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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 10-Q

(Mark One)

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

For the quarterly period ended March 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)	**(I.R.S. Employer Identification No.)**

100 Cardinal Way
Redwood City, CA
(Address of principal executive offices)

94063
(Zip Code)

(650) 656-9323
(Registrant's telephone number, including area code)

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, $0.0001 par value	**ADVM**	**The NASDAQ Stock Market LLC (Nasdaq Capital Market)**

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 x 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 x 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 an emerging growth company. See 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	x	Smaller reporting company	x
		Emerging growth company	☐

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

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

As of May 3, 2024, there were 20,756,850 shares of the registrant's common stock, par value $0.0001 per share, outstanding.

Adverum Biotechnologies, Inc.

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RISK FACTORS SUMMARY

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

- We have incurred significant operating losses since inception, and we expect to incur significant losses for the foreseeable future. We may never become profitable or, if achieved, be able to sustain profitability.
- We expect that our cash, cash equivalents, and short-term investments will be sufficient to fund our planned operations into late 2025. If this expectation proves to be wrong, we may be forced to delay, limit or terminate certain of our development efforts before then.
- We will need to raise additional funding, which may not be available on acceptable terms, or at all. If we fail to obtain additional capital necessary to fund our operations, we will be unable to successfully develop and commercialize our product candidates.
- 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 product candidates at acceptable costs, we may be unable to meet clinical or potential commercial demand, lose potential revenue, have reduced margins, or be forced to terminate a program.
- We and our contractors are subject to significant regulation with respect to manufacturing and testing our product candidates. We have a limited number of vendors on which we rely, including, in some cases, single source vendors, and the contract vendors on which we rely may not continue to meet regulatory requirements, may have limited capacity, or may have other factors limiting their ability to comply with their contracts with us.
- We are subject to many manufacturing and distribution risks, any of which could substantially increase our costs and limit supply of our product candidates.
- We have relied, and expect to continue to rely, on third parties under contracts and partnerships to conduct some or all aspects of our research and development, including vector production, process development, assay development, product candidates and product manufacturing and testing, protocol development, clinical trials, product distribution, commercialization, nonclinical studies, research and related activities, and these third parties may not perform satisfactorily.
- We will rely on third parties to conduct some nonclinical testing and all of our planned clinical trials. If these third parties do not meet our deadlines or otherwise fail to conduct the trials as required, our clinical development programs could be delayed or unsuccessful and we may not be able to obtain regulatory approval for or commercialize our product candidates when expected or at all.
- Our success depends on our ability to protect our intellectual property and our proprietary technologies.
- Claims by third parties that we infringe their proprietary rights may result in liability for damages or prevent or delay our developmental and commercialization efforts.
- We may not be successful in obtaining or maintaining necessary rights to our product candidates through acquisitions and in-licenses.
- Our rights to develop and commercialize our product candidates are subject in part to the terms and conditions of licenses granted to us by other companies and universities.
- The patent protection and patent prosecution for some of our product candidates are dependent on third parties.

- We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.
- Third party patent rights could delay or otherwise adversely affect our planned development and sale of product candidates of our programs.
- We may not be able to obtain intellectual property rights or protect our intellectual property rights throughout the world.
- Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.
- If we do not obtain patent term extensions for patents covering our product candidates, our business may be materially harmed.
- Any suspension of, or delays in the commencement or completion of, clinical trials for our product candidates could result in increased costs to us, delay or limit our ability to generate revenue and adversely affect our commercial prospects.
- Final marketing approval for our product candidates by the FDA or other regulatory authorities outside the U.S. for commercial use may be delayed, limited or denied, any of which would adversely affect our ability to generate operating revenue.
- Even if we receive regulatory approval, we still may not be able to successfully commercialize any of our product candidates, and the revenue that we generate from its sales, if any, could be limited.
- If our competitors develop treatments for the target indications of our product candidates that are approved, marketed more successfully, or demonstrated to be safer or more effective or easier to administer than our product candidates, our commercial opportunity will be reduced or eliminated.
- Even if we obtain marketing approval for any of our product candidates, they could be subject to restrictions or withdrawal from the market, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our product candidates, when and if any of them are approved.
- Coverage and reimbursement may be limited or unavailable in certain market segments for our product candidates, which could make it difficult for us to sell our product candidates profitably.
- Healthcare and other reform legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and, if approved, may affect the prices we may obtain.
- Negative public opinion and increased regulatory scrutiny of gene therapy and genetic research may damage public perception of our product candidates or adversely affect our ability to conduct our business or obtain marketing approvals for our product candidates.
- We are dependent on the services of our key executives and clinical and scientific staff, and if we are not able to retain these members of our management or recruit additional management, clinical and scientific personnel, our business will suffer.
- We may encounter difficulties in managing our growth and expanding our operations successfully.
- If our information technology systems or those of third parties upon which we rely, 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.
- Failure or perceived failure to comply with existing or future laws, regulations, contracts, self-regulatory schemes, standards, and other obligations related to data privacy and security (including security incidents) could harm our business. Compliance or the actual or perceived failure to comply with such obligations could increase the costs of our services, limit their use or adoption, and otherwise negatively affect our operating results and business.
- The trading price of the shares of our common stock has been and could continue to be highly volatile, and purchasers of our common stock could incur substantial losses.
- If we sell shares of our common stock or securities convertible into or exercisable for shares of our common stock in future financings, pursuant to licensing, collaboration or other arrangements, stockholders may experience immediate dilution and, as a result, our stock price may decline.

PART I—FINANCIAL INFORMATION

Item 1. Financial Statements

Adverum Biotechnologies, Inc.
Condensed Consolidated Balance Sheets
(In thousands)
(Unaudited)

	March 31, 2024	December 31, 2023
Assets		
Current assets:		
Cash and cash equivalents	$ 149,608	$ 75,000
Short-term investments	43,720	21,526
Prepaid expenses and other current assets	5,802	6,247
Total current assets	199,130	102,773
Operating lease right-of-use assets	51,760	52,266
Property and equipment, net	13,766	14,764
Restricted cash	1,976	1,976
Deposit and other long-term assets	1,196	1,231
Total assets	$ 267,828	$ 173,010
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 1,897	$ 1,921
Accrued expenses and other current liabilities	9,160	12,584
Lease liability, current portion	10,492	10,409
Total current liabilities	21,549	24,914
Long-term liabilities:		
Lease liability, net of current portion	63,991	64,627
Total liabilities	85,540	89,541
Stockholders' equity:		
Preferred stock	—	—
Common stock	2	1
Additional paid-in capital	1,127,383	1,003,718
Accumulated other comprehensive loss	(533)	(473)
Accumulated deficit	(944,564)	(919,777)
Total stockholders' equity	182,288	83,469
Total liabilities and stockholders' equity	$ 267,828	$ 173,010

See accompanying notes to condensed consolidated financial statements

Adverum Biotechnologies, Inc.
Condensed Consolidated Statements of Operations and Comprehensive Loss
(In thousands, except per share data)
(Unaudited)

	Three Months Ended March 31,	
	2024	2023
License revenue	$ —	$ 3,600
Operating expenses:		
Research and development	15,410	21,059
General and administrative	11,429	12,780
Total operating expenses	26,839	33,839
Operating loss	(26,839)	(30,239)
Other income, net	2,052	1,200
Net loss before income taxes	(24,787)	(29,039)
Income tax provision	—	(17)
Net loss	(24,787)	(29,056)
Other comprehensive loss:		
Net unrealized (loss) gain on marketable securities	(41)	739
Foreign currency translation adjustment	(19)	(7)
Comprehensive loss	$ (24,847)	$ (28,324)
Net loss per share — basic and diluted	$ (1.50)	$ (2.90)
Weighted-average common shares used to compute net loss per share - basic and diluted	16,479	10,030

See accompanying notes to condensed consolidated financial statements

Adverum Biotechnologies, Inc.
Condensed Consolidated Statements of Stockholders' Equity
(In thousands)
(Unaudited)

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2023	10,143	$ 1	$ 1,003,718	$ (473)	$ (919,777)	$ 83,469
Stock-based compensation expense	—	—	4,166	—	—	4,166
Issuance of common stock and pre-funded warrants for cash in private placements, net of issuance costs of $8,449	10,573	1	119,360	—	—	119,361
Common stock issued upon exercise of stock options	14	—	139	—	—	139
Common stock issued upon release of restricted stock units	25	—	—	—	—	—
Foreign currency translation adjustments	—	—	—	(19)	—	(19)
Unrealized loss on marketable securities, net	—	—	—	(41)	—	(41)
Net loss	—	—	—	—	(24,787)	(24,787)
Balance at Balance at March 31, 2024	20,755	$ 2	$ 1,127,383	$ (533)	$ (944,564)	$ 182,288
Balance at December 31, 2022	10,012	$ 1	$ 985,660	$ (1,531)	$ (802,612)	$ 181,518
Stock-based compensation expense	—	—	4,563	—	—	4,563
Common stock issued upon release of restricted stock units	45	—	—	—	—	—
Foreign currency translation adjustments	—	—	—	(7)	—	(7)
Unrealized gain on marketable securities, net	—	—	—	739	—	739
Net loss	—	—	—	—	(29,056)	(29,056)
Balance at March 31, 2023	10,057	$ 1	$ 990,223	$ (799)	$ (831,668)	$ 157,757

See accompanying notes to condensed consolidated financial statements.

Adverum Biotechnologies, Inc.
Condensed Consolidated Statements of Cash Flows
(In thousands)
(Unaudited)

	Three Months Ended March 31,	
	2024	**2023**
Cash flows from operating activities:		
Net loss	$ (24,787)	$ (29,056)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	997	1,592
Stock-based compensation expense	4,166	4,563
Net accretion of discount on marketable securities, net	(333)	(960)
Non-cash lease expense	506	1,427
Other	(19)	19
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	480	924
Deposit and other long-term assets and deferred rent receivable	35	62
Accounts payable	(347)	631
Accrued expenses and other liabilities	(3,391)	(749)
Lease liability	(552)	(865)
Net cash used in operating activities	(23,245)	(22,412)
Cash flows from investing activities:		
Purchases of marketable securities	(26,937)	(20,232)
Maturities of marketable securities	5,000	41,850
Purchases of property and equipment	(90)	(85)
Net cash (used in) provided by investing activities	(22,027)	21,533
Cash flows from financing activities:		
Proceeds from issuance of common stock and pre-funded warrants in private placements, net of issuance costs	119,741	—
Proceeds from issuance of common stock pursuant to option exercises	139	—
Net cash provided by financing activities	119,880	—
Net increase (decrease) in cash and cash equivalents and restricted cash	74,608	(879)
Cash and cash equivalents and restricted cash at beginning of period	76,976	70,934
Cash and cash equivalents and restricted cash at end of period	$ 151,584	$ 70,055
Cash and cash equivalents	149,608	67,552
Restricted cash	1,976	2,503
Cash and cash equivalents and restricted cash at end of period	$ 151,584	$ 70,055
Supplemental schedule of noncash investing and financing information		
Issuance costs included in accounts payable	$ 380	$ —
Remeasurement of operating lease right-of-use assets	$ —	$ 8,004
Property and equipment in accounts payable, accrued expenses and other current liabilities	$ —	$ 17

See accompanying notes to condensed consolidated financial statements.

Adverum Biotechnologies, Inc.
Notes to Condensed Consolidated Financial Statements
(Unaudited)

1. Organization and Basis of Presentation

Adverum Biotechnologies, Inc. (the “Company” or “Adverum”) was incorporated in Delaware on July 17, 2006 and is headquartered in Redwood City, California. The Company aims to establish gene therapy as a new standard of care for highly prevalent ocular diseases. The Company develops gene therapy product candidates intended to provide durable efficacy by inducing sustained expression of a therapeutic protein.

The Company has not generated any revenue from the sale of products since its inception. The Company has experienced net losses since its inception and had an accumulated deficit of $944.6 million as of March 31, 2024. The Company expects to incur losses and have negative net cash flows from operating activities as it engages in further research and development activities. As of March 31, 2024, the Company had cash, cash equivalents and short-term investments of $193.3 million, which the Company believes will be sufficient to fund its operations into late 2025.

Basis of Presentation — The accompanying unaudited condensed consolidated financial statements have been prepared in accordance with U.S. generally accepted accounting principles (“U.S. GAAP”) and follow the requirements of the Securities and Exchange Commission (“SEC”) for interim reporting. As permitted under those rules, certain footnotes or other financial information that are normally required by U.S. GAAP can be condensed or omitted. These unaudited condensed consolidated financial statements have been prepared on the same basis as the Company’s annual consolidated financial statements and, in the opinion of management, reflect all adjustments, consisting only of normal recurring adjustments, which are necessary for a fair statement of the Company’s consolidated financial information. The condensed consolidated financial statements include the accounts of the Company and its wholly owned subsidiaries. All intercompany balances and transactions have been eliminated in consolidation. The results of operations for the three months ended March 31, 2024 are not necessarily indicative of the results to be expected for the full year or any other future period. The balance sheet as of December 31, 2023 is derived from the audited consolidated financial statements at that date but does not include all of the information required by U.S. GAAP for complete consolidated financial statements.

The accompanying unaudited condensed consolidated financial statements and related financial information should be read in conjunction with the audited consolidated financial statements and the related notes thereto included in the Company’s Annual Report on Form 10-K for the year ended December 31, 2023 filed with the SEC.

2. Summary of Significant Accounting Policies

Use of Estimates

The preparation of condensed consolidated financial statements in conformity with U.S. GAAP requires management to make judgments, 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 it believes 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 judgments are inherently uncertain, and 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 financial statements and the notes thereto have been adjusted retroactively, where applicable, to reflect this reverse stock split.

Recent Accounting Pronouncements

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. Early adoption is permitted. 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 information. 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.

3. Fair Value Measurements and Fair Value of Financial Instruments

The authoritative guidance on the fair value hierarchy for disclosure of fair value measurements is 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.

Level 1 securities consist of highly liquid money market funds. U.S. government and agency securities and commercial paper 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:

	March 31, 2024			
	Amortized Cost Basis	Unrealized Gains	Unrealized Losses	Estimated Fair Value
	(In thousands)			
Level 1:				
Money market funds	$ 5,333	$ —	$ —	$ 5,333
Level 2:				
Commercial paper	142,377	—	(78)	142,299
U.S. government and agency securities	35,485	—	(11)	35,474
Total cash equivalents and short-term investments	183,195	—	(89)	183,106
Less: Cash equivalents	(139,451)	—	65	(139,386)
Total short-term investments	$ 43,744	$ —	$ (24)	$ 43,720

	December 31, 2023			
	Amortized Cost Basis	Unrealized Gains	Unrealized Losses	Estimated Fair Value
	(In thousands)			
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 of March 31, 2024, the stated maturities of the Company's investments portfolio are generally less than one year, except for $2.9 million that have remaining maturities between one and two years. The Company classifies its investments as short-term marketable securities even though the stated maturities may be one year or more beyond of the current balance sheet date as the Company has the ability to sell these securities at any time for use in current operations. The aggregate fair value of debt securities in an unrealized loss position at March 31, 2024 and December 31, 2023 was $174.9 million and $71.3 million, respectively, which are highly liquid funds with high credit ratings that have final maturity of less than two years from date of purchase. The Company has not recorded an allowance for credit losses as of March 31, 2024 and December 31, 2023 related to these securities. The accrued interest receivable on available-for-sale marketable securities was immaterial at March 31, 2024 and December 31, 2023. The Company held 41 securities that were in unrealized loss positions as of March 31, 2024. There were no individual securities that were in a significant unrealized loss position as of March 31, 2024 and December 31, 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 had not recorded any impairment charges on available-for-sale securities as of March 31, 2024 and December 31, 2023.

4. License 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.

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 achieved the first development milestone; accordingly, the Company is eligible to receive additional payments. Therefore, the Company recognized $3.5 million of license revenue during the three months ended March 31, 2023. No milestones were achieved and no license revenue was recognized during the three months ended March 31, 2024.

5. 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 $1.9 million, which is classified as restricted cash under long term assets on the Company's condensed 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 $8.3 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

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

On October 26, 2021, the Company entered into a sublease agreement with a subtenant for the NC Premises through October 2037, the remainder of the lease term, and concurrently changed the lease payment 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 the subtenant. This change in the Company's payment terms with the landlord at the time of the sublease was considered to be a lease modification and the Company remeasured the lease liability and right-of-use asset on the modification date, with no amounts recognized in the consolidated statement of operations. The base annual rental rates, payment schedules and amounts under the sublease agreement are substantially the same as the original payment terms by Adverum to the landlord.

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 a reduction to the lease liability with a corresponding reduction of the right-of-use asset of $5.7 million in the quarter ended June 30, 2023. There was no charge recognized in the consolidated statement of operations.

Sublease income was $1.3 million and $1.4 million for the three months ended March 31, 2024 and 2023, respectively, which was classified as a reduction of rent expense in general and administrative expense.

6. Balance Sheet Components

Property and Equipment, Net

Property and equipment, net consists of the following:

	March 31, 2024	December 31, 2023
	(In thousands)	
Laboratory equipment	$ 14,788	$ 14,638
Leasehold improvements	13,586	13,586
Computer equipment and software	901	868
Construction in progress	—	184
Total property and equipment	29,275	29,276
Less: Accumulated depreciation and amortization	(15,509)	(14,512)
Property and equipment, net	$ 13,766	$ 14,764

Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consist of the following:

	March 31, 2024	December 31, 2023
	(In thousands)	
Employee compensation	$ 4,169	$ 8,040
Accrued nonclinical, clinical and process development costs	3,298	3,367
Accrued professional services	674	351
State income tax payable	109	101
Other	910	725
Total accrued expenses and other current liabilities	$ 9,160	$ 12,584

7. 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 March 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.

Equity Incentive Awards

Stock Options

The following table summarizes the Company’s option activity and related information:

	Number of Options (in thousands)	Weighted-Average Exercise Price
Balance at December 31, 2023	2,303	$ 48.71
Options granted	557	18.51
Options exercised	(14)	10.14
Options forfeited	(86)	28.44
Balance at March 31, 2024	2,760	$ 43.43
Exercisable as of March 31, 2024	1,253	$ 73.42

Restricted Stock Units ("RSUs")

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

	Number of Units (in thousands)	Weighted-Average Grant-Date Fair Value
Outstanding at December 31, 2023	154	$ 21.73
Granted	73	19.21
Vested and released	(25)	27.41
Forfeited	(4)	10.81
Outstanding at March 31, 2024	198	$ 20.33

Stock-Based Compensation Expense

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

	Three Months Ended March 31,	
	2024	2023
	(In thousands)	
Research and development	$ 1,120	$ 1,381
General and administrative	3,046	3,182
Total stock-based compensation expense	$ 4,166	$ 4,563

8. 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 rights under the 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.

For the three months ended March 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:

	March 31, 2024	March 31, 2023
	(In thousands)	
Stock options	2,760	2,331
Restricted stock units	198	173
ESPP	42	115
	3,000	2,619

Item 2. Management's Discussion and Analysis of Financial Condition and Results of Operations

The interim financial statements included in this Quarterly Report on Form 10-Q and this Management's Discussion and Analysis of Financial Condition and Results of Operations should be read in conjunction with the financial statements and notes thereto for the year ended December 31, 2023, and the related Management's Discussion and Analysis of Financial Condition and Results of Operations, contained in our Annual Report on Form 10-K, as filed with the U.S. Securities and Exchange Commission (SEC) on March 18, 2024. In addition to historical information, this discussion and analysis contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended ("Securities Act"), and Section 21E of the Securities Exchange Act of 1934, as amended ("Exchange Act"). 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 Quarterly Report on Form 10-Q, 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 forward-looking and other statements are subject to risks and uncertainties, including those discussed in the section titled "Risk Factors," set forth in Part II – Other Information, Item 1A below and elsewhere in this report that could cause actual results to differ materially from historical results or anticipated results.

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, and is being evaluated in the ongoing LUNA Phase 2 clinical trial. 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.

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 cutoff date of August 23, 2023, 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 of mean best-corrected visual acuity ("BCVA") and maintenance to improvement of mean central subfield thickness ("CST"), currently out to three years, and stable aflibercept protein levels through the latest reported follow-up, which is currently up to 4.5 years. Ixo-vec has been generally well tolerated, with the most common adverse events being dose-dependent adeno-associated virus ("AAV") associated ocular inflammation that has been responsive to topical corticosteroid therapy.

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 will assess enhanced prophylactic corticosteroid regimens, including local corticosteroids and combinations of local and systemic corticosteroids to test the relative contribution of local versus systemic AAV exposure on ocular inflammation. The endpoints are similar to the OPTIC trial and focus on mean change in BCVA, CST and treatment burden from baseline to one year, and incidence and severity of adverse events. In August 2023, we announced that LUNA was fully enrolled, with a total of 60 subjects randomized equally between the 2E11 and 6E10 doses.

In February 2024, we announced LUNA preliminary safety and efficacy data suggesting that both the 2E11 and 6E10 doses demonstrated maintenance of 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, consistent with results observed in the OPTIC trial. In those subjects who had completed 26 weeks of follow-up, at the 6E10 (n=19) and 2E11 (n=20) doses, Ixo-vec demonstrated reduction in annualized anti-VEGF injection rates of 90% and 94%, respectively, and injection free rates of 68% and 85%, respectively. In addition, Ixo-vec was well-tolerated, and when present intraocular inflammation was responsive to per-protocol local corticosteroids. Preliminary data suggest that Ozurdex® plus difluprednate eye drops may be a promising prophylactic regimen for future pivotal studies. In this potential "go-forward" regimen, the vast majority of patients had no inflammation, with over 90% of these patients having no or minimal inflammation. We plan to initiate a Phase 3 clinical trial of Ixo-vec in wet AMD in the first half of 2025.

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").

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.

Financial Overview

Summary

We have not generated positive cash flow or net income from operations since our inception and, as of March 31, 2024, we had an accumulated deficit of $944.6 million. We expect to incur substantial expenses and continuing losses from operations in the foreseeable future as we conduct our research and development efforts, advance our product candidates through nonclinical and clinical development, manufacture clinical study materials, seek regulatory approval, and prepare for and, if approved, proceed to commercialization. We are at an early stage of development and may never be successful in developing or commercializing our product candidates.

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

We currently have no operational clinical or commercial manufacturing facilities, and all of our clinical manufacturing activities are currently contracted out to third parties. Additionally, we use third-party contract research organizations ("CROs") to carry out our clinical development and we do not have a sales organization.

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

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 Quarterly Report on Form 10-Q have been adjusted retroactively, where applicable, to reflect this reverse stock split.

As of March 31, 2024, we had $193.3 million in cash, cash equivalents and short-term investments. 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”). We believe that our cash, cash equivalents and short-term investments are sufficient to fund our planned operations into late 2025. However, we may need to raise additional funds sooner as a result of a number of risks and uncertainties, including those set forth in Part II, Item 1A. Risk Factors – “We expect that our cash, cash equivalents, and short-term investments will be sufficient to fund our planned operations into late 2025. If this expectation proves to be wrong, we may be forced to delay, limit or terminate certain of our development efforts before then.”

Revenue

To date we have not generated any revenue from the sale of our products. We have generated revenue through research, collaboration and license arrangements with strategic partners. Our ability to generate product revenue and become profitable depends upon our ability to successfully develop and commercialize our product candidates. Because of the numerous risks and uncertainties associated with product development, we are unable to predict the amount or timing of product revenue. Even if we are able to generate revenue from the sale of our products, our sales may not be sufficient to generate cash from operations, in which case we may be unable to continue our operations at planned levels and be forced to reduce our operations.

Research and Development Expenses

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

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

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

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

General and Administrative Expenses

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

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 unaudited condensed consolidated financial statements, which have been prepared in accordance with U.S. GAAP. The preparation of these condensed 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 condensed consolidated financial statements, as well as the 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.

There have been no significant changes in our critical accounting judgments and estimates during the three months ended March 31, 2024 as compared to the critical accounting judgments and estimates disclosed in the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" included in our most recent Annual Report on Form 10-K filed with the SEC on March 18, 2024.

Results of Operations

Comparison of the Three Months Ended March 31, 2024 and 2023

	Three Months Ended March 31,		
	2024	2023	Change
	(In thousands)		
License revenue	$ —	$ 3,600	$ (3,600)
Operating expenses:			
Research and development	15,410	21,059	(5,649)
General and administrative	11,429	12,780	(1,351)
Total operating expenses	26,839	33,839	(7,000)
Operating loss	(26,839)	(30,239)	3,400
Other income, net	2,052	1,200	852
Net loss before income taxes	(24,787)	(29,039)	4,252
Income tax provision	—	(17)	17
Net loss	$ (24,787)	$ (29,056)	$ 4,269

License Revenue

The $3.6 million of license revenue for the three months ended March 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, pursuant to which we granted Lexeo an exclusive license to the intellectual property rights, pre-clinical data and knowhow associated with our Friedreich's Ataxia program.

Research and Development Expense

The following table summarizes our research and development expenses for the three months ended March 31, 2024 and 2023:

	Three months ended March 31,		Increase/ (Decrease)
	2024	2023	
	(In thousands)		
Direct research and development expenses:			
Ixo-vec	$ 3,731	$ 6,557	$ (2,826)
Other programs	620	1,652	(1,032)
Indirect research and development expenses:			
Personnel related (including stock-based compensation)	8,124	8,850	(726)
Facilities and other unallocated research and development expenses	2,935	4,000	(1,065)
Total research and development expenses	$ 15,410	$ 21,059	$ (5,649)

Research and development expense decreased by $5.6 million to $15.4 million for the three months ended March 31, 2024 from $21.1 million for the three months ended March 31, 2023. This overall decrease was primarily related to a decrease of $2.8 million in spending on Ixo-vec due to completion of two clinical trials, a decrease of $1.1 million in facilities expenses driven by a lease termination in the prior year, a decrease of $1.0 million in other programs arising from license costs driven by the Lexeo revenue, and a decrease of $0.7 million in personnel-associated costs due to restructuring expense in the prior year. Stock-based compensation expense included in research and development expenses was $1.1 million for the three months ended March 31, 2024, compared to $1.4 million for the three months ended March 31, 2023.

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

General and Administrative Expense

General and administrative expense decreased $1.4 million to $11.4 million for the three months ended March 31, 2024 from $12.8 million for the three months ended March 31, 2023, primarily related to $0.7 million in depreciation on leasehold improvements driven by a lease termination in the prior year, $0.5 million in costs related to consultants and contractors, and decreases of $0.3 million in facilities costs. Stock-based compensation expense included in general and administrative expenses was $3.0 million for the three months ended March 31, 2024, compared to $3.2 million for the three months ended March 31, 2023.

Other Income, Net

Other income, net was $2.1 million for the three months ended March 31, 2024 and $1.2 million for the three months ended March 31, 2023 as a result of higher average invested balances.

Income Tax Provision

We recognized no income tax provision for the three months ended March 31, 2024, and $17,000 for the three months ended March 31, 2023, related to foreign operations.

Liquidity and Capital Resources

We have not generated positive cash flow or net income from operations since our inception and as of March 31, 2024, we had an accumulated deficit of $944.6 million. As of March 31, 2024, we had $193.3 million in cash, cash equivalents and short-term investments compared to $96.5 million as of December 31, 2023. On February 7, 2024, we completed 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 for total gross proceeds of $127.8 million, before deducting placement agent fees and offering expenses. Additionally, 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 May 9, 2024, no sales have been made pursuant to the Sales Agreement. We believe that our existing cash and cash equivalents and short-term investments as of March 31, 2024 will be sufficient to fund our operations and meet our existing contractual obligations and other cash requirements into late 2025. However, we may need to raise additional funds sooner as a result of a number of risks and uncertainties, including those set forth in Part II, Item 1A. Risk Factors – “We expect that our cash, cash equivalents, and short-term investments will be sufficient to fund our planned operations into late 2025. If this expectation proves to be wrong, we may be forced to delay, limit or terminate certain of our development efforts before then.”

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

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

- the initiation, progress, timing, costs and results of nonclinical studies and any clinical trials for our product candidates;
- the outcome, timing of and costs involved in, seeking and obtaining approvals from the FDA and other regulatory authorities, including the potential for the FDA and other regulatory authorities to require that we perform more studies than those that we currently expect;
- the ability of our product candidates to progress through clinical development activities successfully;
- our need to expand our research and development activities;
- the rate of progress and cost of commercialization of our products;
- the cost of preparing to manufacture our products on a larger scale;
- the costs of commercialization activities including product sales, marketing, manufacturing and distribution;
- the degree and rate of market acceptance of any products launched by us or future partners;
- the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights;
- our need to implement additional infrastructure and internal systems;
- our ability to hire additional personnel;
- our ability to enter into additional collaboration, licensing, commercialization or other arrangements and the terms and timing of such arrangements; and
- the emergence of competing technologies or other adverse market developments.

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

Cash Flows

	Three Months Ended March 31,	
	2024	2023
	(in thousands)	
Net cash used in operating activities	$ (23,245)	$ (22,412)
Net cash (used in) provided by investing activities	(22,027)	21,533
Net cash provided by financing activities	119,880	—
Net increase (decrease) in cash and cash equivalents and restricted cash	$ 74,608	$ (879)

Cash Used in Operating Activities

During the three months ended March 31, 2024, net cash used in operating activities was $23.2 million, primarily as a result of net loss of $24.8 million due to our continued research and development activities, partially offset by $5.3 million of non-cash charges mainly related to $4.2 million of stock-based compensation expense, $1.0 million of depreciation and amortization expenses, $0.5 million of non-cash lease expense, and by $3.8 million of change in operating assets and liabilities, which fluctuate due to timing of expenses and payments.

During the three months ended March 31, 2023, net cash used in operating activities was $22.4 million, primarily as a result of net loss of $29.1 million due to the continued activities developing our product candidates, partially offset by $6.6 million of non-cash charges mainly related to $4.6 million of stock-based compensation expense and $1.6 million of depreciation and amortization expenses.

Cash (Used in) Provided by Investing Activities

Net cash used in investing activities for the three months ended March 31, 2024 consisted of $21.9 million of net purchases from our marketable securities and $0.1 million of purchases of property and equipment.

Net cash provided by investing activities for the three months ended March 31, 2023 consisted of $21.6 million of maturities from our marketable securities, partially offset by $0.1 million of purchases of property and equipment.

Cash Provided by Financing Activities

Net cash provided by financing activities for the three months ended March 31, 2024 consisted mainly of $119.7 million of proceeds from issuance of common stock and pre-funded warrants in the Private Placements and $0.1 million of proceeds from the exercise of stock options.

Item 3. 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 4. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Management, including our Chief Executive Officer and Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, as of March 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 Quarterly Report on Form 10-Q. 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.

Based on that evaluation, our Chief Executive Officer and Chief Financial Officer concluded that, as of March 31, 2024, our disclosure controls and procedures were effective to provide reasonable assurance that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is (i) recorded, processed, summarized and reported as and when required and (ii) accumulated and communicated to our management, including our Chief Executive Officer and our Chief Financial Officer, as appropriate to allow timely discussion regarding required disclosure.

Limitations on the Effectiveness of Controls

Our management, including our Chief Executive Officer and Chief Financial Officer, does not expect that our disclosure controls and procedures or our internal control over financial reporting will prevent all error and all fraud. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Further, the design of a control system must reflect the fact that there are resource constraints, and the benefit of controls must be considered relative to their costs. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within Adverum have been detected. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting that occurred during our most recent fiscal quarter that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II – OTHER INFORMATION

Item 1. Legal Proceedings

On April 9, 2024, the Delaware Court of Chancery entered an Order and Final Judgment approving settlement of a stockholder derivative action (Pazyuk v. Machado, et al., C.A. No. 2022-1062-MTZ), pursuant to which we agreed to implement and maintain certain limits to our non-employee director compensation policy, to be in effect for three years: (i) a $150,000 cap on non-employee director annual compensation while our market capitalization is below $250 million, (ii) a $250,000 cap on non-employee director annual compensation while our market capitalization is greater than $250 million and less than $500 million, (iii) a $400,000 cap on non-employee director annual compensation while our market capitalization is greater than $500 million and less than $1 billion, (iv) a $475,000 cap on non-employee director annual compensation while our market capitalization is greater than $1 billion and (v) a limit on the grant date fair value of one-time equity awards made to new directors equal to two times the grant date fair value of the annual option grant award made to continuing non-employee directors.

Item 1A. Risk Factors

You should consider carefully the risks and uncertainties described below, together with all of the other information in this Quarterly Report on Form 10-Q. 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

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 expect that our cash, cash equivalents, and short-term investments will be sufficient to fund our planned operations into late 2025. If this expectation proves to be wrong, we may be forced to delay, limit or terminate certain of our development efforts before then.

We currently expect our cash, cash equivalents and short-term investments to fund our planned operations into late 2025. However, this estimate is based on a number of assumptions that may prove to be wrong, including our expectations about the timing of planned clinical trials, investments into our manufacturing capabilities, the scope of our research and development activities, continued compliance with and receipt of rental income under our sublease, and changing circumstances beyond our control, that may cause capital to be consumed more rapidly than currently anticipated. As a result, our operating plan may change, and we may need to seek additional funds sooner than planned through collaboration agreements and public or private financings. If we run low on capital and are unable to successfully raise additional funds on terms acceptable to us, we may need to significantly curtail some or all of our development activities.

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

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

- the type, number, scope, progress, costs, results of and timing of any future nonclinical studies and clinical trials of any of our product candidates that we are pursuing or may choose to pursue in the future;
- the need for, and the progress, costs and results of, any additional clinical trials or nonclinical studies of our product candidates we may initiate based on the results of any clinical trials that we may plan or discussions with the United States Food and Drug Administration ("FDA") or other regulatory authorities outside the United States ("U.S."), including any additional clinical trials or nonclinical studies the FDA or other regulatory authorities outside the U.S. may require evaluating the safety of our product candidates;
- the costs of obtaining, maintaining and enforcing our patents and other intellectual property rights;
- the costs and timing of obtaining or maintaining manufacturing for our product candidates, including internal and external commercial manufacturing;
- the availability and cost of acquiring and shipping of supplies necessary for manufacturing and clinical trials;
- the costs and timing of establishing sales, marketing, distribution and other commercial capabilities;
- the terms and timing of establishing collaborations, license agreements and other partnerships;
- costs associated with any new product candidates that we may develop, in-license or acquire;
- the effect of competing technological and market developments;
- our ability to establish and maintain partnering arrangements for development and/or commercialization;
- the cost and timing of establishing enhanced internal controls over financial reporting; and
- the costs associated with being a public company.

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

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

Additional funding may not be available to us on acceptable terms or at all and the terms of any financing may adversely affect the holdings or the rights of our stockholders. General market conditions resulting from high interest rates, inflation, bank failures, domestic politics, global supply chain issues, and ongoing military conflicts, as well as other market conditions, may make it difficult for us to obtain adequate additional financing when needed or on attractive terms, or at all. In addition, the issuance of additional shares by us, or the possibility of such issuance, may cause the market price of our shares to decline.

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

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 biologics license application ("BLA") to the FDA or marketing authorization application ("MAA") to the European Medicines Agency ("EMA"), and even fewer are approved for commercialization. Furthermore, even if we do receive regulatory approval to market any of our product candidates, any such approval may be subject to limitations on the indicated uses for which we may market the product, or limitations related to its distribution, or be conditional on future development activities and clinical results. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development programs, there can be no assurance that any of our product candidates will be successfully developed or commercialized. If we or any of our future development partners are unable to develop, or obtain regulatory approval, or, if approved, successfully commercialize, any of our product candidates, we may not be able to generate sufficient revenue to continue our business.

Drug development is a long, expensive and uncertain process, and delay or failure can occur at any stage of development, including after commencement of any of our clinical trials or any clinical trials using our proprietary viral vectors.

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

We, or any licensee or development partner, will be required to demonstrate through adequate and well-controlled clinical trials that our product candidate or another party's product candidate containing one of our proprietary viral vectors is safe and effective for use in its target indications before seeking regulatory approvals for commercial sale. Drug development is a long, expensive and uncertain process, and delay or failure can occur at any stage of development, including after commencement of any of our clinical trials or any clinical trials using our proprietary viral vectors. Any such delay or failure could significantly harm our business prospects, financial condition and results of operations.

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

During the conduct of nonclinical studies and clinical trials, animal models and human subjects may experience changes in their health, including illnesses, injuries and discomforts. 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, 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 intraocular 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 February 2024, we announced LUNA preliminary safety and efficacy data. Ixo-vec was well-tolerated, and when present intraocular inflammation was responsive to per protocol local corticosteroids. Preliminary data suggest that Ozurdex® plus difluprednate eye drops may be a promising prophylactic regimen for future pivotal studies. The use of an Ozurdex® plus 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.

Even if we achieve marketing approval, doctors may not prescribe, and patients may not use, Ixo-vec or our other product candidates if they deem the levels or risk of inflammation to be unacceptable or if they are unwilling or unable to use the required prophylactic corticosteroid regimen. Further, patients treated with Ixo-vec could develop antibodies against AAV.7m8 capsid and/or aflibercept protein. These antibodies could preclude these patients from receiving other AAV-based gene therapies in the future. In addition, patients previously treated with or exposed to other AAV-based gene therapies could develop antibodies against AAV.7m8 and/or the aflibercept protein, which could reduce or eliminate the effectiveness of Ixo-vec or could cause unanticipated adverse reactions to Ixo-vec. Studies have also found that intravenous delivery of certain AAV vectors at high doses may result in adverse events and have prompted the recommendation that studies involving high doses of AAV vectors should be monitored carefully for such adverse events. In addition, patients given infusions of any therapeutic protein or injection of gene therapies that express a therapeutic protein may develop severe hypersensitivity reactions, infusion reactions, or serious side effects including transaminitis. With respect to our product candidates that are being or may be studied in diseases of the eye, there are additional potential serious complications related to 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 higher than the level of protein expression achieved in humans. Similarly, human subjects administered our product candidates may develop side effects that were not observed in animal models and/or are more severe than those observed in animal models. In addition, even industry-accepted animal models may not accurately replicate human disease. Success in nonclinical studies or in early clinical trials does not mean that later clinical trials will be successful, because product candidates in later-stage clinical trials may fail to demonstrate sufficient safety or efficacy despite having progressed through nonclinical and initial clinical testing. Further, safety and/or efficacy issues with a product candidate may become apparent only when the product candidate is tested in human subjects suffering from the relevant disease. Furthermore, the initiation of future trials for a product candidate will be dependent upon demonstrating sufficient safety and efficacy to the relevant regulatory authorities in preceding or other ongoing trials using the same product candidate. We will still need to conduct Phase 3 pivotal trials in which we anticipate Ixo-vec will be compared to available therapies and utilize longer term endpoints in order to support submission and approval of a BLA or equivalent outside of the U.S. Companies frequently suffer significant setbacks in advanced clinical trials, even after earlier clinical trials have shown promising results. In addition, only a small percentage of products under development result in the submission of a marketing application and even fewer are approved for commercialization. Even if our clinical trials successfully meet their endpoints for safety and efficacy, the FDA and/or other regulatory authorities outside the U.S. may still conclude that the product candidate has not demonstrated a beneficial 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 products. The regulatory approval process for novel gene therapy products such as ours can be more expensive and take longer than for other treatment modalities, which are better known or more extensively studied to date. To date, approvals for gene therapy products by the FDA have been generally for rare diseases with limited treatment options. Because we are targeting a broad population of patients with wet AMD, for which there is an approved and widely adopted standard of care, the benefit-risk profile of Ixo-vec may be subject to greater scrutiny by regulatory authorities. Regulatory approaches and requirements for gene therapy products continue to evolve, and any changes could create significant delay and unpredictability for product development and approval as compared to technologies with which regulatory authorities have more substantial experience, including, for example, reevaluating whether to require a companion diagnostic for gene therapy products.

Before a clinical trial can begin to enroll at a clinical site, the site's Institutional Review Board ("IRB") 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 have neutralizing antibodies at titer levels that would prevent them from being enrolled in a clinical trial for any of our product candidates, or may meet other exclusion criteria. As a consequence, enrollment in our clinical trials may be limited or slowed. We also may encounter difficulties in identifying and enrolling patients with a stage of disease appropriate for such future clinical trials. We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics to achieve diversity in a trial.

We plan to seek initial marketing approval of our product candidates in the U.S. and/or the EU 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; or
- the approval policies or regulations of such authorities may significantly change in a manner rendering our or any of our future development partners' clinical data insufficient for approval.

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

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

From time to time, we may announce or publish preliminary or interim data from our clinical trials. Preliminary and interim results of a clinical trial are not necessarily predictive of final results. Preliminary and interim data are subject to the risk that one or more of the clinical outcomes may materially change as subject enrollment continues or further subject follow up occurs and more subject data become available. In addition, in certain clinical trials, such as our OPTIC trial, individual cohorts of subjects were enrolled with different dosages and other treatment conditions under our protocol. These different doses, populations, and other treatment conditions may affect clinical outcomes, including safety profiles or efficacy, such as the number of supplemental injections required, in each of the cohorts. As a result, preliminary and interim data should be viewed with caution and not relied upon until the final data from a locked database for the entire clinical trial are available. Material changes in the final data compared to preliminary or interim data could significantly harm our business prospects.

Fast Track designation by the FDA, 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 rolling review, where the FDA reviews portions of a marketing application before the sponsor submits the complete application.

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 new 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, 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 does 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 each 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 or through third parties, we will likely face technical and scientific challenges, considerable capital costs, and potential difficulty in recruiting and hiring experienced, qualified personnel. There may also be unexpected technical or operational issues during clinical manufacturing campaigns or process validation campaigns. For example, all Good Manufacturing Practices (“GMP”) activities at our Redwood City facility, and external manufacturing, testing, and distribution partners are subject to significant health authority regulation with respect to manufacturing and testing our product candidates. If we are unable to satisfy these regulatory requirements, or if we are unable to solve the technical, scientific, and other challenges described above, we may be unable to manufacture a sufficient supply of our product candidates for our clinical trials and may be forced to delay or terminate our development programs. Additionally, changes in manufacturing processes (including cell lines 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, or from a third-party facility to one of our facilities) may require us to conduct additional studies to demonstrate comparability in order to receive regulatory approval of any manufacturing modifications. As a result, we could experience manufacturing delays that prevent us from 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 also will increase if we experience delays in testing or regulatory approvals.

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

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

As we develop, seek to optimize and operate the Ixo-vec manufacturing process internally or through third parties, we will likely face technical and scientific challenges, considerable costs, and potential difficulty in recruiting and hiring experienced, qualified personnel. 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 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 we may be unable to transfer or sublicense the intellectual property rights we may have with respect to such activities, and may be unable to acquire such rights, to the extent that we do not already have them.

All entities involved in the preparation of therapeutics for clinical trials or commercial sale, including our existing contract vendors for our product candidates, are subject to extensive regulation. Components of a finished therapeutic product used in clinical trials or approved for commercial sale must be manufactured and tested in accordance with GMP regulations. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing.

We or our contract manufacturers must supply all necessary documentation in support of a BLA on a timely basis and must adhere to the FDA's GMP regulations enforced by the FDA through its facilities inspection program as well as other 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 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 foresees a three-year transition period. The extent to which ongoing and new clinical trials will be governed by the CTR varies. For clinical trials in relation to which application for approval was made on the basis of the Clinical Trials Directive before January 31, 2023, the Clinical Trials Directive will continue to apply on a transitional basis until January 31, 2025. By that date, all ongoing trials will become subject to the provisions of the CTR. The CTR will apply to clinical trials from an earlier date if the related clinical trial application was made on the basis of the CTR or if the clinical trial has already transitioned to the CTR framework before January 31, 2025. 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. 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.

On January 31, 2020, the UK withdrew from the European Union ("EU"), commonly referred to as Brexit. Pursuant to the formal withdrawal arrangements agreed between the UK and the EU, the UK was subject to a transition period until December 31, 2020, or the Transition Period, during which EU rules continued to apply. The UK-EU Trade and Cooperation Agreement, which has applied since the end of the Transition Period, provides for tariff-free trade of goods, but not services, between the UK and the EU. There may, however, be additional non-tariff costs which did not exist prior to the end of the Transition Period. Further, should the UK further diverge from the EU from a regulatory perspective in relation to medical products, tariffs could be put into place in the future.

Although the body of the UK-EU Trade and Cooperation Agreement includes general terms which apply to medicinal products, greater detail on sector-specific issues is provided in an Annex to the Agreement. The Annex provides a framework for the recognition of GMP inspections and for the exchange and acceptance of official GMP documents. The regime does not, however, extend to procedures such as batch release certification, and Great Britain (England, Scotland and Wales) is treated as a third country. Northern Ireland, has continued to follow EU regulatory rules, but pursuant to the Windsor Framework, a post-Brexit legal agreement entered into between the EU and UK Northern Ireland will no longer be subject to EU Regulations as of January 1, 2025. As part of the UK-EU Trade and Cooperation Agreement, the EU and the UK will recognize GMP inspections carried out by the other Party and the acceptance of official GMP documents issued by the other Party. The UK-EU Trade and Cooperation Agreement also encourages, although it does not oblige, the parties to consult one another on proposals to introduce significant changes to technical regulations or inspection procedures. Among the areas of absence of mutual recognition are batch testing and batch release. The UK continues to accept EU batch testing and batch release, but has recently conducted a consultation as to the future strategy for batch testing policy; two years notice will be provided of any change to such a policy. However, the EU continues to apply EU laws that require batch testing and batch release to take place in the EU territory. As regards marketing authorizations, Great Britain has a separate regulatory submission process, approval process and a separate national marketing authorization. Northern Ireland has continued to be covered by centralized marketing authorizations granted by the European Commission ("EC"). but the Windsor Framework provides that the UK MHRA will be the sole regulatory body responsible for granting marketing authorizations for Northern Ireland as of January 1, 2025.

There are currently delays on cross-border trade between the UK and the EU as businesses and governmental bodies adapt to the arrangements. We and our contract vendors currently rely on other contractors based in the UK. The implementation of new governmental policies associated with Brexit may affect our UK-based contractors' ability to comply with applicable regulations, including existing EU regulations. If they are unable to return to compliance, or if an acceptable substitute vendor cannot be identified, it may negatively impact our business. Further, to the extent that our UK-based contractors have supply relationships with vendors in the EU, these contractors may experience difficulties, delay or increased costs in receiving materials from their vendors in the EU, which could have a material adverse effect on our UK-based contractors' ability to provide the services or materials to us.

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 contaminations are discovered in our product candidates or in the manufacturing facility in which our product candidates are made, such manufacturing facility may need to be closed for an extended period of time to investigate and remedy the contamination.
- The manufacturing facilities in which our product candidates are made could be adversely affected by equipment failures, labor shortages, contaminants, raw materials shortages, natural disasters, power failures, and numerous other factors.
- We and our contract manufacturers must comply with the FDA's 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 for late-stage clinical product, and our current process has not been fully characterized and therefore is open to potential variations that could lead to defective product substance that does not meet specification.
- Problems with the manufacturing, storage or distribution of our product candidates, including even minor deviations from our established parameters, could result in product defects or manufacturing failures that result in lot failures, product recalls, product liability claims and insufficient inventory.
- Some of the raw materials required in our manufacturing process are derived from biological sources. Such raw materials are difficult to procure and may also be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our product candidates could adversely impact or disrupt commercialization.

Any adverse developments affecting manufacturing operations for our product candidates may result in shipment delays, inventory shortages, lot failures, product withdrawals or recalls, or other interruptions in the supply of our product candidates, 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 be more costly. Our reliance on these third parties for vector production, process development, assay development, product and product candidate manufacturing and testing, protocol development, clinical trials, product distribution, commercialization, nonclinical studies, research and related activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations. If any of these third parties on which we rely do not perform satisfactorily, we will remain responsible for ensuring that:

- each of our nonclinical studies and clinical trials are conducted in accordance with the study plan and protocols and applicable regulatory requirements;
- vector production, product and product candidate manufacturing and testing are conducted in accordance with applicable GMP requirements and other applicable regulatory requirements; and
- other research, process development, and assay development are conducted in accordance with applicable industry and regulatory standards and norms;

any of which we may not be able to do.

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

- the inability to negotiate manufacturing, supplier agreements, partnerships or other agreements with third parties under commercially reasonable terms;
- reduced control as a result of using third-party manufacturers or partners for some or all aspects of manufacturing activities;
- termination or nonrenewal of manufacturing agreements, partnerships, or supplier agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers or suppliers caused by conditions unrelated to our business or operations, including the acquisition, change in control, or bankruptcy of the manufacturer, supplier or partner, or their commitments to other vaccine and therapeutics production projects that may reduce available manufacturing capacity.

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

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

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

There is no guarantee that any CROs, investigators or other third parties on which we rely for administration and conduct of our clinical trials will devote adequate time and resources to such trials or perform as contractually required. If any of these third parties fails to meet expected deadlines, fails to adhere to our clinical protocols, fails to meet regulatory requirements, or otherwise performs in a substandard manner, our clinical trials may be extended, delayed or terminated. If any of our clinical trial sites terminates for any reason, we may experience the loss of follow-up information on subjects enrolled in our ongoing clinical trials unless we are able to transfer those subjects to another qualified clinical trial site.

In addition, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and may receive compensation in connection with such services. If these relationships and any related compensation result in perceived or actual conflicts of interest, the utility of certain data from the clinical trial may be questioned and the utility of the clinical trial itself may be jeopardized, which could result in the delay or rejection of any IND or BLA we submit to the FDA, or equivalent submissions to other regulatory authorities outside the U.S. Any such delay or rejection could prevent us from commercializing our product candidates.

Risks Relating to Our Intellectual Property

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

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

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

We own and license certain method-of-use patents and applications covering methods of treating certain diseases with our product candidates. Method-of-use patents protect the use of a product for the specified method or for treatment of a particular indication. However, methods of treating human diseases are considered unpatentable in many jurisdictions, and even where available this type of patent does not prevent a competitor from making and marketing a product that is identical to our product candidate for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products "off-label." Although off-label prescriptions may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent or prosecute.

The patent application process is subject to numerous risks and uncertainties, and there can be no assurance that we or any of our future development partners will be successful in protecting our product candidates by obtaining and defending patents. These risks and uncertainties include the following:

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

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

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

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

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

Because we rely on third parties to conduct research and to develop and manufacture our product candidates, we must, at times, share confidential information, including trade secrets, with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements containing confidentiality provisions with our advisors, employees, third-party contractors and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, including our trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that they become known by our competitors, are purposefully or inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Public disclosure of our confidential information also prevents us from seeking patent protection for that or related discoveries. Given that our proprietary position is based, in part, on our know-how and trade secrets, the unauthorized use or disclosure of our trade secrets would impair our competitive position and may have a material adverse effect on our business, financial conditions, results of operations and prospects.

In addition, these agreements typically restrict the ability of our advisors, employees, third-party contractors and consultants to publish data potentially relating to our confidential information and trade secrets, although our agreements may contain certain limited publication rights. For example, academic institutions that we collaborate with often require rights to publish data arising out of such collaboration, provided that we are notified in advance and given the opportunity to delay publication for a limited time period in order for us to secure patent protection of intellectual property rights arising from the collaboration, in addition to the opportunity to remove confidential information or trade secrets from any such publication. However, we may fail to recognize or identify to our collaborator such confidential information or trade secrets during the appropriate timeframe prior to publication, and they may be publicly disclosed without us filing for patent or other protection. In the future we may also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development or similar agreements.

Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, including through breach of our agreements with third parties, failure of our security measures or publication of information by any of our third-party collaborators, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions. A competitor’s discovery of our trade secrets could impair our competitive position and have an adverse impact on our business, financial condition, results of operations and prospects.

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

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

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

Others may hold proprietary rights that could prevent our product candidates from being marketed. Any patent-related legal action against us claiming damages and seeking to enjoin commercial activities relating to our product candidate or processes could subject us to potential liability for damages and require us to obtain a license to continue to manufacture or market our product candidates. We cannot predict whether we would prevail in any such actions or that any license required under any of these patents would be made available on commercially acceptable terms, if at all. In addition, we cannot be sure that we could redesign our product candidate or processes to avoid infringement, if necessary. Accordingly, an adverse determination in a judicial or administrative proceeding, or the failure to obtain necessary licenses, could prevent us from developing and commercializing our product candidates, which could harm our business, financial condition, results of operations and prospects.

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

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

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

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

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

We currently are heavily reliant upon licenses of certain patent rights and proprietary technology from third parties that are important or necessary to the development of our technology and products, including technology related to our manufacturing process and our gene therapy product candidates. These and other licenses may not provide adequate rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and products in the future, or may contain other limitations on our ability to use such intellectual property or technology. As a result, our ability to develop or commercialize our processes and product candidates may be limited by the terms of such agreements. Further, the third parties from whom we license certain patent rights and proprietary technology may attempt to terminate their agreements with us. For example, in 2019 we received from Virovek a notice of intent to terminate our non-exclusive license to certain Virovek technology and know-how related to methods and materials for manufacturing adeno-associated virus. Although no further action has been taken in that matter, it illustrates that if one of our licenses were to be terminated, we may be unable to obtain a new license to that technology on commercially reasonable terms, if at all. If we need to develop or acquire alternative manufacturing technology, our product development activities may be significantly delayed, and if we were unable to develop or acquire alternative manufacturing technology, it could have a material adverse effect on our business. In addition, we may not be able to prevent competitors from developing and commercializing competitive products to the extent our licenses to patents are non-exclusive or limited with respect to fields of use or territories.

We anticipate that licenses to additional third-party technology will be required to advance our current development programs, as well as additional development programs we may initiate in the future. If these licenses are not available on commercially reasonable terms or at all, we may not be able to commercialize our current and future development programs, which will have a material adverse effect on our business and financial condition, results of operations and prospects.

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

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

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

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

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

We are aware of patent rights held by third parties that could be construed to cover certain aspects of our product candidates. In addition, changes to our product candidates or their uses or manufacture may cause them to infringe patents held by third parties. A patent holder has the right to prevent others from making, using, 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;
- 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. 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.

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;
- 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, REGENXBIO is developing RGX-314, an AAV-based gene therapy delivering a gene encoding a therapeutic antibody fragment similar to ranibizumab (LUCENTIS®) for the treatment of wet AMD and diabetic retinopathy, which competes for the same patients, study site resources, and personnel as Ixo-vec. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

New developments, including the development of other biotechnology and gene therapy technologies and methods of treating disease, occur in the pharmaceutical, biotechnology and gene therapy industries at a rapid pace. Developments by competitors may render our product candidates obsolete or noncompetitive. Competition in drug development is intense. In addition, we believe that duration of efficacy is an important consideration by physicians and patients when choosing a therapy. However, we do not know and may not know prior to any potential approval the duration of efficacy of our product candidates. We anticipate that we will face intense and increasing competition as new treatments enter the market and advanced technologies become available.

Even if we obtain regulatory approval for our product candidates, the availability and price of our competitors' products could limit the demand, and the price we are able to charge, for our product candidates. For example, LUCENTIS (and biosimilars thereto), EYLEA and VABYSMO are currently available in the U.S. and the EU for treatment of wet AMD. We will not achieve our business plan if the acceptance of our product candidates is inhibited by price competition or the reluctance of physicians to switch from existing methods of treatment to our product candidates, or if physicians switch to other new drug products or choose to reserve our product candidates for use in limited circumstances. Our inability to compete with existing or subsequently introduced drug products or other therapies would have a material adverse impact on our business, prospects, financial condition and results of operations.

Our potential competitors in these diseases may be developing novel therapies that may be safer or more effective or easier to administer than our product candidates. For example, if we continue clinical development of, and seek to commercialize, Ixo-vec for the treatment of wet AMD, it will compete with a variety of therapies currently marketed and in development for wet AMD, using therapeutic modalities such as biologics, small molecules, long-acting delivery devices and gene therapy.

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 significant number of product candidates in development or recently approved for chronic retinal conditions that respond to anti-VEGF therapy, including wet AMD:

- biosimilar anti-VEGFs (e.g., FYB201);
- bispecific / combination / add-on therapy for efficacy or durability improvement (e.g., Vabysmo and OPT-302);
- next-generation anti-VEGF for durability improvement (e.g., EYLEA HD);
- long-acting delivery device / gene therapy to lower treatment frequency (e.g., 4D-150, RGX-314 and Susvimo, which is Roche's Port Delivery System with ranibizumab); and
- other molecules that inhibit neovascularization in wet AMD (e.g., tyrosine kinase inhibitors such as OKT-TKI and EYP-1901).

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. The U.S. government, state legislatures, and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement, and requirements for substitution of generic products for branded prescription drugs.

By way of example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act (collectively, the "Affordable Care Act"), was enacted with a goal of reducing the cost of healthcare and substantially changing the way healthcare is financed by both government and private insurers. The Affordable Care Act, among other things, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program, extended the rebate program to individuals enrolled in Medicaid managed care organizations and established annual fees and taxes on manufacturers of certain prescription drugs.

Certain provisions of the Affordable Care Act have been subject to executive, Congressional, and judicial challenges as well as efforts to repeal, replace, or otherwise modify them or alter their interpretation and implementation. For example, the Tax Cuts and Jobs Act ("TCJA") included a provision that repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." Additionally, on June 17, 2021 the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Further, prior to the U.S. Supreme Court ruling, on January 28, 2021, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the Affordable Care Act marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including, among others, policies that undermine protections for people with pre-existing conditions, demonstrations and waivers under Medicaid and the Affordable Care Act that may reduce coverage or undermine the programs thereunder, including work requirements, and policies that make it more difficult to access health benefits through Medicaid or the Affordable Care Act. On August 16, 2022, President Biden signed the Inflation Reduction Act of 2022 (the "Inflation Reduction Act") into law, which among other things, extends enhanced subsidies for individuals purchasing health insurance coverage in Affordable Care Act marketplaces through plan year 2025. The Inflation Reduction Act also eliminates the "donut hole" under the Medicare Part D program beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket cost and through a newly established manufacturer discount program. Additional legislative changes, regulatory changes, and judicial challenges related to the Affordable Care Act remain possible. Any such changes could affect the number of individuals with health coverage. It is possible that the Affordable Care Act, as currently enacted or as it may be amended in the future, and other healthcare reform measures that may be adopted in the future could have a material adverse effect on our industry generally and on our ability to successfully commercialize our product candidates, if approved.

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, Congress is considering additional health reform measures.

These cost reduction initiatives could decrease the coverage and reimbursement that we receive for any approved products and could seriously harm our business. The Biden administration expressed its intent to pursue certain policy initiatives to reduce drug prices. For example, in July 2021, the Biden administration released an executive order, "Promoting Competition in the American Economy," with multiple provisions aimed at prescription drugs. In response to Biden's executive order, on September 9, 2021, the U.S. Department of Health and Human Services ("HHS") released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue to advance these principles. Further, the Inflation Reduction Act, among other things, (1) directs HHS to negotiate the price of certain single-source drugs and biologics covered under Medicare and (2) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. These provisions began to take effect beginning fiscal year 2023. On August 29, 2023, HHS announced the list of the first ten drugs that will be subject to price negotiations, although the Medicare drug price negotiation program is currently subject to legal challenges. 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. It is unclear how the Inflation Reduction Act will be implemented but is likely to have a significant impact on the pharmaceutical industry. In response to the Biden administration's October 2022 executive order, on February 14, 2023, HHS released a report outlining three new models for testing by the CMS Innovation Center which will be evaluated on their ability to lower the cost of drugs, promote accessibility, and improve quality of care. It is unclear whether the models will be utilized in any health reform measures in the future. Further, on December 7, 2023, the Biden administration announced an initiative to control the price of prescription drugs through the use of march-in rights under the Bayh-Dole Act. 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 will apply as of January 2025, 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 will permit 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 or other strategic collaborations, which could adversely affect our ability to develop and commercialize product candidates and receive milestone and/or royalty payments.

We have entered into development or other strategic collaborations with biotechnology and pharmaceutical companies in the past and may do so again in the future. Research activities under our collaboration agreements 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 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 invest significant amounts of financial and management resources to develop internal sales, marketing, distribution, or market access and reimbursement capabilities, some of which will be committed prior to any confirmation that any of our product candidates will be approved, if at all. We may not be able to hire consultants or external service providers to assist us in sales, marketing, distribution, or market access and reimbursement functions on acceptable financial terms or at all. Even if we determine to perform sales, marketing, distribution, or market access and reimbursement functions ourselves, we could face a number of additional related risks, including:

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

Risks Related to Our Business Operations

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

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

More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop. Trials using early versions of retroviral vectors, which integrate into, and thereby alter, the host cell's DNA, have led to several well-publicized adverse events. Although none of our current product candidates utilize retroviruses and we believe AAVs used in our product candidates have low-integrating potential and are not known to cause disease in humans, our product candidates do use a viral vector delivery system. The risk of serious adverse events, such as the dose-limiting toxicity at the 6E11 dose tested in our INFINITY trial, remains a concern for gene therapy and we cannot assure that it will not occur in any of our current or future clinical trials. In addition, there is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biological activity of the genetic material or other components of products used to carry the genetic material.

Adverse events in trials or studies conducted by us or other parties, in particular involving the same or similar AAV serotypes to the ones we are using, even if not ultimately attributable to our product candidates or to an AAV serotype that we employ, and resulting publicity, could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates. Similarly, our lead product candidate, Ixo-vec, expresses the aflibercept protein, which is also the active component in EYLEA. If safety or efficacy issues occur relating to EYLEA, even if not ultimately attributable to aflibercept, this may negatively impact our product candidate. If any such adverse events or issues occur, development and commercialization of our product candidates or advancement of any potential clinical trials could be halted or delayed, which would have a material adverse effect on our business and operations.

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

We are dependent on the principal members of our management, clinical and scientific staff. The loss of service of any of our management or clinical or scientific staff could harm our business. In addition, we are dependent on our continued ability to attract, retain and motivate highly qualified additional management, clinical and scientific personnel. If we are not able to retain our management, and to attract, on acceptable terms, additional qualified personnel necessary for the continued development of our business, we may not be able to sustain our operations or grow. Although we have executed employment agreements with each member of our current executive management team, these agreements are terminable at will with or without notice and, therefore, we may not be able to retain their services as expected. We 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. Our industry has experienced a high rate of turnover of management and scientific personnel in recent years. If we are not able to attract, retain and motivate necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our development objectives, our ability to raise additional capital and our ability to implement our business strategy.

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

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

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

If our information technology systems or those third parties upon which we rely, 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 upon which we rely, 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 upon which we rely. 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 upon which we rely may be vulnerable to a heightened risk of these attacks, including retaliatory cyber-attacks, that could materially disrupt our systems and operations, supply chain, and ability to produce, sell and distribute our goods and services.

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

We rely on third-party service providers and technologies 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 our third-party service providers experience a security incident or other interruption, we could experience adverse consequences. While we may be entitled to damages if our third-party service providers fail to satisfy their privacy or security-related obligations to us, any award may be insufficient to cover our damages, or we may be unable to recover such award.

In addition, supply-chain attacks have increased in frequency and severity, and we cannot guarantee that third parties' infrastructure in our supply chain or our third-party partners' supply chains have not been compromised. While we may be entitled to damages if our third-party service providers fail to satisfy their privacy or security-related obligations to us, any award may be insufficient to cover our damages, or we may be unable to recover such award. In addition, supply-chain attacks have increased in frequency and severity, and we cannot guarantee that third parties' infrastructure in our supply chain or our third-party partners' supply chains have not been compromised.

Any of the previously identified or similar threats could cause a security incident or other interruption that could result in unauthorized, unlawful, or accidental acquisition, modification, destruction, loss, alteration, encryption, disclosure of, or access to our sensitive information or our information technology systems, or those of the third parties upon whom we rely. A security incident or other interruption could disrupt our ability (and that of third parties upon whom we rely) to provide our services. We may expend significant resources or modify our business activities (including our clinical trial activities) to try to protect against security incidents. Certain data privacy and security obligations may require us to implement and maintain specific security measures, industry-standard or reasonable security measures to protect our information technology systems and confidential, sensitive, or proprietary information. For example, the loss of clinical trial information from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the information.

While we have implemented security measures designed to protect against security incidents, there can be no assurance that these measures will be effective. 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 upon which we rely). We may not, however, detect and remediate all such vulnerabilities including on a timely basis. Further, we may experience delays in 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 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 upon whom we rely. A security incident or other interruption could disrupt our ability (and that of third parties upon whom we rely) to provide our services. We may expend significant resources or modify our business activities (including our clinical trial activities) to try to protect against security incidents. Certain data privacy and security obligations may require us to implement and maintain specific security measures or industry-standard or reasonable security measures to protect our information technology systems and sensitive information.

Applicable data privacy and security obligations may require us to notify relevant stakeholders, such as governmental authorities, partners, and affected individuals, of security incidents. Such disclosures may involve inconsistent requirements and are costly, and the disclosures or the failure to comply with such requirements could lead to adverse consequences. If we (or a third party upon whom we rely) experience a security incident or are perceived to have experienced a security incident, we may experience adverse consequences, 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 consequences may prevent or cause customers to stop using our platform/products/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 data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development and commercialization of our product candidates could be delayed. In addition, there can be no assurance that we will promptly detect any such disruption or security incident, if at all.

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

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

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

The federal civil False Claims Act, which prohibits, among other things, individuals or entities from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment of government funds, or knowingly making, using or causing to be made or used, a false record or statement material to an obligation to pay money to the government or knowingly concealing or knowingly and improperly avoiding, decreasing or concealing an obligation to pay money to the federal government. Actions under the False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Violations of the False Claims Act can result in significant monetary penalties and treble damages. Pharmaceutical and other healthcare companies have faced enforcement actions under the federal civil False Claims Act for, among other things, allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product and for allegedly causing false claims to be submitted because of the companies' marketing of the product for unapproved, and thus non-reimbursable, uses. In addition, a claim can be deemed to be false due to failure to comply with legal or regulatory requirements material to the government's payment decision. False Claims Act liability is potentially significant in the healthcare industry because the statute provides for treble damages and significant mandatory penalties per false claim or statement. Pharmaceutical and other healthcare companies also are subject to other federal false claims laws, including, among others, federal criminal healthcare fraud and false statement statutes.

In addition, there has been a recent trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The Affordable Care Act, among other things, imposed new reporting requirements on drug manufacturers, under the federal Physician Payments Sunshine Act, for payments and other transfers of value made by them to physicians (defined to include doctors, dentists, optometrists, podiatrists, and chiropractors), certain other healthcare professionals (such as a physician assistants and nurse practitioners), and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in significant civil monetary penalties, for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. Certain states and localities also mandate implementation of commercial compliance programs, restrict the ability of manufacturers to offer co-pay support to patients for certain prescription drugs, impose restrictions on drug manufacturer marketing practices, require the tracking and reporting of gifts, compensation and other remuneration to physicians and/or require the registration of pharmaceutical sales representatives.

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

In the ordinary course of business, we 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 Health Information Technology for Economic and Clinical Health Act ("HITECH"), imposes specific requirements relating to the privacy, security, and transmission of individually identifiable protected health information. We may obtain health information from third parties, such as research institutions, that are subject to privacy and security requirements under HIPAA. Although we are not directly subject to HIPAA other than with respect to providing certain employee benefits, we could potentially be subject to penalties if we, our affiliates, or our agents obtain, use, or disclose individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA.

In the past few years, numerous U.S. states—including California, Virginia, Colorado, Connecticut, and Utah—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, as amended by the California Privacy Rights Act of 2020 ("CPRA"), (collectively, "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 of up to $7,500 per intentional violation and allows private litigants affected by certain data breaches to recover significant statutory damages.

Although the CCPA exempts some data processed in the context of clinical trials, the CCPA increases compliance costs and potential liability with respect to other personal data we maintain about California residents. 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. While these states, like the CCPA, also exempt some data processed in the context of clinical trials, these developments further complicate compliance efforts, and increase legal risk and compliance costs for us and the third parties upon whom we rely.

Outside the U.S., an increasing number of laws, regulations, and industry standards 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"), 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. EU member states are also able to legislate separately on health and genetic information, and we must comply with these local laws where we operate.

In the ordinary course of business, we may 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 similarly stringent interpretations of their data localization and cross-border data transfer laws.

Although there are currently various mechanisms that may be used to transfer personal 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.

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. We may also be bound by contractual obligations related to data privacy and security, and our efforts to comply with such obligations may not be successful.

We publish privacy policies, marketing materials 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 on whom we rely may fail to comply with such obligations, which could negatively impact our business operations. If we or the third parties on which we rely fail, or are perceived to have failed, to address or comply with applicable data privacy and security obligations, we could face significant consequences, 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 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); 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 future development partners will be required to report to regulatory authorities if any of our approved products cause or contribute to adverse medical events, and any failure to do so would result in sanctions that would materially harm our business.

If we and any of our future development partners 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 TCJA, 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 owns at least 5% of a corporation’s stock within a specified testing period. Similar rules may apply under state tax laws. We may have experienced an ownership change as a result of the August 2020 underwritten public offering of our common stock and/or the February 2024 private placements of shares of common stock and pre-funded warrants, and may in the future experience ownership changes from future offerings or other changes in the ownership of our stock.

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

Risks Related to Our Common Stock

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

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

- our ability to enroll and dose subjects in any clinical trials that are on-going, or that we plan to conduct in the future;
- our ability to obtain regulatory approvals for our product candidates and delays or failure to obtain such approvals;
- our plans to conduct nonclinical studies to determine the best gene therapy candidates to advance in development;
- results of any clinical trials of our product candidates and the results of trials of competing product candidates or of other companies in our market sector;
- investor perception and analysis of the results of our clinical trials, which may be different than our own;

- regulatory developments in the U.S. and foreign countries;
- our financial results, variations in our financial results and the adequacy of our cash runway to achieve key milestones, or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems, especially in light of current reforms to the U.S. healthcare system;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures or capital commitments;
- failure to maintain our existing third-party license and collaboration agreements;
- delays in manufacturing adequate supply of our product candidates;
- adverse publicity relating to gene therapy and to biotechnology generally, including with respect to other products and potential products in such markets;
- market conditions in the pharmaceutical and biotechnology sectors and issuance of securities analysts' reports or recommendations;
- 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.

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

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, licensing, collaboration or similar arrangements, grants, debt and other financings. We do not have any committed external source of funds. As a result, we may from time to time issue additional shares of common stock or securities convertible into or exercisable for shares of our common stock. To the extent that we raise additional capital through the sale of equity or convertible debt securities, 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 financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends or other distributions. Furthermore, we may issue common stock as consideration in acquisitions. If we issue common stock or securities convertible into common stock, our common stockholders would experience additional dilution and, as a result, our stock price may decline.

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

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

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

- the authorization of the issuance of "blank check" preferred stock, the terms of which may be established and shares of which may be issued without stockholder approval;
- the limitation of the removal of directors by the stockholders;
- a staggered board of directors;

- the prohibition of stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders;
- the elimination of the ability of stockholders to call a special meeting of stockholders;
- the ability of our board of directors to accelerate the vesting of outstanding option grants, restricted stock units or other equity awards upon certain transactions that result in a change of control; and
- the establishment of advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted upon at stockholder meetings.

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

We are obligated to develop and maintain proper and effective internal control over financial reporting. In the future, we may not complete our execution of our internal control over financial reporting in a timely manner, or these internal controls may not be determined to be effective, which may result in material misstatements in our consolidated financial statements and may adversely affect investor confidence in our company and, as a result, the value of our common stock.

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. Additionally, if we identify one or more material weaknesses in our internal control over financial reporting, we will not be able to assert that our internal controls are effective. 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. As of December 31, 2022, we identified a deficiency in the operating effectiveness of controls in our financial statement close process that we considered to be a material weakness. An immaterial non-cash lease accounting error was identified in previously issued financial statements. While the identified error was not material, we considered the magnitude of the potential errors that could arise from the operating deficiency as potentially material. This material weakness did not result in the restatement of prior quarterly or annually filed financial statements. During 2023, management conducted a remediation plan to address its material weakness, which included increasing the rigor with which management evaluates the accounting of material non-routine transactions by engaging additional outside financial reporting and technical accounting expertise. As of December 31, 2023, we have remediated the material weakness related to our internal controls over financial reporting that were determined to be ineffective as of December 31, 2022.

Even though we remediated this material weakness as of December 31, 2023, we cannot be certain that other material weaknesses and control deficiencies will not be discovered in the future. If our efforts are not successful or other 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 condensed consolidated financial statements and we could fail to meet our financial reporting obligations. As a result, 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 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 2. Unregistered Sales of Equity Securities and Use of Proceeds

There were no sales of equity securities during the period covered by this report that were not registered under the Securities Act and were not previously reported in a Current Report on Form 8-K filed by the Company.

Item 3. Defaults Upon Senior Securities

None.

Item 4. Mine Safety Disclosures

Not applicable.

Item 5. Other Information

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 6. Exhibits

EXHIBIT INDEX

EXHIBIT NUMBER	EXHIBIT DESCRIPTION	INCORPORATED BY REFERENCE				PROVIDED HEREWITH
		FILE NUMBER	FORM	DATE	EXHIBIT OR ITEM NUMBER	
3.1	Restated Certificate of Incorporation.	001-36579	8-K	March 20, 2024	3.2	
3.2	Amended and Restated Bylaws.	001-36579	8-K	June 29, 2020	3.1	
4.1	Reference is made to Exhibits 3.1 through 3.2.					
4.2	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	
4.3	Form of Pre-Funded Warrant.	001-36579	8-K	February 5, 2024	4.1	
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 Officer pursuant to 18 U.S.C. section 1350, as adopted pursuant to section 906 of the Sarbanes-Oxley Act of 2002.					X
101.INS	XBRL Instance Document- the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL 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 Labels Linkbase Document.					
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document.					
104	XBRL tags for the cover page from the Company's Quarterly Report on Form 10-Q for the quarter ended March 31, 2024, are embedded with the Inline XBRL document.					

* The certifications attached as Exhibit 32.1 and 32.2 that accompany this Quarterly Report on Form 10-Q are not deemed filed with the SEC and are 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-Q, irrespective of any general incorporation language contained in such filing.

SIGNATURES

Pursuant to the requirements 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.

ADVERUM BIOTECHNOLOGIES, INC.

Date: May 9, 2024

By: /s/ Laurent Fischer

Laurent Fischer, M.D.

President and Chief Executive Officer
(Principal Executive Officer)

Date: May 9, 2024

By: /s/ Linda Rubinstein

Linda Rubinstein

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

Exhibit 31.1

CERTIFICATION OF THE PRINCIPAL EXECUTIVE OFFICER

PURSUANT TO SECTION 302 OF
THE SARBANES-OXLEY ACT OF 2002

I, Laurent Fischer, certify that:

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

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

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

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

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

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

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

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

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

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

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

Date: May 9, 2024

By: /s/ Laurent Fischer

Name: Laurent Fischer, M.D.

Title: President and Chief Executive Officer

(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION OF THE PRINCIPAL FINANCIAL AND ACCOUNTING OFFICER

PURSUANT TO SECTION 302 OF
THE SARBANES-OXLEY ACT OF 2002

I, Linda Rubinstein, certify that:

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

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

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

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

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

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

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

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

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

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

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

Date: May 9, 2024

By: /s/ Linda Rubinstein

Name: Linda Rubinstein

Title: Chief Financial Officer

(Principal Financial Officer and Principal Accounting Officer)

Exhibit 32.1

CERTIFICATION
PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Quarterly Report on Form 10-Q of Adverum Biotechnologies, Inc. for the fiscal quarter ended March 31, 2024 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Laurent Fischer, in his capacity as Chief Executive Officer of Adverum Biotechnologies, Inc., hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to the best of his knowledge, the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of Adverum Biotechnologies, Inc.

Date: May 9, 2024

By: /s/ Laurent Fischer
Laurent Fischer, M.D.
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 32.2

CERTIFICATION
PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Quarterly Report on Form 10-Q of Adverum Biotechnologies, Inc. for the fiscal quarter ended March 31, 2024 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Linda Rubinstein, in her capacity as Chief Financial Officer, of Adverum Biotechnologies, Inc., hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to the best of her knowledge, the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of Adverum Biotechnologies, Inc.

Date: May 9, 2024

By: /s/ Linda Rubinstein
Linda Rubinstein
Chief Financial Officer
(Principal Financial Officer and Principal Accounting Officer)