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, 2024

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**	**The Nasdaq Stock Market LLC (Nasdaq Capital 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, 2024, 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 $136.7 million, based on the closing price of the registrant's common stock on the Nasdaq Capital Market on June 30, 2024 of $6.86 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 April 4, 2025, the registrant had 20,890,540 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 2025 Annual Meeting of Stockholders of the registrant are incorporated by reference into Part III of this Annual Report on Form 10-K. If the Proxy Statement is not filed by April 30, 2025, 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.

EXPLANATORY NOTE

On March 28, 2025, the Audit Committee of the Board of Directors (the "Audit Committee") of Adverum Biotechnologies, Inc. (the "Company"), following consultation with the Company's management and independent registered public accounting firm, Ernst & Young LLP, concluded that certain of the Company's previously issued financial statements should no longer be relied upon due to non-cash errors identified in the accounting for tenant improvement allowances associated with an operating lease and sublease related to a building in North Carolina (the "NC Premises").

In January 2021, the Company entered into the operating lease for the NC Premises, and in October 2021, the Company entered into the sublease agreement with Jaguar Gene Therapy, LLC, who subsequently assigned the sublease to Advanced Medicine Partners, LLC as the subtenant for the NC Premises, through the remainder of the lease term. While preparing the consolidated financial statements as of and for the year ended December 31, 2024, management discovered non-cash errors in the Company's accounting for its operating lease and sublease of the NC Premises. The errors relate solely to the Company's accounting for tenant improvement allowances provided by the landlord to the Company under its operating lease, which were subsequently conveyed from the Company to the subtenant under the sublease, and to a lesser extent, to the assessment of the probability of collection of the lease payments from the subtenant over the remaining term of the sublease. The errors affect the reported amounts of non-cash assets and liabilities, and non-cash general and administrative expenses, related to the lease and sublease (the "Misstatements").

The Misstatements relate solely to the NC Premises and require non-cash corrections to the Company's previously issued audited consolidated financial statements as of and for the years ended December 31, 2022 and 2023, included in the Company's Annual Report on Form 10-K for the year ended December 31, 2023 (the "2023 Annual Report"), as well as the unaudited condensed consolidated quarterly financial information for the quarterly periods in the years ended December 31, 2023 and 2024 (collectively the "Restated Periods"), included in the Company's Quarterly Reports on Form 10-Q for the quarterly periods within those years ("Quarterly Reports" and, together with the 2023 Annual Report, the "Affected Reports"). The Audit Committee concluded that it is appropriate to correct the Misstatements by restating the financial statements for the Restated Periods.

The previously issued financial statements included in the Affected Reports should no longer be relied upon. The Company does not intend to separately amend the Affected Reports.

Accordingly, investors and other readers should rely only on the financial statements for the Restated Periods included in this Annual Report on Form 10-K and in any other future filings with the SEC (as applicable).

Restatement of Financial Statements

This Annual Report on Form 10-K includes restated financial statements for the Restated Periods. In these restated financial statements, the Company has corrected the Misstatements, and has corrected certain other immaterial errors. For additional information, see Note 2, Restatement of Previously Issued Financial Statements and Note 14, Quarterly Financial Information (Unaudited), to the consolidated financial statements included in this Annual Report on Form 10-K.

Internal Control Considerations

In connection with the restatement, management has concluded that the Misstatements are indicative of a material weakness in the Company's internal control over financial reporting as of December 31, 2024, with respect to the operating effectiveness of the Company's controls over lease accounting. For a discussion of management's considerations of the Company's disclosure controls and procedures, internal control over financial reporting, and material weakness identified, see Part II, Item 9A of this Annual Report on Form 10-K.

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:

- our ability to mitigate the substantial doubt about our ability to continue as a going concern;
- our estimates regarding expenses, future revenue, capital requirements, uses of cash and needs for additional financing and the period for which our resources will be sufficient to meet our operational requirements;
- our ability to enter into collaborations, or other strategic arrangements, or obtain additional funding;
- 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 expectations regarding the potential market sizes for our product candidates;
- our intellectual property position;
- the potential benefits of our strategic collaborations;
- developments and projections relating to our competitors and our industry;
- the safety, efficacy and projected development timeline and commercial potential of any product candidates; and
- our ability to remediate the material weakness in our internal control over financial reporting described in Part II, Item 9A of this Annual Report on Form 10-K.

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.

- There is substantial doubt regarding our ability to continue as a going concern. We will need to raise substantial additional funding to finance our operations through regulatory approval of our lead program and beyond, which may not be available on acceptable terms, or at all. If we fail to obtain additional capital necessary to fund our operations, we could be forced to delay, limit, reduce or terminate our product development programs, commercialization efforts or other operations, or to cease operations or liquidate our assets.
- If we sell shares of our common stock or securities convertible into or exercisable for shares of our common stock in future financings, or pursuant to licensing, collaboration or other arrangements, stockholders may experience immediate dilution and, as a result, our stock price may decline.
- The report of our independent registered public accounting firm for the year ended December 31, 2024 contains an explanatory paragraph regarding substantial doubt about our ability to continue as a going concern.
- 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 are subject to risks associated with subletting our leased premises, including risks associated with subtenant defaults, which have occurred and we expect to continue to occur.
- 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.
- Changes in methods of manufacturing or formulation of our product candidates may result in additional costs or delays.
- 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, face delayed timelines, 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 ongoing and 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 product 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.
- If our information technology systems or those third parties with whom we work, or our data, 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.
- 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.
- We have identified a material weakness in our internal control over financial reporting. If we are unable to remedy the material weakness, or if we fail to maintain an effective system of internal control over financial reporting in the future, we may not be able to accurately report our financial condition, results of operations or cash flows, which may adversely affect investor confidence in us and, as a result, the value of our common stock.

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 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 is currently being developed for the treatment of patients with wet age-related macular degeneration ("wet AMD"), also known as neovascular AMD. In November 2024 we announced top-line 52 week results from the ongoing LUNA Phase 2 clinical trial. In March 2025, we initiated ARTEMIS, the first of two Phase 3 clinical trials of Ixo-vec in wet AMD. We intend to initiate AQUARIUS, the second phase 3 trial of Ixo-vec in wet AMD, in the second half of 2025. We intend to conduct ARTEMIS at U.S. sites and AQUARIUS globally. We are also developing an early-stage pipeline of gene therapy programs targeting the treatment of other highly prevalent ocular diseases. Our core capabilities include novel vector evaluation, cassette engineering, ocular IND-enabling nonclinical and clinical development, scalable process development, assay development, and current Good Manufacturing Practices ("GMP") quality control.

Ixo-vec (formerly known as ADVM-022)

Ixo-vec utilizes an engineered, proprietary capsid, AAV.7m8, which along with a proprietary expression cassette is capable of transducing retinal cells and expressing aflibercept after a single in-office IVT injection. This product candidate is intended to improve both real-world vision outcomes and quality of life for patients.

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. Up to 42% of patients with wet AMD experience neovascularization in the second eye in the first two to three years following diagnosis in the first eye.

The current standard of care for wet AMD requires frequent and lifelong anti-VEGF IVT injections. Undertreatment is associated with persistent macular fluid and resulting in loss of vision over time. Additionally, fluid fluctuations associated with bolus anti-VEGF therapy may impair vision over time even in well treated wet AMD patients. A significant proportion of patients discontinue anti-VEGF treatment within two to five years. Key unmet needs in the treatment of wet AMD include therapeutics with greater durability.

In November 2018, we initiated the OPTIC trial, designed as an open-label, dose-ranging trial evaluating the safety and efficacy 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. OPTIC was a two-year trial, which the last subject completed in June 2022, and we continue to follow subjects in the OPTIC extension trial for an additional three years, for a total of five years. Through the most recent data cut-off date of August 21, 2024, 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 maintenance to improvement in best-corrected visual acuity ("BCVA") and maintenance to improvement of central subfield thickness ("CST"), currently out to four years, and stable aflibercept protein levels through latest reported follow-up, which is currently up to five years. Following Ixo-vec treatment, OPTIC patients experienced a robust treatment burden reduction, with subjects who had received the 2E11 dose seeing an 86% reduction in annualized anti-VEGF injections through four years. Nearly 50% of patients were injection free through four years following Ixo-vec treatment. Ixo-vec has been generally well tolerated, with the most common adverse events being dose-related anterior inflammation and pigmentary changes.

In September 2022, we dosed the first subject in our LUNA Phase 2 trial of Ixo-vec. The LUNA trial is a multicenter, double-masked, randomized, parallel-group trial evaluating two doses of Ixo-vec - 2E11, the lower dose used in the OPTIC trial, and a new, lower 6 x 10^10 vg/eye dose ("6E10") dose. In addition, LUNA assesses enhanced prophylactic corticosteroid regimens, including local corticosteroids and combinations of local and systemic corticosteroids, to test the relative contribution of local versus systemic adeno-associated virus ("AAV") exposure on ocular inflammation. The endpoints are similar to the OPTIC trial and focus on mean change in BCVA and CST from baseline to one year, and incidence and severity of adverse events. LUNA enrolled 60 subjects who were randomized equally between the 2E11 and 6E10 doses. LUNA subjects were assessed for the primary and other endpoints at 52 weeks, and we will continue to follow them for an additional four years, for a total of five years. In November 2024, we announced top-line 52 week results with a data cut-off date of August 29, 2024 from the LUNA Phase 2 trial demonstrating that both the 2E11 and 6E10 doses maintained visual and anatomic outcomes. Notably, both doses resulted in favorable reductions in annualized anti-VEGF injections and percentages of subjects remaining free of injections which were consistent with results observed in the OPTIC trial. In those subjects who had completed 52 weeks of follow-up, at the 6E10 (n=28) and 2E11 (n=29) doses, Ixo-vec demonstrated reduction in annualized anti-VEGF injection rates of 88% and 92%, respectively, and injection free rates of 54% and 69%, respectively. In addition, Ixo-vec was well-tolerated, with the most common adverse events being dose-related anterior inflammation and pigmentary changes. Data demonstrated that difluprednate eye drops alone is a promising prophylactic regimen for our planned pivotal studies. Additionally, our LUNA pre-specified patient preference survey demonstrated a strong preference for Ixo-vec over prior anti-VEGF therapies and acceptability of the topical eye drops steroid regimen.

Our Phase 3 program is planned to include two registrational trials in wet AMD. We have selected the 6E10 dose and a difluprednate topical-eye-drops-only prophylactic regimen to evaluate in the Phase 3 program. In March 2025, we initiated ARTEMIS, the first of two Phase 3 clinical trials of Ixo-vec in wet AMD. We intend to initiate AQUARIUS, the second phase 3 trial of Ixo-vec in wet AMD, in the second half of 2025. We intend to conduct ARTEMIS at U.S. sites and AQUARIUS globally.

Regulatory Designations for Ixo-vec

In September 2018, we announced that the FDA had granted Ixo-vec Fast Track designation. Fast Track is a process designed to facilitate the development and expedite the review of drugs and biologics to treat serious conditions and fill unmet medical needs. In June 2022, we announced that the European Medicines Agency ("EMA") had granted Ixo-vec Priority Medicines ("PRIME") designation. PRIME is a voluntary scheme aimed at enhancing the EMA's support for the development of medicinal products that target unmet medical needs. Eligible products must target conditions for which there is an unmet medical need (there is no satisfactory method of diagnosis, prevention or treatment in the EU or, if there is, the new medicinal product will bring a major therapeutic advantage) and they must demonstrate the potential to address the unmet medical need by introducing new methods of therapy or improving existing ones. In April 2023, we announced that the Medicines and Healthcare products Regulatory Agency ("MHRA") had granted Ixo-vec an Innovation Passport under the Innovative Licensing and Access Pathway ("ILAP"). The Innovation Passport is the first step in the ILAP process, triggering the MHRA and its partner agencies to partner with Adverum to charter a roadmap for regulatory and development milestones with the goal of early patient access in the United Kingdom ("UK"). Additionally, in August 2024, the FDA granted Ixo-vec the Regenerative Medicine Advanced Therapy designation ("RMAT"). RMAT is a dedicated program designed to expedite the drug development and review processes for promising pipeline products, including genetic therapies. RMAT provides the benefits of intensive FDA guidance on efficient drug development, including potential priority review of the biologics license application ("BLA"), and other opportunities to expedite development and review.

Ixo-vec Manufacturing

As we advance Ixo-vec for wet AMD, we are continuing to develop our manufacturing expertise for ongoing supply and implementing strategies for large-scale manufacturing and supply. We collaborate with external vendors to manufacture our viral banks, drug supply and drug product, while maintaining control of key aspects of the manufacturing process including development of scalable processes, assay development, and GMP quality controls. This approach to large-scale production is essential for addressing the needs of highly prevalent diseases like wet AMD and sets us apart from many existing gene therapies, which are approved or in development for conditions affecting smaller patient populations.

Our Strengths

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

- Ixo-vec, for which we have reported top-line 52 week results from the LUNA Phase 2 trial demonstrating that Ixo-vec maintained visual and anatomic outcomes, while being generally well tolerated and achieving a robust treatment burden reduction and high patient preference over prior anti-VEGF injections, and for which we have seen in our OPTIC clinical trial strong signals of therapeutic efficacy out to four years and stable aflibercept protein levels through the latest reported follow-up, which is currently up to five years;
- 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 early stage gene therapy programs targeting the treatment of other highly prevalent ocular diseases;
- deep expertise developing and conducting clinical trials with a focus on regulatory compliance in the U.S and Europe;
- gene therapy manufacturing expertise, specifically in scalable process development, assay development, and cGMP 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, manufacturing, 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, such as those impacted by wet AMD.** 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 and a large percentage of wet AMD patients experiencing neovascularization in the second eye.
- **With Ixo-vec, target a well characterized and proven mechanism of action, leveraging anti-VEGF within a gene therapy for wet AMD, a retinal condition that is known to respond to anti-VEGF therapy.** Unlike with many gene therapies designed to replace a defective or missing gene, with Ixo-vec we are leveraging gene therapy to deliver an already approved drug. For wet AMD, Ixo-vec is designed for continuous delivery of aflibercept anti-VEGF therapy by a single IVT injection. This innovative method allows us to harness the benefits of gene therapy while providing a well-understood and established therapeutic agent. 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 approximately $14 billion worldwide in sales in 2023, underscoring the demand for this class of therapy.
- **Develop single-intravitreal-injection gene therapy treatments, which in wet AMD have the potential to relieve the burden of frequent, chronic injections and improve real-world vision outcomes and quality of life.** Our product candidates are designed as a single, in-office IVT injection therapy to address the unmet needs of patients with highly prevalent ocular diseases. The current standard of care for wet AMD requires frequent injections for the duration of the disease. A significant proportion of patients discontinue anti-VEGF treatment, estimated at up to 40% within two years and up to 57% within five years. In addition, even well-treated wet AMD patients can experience a loss of vision over time, which is thought to arise from fluctuations in macular fluid that can be pronounced with standard-of-care bolus anti-VEGF therapy. We believe that a durable treatment option has the potential to reduce injection frequency and thereby mitigate challenges with treatment compliance and to control fluid fluctuations and to improve long-term visual outcomes.

- **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 established regulatory paths. In wet AMD, aflibercept is an approved standard-of-care IVT injection treatment both as Eylea® and Eylea HD®, and Ixo-vec utilizes our proprietary vector capsid, AAV.7m8, which is designed to provide a codon optimized cassette of aflibercept enabling patients to generate their own aflibercept through a single IVT injection. In February 2023, the FDA published a draft guidance document (for comment purposes only) for drugs being developed for the treatment of wet AMD, which offered the FDA's recommendations for clinical trials including eligibility criteria, clinical trial designs, and efficacy endpoints.
- **Expand our process capabilities to support 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 European Commission 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.
- **Prepare for commercialization of Ixo-vec and our other programs, including by building a U.S. commercial organization and/or leveraging partnerships for the U.S. and global distribution.** We may seek to build a specialty sales force for our ocular gene therapies to target the approximately 2,500 retina specialists in the U.S. Alternatively, we may seek to leverage partnerships in the U.S. and/or to extend our reach, ensuring global access to our therapies. We are open to partnering with one or more pharmaceutical companies to develop and commercialize Ixo-vec and our other programs.
- **Advance our pipeline by leveraging our industry-leading capabilities in AAV vector and cassette optimization and moving our early-stage research assets into our development pipeline.** Integrating our AAV engineering, cassette optimization, and innovation together with our manufacturing expertise, we have the capability to generate high-quality recombinant AAV product candidates for ocular gene therapy. By expanding our understanding of AAV-induced inflammation and ocular inflammatory responses, we are better able to generate optimal prophylaxis strategies to support IVT product candidates with favorable attributes. 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 programs. Our AAV.7m8 vector is part of three clinical-stage gene therapy product candidates, including Ixo-vec.

Gene Therapy Background

Gene therapy is a powerful treatment modality to address disease biology in a targeted, efficient and sustained way. 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. In many gene therapies, patients receive viral vectors containing a new gene, called a transgene, that encodes for the desired therapeutic protein or functional version of a mutated protein, and a promoter to control expression of the transgene. Once a patient's cells are transduced with the transgene, the cells have the potential to continue to produce the therapeutic protein encoded by that transgene for years. We are currently advancing this field by focusing on localized ocular gene therapies. We believe this approach is particularly promising due to the ocular environment's privileged immune status and presents several advantages over systemic gene therapies. For instance, our product candidates require smaller doses than systemic gene therapies, which reduces the manufacturing burden and would result in lower cost of goods sold.

Our strategy takes a 'biofactory' approach. Unlike many gene therapies designed to replace a defective or missing gene, with Ixo-vec we are leveraging gene therapy to deliver an already approved drug. For wet AMD, Ixo-vec is designed for continuous delivery of aflibercept anti-VEGF therapy by a single IVT injection. This innovative method allows us to harness the benefits of gene therapy while providing a well-understood and established therapeutic agent.

Similar to existing classes of protein or biologic therapies such as monoclonal antibodies and antibody-drug conjugates, gene therapy has taken a number of years to evolve from a research tool into a viable and compelling treatment modality.

Our Novel AAV Vector Platform

Our ocular gene therapy platform relies on vectors derived from AAV, a small, non-pathogenic virus carrying DNA encoding a therapeutic gene instead of viral genes. These AAV vectors are utilized to deliver the transgene into a targeted cell population, ensuring sustained protein production upon expression. We believe AAV vectors offer distinct advantages in ocular gene therapy, including enhancing safety, applicability across various indications, and potential long-term efficacy. Noteworthy features include high efficiency in transferring the gene of interest, non-pathogenic nature, non-replicating behavior, provision of long-term expression, and low integrating potential. These characteristics collectively contribute to the potential success and safety of AAV-based vectors in ocular gene therapy, making them a promising choice for sustained therapeutic benefits.

However, natural capsid-based vectors exhibit inherent limitations, stemming either from their limited tropism or constrained permeation through biological barriers. Directed evolution, a multi-step process, addresses these limitations by utilizing a library of engineered AAV capsid genes with properties distinct from natural AAVs. Millions of AAV variants are created and screened *in vivo* for novel properties, such as specific cell type transduction. The identified capsids undergo further optimization, resulting in a select number of engineered AAVs with desired characteristics.

Adverum utilizes the AAV.7m8 capsid as a key platform for IVT delivery. This engineered variant, derived from natural AAV2, was developed through directed evolution for its ability to transduce neural retinal cells upon IVT administration. AAV.7m8 capsid has a 10-amino acid insertion that has been reported to reduce the binding of AAV2 to heparan sulfate proteoglycan (HSPG). The altered HSPG binding is believed to facilitate spread of the vector in the retina. More specifically, AAV.7m8 has exhibited the capability to cross the inner limiting membrane in the retina, a hurdle for naturally occurring AAV serotypes, including its parental AAV2, which displays limited penetration from vitreous. The AAV.7m8 vector has demonstrated widespread transduction of the retina and robust transgene expression in animal models post IVT delivery. As shown in non-human primates (“NHPs”), retinal transduction is primarily located in the macula, or central retina, and retinal periphery. AAV.7m8-based vectors have also been demonstrated to transduce retinal ganglion cells, cells in the inner nuclear layer, and photoreceptors, particularly foveal cones.

Key advantages of the AAV.7m8 capsid over standard AAV2 include:

- **Enables Intravitreal Delivery:** AAV.7m8 capsid has been engineered to achieve retinal transduction through IVT injection, the standard in-office procedure for wet AMD standard of care. The IVT route of administration is a routine and less invasive alternative to both the sub-retinal and suprachoroidal routes. The former can pose risks to the structure and function of the retina, particularly in cases where the patient's retina is already compromised or undergoing degeneration, while the latter relies on a novel specialized medical device and can be associated with complications related to the device or the procedure.
- **Enhanced Retinal Transduction:** AAV.7m8 has been engineered to achieve widespread retinal transduction through IVT administration, facilitating the delivery of the gene of interest to cells in the deeper retinal layers. This capability is crucial for therapies targeting retinal diseases.
- **Potential for Lower Dosing, Increased Efficacy:** AAV.7m8's efficient IVT dosing overcomes therapy barriers, enabling high gene expression in the retina. This allows for lower doses, potentially enhancing efficacy and reducing the immune response and inflammation associated with higher doses of vectors with limited permeability from the vitreous to the retina.
- **Efficacy and Inflammation Balance:** With its highly efficient retinal transduction profile, AAV.7m8-based vectors, when coupled with appropriate corticosteroid prophylaxis, may provide an optimal therapeutic window and a favorable benefit/risk profile.
- **Retina as a Biofactory:** AAV.7m8-based vectors, administered intravitreally, leverage ocular cells as a biofactory to release secretable therapeutic proteins. This approach can eliminate the necessity for repetitive IVT dosing, as a single injection may sustain the continuous delivery of therapeutic proteins throughout an individual's lifetime.
- **Benchmark for IVT Delivery:** AAV.7m8 has set the standard for IVT delivery of therapeutic vectors, given its optimal retinal transduction profile.
- **Well Studied:** Several gene therapy product candidates using AAV.7m8 have shown positive results in clinical and/or non-clinical studies. As of December 31, 2024, three product candidates using AAV.7m8 are in clinical development.

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. Ixo-vec is designed to deliver long-term, durable therapeutic levels of aflibercept associated with a robust, sustained treatment response and reducing the treatment burden and fluctuations in macular fluid associated with bolus anti-VEGF IVT injections. Ixo-vec utilizes an engineered, proprietary capsid, AAV.7m8, carrying a codon-optimized aflibercept coding sequence under the control of a proprietary expression cassette capable of transducing retinal cells after a single in-office IVT injection.

Ixo-vec is designed to provide long-term efficacy, which would address one of the major challenges in managing wet AMD – the frequent need for anti-VEGF injections. By potentially reducing or eliminating the need for these regular injections, if approved, Ixo-vec would offer a more convenient and less burdensome treatment regimen. This product is intended to improve both real-world vision outcomes and quality of life for patients. This approach could optimize patient compliance and lead to better overall vision outcomes, making it a significant advancement in the treatment of wet AMD.

Current Market for Wet AMD and Unmet Medical Needs

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, is an advanced form of AMD, affecting approximately 10% of patients living with AMD. In patients with wet AMD, the abnormal blood vessels 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. 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. Up to 42% of wet AMD patients experience neovascularization in the second eye in the first two to three years following diagnosis in the primary eye.

Greater durability of therapeutics is a key unmet need in wet AMD. The current standard of care for wet AMD requires frequent and lifelong anti-VEGF injections. Most patients with wet AMD are commonly treated with bevacizumab, often used off-label, or with specific wet AMD therapies. Bevacizumab, while not originally developed for wet AMD, has found widespread use due to its efficacy and cost-effectiveness. In contrast, Lucentis® (ranibizumab), Eylea (aflibercept), Vabysmo® (faricimab), and the high-dose formulation Eylea HD are FDA-approved treatments specifically designed for wet AMD. While effective for many patients, these options 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 and resulting in loss of vision over time. A significant proportion of patients discontinue anti-VEGF treatment, estimated at up to 40% within two years and up to 57% within 5 years.

Even well-treated wet AMD patients can experience a loss of vision over time. This is thought to arise from fluctuations in macular fluid. These fluctuations can be pronounced with standard-of-care bolus anti-VEFG therapy, in which patients see fluid levels fall after receiving an injection only to rise before their next injection. A growing scientific consensus views controlling fluid fluctuations as crucial for maintaining visual acuity in patients undergoing anti-VEGF therapy for wet AMD. 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 approximately $14 billion worldwide in sales in 2023.

Ixo-Vec Addresses Unmet Medical Needs for Wet AMD

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. We believe that durable treatment to reduce injection frequency, reduce fluctuations of macular fluid, 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. Ixo-vec has the potential to revolutionize this paradigm, shifting from the traditional "treat-and-extend" approach to a model focused on sustained anti-VEGF delivery, potentially effective for the patient's lifetime. 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.

Advantages over Other Biofactory Approaches

We believe IVT injection of ocular gene therapy for the treatment of wet AMD, as with Ixo-vec, offers substantial advantages compared to subretinal and suprachoroidal administration. The earliest ophthalmic gene therapies have been delivered subretinally. Subretinal administration requires that a victrectomy be performed via intraocular surgery, which carries inherent risks such as retinal detachment or infection and involves a recovery period that can be uncomfortable for the patient. In addition, subretinal gene therapy may be administered only to pseudophakic patients, that is, those patients who have had an artificial lens implanted, typically during cataract surgery.

The more recently developed suprachoroidal approach, while less invasive than subretinal surgery, relies on specialized medical devices to inject into a highly vascularized virtual space. This approach can be associated with complications related to the device or the procedure itself, and systemic absorption may lead to off-target effects. In animal models it has been observed that suprachoroidal delivery may result in higher potential for development of the immune response against the transgenic protein, potentially linked to the vector's exposure to inflammatory cells outside the blood-retinal barrier within scleral and uveal tissue. Furthermore, suprachoroidal administration in NHPs revealed a diffuse, peripheral, and circumferential pattern of transduction, with the retinal pigment epithelium, and scleral tissues identified as primary targets. Thus, when suprachoroidal delivery is utilized as a biofactory method for delivering therapeutic proteins to the retina, these proteins must overcome barriers by diffusing effectively to reach the targeted disease site in the retina, to provide optimal effectiveness. Suprachoroidal gene therapy appears to require higher doses than subretinal IVT gene therapy, which increases manufacturing costs and may have implications for potential inflammation.

In contrast, Ixo-vec is administered via a straightforward, one-time IVT injection. This simple procedure is performed during an office visit and is the mode of administration for current standard-of-care therapies for wet AMD. The IVT method significantly reduces the procedural risks and potential complications associated with the more invasive surgical techniques. It simplifies the treatment process and fits into existing retina practice workflows, making it more patient-friendly and accessible.

OPTIC Clinical Trial in Wet AMD

In November 2018, we initiated the Ixo-vec clinical trial entitled "An Open Label Phase 1 Study of Ixo-vec (AAV.7m8-aflibercept) in Neovascular (Wet) Age-Related Macular Degeneration" ("OPTIC"). The last subject completed the two-year OPTIC trial in June 2022. We will continue to follow subjects enrolled in the OPTIC three-year extension out to a total of five years.

OPTIC Trial Design. 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.

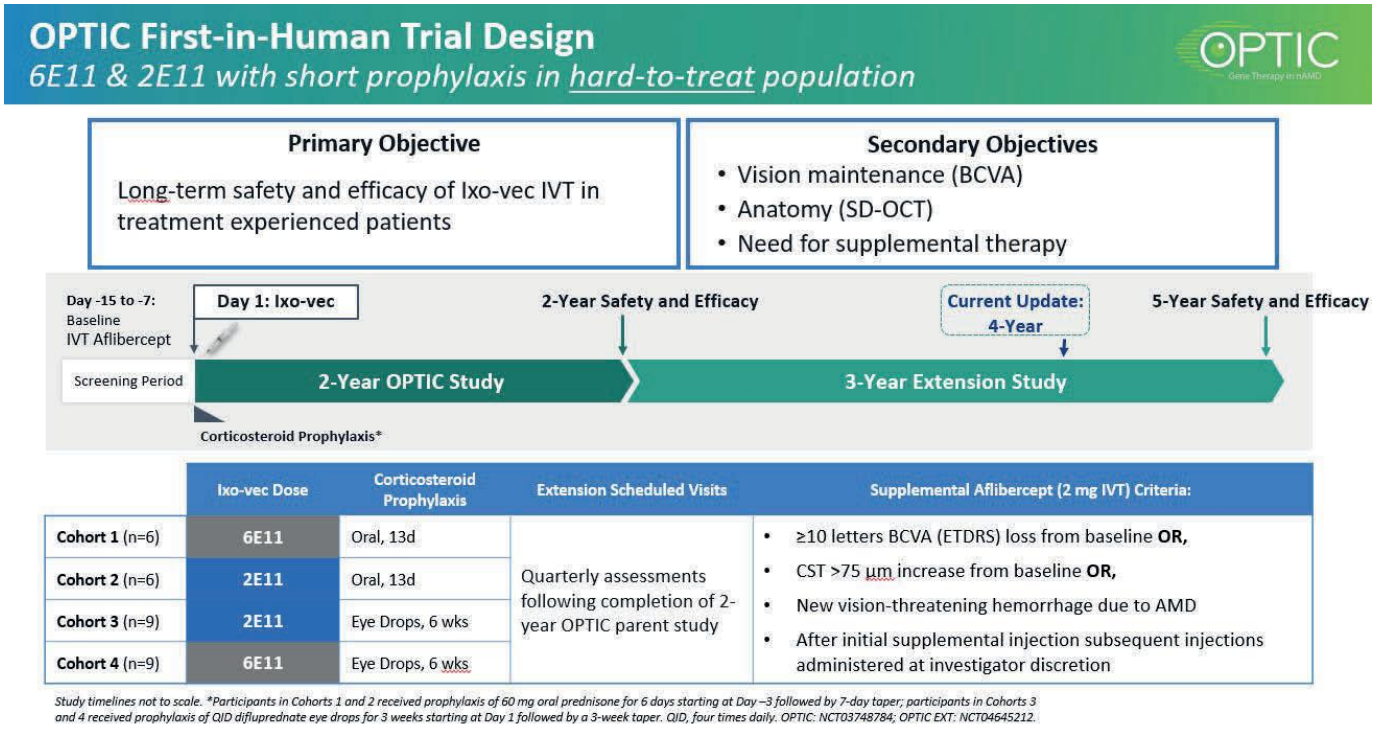
In OPTIC, subjects were dosed with a single IVT injection of Ixo-vec. Subjects in cohort 1 (n=6) were treated with a 6E11 dose of Ixo-vec. Subjects in cohort 2 (n=6) were treated with a three-fold lower 2E11 dose of Ixo-vec. Subjects in cohorts 1 and 2 received a 13-day tapering course of prophylactic 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 included changes in BCVA, measurement of 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. 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.

OPTIC Two-Year Data. The last subject completed the OPTIC study in June 2022. On average, subjects had significant disease, having received an average of approximately 10 annualized injections of anti-VEGF therapy in the year prior to receiving Ixo-vec. In OPTIC, Ixo-vec showed a robust treatment response from both doses through 104 weeks. Subjects who received the 6E11 dose 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 the 2E11 dose of Ixo-vec, Cohorts 2 and 3, experienced an 80% reduction in annualized anti-VEGF injections and 53% remained supplemental anti-VEGF injection free. Subjects also experienced maintenance of BCVA and a reduction of CST, followed by maintenance of those lower CST levels. Subjects experienced sustained stable aflibercept protein levels from 10 weeks through the end of the study. Despite the short duration of prophylactic corticosteroid therapy, Ixo-vec was generally well tolerated, with the most common adverse event ("AE") of dose-related anterior inflammation and asymptomatic pigmentary changes, including iris hyperpigmentation and iris transillumination defects. In December 2023, the OPTIC two-year results were published in the Lancet's *eClinical Medicine*.

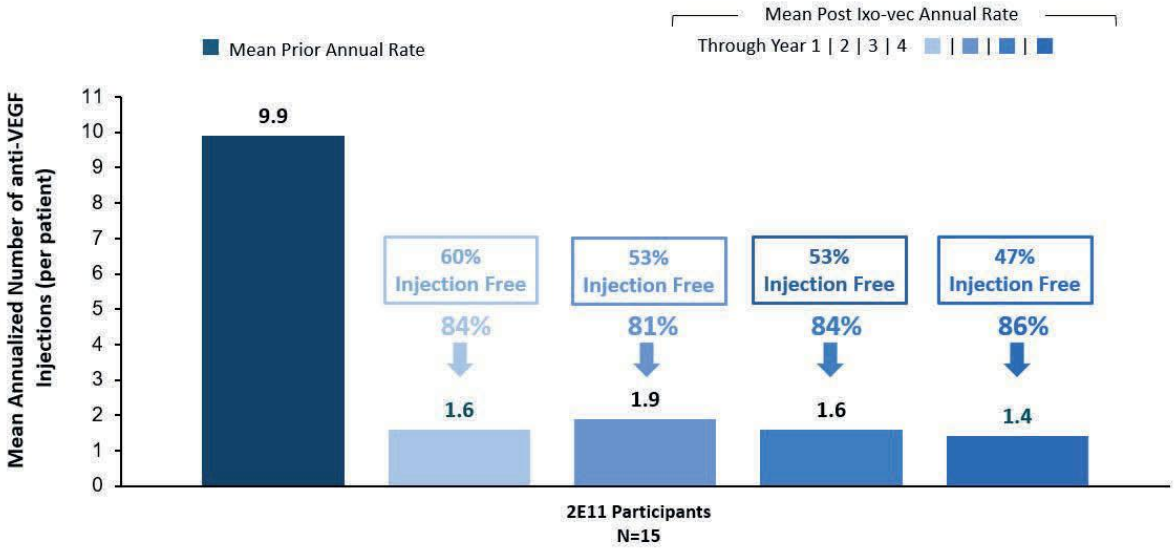
OPTIC Four-Year Data. In November 2024, we presented four-year results from the OPTIC parent and extension trials. Following Ixo-vec treatment, subjects who had received the 2E11 dose, the dose taken forward into LUNA, experienced an 86% reduction in annualized anti-VEGF injections through four years, with a robust treatment burden reduction demonstrated in each year and nearly half of the subjects injection free through four years. Subjects continued to experience maintenance of BCVA and CST levels. Subjects also demonstrated sustained aflibercept protein levels, measured through the latest reported follow-up, which is currently up to five years in the earliest subjects enrolled. Ixo-vec at the 2E11 dose continues to be generally well tolerated in the extension study.

Below is a schematic of the OPTIC and OPTIC extension trial and selected OPTIC four-year data showing treatment burden reduction and BCVA and CST reduction and maintenance.



Ixo-vec Reduced Treatment Burden Through 4 Years

2E11 shows >80% reduction in annualized anti-VEGF injections in every year

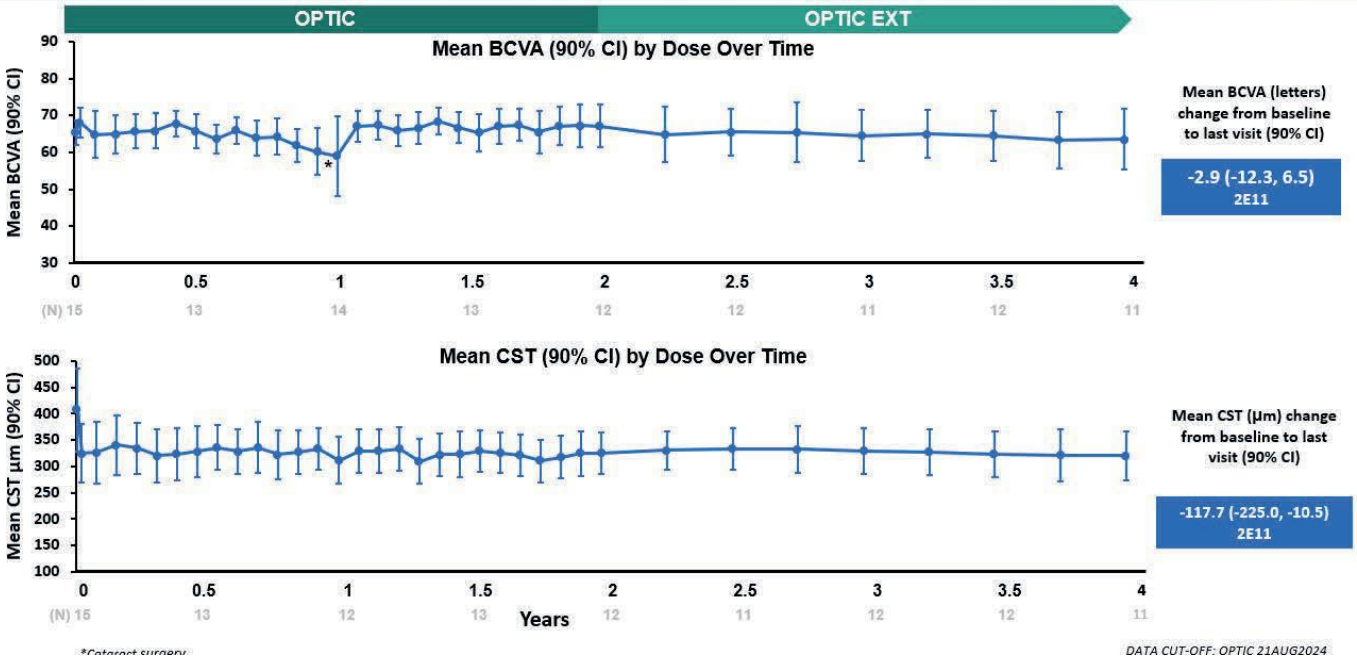


Annualized rate (Prior) = (number of IVTs in 12 months prior to Ixo-vec) / (days from the first IVT in the past 12 months to Ixo-vec / 365.25).
Annualized rate (Post) = (number of aflibercept IVTs since Ixo-vec) / (days from Ixo-vec to the last study follow-up / 365.25).
Analysis includes all participants from the OPTIC study.

DATA CUT-OFF: OPTIC 21AUG2024

Ixo-vec Maintains BCVA & CST through 4 Years

Demonstrated robust and durable activity



DATA CUT-OFF: OPTIC 21AUG2024

LUNA Phase 2 Clinical Trial in Wet AMD

In September 2022, we dosed the first subject in our LUNA Phase 2 trial of Ixo-vec. LUNA 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. LUNA is assessing four new enhanced prophylactic corticosteroid regimens, including difluprednate drops alone or in combination with IVT Ozurdex, a bioerodable implant of dexamethasone, and both local regimens with or without oral prednisone. Participants were randomized approximately 2:1 to receive local versus local plus oral prophylaxis.

The primary endpoints are similar to the OPTIC trial and focus on mean change in BCVA and CST from baseline to one year, and incidence and severity of adverse events. Other endpoints include aflibercept protein levels at 14 weeks, reductions in fluctuations in CST and in treatment burden, and patient preferences. The study is also evaluating the effectiveness and tolerability of the prophylactic corticosteroid regimens. In August 2023, we announced that the Phase 2 LUNA trial was fully enrolled, with a total of 60 subjects randomized equally between the 2E11 and 6E10 doses across 34 sites in the U.S.

In November 2024, we announced top-line 52 week results from the LUNA Phase 2 trial with a data cut-off date of August 29, 2024, demonstrating that both the 2E11 and 6E10 doses maintained visual and anatomic outcomes. Notably, both doses resulted in favorable reductions in annualized anti-VEGF injections and the percentage of subjects remaining free of injections was consistent with results observed in the OPTIC trial at one year. Subjects enrolled in the study had a high treatment burden, receiving an average of approximately 10 anti-VEGF injections in the year prior to receiving Ixo-vec.

Treatment Burden Reduction. In those subjects who had completed 52 weeks of follow-up, at the 6E10 (n=28) and 2E11 (n=29) doses, Ixo-vec demonstrated reduction in annualized anti-VEGF injection rates of 88% and 92%, respectively, and injection free rates of 54% and 69%, respectively.

Visual and Anatomic Outcomes. Visual acuity (BCVA) and anatomic endpoints (CST) were maintained at both dose levels. In a sub-group analysis of patients with higher baseline CST, a greater reduction in CST was demonstrated, indicating the efficacy potential of Ixo-vec gene therapy.

Aflibercept Levels. Aqueous humor aflibercept protein levels at 14 weeks suggest that both doses deliver aflibercept levels that are within the therapeutic range observed in OPTIC. Importantly, early aflibercept levels are associated with sustained long-term protein levels in OPTIC through the latest reported follow-up, which is currently through four years at the 2E11 dose. No minimum aqueous humor aflibercept threshold for clinical benefit was observed. We revised the LUNA study to stop the collection of aqueous humor samples.

Safety Profile and "Go-Forward" Corticosteroid Prophylaxis Regimen. Ixo-vec was well-tolerated, and when present inflammation was responsive to local corticosteroids. No Ixo-vec related serious adverse events were reported. No Ixo-vec related episcleritis, vasculitis, retinitis, choroiditis, vascular occlusion or hypotony were reported. Consistent with OPTIC 2E11, the most common Ixo-vec related AEs observed in LUNA were dose-related anterior inflammation and asymptomatic pigmentary changes, including iris transillumination defects and anterior chamber pigmentation.

Data suggest corticosteroid prophylaxis optimization at both the 2E11 and 6E10 doses appears to result in improved inflammatory profiles in LUNA as compared to OPTIC trial results. Specifically, data demonstrated that difluprednate topical eye drops alone is a promising prophylactic regimen. Data indicated that Ozurdex alone or with oral corticosteroids does not provide prophylaxis of sufficient duration, and oral corticosteroids showed no incremental benefit. We have selected difluprednate eye drops alone as the "go-forward" prophylactic regimen for the pivotal studies.

Patient Preference Survey. Results from our pre-specified LUNA patient preference survey demonstrate strong preference for Ixo-vec over prior anti-VEGF therapies, plus the acceptability of local prophylactic steroid regimens. 93% (n=56) of LUNA patients at 52 weeks preferred Ixo-vec, including accompanying steroid regimen, over prior treatments, up from 88% (n=57) at 26 weeks; 95% (n=56) would elect to receive Ixo-vec in the other eye if both eyes had wet AMD; and 96% (n=56) would recommend Ixo-vec to their family or friends with wet AMD. 100% (n=10) of patients who received the 6E10 dose and topical-eye-drop-only steroid regimen preferred Ixo-vec over their prior treatments for wet AMD, would elect to receive Ixo-vec in the other eye if both eyes had wet AMD, and would recommend Ixo-vec to their family or friends with wet AMD. No patients receiving topical eye drop alone prophylaxis (n=20) stated it was difficult to manage.

The graphics below show a schematic of the LUNA trial design and selected data from the November 2024 LUNA data announcement including treatment burden reduction; BCVA and CST maintenance; the greater reduction in CST levels in a subgroup of patients with higher baseline CST levels; aflibercept levels overlaid onto aflibercept levels observed at the 2E11 dose in OPTIC through the latest reported follow-up, which is currently through four years at the 2E11 dose; and results from the patient preference survey.

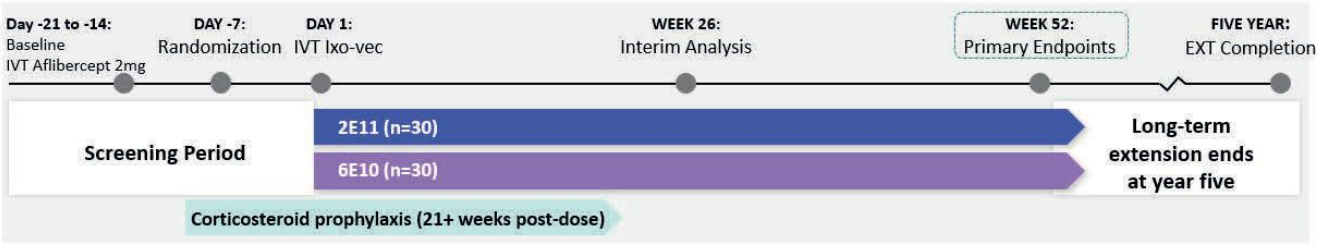
LUNA Phase 2 Trial Design

6E10 & 2E11 with extended prophylaxis in hard-to-treat patients

LUNA

Multicenter, double-masked, randomized, parallel-group Phase 2 study

Key inclusion criteria: demonstrated response to anti-VEGF therapy and under active treatment for CNV secondary to nAMD (received a minimum of 2 injections within 4 months of entry), study eye BCVA in the range of 25 – 83 ETDRS letters



Corticosteroid Prophylaxis Regimen

- Difluprednate 22 wks ± prednisone oral 10 wks
- Ozurdex IVT + difluprednate after week 4 ± prednisone oral 10 wks*
- Randomized 2:1 local versus local + oral

Supplemental Injection Criteria

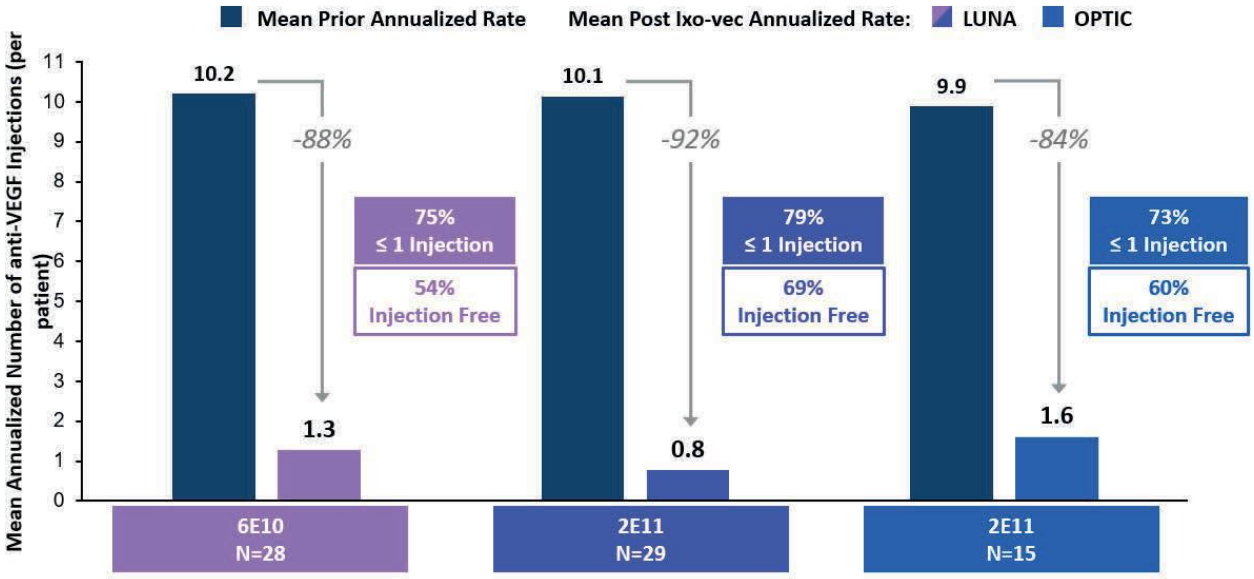
- Increase in CST > 75 µm from BL confirmed by the CRC **OR**
- Loss of ≥ 10 letters in BCVA from BL due to new/worsening IRF or SRF **OR**
- New vision-threatening hemorrhage due to nAMD

*Study timeline and length of arrows depicted are not to scale. Baseline is defined as the day screening aflibercept is administered. *Protocol amended early in study to include difluprednate starting at week 4 to match the taper in difluprednate regimens; if initiated after week 4 visit, difluprednate may be adjusted at the discretion of investigator in consult with medical monitors (6 participants did not receive difluprednate as part of prophylaxis).*

52-Week LUNA and OPTIC Injection Burden Reduction are Consistent

>80% reduction in annualized anti-VEGF injections, >50% injection free

LUNA OPTIC



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 last follow-up within the interim analysis period / 365.25).

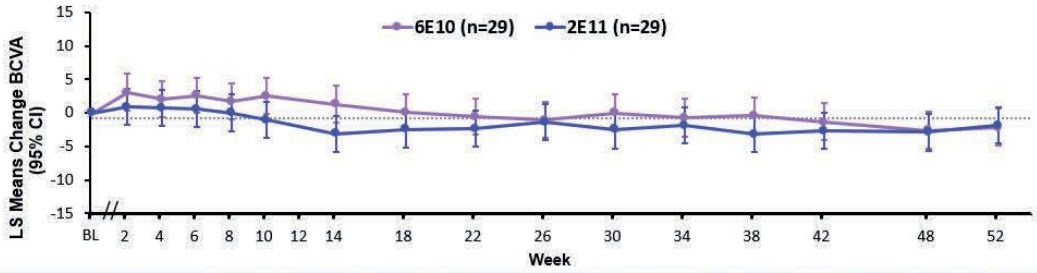
DATA CUT-OFF: OPTIC 21AUG2024, LUNA 29AUG2024

Ixo-vec Maintains BCVA & CST

Both doses demonstrate robust and durable activity, consistent with OPTIC

LUNA

Least Squares Means Change in Best Corrected Visual Acuity (BCVA) Over Time by Dose*

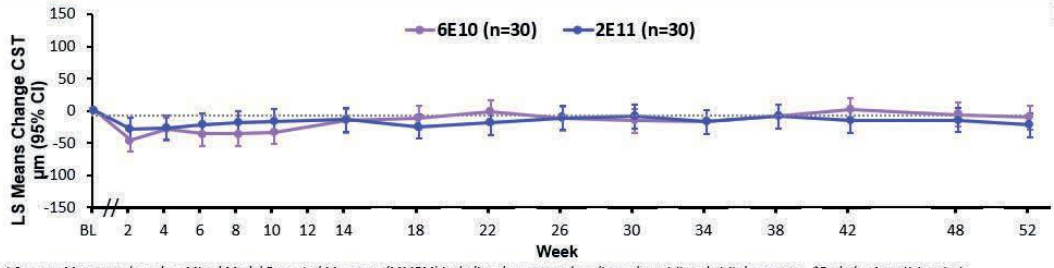


LS Means BCVA Change from Baseline at Week 52, Letters (95% CI)

-2.1 (-4.8, 0.7) 6E10

-1.8 (-4.6, 0.9) 2E11

Least Squares Means Change in Central Subfield Thickness (CST) Over Time by Dose



LS Means CST Change from Baseline at Week 52, µm (95% CI)

-10.2 (-29.0, 8.5) 6E10

-21.9 (-40.4, -3.3) 2E11

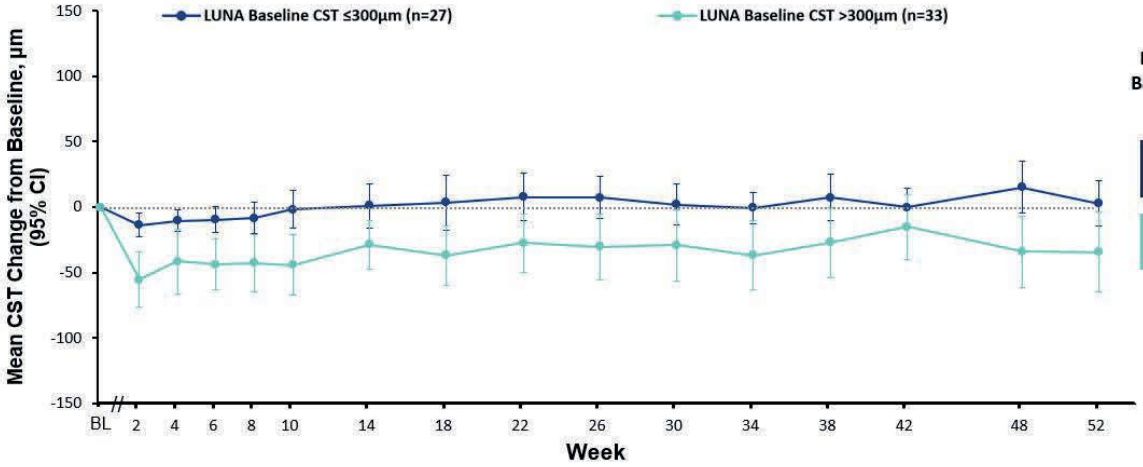
*Least Squares Means are based on Mixed Model Repeated Measures (MMRM) including dose group, baseline value, visit and visit dose group. *Excludes 1 participant at each dose with letter loss due to cataract*

DATA CUT-OFF: LUNA 29AUG2024

Consistent Anatomic Benefit in Broad Population

Fluid reduction in patients with baseline CST >300 µm; maintenance in ≤300 µm

LUNA



Mean CST Change from Baseline at Week 52, µm (95% CI)

2.9 (-14.3, 20.2) BL ≤300 µm, All

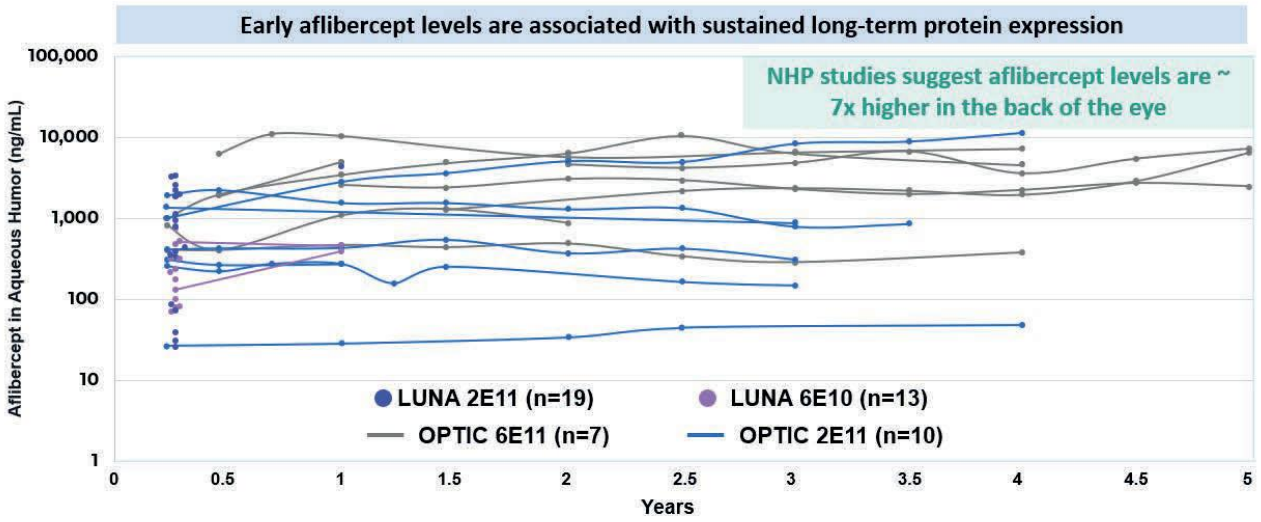
-34.4 (-64.9, -3.9) BL >300 µm, All

Baseline Characteristic for Subgroup	CST ≤300 µm All Participants	CST >300 µm All Participants
Mean CST, µm (SD)	269.9 (18.7)	416.6 (119.1)

DATA CUT-OFF: LUNA 29AUG2024

Ixo-vec Demonstrates Durable Therapeutic Levels After One Injection

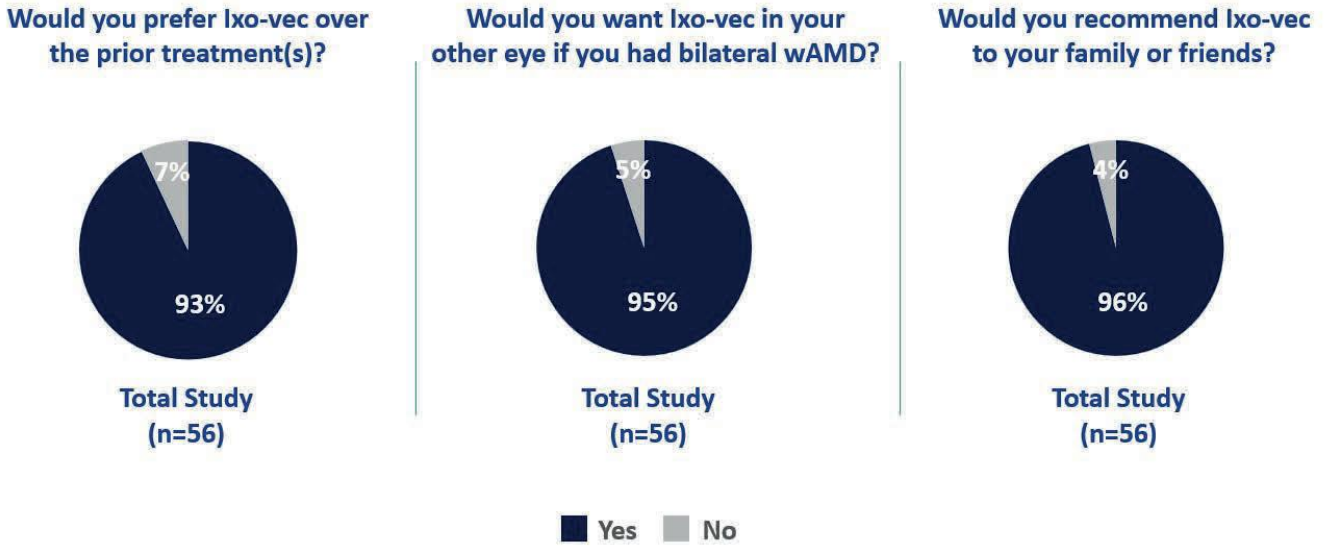
Sustained aqueous aflibercept levels up to 5 years



DATA CUT-OFF: OPTIC 21AUG2024, LUNA 29AUG2024

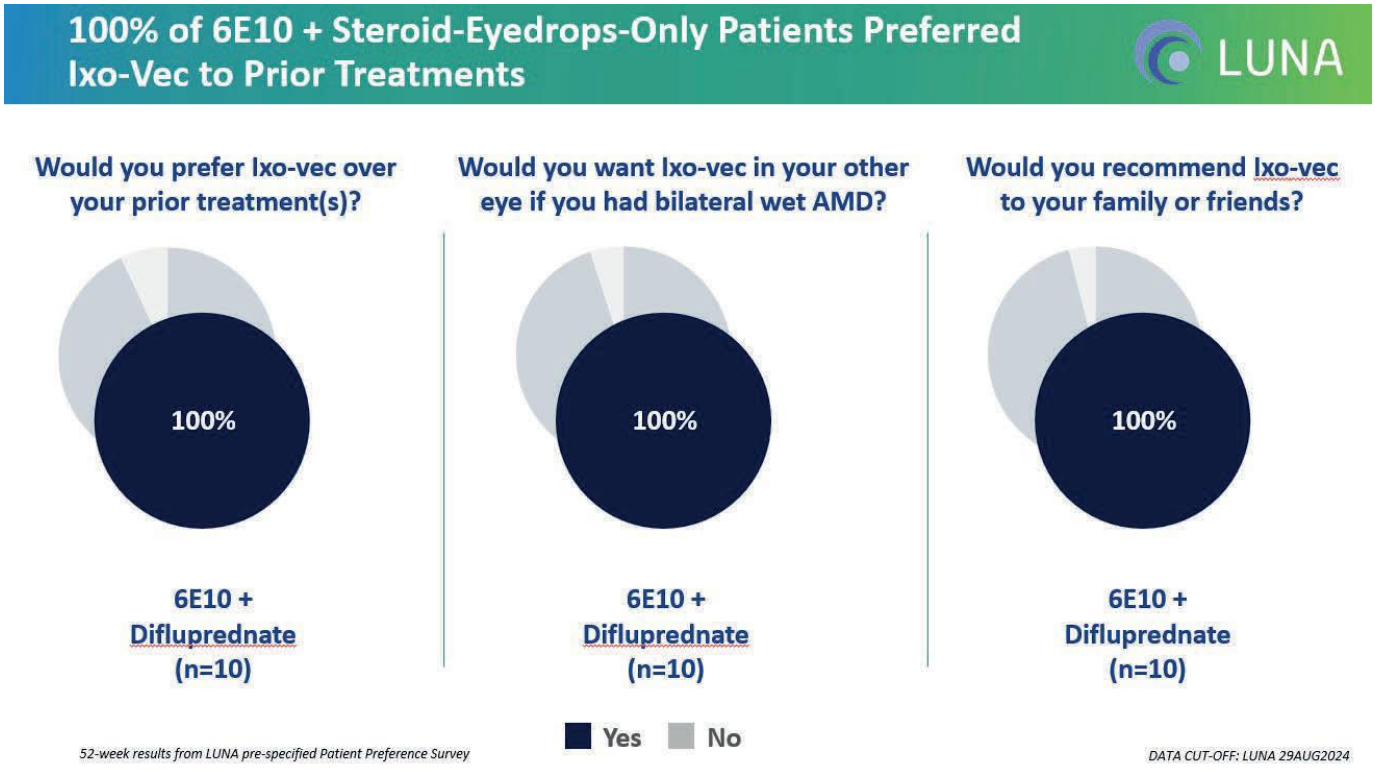
In OPTIC, all subjects tested had quantifiable aqueous humor aflibercept levels (one subject had levels above and below the limit of quantification of the assay [25 ng/mL] at multiple time points). In LUNA, 32 of 38 subjects (84%) had quantifiable aqueous humor aflibercept levels; the patients who had aflibercept concentrations measured below the limit of quantification (BLOQ) included patients at both doses who remained injection free or experienced treatment burden reduction. Measurements BLOQ of the assay or within 8 weeks of supplemental aflibercept injections are not shown. LUNA revised to stop collection of AH samples. NHP data: Kiss, Szilárd et al, Molecular Therapy Methods & Clinical Development, Volume 18, 345 - 353

>90% of Patients Preferred Ixo-vec over Today's Standard of Care



52-week results from LUNA pre-specified Patient Preference Survey

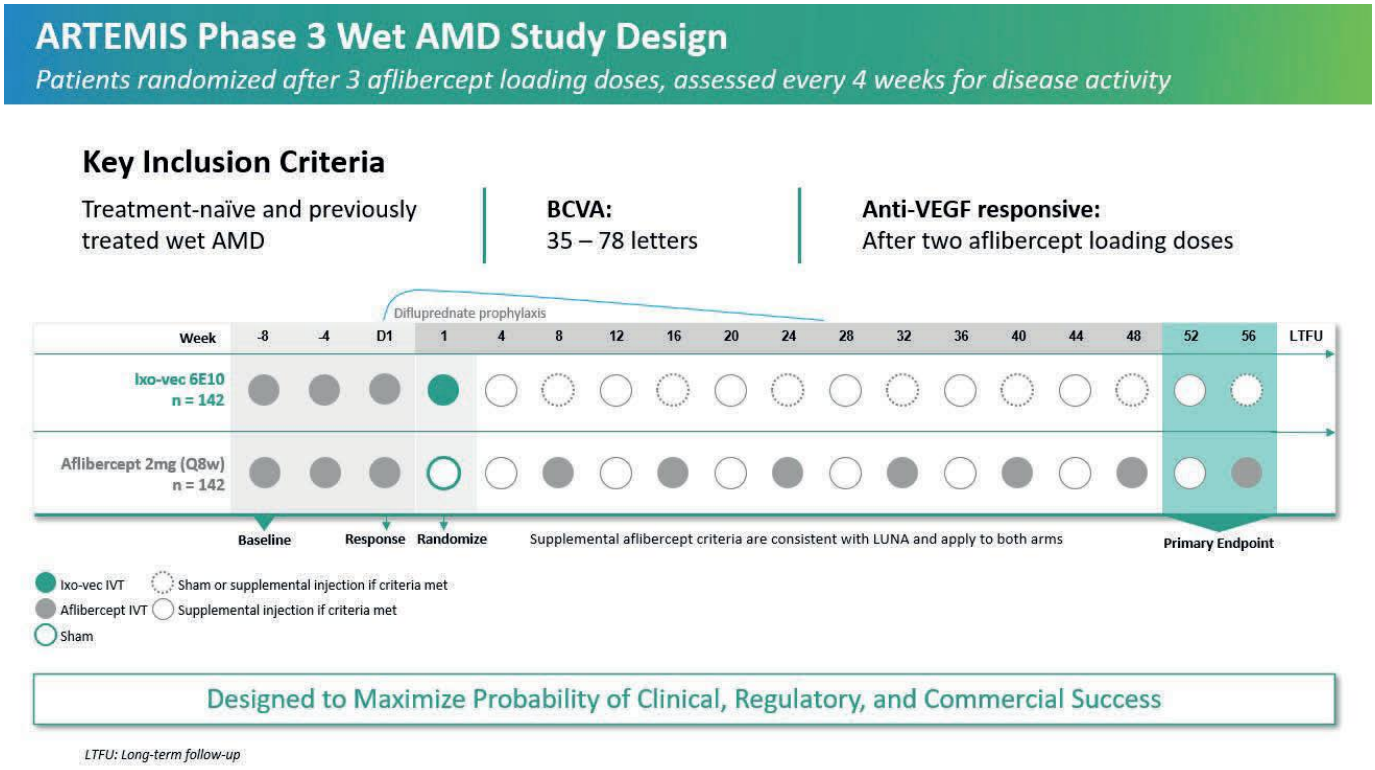
DATA CUT-OFF: LUNA 29AUG2024



Phase 3 Program for Ixo-vec in Wet AMD

We plan to conduct two, double-masked, randomized Phase 3 clinical trials evaluating Ixo-vec in wet AMD. We are conducting the first Phase 3 trial, ARTEMIS, at U.S. sites and intend to conduct the second Phase 3 trial, AQUARIUS, at both U.S. and non-U.S. sites.

The 284-patient ARTEMIS Phase 3 trial is designed to enroll a broad patient population, including both treatment-naïve and treatment-experienced wet AMD patients. The primary endpoint, measured at an average of weeks 52 and 56, is non-inferiority in mean BCVA change from baseline between Ixo-vec (6E10) and aflibercept (2mg Q8W). The non-inferiority margin for this study is -4.5 letters. All patients will receive three monthly loading doses of aflibercept prior to Ixo-vec. The study will utilize sham injections in the control arm to support masking. Patients in both arms will be eligible for supplemental injections of aflibercept and will receive topical steroid eye drops. We initiated ARTEMIS in March 2025. The schematic below shows the ARTEMIS trial design.



INFINITY Phase 2 Clinical Trial in DME

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 microvascular 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, OPTIC, or LUNA trials or the 6E11 dose in the OPTIC trial.

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 in LUNA, OPTIC and INFINITY and all of our nonclinical data by internal and external experts, we believe that utilizing the 6E10 dose along with enhanced topical-eye-drop steroid prophylaxis, as we are currently evaluating in the ongoing LUNA and ARTEMIS trials, may allow us to minimize post-prophylaxis inflammation in our wet AMD trial subjects going forward.

Ixo-vec Regulatory Designations

In September 2018, we announced that the FDA had granted Ixo-vec Fast Track designation. Fast Track is a process designed to facilitate the development and expedite the review of drugs and biologics to treat serious conditions and fill unmet medical needs. The designation enables more frequent meetings and communication with the FDA throughout a product candidate's development and review process, often leading to earlier drug approval and access by patients. The designation also provides eligibility for Priority Review, Accelerated Approval, and Rolling Review, which may potentially result in a shorter FDA review process. The purpose of the Fast Track process is to get important new drugs and biologics to patients earlier.

In June 2022, we announced that the European Medicines Agency EMA granted Ixo-vec Priority Medicines PRIME designation. PRIME voluntary scheme intended to enhance the EMA's support for the development of medicinal products that target unmet medical needs. Eligible products must target conditions for which there is an unmet medical need (i.e. there is no satisfactory method of diagnosis, prevention or treatment in the EU or, if such a method exists, the new medicinal product will bring a major therapeutic advantage) and they must be demonstrated to have the potential to address the unmet medical need by introducing new methods of therapy or improving existing ones.

In April 2023, we announced that the MHRA granted Ixo-vec an Innovation Passport under the ILAP. The Innovation Passport is the first step in the ILAP process, triggering the MHRA and its partner agencies, including the All Wales Therapeutics and Toxicology Centre, the National Institute for Health and Care Excellence, and the Scottish Medicines Consortium to partner with Adverum to charter a roadmap for regulatory and development milestones with the goal of early patient access in the U.K.

In August 2024, we announced the FDA had granted Ixo-vec the Regenerative Medicine Advanced Therapy ("RMAT") designation. RMAT designation is a dedicated program designed to expedite the drug development and review processes for promising pipeline products, including genetic therapies. The RMAT designation provides the benefits of intensive FDA guidance on efficient drug development, including potential priority review of the BLA, and other opportunities to expedite development and review.

Additional Programs

Dry AMD / Geographic Atrophy Program

In May 2023, we presented nonclinical data on an IVT gene therapy for the treatment of geographic atrophy secondary to dry age-related macular degeneration ("dry AMD") via expression of Complement Factor I at the American Society of Gene & Cell Therapy's ("ASGCT") 2023 Annual Meeting. Dry AMD is a highly prevalent disease in which patients experience a chronic progressive deterioration of the macula, leading to central blind spots and permanent vision loss. Geographic atrophy can be seen as part of late-stage AMD.

Optogenetics Program

In May 2023, we presented data on an optogenetic approach to vision restoration at ASGCT's 2023 Annual Meeting. Melanopsin, through its ability to regenerate chromophore, has the potential to be an effective light sensor candidate by generating pseudo-photoreceptors. Our engineered melanopsin demonstrated favorable kinetics *in vitro* and may have utility as a therapeutic transgene for optogenetic vision restoration.

Other Partnered Programs

BGTF-027 (AAV.7m8-L-opsin), formerly known as ADVM-062, is a novel gene therapy product candidate designed 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. BGTF-027 utilizes Adverum's propriety vector capsid, AAV.7m8. In January 2022, we announced that the FDA granted Orphan Drug Designation to BGTF-027. In September 2023, we granted an exclusive license for the rights to BGTF-027 to Blue Gen Therapeutics Foundation, a non-profit organization dedicated to advancing gene therapy treatments for rare inherited retinal diseases, that will now lead all research and development activities for the program.

We have licensed to GenSight rights to use AAV.7m8 for GS030, GenSight's gene therapy encoding for channelrhodopsin protein. In October 2018, GenSight began its PIONEER Phase 1/2 clinical trial in retinitis pigmentosa in the U.S., France, and U.K. and in February 2023 announced one-year safety data and efficacy signals from the trial. In October 2021, GenSight announced it had been granted Fast Track Designation by the FDA for GS030.

We have licensed to Ray Therapeutics rights to use AAV.7m8 in conjunction with Ray's RTx-015 optogenetics payload for ocular diseases. Ray Therapeutics is developing RTx-015 in retinitis pigmentosa, a degenerative retinal disease with significant unmet medical need. In September 2024, Ray Therapeutics advanced RTx-015 into a Phase 1 clinical trial in retinitis pigmentosa.

We have licensed to LEXEO Therapeutics rights to the intellectual property and pre-clinical data package for LX2006, an investigational gene therapy for Friedreich's ataxia.

Manufacturing

As we advance Ixo-vec for wet AMD, we are continuing to develop our manufacturing expertise for ongoing supply. We currently have no operational clinical or commercial manufacturing facilities, and all of our clinical manufacturing activities are currently contracted out to third parties. We maintain control of key aspects of the manufacturing process, specifically in development of scalable processes, 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 European-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 and infection by adventitious agents in humans.
- **High yield and cost effectiveness.** Because of its scalability, our BEVS system may allow the production of large quantities of AAV vectors, up to the 2000-liter scale, providing further economies of 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 together with 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, expandibility and flexibility as we prepare to potentially deliver one of the first gene therapies for large indications.

Our CMOs have produced multiple batches of Ixo-vec at our proposed commercial scale that we have used in LUNA and intend to use in our Phase 3 clinical trials.

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 IVT approach for the treatment of wet AMD, our AAV-based 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 Ixo-vec gene therapy product candidate for wet AMD utilizes a proprietary vector, is administered through a single IVT 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.

In the United States, most patients receive off-label bevacizumab, including as a first-line treatment. Many patients go on to receive Eylea, Eylea HD and Vabysmo® (faricimab). We know of a number of additional product candidates in development or approved for chronic retinal conditions that respond to anti-VEGF therapy, including wet AMD. These product candidates and products include:

- biosimilar anti-VEGFs;
- bispecific / combination / add-on therapies for efficacy or durability improvement;
- long-acting delivery devices and tyrosine kinase inhibitor implants to lower treatment frequency;
- gene therapy to lower treatment frequency and offer the potential for lifelong injection freedom; and
- other molecules that inhibit neovascularization in wet AMD.

There are several other companies in the U.S. or Europe 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, AbbVie, Bayer, Clearside Biomedical, EyePoint Pharmaceuticals, Kodiak Sciences, Novartis, Ocular Therapeutix, Opthea, Outlook Therapeutics, Regeneron, REGENXBIO and Roche.

These companies, as well as any other 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 we in obtaining approval for treatments and achieving widespread market acceptance. Our competitors' treatments may be more effective, have fewer side effects, or be 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 1/2 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 1/2 clinical trial for retinitis pigmentosa.

Ray Therapeutics

In February 2023, we entered into an agreement with Ray Therapeutics ("Ray"), pursuant to which we granted Ray a non-exclusive license to our proprietary AAV.7m8 vector to be used in conjunction with Ray's optogenetics payload. 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 Ray's licensed products.

Ray is currently developing RTx-015, an optogenetic gene therapy which incorporates our AAV.7m8 capsid. Ray is conducting a Phase 1 trial with RTx-015 to treat 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 January 7, 2025, we own or license more than 430 issued patents that are still in force, including more than 30 issued U.S. patents and 15 European patents validated cumulatively in more than 275 countries, as well as more than 197 patent applications pending in the U.S. and foreign jurisdictions, 10 of which have been allowed. These numbers include more than 44 patents and 8 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 five 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. Twenty patents in this family have issued in the U.S., elsewhere in North America, Europe and the Asia/Pacific region, and seven 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, eight patents are issued in North America, the Asia/Pacific region, Israel and South Africa, and at least sixteen 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 Australia, Europe (validated in 37 countries), Hong Kong, and 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 28 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 2040 subject to possible patent term adjustments and patent term extensions. The fifth family is an international application (i.e., Patent Cooperation Treaty ("PCT") application) directed to methods of treating neovascular diseases of the eye, including wet AMD and diabetic retinopathy, with low dose AAV.7m8-aflibercept. Patents that may eventually issue from this family, if any, are generally expected to expire in 2043.

We also own over 20 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 2043, 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 two granted patents in the U.S. The patents in this family are projected to expire between 2027 and 2029 in the U.S., 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 IVT injection, and which we utilize in our product candidate ADVM-022. This family includes at least thirty-four issued patents in the U.S., elsewhere in North America, Europe, Asia, and the Pacific, including three European patents each validated in thirty-seven countries. Seven 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 and 2030.

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 India, one in Mexico, one in New Zealand and two in South Africa. There are ten 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 ("PHS Act"), as well as corresponding implementing regulations promulgated by the FDA. These laws and regulations govern, among other things, the testing, manufacturing, safety, efficacy, purity, potency, labeling, packaging, storage, record keeping, reporting, advertising and promotion, distribution, post-approval monitoring and reporting, sampling, and export and import of biological 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 Therapeutic Products ("OTP"). The FDA has also established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER in its review.

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 go into effect 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 biological product for its proposed indication;
- Submission to the FDA of a Biologics License Application ("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 facilities, 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 inspection(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 an advisory committee review if the FDA convenes an advisory committee; and

- Payment of user fees and the FDA review and licensure of the BLA prior to any commercial marketing, sale or shipment of the biological 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 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 (and its amendments) 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 gene therapy products, 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. Some studies employ a Data Monitoring Committee (DMC), independent from the study sponsor, to monitor clinical trial conduct and safety, assess risks and benefits, and make recommendations to protect the study participants of clinical trials.

All clinical research performed in the 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 human subjects and tested for safety. 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 to further evaluate dosage, clinical efficacy, potency, and safety in an expanded patient population at geographically dispersed clinical study sites. These clinical studies are intended to establish the overall risk/benefit ratio of the product and to provide an adequate basis for product approval and labeling. 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 follow-up. Phase 4 clinical trials may be required by the FDA as a condition of approval. Additionally, FDA recommends that sponsors observe study participants for potential gene therapy-related delayed adverse events for as long as 15 years.

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 using the proprietary 7m8 capsid, 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 expedited 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 DMC 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. In the EU, clinical trials are governed by the EU Clinical Trial Regulation 536/2014 ("CTR"), which entered into application on January 31, 2022 repealing and replacing the former Clinical Trials Directive 2001/20 ("CTD"). The CTR is intended to harmonize and streamline clinical trial authorizations, simplify adverse-event reporting procedures, improve the supervision of clinical trials and increase transparency. Specifically, the Regulation, which is directly applicable in all EU Member States, introduces a streamlined application procedure through a single-entry point, the "EU portal", the Clinical Trials Information System; a single set of documents to be prepared and submitted for the application; as well as simplified reporting procedures for clinical trial sponsors. A harmonized procedure for the assessment of applications for clinical trials has been introduced and is divided into two parts. Part I assessment is led by the competent authorities of a reference Member State selected by the trial sponsor and relates to clinical trial aspects that are considered to be scientifically harmonized across EU Member States. This assessment is then submitted to the competent authorities of all concerned Member States in which the trial is to be conducted for their review. Part II is assessed separately by the competent authorities and Ethics Committees in each concerned EU Member State. Individual EU Member States retain the power to authorize the conduct of clinical trials on their territory.

The extent to which on-going clinical trials will be governed by the CTR will depend on the duration of the individual clinical trial. For clinical trials in relation to which an application for approval was made on the basis of the CTD before January 31, 2023, the CTD continued to apply on a transitional basis until January 31, 2025. All ongoing trials are now subject to the provisions of the CTR.

In all cases, clinical trials must be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki. Medicines used in clinical trials, including ATMPs, must be manufactured in accordance with the guidelines on cGMP and in a GMP licensed facility, which can be subject to GMP inspections.

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, assist researchers and others involved in human gene therapy clinical studies, and manages information about science and safety of gene therapy 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 clinical development and the FDA usually recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for up to five years for nonintegrating vectors such as AAV vectors.

The responsible party for an applicable clinical trial must register the clinical trial of FDA-regulated products on the ClinicalTrials.gov website, including the registry of new, on-going, and completed clinical trials of drugs, biologics, and device products, including the publication of the study results.

Biologics License Applications and Marketing Authorization Applications

The results of nonclinical studies and clinical trials, 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. Under the Prescription Drug User Fee Act ("PDUFA"), 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 PDUFA, the FDA has a performance goal to review applications within six months from successful filing of the application for priority reviews or ten 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 for the FDA reviewers to complete their review of the BLA. As with new BLAs, the review process could also be extended by FDA requests for additional information or clarification.

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. During the biological product approval process, the FDA also will determine whether a Risk Evaluation and Mitigation Strategy (REMS) is necessary to assure the safe use of the biological product upon marketing. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS; the FDA will not approve the BLA without a REMS, if required.

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 approving a BLA, the FDA will inspect the facilities at which the biologic is manufactured and will not license the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with cGMPs. Additionally, before approving a BLA, the FDA may also inspect one or more clinical sites to assure that the clinical studies were conducted in compliance with IND study requirements and GCP requirements. The FDA may also inspect the facilities of the sponsor to ensure that processes and procedures are in compliance with GMP/GCP requirements.

After FDA evaluates a BLA and conducts inspections of manufacturing facilities where the investigational product and/or its drug substance will be produced, the FDA may issue an approval letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. 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. FDA intends to review and act on the manufacturing supplement within six months of receipt.

A biological product approved under section 351(a) of the PHS Act (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 the 27 Member States of the EU plus Norway, Iceland, and Liechtenstein), medicinal products can only be commercialized after a related Marketing Authorization ("MA") has been granted. To obtain an MA for a product in the EU, an applicant must submit a Marketing Authorization Application ("MAA"), either a centralized procedure administered by the European Medicines Agency ("EMA"), or one of the procedures administered by the competent authorities of EU Member States (mutual recognition procedure, decentralized procedure, or national procedure). An MA may be granted only to an applicant established in the EEA.

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 European Commission will grant a single centralized MA that is valid throughout the EEA.

The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, advanced therapy medicinal products (ATMPs, such as gene therapy products), orphan medicinal products, and medicinal products containing a new active substance to treat some diseases like HIV/AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and other immune dysfunctions and viral diseases. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, authorization through the centralized procedure is optional on related approval.

Under the centralized procedure, the EMA's Committee for Medicinal Products for Human Use ("CHMP") conducts the initial assessment of a product. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing MA. The maximum timeframe for the evaluation of an MAA under the centralized procedure is 210 days, excluding clock stops when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP.

Unlike the centralized authorization procedure, the decentralized MA procedure requires a separate application to, and leads to separate approval by, the competent authorities of each EU Member State in which the product is to be marketed. This application is identical to the application that would be submitted to the EMA for authorization through the centralized procedure. The reference EU Member State prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. The resulting assessment report is submitted to the concerned EU Member States who, within 90 days of receipt, must decide whether to approve the assessment report and related materials. If a concerned EU Member State cannot approve the assessment report and related materials due to concerns relating to a potential serious risk to public health, disputed elements may be referred to the Heads of Medicines Agencies' Coordination Group for Mutual Recognition and Decentralised Procedures – Human ("CMDh"), for review. The subsequent decision of the European Commission is binding on all EU Member States.

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. Like the decentralized procedure, the mutual recognition procedure is based on the acceptance by the competent authorities of the EU Member States of the MA of a medicinal product by the competent authorities of other EU Member States. The holder of a national MA may submit an application to the competent authority of an EU Member State requesting that this authority recognize the MA delivered by the competent authority of another EU Member State.

An MA has, in principle, an initial validity of five years. The MA may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the EU Member State in which the original MA was granted. To support the application, the MA holder must provide the EMA or the competent authority with a consolidated version of the Common Technical Document providing up-to-date data concerning the quality, safety and efficacy of the product, including all variations introduced since the MA was granted, at least nine months before the MA ceases to be valid. The European Commission or the competent authorities of the EU Member States may decide on justified grounds relating to pharmacovigilance, to proceed with one further five-year renewal period for the MA. Once subsequently renewed, the MA shall be valid for an unlimited period. Any authorization which is not followed by the actual placing of the medicinal product on the EU market (for a centralized MA) or on the market of the authorizing EU Member State within three years after authorization ceases to be valid (the so-called sunset clause).

In the EU, a "conditional" MA may be granted in cases where all the required safety and efficacy data are not yet available. The European Commission may grant a conditional MA for a medicinal product if it is demonstrated that all of the following criteria are met: (i) the benefit-risk balance of the medicinal product is positive; (ii) it is likely that the applicant will be able to provide comprehensive data post-authorization; (iii) the medicinal product fulfills an unmet medical need; and (iv) the benefit of the immediate availability to patients of the medicinal product is greater than the risk inherent in the fact that additional data are still required. The conditional MA is subject to conditions to be fulfilled for generating the missing data or ensuring increased safety measures. It is valid for one year and must be renewed annually until all related conditions have been fulfilled. Once any pending studies are provided, the conditional MA can be converted into a traditional MA. However, if the conditions are not fulfilled within the timeframe set by the EMA and approved by the European Commission, the MA will cease to be renewed.

An MA may also be granted "under exceptional circumstances" where the applicant can show that it is unable to provide comprehensive data on efficacy and safety under normal conditions of use even after the product has been authorized and subject to specific procedures being introduced. These circumstances may arise in particular when the intended indications are very rare and, in the state of scientific knowledge at that time, it is not possible to provide comprehensive information, or when generating data may be contrary to generally accepted ethical principles. Like a conditional MA, an MA granted in exceptional circumstances is reserved for medicinal products intended to be authorized for treatment of rare diseases or unmet medical needs for which the applicant does not hold a complete data set that is required for the grant of a standard MA. However, unlike the conditional MA, an applicant for authorization in exceptional circumstances is not subsequently required to provide the missing data. Although the MA "under exceptional circumstances" is granted definitively, the risk-benefit balance of the medicinal product is reviewed annually, and the MA will be withdrawn if the risk-benefit ratio is no longer favorable.

The EU provides opportunities for data and market exclusivity related to MAs. Upon receiving an MA, innovative medicinal products are generally entitled to receive eight years of data exclusivity and 10 years of market exclusivity. Data exclusivity, if granted, 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 MAA can be submitted, and the innovator's data may be referenced. The market exclusivity period prevents a successful generic or biosimilar applicant from commercializing its product in the EU until 10 years have elapsed from the initial MA of the reference product in the EU. The overall ten-year period may, occasionally, be extended for a further year to a maximum of 11 years if, during the first eight years of those ten years, the MA 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. However, there is no guarantee that a product will be considered by the EU's regulatory authorities to be a new chemical/biological entity, and products may not qualify for data exclusivity

In the EU, there is a special regime for biosimilars, or biological medicinal products that are similar to a reference medicinal product but that do not meet the definition of a generic medicinal product. For such products, the results of appropriate preclinical or clinical trials must be provided in support of an application for MA. Guidelines from the EMA detail the type of quantity of supplementary data to be provided for different types of biological products.

Advanced Therapy Medicinal Products in the EU

Advanced Therapy Medicinal Products, ("ATMPs") include gene therapy products as well as somatic cell therapy products and tissue engineered products. The grant of marketing authorization in the EU for products containing viable human tissues or cells such as gene therapy medicinal products is governed by Regulation (EC) No. 1394/2007 on ATMPs, read in combination with Directive (EC) No. 2001/83 of the European Parliament and of the Council, commonly known as the Community code on medicinal products. Regulation (EC) No. 1394/2007 establishes specific rules concerning the authorization, supervision and pharmacovigilance of gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products. Manufacturers of advanced therapy medicinal products must demonstrate the quality, safety and efficacy of their products to the EMA which is required to provide an opinion regarding the application for marketing authorization. The European Commission grants or refuses marketing authorization in light of the opinion delivered by the EMA.

Cell-based products must also comply with Directive (EC) No. 2004/23 of the European Parliament and of the Council of March 31, 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells ("the Tissues and Cells Directive"), as well as its technical implementing directives. This Directive describes the conditions and quality requirements which must be applied when sourcing the cells intended for manufacturing of the cell-based medicinal product. The EU Member States have transposed the Tissues and Cells Directive into their national laws. However, various interpretations of the Tissue and Cells Directive have occurred and are reflected in individual EU Member States national implementing legislation which have led to diverging approaches.

Pediatric Development in the EU

In the EU, Regulation (EC) No 1901/2006 provides that all MAAs for new medicinal products have to include the results of trials conducted in the pediatric population, in compliance with a pediatric investigation plan ("PIP"), agreed with the EMA's Pediatric Committee ("PDCO"). The PIP sets out the timing and measures proposed to generate data to support a pediatric indication of the medicinal product for which MA is being sought. The PDCO can grant a deferral of the obligation to implement some or all of the measures provided in the PIP until there are sufficient data to demonstrate the efficacy and safety of the product in adults. Further, the obligation to provide pediatric clinical trial data can be waived by the PDCO when these data are not needed or appropriate because the product is likely to be ineffective or unsafe in children, the disease or condition for which the product is intended occurs only in adult populations, or when the product does not represent a significant therapeutic benefit over existing treatments for pediatric patients. Once the MA is obtained in all EU Member States and study results are included in the product information, even when negative, the product is eligible for a six-month extension to the Supplementary Protection Certificate ("SPC"), if any is in effect at the time of authorization or, in the case of orphan medicinal products, a two-year extension of orphan market exclusivity.

Expedited Development and Review Programs

The FDA has created programs intended to facilitate and expedite the development and review of new drugs to address the unmet medical need in the treatment of a serious or life-threatening condition.

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 (under which FDA sets a target date for FDA action of the BLA at six months after FDA accepts that application for filing), and the ability to have greater interactions with the FDA.

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. A product candidate intended to treat a serious or life-threatening disease or condition may also be eligible for breakthrough therapy designation to expedite its development and review, if preliminary clinical data indicate that the product 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.

RMAT designation. A designation given to a product candidate that is a regenerative medicine therapy intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the candidate has the potential to address the unmet medical needs for the disease or condition. The FDA has indicated that gene therapies may qualify as regenerative medicine therapies. Advantages of RMAT designation include all the benefits of breakthrough therapy designation, early and frequent 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 six-month goal for reviewing the marketing application or efficacy supplement.

Accelerated approval. The Accelerated Approval Program is a drug development pathway that offers an approval based on a "surrogate" marker in a clinical trial. A surrogate marker is a biomarker or clinical marker that can be measured at an earlier point in a trial than the type of endpoints that may be used in a traditional 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. As a condition of approval, the FDA may require that a sponsor conduct post-marketing clinical trials.

In the EU, innovative products that target an unmet medical need and are expected to be of major public health interest may be eligible for a number of expedited development and review programs, such as the Priority Medicines ("PRIME") scheme, which provides incentives similar to the breakthrough therapy designation in the U.S. PRIME is a voluntary scheme aimed at enhancing the EMA's support for the development of medicinal products that target unmet medical needs. Eligible products must target conditions for which there is an unmet medical need (there is no satisfactory method of diagnosis, prevention or treatment in the EU or, if there is, the new medicinal product will bring a major therapeutic advantage) and they must demonstrate the potential to address the unmet medical need by introducing new methods of therapy or improving existing ones. Benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and potentially accelerated MAA assessment once a dossier has been submitted.

Accelerated assessment may be granted by the CHMP in exceptional cases, when a medicinal product targeting an unmet medical need is expected to be of major interest from the point of view of public health and, in particular, from the viewpoint of therapeutic innovation. If the CHMP accepts a request for accelerated assessment, the time limit of 210 days will be reduced to 150 days (excluding clock stops). The CHMP can, however, revert to the standard time limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment.

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. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. 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.

Orphan drug products are also eligible for Rare Pediatric Disease Designation if greater than 50% of patients living with the disease are under age 18. A priority review voucher will be given to the sponsor of a product with a Rare Pediatric Disease Designation at the time of product approval that is transferable to another company.

In the EU, Regulation (EC) No. 141/2000, as implemented by Regulation (EC) No. 847/2000 provides that a medicinal product can be designated as an orphan medicinal product by the European Commission if its sponsor can establish that: (i) the product is intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions; (ii) either (a) such conditions affect not more than 5 in 10,000 persons in the EU when the application is made, or (b) the product without the benefits derived from orphan status, would not generate sufficient return in the EU to justify the necessary investment in developing the medicinal product; and (iii) there exists no satisfactory authorized method of diagnosis, prevention, or treatment of the condition that has been authorized in the EU, or even if such method exists, the product will be of significant benefit to those affected by that condition.

Regulation (EC) No 847/2000 sets out further provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product. An application for the designation of a medicinal product as an orphan medicinal product must be submitted at any stage of development of the medicinal product but before filing of an MAA. An MA for an orphan medicinal product may only include indications designated as orphan. For non-orphan indications treated with the same active pharmaceutical ingredient, a separate marketing authorization has to be sought.

Orphan medicinal product designation entitles an applicant to incentives such fee reductions or fee waivers, protocol assistance, and access to the centralized marketing authorization procedure. Upon grant of a marketing authorization, orphan medicinal products are entitled to a ten-year period of market exclusivity for the approved therapeutic indication, which means that the EMA cannot accept another marketing authorization application or accept an application to extend for a similar product and the European Commission cannot grant a marketing authorization for the same indication for a period of ten years. The period of market exclusivity is extended by two years for orphan medicinal products that have also complied with an agreed PIP. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications. Orphan medicinal product designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The period of market exclusivity may, however, be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria on the basis of which it received orphan medicinal product destination, including where 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 or where the prevalence of the condition has increased above the threshold. Additionally, an MA may be granted to a similar medicinal product with the same orphan indication during the 10-year period if: (i) if the applicant consents to a second original orphan medicinal product application, (ii) if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities; or (iii) if the second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior to the original orphan medicinal product. A company may voluntarily remove a product from the register of orphan products.

Other Regulatory Requirements

Any biologics manufactured or distributed by us or our collaborators pursuant to FDA or European Commission and other regulatory authorities' approvals would be subject to continuing regulation by the FDA, the EMA, the European Commission, the national competent authorities of EU Member States and other regulatory authorities, including in relation to regulatory requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. Biologic manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies and comparable foreign regulatory authorities.

In addition to an MA, various other requirements apply to the manufacturing and placing on the EU market of medicinal products. The manufacturing of medicinal products in the EU requires a manufacturing authorization and import of medicinal products into the EU requires a manufacturing authorization allowing for import. The manufacturing authorization holder must comply with various requirements set out in the applicable EU laws, regulations and guidance, including EU cGMP standards. Similarly, the distribution of medicinal products within the EU is subject to compliance with the applicable EU laws, regulations and guidelines, including the requirement to hold appropriate authorizations for distribution granted by the competent authorities of EU Member States. Marketing authorization holders and/or manufacturing and import authorization, or MA holders and/or distribution authorization holders may be subject to civil, criminal or administrative sanctions, including suspension of manufacturing authorization, in case of non-compliance with the EU or EU Member States' requirements applicable to the manufacturing of medicinal products.

We, or our third-party manufacturers may be subject to periodic unannounced inspections by the FDA, certain state agencies, national competent authorities of EU Member States and comparable foreign regulatory 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 comparable foreign regulatory requirements. If we or our present or future third-party manufacturers or suppliers are not able to comply with these requirements, the FDA, national competent authorities of EU Member State or other regulatory authorities may impose sanctions on us, including shutdown of the third-party vendor or invalidation of drug product lots or processes, fines, injunctions, civil penalties, delays, suspension, variation or withdrawal of approvals, license revocation, seizures or recalls of product candidates or drugs, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products, if approved, and significantly harm our business, financial condition, results of operations and prospects.

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.

Where an MA is granted in relation to a medicinal product in the EU, the holder of the MA is required to comply with a range of regulatory requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. Similar to the United States, both MA holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA, the European Commission and/or the competent regulatory authorities of the individual EU Member States. The holder of an MA must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance who is responsible for oversight of that system. Key obligations include expedited reporting of suspected serious adverse reactions and submission of periodic safety update reports ("PSURs").

All new MAAs must include a risk management plan, describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the MA. Such risk- minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies.

In the EU, the advertising and promotion of pharmaceutical products are subject to EU and EU Member States' laws governing promotion of medicinal products, interactions with physicians and other healthcare professionals, misleading and comparative advertising and unfair commercial practices. General requirements for advertising and promotion of medicinal products, such as direct-to-consumer advertising of prescription medicinal products are established in EU law. However, the details are governed by regulations in individual EU Member States and can differ from one country to another. For example, applicable laws require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics ("SmPC"), as approved by the competent authorities in connection with a marketing authorization approval. The SmPC is the document that provides information to physicians and other healthcare professionals 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 result in reputational risk, public reprimands, administrative measures, fines and imprisonment.

Data Privacy and Security Laws

In the ordinary course of our business, we process confidential, sensitive, and proprietary information, including personal data. 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 related to data privacy, security, and protection. Such obligations may include, without limitation, the Federal Trade Commission Act, the Telephone Consumer Protection Act of 1991, the Controlling the Assault of Non-Solicited Pornography And Marketing Act of 2003, the California Consumer Privacy Act of 2018 ("CCPA"), the European Union's General Data Protection Regulation 2016/679 ("EU GDPR"), the EU GDPR as it forms part of UK law by virtue of section 3 of the European Union (Withdrawal) Act 2018 ("UK GDPR"), the ePrivacy Directive, 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"). Several states within the United States have enacted or proposed data privacy laws.

The CCPA and EU GDPR are examples of the increasingly stringent and evolving regulatory frameworks related to personal data processing that may increase our compliance obligations and exposure for any noncompliance. For example, the CCPA imposes obligations on covered businesses to provide specific disclosures related to a business's collecting, using, and disclosing personal data and to respond to certain requests from California residents related to their personal data (for example, requests to know of the business's personal data processing activities, to delete the individual's personal data, and to opt out of certain personal data disclosures). Also, the CCPA provides for civil penalties and a private right of action for data breaches which may include an award of statutory damages.

Foreign data privacy and security laws (including but not limited to the EU GDPR and UK GDPR) impose significant and complex compliance obligations on entities that are subject to those laws. As one example, the EU GDPR applies to any company established in the EEA and to companies established outside the EEA that process personal data in connection with the offering of goods or services to data subjects in the EEA or the monitoring of the behavior of data subjects in the EEA. These obligations may include limiting personal data processing to only what is necessary for specified, explicit, and legitimate purposes; requiring a legal basis for personal data 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 data; 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 data; mandating notice of certain personal data 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.

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 their immediate family members;
- Outside the U.S., interactions between pharmaceutical companies and physicians and other healthcare professionals are also governed by strict laws, such as national anti-bribery laws of European countries, national sunshine rules, regulations, industry self-regulation codes of conduct and physicians' codes of professional conduct. Certain EU member states, or industry codes of conduct, require that payments made to physicians be publicly disclosed. Moreover, agreements with healthcare professionals may require prior notification and approval by the healthcare professional'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 and foreign 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 professionals and other potential referral sources; state and foreign 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 and foreign 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.

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 and 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.

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. Further, coverage policies and third-party payer reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained more products for which we receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future. 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 healthcare 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. The Affordable Care Act has been subject to legislative and judicial challenges and amendments, including efforts to repeal, replace, or otherwise modify or to alter its interpretation and implementation. For example, on August 16, 2022, the Inflation Reduction Act of 2022 "Inflation Reduction Act" was signed 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 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 2032 unless additional congressional action is taken. Further, Congress may consider 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, the Inflation Reduction Act also, among other things, (1) directs the U.S. Department of Health and Human Services ("HHS") to negotiate the price of certain single-source biologics that have been on the market for at least 11 years covered under Medicare (the "Medicare Drug Price Negotiation Program") and (2) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. These provisions began to take effect progressively in fiscal year 2023. On August 15, 2024, HHS announced the agreed-upon price of the first ten drugs that were subject to price negotiations, although the Medicare Drug Price Negotiation Program is currently subject to legal challenges. On January 17, 2025, HHS selected fifteen additional products covered under Part D for price negotiation in 2025. Each year thereafter more products covered under Part B and Part D will become subject to the Medicare Drug Price Negotiation Program. Further, on December 7, 2023, an initiative to control the price of prescription drugs through the use of march-in rights under the Bayh-Dole Act was announced. On December 8, 2023, the National Institute of Standards and Technology published for comment a Draft Interagency Guidance Framework for Considering the Exercise of March-In Rights which for the first time includes the price of a product as one factor an agency can use when deciding to exercise march-in rights. While march-in rights have not previously been exercised, it is uncertain if that will continue under the new framework. 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.

In the EU, pricing and reimbursement schemes vary widely from country to country. Some EU Member States may approve a specific price for a product, or they may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other EU Member States allow companies to fix their own prices for products but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions.

In addition, some EU Member States may require the completion of additional studies that compare the cost-effectiveness of a particular medicinal product candidate to currently available therapies. This Health Technology Assessment, or HTA, process 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. 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. In December 2021, Regulation No. 2021/2282 on Health Technology Assessment, or HTA Regulation, was adopted. This Regulation, which entered into force in January 2022 and began to apply on January 12, 2025, through a phased implementation, is intended to boost cooperation among EU Member States in assessing health technologies, including new medicinal products, and provides the basis for cooperation at EU level for joint clinical assessments in these areas. The Regulation permits EU Member States to use common HTA tools, methodologies, and procedures across the EU, working together in four main areas, including joint clinical assessment of the innovative health technologies with the most potential impact for patients, joint scientific consultations whereby developers can seek advice from HTA authorities, identification of emerging health technologies to identify promising technologies early, and continuing voluntary cooperation in other areas. Individual EU Member States continue to be responsible for assessing non-clinical (e.g., economic, social, ethical) aspects of health technologies, and making decisions on pricing and reimbursement. If we are unable to maintain favorable pricing and reimbursement status in EU Member States for drug candidates that we may successfully develop and for which we may obtain regulatory approval, any anticipated revenue from and growth prospects for those products in the EU could be negatively affected.

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.

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, in specific circumstances, 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.

Brexit. The United Kingdom's, or UK, withdrawal from the EU on January 31, 2020, commonly referred to as Brexit, has changed the regulatory relationship between the UK and the EU. The Medicines and Healthcare products Regulatory Agency, or MHRA, is now the UK's standalone regulator for medicinal products and medical devices. The United Kingdom is no longer subject to EU regulations (Northern Ireland continues to follow certain limited EU regulatory rules, including in relation to medical devices, but not in relation to medicinal products).

The UK regulatory framework in relation to clinical trials is governed by the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, which is derived from the CTD, as implemented into UK national law through secondary legislation. On January 17, 2022, the UK Medicines and Healthcare products Regulatory Agency, or MHRA, launched an eight-week consultation on reframing the UK legislation for clinical trials. The UK Government published its response to the consultation on March 21, 2023 confirming that it would bring forward changes to the legislation and such changes were laid in parliament on December 12, 2024. These resulting legislative amendments will, if implemented in their current form, bring the UK into closer alignment with the EU CTR. In October 2023, the MHRA announced a new Notification Scheme for clinical trials which enables a more streamlined and risk-proportionate approach to initial clinical trial applications for Phase 4 and low-risk Phase 3 clinical trial applications.

Marketing authorizations in the UK are governed by the Human Medicines Regulations (SI 2012/1916), as amended. Since January 1, 2021, an applicant for the EU centralized procedure marketing authorization can no longer be established in the UK. As a result, since this date, companies established in the UK cannot use the EU centralized procedure and instead must follow one of the UK national authorization procedures or one of the remaining post-Brexit international cooperation procedures to obtain a marketing authorization to market products in the UK. All existing EU marketing authorizations for centrally authorized products were automatically converted or grandfathered into UK marketing authorization, effective in Great Britain only, free of charge on January 1, 2021, unless the marketing authorization holder opted-out of this possibility. Northern Ireland remained within the scope of EU authorizations in relation to centrally authorized medicinal products until January 1, 2025. However, on January 1, 2025, a new arrangement as part of the so-called "Windsor Framework" came into effect and reintegrated Northern Ireland under the regulatory authority of the MHRA with respect to medicinal products. The Windsor Framework removes EU licensing processes and EU labelling and serialization requirements in relation to Northern Ireland and introduces a UK -wide licensing process for medicines.

The MHRA has also introduced changes to national marketing authorization procedures. This includes introduction of procedures to prioritize access to new medicines that will benefit patients, including a 150-day assessment route, a rolling review procedure and the International Recognition Procedure. Since January 1, 2024, the MHRA may rely on the International Recognition Procedure, or IRP, when reviewing certain types of marketing authorization applications. This procedure is available for applicants for marketing authorization who have already received an authorization for the same product from a reference regulator. These include the FDA, the EMA, and national competent authorities of individual EEA countries. A positive opinion from the EMA and CHMP, or a positive end of procedure outcome from the mutual recognition or decentralized procedures are considered to be authorizations for the purposes of the IRP.

There is no pre-marketing authorization orphan designation for medicinal products in the UK. Instead, the MHRA reviews applications for orphan designation in parallel to the corresponding marketing authorization application. The criteria are essentially the same as those in the EU, but have been tailored for the market. This includes the criterion that prevalence of the condition in the UK, rather than the EU, must not be more than five in 10,000. Upon the grant of a marketing authorization with orphan status, the medicinal product will benefit from up to 10 years of market exclusivity from similar products in the approved orphan indication. The start of this market exclusivity period will be set from the date of first approval of the product in the UK.

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, 2024, we had approximately 155 full-time employees. Of these employees, 35 hold Ph.D. or M.D. degrees, 114 are engaged in research and development, and 41 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 in 2021, 2022, 2023 and 2024 by the San Francisco Chronicle.

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.

Equity, Inclusion and Diversity

We are committed to inclusion across all aspects of our company, including hiring, promotion and development practices. Our employees bring diverse perspectives 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 support employee-led resource groups ("ERGs") and provide resources for our employees to support equity and engagement. We currently have one ERG that represents and supports women in our workforce: SOAR (Supporting Women of All Ranks ERG), providing support and mentorship for our female workforce, including guidance on career advancement. Overall, the goal of ERG programs at Adverum are to 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.

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 Capital 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.

Risks Related to Our Financial Position and Need for Capital

There is substantial doubt regarding our ability to continue as a going concern. We will need to raise substantial additional funding to finance our operations through regulatory approval of our lead program and beyond, which may not be available on acceptable terms, or at all. If we fail to obtain additional capital necessary to fund our operations, we could be forced to delay, limit, reduce or terminate our product development programs, commercialization efforts or other operations, or to cease operations or liquidate our assets.

As of December 31, 2024, our cash, cash equivalents and short-term investments totaled $125.7 million, which we expect to fund our operations into the second half of 2025. We have determined that our existing cash and cash equivalents as of December 31, 2024 would be insufficient to fund our operations through one year from the filing date of this Annual Report on Form 10-K. Because our cash and cash equivalents will not be adequate to fund our operations through at least 12 months from the date the consolidated financial statements in this Annual Report on Form 10-K are issued, there is substantial doubt regarding our ability to continue as a going concern. As a result, the report from our independent registered public accounting firm issued in connection with this Annual Report on Form 10-K contains statements expressing substantial doubt about our ability to continue as a going concern.

Any future clinical trials or ongoing clinical trials of our product candidates could cause an increase in our spending levels, as could 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 or other regulatory authorities outside the United States, 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 commercial validation and 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 effects of competing technological and market developments;
- our ability to establish and maintain partnering arrangements for development and/or commercialization;
- the cost and timing of establishing enhanced internal controls over financial reporting; and
- the costs associated with being a public company.

We may never generate the necessary data or results required to obtain regulatory approval in order to generate revenue from product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products that we do not expect to be commercially available for several years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. We will need to raise substantial additional funding to finance our operations through clinical development of our product candidates and potentially to commercialize these candidates. We continue to analyze various alternatives, including public or private equity or debt financings, third-party funding, revenue interest arrangements, collaborations, strategic alliances and licensing arrangements, or any combination of these approaches. Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. We may experience difficulties in accessing the capital markets due to external factors beyond our control, such as volatility in the equity markets for emerging biotechnology companies and general economic and market conditions both in the U.S. and abroad. For example, our ability to raise additional capital may be adversely impacted by global economic conditions and disruptions to and volatility in the credit and financial markets in the U.S. and worldwide, such as have been experienced recently due in part to, among other things, the impacts of inflation, ongoing overseas conflicts, and disruptions in access to bank deposits and lending commitments due to bank failures. We may be unable to raise additional funds or to enter into such agreements or arrangements on favorable terms, or at all.

If we fail to obtain additional capital necessary to fund our operations, we could be forced to delay, limit, reduce or terminate our product development programs, commercialization efforts or other operations, or to cease operations or liquidate our assets. Although we have been successful in raising capital in the past, there is no assurance that we will be successful in obtaining additional financing. Therefore, we cannot be certain that our plans to raise additional capital will be successful in alleviating the substantial doubt regarding our ability to continue as a going concern. Failure to manage discretionary spending or raise additional financing, as needed, may adversely impact our ability to achieve our intended business objectives. If we do not obtain additional financing and are required to terminate our operations, our stockholders will lose all or a part of their investment.

If we sell shares of our common stock or securities convertible into or exercisable for shares of our common stock in future financings or 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 public or private equity or debt financings, third-party funding, revenue interest arrangements, as well as other collaborations, strategic alliances and licensing arrangements or any combination of these approaches, grants, debt and other financings. We do not have any committed external source of funds. To the extent that we raise additional capital, if available, through the sale of equity or convertible debt securities, including through our “at-the-market” offering program, the ownership interests of our existing stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect such holders' rights as a holder of our common stock. Debt and revenue interest 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 collaborations, strategic alliances, third-party licensing arrangements 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.

The report of our independent registered public accounting firm for the year ended December 31, 2024 contains an explanatory paragraph regarding substantial doubt about our ability to continue as a going concern.

Due to the uncertainty of our ability to meet our current operating and capital expenses, in the auditor’s report on our audited annual financial statements as of and for the year ended December 31, 2024, our independent auditors included a paragraph regarding our ability to continue as going concern. Substantial doubt about our ability to continue as a going concern may materially and adversely affect the price per share of our common stock and we may have a more difficult time obtaining financing. Further, the perception that we may be unable to continue as a going concern may impede our ability to raise additional funds or operate our business due to concerns regarding our ability to discharge our contractual obligations.

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 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 are subject to risks associated with subletting our leased premises, including risks associated with subtenant defaults, which have occurred and we expect to continue to occur.

In January 2021, we entered into an operating lease agreement for a building in North Carolina ("NC Premises") and in October 2021, we entered into a sublease agreement with Jaguar Gene Therapy, LLC, ("Jaguar"), who subsequently assigned the sublease to Advanced Medicine Partners, LLC ("AMP" or the "subtenant") as the subtenant for the NC Premises, through the remainder of the lease term (ending in October 2037). Pursuant to the sublease and the notice and waiver of assignment (the "assignment agreement"), Jaguar remained obligated for AMP's proper performance under the sublease. In February 2025, a lien in the amount of $4.8 million was filed by a third-party contractor against the subtenant's interest in the NC Premises. We discharged the lien in March 2025 by depositing cash in the full amount with the applicable court in order to avoid a default under the head lease. Further liens by third-party subcontractors or other contractors have been or may in the future be filed against the subtenant's interest in the NC Premises, and we may need to also discharge such liens to avoid a default under the head lease. The subtenant and Jaguar failed to remit the March 2025 rent and subsequent rent payments and defaulted, and failed to cure such defaults, under the sublease and the assignment agreement for the NC Premises. As a result, we assumed responsibility for such payments in March 2025. As of April 7, 2025, we have made payments in the total amount of $1.9 million to satisfy outstanding rent and common area management fee obligation, and we remain obligated under the head lease, including for all future remaining rent payments in an aggregate amount of up to $119.7 million for the remainder of the head lease term, of which $5.7 million is due between April 8 and December 31, 2025. As a result of the uncured defaults, we terminated the sublease and initiated a lawsuit against the subtenant and Jaguar in the Superior Court of Wake County, North Carolina to enforce our rights under the sublease and to seek recovery of losses and damages due to the defaults by the subtenant and Jaguar. In the event we are unsuccessful in collecting from the subtenant or Jaguar or are unable to obtain a new subtenant on acceptable terms or at all, we will be required to satisfy our obligations directly to the landlord under the head lease in accordance with its terms.

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 gene therapies, biologics and drugs in development in the pharmaceutical industry, only a small percentage result in the submission of a 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 the operation of our business. In addition, difluprednate eye drops are not approved or commercially available in certain geographies where we intend or may choose to conduct Phase 3 clinical trials and to commercialize Ixo-vec, if approved, which could have an adverse effect on our ability to complete Phase 3 clinical trials or commercialize Ixo-vec in such jurisdictions or on our expected timelines.

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 Ixo-vec is a gene therapy and the broad patient population that it is intended to treat mean 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. Results in trials of competing product candidates or of other companies in our market sector may influence the perception of our product candidates. In addition, we may be adversely impacted if adverse events are reported for our or another party's product or product candidate containing one of our proprietary viral vectors.

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. It is not always possible to accurately 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 could then be 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 if 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, varied or suspended 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 attributed to Ixo-vec, the trial and any 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 and LUNA 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, pigmentary changes, including iris transillumination defects and anterior chamber pigmentation, 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 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. Our LUNA trial is evaluating 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. In November 2024, we announced LUNA 52-week data with a cut-off date of August 29, 2024. Ixo-vec was well-tolerated, and when present inflammation was responsive to per protocol local corticosteroids. Our 52-week data suggest that difluprednate eye drops alone are a promising "go forward" prophylactic regimen for our future pivotal studies. The use of a difluprednate eye drop prophylactic regimen may not be as successful in managing or mitigating inflammation in future, larger clinical trials or commercial use, and our reliance on the availability of these corticosteroids makes us vulnerable to drug shortage or other supply problems. In addition, difluprednate eye drops are not approved or commercially available in certain geographies where we intend or choose to conduct Phase 3 clinical trials, which could have an adverse effect on our ability to complete Phase 3 clinical trials in these jurisdictions on our expected timelines.

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 cause expression of 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 IVT injection and taking aqueous fluid samples from the eye ("aqueous tap"), 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 different 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 benefit-risk 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, EU competent authorities 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 product. 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. 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 are multiple approved and widely adopted standard-of-care therapies, 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") or Ethics Committee and its Institutional Biosafety Committee must review the proposed clinical trial to assess the 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 authorities, 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. We have in the past and may in the future experience difficulties or delays enrolling patients in our clinical trials.

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. 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 meet exclusion criteria that would prevent them from being enrolled in a clinical trial for any of our product candidates. 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., EU and/or other countries 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 EU 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, negative publicity from other adverse events in the biotechnology or gene therapy sector, 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. Similar approvals are required to market our product candidates outside of the U.S. 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 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 in the manufacturing processes, analytical testing or facilities of third-party manufacturers or testing laboratories with which we or any of our future development partners contract for clinical and commercial supplies;
- 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; or
- approval from such authorities may be conditioned on the collection of additional data or otherwise contain significant post-marketing obligations.

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. 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 and Regenerative Medicine Advanced Therapy ("RMAT") designations by the FDA, PRIME designation by the EMA and the Innovation Passport by the MHRA for Ixo-vec may not lead to a faster development, regulatory review or approval, and they do 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 an unmet medical need. 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 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 Priority Review and Rolling Review, which may potentially result in a shorter FDA review process.

In July 2024, FDA granted RMAT designation for Ixo-vec for the treatment of wet AMD. An investigational drug product is eligible for the RMAT designation if: (1) it meets the definition of a regenerative therapy medicine, which includes cell therapies, therapeutic tissue engineering products, human cell and tissue products, or combination products using such therapies or products, with limited exceptions; (2) the product is intended to treat, modify, reverse, or cure a serious disease or condition; and (3) preliminary clinical evidence indicates that the regenerative medicine therapy has the potential to address unmet medical needs for such disease or condition. RMAT designation offers potential benefits that include increased collaboration with the FDA to accelerate development including the potential for Priority Review.

The 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 the potential to target a significant unmet medical need on the basis of data showing a meaningful improvement of clinical outcomes. This regulatory program offers sponsors 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.

The United Kingdom's MHRA granted Ixo-vec an Innovation Passport under the Innovative Licensing and Access Pathway ("ILAP") in April 2023. ILAP is a pathway supporting innovative approaches to the safe, timely, and efficient development of medicines aiming to accelerate the time to market, facilitating patient access to medicines. ILAP is comprised of the Innovation Passport designation and a Target Development Profile and provides applicants with access to a toolkit to support the design, development and approvals process. The Innovation Passport is the first step in the ILAP process, triggering the MHRA and its partner agencies, including the All Wales Therapeutics and Toxicology Centre, the National Institute for Health and Care Excellence, and the Scottish Medicines Consortium to partner with Adverum to charter a roadmap for regulatory and development milestones with the goal of early patient access in the United Kingdom ("UK").

However, Fast Track, RMAT, PRIME and ILAP 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 do not assure ultimate approval by the FDA, the European Commission, or MHRA. In addition, the FDA and MHRA can rescind or revoke the designations for Ixo-vec if the regulatory agencies later determine that Ixo-vec no longer meets the qualifying criteria for such designation. The EMA can remove Ixo-vec from the PRIME eligibility list if Ixo-vec no longer meets the eligibility criteria.

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 and/or through third parties such as CMOs or potential partners, 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, whether conducted at our Redwood City facility, or by external manufacturing, testing, and distribution vendors or potential 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 and viral banks), equipment or facilities (including moving manufacturing or testing from one of our facilities to another one of our facilities or a third-party facility, such as CMOs or potential partners, or from a third-party facility, such as CMOs or potential partners, 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 commencing or completing our clinical studies on the timelines we anticipate, 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, which could delay our commencement or completion of clinical trials.

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 will also 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, face delayed timelines, 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 delay our clinical and/or commercialization timelines, 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. We have in the past and may in the future experience unexpected technical or operational issues during clinical or commercial manufacturing campaigns. As a result, we could experience manufacturing delays that prevent us from commencing or completing clinical studies or 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 canceled or delayed in order to prioritize other projects, we may be unable to produce sufficient quantities of our product candidates for our development programs and for commercialization.

Changes in methods of manufacturing or formulation of our product candidates may result in additional costs or delays.

As our product candidates progress through preclinical to late-stage clinical trials to marketing approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods, formulation, and manufacturing sites are altered along the way in an effort to optimize yield and manufacturing batch size, reduce costs and achieve consistent quality and results. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause our product candidates to perform differently and affect the results of our ongoing and planned clinical trials or other future clinical trials conducted with the altered materials. This could delay completion of clinical trials, require the conduct of bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidates and jeopardize our ability to commercialize our product candidates, if approved, and generate revenue.

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 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. If we or a contract manufacturer are unable to do so, we may experience clinical or commercialization delays or be required to expend significant resources to work with an alternative contract manufacturer. We and our contract manufacturers must also adhere to the FDA's GMP regulations enforced by the FDA through its facilities inspection program as well as other comparable 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.

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 shutdown of the third-party vendor or invalidation of drug product lots or processes, fines, injunctions, civil penalties, delays, suspension, variation or withdrawal of approvals, license revocation, seizures or recalls of product candidates or drugs, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products, if approved, and significantly harm our business, financial condition, results of operations and prospects.

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 the 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 may face difficulties from changes to current regulations and future legislation.

We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the U.S. or abroad. The policies of the FDA, the competent authorities of the EU Member States, the EMA, the European Commission and other comparable regulatory authorities responsible for clinical trials may change and additional government regulations may be enacted. For instance, the regulatory landscape related to clinical trials in the EU recently evolved. The EU Clinical Trials Regulation ("CTR"), which was adopted in April 2014 and repeals the EU Clinical Trials Directive, became applicable on January 31, 2022. The CTR allows sponsors to make a single submission to both the competent authority and an ethics committee in each EU Member State, leading to a single decision for each EU Member State. The assessment procedure for the authorization of clinical trials has been harmonized as well, including a joint assessment by all EU Member States concerned, and a separate assessment by each EU Member State with respect to specific requirements related to its own territory, including ethics rules. Each EU Member State's decision is communicated to the sponsor via the centralized EU portal. Once the clinical trial approved, clinical study development may proceed. The CTR foresaw a three-year transition period that ended on January 31, 2025. Since this date, all new or ongoing trials are subject to the provisions of the CTR. Compliance with the CTR requirements by us and our third-party service providers, such as CROs, may impact our developments plans.

In addition, on April 26, 2023, the European Commission adopted a proposal for a new Directive and Regulation to revise the existing pharmaceutical legislation and on April 10, 2024, the Parliament adopted its related position. The proposed revisions remain to be agreed and adopted by the European Council. Moreover, on December 1, 2024, a new European Commission took office. The proposal could, therefore, still be subject to revision. If adopted in the form proposed, the recent European Commission proposals to revise the existing EU laws governing authorization of medicinal products may result in a decrease in data and market exclusivity opportunities for our product candidates in the EU and make them open to generic or biosimilar competition earlier than is currently the case with a related reduction in reimbursement status.

The United Kingdom's withdrawal from the EU may have a negative effect on global economic conditions, financial markets and our business.

Following Brexit, the UK and the EU signed a EU-UK Trade and Cooperation Agreement, which became provisionally applicable on January 1, 2021 and entered into force on May 1, 2021. This agreement provides details on how some aspects of the UK and EU's relationship will operate going forwards however there are still uncertainties. The EU-UK Trade and Cooperation Agreement primarily focuses on ensuring free trade between the EU and the UK in relation to goods, including medicinal products. Among the changes that have occurred are that the UK is treated as a "third country", a country that is not a member of the EU and whose citizens do not enjoy the EU right to free movement (Northern Ireland continues to follow certain limited EU regulatory rules, including in relation to medical devices, but not in relation to medicinal products). As part of the EU-UK Trade and Cooperation Agreement, the EU and the UK recognize GMP inspections carried out by the other party and the acceptance of official GMP documents issued by the other party. The EU-UK 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 has unilaterally agreed to accept EU batch testing and batch release. 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.

On February 27, 2023, the UK Government and the European Commission reached a political agreement on the so-called "Windsor Framework". The Windsor Framework is intended to revise the Northern Ireland Protocol to address some of the perceived shortcomings in its operation. The agreement was adopted at the Withdrawal Agreement Joint Committee on March 24, 2023 and the arrangements under the Windsor Framework relating to medicinal products took effect on January 1, 2025. As it relates to marketing authorizations, the United Kingdom has a separate regulatory submission process, approval process and a separate national marketing authorization. Northern Ireland continued, until January 1, 2025 to be covered by the marketing authorizations granted by the European Commission but the Windsor Framework provides that the UK MHRA is the sole regulatory body responsible for granting marketing authorizations for Northern Ireland as of January 1, 2025.

A significant proportion of the regulatory framework in the UK applicable to medicinal products is currently derived from EU Directives and Regulations. The potential for UK legislation to diverge from EU legislation following Brexit could materially impact the regulatory regime with respect to the development, manufacture, import, approval, and commercialization of our product candidates in the UK or the EU. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies governing clinical trials, our development plans may be impacted.

All of these changes could increase our costs and otherwise adversely affect our business. Any delay in obtaining, or an inability to obtain, any regulatory approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the UK or the EU and restrict our ability to generate revenue and achieve and sustain profitability. In addition, we may be required to pay taxes or duties or be subjected to other hurdles in connection with the importation of our product candidates into the EU. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the UK or the EU for our product candidates, or incur significant additional expenses to operate our business, which could significantly and materially harm or delay our ability to generate revenues or achieve profitability of our business. Any further changes in international trade, tariff and import/export regulations as a result of Brexit or otherwise may impose unexpected duty costs or other non-tariff barriers on us. These developments, or the perception that any of them could occur, may significantly reduce global trade and, in particular, trade between the impacted nations and the UK. It is also possible that Brexit may negatively affect our ability to attract and retain employees, particularly those from the EU.

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 contamination is discovered in our product candidates or in a 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 and comparable foreign regulatory authorities' 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, variation 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, 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, which could affect the timing of our commencement and completion of clinical studies. 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, EU 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 regulatory filings 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 reduces our control over these activities but does 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 entail 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 rely and will continue to rely on third parties to conduct some nonclinical testing and all of our ongoing and 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 have in the past attempted and may in the future attempt to terminate their agreements with us. We may be unable to obtain a new license to that technology on commercially reasonable terms. 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, importing 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 Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Act") 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 was introduced in 2023. Under the unitary patent system, European applications will 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 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 ("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;
- 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 about the product candidate's chemistry, manufacturing, and controls and our proposed clinical trial protocol, as part of an IND. Similar requirements may apply to conduct clinical trials outside the U.S. 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 or comparable foreign applications 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 outside the U.S. may require us to conduct additional nonclinical testing for any of our product candidates before they allow us to initiate clinical trials 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;
- availability of appropriate prophylaxis in geographies where we intend to conduct our Phase 3 clinical trials and to commercialize Ixo-vec, if approved;
- 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 or Ethics Committee 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 foreign equivalent 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 or Ethics Committees 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 competent authorities, IRBs or Ethics Committees for review and approval, which may impact the costs, timing or successful completion of a clinical trial. If we experience delays in the completion of our clinical trials, or if we, the FDA or other regulatory authorities outside the U.S., the IRB or Ethics Committee, 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, the 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 clinical trial protocols and from time to time may further amend our clinical trial protocols 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. For example, difluprednate eye drops are not approved or commercially available in certain geographies where we intend or may choose to seek regulatory approval for Ixo-vec, and we cannot assure you that the appropriate prophylaxis will be available in such jurisdictions to enable us to obtain regulatory approval to commercialize Ixo-vec. 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's or comparable foreign regulatory authorities' 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.

Disruptions at the FDA or other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, the U.S. government shut down several times and certain regulatory agencies, such as the FDA, furloughed critical employees and ceased critical activities. More recently, such agencies, including the FDA, have conducted layoffs and may, from time to time, conduct additional layoffs. If a prolonged government shutdown or significant layoffs occur, it could significantly impact the ability of the FDA and applicable foreign authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

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 competitive products, some of which are more established than our product candidates;
- availability and market acceptance of an appropriate prophylaxis regimen in geographies where we intend to commercialize Ixo-vec, if approved;
- the limitation of our targeted patient population and other limitations or warnings contained in any labeling approved for our product candidates 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 healthcare providers to potential serious side effects associated with using a product or the imposition of a Risk Evaluation and Mitigation Strategy ("REMS") or comparable foreign strategies;

- acceptance of new therapeutic options by healthcare 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 or foreign equivalents, private health insurers and other third-party payers; 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, 4D Molecular Therapeutics is developing 4D-150, an AAV-based gene therapy delivering two transgenes and encoding a therapeutic antibody fragment similar to aflibercept (Eylea) for the treatment of wet AMD and diabetic macular edema, 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 biosimilars thereto), EYLEA (and any biosimilars thereto) and VABYSMO (and any biosimilars thereto) are currently available or will become available in the U.S. and the EU for treatment of wet AMD. We may 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.

In the United States, most patients receive off-label bevacizumab, including as a first-line treatment. Many patients go on to receive Eylea, Eylea HD or Vabysmo® (faricimab-svoa). We know of a number of additional product candidates in development or approved for chronic retinal conditions that respond to anti-VEGF therapy, including wet AMD:

- biosimilar anti-VEGFs;
- bispecific / combination / add-on therapy for efficacy or durability improvement;
- long-acting delivery device and tyrosine kinase inhibitor implants to lower treatment frequency;
- gene therapy to lower treatment frequency and offer the potential for lifelong injection freedom; and
- other molecules that inhibit neovascularization in wet AMD.

There are several other companies in the U.S. or Europe 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, AbbVie, Bayer, Clearside Biomedical, EyePoint Pharmaceuticals, Kodiak Sciences, Novartis, Ocular Therapeutix, Opthea, Outlook Therapeutics, Regeneron, REGENXBIO and Roche.

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 regulatory approval is obtained, the FDA or comparable foreign regulatory authorities 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 and comparable foreign 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 authority 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 authority 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 authority may:

- issue warning letters or untitled letters;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend, vary 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. Similar restrictions may be imposed by foreign regulatory authorities outside the U.S.

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 us to sell our products at a profit. Further, coverage policies and third-party payer reimbursement rates may change at any time. Therefore, even if favorable coverage and reimbursement status is attained for one or more products for which we receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future. 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 amendments and executive, Congressional, and judicial challenges as well as efforts to repeal, replace, or otherwise modify them or alter their interpretation and implementation. For example, on August 16, 2022, the Inflation Reduction Act of 2022 (the "Inflation Reduction Act") was signed 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.

Outside the United States, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. The EU provides options for EU Member States to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. An EU Member State may approve a specific price for the medicinal product, it may refuse to reimburse a product at the price set by the manufacturer or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. Many EU Member States also periodically review their reimbursement procedures for medicinal products, which could have an adverse impact on reimbursement status.

Moreover, in order to obtain reimbursement for our products in some European countries, including some EU Member States, we may be required to compile additional data comparing the cost-effectiveness of our products to other available therapies. This 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 those representing the larger markets. The HTA process is the procedure to assess therapeutic, economic and societal impact of a given medicinal product in the national healthcare systems of the individual country. The outcome of an HTA will often influence the pricing and reimbursement status granted to these medicinal products by the competent authorities of individual EU Member States. The extent to which pricing and reimbursement decisions are influenced by the HTA of the specific medicinal product currently varies between EU Member States.

Legislators, policymakers and healthcare insurance funds in the EU and the United Kingdom may continue to propose and implement cost-containing measures to keep healthcare costs down. These measures could include limitations on the prices we would be able to charge for product candidates that we may successfully develop and for which we may obtain regulatory approval or the level of reimbursement available for these products from governmental authorities or third-party payers. Further, an increasing number of EU and other foreign countries use prices for medicinal products established in other countries as "reference prices" to help determine the price of the product in their own territory. Consequently, a downward trend in prices of medicinal products in some countries could contribute to similar downward trends elsewhere.

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 2032 unless additional congressional action is taken. Further, there may be additional health reform measures, particularly in light of recent U.S. presidential and congressional elections.

These cost reduction initiatives could decrease the coverage and reimbursement that we receive for any approved products and could seriously harm our business. For example, the Inflation Reduction Act, among other things, (1) directs the U.S. Department of Health and Human Services ("HHS") to negotiate the price of certain single-source biologics that have been on the market for at least 11 years covered under Medicare (the "Medicare Drug Price Negotiation Program") and (2) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. These provisions began to take effect beginning fiscal year 2023. On August 15, 2024, HHS announced the agreed-upon reimbursement price of the first ten drugs that were subject to price negotiations, although the Medicare Drug Price Negotiation Program is currently subject to legal challenges. On January 17, 2025, HHS selected fifteen additional products covered under Part D for price negotiation in 2025. Each year thereafter more products covered under Part B and Part D will become subject to the Medicare Drug Price Negotiation Program. The Inflation Reduction Act permits HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. HHS has and will continue to issue and update guidance as these programs are implemented. Further, on December 7, 2023, an initiative to control the price of prescription drugs through the use of march-in rights under the Bayh-Dole Act was announced. On December 8, 2023, the National Institute of Standards and Technology published for comment a Draft Interagency Guidance Framework for Considering the Exercise of March-In Rights which for the first time includes the price of a product as one factor an agency can use when deciding to exercise march-in rights. While march-in rights have not previously been exercised, it is uncertain if that will continue under the new framework.

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.

In December 2021, Regulation No 2021/2282 on HTA amending Directive 2011/24/EU, was adopted in the EU. This Regulation, which entered into force in January 2022 and began to apply on January 12, 2025, through a phased implementation, is intended to boost cooperation among EU Member States in assessing health technologies, including new medicinal products, and providing the basis for cooperation at EU level for joint clinical assessments in these areas. The Regulation foresees a three-year transitional period and permits EU Member States to use common HTA tools, methodologies, and procedures across the EU, working together in four main areas, including joint clinical assessment of the innovative health technologies with the most potential impact for patients, joint scientific consultations whereby developers can seek advice from HTA authorities, identification of emerging health technologies to identify promising technologies early, and continuing voluntary cooperation in other areas. Individual EU Member States will continue to be responsible for assessing non-clinical (e.g., economic, social, ethical) aspects of health technologies, and making decisions on pricing and reimbursement. If we are unable to maintain favorable pricing and reimbursement status in EU Member States for product candidates that we may successfully develop and for which we may obtain regulatory approval, any anticipated revenue from and growth prospects for those products in the EU could be negatively affected. In light of the fact that the United Kingdom has left the EU, Regulation No 2021/2282 on HTA will not apply in the United Kingdom. However, the UK MHRA is working with UK HTA bodies and other national organizations, such as the Scottish Medicines Consortium ("SMC"), the National Institute for Health and Care Excellence ("NICE"), and the All-Wales Medicines Strategy Group, to introduce new pathways supporting innovative approaches to the safe, timely and efficient development of medicinal products.

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, which is a leading cause of blindness in patients over 65 years of age. 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 its 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 outside the U.S. 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, commercialization 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 in the future enter into additional development, commercialization or other strategic collaborations. Research activities under our collaboration agreements may be 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 establish a partnering arrangement and/or 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 receives regulatory approval, we may not be able to effectively market and distribute the product candidate. We would have to establish a partnering arrangement for commercialization and/or 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, leads to expression of a codon-optimized version of 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 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. Previously, we have had significant changes in our executive management team, and from time to time, may experience additional changes in our executive management team resulting from the hiring or departure of executives. While we seek to manage these transitions carefully, these and any other such changes may result in a loss of institutional knowledge and cause disruptions to our business.

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

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

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

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

If our information technology systems or those third parties with whom we work, or our data, 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 the third parties with whom we work, process, collect, receive, store, process, generate, use, transfer, disclose, make accessible, protect, secure, dispose of, transmit and share (collectively, process) proprietary, confidential, and sensitive data, including personal data (such as health-related data), intellectual property and trade secrets (collectively, sensitive information).

Cyber-attacks, malicious internet-based activity, online and offline fraud, and other similar activities threaten the confidentiality, integrity, and availability of our sensitive information and information technology systems, and those of the third parties with whom we work. Such threats are prevalent and continue to rise, are increasingly difficult to detect, and come from a variety of sources, including traditional computer “hackers,” threat actors, “hacktivists,” 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 with whom we work, 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 goods and services.

We and the third parties with whom we work are subject to a variety of evolving threats, including but not limited to social-engineering attacks (including through deep fakes, which may be increasingly more difficult to identify as fake, and phishing attacks), malicious code (such as viruses and worms), malware (including as a result of advanced persistent threat intrusions), denial-of-service attacks, credential stuffing attacks, 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, earthquakes, fires, floods, attacks enhanced or facilitated by AI, and other similar threats.

In particular, severe ransomware attacks are becoming increasingly prevalent and can lead to significant interruptions in our operations, disruptions of clinical trials, ability to provide our services, loss of sensitive 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 such payments.

Remote work 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. 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.

We rely on third parties to operate critical business systems to process sensitive information 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. 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 the third parties with whom we work experience a security incident or other interruption, we could experience adverse consequences. While we may be entitled to damages if the third parties with whom we work 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 that of the third parties with whom we work have not been compromised. While we have implemented security measures designed to protect against security incidents, there can be no assurance that these measures will be effective.

We take steps designed to detect, mitigate, and remediate vulnerabilities in our information systems (such as our hardware and/or software, including that of third parties with whom we work). We may not, however, detect and remediate all such vulnerabilities including on a timely basis. Further, we may experience delays in developing and deploying remedial measures and patches designed to address identified vulnerabilities. Vulnerabilities could be exploited and result in a security incident.

Any of the previously identified or similar threats could cause a security incident or other interruption that could result in the unauthorized, unlawful, or accidental acquisition, modification, destruction, loss, alteration, encryption, disclosure of, or access to our sensitive information or our information technology systems, or those of the third parties with whom we work. For example, in December 2024, we were the target of nine unsuccessful phishing attempts and expect such attempts will continue in the future and we cannot guarantee that our employees will not succumb to, or that our security measures will adequately detect or prevent, such phishing attacks. A security incident or other interruption could disrupt our ability (and that of third parties with whom we work) to provide our services.

We 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 require us to implement and maintain specific security measures, industry-standard or reasonable security measures to protect our information technology systems and sensitive 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.

Applicable data privacy and security obligations may require us, or we may voluntarily choose, to notify relevant stakeholders, including partners, affected individuals, regulators, and investors of security incidents, or to take other actions, such as providing credit monitoring and identity theft protection services. Such disclosures and related actions can be costly, and the disclosures or the failure to comply with such applicable requirements could lead to adverse consequences.

If we (or a third-party with whom we work) experience a security incident or are perceived to have experienced a security incident, we may experience material adverse consequences, such as government enforcement actions (for example, investigations, fines, penalties, audits, and inspections); additional reporting requirements and/or oversight; restrictions on processing sensitive information (including personal data); litigation (including class claims); indemnification obligations; negative publicity; reputational harm; monetary fund diversions; diversion of management attention; interruptions in our operations (including availability of data); financial loss; and other similar harms.

Security incidents and attendant material consequences may prevent or cause customers to stop using our services, deter new customers from using our services, and negatively impact our ability to grow and operate our business. 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 sensitive information or applications, or inappropriate disclosure of such sensitive 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 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 sensitive 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. Additionally, our sensitive information could be leaked, disclosed, or revealed as a result of or in connection with employees', contractors' or vendors' use of generative artificial intelligence ("AI") technologies.

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, or foreign equivalents.

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, and foreign equivalents. 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.

HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act ("HITECH") and their respective implementing regulations, which impose obligations on covered health care providers, health plans, and health care clearinghouses, as well as their business associates that create, receive, maintain, or transmit individually identifiable health information for or on behalf of a covered entity and their subcontractors that use, disclose, access, or otherwise process protected health information, with respect to safeguarding the privacy, security and transmission of individually identifiable health information.

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 is an increase in 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.

Outside the United States, interactions between pharmaceutical companies and health care professionals are also governed by strict laws, such as national anti-bribery laws of European countries, national sunshine rules, regulations, industry self-regulation codes of conduct and physicians' codes of professional conduct. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

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 and the third parties with whom we work are subject to stringent and evolving U.S. and foreign laws, regulations, rules, contractual obligations, industry standards, policies, and other obligations related to data privacy and security. Our (or the third parties with whom we work) actual or perceived failure to comply with such obligations could lead to regulatory investigations or actions, litigation (including class claims) and mass arbitration demands, 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 process sensitive information, including personal data, business data, trade secrets, intellectual property, and data we collect about trial participants in connection with clinical trials. Our data processing activities subject us to numerous data privacy and security obligations, such as various laws, regulations, guidance, industry standards, external and internal privacy and security policies, contractual requirements, and other obligations relating to data privacy and security, including information that we collect or will collect about clinical trial 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, including data breach notification laws, personal data privacy laws, consumer protection laws (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 HITECH, imposes specific requirements relating to the privacy, security, and transmission of individually identifiable protected health information. We 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.

Numerous U.S. states have enacted comprehensive privacy laws that impose certain obligations on covered businesses, including providing specific disclosures in privacy notices and affording residents with certain rights concerning their personal data. As applicable, such rights may include the right to access, correct, or delete certain personal data, and to opt-out of certain data processing activities, such as targeted advertising, profiling, and automated decision-making. The exercise of these rights may impact our business and ability to provide our products and services. Certain states also impose stricter requirements for processing certain personal data, including sensitive information, such as conducting data privacy impact assessments. These state laws allow for statutory fines for noncompliance. For example, the California Consumer Privacy Act of 2018 (the "CCPA") applies to personal data of consumers, business representatives, and employees who are California residents, and requires businesses to provide specific disclosures in privacy notices and honor requests of such individuals to exercise certain privacy rights. The CCPA provides for fines and allows private litigants affected by certain data breaches to recover significant statutory damages.

The CCPA and other comprehensive U.S. privacy laws exempt some data processed in the context of clinical trials, but these developments may further complicate compliance efforts, and increase legal risk and compliance costs for us, and the third parties with whom we work. Similar laws are being considered in several other states, as well as at the federal and local levels, and we expect more states to pass similar laws in the future.

Outside the U.S., an increasing number of laws, regulations, and industry standards govern data privacy and security. For example, the European Union's General Data Protection Regulation 2016/679 ("EU GDPR"), the United Kingdom's GDPR ("UK GDPR", and, together with the EU GDPR, the "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 data. For example, under the GDPR, companies may face temporary or definitive bans on data processing and other corrective actions; fines of up to 20 million Euros under the EU GDPR, 17.5 million pounds sterling under the UK GDPR or, in each case, 4% of annual global revenue, whichever is greater; or private litigation related to processing of personal data brought by classes of data subjects or consumer protection organizations authorized by law to represent their interests.

In the ordinary course of business, we transfer personal data from Europe and other jurisdictions to the U.S. or other countries. Europe and other jurisdictions have enacted laws requiring data to be localized or limiting the transfer of personal data to other countries. In particular, the EEA and the UK have significantly restricted the transfer of personal data to the U.S. and other countries whose privacy laws it generally believes are inadequate. Other jurisdictions may adopt or have already adopted similarly stringent data localization and cross-border data transfer laws.

Although there are currently various mechanisms that may be used to transfer personal data from the EEA and UK to the U.S. in compliance with law, such as the EEA's standard contractual clauses, the UK's International Data Transfer Agreement / Addendum, and the EU-U.S. Data Privacy Framework and the UK extension thereto (which allows for transfers to relevant U.S.-based organizations who self-certify compliance and participate in the Framework), 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 data to the U.S.

If there is no lawful manner for us to transfer personal data from the EEA, 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 (such as Europe) 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 data necessary to operate our business. Additionally, companies that transfer personal data out of the EEA and UK to other jurisdictions, particularly to the U.S., are subject to increased scrutiny from regulators, individual litigants, and activist groups. Some European regulators have ordered certain companies to suspend or permanently cease certain transfers of personal data out of Europe for allegedly violating the GDPR's cross-border data transfer limitations.

In addition to data privacy and security laws, we are contractually subject to industry standards adopted by industry groups and, we are, or may become subject to such obligations in the future. We are also bound by contractual obligations related to data privacy and security, and our efforts to comply with such obligations may not be successful. For example, certain privacy laws, such as the GDPR and the CCPA, require our customers to impose specific contractual restrictions on their service providers.

Our employees and contractors use generative AI technologies to perform work, and the disclosure and use of personal data in generative AI technologies is subject to various privacy laws and other privacy obligations. Governments have passed and are likely to pass additional laws regulating generative AI. Our use of this technology could result in additional compliance, costs, regulatory investigations and actions, and lawsuits. If we are unable to use generative AI, it could make our business less efficient and result in competitive disadvantages.

Obligations related to data privacy and security (and consumers' data privacy expectations) are quickly changing, becoming increasingly stringent, and creating 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 us to devote significant resources, which may necessitate changes to our services, information technologies, systems, and practices and to those of any third parties that process personal data on our behalf. In addition, these obligations may require us to change our business model.

We publish privacy policies, marketing materials, presentations, and other statements regarding data privacy and security. If these policies, materials or statements are found to be deficient, lacking in transparency, deceptive, unfair, or misrepresentative of our practices, we may be subject to investigation, enforcement actions by regulators or other adverse consequences.

We may at times fail (or be perceived to have failed) in our efforts to comply with our data privacy and security obligations. Moreover, despite our efforts, our personnel or third parties with whom we work may fail to comply with such obligations, which could negatively impact our business operations. If we or the third parties with whom we work fail, or are perceived to have failed, to address or comply with applicable data privacy and security obligations, we could face significant consequences, including but not limited to: government enforcement actions (e.g., investigations, fines, penalties, audits, inspections, and similar); litigation (including class-action claims) and mass arbitration demands; additional reporting requirements and/or oversight; bans or restrictions on processing personal data; orders to destroy or not use personal data; and imprisonment of company officials. In particular, plaintiffs have become increasingly more active in bringing privacy-related claims against companies, including class claims and mass arbitration demands. Some of these claims allow for the recovery of statutory damages on a per violation basis, and, if viable, carry the potential for monumental statutory damages, depending on the volume of data and the number of violations. 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, as relevant, clinical trials); interruptions or stoppages of data collection needed to train our algorithms; inability to process personal data 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 substantial changes to our business model or 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 manufacturers 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 manufacturers 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 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 development partners are successful in commercializing our products, the FDA and foreign regulatory authorities will 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 or comparable foreign regulations, including those laws requiring the reporting of true, complete and accurate information to regulatory authorities, (2) manufacturing standards, (3) federal, state and foreign 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 or comparable foreign 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.

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 Tax Cuts and Jobs Act, federal net operating losses ("NOL") 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 2020 is limited. In addition, under Section 382 of the Internal Revenue Code of 1986, 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 own at least 5% of a corporation's stock within a specified testing period. Similar rules may apply under state tax laws. We are conducting a Section 382 study, which is still subject to finalization, but which may show that we experienced an ownership change in 2024. If such ownership change has occurred, up to the vast majority of the NOLs, capital losses and research credit carryforwards presented in our consolidated financial statements would be subject to limitations and therefore may expire unutilized. In addition, states may suspend the ability to use NOLs and research credits which could further limit our ability to use our NOLs and research credits to offset state taxable income and taxes.

For example, California has enacted legislation that, with certain exceptions, suspends the ability to use California net operating losses to offset California income and limits the ability to use California business tax credits to offset California taxes, for taxable years beginning on or after January 1, 2024, and before January 1, 2027.

Potential natural disasters, some possibly related to the increasing effects of climate change, could damage, destroy or disrupt operations at our office and laboratories, CMO premises, study sites, and/or other third-party vendor sites, which could have a significant negative impact on our operations.

We are vulnerable to the increasing impact of climate change and other natural disasters. Volatile changes in weather conditions, including extreme heat or cold, could increase the risk of wildfires, floods, blizzards, hurricanes and other weather-related disasters. Such extreme weather events, or other natural disasters such as earthquakes, can cause power outages and network disruptions that may result in damage, destruction or disruption to operations at our offices, laboratories, CMO premises, or other third-party vendor sites and may impact our ability to continue or complete our clinical studies or to produce, characterize or otherwise develop our product candidate which could negatively impact our operations and delay our plans to commercialize our product candidates. They could also cause significant damage to or destruction of our clinical study sites resulting in temporary or long-term closures of these facilities. Such disasters could also result in loss or damage to our office buildings, laboratories, CMO premises, employee and/or patient homes, employees and/or patients relocating to other parts of the country or being unwilling to travel to the clinical study site locations, and the inability to recruit key employees and/or enroll patients. This could result in adverse impacts to the available workforce and/or patient enrollment in our clinical studies, damage to or destruction of materials and/or data, or the inability to conduct clinical studies and deliver new data.

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;
- sales of our stock by insiders and stockholders;
- trading volume of our common stock;
- general economic, industry and market conditions other events or factors, many of which are beyond our control;
- additions or departures of key personnel; and
- intellectual property, product liability or other litigation against us.

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

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 are unable to remedy the material weakness, or if we fail to maintain an effective system of internal control over financial reporting in the future, we may not be able to accurately report our financial condition, results of operations or cash flows, which may adversely affect investor confidence in our company and, as a result, the value of our common stock.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal control over financial reporting and disclosure controls and procedures. We are required, pursuant to Section 404 of the Sarbanes-Oxley Act, to furnish a report by management on, among other things, the effectiveness of our internal control over financial reporting.

Complying with Section 404 requires a rigorous compliance program as well as adequate time and resources. We may not be able to complete our internal control evaluation, testing and any required remediation in a timely fashion.

As more fully described in Part II, Item 9A, in connection with our preparation of the consolidated financial statements for the year ended December 31, 2024 we have identified non-cash errors in the accounting for tenant improvement allowances that resulted in the restatement of our consolidated financial statements as of and for the year ended December 31, 2023, as well as the unaudited condensed consolidated quarterly financial information for the quarterly periods in the years ended December 31, 2023 and 2024. These errors were indicative of a material weakness in our controls over lease accounting as of December 31, 2024. A material weakness is a deficiency, or combination of deficiencies, in internal control over financial reporting such that there is a reasonable possibility that a material misstatement of the Company's annual or interim financial statements will not be prevented or detected on a timely basis. We previously identified a material weakness as of December 31, 2022, related to a non-cash lease accounting error related to another operating lease in previously issued financial statements. We have also identified other control deficiencies. We cannot be certain that additional material weaknesses and control deficiencies will not be discovered in the future. If our efforts to remediate the material weakness are not successful, material weaknesses are identified in the future or we are not able to comply with the requirements of Section 404 in a timely manner, our reported financial results could be materially misstated, and we could be subject to investigations or sanctions by regulatory authorities, which would require additional financial and management resources, and the value of our common stock could decline. To the extent we identify future weaknesses or deficiencies, there could be material misstatements in our consolidated financial statements, and we could fail to meet our financial reporting obligations. As a result of failure to remediate the material weakness or future weaknesses or deficiencies, our ability to obtain additional financing, or obtain additional financing on favorable terms, could be materially and adversely affected, which, in turn, could materially and adversely affect our business, our financial condition and the value of our common stock. If we are or remain unable to assert that our internal control over financial reporting is effective in the future, investor confidence in the accuracy and completeness of our financial reports could be further eroded, which would have a material adverse effect on the price of our common stock.

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 1C. Cybersecurity

Risk Management and Strategy

We have implemented and maintain various information security processes designed to identify, assess and manage material risks from cybersecurity threats to our critical computer networks, third-party hosted services, communications systems, hardware and software, and our critical data, including intellectual property, confidential information that is proprietary, strategic or competitive in nature, and clinical trial data ("Information Systems and Data").

Our information security function, which includes our Vice President of Information Technology ("IT") and third-party service providers, legal department and security committee, helps identify, assess, and manage the Company's cybersecurity threats and risks. Our information security function identifies and assesses risks from cybersecurity threats by monitoring and evaluating our threat environment using various methods including, for example: using automated tools, conducting audits, evaluating threats, and performing vulnerability assessments.

Depending on the environment, systems, and data at issue, we implement and maintain various technical, physical, and organizational measures, processes, and policies designed to manage and mitigate material risks from cybersecurity threats to our Information Systems and Data, including, for example: cybersecurity insurance, physical security, incident detection and response, access controls, employee training, penetration testing, and systems monitoring.

Our assessment and management of material risks from cybersecurity threats are integrated into the Company's overall risk management processes. For example, our Vice President of IT, works with management to prioritize our risk management processes and mitigate cybersecurity threats that are more likely to lead to a material impact to our business.

We use third-party service providers to assist us from time to time to identify, assess, and manage material risks from cybersecurity threats, including for example: cybersecurity software providers, managed cybersecurity service providers, penetration testing firms, and cybersecurity consultants.

We use third-party service providers to perform a variety of functions throughout our business, such as contract research organizations, contract manufacturing organizations, and supply chain resources. We have a vendor management process to manage cybersecurity risks associated with certain of these providers. Depending on the nature of the services provided, the sensitivity of the Information Systems and Data at issue, and the identity of the provider, our vendor management process may involve different levels of diligence designed to help identify cybersecurity risks associated with a provider such as risk assessments and reviewing security assessments and reports.

For a description of the risks from cybersecurity threats that may materially affect the Company and how they may do so, see our risk factors under Part 1. Item 1A. Risk Factors in this Annual Report on Form 10-K, including the risk factor entitled: ***If our information technology systems or those third parties with whom we work, or our data, 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.***

Governance

Our Board of Directors addresses the Company's cybersecurity risk management as part of its general oversight function. The Board of Directors is responsible for overseeing Company's cybersecurity risk management processes, including oversight of mitigation of risks from cybersecurity threats.

Our cybersecurity risk assessment and management processes are implemented and maintained by certain Company management, including our Vice President of IT, who holds a Bachelor of Science in Computer Methods from California State University-Long Beach and has previously served as a Director and Associate Director of IT for large pharmaceutical companies.

Our management, including our Chief Operating Officer and Vice President of IT, is responsible for hiring appropriate information security personnel, helping to integrate cybersecurity risk considerations into the Company's overall risk management strategy, and helping prepare for cybersecurity incidents.

Our cybersecurity incident response processes are designed to escalate certain cybersecurity incidents to members of management depending on the circumstances, including our Vice President of IT and General Counsel, who work with the Company's incident response team to help the Company mitigate and remediate cybersecurity incidents of which they are notified. In addition, the Company's incident response process includes reporting to the Audit Committee of the Board of Directors for certain cybersecurity incidents.

The Board of Directors receives periodic reports from the management concerning the Company's significant cybersecurity threats and risk and the processes the Company has implemented to address them. The Board of Directors also has access to various reports, summaries or presentations related to cybersecurity threats, risk, and mitigation.

Item 2. Properties

Our corporate headquarters are located in Redwood City, California, consisting of approximately 79,675 square feet of office and laboratory space under a lease that will expire in December 2031.

In addition, we lease a manufacturing facility in North Carolina, consisting of approximately 173,820 square feet, under a lease that will expire in 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

In October 26, 2021, we entered into a sublease agreement with Jaguar, who subsequently assigned the sublease to AMP, as the subtenant for the NC Premises, for the remainder of the underlying lease term (ending in October 2037). Pursuant to the sublease and the assignment agreement, Jaguar remained obligated for AMP's proper performance under the sublease. In February 2025, a lien in the amount of $4.8 million was filed by a third-party contractor against the subtenant's interest in the NC Premises. We discharged the lien in March 2025 by depositing cash in the full amount with the applicable court in order to avoid a default under the head lease. Further liens by third-party subcontractors or other contractors have been or may in the future be filed against the subtenant's interest in the NC Premises and we may need to also discharge such liens to avoid a default under the head lease. The subtenant and Jaguar failed to remit March 2025 rent and subsequent rent payments and defaulted, and failed to cure such defaults, under the sublease and the assignment agreement for the NC Premises. As a result, we assumed responsibility for such payments in March 2025. As of April 7, 2025, we have made payments in the total amount of $1.9 million to satisfy outstanding rent and common area management fee obligation, and we remain obligated under the head lease, including for all future remaining rent payments in an aggregate amount of up to $119.7 million for the remainder of the head lease term, of which $7.1 million is due between April 8 and December 31, 2025. As a result of the uncured defaults, we terminated the sublease and initiated a lawsuit against the subtenant and Jaguar in the Superior Court of Wake County, North Carolina to enforce our rights under the sublease and seek recovery of losses and damages due to the defaults by the subtenant and Jaguar.

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 Capital Market under the symbol "ADVM".

Holders of Record

As of April 4, 2025, we had approximately 10 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, 2024, we had an accumulated deficit of $1.1 billion. 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 still in clinical 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.

On March 21, 2024, we effected a 1-for-10 reverse stock split of our common stock. The par value and the authorized shares of our common stock were not adjusted as a result of the reverse stock split. All equity-related information including per share amounts for all periods presented in this Annual Report on Form 10-K have been adjusted retroactively, where applicable, to reflect this reverse stock split.

Private Placements

On February 7, 2024, we completed a private placement of 10.5 million shares of our common stock and, in lieu of common stock, prefunded warrants to purchase an aggregate of 75,000 shares of common stock (the "Pre-Funded Warrants") to certain institutional and accredited investors and a concurrent private placement to certain directors of 23,000 shares of our common stock for total gross proceeds of $127.8 million, before deducting placement agent fees and offering expenses (the "Private Placements").

Restatement of Previously Issued Financial Statements

On March 28, 2025, the Audit Committee of our Board of Directors (the "Audit Committee"), following consultation management and our independent registered public accounting firm, Ernst & Young LLP, concluded that certain of our previously issued financial statements should no longer be relied upon due to non-cash errors identified in the accounting for tenant improvement allowances associated with an operating lease and sublease related to a building in North Carolina (the "NC Premises").

In January 2021, we entered into the operating lease for the NC Premises, and in October 2021, we entered into the sublease agreement with Jaguar Gene Therapy, LLC ("Jaguar"), who subsequently assigned the sublease to Advanced Medicine Partners, LLC ("AMP" or the "subtenant") as the subtenant for the NC Premises, through the remainder of the lease term. While preparing the consolidated financial statements as of and for the year ended December 31, 2024, management discovered non-cash errors in our accounting for our operating lease and sublease of the NC Premises. The errors relate solely to our accounting for tenant improvement allowances provided by the landlord to the Company under the operating lease, which were subsequently conveyed from the Company to the subtenant under the sublease, and to a lesser extent, to the assessment of the probability of collection of the lease payments from the subtenant over the remaining term of the sublease. The errors affect the reported amounts of non-cash assets and liabilities, and non-cash general and administrative expenses, related to the lease and sublease (the "Misstatements").

The Misstatements relate solely to the NC Premises and require non-cash corrections to our previously issued audited consolidated financial statements as of and for the years ended December 31, 2022 and 2023, included in our Annual Report on Form 10-K for the year ended December 31, 2023 (the "2023 Annual Report"), as well as the unaudited condensed consolidated quarterly financial information for the quarterly periods in the years ended December 31, 2023 and 2024 (collectively the "Restated Periods"), included in the Company's Quarterly Reports on Form 10-Q for the quarterly periods within those years ("Quarterly Reports" and, together with the 2023 Annual Report, the "Affected Reports"). The Audit Committee concluded that it is appropriate to correct the Misstatements by restating the financial statements for the Restated Periods.

The restated financial statements for the Restated Periods are included in this Annual Report on Form 10-K and we do not intend to separately amend the Affected Reports.

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.

Other Income, Net

Other income, 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 Research and Development Expense

We estimate our accrued 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.

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

- contract manufacturers in connection with the production of clinical trial materials;
- vendors in connection with nonclinical development activities; and
- service 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. Due to the nature of these estimates, we cannot assure you that we will not materially 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, 2024 and 2023, there were no material changes from our prior estimates of accrued research and development expenses.

Leases

For our long-term operating leases, we recognize a right-of-use asset and a lease liability on our consolidated balance sheets. We determine if an arrangement contains a lease and the classification of the lease at inception based on the unique facts and circumstances present in the arrangement. Lease liabilities and their corresponding right-of-use assets are recorded based on the present value of lease payments and lease incentives over the expected lease term. Lease incentives are included in the measurement of the consideration in the contract at lease commencement when we are reasonably certain to incur costs to construct lessee assets. In order to determine the incremental borrowing rate, we determine 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. The incremental borrowing rate, the ROU asset and the lease liability are reevaluated upon a lease modification. We elected to combine lease and non-lease components for all underlying assets groups. We determine the lease term at the commencement date by considering whether renewal options and termination options are reasonably assured of exercise. For short term leases, we do not recognize a right-of-use asset and lease liability and recognize the lease expense over the term of the lease on a straight-line basis.

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.

We assess the probability of collecting lease payments under our sublease at each reporting date. We currently believe that collection of lease payments is improbable and therefore sublease income is constrained at the lesser of cash payments or straight-line sublease income. Sublease income/loss for operating leases is classified in general and administrative expenses based on payments collected and tenant improvement allowance disbursed to the subtenant.

Recent Accounting Pronouncements

Information regarding recent accounting pronouncements applicable to us is included in Note 3. Summary of Significant Accounting Policies to the consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Results of Operations

Comparison of Results of Operations for the Years Ended December 31, 2024 and 2023

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

	Years ended December 31,		
	2024	2023 As Restated	Increase/ (Decrease)
		(In thousands)	
License revenue	$ 1,000	$ 3,600	$ (2,600)
Operating expenses:			
Research and development	77,041	77,486	(445)
General and administrative	63,118	55,056	8,062
Total operating expenses	140,159	132,542	7,617
Operating loss	(139,159)	(128,942)	(10,217)
Other income, net	8,232	5,748	2,484
Net loss before income taxes	(130,927)	(123,194)	(7,733)
Income tax benefit	—	1,078	(1,078)
Net loss	$ (130,927)	$ (122,116)	$ (8,811)

License Revenue

The $1.0 million of license revenue for the year ended December 31, 2024 was related to a milestone payment received from Ray Therapeutics, Inc. (“Ray”) pursuant to a license agreement we had entered into with Ray in February 2023. The $3.6 million of license revenue for the year ended December 31, 2023 was primarily related to a milestone payment received from Lexeo Therapeutics, Inc.(“Lexeo”) pursuant to a license agreement we had entered into with Lexeo in January 2021.

Research and Development Expense

The following table summarizes our research and development expenses for the years ended December 31, 2024 and 2023:

	Years ended December 31,		
	2024	2023 As Restated	Increase/ (Decrease)
		(In thousands)	
Direct research and development expenses			
Ixo-vec	$ 28,552	$ 23,256	$ 5,296
Other programs	2,865	2,630	235
Indirect research and development expense			
Personnel related (including stock-based compensation)	33,041	30,716	2,325
Facilities and other unallocated research and development expenses	12,583	20,884	(8,301)
Total research and development expenses	$ 77,041	$ 77,486	$ (445)

Research and development expenses decreased by $0.5 million to $77.0 million for the year ended December 31, 2024 from $77.5 million for the year ended December 31, 2023. This overall decrease was primarily related to a decrease of $8.3 million in rent expense driven by a lease termination in the prior year, partially offset by an increase of $5.3 million in spending on Ixo-vec in preparation for Phase 3 clinical development, an increase of $2.3 million in personnel-associated costs due to higher headcount, and an increase of $0.2 million related to other programs.

For the periods presented, our research and development activities were attributable to Ixo-vec and our earlier-stage research programs. We expect that research and development expenses will increase in future periods as we focus on advancing Ixo-vec for the treatment of wet AMD into Phase 3.

General and Administrative Expense

General and administrative expense increased by $8.1 million to $63.1 million for the year ended December 31, 2024 from $55.1 million for the year ended December 31, 2023, primarily related to an increase of $14.3 million in facilities expenses driven by non-cash tenant improvement allowances made available to the subtenant of the NC Premises and a $0.6 million increase in professional services. These increases were partially offset by a $6.3 million decrease in depreciation expense and rent expense driven by the lease termination in the prior year and a decrease of $0.7 million in insurance costs due to a decrease in premiums.

We expect that general and administrative expenses will increase in future periods as we focus on advancing Ixo-vec for the treatment of wet AMD.

Other Income, Net

The increase of $2.5 million in other income, net for the year ended December 31, 2024 as compared to 2023 was primarily due to higher average yields on investments.

Income Tax Benefit

There was no income tax benefit during the year ended December 31, 2024. We derecognized the liability of $1.1 million for the year ended December 31, 2023 arising from an uncertain tax position related to foreign operations.

Liquidity, Capital Resources and Plan of Operations

Overview

We have funded our operations primarily through the sale of equity. We have not generated positive cash flow or net income from operations since our inception and as of December 31, 2024, we had an accumulated deficit of $1.1 billion. As of December 31, 2024, we had $125.7 million in cash, cash equivalents and short-term investments compared to $96.5 million as of December 31, 2023. Based on our available cash resources and current operating plan, there is substantial doubt regarding our ability to continue as a going concern for a period of one year after the date that our financial statements for the year ended December 31, 2024 are issued.

Private Placements

On February 7, 2024, we completed the Private Placements of 10.6 million shares of our common stock and, in lieu of common stock, Pre-Funded Warrants to purchase an aggregate of 75,000 shares of common stock to certain institutional and accredited investors and directors for total gross proceeds of $127.8 million, before deducting placement agent fees and offering expenses.

At-the-Market Offering Program

We are party to a sales agreement (the “Sales Agreement”) with Cowen & Company, LLC (“Cowen”) pursuant to which we may, from time to time, sell up to an aggregate amount of $100.0 million of our common stock through Cowen in an “at-the-market” offering. We are not required to sell shares under the Sales Agreement. We will pay Cowen a commission of up to 3.0% of the aggregate gross proceeds of any shares of common stock sold pursuant to the Sales Agreement. As of April 15, 2025, no sales have been made pursuant to the Sales Agreement.

Going Concern

As of December 31, 2024, we have devoted substantially all of our efforts to product development and have not realized product sales revenue from our planned principal operations. We have a limited operating history, and the sales and income potential of our business and market are unproven. We have experienced net losses since our inception and, as of December 31, 2024, we had an accumulated deficit of $1.1 billion. We used $92.5 million of cash in operations during the year ended December 31, 2024. We expect to continue to incur net losses and operating cash outflows for at least the next several years 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. As of December 31, 2024, we had cash, cash equivalents and short-term investments of $125.7 million, which we expect to fund our operations into the second half of 2025. We have determined that our existing cash and cash equivalents as of December 31, 2024 would be insufficient to fund our operations through at least 12 months from the date the consolidated financial statements in this Annual Report on Form 10-K are issued, and therefore there is substantial doubt regarding our ability to continue as a going concern. Accordingly, the report from our independent registered public accounting firm for the years ended December 31, 2024 includes an explanatory paragraph stating that our recurring losses since inception raise substantial doubt about our ability to continue as a going concern. See Part I, Item 1A. Risk Factors under the header “Risks Related to Our Financial Position and Need for Capital” for additional information.

We will need to raise substantial additional funding to finance our operations through clinical development of our product candidates and potentially to commercialize these candidates. We continue to analyze various alternatives, including public or private equity or debt financings, third-party funding, revenue interest arrangements, collaborations, strategic alliances and licensing arrangements, or any combination of these approaches. There is no assurance, however, that we will receive any additional financing or any revenue-generating collaboration will be available when needed, that management will be able to obtain financing or enter into a collaboration on terms acceptable to us, or that any additional financing or revenue generated through third-party collaborations will be sufficient to fund our operations for at least 12 months from the date the consolidated financial statements in this Annual Report on Form 10-K are issued. If we fail to obtain additional capital necessary to fund our operations, we could be forced to delay, limit, reduce or terminate our product development programs, commercialization efforts or other operations, or to cease operations or liquidate our assets. Although we have been successful in raising capital in the past, there is no assurance that we will be successful in obtaining such additional financing. Therefore, it is not considered probable that our plans to raise additional capital will alleviate the substantial doubt regarding our ability to continue as a going concern. Failure to manage discretionary spending or raise additional financing, as needed, may adversely impact our ability to achieve our intended business objective. The actual amount of cash that we will need to operate is subject to many factors, including those described in the section titled “Risk Factors.” Our consolidated financial statements do not include any adjustments that might be necessary if we are unable to continue as a going concern.

Funding Requirements

We expect to incur substantial expenditures in the foreseeable future, contingent upon receipt of additional funding, 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 public or private equity or debt financings, third-party funding, revenue interest arrangements, collaborations, strategic alliances and licensing arrangements, or any combination of these approaches. Adequate additional funding may not be available to us on acceptable terms or at all. As a result, we have concluded that management’s plans do not alleviate substantial doubt about the Company’s ability to continue as a going concern. 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:

- our ability to realize savings from any restructuring plans or cost-containment measures we have implemented or additional measures we may implement;
- security breaches, data losses or other disruptions affecting our information systems;
- our need and ability to retain key management and hire scientific, technical, business, and engineering personnel;

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

If we are unable to raise additional funds when needed, we may be required to delay, limit, reduce, or terminate our product development programs, commercialization efforts or other operations, or to cease operations or liquidate our assets. 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.

Material Cash Requirements

Our material cash requirements as of December 31, 2024 included operating lease commitments, including the lease of our headquarters office in Redwood City, CA, and the NC Premises. As of December 31, 2024, we had fixed lease payment obligations of $167.2 million, with $12.1 million payable within 12 months. See Note 6, Leases to our financial statements for additional information. As described in Note 15, Subsequent Events to our financial statements, the subtenant, AMP, and Jaguar defaulted, and failed to cure such defaults, under the sublease and the notice and waiver of assignment (the "assignment agreement") for the NC Premises. In February 2025, a lien in the amount of $4.8 million was filed by a third-party contractor against the subtenant’s interest in the NC Premises. We discharged the lien in March 2025 by depositing cash in the full amount with the applicable court in order to avoid default under the head lease. Further liens by third-party subcontractors or other contractors have been or may in the future be filed against the subtenant’s interest in the NC Premises and we may need to also discharge such liens to avoid a default under the head lease. The subtenant and Jaguar failed to remit the March 2025 rent and subsequent rent payments. As a result, we assumed responsibility for such payments in March 2025. As of April 7, 2025, we had made payments in the total amount of $1.9 million to satisfy outstanding rent and common area management fee obligation, and we remain obligated under the head lease, including for all future remaining rent payments in an aggregate amount of up to $119.7 million for the remainder of the head lease term, of which $5.7 million is due between April 8 and December 31, 2025. As a result of the uncured defaults, we terminated the sublease and initiated a lawsuit against the subtenant and Jaguar in the Superior Court of Wake County, North Carolina to enforce our rights under the sublease and seek recovery of losses and damages incurred due the defaults by the subtenant and Jaguar.

Except as disclosed above, we have no long-term debt and no material non-cancelable purchase commitments with service providers, as we have generally contracted on a cancelable, purchase-order basis. We enter into contracts in the normal course of business with CROs, CMOs and other third parties for clinical trials, preclinical research studies and testing, and manufacturing services. These contracts are cancelable by us upon prior notice. Payments due upon cancellation consist of payments for services provided or expenses incurred, including noncancelable obligations of our service providers, up to the date of cancellation. These payments are not determinable.

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,	
	2024	2023 As Restated
	(In thousands)	
Net cash (used in) provided by:		
Operating activities	$ (92,462)	$ (90,902)
Investing activities	(41,889)	96,875
Financing activities	120,003	69
Net (decrease) increase in cash, cash equivalents and restricted cash	$ (14,348)	$ 6,042

Cash Used in Operating Activities

During the year ended December 31, 2024, net cash used in operating activities was $92.5 million, primarily as a result of net loss of $130.9 million due to the continued activities developing our product candidates, partially offset by $37.6 million of non-cash charges mainly related to $14.4 million of stock-based compensation expense, $14.0 million of non-cash sublease loss, $7.5 million of non-cash lease expense, $3.7 million of depreciation and amortization expenses, and $0.9 million of net increase in cash from changes in operating assets and liabilities, which fluctuate due to timing of expenses and payments.

During the year ended December 31, 2023, net cash used in operating activities was $90.9 million, primarily as a result of net loss of $122.1 million due to the continued activities developing our product candidates, partially offset by $39.7 million of non-cash charges mainly related to $18.3 million of non-cash lease expense, $17.6 million of stock-based compensation expense, and $5.6 million of depreciation and amortization expenses; partially offset by $8.5 million of net decrease in cash from changes in operating assets and liabilities, which fluctuate due to timing of expenses and payments.

Cash (Used In) Provided by Investing Activities

Net cash used in investing activities for the year ended December 31, 2024 consisted of $41.5 million of net purchases of marketable securities and by $0.4 million of purchases of property and equipment primarily related to facilities.

Net cash provided by investing activities for the year ended December 31, 2023 consisted of $97.7 million of net maturities of marketable securities, partially offset by $0.8 million of purchases of property and equipment primarily related to facilities.

Cash Provided by Financing Activities

Net cash provided by financing activities for the year ended December 31, 2024 consisted of $119.4 million of proceeds from issuance of common stock and pre-funded warrants in the Private Placements, $0.5 million in proceeds from our employee stock purchase plan and $0.1 million in proceeds from the exercise of stock options.

Net cash provided by financing activities for the year ended December 31, 2023 consisted of $0.5 million in proceeds from employee stock purchase plan, almost entirely offset by $0.4 million in payments for deferred offering costs.

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, 2024 AND 2023

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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, 2024 and 2023, the related consolidated statements of operations and comprehensive loss, stockholders' equity, and cash flows for each of the two years in the period ended December 31, 2024, 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 at December 31, 2024 and 2023, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2024, in conformity with U.S. generally accepted accounting principles.

The Company's Ability to Continue as a Going Concern

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 1 to the consolidated financial statements, the Company has incurred recurring losses from operations and negative cash flows from operating activities and has stated that substantial doubt exists about the Company's ability to continue as a going concern. Management's evaluation of the events and conditions and management's plans regarding these matters are also described in Note 1. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty.

Restatement of 2023 Consolidated Financial Statements

As discussed in Note 2 to the consolidated financial statements, the 2023 consolidated financial statements have been restated to correct certain misstatements.

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 Matters

The critical audit matters communicated below are matters arising from the current period audit of the financial statements that were communicated or required to be communicated to the audit committee and that: (1) relate to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of critical audit matters 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 matters below, providing separate opinions on the critical audit matters or on the accounts or disclosures to which they relate.

Accrued research and development expenses – clinical trials

Description of the Matter The Company recorded accrued research and development expenses of $2.6 million as of December 31, 2024. As described in Note 3, the Company estimates clinical trial expenses based on the services performed pursuant to contracts with contract research organizations that conduct and manage clinical trials on the Company's behalf.

Auditing the Company's accrued research and development expenses for clinical trials was challenging due to the complex nature of evaluating the completeness and accuracy of the information used to estimate clinical trial expenses. Research and development expenses are incurred as the services are performed by vendors. This requires management to accurately monitor the activity of the vendors to determine the level of effort incurred during the reporting period.

How We Addressed the Matter in Our Audit To test the completeness and accuracy of information used to estimate clinical trial expenses, 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 accrued expenses, and making inquiries of individuals outside the finance function.

Accounting for North Carolina leases

Description of the Matter At December 31, 2024, the Company's operating lease right-of-use assets and operating lease liabilities were $33.6 million and $91.7 million, respectively. The Company recorded rent expense of $13.3 million and sublease loss of $14.0 million for the year ended December 31, 2024. As discussed in Note 6, the Company has an operating lease agreement ("head lease") for use of a building in North Carolina that it subleased to a subtenant ("sublease"). Tenant improvement allowances provided by the landlord to the Company under the head lease were subsequently conveyed from the Company to the subtenant under the sublease.

Auditing the Company's accounting for the head lease and sublease was challenging due to the complex nature of the tenant improvement allowances provided under the head lease and sublease and because of the judgment involved in assessing the collectibility of future lease payments from the subtenant

How We Addressed the Matter in Our Audit To test the accounting for the effects of the tenant improvement allowances provided under the head lease and sublease, our procedures included, among others, reviewing the head lease and sublease agreement to understand the terms and conditions related to the tenant improvement allowances and evaluating whether the tenant improvements related to the incentives were lessor or lessee assets. To test the sublease loss recognized, we performed audit procedures that included, among others, confirming tenant improvement allowance payments and rent payments directly with the landlord and evaluating the collectibility of future lease payments. For example, we assessed the subtenant's payment history and factors contributing to the financial strength of the subtenant.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2018.
San Francisco, California
April 15, 2025

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

	As of December 31,	
	2024	2023 As Restated
Assets		
Current assets:		
Cash and cash equivalents	$ 60,652	$ 75,000
Short-term investments	65,039	21,526
Prepaid expenses and other current assets	5,609	6,247
Total current assets	131,300	102,773
Operating lease right-of-use assets	33,611	35,024
Property and equipment, net	11,607	14,764
Restricted cash	1,976	1,976
Deposit and other long-term assets	1,347	1,231
Total assets	$ 179,841	$ 155,768
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 1,610	$ 1,921
Accrued expenses and other current liabilities	15,620	12,584
Lease liability, current portion	5,668	5,476
Total current liabilities	22,898	19,981
Long-term liabilities:		
Lease liability, net of current portion	86,037	68,565
Other non-current liabilities	192	—
Total liabilities	109,127	88,546
Commitments and contingencies (Note 8)		
Stockholders' equity:		
Preferred stock, $0.0001 par value, 5,000 shares authorized; no shares issued and outstanding	—	—
Common stock, $0.0001 par value, 300,000 shares authorized at December 31, 2024: 20,848 and 10,143 shares issued and outstanding at December 31, 2024 and 2023, respectively	2	1
Additional paid-in capital	1,138,070	1,003,718
Accumulated other comprehensive loss	(407)	(473)
Accumulated deficit	(1,066,951)	(936,024)
Total stockholders' equity	70,714	67,222
Total liabilities and stockholders' equity	$ 179,841	$ 155,768

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,	
	2024	2023 As Restated
License revenue	$ 1,000	$ 3,600
Operating expenses:		
Research and development	77,041	77,486
General and administrative	63,118	55,056
Total operating expenses	140,159	132,542
Operating loss	(139,159)	(128,942)
Other income, net	8,232	5,748
Net loss before income taxes	(130,927)	(123,194)
Income tax benefit	—	1,078
Net loss	$ (130,927)	$ (122,116)
Other comprehensive gain (loss):		
Net unrealized gain on marketable securities	105	1,057
Foreign currency translation adjustment	(39)	1
Comprehensive loss	$ (130,861)	$ (121,058)
Net loss per share - basic and diluted	$ (6.62)	$ (12.11)
Weighted-average common shares outstanding - basic and diluted	19,782	10,082

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, 2022 As Restated	**10,012**	**$ 1**	**$ 985,660**	**$ (1,531)**	**$ (813,908)**	**$ 170,222**
Stock-based compensation expense	—	—	17,569	—	—	17,569
Common stock issued upon exercise of stock options	—	—	1	—	—	1
Common stock issued under employee stock purchase plan	82	—	488	—	—	488
Common stock issued upon release of restricted stock units	49	—	—	—	—	—
Net unrealized gain on marketable securities	—	—	—	1,057	—	1,057
Foreign currency translation adjustments	—	—	—	1	—	1
Net loss	—	—	—	—	(122,116)	(122,116)
Balance at December 31, 2023 As Restated	**10,143**	**1**	**1,003,718**	**(473)**	**(936,024)**	**67,222**
Stock-based compensation expense	—	—	14,350	—	—	14,350
Issuance of common stock and warrants for cash in private placement, net of issuance costs of $8,449	10,573	1	119,360	—	—	119,361
Common stock issued upon exercise of stock options	15	—	146	—	—	146
Common stock issued under employee stock purchase plan	88	—	496	—	—	496
Common stock issued upon release of restricted stock units	29	—	—	—	—	—
Net unrealized gain on marketable securities	—	—	—	105	—	105
Foreign currency translation adjustments	—	—	—	(39)	—	(39)
Net loss	—	—	—	—	(130,927)	(130,927)
Balance at December 31, 2024	**20,848**	**$ 2**	**$ 1,138,070**	**$ (407)**	**$ (1,066,951)**	**$ 70,714**

See accompanying notes to consolidated financial statements.

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

	Years ended December 31,	
	2024	**2023 As Restated**
Cash flows from operating activities:		
Net loss	$ (130,927)	$ (122,116)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	3,653	5,644
Stock-based compensation expense	14,350	17,569
Net accretion of discount on marketable securities	(1,907)	(1,935)
Non-cash lease expense	7,495	18,257
Non-cash sublease loss/(income)	14,000	(89)
Loss on disposal of property and equipment	2	50
Other	(39)	225
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	638	298
Deposit and other long-term assets	(68)	182
Accounts payable	(262)	(369)
Accrued expenses and other liabilities	3,021	(5,396)
Lease liability	(2,418)	(3,222)
Net cash used in operating activities	(92,462)	(90,902)
Cash flows from investing activities:		
Purchases of marketable securities	(101,901)	(36,718)
Maturities of marketable securities	60,400	134,401
Purchases of property and equipment	(388)	(808)
Net cash (used in) provided by investing activities	(41,889)	96,875
Cash flows from financing activities:		
Proceeds from issuance of common stock and pre-funded warrants in private placement, net of issuance costs	119,361	—
Payment of deferred offering costs	—	(420)
Proceeds from issuance of common stock pursuant to option exercises	146	1
Proceeds from employee stock purchase plan	496	488
Net cash provided by financing activities	120,003	69
Net (decrease) increase in cash, cash equivalents and restricted cash	(14,348)	6,042
Cash, cash equivalents and restricted cash at beginning of period	76,976	70,934
Cash, cash equivalents and restricted cash at end of period	$ 62,628	$ 76,976
Cash and cash equivalents	$ 60,652	$ 75,000
Restricted cash	1,976	1,976
Cash, cash equivalents and restricted cash at end of period	$ 62,628	$ 76,976
Supplemental schedule of noncash information		
Non-cash settlement of operating lease liability	$ —	$ 14,903
Remeasurement of operating lease right-of-use assets and liabilities	$ —	$ 7,632
Fixed assets in accounts payable and current liabilities	$ 201	$ 91

See accompanying notes to consolidated financial statements.

1. Description of the Business

Nature of the 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.

Going Concern, Liquidity, Risks and Uncertainties—As of December 31, 2024, the Company has devoted substantially all of its efforts to product development and has not realized product sales revenues from its planned principal operations. The Company has a limited operating history, and the sales and income potential of the Company's business and market are unproven. The Company has experienced net losses since its inception and, as of December 31, 2024, had an accumulated deficit of $1.1 billion. The Company used $92.5 million of cash in operations during the year ended December 31, 2024. The Company expects to continue to incur net losses and operating cash outflows for at least the next several years. A successful transition to attaining profitable operations is dependent upon achieving a level of revenue adequate to support the Company's cost structure.

As of December 31, 2024, the Company had cash, cash equivalents and short-term investments of $125.7 million, which are expected to fund the Company's operations into the second half of 2025. The Company has determined that its cash and cash equivalents as of December 31, 2024 would be insufficient to fund its operations for a period of at least twelve months from the date these financial statements are issued, which raises substantial doubt regarding the Company's ability to continue as a going concern.

The Company's financial statements have been prepared using the going concern basis of accounting, which contemplates the continuity of operations, realization of assets and the satisfaction of liabilities and commitments in the ordinary course of business. The financial statements do not include any adjustments relating to the recoverability and classification of recorded asset amounts or the amounts and classification of liabilities that might result from the outcome of the uncertainties described above.

Management expects operating losses to continue for the foreseeable future. The Company plans to raise substantial additional capital to continue as a going concern, including through public or private equity or debt financings, third-party funding, revenue interest arrangements, collaborations, strategic alliances and licensing arrangements, or any combination of these approaches. The Company may be unable to raise additional funds or to enter into such agreements or arrangements on favorable terms, or at all. If the Company is unable to raise capital or enter into such agreements as and when needed, it may have to delay, limit, reduce or terminate its product development programs, commercialization efforts or other operations, or to cease operations or liquidate its assets. Although the Company has been successful in raising capital in the past, there is no assurance that it will be successful in obtaining such additional financing. Therefore, it is not considered probable that the Company's plans to raise additional capital will alleviate the substantial doubt regarding its ability to continue as a going concern.

2. Restatement of Previously Issued Financial Statements

The Company has restated herein its audited consolidated financial statements for the year ended December 31, 2023 in accordance with Accounting Standards Codification ("ASC") Topic 250, Accounting Changes and Error Corrections. In March 2025, the Company discovered that there were errors in its lease accounting related to tenant improvement allowances in connection with an operating lease agreement for a building in North Carolina, which the Company entered into in January 2021 and subsequently subleased in October 2021 (the operating lease agreement and sublease agreements, with their respective amendments, collectively, the "NC Leases"). The Company inappropriately omitted accounting for available tenant improvement allowance that resulted in a misstatement of its operating lease right-of-use asset and related lease liability. Additionally, the Company did not account for tenant improvement allowances that were conveyed to the subtenant, resulting in an overstatement of sublease income. The tables below reflect the adjustments related to this restatement, the amounts of which are included with reference (a).

The Company has also restated interim period financial statements for the first, second and third quarters of 2024 and 2023 as a result of these errors. See Note 14 Quarterly Financial Information (Unaudited) for additional information on the restated interim financial statements for the first, second, and third quarters of 2024 and 2023.

As part of this restatement, the Company has corrected certain other immaterial errors. While these other errors are quantitatively and qualitatively immaterial, individually and in the aggregate, because the Company is restating its consolidated financial statements for material errors, the Company has corrected other immaterial errors as well. These adjustments are described in more detail in references (b) and (c) and elsewhere in the section titled *"Other Adjustments"* below.

Other Adjustments

The adjustments to correct other errors that are quantitatively and qualitatively immaterial, individually and in the aggregate are as follows:

(b) The Company had previously recorded an out of period adjustment related to research and development expenses in the first quarter of 2023 that was the result of not recording a severance accrual of $0.2 million in 2022.

(c) The Company had previously understated its right-of-use assets and lease liability by $0.3 million related to its facilities in Redwood City, California at each balance sheet in 2024 and 2023.

The Company also identified certain errors as a result of imprecise calculations related to its research and development tax credits that should have been corrected in the consolidated financial statements for the year ended December 31, 2023. Such amounts are deemed immaterial to the Company's income tax provision for the years ended December 31, 2024 and 2023.

The remainder of the notes to the Company's financial statements have been restated, as applicable, to reflect the impacts from the restatement discussed above.

Impact of the Restatement

The following tables represent the restated amounts in the Consolidated Balance Sheet, Statement of Operations and Comprehensive Loss, and Statement of Cash Flows for the year ended December 31, 2023 (in thousands, except per share data).

The amounts as previously reported for fiscal year 2023 were derived from the Annual Report on Form 10-K for the fiscal year ended December 31, 2023, filed on March 18, 2024 and the amounts previously reported for the unaudited condensed consolidated quarterly financial information for the quarterly periods in the years ended December 31, 2023 and 2024 were derived from the Company's Quarterly Reports on Form 10-Q for the quarterly periods within those years (the "Previously Reported Amounts"). The Previously Reported Amounts are labeled as "As Reported" in the tables below. The amounts labeled "Adjustment" represent the effects of this restatement described above.

The cumulative effect of the error on periods prior to 2023 was $11.3 million which is included in the beginning balance of the accumulated deficit of the restated Consolidated Balance Sheet for the year ended December 31, 2023.

Consolidated Balance Sheet

	As of December 31, 2023			
	As Previously Reported	Adjustment	Reference	As Restated
Assets				
Current assets:				
Cash and cash equivalents	$ 75,000	$ —		$ 75,000
Short-term investments	21,526	—		21,526
Prepaid expenses and other current assets	6,247			6,247
Total current assets	102,773	—		102,773
Operating lease right-of-use assets	52,266	(17,242)	(a) (c)	35,024
Property and equipment, net	14,764	—		14,764
Restricted cash	1,976	—		1,976
Deposit and other long-term assets	1,231			1,231
Total assets	$ 173,010	$ (17,242)		$ 155,768
Liabilities and stockholders' equity				
Current liabilities:				
Accounts payable	$ 1,921	$ —		$ 1,921
Accrued expenses and other current liabilities	12,584	—		12,584
Lease liability, current portion	10,409	(4,933)	(a)	5,476
Total current liabilities	24,914	(4,933)		19,981
Long-term liabilities:				
Lease liability, net of current portion	64,627	3,938	(a) (c)	68,565
Total liabilities	89,541	(995)		88,546
Commitments and contingencies				
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, 2023: 10,143 shares issued and outstanding at December 31, 2023	1	—		1
Additional paid-in capital	1,003,718	—		1,003,718
Accumulated other comprehensive loss	(473)	—		(473)
Accumulated deficit	(919,777)	(16,247)	(a) (b)	(936,024)
Total stockholders' equity	83,469	(16,247)		67,222
Total liabilities and stockholders' equity	$ 173,010	$ (17,242)		$ 155,768

Consolidated Statement of Operations and Comprehensive Loss

	Year ended December 31, 2023			
	As Previously Reported	Adjustment	Reference	As Restated
License revenue	$ 3,600	$ —		$ 3,600
Operating expenses:				
Research and development	77,676	(190)	(b)	77,486
General and administrative	49,915	5,141	(a)	55,056
Total operating expenses	127,591	4,951		132,542
Operating loss	(123,991)	(4,951)		(128,942)
Other income, net	5,748	—		5,748
Net loss before income taxes	(118,243)	(4,951)		(123,194)
Income tax benefit	1,078	—		1,078
Net loss	$ (117,165)	$ (4,951)		$ (122,116)
Other comprehensive gain:				
Net unrealized gain on marketable securities	1,057	—		1,057
Foreign currency translation adjustment	1	—		1
Comprehensive loss	$ (116,107)	$ (4,951)		$ (121,058)
Net loss per share - basic and diluted	$ (11.62)	$ —		$ (12.11)
Weighted-average common shares outstanding - basic and diluted	10,082	—		10,082

Consolidated Statement of Cash Flows

	Year ended December 31, 2023			
	As Previously Reported	Adjustment	Reference	As Restated
Cash flows from operating activities:				
Net loss	$ (117,165)	$ (4,951)	(a) (b)	$ (122,116)
Adjustments to reconcile net loss to net cash used in operating activities:				
Non-cash lease expense	13,027	5,230	(a)	18,257
Non-cash sublease income	—	(89)		(89)
Changes in operating assets and liabilities:				
Accrued expenses and other liabilities	(5,206)	(190)	(b)	(5,396)
Supplemental schedule of noncash information				
Remeasurement of operating lease right-of-use assets and liabilities	$ 13,711	$ (6,079)	(a) (c)	$ 7,632

There was no impact on net cash used in operating activities or within any line items within investing and financing activities.

3. 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 judgements, estimates and assumptions that affect the reported amounts of assets, liabilities, revenue and expenses, and related disclosures. Management bases its estimates on historical experience and on various other assumptions that are believed to be reasonable under the circumstances. These estimates form the basis for making judgments about the carrying values of assets and liabilities when these values are not readily apparent from other sources. Accounting estimates and judgements are inherently uncertain, and the actual results could differ from these estimates.

March 2024 Reverse Stock Split—On March 21, 2024, the Company effected a 1-for-10 reverse stock split of its common stock. The par value and the authorized shares of the common stock were not adjusted as a result of the reverse stock split.

All equity related information including per share amounts for all periods presented in these consolidated financial statements and the notes thereto have been adjusted retroactively, where applicable, to reflect this reverse stock split.

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, net.

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 6, Leases for additional information.

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. 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 assesses available-for-sale debt securities on a quarterly basis to see whether any unrealized loss is due to credit-related factors. Factors considered in determining whether an impairment is credit-related include the extent to which the investment’s fair value is less than its cost basis, declines in published credit ratings, changes in interest rates, and any other adverse factors related to the security. If it is determined that a credit-related impairment exists, the Company will measure the credit loss based on a discounted cash flow model. Credit-related impairments on available-for-sale debt securities are recognized as an allowance for credit losses with a corresponding adjustment to other income, net in the Company’s consolidated statement of operations. The unrealized loss position that is not credit-related is recorded, net of any related tax effects, in other comprehensive income until realized. There were no credit-related losses recognized for the periods presented.

Accrued Interest Receivable—Accrued interest receivable related to the Company’s available-for-sale debt securities is presented within prepaid expenses and other current assets on the Company’s consolidated balance sheets. The Company has elected to exclude accrued interest receivable from both the fair value and the amortized cost basis of available-for-sale debt securities for the purposes of identifying and measuring any impairment. The Company writes off accrued interest receivable once it has determined that the asset is not realizable. Any write offs of accrued interest receivable are recorded by reversing interest income, recognizing credit loss expense, or a combination of both. To date, the Company has not written off any accrued interest receivables associated with its available-for-sale debt securities.

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 ("CODM"), assesses segment performance and decides how to allocate resources based on total operating expenses as reported on the consolidated statements of operations and comprehensive loss. See Note 11, Segment Reporting, for additional information.

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.

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.

Impairment of Long-Lived Assets—Long-lived assets, including property and equipment and finite-lived intangible assets, are reviewed for impairment whenever facts or circumstances either internally or externally may indicate that the carrying value of an asset may not be recoverable. If there is an indication of impairment, the Company tests for recoverability by comparing the estimated undiscounted future cash flows expected to result from the use of the asset to the carrying amount of the asset or asset group. If the asset or asset group is determined to be impaired, any excess of the carrying value of the asset or asset group over its estimated fair value is recognized as an impairment loss.

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 Company determines if an arrangement contains a lease and the classification of the lease at inception. An arrangement contains a lease if there is an identified asset and if the Company controls the use of the identified asset throughout the period of use. The lease liability is determined as the present value of future lease payments and lease incentives over the expected lease term. Lease incentives are included in the measurement of the consideration in the contract at lease commencement when the Company is reasonably certain to incur costs to construct lessee assets. In order to determine the incremental borrowing rate, the Company determines 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. The incremental borrowing rate, the ROU asset and the lease liability are reevaluated upon a lease modification. It bases the ROU asset on the lease liability adjusted for any prepaid or deferred rent. The Company elected to combine lease and non-lease components for all underlying assets groups. The Company determines the lease term at the commencement date by considering whether renewal options and termination options are reasonably assured of exercise. 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.

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.

The Company assesses the probability of collecting lease payments under its sublease at each reporting date. The Company currently does not deem the collection of lease payments probable and therefore sublease income is constrained at the lesser of cash payments or straight-line sublease income. Sublease income/loss for operating leases is classified in general and administrative expenses based on payments collected and tenant improvement allowance disbursed to the subtenant.

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

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, Revenue from Contracts with Customers, 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 contract research organizations ("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 approximate their fair values due to their short-term maturities. See Note 4, Fair Value Measurements 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 records 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, 2024 and 2023, 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 gain or 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 November 2024, the FASB issued ASU 2024-03, *Income Statement - Reporting Comprehensive Income - Expense Disaggregation Disclosures* ("ASU 2024-03"). ASU 2024-03 requires disaggregated disclosures of certain categories of expenses in the notes to the financial statements that are included in expense line items on the face of the income statement in annual and interim periods. ASU 2024-03 is effective for annual periods beginning after December 15, 2026 and interim periods beginning after December 15, 2027. The Company is evaluating the impact of this guidance on its financial statements and related disclosures.

In December 2023, the FASB issued ASU 2023-09, *Income Taxes (Topic 740): Improvements to Income Tax Disclosures* ("ASU 2023-09"). ASU 2023-09 requires enhanced annual disclosures regarding the rate reconciliation and income taxes paid. ASU 2023-09 is effective for annual periods beginning after December 15, 2024 and may be adopted on a prospective or retrospective basis. Early adoption is permitted. The Company is evaluating the impact of this guidance on its financial statements and related disclosures.

In November 2023, the FASB issued ASU 2023-07, *Segment Reporting (Topic 280): Improvements to Reportable Segment Disclosures* ("ASU 2023-07"). The amendments in ASU 2023-07 are intended to improve reportable segment disclosure, primarily through enhanced disclosures about significant segment expenses. ASU 2023-07 is effective for annual periods beginning after December 15, 2023, and interim periods beginning after December 15, 2024. The amendments in this ASU should be applied retrospectively to all prior periods presented in the financial statements. The Company retrospectively adopted ASU 2023-07 on December 31, 2024. The adoption of ASU 2023-07 did not have a material financial impact on the Company's consolidated financial statements.

4. 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 and corporate bonds 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, 2024			
	Amortized Cost Basis	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Level 1				
Money market funds	$ 165	$ —	$ —	$ 165
Level 2				
Commercial paper	78,500	10	(9)	78,501
U.S. government and agency securities	41,210	56	—	41,266
Total cash equivalents and short-term investments	119,875	66	(9)	119,932
Less: Cash equivalents	(54,901)	—	8	(54,893)
Total short-term investments	$ 64,974	$ 66	$ (1)	$ 65,039

	December 31, 2023			
	Amortized Cost Basis	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Level 1				
Money market funds	$ 10,204	$ —	$ —	$ 10,204
Level 2				
Commercial paper	64,693	—	(35)	64,658
U.S. government and agency securities	17,616	4	(17)	17,603
Total cash equivalents and short-term investments	92,513	4	(52)	92,465
Less: Cash equivalents	(70,972)	—	33	(70,939)
Total short-term investments	$ 21,541	$ 4	$ (19)	$ 21,526

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 sheets. As of December 31, 2024, all marketable securities had a remaining maturity of less than one year. The Company held 14 debt securities in an unrealized loss position with an aggregate fair value at December 31, 2024 of $54.2 million. These are highly liquid funds with high credit ratings with final maturity of less than one year from the balance sheet date. There were no individual securities that were in a significant unrealized loss position as of December 31, 2024 and 2023. The Company has not recorded an allowance for credit losses as of December 31, 2024 or 2023 related to these securities. The accrued interest receivable on available-for-sale marketable securities was immaterial at December 31, 2024 or 2023. The Company regularly reviews the securities in an unrealized loss position and evaluates the current expected credit loss by considering factors such as historical experience, market data, issuer-specific factors, and current economic conditions. The Company does not intend to sell the investments and it is not more likely than not that the Company will be required to sell the investments before recovery of their amortized cost bases. The Company has not recorded any impairment charges on available-for-sale securities.

5. 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.

In February 2023, Lexeo notified the Company that it had achieved the first development milestone; accordingly, the Company received and recognized $3.5 million of license revenue during the year ended December 31, 2023.

Ray

On February 6, 2023, the Company and Ray Therapeutics, Inc ("Ray") entered into a License Agreement pursuant to which the Company granted Ray a non-exclusive, worldwide, royalty-bearing license to certain of the Company's intellectual property to develop, manufacture, and commercialize a gene therapy product to treat retinitis pigmentosa and the right to develop the technology to treat other ocular diseases and disorders. Under the terms of the agreement, the Company is eligible to receive development, regulatory and commercial milestone payments and royalties on net sales once commercialized.

In September 2024, Ray notified the Company that it achieved the first development milestone. Accordingly, the Company recognized $1.0 million of license revenue during the year ended December 31, 2024.

6. Leases

Redwood City

The Company has a lease for facilities in Redwood City, California ("Redwood City Premises"), which expires December 31, 2031, with an option to extend for a period of eight years. Related to this lease, the Company provided the landlord with a letter of credit, as amended, in the amount of $2.0 million, which is classified as restricted cash under long-term assets on the Company's consolidated balance sheets.

Prior to September 30, 2023, the Company had two facility leases in Redwood City. In March 2023, the Company entered into an amendment to accelerate the expiration of the lease for one of the facilities in its Redwood City Premises from December 31, 2031 to September 30, 2023. Concurrently, the Company entered into an agreement for additional tenant improvement allowance towards its other Redwood City Premises. The Company accounted for this amendment as a lease modification in accordance with ASC 842-10-25-11(d). As a result of the modification the Company revalued the lease liability based on the new and remaining lease terms, which resulted in a reduction to the lease liability of $7.9 million, and recognized the remeasurement to the lease liabilities as an adjustment to the right-of-use asset. The estimated value of non-cash consideration, composed primarily of leasehold improvements and furniture and fixtures, was $14.9 million, which was fully amortized as of September 30, 2023. There was no charge recognized in the consolidated statement of operations.

North Carolina

The Company has restated amounts related to this lease. See Notes 2 and 14.

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 Jaguar Gene Therapy, LLC ("Jaguar") for the NC Premises through October 2037, the remainder of the lease term, and concurrently changed the terms of the head lease. In addition, the remainder of the tenant improvement allowance under the original lease of approximately $22.7 million was transferred to Jaguar.

On April 3, 2023, the Company entered into an amendment of the lease of its NC Premises with the landlord and subtenant. Under this amendment, the parties agreed to substantially reduce the total tenant improvement allowance in exchange for lower monthly rent. The Company accounted for this amendment as a lease modification in accordance with ASC 842-10-25-11(d). The Company remeasured the lease liability, resulting in an increase in the lease liability with a corresponding increase of the right-of-use asset of $0.3 million in the quarter ended June 30, 2023. There was no charge recognized in the consolidated statement of operations.

During the year ended December 31, 2022, management reassessed the probability of collection of the lease payments from Jaguar over the remaining term of a sublease. At that time, management assessed the collectibility to be less than probable and recognized an adjustment to eliminate the deferred rent receivable as a current period adjustment during the year ended December 31, 2022. Deferred rent receivable was zero as of December 31, 2024 and 2023. In April 2023, Jaguar assigned the sublease to Advanced Medicine Partners, LLC (at that time, a wholly-owned subsidiary of Jaguar, "AMP" or the "subtenant") as the subtenant for the NC Premises for the remainder of the lease term. Pursuant to the sublease and the notice and waiver of assignment (the "assignment agreement"), Jaguar remained obligated for AMP's proper performance under the sublease.

In February 2025, a lien totaling $4.8 million was filed by a third–party contractor against the subtenant's interest in the NC Premises. The Company discharged the lien in March 2025 by depositing cash in the full amount with the applicable court in order to avoid a default under the head lease. Subsequently, the subtenant and Jaguar failed to remit the March 2025 rent and subsequent rent payments and defaulted, and failed to cure such defaults, under the sublease and the assignment agreement for the NC Premises. Subsequent to December 31, 2024, the subtenant made payments totaling $1.4 million for January and February 2025 rent and drew $2.3 million from the available tenant improvement allowance, at which point the subtenant discontinued rent payments. The Company assumed responsibility for rent payments in March 2025 and as of April 7, 2025 had made payments in the total payment of $1.9 million to satisfy outstanding rent and common area management fee obligations. See Note 15 Subsequent Events.

The Company recorded sublease loss of $14.0 million and sublease income of $0.1 million for the years ended December 31, 2024 and 2023, respectively, which was recognized in general and administrative expense.

As of December 31, 2024, the weighted-average remaining lease term was 11.2 years for the Company's leases and the weighted-average Incremental Borrowing Rate ("IBR") was 11.6%. As of December 31, 2023, the weighted-average remaining lease term was 11.6 years for the Company's leases and the weighted-average IBR was 11.7%.

The following table summarizes the undiscounted future non-cancellable lease payments under the lease agreements as of December 31, 2024 (in thousands):

December 31,	Operating Leases
2025	$ 12,142
2026	14,892
2027	15,278
2028	15,677
2029	16,089
Thereafter	93,087
Total undiscounted lease payments	$ 167,165
Less: Imputed Interest	(75,460)
Total	$ 91,705

Rent expense for the years ended December 31, 2024, and 2023 was $13.3 million and $25.3 million, respectively. Included in rent expense for the years ended December 31, 2024, and 2023 were variable lease costs for utilities, parking, maintenance, and real estate taxes of $2.3 million and $2.4 million, respectively. Cash paid for amounts included in the measurement of lease liabilities was $5.8 million and $7.5 million for the twelve months ended December 31, 2024 and 2023, respectively. During the years ended December 31, 2024 and 2023, the landlord made payments to the subtenant on the Company's behalf for tenant improvement allowances in the amount of $20.5 million and $5.4 million and the subtenant made rent payments to the landlord on the Company's behalf in the amount of $6.5 million and $5.5 million, respectively.

7. Balance Sheet Components

Property and Equipment, Net

Property and equipment, net consisted of the following:

	December 31,	
	2024	2023
	(In thousands)	
Laboratory equipment	$ 14,963	$ 14,638
Leasehold improvements	13,779	13,586
Computer equipment and software	901	868
Construction in progress	9	184
Total property and equipment	29,652	29,276
Less accumulated depreciation and amortization	(18,045)	(14,512)
Property and equipment, net	$ 11,607	$ 14,764

Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consist of the following:

	December 31,	
	2024	2023
	(In thousands)	
Employee compensation	$ 9,540	$ 8,040
Accrued nonclinical, clinical and process development costs	4,401	3,367
Accrued professional fees	554	351
State income tax payable	123	101
Other	1,002	725
Total accrued expenses and other current liabilities	$ 15,620	$ 12,584

8. 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. The Company recognized license revenue of $1.0 million for the first development milestone in the Ray License Agreement and $3.5 million for the first development milestone in the Lexeo License Agreement during the years ended December 31, 2024 and 2023, respectively. See Note 5, Revenue, for additional information. Because achievement of these future milestones is not fixed and determinable, such amounts have not been included on the Company's consolidated statements of operations and comprehensive loss.

9. Stockholders' Equity

February 2024 Private Placements

On February 7, 2024, the Company entered into a securities purchase agreement, pursuant to which the Company sold 10.5 million shares of its common stock and, in lieu of common stock, pre-funded warrants to purchase an aggregate of 75,000 shares of common stock (the "Pre-Funded Warrants") to certain institutional and accredited investors in a private placement. The purchase price per share was $12.00, or $11.999 per Pre-Funded Warrant, which represents the purchase price per share minus the $0.001 per share exercise price of each Pre-Funded Warrant. Such Pre-Funded Warrants can be exercised at any time and have no expiration date.

The exercise of the outstanding Pre-Funded Warrants is subject to a beneficial ownership limitation of 9.99%. The Pre-Funded Warrants were classified as a component of stockholders' equity. As of December 31, 2024, none of the Pre-Funded Warrants had been exercised.

Concurrently, the Company also entered into a securities purchase agreement with two directors of the Company (together with the private placement to certain institutional and accredited investors, the "Private Placements"). The Company issued and sold 23,000 shares at $13.50 per share on otherwise substantially the same terms as those set forth in the Securities Purchase Agreement.

At the close of the Private Placements on February 7, 2024, the Company received total gross proceeds of $127.8 million, before deducting placement agent fees and offering expenses.

Accumulated Other Comprehensive Loss

Accumulated other comprehensive loss included $0.5 million and $0.4 million of accumulated currency translation adjustments as of December 31, 2024 and 2023, respectively.

Equity Incentive Plans

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"). The 2014 Plan provided 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 June 2024, the Company adopted the 2024 Equity Incentive Award Plan (the "2024 Plan"). The Company reserved 4,688,345 shares for issuance pursuant to awards under the 2024 Plan. As of the effective date of the 2024 Plan, no further awards may be granted under the 2014 Plan.

In October 2017, the Company adopted the 2017 Inducement Plan (the "Inducement Plan"). The Company originally 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 the 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 2014 Plan, 2024 Plan and Inducement Plan are referred to collectively as the Plans. As of December 31, 2024, a total of 1,277,999 shares were available for future issuance under the Plans.

Stock Options

Stock options under the 2024 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, 2023	2,303	$ 48.70	6.8	$ 99
Granted	1,971	10.39		
Exercised	(15)	9.97		
Canceled/forfeited	(350)	50.28		
Balance at December 31, 2024	3,909	$ 29.39	8.1	$ —
Vested and expected to vest as of December 31, 2024	3,909	$ 29.39	8.1	$ —
Exercisable at December 31, 2024	1,504	$ 58.95	6.5	$ —

(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, 2024 and 2023 was not material.

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,	
	2024	2023	2024	2023
Expected volatility	95%	90%	83%	78%
Expected term (in years)	6.0	6.0	1.3	1.3
Expected dividend yield	—	—	—	—
Risk-free interest rate	3.9%	4.2%	4.3%	5.0%

The weighted-average fair values of options granted during the years ended December 31, 2024 and 2023 were $8.12 and $7.96, respectively.

As of December 31, 2024, there was $17.1 million of unrecognized stock-based compensation expense related to stock options that was 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 three-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, 2023	154	21.73	1.4
Granted	160	12.04	
Vested and released	(29)	26.20	
Forfeited	(26)	14.22	
Balance at December 31, 2024	259	$ 16.00	1.2

During the years ended December 31, 2024 and 2023, total fair value of RSUs vested was $0.8 million and $1.5 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, 2024, there was $1.7 million of unrecognized compensation cost related to unvested RSUs that is expected to be recognized over a weighted-average period of 1.8 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 years ended December 31, 2024 and 2023, 88,199 and 82,422 shares were issued under the ESPP, respectively. As of December 31, 2024, a total of 533,978 shares of common stock were available for future issuance under the ESPP. As of December 31, 2024, there was $0.5 million of unrecognized compensation cost related to the ESPP.

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

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

	Years ended December 31,	
	2024	2023
	(In thousands)	
Research and development	$ 4,544	$ 4,969
General and administrative	9,806	12,600
Total share-based compensation expense	$ 14,350	$ 17,569

10. 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, 2024 and 2023 was $0.9 million.

11. Segment Reporting

Segment Reporting

The CODM assesses performance for the Company's single reportable segment and decides how to allocate resources based on the Company's total operating expenses as reported on the consolidated statements of operations and comprehensive loss. The CODM's review of total operating expenses at the consolidated level is used to monitor the Company's spending as well as budget versus actual results. The Company's reportable segment primarily generates revenue through its license agreements (see Note 5).

As part of the CODM's review of the segment's performance, the CODM reviews the Company's operating expense information, grouped by certain detailed line items from the internal income statement reporting. This includes research and development costs as well as general and administrative expenses. Based upon the operating expense information, the CODM can reconcile to net loss as reported on the consolidated statements of operations and comprehensive loss, shown in the table below.

The following table presents the segment loss, including significant segment expenses, for the years ended December 31, 2024 and 2023 (in thousands):

	Years ended December 31,	
	2024	2023 As Restated
	(In thousands)	
License Revenue	$ 1,000	$ 3,600
Less:		
Compensation and benefits expenses	56,546	54,572
Clinical trial and manufacturing	22,333	20,235
Facilities and IT	37,841	39,114
Other research and development expense	4,728	4,985
Other segment expenses[(a)]	18,711	13,636
Total operating expenses	**140,159**	**132,542**
Operating loss	**(139,159)**	**(128,942)**
Other income, net	8,232	5,748
Net loss before income taxes	(130,927)	(123,194)
Income tax benefit (provision)	—	1,078
Segment and consolidated net loss	**$ (130,927)**	**$ (122,116)**

(a) Other segment expenses include professional services, consultants and contractors, travel and entertainment expenses, and general business expenses.

As of December 31, 2024 and 2023, all of the Company's property and equipment was maintained in the United States. For each of the years ended December 31, 2024 and 2023, all of the Company's license revenue was generated in the United States.

12. Income Taxes

As part of the restatement, the Company adjusted the 2023 California research and development tax credit amounts as a result of a research and development credit study performed during 2024. This resulted in a net decrease of $3.4 million in the deferred tax asset balance related to the California research and development tax credit (net of a decrease in unrecognized tax benefits of $1.9 million) and a corresponding decrease in valuation allowance in 2023.

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

	Years ended December 31,	
	2024	2023 As Restated
	(In thousands)	
U.S.	$ (130,768)	$ (123,040)
Foreign	(159)	(154)
Loss before income taxes	$ (130,927)	$ (123,194)

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

	Years ended December 31,	
	2024	2023 As Restated
	(In thousands)	
Current:		
Foreign	$ —	$ (1,078)
Total current tax (benefit) provision	—	(1,078)
Deferred		
Foreign	—	—
Total deferred tax provision	—	—
Total income tax (benefit) provision	$ —	$ (1,078)

The income tax provision for the years ended December 31, 2024 and 2023 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,	
	2024	2023 As Restated
	(In thousands)	
Federal income tax benefit at statutory rate	$ (27,495)	$ (25,871)
Stock compensation	3,189	6,001
Non-deductible expenses	41	21
Research and development tax credits	(5,642)	(1,810)
Change in valuation allowance	23,801	19,558
Foreign rate differential	(14)	(14)
Impact of internal reorganization	—	1,323
Uncertain tax positions	6,100	(1,078)
Other	20	792
Total tax (benefit) provision	$ —	$ (1,078)

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,	
	2024	2023 As Restated
	(In thousands)	
Deferred tax assets:		
Net operating loss carryforwards	$ 137,140	$ 128,171
Accruals, reserve and other	1,972	1,749
Tax credit carryforwards	29,263	21,254
Stock-based compensation	6,349	7,274
Intangibles	7	11
Lease obligation	19,622	17,322
Capital losses	9,850	9,850
Section 174 R&D capitalization	35,842	29,688
Other	5	3
Total deferred tax assets before valuation allowance	240,050	215,322
Valuation allowance	(232,058)	(205,861)
Total deferred tax assets	7,992	9,461
Deferred tax liabilities:		
Right-of-use assets	(7,149)	(8,153)
Property and equipment	(843)	(1,308)
Total deferred tax liabilities	$ (7,992)	$ (9,461)
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, 2024 and 2023. The valuation allowance increased approximately $26.2 million and $17.7 million during the years ended December 31, 2024 and 2023, respectively, mainly driven by net operating losses ("NOLs").

As of December 31, 2024, the Company had U.S. federal NOLs carryforwards of approximately $552.7 million to offset any future federal income. Approximately $57.3 million of NOLs expire at various years beginning with 2032. As of December 31, 2024, the Company also had U.S. state NOL carryforwards of approximately $345.2 million to offset any future state income. U.S. state NOLs expire at various years beginning with 2037. At December 31, 2024, the Company also had approximately $49.5 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, 2024, the Company had federal research and development tax credit carryforwards of approximately $25.1 million available to reduce future tax liabilities which expire at various years beginning with 2036. As of December 31, 2024, the Company had state credit carryforwards of approximately $13.8 million available to reduce future tax liabilities which do not expire.

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 the Company has 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. The Company is conducting a Section 382 study, which is still subject to finalization, but which may show that the Company experienced an ownership change in 2024. If such an ownership change has occurred then up to vast majority of the NOLs, capital losses and research credit carryforwards presented in the consolidated financial statements would be subject to limitations and therefore may expire unutilized.

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, 2019 through December 31, 2023. 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, 2024 and 2023 of approximately $27.2 million and $22.8 million, respectively. If the unrecognized tax benefits for uncertain tax positions as of December 31, 2023, is recognized, there will be no impact to the effective tax rate as the tax benefit would increase the net deferred tax assets, which is currently offset with a full valuation allowance. A reconciliation of the unrecognized tax benefits is as follows:

	Years ended December 31,	
	2024	2023 As Restated
	(In thousands)	
Unrecognized tax benefits as of the beginning of the year	$ 22,758	$ 23,069
Increase related to tax positions taken during the prior year	—	43
Decrease related to tax positions taken during the prior year	(2,880)	—
Increase related to tax position taken during the current year	7,310	3,121
Decrease related to tax position taken during the current year	—	(3,475)
Unrecognized tax benefits as of the end of the year	$ 27,188	$ 22,758

The Company recognizes interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2024 and 2023, the Company had no accrued interest and penalties related to uncertain tax positions and no amount has been recognized in the Company's consolidated statement of operations and comprehensive loss. There are no ongoing examinations by taxing authorities at this time.

13. Net Loss per Share

For the year ended December 31, 2024, the Pre-Funded Warrants to purchase the Company's shares of common stock issued in the Private Placements were included in the basic and diluted net loss per share calculation as the exercise price is non-substantive and virtually assured.

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,	
	2024	2023
	(In thousands)	
Stock options	3,909	2,303
Restricted stock units	259	154
ESPP	32	17
	4,200	2,474

14. Quarterly Financial Information (Unaudited)

The previously reported financial information for the three months ended March 31, 2024, three and six months ended June 30, 2024 and the three and nine months ended September 30, 2024 and the comparable periods in 2023, has been restated. Relevant restated financial information for each period is included in this restatement and for other immaterial adjustments in the tables that follow.

Restatement Related to NC Premises

As described in Note 2, the Company inappropriately omitted accounting for available tenant improvement allowance that resulted in a misstatement of its operating lease right-of-use asset and related lease liability. Additionally, the Company did not account for a tenant improvement allowances that were conveyed to the subtenant resulting in an overstatement of sublease income. The tables below reflect the adjustments related to this restatement, the amounts of which are included with reference (a).

During the quarter ended June 30, 2024, the Company inappropriately assessed the collectibility of the sublease payments as probable and recorded a deferred rent receivable of $7.0 million. The Company corrected its collectibility assessment and recognized an adjustment to eliminate the $7.0 million and $7.1 million deferred rent receivable in the second and third quarters of 2024, respectively, the amounts of which are included in the tables below with reference (b).

Other Adjustments

As part of this restatement, the Company has corrected certain other immaterial errors. These adjustments are described in more detail references (c) and (d) as follows:

(c) The Company had previously recorded an out of period adjustment related to research and development expenses in the first quarter of 2023 that was the result of not recording a severance accrual of $0.2 million in 2022.

(d) The Company had previously understated its right-of-use assets and lease liability by $0.3 million related to its facilities in Redwood City, California at each balance sheet date in 2024 and 2023.

The unaudited interim financial statements reflect all adjustments which are, in the opinion of management, necessary for a fair statement of the results for the interim periods presented (in thousands, except per share data).

Condensed Consolidated Balance Sheets

	September 30, 2024 (unaudited)			
	As Previously Reported	Adjustment	Reference	As Restated
Assets				
Current assets:				
Cash and cash equivalents	$ 92,851	$ —		$ 92,851
Short-term investments	60,390	—		60,390
Prepaid expenses and other current assets	7,839	—		7,839
Total current assets	161,080	—		161,080
Operating lease right-of-use assets	50,695	(17,015)	(a) (d)	33,680
Property and equipment, net	12,215	—		12,215
Deferred rent receivable	7,116	(7,116)	(b)	—
Restricted cash	1,976	—		1,976
Deposit and other long-term assets	1,293	—		1,293
Total assets	$ 234,375	$ (24,131)		$ 210,244
Liabilities and stockholders' equity				
Current liabilities:				
Accounts payable	$ 2,110	—		$ 2,110
Accrued expenses and other current liabilities	14,886	—		14,886
Lease liability, current portion	10,661	(5,044)	(a)	5,617
Total current liabilities	27,657	(5,044)		22,613
Long-term liabilities:				
Lease liability, net of current portion	62,602	16,759	(a) (d)	79,361
Total liabilities	90,259	11,715		101,974
Commitments and contingencies				
Stockholders' equity:				
Preferred stock	—	—		—
Common stock	2	—		2
Additional paid-in capital	1,134,556	—		1,134,556
Accumulated other comprehensive loss	(268)	—		(268)
Accumulated deficit	(990,174)	(35,846)	(a) (b)	(1,026,020)
Total stockholders' equity	144,116	(35,846)		108,270
Total liabilities and stockholders' equity	$ 234,375	$ (24,131)		$ 210,244

	June 30, 2024 (unaudited)			
	As Previously Reported	Adjustment	Reference	As Restated
Assets				
Current assets:				
Cash and cash equivalents	$ 127,321	$ —		$ 127,321
Short-term investments	46,506	—		46,506
Prepaid expenses and other current assets	5,591	—		5,591
Total current assets	179,418	—		179,418
Operating lease right-of-use assets	51,237	(17,241)	(a) (d)	33,996
Property and equipment, net	13,047			13,047
Deferred rent receivable	6,963	(6,963)	(b)	—
Restricted cash	1,976	—		1,976
Deposit and other long-term assets	1,162	—		1,162
Total assets	$ 253,803	$ (24,204)		$ 229,599
Liabilities and stockholders' equity				
Current liabilities:				
Accounts payable	1,973	—		1,973
Accrued expenses and other current liabilities	9,912	—		9,912
Lease liability, current portion	10,576	(5,006)	(a)	5,570
Total current liabilities	22,461	(5,006)		17,455
Long-term liabilities:				
Lease liability, net of current portion	63,313	11,431	(a) (d)	74,744
Total liabilities	85,774	6,425		92,199
Commitments and contingencies				
Stockholders' equity:				
Preferred stock	—	—		—
Common stock	2	—		2
Additional paid-in capital	1,131,592	—		1,131,592
Accumulated other comprehensive loss	(525)	—		(525)
Accumulated deficit	(963,040)	(30,629)	(a) (b)	(993,669)
Total stockholders' equity	168,029	(30,629)		137,400
Total liabilities and stockholders' equity	$ 253,803	$ (24,204)		$ 229,599

	March 31, 2024 (unaudited)			
	As Previously Reported	Adjustment	Reference	As Restated
Assets				
Current assets:				
Cash and cash equivalents	$ 149,608	$ —		$ 149,608
Short-term investments	43,720	—		43,720
Prepaid expenses and other current assets	5,802	—		5,802
Total current assets	199,130	—		199,130
Operating lease right-of-use assets	51,760	(17,282)	(a) (d)	34,478
Property and equipment, net	13,766	—		13,766
Restricted cash	1,976	—		1,976
Deposit and other long-term assets	1,196	—		1,196
Total assets	$ 267,828	$ (17,282)		$ 250,546
Liabilities and stockholders' equity				
Current liabilities:				
Accounts payable	1,897	—		1,897
Accrued expenses and other current liabilities	9,160	—		9,160
Lease liability, current portion	10,492	(4,971)	(a)	5,521
Total current liabilities	21,549	(4,971)		16,578
Long-term liabilities:				
Lease liability, net of current portion	63,991	6,296	(a) (d)	70,287
Total liabilities	85,540	1,325		86,865
Commitments and contingencies				
Stockholders' equity:				
Preferred stock	—	—		—
Common stock	2	—		2
Additional paid-in capital	1,127,383	—		1,127,383
Accumulated other comprehensive loss	(533)	—		(533)
Accumulated deficit	(944,564)	(18,607)	(a)	(963,171)
Total stockholders' equity	182,288	(18,607)		163,681
Total liabilities and stockholders' equity	$ 267,828	$ (17,282)		$ 250,546

	September 30, 2023 (unaudited)			
	As Previously Reported	Adjustment	Reference	As Restated
Assets				
Current assets:				
Cash and cash equivalents	$ 105,366	$ —		$ 105,366
Short-term investments	11,716	—		11,716
Prepaid expenses and other current assets	7,514	—		7,514
Total current assets	124,596	—		124,596
Operating lease right-of-use assets	52,757	(17,158)	(a) (d)	35,599
Property and equipment, net	15,497	—		15,497
Restricted cash	2,650	—		2,650
Deposit and other long-term assets	1,270	—		1,270
Total assets	$ 196,770	$ (17,158)		$ 179,612
Liabilities and stockholders' equity				
Current liabilities:				
Accounts payable	2,170	—		2,170
Accrued expenses and other current liabilities	16,362	—		16,362
Lease liability, current portion	10,324	(4,897)	(a)	5,427
Total current liabilities	28,856	(4,897)		23,959
Long-term liabilities:				
Lease liability, net of current portion	65,200	3,196	(a) (d)	68,396
Total liabilities	94,056	(1,701)		92,355
Commitments and contingencies				
Stockholders' equity:				
Preferred stock	—	—		—
Common stock	1	—		1
Additional paid-in capital	999,328	—		999,328
Accumulated other comprehensive loss	(552)	—		(552)
Accumulated deficit	(896,063)	(15,457)	(a) (c)	(911,520)
Total stockholders' equity	102,714	(15,457)		87,257
Total liabilities and stockholders' equity	$ 196,770	$ (17,158)		$ 179,612

	June 30, 2023 (unaudited)			
	As Previously Reported	Adjustment	Reference	As Restated
Assets				
Current assets:				
Cash and cash equivalents	$ 111,187	$ —		$ 111,187
Short-term investments	30,266	—		30,266
Prepaid expenses and other current assets	5,690	—		5,690
Total current assets	147,143	—		147,143
Operating lease right-of-use assets	58,287	(17,054)	(a) (d)	41,233
Property and equipment, net	32,041	—		32,041
Restricted cash	2,650	—		2,650
Deposit and other long-term assets	1,308	—		1,308
Total assets	$ 241,429	$ (17,054)		$ 224,375
Liabilities and stockholders' equity				
Current liabilities:				
Accounts payable	1,418	—		1,418
Accrued expenses and other current liabilities	17,704	—		17,704
Lease liability, current portion	25,396	(4,861)	(a)	20,535
Total current liabilities	44,518	(4,861)		39,657
Long-term liabilities:				
Lease liability, net of current portion	65,756	2,734	(a) (d)	68,490
Total liabilities	110,274	(2,127)		108,147
Commitments and contingencies				
Stockholders' equity:				
Preferred stock	—	—		—
Common stock	1	—		1
Additional paid-in capital	994,938	—		994,938
Accumulated other comprehensive loss	(606)	—		(606)
Accumulated deficit	(863,178)	(14,927)	(a) (c)	(878,105)
Total stockholders' equity	131,155	(14,927)		116,228
Total liabilities and stockholders' equity	$ 241,429	$ (17,054)		$ 224,375

	March 31, 2023 (unaudited)			
	As Previously Reported	Adjustment	Reference	As Restated
Assets				
Current assets:				
Cash and cash equivalents	$ 67,552	$ —		$ 67,552
Short-term investments	96,733	—		96,733
Prepaid expenses and other current assets	4,588	—		4,588
Total current assets	168,873	—		168,873
Operating lease right-of-use assets	69,503	(22,905)	(a) (d)	46,598
Property and equipment, net	33,347	—		33,347
Restricted cash	2,503	—		2,503
Deposit and other long-term assets	1,351	—		1,351
Total assets	$ 275,577	$ (22,905)		$ 252,672
Liabilities and stockholders' equity				
Current liabilities:				
Accounts payable	2,863	—		2,863
Accrued expenses and other current liabilities	17,344	—		17,344
Lease liability, current portion	26,265	(5,531)	(a)	20,734
Total current liabilities	46,472	(5,531)		40,941
Long-term liabilities:				
Lease liability, net of current portion	71,348	(3,462)	(a) (d)	67,886
Total liabilities	117,820	(8,993)		108,827
Commitments and contingencies				
Stockholders' equity:				
Preferred stock	—	—		—
Common stock	1	—		1
Additional paid-in capital	990,223	—		990,223
Accumulated other comprehensive loss	(799)	—		(799)
Accumulated deficit	(831,668)	(13,912)	(a) (c)	(845,580)
Total stockholders' equity	157,757	(13,912)		143,845
Total liabilities and stockholders' equity	$ 275,577	(22,905)		$ 252,672

Quarterly and Year to Date Condensed Consolidated Statements of Operations and Comprehensive Loss

	Three Months Ended September 30, 2024 (unaudited)				Nine Months Ended September 30, 2024 (unaudited)			
	As Previously Reported	Adjustment	Reference	As Restated	As Previously Reported	Adjustment	Reference	As Restated
License revenue	$ 1,000	$ —		$ 1,000	$ 1,000	$ —		$ 1,000
Operating expenses:								
Research and development	20,439	—		20,439	52,946	—		52,946
General and administrative	9,782	5,217	(a)	14,999	24,996	19,599	(a) (b)	44,595
Total operating expenses	30,221	5,217		35,438	77,942	19,599		97,541
Operating loss	(29,221)	(5,217)		(34,438)	(76,942)	(19,599)		(96,541)
Other income, net	2,087	—		2,087	6,545	—		6,545
Net loss	(27,134)	(5,217)		(32,351)	(70,397)	(19,599)		(89,996)
Other comprehensive gain (loss):								
Net unrealized gain on marketable securities	241	—		241	198	—		198
Foreign currency translation adjustment	16	—		16	7	—		7
Comprehensive loss	$ (26,877)	$ (5,217)		$ (32,094)	$ (70,192)	$ (19,599)		$ (89,791)
Net loss per share — basic and diluted	$ (1.30)	—		$ (1.55)	$ (3.63)	—		$ (4.64)
Weighted-average common shares used to compute net loss per share - basic and diluted	20,876	—		20,876	19,408	—		19,408

	Three Months Ended June 30, 2024 (unaudited)				Six Months Ended June 30, 2024 (unaudited)			
	As Previously Reported	Adjustment	Reference	As Restated	As Previously Reported	Adjustment	Reference	As Restated
Operating expenses:								
Research and development	$ 17,097	$ —		$ 17,097	$ 32,507	$ —		$ 32,507
General and administrative	3,785	12,022	(a) (b)	15,807	15,214	14,382	(a) (b)	29,596
Total operating expenses	20,882	12,022		32,904	47,721	14,382		62,103
Operating loss	(20,882)	(12,022)		(32,904)	(47,721)	(14,382)		(62,103)
Other income, net	2,406	—		2,406	4,458	—		4,458
Net loss	(18,476)	(12,022)		(30,498)	(43,263)	(14,382)		(57,645)
Other comprehensive gain (loss):								
Net unrealized loss on marketable securities	(2)	—		(2)	(43)	—		(43)
Foreign currency translation adjustment	10	—		10	(9)	—		(9)
Comprehensive loss	$ (18,468)	(12,022)		$ (30,490)	$ (43,315)	$ (14,382)		$ (57,697)
Net loss per share — basic and diluted	$ (0.89)	—		$ (1.46)	$ (2.31)	—		$ (3.08)
Weighted-average common shares used to compute net loss per share - basic and diluted	20,852	—		20,852	18,713	—		18,713

	Three Months Ended March 31, 2024 (unaudited)			
	As Previously Reported	Adjustment	Reference	As Restated
Operating expenses:				
Research and development	$ 15,410	$ —		$ 15,410
General and administrative	11,429	2,360	(a)	13,789
Total operating expenses	26,839	2,360		29,199
Operating loss	(26,839)	(2,360)		(29,199)
Other income, net	2,052	—		2,052
Net loss	(24,787)	(2,360)		(27,147)
Other comprehensive gain (loss):				
Net unrealized loss on marketable securities	(41)	—		(41)
Foreign currency translation adjustment	(19)	—		(19)
Comprehensive loss	$ (24,847)	$ (2,360)		$ (27,207)
Net loss per share — basic and diluted	$ (1.50)	—		$ (1.65)
Weighted-average common shares used to compute net loss per share - basic and diluted	16,479	—		16,479

	Three Months Ended September 30, 2023 (unaudited)				Nine Months Ended September 30, 2023 (unaudited)			
	As Previously Reported	Adjustment	Reference	As Restated	As Previously Reported	Adjustment	Reference	As Restated
License revenue	$ —	$ —		$ —	$ 3,600	$ —		$ 3,600
Operating expenses:								
Research and development	20,740	—		20,740	62,398	(190)	(c)	62,208
General and administrative	13,789	530	(a)	14,319	39,035	4,351	(a)	43,386
Total operating expenses	34,529	530		35,059	101,433	4,161		105,594
Operating loss	(34,529)	(530)		(35,059)	(97,833)	(4,161)		(101,994)
Other income, net	1,661	—		1,661	4,437	—		4,437
Net loss before income taxes	(32,868)	(530)		(33,398)	(93,396)	(4,161)		(97,557)
Income tax provision	(17)			(17)	(55)			(55)
Net loss	(32,885)	(530)		(33,415)	(93,451)	(4,161)		(97,612)
Other comprehensive gain (loss):								
Net unrealized gain on marketable securities	66	—		66	1,003	—		1,003
Foreign currency translation adjustment	(12)	—		(12)	(24)	—		(24)
Comprehensive loss	$ (32,831)	(530)		$ (33,361)	$ (92,472)	$ (4,161)		$ (96,633)
Net loss per share — basic and diluted	$ (3.26)	—		$ (3.31)	$ (9.28)	—		$ (9.69)
Weighted-average common shares used to compute net loss per share - basic and diluted	10,099	—		10,099	10,069	—		10,069

	Three Months Ended June 30, 2023 (unaudited)				Six Months Ended June 30, 2023 (unaudited)			
	As Previously Reported	Adjustment	Reference	As Restated	As Previously Reported	Adjustment	Reference	As Restated
License revenue	$ —	$ —		$ —	$ 3,600	$ —		$ 3,600
Operating expenses:								
Research and development	$ 20,599	$ —		$ 20,599	$ 41,658	$ (190)	(c)	$ 41,468
General and administrative	12,466	1,015	(a)	13,481	25,246	3,821	(a)	29,067
Total operating expenses	33,065	1,015		34,080	66,904	3,631		70,535
Operating loss	(33,065)	(1,015)		(34,080)	(63,304)	(3,631)		(66,935)
Other income, net	1,576	—		1,576	2,776	—		2,776
Net loss before income taxes	(31,489)	(1,015)		(32,504)	(60,528)	(3,631)		(64,159)
Income tax provision	(21)			(21)	(38)			(38)
Net loss	(31,510)	(1,015)		(32,525)	(60,566)	(3,631)		(64,197)
Other comprehensive gain (loss):								
Net unrealized gain on marketable securities	198	—		198	937	—		937
Foreign currency translation adjustment	(5)	—		(5)	(12)	—		(12)
Comprehensive loss	$ (31,317)	(1,015)		$ (32,332)	$ (59,641)	$ (3,631)		$ (63,272)
Net loss per share — basic and diluted	$ (3.13)	—		$ (3.23)	$ (6.02)	—		$ (6.39)
Weighted-average common shares used to compute net loss per share - basic and diluted	10,076	—		10,076	10,053	—		10,053

	Three Months Ended March 31, 2023 (unaudited)			
	As Previously Reported	Adjustment	Reference	As Restated
License revenue	$ 3,600	$ —		$ 3,600
Operating expenses:				
Research and development	$ 21,059	$ (190)	(c)	$ 20,869
General and administrative	12,780	2,806	(a)	15,586
Total operating expenses	33,839	2,616		36,455
Operating loss	(30,239)	(2,616)		(32,855)
Other income, net	1,200	—		1,200
Net loss before income taxes	(29,039)	(2,616)		(31,655)
Income tax provision	(17)	—		(17)
Net loss	(29,056)	(2,616)		(31,672)
Other comprehensive gain (loss):				
Net unrealized gain on marketable securities	739	—		739
Foreign currency translation adjustment	(7)	—		(7)
Comprehensive loss	$ (28,324)	(2,616)		$ (30,940)
Net loss per share — basic and diluted	$ (2.90)	—		$ (3.16)
Weighted-average common shares used to compute net loss per share - basic and diluted	10,030	—		10,030

Condensed Consolidated Statements of Cash Flows

The effects of this restatement on certain line items of the condensed consolidated statements of cash flows are summarized in the following tables (in thousands). There was no impact on net cash used in operating activities or within any line items within investing and financing activities.

	Nine Months Ended September 30, 2024			
	As Previously Reported	Adjustments	Reference	As Restated
Cash flows from operating activities:				
Net loss	$ (70,397)	$ (19,599)	(a) (b)	$ (89,996)
Adjustments to reconcile net loss to net cash used in operating activities:				
Non-cash lease expense	1,571	4,006	(a)	5,577
Non-cash sublease loss	—	8,477	(a)	8,477
Changes in operating assets and liabilities:				
Deposit and other long-term assets and deferred rent receivable	(7,178)	7,116	(b)	(62)

	Six Months Ended June 30, 2024			
	As Previously Reported	Adjustments	Reference	As Restated
Cash flows from operating activities:				
Net loss	$ (43,263)	$ (14,382)	(a) (b)	$ (57,645)
Adjustments to reconcile net loss to net cash used in operating activities:				
Non-cash lease expense	1,029	2,654	(a)	3,683
Non-cash sublease loss	—	4,765	(a)	4,765
Changes in operating assets and liabilities:				
Deposit and other long-term assets and deferred rent receivable	(6,894)	6,963	(b)	69

	Three Months Ended March 31, 2024			
	As Previously Reported	Adjustments	Reference	As Restated
Cash flows from operating activities:				
Net loss	$ (24,787)	$ (2,360)	(a)	$ (27,147)
Adjustments to reconcile net loss to net cash used in operating activities:				
Non-cash lease expense	506	1,314	(a)	1,820
Non-cash sublease loss	—	1,046	(a)	1,046

	Nine Months Ended September 30, 2023			
	As Previously Reported	Adjustments	Reference	As Restated
Cash flows from operating activities:				
Net loss	$ (93,451)	$ (4,161)	(a) (c)	$ (97,612)
Adjustments to reconcile net loss to net cash used in operating activities:				
Non-cash lease expense	12,466	3,916	(a)	16,382
Non-cash sublease loss	—	435	(a)	435
Changes in operating assets and liabilities:				—
Accrued expenses and other liabilities	(1,452)	(190)	(c)	(1,642)
Supplemental schedule of noncash information				
Remeasurement of operating lease right-of-use assets	$ 13,711	$ (6,079)		$ 7,632

	Six Months Ended June 30, 2023			
	As Previously Reported	Adjustments	Reference	As Restated
Cash flows from operating activities:				
Net loss	$ (60,566)	$ (3,631)	(a) (c)	(64,197)
Adjustments to reconcile net loss to net cash used in operating activities:				
Non-cash lease expense	6,936	2,602	(a)	9,538
Non-cash sublease loss	—	1,219	(a)	1,219
Changes in operating assets and liabilities:				
Accrued expenses and other liabilities	(525)	(190)	(c)	(715)
Supplemental schedule of noncash information				
Remeasurement of operating lease right-of-use assets	$ 13,711	$ (6,079)		$ 7,632

	Three Months Ended March 31, 2023			
	As Previously Reported	Adjustments	Reference	As Restated
Cash flows from operating activities:				
Net loss	$ (29,056)	$ (2,616)	(a) (c)	$ (31,672)
Adjustments to reconcile net loss to net cash used in operating activities:				
Non-cash lease expense	1,427	1,239	(a)	2,666
Non-cash sublease loss	—	1,567		1,567
Changes in operating assets and liabilities:				—
Accrued expenses and other liabilities	(749)	(190)	(c)	(939)
Supplemental schedule of noncash information				
Remeasurement of operating lease right-of-use assets	$ 8,004	$ (104)		$ 7,900

15. Subsequent Events

In February 2025, a lien in the amount of $4.8 million was filed by a third-party contractor against the subtenant's interest in the NC Premises. The Company discharged the lien in March 2025 by depositing cash in the full amount with the applicable court in order to avoid a default under the head lease. Subsequently, the subtenant and Jaguar failed to remit the March 2025 rent and subsequent rent payments and defaulted, and failed to cure such defaults, under the sublease and the assignment agreement for the NC Premises.

As a result, the Company assumed responsibility for such payments in March 2025 and as of April 7, 2025 had made a total amount of $1.9 million to satisfy outstanding rent and common area management fee obligations. The Company remains obligated under the head lease, including for all future remaining rent payments in an aggregate amount of up to $119.7 million for the remainder of the head lease term, of which $5.7 million is due between April 8 and December 31, 2025. As a result of the uncured defaults, the Company terminated the sublease and initiated a lawsuit against the subtenant and Jaguar in the Superior Court of Wake County, North Carolina to enforce its rights under the sublease and to seek recovery of losses and damages incurred due to the defaults by the subtenant and Jaguar.

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 Fischer, 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, 2024. 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.

As a result of the existence of the material weakness in our internal control over financial reporting described below, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were not effective as of December 31, 2024.

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.

Under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, we assessed our internal control over financial reporting as of December 31, 2024, the end of our fiscal year, based on the framework 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 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.

Management identified a material weakness in the Company's internal control over financial reporting as of December 31, 2024 with respect to the design and operating effectiveness of the Company's controls over lease accounting. The material weakness resulted in misstatements in the Company's previously issued financial statements.

Based on our assessment, management has concluded that our internal control over financial reporting was not effective as of December 31, 2024 due to the material weakness. The results of management's assessment were reviewed with the Audit Committee.

Remediation Plan

To address our material weakness, we have implemented and continue to implement increased rigor to ensure controls operate with regard to lease accounting. Consistent with past practice, the preparation of technical accounting memos will occur for all material lease agreements, including modifications of existing agreements. Management will engage additional outside financial reporting and technical accounting expertise to assist in the analysis of potential accounting impacts of new or amended lease agreements and will improve the process to monitor accounting conclusions for existing lease agreements. In addition, management will enhance the process to monitor creditworthiness of subtenants and increase the oversight over any subtenant activities, including obtaining robust support of lease payments and tenant improvement allowance payments.

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 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 weakness 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 lease accounting during the quarter ended December 31, 2024. 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, 2024 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

Termination of Sublease for NC Premises

In January 2021, we entered into the operating lease related to the "NC Premises", and in October 2021, we entered into a sublease agreement with Jaguar, who subsequently assigned the sublease to AMP as the subtenant for the NC Premises, through the remainder of the lease term (ending in October 2037). Pursuant to the sublease and the assignment agreement, Jaguar remained obligated for AMP's proper performance under the sublease. In February 2025, a lien in the amount of $4.8 million was filed by a third-party contractor against the subtenant's interest in the NC Premises. We discharged the lien in March 2025 by depositing cash in the full amount with the applicable court to avoid a default under the head lease. Further liens by third-party subcontractors or other contractors have been or may in the future be filed against the subtenant's interest in the NC Premises and we may need to also discharge such liens to avoid a default under the head lease. The subtenant and Jaguar failed to remit March 2025 rent and subsequent rent payments, and defaulted and failed to cure such defaults under the sublease for the NC Premises. As a result, we assumed responsibility for such payments in March 2025. As of April 7, 2025, we had made payments in the total amount of $1.9 million to satisfy outstanding rent and common area management fee obligation, and we remain obligated under the head lease, including for all future rent payments in an aggregate amount of up to $119.7 million for remainder of the head lease term, of which $5.7 million is due between April 8 and December 31, 2025. As a result of the uncured defaults, we terminated the sublease on April 9, 2025 and initiated a lawsuit against the subtenant and Jaguar in the Superior Court of Wake County, North Carolina to enforce our rights under the sublease and to seek recovery of losses and damages incurred due to the defaults by the subtenant and Jaguar. In the event we are unsuccessful in collecting from the subtenant or identify a new subtenant on acceptable terms or at all, we will be required to satisfy our obligations directly to the landlord under such original lease in accordance with its terms.

10b5-1 Plans

None of our directors or officers (as defined in Section 16 of the Securities Exchange Act of 1934, as amended) adopted or terminated any contract, instruction or written plan for the purchase or sale of our securities that was intended to satisfy the affirmative defense conditions of Rule 10b5-1(c) or any "non-Rule 10b5-1 trading arrangement," as defined in Item 408(a) of Regulation S-K.

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 2025 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, 2024, 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 Code of Business Conduct and Ethics that applies to all of our employees, officers and directors, including those officers responsible for financial reporting. The Code of Business Conduct and Ethics is publicly available on our website at http://investors.adverum.com. We intend to promptly disclose on our website or in a Current Report on Form 8-K in the future (i) the date and nature of any amendment (other than technical, administrative or other non-substantive amendments) to the Code of Business Conduct and Ethics that applies to our principal executive officer, principal financial officer, principal accounting officer or controller or persons performing similar functions and relates to any element of the code of ethics definition enumerated in Item 406(b) of Regulation S-K and (ii) the nature of any waiver, including an implicit waiver, from a provision of the Code of Business Conduct and Ethics that is granted to one of these specified individuals that relates to one or more of the elements of the code of ethics definition enumerated in Item 406(b) of Regulation S-K, the name of such person who is granted the waiver and the date of the waiver.

We have adopted insider trading policies and procedures governing the purchase, sale, and/or other dispositions of our securities by directors, officers and employees. In addition, it is the Company's intent to comply with the applicable laws and regulations relating to insider trading. A copy of our insider trading policy is filed as an exhibit to this Form 10-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	Restated Certificate of Incorporation.	001-36579	10-Q	November 4, 2024	3.1	
3.2	Amended and Restated Bylaws.	001-36579	8-K	June 29, 2020	3.1	
4.2	Form of Pre-Funded Warrant.	001-36579	8-K	February 5, 2024	4.1	
4.3	Form of Registration Rights Agreement, dated February 5, 2024, by and among Adverum Biotechnologies, Inc. and the investors party thereto.	001-36579	8-K	February 5, 2024	10.2	
4.4	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.	001-36579	10-K	March 30, 2023	10.4D	
10.4E	Fourth Amendment to Lease between Adverum Biotechnologies, Inc. and HCP LS Redwood City, LLC, dated as of March 24, 2023.	001-36579	10-K	March 30, 2023	10.4E	
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	

EXHIBIT NUMBER	EXHIBIT DESCRIPTION	INCORPORATED BY REFERENCE				PROVIDED HEREWITH
		FILE NUMBER	FORM	DATE	EXHIBIT NUMBER	
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	
10.5C	Third Amendment to Lease and First Amendment to Consent to Sublease between Adverum NC, LLC (a wholly owned subsidiary of the Company), ARE-NC REGION NO. 21, LLC and Jaguar Gene Therapy, LLC, dated as of April 3, 2023.	001-36579	10-Q	May 11, 2023	10.3	
10.6A(#)	2017 Inducement Plan, as amended and restated	333-285358	S-8	February 27, 2024	99.1	
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	
10.9A(#)	Adverum Biotechnologies, Inc. 2024 Equity Incentive Award Plan.	333-280567	S-8	June 28, 2024	99.1	
10.9B(#)	Form of Stock Option Grant Notice and Stock Option Agreement under the 2024 Equity Incentive Award Plan.	333-280567	S-8	June 28, 2024	99.2	
10.9C(#)	Form of Restricted Stock Unit Award Grant Notice and Restricted Stock Unit Award Agreement under the 2024 Equity Incentive Award Plan.	333-280567	S-8	June 28, 2024	99.3	
10.10(#)	Form of Change in Control and Severance Agreement for executive officers other than the chief executive officer.	001-36579	10-Q	August 10, 2023	10.6	
10.11(#)	Form of Indemnification Agreement for directors and executive officers.	001-36579	10-Q	May 28, 2020	10.1	
10.12(#)	Non-Employee Director Compensation Policy, adopted May 5, 2021.	001-36579	10-Q	May 6, 2021	10.7	

EXHIBIT NUMBER	EXHIBIT DESCRIPTION	INCORPORATED BY REFERENCE				PROVIDED HEREWITH
		FILE NUMBER	FORM	DATE	EXHIBIT NUMBER	
10.13(#)	Non-Employee Director Compensation Policy, adopted May 22, 2024.	001-36579	10-Q	August 12, 2024	10.4	
10.14A(#)	Offer Letter between Adverum Biotechnologies, Inc. and Laurent Fischer, dated as of June 11, 2020.	001-36579	10-Q	August 10, 2020	10.1	
10.14B(#)	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	
10.15(#)	Offer Letter between Adverum Biotechnologies, Inc. and Peter Soparkar, dated as of October 11, 2019.	001-36579	10-Q	November 7, 2019	10.2	
10.16(#)	Offer Letter between Adverum Biotechnologies, Inc. and Setareh Seyedkazemi, dated as of December 3, 2021.	001-36579	10-K	March 29, 2022	10.21	
10.17(#)	Offer Letter between Adverum Biotechnologies, Inc. and Linda Rubinstein, dated as of August 3, 2023.	001-36579	10-Q	August 10, 2023	10.5	
10.18(#)	Offer Letter between Adverum Biotechnologies, Inc. and Rabia Gurses Ozden, dated as of June 10, 2024.					X
10.19	Sales Agreement, dated May 11, 2023, by and between Adverum Biotechnologies, Inc. and Cowen and Company, LLC.	001-36579	8-K	May 11, 2023	1.1	
19.1	Insider Trading Policy.					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 Principal 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
97.1	Incentive Compensation Recoupment Policy.	001-36579	10-K	March 18, 2024	97.1	
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: April 15, 2025

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)*	April 15, 2025
/s/ Linda Rubinstein Linda Rubinstein	Chief Financial Officer *(Principal Financial Officer and Principal Accounting Officer)*	April 15, 2025
/s/ Patrick Machado Patrick Machado	Chairman of the Board	April 15, 2025
/s/ Soo Hong Soo Hong	Director	April 15, 2025
/s/ Szilárd Kiss, M.D. Szilárd Kiss, M.D.	Director	April 15, 2025
/s/ Mark Lupher Mark Lupher, Ph.D.	Director	April 15, 2025
/s/ C. David Nicholson C. David Nicholson, Ph.D.	Director	April 15, 2025
/s/ James Scopa James Scopa	Director	April 15, 2025
/s/ Dawn Svoronos Dawn Svoronos	Director	April 15, 2025
/s/ Reed Tuckson Reed Tuckson, M.D.	Director	April 15, 2025
/s/ Scott Whitcup Scott Whitcup, M.D.	Director	April 15, 2025