment that such Tenant Improvements do not need to be restored and provides written notice to Tenant at the time Landlord provides consent to the proposed Expansion Tenant Improvements and the same constitute "Specialty Improvements" (as hereinafter defined). As used herein, "**Specialty Improvements**" means, any alterations, additions or improvements made to the 100 Premises which are not typical alterations, additions or improvements found in the premises of tenants of similar, First Class Life Sciences Projects.

3. **Letter of Credit**. Pursuant to the terms of Section 4 of the Third Amendment, following the reduction of the L-C due to the termination of the Lease with respect to the 900 Premises, the L-C to be held by Landlord shall be in the amount of $1,881,586.10 (the "**Current L-C Amount**"). In the event Tenant exercises its right to use all or any portion of the Second Additional TI Allowance, then notwithstanding anything in the Lease to the contrary, Tenant shall be required to increase such Current L-C Amount by an amount equal to ten percent (10%) of the Utilized Amount (the "**L-C Increase Amount**"). Accordingly, within ten (10) business days of Tenant's election to utilize all or any portion of the Second Additional TI Allowance, Tenant shall provide an L-C (via delivery of a new L-C in an amount equal to the sum of the Current L-C Amount and the L-C Increase Amount or an amendment to the existing L-C increasing the L-C by the L-C Increase Amount) which shall in either event be in a form reasonably acceptable to Landlord and in conformance with the terms of the Lease. To the extent that Tenant delivers a new, replacement L-C (rather than an amendment to the existing L-C), Landlord shall return the existing L-C within ten (10) business days following receipt of such new, replacement L-C. To the extent that the total amount held by Landlord at any time as security for the Lease, as hereby amended, is less than the amount required, Tenant shall provide the difference to Landlord pursuant to the terms of the Lease. Landlord and Tenant will enter into a lease amendment to confirm the terms of this Section 3 in the event Tenant elects to utilize all or any portion of the Second Additional TI Allowance.

4. **No Mortgage**. Landlord represents and warrants that there is no mortgage or deed of trust encumbering the 100 Building.

5. **Counterparts; Signatures**. This Fourth Amendment may be executed in counterparts, each of which shall be deemed an original, but such counterparts, when taken together, shall constitute one agreement. The parties hereto consent and agree that this Fourth Amendment may be signed and/or transmitted by facsimile, e-mail of a .pdf document or using electronic signature technology (e.g., via DocuSign or similar electronic signature technology), and that such signed electronic record shall be valid and as effective to bind the party so signing as a paper copy bearing such party's handwritten signature. The parties further consent and agree that (1) to the extent a party signs this Fourth Amendment using electronic signature technology,

by clicking "SIGN", such party is signing this Fourth Amendment electronically, and (2) the electronic signatures appearing on this Fourth Amendment shall be treated, for purposes of validity, enforceability and admissibility, the same as handwritten signatures.

6. **Binding Effect**. This Fourth Amendment shall inure to the benefit of, and shall be binding upon, the parties hereto and their respective legal representatives, successors and assigns.

7. **Time of the Essence**. Time is of the essence of this Fourth Amendment and the provisions contained herein.

8. **Further Assurances**. Landlord and Tenant hereby agree to execute such further documents or instruments as may be necessary or appropriate to carry out the intention of this Fourth Amendment.

9. **Voluntary Agreement**. The parties have read this Fourth Amendment and mutual release as contained herein, and on the advice of counsel they have freely and voluntarily entered into this Fourth Amendment.

10. **No Further Modification**. Except as set forth in this Fourth Amendment, all of the terms and provisions of the Lease shall remain unmodified and in full force and effect.

[SIGNATURES APPEAR ON THE FOLLOWING PAGE]

IN WITNESS WHEREOF, Landlord and Tenant have executed this Fourth Amendment as of the day and year first above written.

"**LANDLORD**"

HCP LS REDWOOD CITY, LLC,
a Delaware limited liability company

By: /s/ Scott Bohn
Name: Scott Bohn
Its: Chief Development Officer

"**TENANT**"

ADVERUM BIOTECHNOLOGIES, INC.,
a Delaware corporation

By: /s/ Peter Soparkar
Name: Peter Soparkar
Its: Chief Operating Officer

Reviewed by ADVM Legal: JR

CONFIDENTIAL CONSULTING AGREEMENT

This Confidential Consulting Agreement (the "Agreement") is executed as of the date shown on the signature page (the "Effective Date"), by and between FLG Partners, LLC, a California limited liability company ("FLG"), and the entity identified on the signature page ("Client").

RECITALS

WHEREAS, FLG is in the business of providing certain financial services;

WHEREAS, Client wishes to retain FLG to provide and FLG wishes to provide such services to Client on the terms set forth herein;

NOW, THEREFORE, in consideration of the mutual covenants set forth herein, the parties hereto agree as follows:

1. Services.

A. Commencing on the Effective Date, FLG will perform those services (the "Services") described in one or more exhibits attached hereto. Such services shall be performed by the member or members of FLG identified in Exhibit A (collectively, the "FLG Member").

B. Client acknowledges and agrees that FLG's success in performing the Services hereunder will depend upon the participation, cooperation and support of Client's most senior management.

C. Notwithstanding anything in Exhibit A or elsewhere in this Agreement to the contrary, neither FLG nor any of its members shall serve as an employee, an appointed officer, or an elected director of Client. Consistent with the preceding: (i) Client shall not appoint FLG Member as a corporate officer in Client's corporate minutes; (ii) Client shall not elect FLG Member to its board of directors or equivalent governing body; and (iii) the FLG Member shall have no authority to sign any documents on behalf of Client, including, but not limited to, federal or state securities filings, tax filings, or representations and warranties on behalf of Client except as pursuant to a specific resolution(s) of Client's board of directors or equivalent governing body granting such authority to FLG Member as a non-employee consultant to Client.

D. The Services provided by FLG and FLG Member hereunder shall not constitute an audit, attestation, review, compilation, or any other type of financial statement reporting engagement (historical or prospective) that is subject to the rules of the California Board of Accountancy, the AICPA, or other similar state or national licensing or professional bodies. Client agrees that any such services, if required, will be performed separately by its independent public accountants or other qualified consultants.

E. During the term of this Agreement, Client shall not hire or retain the FLG Member as an employee, consultant or independent contractor except pursuant to this Agreement.

2. Compensation; Payment; Deposit; Expenses.

A. As compensation for Services rendered by FLG hereunder, Client shall pay FLG the amounts set forth in Exhibit A for Services performed by FLG hereunder (the "Fees"). The Fees shall be net of any and all taxes, withholdings, duties, customs, bank fees, social contributions or other reductions imposed by any and all authorities which are required to be withheld or collected by Client or FLG, including ad valorem, sales, gross receipts or similar taxes, but excluding US income taxes based upon FLG's or FLG Member's net taxable income.

B. Consistent with common practice in professional services, FLG reserves the right to increase the Fee set forth in Exhibit A no more frequently than on the annual anniversary of the Effective Date, and no sooner than the first anniversary of the Effective Date. Notice of any such increase will be made no less than thirty (30) days in advance of such of Fee increase.

B. As additional compensation to FLG, Client will pay FLG the incentive bonus or warrants or options, if any, set forth in Exhibit A.

C. Client shall pay FLG all amounts owed to FLG under this Agreement upon Client's receipt of invoice, with no purchase order required. Invoices should be addressed to Adverum Biotechnologies, Inc., Attn: Accounts Payable via e-mail at: invoices@adverum.coupahost.com, with a copy to Laurent Fischer via email at: lfischer@adverum.com and must include detail supporting the amounts that are billed. Upon execution of this Agreement, an authorized Purchase Order will be issued. The Purchase Order number should be included on each invoice. Any invoices more than thirty (30) days overdue will accrue a late payment fee at the rate of one and 50/100 percent (1.5%) per month. FLG shall be entitled to recover all costs and expenses (including, without limitation, attorneys' fees) incurred by it in collecting any amounts overdue under this Agreement.

D. Client hereby agrees to pay FLG a deposit as set forth on Exhibit A (the "Deposit") to be held in its entirety as security for Client's future payment obligations to FLG under this Agreement. Upon termination of this Agreement, all amounts then owing to FLG under this Agreement shall be charged against the Deposit and the balance thereof, if any, shall be refunded to Client.

E. Within ten (10) days of Client's receipt of an expense report from FLG's personnel performing Services hereunder, Client shall immediately reimburse FLG personnel directly for reasonable travel and out-of-pocket business expenses detailed in such expense report. Any required air travel, overnight accommodation and resulting per diem expenses shall be consistent with Client's travel & expense policies for Client's employed executive staff.

3. Relationship of the Parties.

A. FLG's relationship with Client will be that of an independent contractor and nothing in this Agreement shall be construed to create a partnership, joint venture, or employer-employee relationship. FLG is not the agent of Client and is not authorized to make any presentation, contract, or commitment on behalf of Client unless specifically requested or authorized to do so by Client in writing. FLG agrees that all taxes payable as a result of compensation payable to FLG hereunder shall be FLG's sole liability. FLG shall defend, indemnify and hold harmless Client, Client's officers, directors, employees and agents, and the administrators of Client's benefit plans from and against any claims, liabilities or expenses relating to such taxes or compensation.

4. Term and Termination.

A. The term of this Agreement shall be for the period set forth in Exhibit A.

B. Either party may terminate this Agreement upon thirty (30) calendar days advance written notice to the other party.

CONFIDENTIAL CONSULTING AGREEMENT

C. Either party may terminate this Agreement immediately upon a material breach of this Agreement by the other party and a failure by the other party to cure such breach within ten (10) days of written notice thereof by the non-breaching party to the breaching party.

D. FLG shall have the right to terminate this Agreement immediately without advance written notice (i) if Client is engaged in, or requests that FLG or the FLG Member undertake or ignore any illegal or unethical activity, or (ii) upon the death or disability of the FLG Member.

E. This Agreement shall be deemed terminated if during any six month period no billable hours occur, with the termination date effective on the date of the last billable hour therein.

F. If at any time during the one (1) year period following termination of this Agreement Client shall hire or retain the FLG Member as an employee, consultant or independent contractor, **AND in so doing induce, compel or cause FLG Member to leave FLG as a precondition to commencing or continuing employment or consultancy with Client**, Client shall immediately pay to FLG in readily available funds a recruiting fee equal to the annualized amount of Fees payable hereunder, which shall equal either (i) 260 multiplied by the daily rate, if this Agreement provides for Fees payable by daily rate, or (ii) 2,100 multiplied by the hourly rate, if this Agreement provides for Fees payable by hourly rate, multiplied by thirty percent (30%).

5. Disclosures

A. IRS Circular 230. To ensure compliance with requirements imposed by the IRS effective June 20, 2005, FLG hereby informs Client that any tax advice offered during the course of providing, or arising out of, the Services rendered pursuant to this Agreement, unless expressly stated otherwise, is not intended or written to be used, and cannot be used, for the purpose of: (i) avoiding tax-related penalties under the Internal Revenue Code, or (ii) promoting, marketing or recommending to another party any tax-related matter(s) said tax advice address(es).

B. Attorney-Client Privilege. Privileged communication disclosed to FLG or FLG Member may waive the privilege through no fault of FLG. FLG strongly recommends that Client consult with legal counsel before disclosing privileged information to FLG or FLG Member. Pursuant to Paragraph 6, neither FLG nor FLG Member will be responsible for damages caused through Client's waiver of privilege, whether deliberate or inadvertent, by disclosing such information to FLG or FLG Member.

6. DISCLAIMERS AND LIMITATION OF LIABILITY.

EXCEPT AS EXPRESSLY SET FORTH HEREIN, ALL SERVICES TO BE PROVIDED BY FLG AND FLG MEMBER (FOR PURPOSES OF THIS PARAGRAPH 6, COLLECTIVELY "FLG") HEREUNDER ARE PROVIDED "AS IS" WITHOUT ANY WARRANTY WHATSOEVER. CLIENT RECOGNIZES THAT THE "AS IS" CLAUSE OF THIS AGREEMENT IS AN IMPORTANT PART OF THE BASIS OF THIS AGREEMENT, WITHOUT WHICH FLG WOULD NOT HAVE AGREED TO ENTER INTO THIS AGREEMENT. FLG EXPRESSLY DISCLAIMS ALL OTHER WARRANTIES, TERMS OR CONDITIONS, WHETHER EXPRESS, IMPLIED, OR STATUTORY, REGARDING THE PROFESSIONAL SERVICES, INCLUDING ANY, WARRANTIES OF MERCHANTABILITY, TITLE, FITNESS FOR A PARTICULAR PURPOSE AND INFRINGEMENT. NO REPRESENTATION OR OTHER AFFIRMATION OF FACT REGARDING THE SERVICES PROVIDED HEREUNDER SHALL BE DEEMED A WARRANTY FOR ANY PURPOSE OR GIVE RISE TO ANY LIABILITY OF FLG WHATSOEVER.

IN NO EVENT SHALL FLG BE LIABLE FOR ANY INCIDENTAL, INDIRECT, EXEMPLARY, SPECIAL, PUNITIVE OR CONSEQUENTIAL DAMAGES, UNDER ANY CIRCUMSTANCES, INCLUDING, BUT NOT LIMITED TO: LOST PROFITS; REVENUE OR SAVINGS; WAIVER BY CLIENT, WHETHER INADVERTENT OR INTENTIONAL, OF CLIENT'S ATTORNEY-CLIENT PRIVILEGE THROUGH CLIENT'S DISCLOSURE OF LEGALLY PRIVILEGED INFORMATION TO FLG; OR THE LOSS, THEFT, TRANSMISSION OR USE, AUTHORIZED OR OTHERWISE, OF ANY DATA, EVEN IF CLIENT OR FLG HAVE BEEN ADVISED OF, KNEW, OR SHOULD HAVE KNOWN, OF THE POSSIBILITY THEREOF. NOTWITHSTANDING ANYTHING IN THIS AGREEMENT TO THE CONTRARY, FLG'S AGGREGATE CUMULATIVE LIABILITY HEREUNDER, WHETHER IN CONTRACT, TORT, NEGLIGENCE, MISREPRESENTATION, STRICT LIABILITY OR OTHERWISE, SHALL NOT EXCEED AN AMOUNT EQUAL TO THE LAST TWO (2) MONTHS OF FEES PAYABLE BY CLIENT UNDER PARAGRAPH 2(A) OF THIS AGREEMENT. CLIENT ACKNOWLEDGES THAT THE COMPENSATION PAID BY IT UNDER THIS AGREEMENT REFLECTS THE ALLOCATION OF RISK SET FORTH IN THIS AGREEMENT AND THAT FLG WOULD NOT ENTER INTO THIS AGREEMENT WITHOUT THESE LIMITATIONS ON ITS LIABILITY. THIS PARAGRAPH SHALL NOT APPLY TO EITHER PARTY WITH RESPECT TO A BREACH OF ITS CONFIDENTIALITY OBLIGATIONS.

A. As a condition for recovery of any amount by Client against FLG, Client shall give FLG written notice of the alleged basis for liability within ninety (90) days of discovering the circumstances giving rise thereto, in order that FLG will have the opportunity to investigate in a timely manner and, where possible, correct or rectify the alleged basis for liability; provided that the failure of Client to give such notice will only affect the rights of Client to the extent that FLG is actually prejudiced by such failure. Notwithstanding anything herein to the contrary, Client must assert any claim against FLG by the sooner of: (i) ninety (90) days after discovery; (ii) ninety (90) days after the termination of this Agreement; (iii) ninety (90) days after the last date on which the Services were performed; or, (iv) sixty (60) days after completion of a financial or accounting audit for the period(s) to which a claim pertains.

7. Indemnification.

A. FLG and FLG Member acting in relation to any of the affairs of Client shall, to the fullest extent permitted by law, as now or hereafter in effect, be indemnified and held harmless, and such right to indemnification shall continue to apply to FLG and FLG Member following the term of this Agreement out of the assets and profits of the Client from and against all actions, costs, charges, losses, damages, liabilities and expenses which FLG or FLG Member, or FLG's or FLG Member's heirs, executors or administrators, shall or may incur or sustain by or by reason for any act done, concurred in or omitted in or about the execution of FLG's or FLG Member's duty or services performed on behalf of Client; and Client shall advance the reasonable attorney's fees, costs and expenses incurred by FLG or FLG's Member in connection with litigation related to the foregoing on the same basis as such advancement would be available to the Client's officers and directors, PROVIDED THAT Client shall not be obligated to make payments to or on behalf of any person (i) in connection with services provided by such person outside the scope of Services contemplated by this Agreement, and not authorized or consented to by Client's CEO or Board of Directors, or (ii) in respect of any (a) gross negligence or willful misconduct of such person, or (b) negligence of such person, but only to the

extent that FLG's errors and omissions liability insurance would cover such person for such negligence without regard to Client's obligation to indemnify FLG hereunder.

B. FLG and FLG Member shall have no liability to Client relating to the performance of its duties under this Agreement except in the event of FLG's or FLG Member's gross negligence or willful misconduct.

C. FLG and FLG Member agree to waive any claim or right of action FLG or FLG Member might have whether individually or by or in the right of Client, against any director, secretary and other officers of Client and the liquidator or trustees (if any) acting in relation to any of the affairs of Client and every one of them on account of any action taken by such director, officer, liquidator or trustee or the failure of such director, officer, liquidator or trustee to take any action in the performance of his duties with or for Client; PROVIDED THAT such waiver shall not extend to any matter in respect of any gross negligence or willful misconduct which may attach to any such persons.

8. Representations and Warranties.

A. Each party represents and warrants to the other that it is authorized to enter into this Agreement and can fulfill all of its obligations hereunder.

B. FLG and FLG Member warrant that they shall perform the Services diligently, with due care, and in accordance with prevailing industry standards for comparable engagements and the requirements of this Agreement. FLG and FLG Member warrant that FLG Member has sufficient professional experience to perform the Services in a timely and competent manner.

C. Each party represents and warrants that it has and will maintain a policy or policies of insurance with reputable insurance companies providing the members, officers and directors, as the case may be, of itself with coverage for losses from wrongful acts. FLG covenants that it has an error and omissions insurance policy in place in the form provided to Client prior to or contemporaneously with the date of execution of this Agreement and will continue to maintain such policy or equivalent policy provided that such policy or equivalent policy shall be available at commercially reasonable rates.

9. Work Product License.

The parties do not anticipate that FLG or FLG Member will create any intellectual property for Client in performing the Services pursuant to this Agreement. However, FLG and FLG Member grant to Client a world-wide, perpetual, exclusive, royalty-free, irrevocable license to use and create derivative works from all tangible and electronic documents, spreadsheets, and financial models (collectively, "Work Product") produced or authored by FLG Member in the course of performing the Services pursuant to this Agreement. Any patent rights arising out of the Services will be assigned to and owned by Client and not FLG or FLG Member. All other rights, including, but not limited to, the residual memory of any methods, discoveries, developments, improvements, know-how, ideas, insights, analytical concepts and skills directly inherent to, or reasonably required for, the competent execution of FLG Member's profession as a chief financial officer are reserved in their entirety by FLG and FLG Member.

10. Miscellaneous.

A. Any notice required or permitted to be given by either party hereto under this Agreement shall be in writing and shall be personally delivered or sent by a reputable courier mail service (e.g., Federal Express) or by facsimile confirmed by reputable courier mail service, to the other party as set forth in this Paragraph 10(A). Notices will be deemed effective two (2) days after deposit with a reputable courier service or upon confirmation of receipt by the recipient from such courier service or the same day if sent by facsimile and confirmed as set forth above.

If to FLG:

U. Heather Ogan
FLG Partners, LLC
228 Hamilton Ave., 3rd Floor,
Palo Alto, CA 94301
PO BOX 192304
San Francisco, CA 94119
Tel: 707-373-0837
Fax: 415-456-1191
E-mail: accounting@flgpartners.com

If to Client: the address, telephone numbers and email address shown below Client's signature on the signature page.

B. This Agreement will be governed by and construed in accordance with the laws of California without giving effect to any choice of law principles that would require the application of the laws of a different jurisdiction.

C. Any claim, dispute, or controversy of whatever nature arising out of or relating to this Agreement (including any other agreement(s) contemplated hereunder), including, without limitation, any action or claim based on tort, contract, or statute (including any claims of breach or violation of statutory or common law protections from discrimination, harassment and hostile working environment), or concerning the interpretation, effect, termination, validity, performance and/or breach of this Agreement ("Claim"), shall be resolved by final and binding arbitration before a single arbitrator ("Arbitrator") selected from and administered by the San Francisco office of JAMS (the "Administrator") in accordance with its then existing commercial arbitration rules and procedures. The arbitration shall be held in San Francisco, California. The Arbitrator shall, within fifteen (15) calendar days after the conclusion of the Arbitration hearing, issue a written award and statement of decision describing the essential findings and conclusions on which the award is based, including the calculation of any damages awarded. The Arbitrator also shall be authorized to grant any temporary, preliminary or permanent equitable remedy or relief he or she deems just and equitable and within the scope of this Agreement, including, without limitation, an injunction or order for specific performance. Each party shall bear its own attorneys' fees, costs, and disbursements arising out of the arbitration, and shall pay an equal share of the fees and costs of the Administrator and the Arbitrator; provided, however, the Arbitrator shall be authorized to determine whether a party is the prevailing party, and if so, to award to that prevailing party reimbursement for its reasonable attorneys' fees, costs and disbursements, and/or the fees and costs of the Administrator and the Arbitrator. The Arbitrator's award may be enforced in any court of competent jurisdiction. Notwithstanding the foregoing, nothing in this Paragraph 10(C) will restrict either party from applying to any court of competent jurisdiction for injunctive relief.

D. Neither party may assign its rights or delegate its obligations hereunder, either in whole or in part, whether by operation of law or otherwise, without the prior written consent of the other party; provided, however, that FLG may assign its rights and delegate its obligations hereunder to any affiliate of FLG. The rights and liabilities of the parties under this Agreement will bind and inure to the benefit of the parties' respective successors and permitted assigns.

E. If any provision of this Agreement, or the application thereof, shall for any reason and to any extent be invalid or unenforceable, the remainder of this Agreement and application of such provision to other persons or circumstances shall be interpreted so as best to

reasonably effect the intent of the parties. The parties further agree to replace such void or unenforceable provision of this Agreement with a valid and enforceable provision that will achieve, to the extent possible, the economic, business and other purposes of the void or unenforceable provision.

F. This Agreement, the Exhibits, and any executed Non-Disclosure Agreements specified herein and thus incorporated by reference constitute the entire understanding and agreement of the parties with respect to the subject matter hereof and thereof and supersede all prior and contemporaneous agreements or understandings, express or implied, written or oral, between the parties with respect hereto. The express terms hereof control and supersede any course of performance or usage of the trade inconsistent with any of the terms hereof.

G. Any term or provision of this Agreement may be amended, and the observance of any term of this Agreement may be waived, only by a writing signed by the parties. The waiver by a party of any breach hereof for default in payment of any amount due hereunder or default in the performance hereof shall not be deemed to constitute a waiver of any other default or succeeding breach or default.

H. Upon completion of the engagement hereunder FLG may place customary "tombstone" advertisements using Client's logo and name in publications of FLG's choice at its own expense, and/or cite the engagement in similar fashion on FLG's website.

I. If Client discloses FLG Member's name on Client's website (such as in an executive biography, for example), press releases, SEC filings and other public documents and media, then Client shall include in the description of FLG Member a sentence substantially the same as "[FLG Member] is also a partner at FLG Partners, a leading CFO services firm in Silicon Valley."

J. If and to the extent that a party's performance of any of its obligations pursuant to this Agreement is prevented, hindered or delayed by fire, flood, earthquake, elements of nature or acts of God, acts of war, terrorism, riots, civil disorders, rebellions or revolutions, or any other similar cause beyond the reasonable control of such party (each, a "Force Majeure Event"), and such non-performance, hindrance or delay could not have been prevented by reasonable precautions of the non-performing party, then the non-performing, hindered or delayed party shall be excused for such non-performance, hindrance or delay, as applicable, of those obligations affected by the Force Majeure Event for as long as such Force Majeure Event continues and such party continues to use its best efforts to recommence performance whenever and to whatever extent possible without delay, including through the use of alternate sources, workaround plans or other means.

K. This Agreement may be executed in any number of counterparts and by the parties on separate counterparts, each of which when executed and delivered shall constitute an original, but all the counterparts together constitute one and the same instrument.

L. This Agreement may be executed by facsimile signatures (including electronic versions of this document in Adobe Acrobat Portable Document Format form which contain scanned or secure, digitally signed signatures) by any party hereto and such signatures shall be deemed binding for all purposes hereof, without delivery of an original signature being thereafter required.

M. Survivability. The following Paragraphs shall survive the termination of this Agreement: 6 ("Disclaimers and Limitation of Liability"); 7 ("Indemnification"); 8 ("Representations and Warranties"); 9 ("Work Product License"); and 10 ("Miscellaneous").

IN WITNESS WHEREOF, the parties hereto have executed this Agreement as of the Effective Date.

CLIENT:
Adverum Biotechnologies, Inc.,
a Delaware C corporation.
By: Peter Soparkar
Signed: /s/ Peter Soparkar
Title: COO
Address: 100 Cardinal Way
Redwood City, CA 94063

Email: psoparkar@adverum.com

FLG:
FLG Partners, LLC,
a California limited liability company.
By: U. Heather Ogan
Signed: /s/ Ugadie Heather Ogan
Title: Administrative Partner
Effective Date: November 22, 2022

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CONFIDENTIAL CONSULTING AGREEMENT

EXHIBIT A

1. Description of Services: CFO level services typical for a publicly held corporation.
2. FLG Member: Linda Rubinstein.
3. Fees: $650 per hour, subject to any hourly maximums that Client may establish from time to time.
4. Additional Compensation: None.
5. Deposit: $10,000.
6. Term: Indefinite, and terminable pursuant to Paragraph 4 of the Agreement.
7. Non-Disclosure Agreement: FLG-Client Mutual Non-Disclosure Agreement dated November 8, 2022 (the "NDA"). FLG hereby expressly consents to the public disclosure of the existence of FLG's relationship with Client, by Client, provided that the terms and conditions herein shall remain confidential pursuant to the terms of the NDA.

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Exhibit 21.1

SUBSIDIARIES OF ADVERUM BIOTECHNOLOGIES, INC.

Name of Subsidiary	Country of Incorporation
Avalanche Australia PTY LTD	Australia
Annapurna Therapeutics, LTD	Ireland
Adverum NC, LLC	North Carolina, USA

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

(1) Registration Statement (Form S-8 No. 333-199296) pertaining to the Amended and Restated 2016 Equity Incentive Plan, as amended, the 2014 Equity Incentive Award Plan and the 2014 Employee Stock Purchase Plan,

(2) Registration Statement (Form S-8 No. 333-203398) pertaining to the 2014 Equity Incentive Award Plan and the 2014 Employee Stock Purchase Plan,

(3) Registration Statement (Form S-8 No. 333-211439) pertaining to the 2014 Equity Incentive Award Plan, the 2014 Employee Stock Purchase Plan, and the Inducement Stock Option Awards,

(4) Registration Statement (Form S-8 No. 333-218465) pertaining to the 2014 Equity Incentive Award Plan, the 2014 Employee Stock Purchase Plan, and the Inducement Restricted Stock Unit and Stock Option Awards,

(5) Registration Statement (Form S-8 No. 333-220894) pertaining to the 2017 Inducement Plan and Inducement Stock Option Awards,

(6) Registration Statement (Form S-8 No. 333-223894) pertaining to the 2014 Equity Incentive Award Plan, the 2014 Employee Stock Purchase Plan, and the Inducement Restricted Stock Unit Awards,

(7) Registration Statement (Form S-8 No. 333-230138) pertaining to the 2014 Equity Incentive Award Plan, as amended and restated, the 2014 Employee Stock Purchase Plan, as amended and restated, and the 2017 Inducement Plan, as amended and restated,

(8) Registration Statement (Form S-8 No. 333-233135) pertaining to the 2017 Inducement Plan, as amended and restated,

(9) Registration Statement (Form S-8 No. 333-237136) pertaining to the 2014 Equity Incentive Award Plan, as amended and restated, and the 2014 Employee Stock Purchase Plan, as amended and restated,

(10) Registration Statement (Form S-8 No. 333-243761) pertaining to the 2017 Inducement Plan, as amended and restated,

(11) Registration Statement (Form S-8 No. 333-253727) pertaining to the 2014 Equity Incentive Award Plan, as amended and restated, the 2014 Employee Stock Purchase Plan, as amended and restated, and the 2017 Inducement Plan, as amended and restated,

(12) Registration Statement (Form S-8 No. 333-263954) pertaining to the 2014 Equity Incentive Award Plan, as amended and restated, and

(13) Registration Statement (Form S-8 No. 333-266794) pertaining to the Amended and Restated 2014 Employee Stock Purchase Plan;

of our report dated March 30, 2023, with respect to the consolidated financial statements of Adverum Biotechnologies Inc. included in this Annual Report (Form 10-K) of Adverum Biotechnologies Inc. for the year ended December 31, 2022.

/s/ Ernst & Young LLP

San Jose, California
March 30, 2023

Exhibit 31.1

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

I, Laurent Fischer, 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 30, 2023

By: /s/ Laurent Fischer

Name: Laurent Fischer, M.D.
Title: President and 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, Linda Rubinstein, 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 30, 2023

By: /s/ Linda Rubinstein

Name: Linda Rubinstein
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, 2022 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Laurent Fischer, as President and 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 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 30, 2023

By: /s/ Laurent Fischer

Laurent Fischer, M.D.
President and 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, 2022 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Linda Rubinstein, as Chief Financial Officer of Adverum Biotechnologies, Inc., hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to the best of her knowledge, the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of Adverum Biotechnologies, Inc.

Date: March 30, 2023

By: /s/ Linda Rubinstein

Linda Rubinstein
Chief Financial Officer
(Principal Financial and Accounting Officer)