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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 September 30, 2020

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.)**

800 Saginaw Drive,
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 Global 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	☐	Smaller reporting company	☒
		Emerging growth company	☐

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

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

As of October 30, 2020, there were 97,477,603 shares of the registrant's common stock, par value $0.0001 per share, outstanding.

Adverum Biotechnologies, Inc.

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PART I—FINANCIAL INFORMATION

Item 1. Financial Statements

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

	September 30, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 72,696	$ 65,897
Short-term investments	381,766	100,138
Prepaid expenses and other current assets	5,238	9,835
Total current assets	459,700	175,870
Operating lease right-of-use assets	19,698	20,963
Property and equipment, net	27,295	24,884
Restricted cash	999	999
Deposit and other long-term assets	19	11
Total assets	$ 507,711	$ 222,727
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 3,034	$ 4,103
Accrued expenses and other current liabilities	8,642	11,271
Lease liability, current portion	4,435	4,034
Total current liabilities	16,111	19,408
Lease liability, net of current portion	26,752	28,214
Other non-current liabilities	136	148
Total liabilities	42,999	47,770
Stockholders' equity:		
Preferred stock	—	—
Common stock	10	7
Additional paid-in capital	930,211	560,704
Accumulated other comprehensive loss	(605)	(725)
Accumulated deficit	(464,904)	(385,029)
Total stockholders' equity	464,712	174,957
Total liabilities and stockholders' equity	$ 507,711	$ 222,727

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 September 30,		Nine Months Ended September 30,	
	2020	2019	2020	2019
Collaboration and license revenue	$ —	$ 250	$ —	$ 250
Operating expenses:				
Research and development	16,653	9,944	50,581	29,045
General and administrative	11,351	7,389	30,989	20,097
Total operating expenses	28,004	17,333	81,570	49,142
Operating loss	(28,004)	(17,083)	(81,570)	(48,892)
Other income, net	235	965	1,695	3,331
Net loss	(27,769)	(16,118)	(79,875)	(45,561)
Other comprehensive loss:				
Net unrealized (loss)/gain on marketable securities	(20)	4	120	27
Foreign currency translation adjustment	13	(11)	—	27
Comprehensive loss	$ (27,776)	$ (16,125)	$ (79,755)	$ (45,507)
Net loss per share — basic and diluted	$ (0.31)	$ (0.25)	$ (0.99)	$ (0.71)
Weighted-average common shares used to compute net loss per share - basic and diluted	88,867	64,484	80,995	63,764

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)/Income	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2019	67,329	$ 7	$ 560,704	$ (725)	$ (385,029)	$ 174,957
Stock-based compensation expense	—	—	3,409	—	—	3,409
Issuance of common stock, net of issuance costs of $332	10,925	1	140,872	—	—	140,873
Common stock issued upon exercise of stock options	1,310	—	9,650	—	—	9,650
Common stock issued upon net exercise of warrants	7	—	—	—	—	—
Common stock issued upon release of restricted stock units	462	—	—	—	—	—
Restricted stock surrendered for taxes	(155)	—	(1,922)	—	—	(1,922)
Foreign currency translation adjustments	—	—	—	(54)	—	(54)
Unrealized loss on marketable securities, net	—	—	—	(54)	—	(54)
Net loss	—	—	—	—	(22,906)	(22,906)
Balance at March 31, 2020	79,878	8	712,713	(833)	(407,935)	303,953
Stock-based compensation expense	—	—	4,785	—	—	4,785
Issuance of common stock, additional issuance costs	—	—	(51)	—	—	(51)
Issuance of common stock upon exercise of stock options	643	—	2,487	—	—	2,487
Common stock issued under employee stock purchase plan	57	—	475	—	—	475
Issuance of common stock upon release of restricted stock units	66	—	—	—	—	—
Restricted stock surrendered for taxes	(5)	—	(121)	—	—	(121)
Foreign currency translation adjustments	—	—	—	41	—	41
Unrealized gain on marketable securities, net	—	—	—	194	—	194
Net loss	—	—	—	—	(29,200)	(29,200)
Balance at June 30, 2020	80,639	8	720,288	(598)	(437,135)	282,563
Stock-based compensation expense	—	—	6,020	—	—	6,020
Issuance of common stock, net of issuance costs of $385	16,675	2	203,381	—	—	203,383
Issuance of common stock upon exercise of stock options	83	—	516	—	—	516
Common stock issued upon net exercise of warrants	29	—	—	—	—	—
Common stock issued under employee stock purchase plan	1	—	6	—	—	6
Issuance of common stock upon release of restricted stock units	43	—	—	—	—	—
Restricted stock surrendered for taxes	(3)	—	—	—	—	—
Foreign currency translation adjustments	—	—	—	13	—	13
Unrealized loss on marketable securities, net	—	—	—	(20)	—	(20)
Net loss	—	—	—	—	(27,769)	(27,769)
Balance at September 30, 2020	97,467	$ 10	$ 930,211	$ (605)	$ (464,904)	$ 464,712

See accompanying notes to condensed consolidated financial statements.

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

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive (Loss)/Income	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2018	62,965	$ 6	$ 522,503	$ (799)	$ (320,543)	$ 201,167
Stock-based compensation expense	—	—	1,762	—	—	1,762
Common stock issued upon exercise of stock options	119	—	162	—	—	162
Common stock issued upon release of restricted stock units	397	—	—	—	—	—
Restricted stock surrendered for taxes	(145)	—	(504)	—	—	(504)
Foreign currency translation adjustments	—	—	—	42	—	42
Unrealized gain on marketable securities, net	—	—	—	3	—	3
Net loss	—	—	—	—	(14,489)	(14,489)
Balance at March 31, 2019	63,336	6	523,923	(754)	(335,032)	188,143
Stock-based compensation expense	—	—	2,626	—	—	2,626
Issuance of common stock, private placement	20	—	134	—	—	134
Common stock issued upon exercise of stock options	823	—	2,312	—	—	2,312
Common stock upon release of restricted stock units	220	—	—	—	—	—
Restricted stock surrendered for taxes	(73)	—	(700)	—	—	(700)
Common stock issued under employee stock purchase plan	51	—	163	—	—	163
Foreign currency translation adjustments	—	—	—	(4)	—	(4)
Unrealized gain on marketable securities, net	—	—	—	20	—	20
Net loss	—	—	—	—	(14,954)	(14,954)
Balance at June 30, 2019	64,377	6	528,458	(738)	(349,986)	177,740
Stock-based compensation expense	—	—	2,661	—	—	2,661
Issuance of common stock upon exercise of stock options	191	1	144	—	—	145
Issuance of common stock upon release of restricted stock units	27	—	—	—	—	—
Restricted stock unit withholdings	(14)	—	—	—	—	—
Taxes paid for RSUs	—	—	(207)	—	—	(207)
Foreign currency translation adjustments	—	—	—	(11)	—	(11)
Unrealized gain on marketable securities, net	—	—	—	4	—	4
Net loss	—	—	—	—	(16,118)	(16,118)
Balance at September 30, 2019	64,581	$ 7	$ 531,056	$ (745)	$ (366,104)	$ 164,214

See accompanying notes to condensed consolidated financial statements.

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

	Nine Months Ended September 30,	
	2020	2019
Cash flows from operating activities:		
Net loss	$ (79,875)	$ (45,561)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	3,081	1,219
Stock-based compensation expense	14,214	7,049
Amortization of premium and accrued interest on marketable securities	(773)	(813)
Other	25	46
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	5,194	(1,868)
Other assets	(8)	—
Operating lease right-of-use asset	1,265	1,620
Accounts payable	1,444	(680)
Accrued expenses and other current liabilities	(573)	1,891
Lease liability	(1,061)	2,762
Net cash used in operating activities	(57,067)	(34,335)
Cash flows from investing activities:		
Purchases of marketable securities	(511,845)	(133,144)
Maturities of marketable securities	223,765	95,155
Sales of marketable securities	6,748	—
Purchases of property and equipment	(10,411)	(10,874)
Net cash used in investing activities	(291,743)	(48,863)
Cash flows from financing activities:		
Proceeds from offerings of common stock, net of issuance costs	344,547	—
Proceeds from issuance of common stock	—	134
Proceeds from issuance of common stock pursuant to option exercises	12,653	2,618
Taxes paid related to net share settlement of restricted stock units	(2,043)	(1,411)
Proceeds from employee stock purchase plan	481	163
Repayment of loan	(29)	(84)
Net cash provided by financing activities	355,609	1,420
Net increase (decrease) in cash and cash equivalents and restricted cash	6,799	(81,778)
Cash and cash equivalents and restricted cash at beginning of period	66,896	155,948
Cash and cash equivalents and restricted cash at end of period	$ 73,695	$ 74,170
Supplemental schedule of noncash investing and financing information		
Fixed assets in accounts payable, accrued expenses and other current liabilities	$ 325	$ 3,625

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") is a clinical-stage gene therapy company targeting unmet medical needs in ocular and rare diseases. The Company develops gene therapy product candidates intended to provide durable efficacy by inducing sustained expression of a therapeutic protein. The Company’s core capabilities include clinical development, novel vector discovery, and in-house manufacturing expertise, specifically in scalable process development, assay development, and current Good Manufacturing Practices (“cGMP”) quality control. Since the Company’s inception, it has devoted its efforts to performing research and development activities, filing patent applications, hiring personnel and raising capital to support these activities.

The Company has not generated any revenue from the sale of products since its inception. The Company has experienced net losses since its inception and had an accumulated deficit of $464.9 million as of September 30, 2020. The Company expects to incur losses and have negative net cash flows from operating activities as it engages in further research and development activities. The Company believes that it has sufficient funds to continue operations into mid-2022.

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 results of operations for the three and nine months ended September 30, 2020 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, 2019 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 full extent to which the novel coronavirus disease ("COVID-19") pandemic will directly or indirectly impact the Company’s business, results of operations and financial condition, including expenses and manufacturing, clinical trials and research and development costs, is dependent upon future developments that are highly uncertain at this time.

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, 2019 filed with the SEC.

2. Summary of Significant Accounting Policies

Use of Estimates

The accompanying condensed consolidated financial statements have been prepared in accordance with U.S. GAAP. The preparation of the condensed consolidated financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent liabilities and the reported amounts of expenses in the condensed consolidated financial statements and the accompanying notes. On an ongoing basis, management evaluates its estimates, including those related to clinical trial accruals, fair value of assets and liabilities, income taxes, and stock-based compensation. Management bases its estimates on historical experience and on various other market-specific and relevant assumptions that management believes to be reasonable under the circumstances. Actual results could differ from those estimates.

Recent Accounting Pronouncements

In June 2016, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") 2016-13, *Financial Instruments – Credit Losses: Measurement of Credit Losses on Financial Instruments* ("*Topic 326*") and also issued subsequent amendments to the initial guidance: ASU 2018-19, ASU 2019-04, ASU 2019-05, and ASU 2019-11. The standard requires that financial assets measured at amortized cost be presented at the net amount expected to be collected. The measurement of expected credit losses is based on historical experience, current conditions, and reasonable and supportable forecasts that affect collectability. Topic 326 also eliminates the concept of "other-than-temporary" impairment when evaluating available-for-sale debt securities and instead focuses on determining whether any impairment is a result of a credit loss or other factors. An entity will recognize an allowance for credit losses on available-for-sale debt securities rather than an other-than-temporary impairment that reduces the cost basis of the investment. Topic 326 will become effective for the Company beginning after December 15, 2022 and interim periods within those fiscal years. Early adoption is permitted. The Company is currently evaluating the impact of adopting Topic 326, but does not expect the effect of adoption to be material.

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.

The fair value of Level 1 securities is determined using quoted prices in active markets for identical assets. Level 1 securities consist of highly liquid money market funds. Financial assets and liabilities are considered Level 2 when their fair values are determined using inputs that are observable in the market or can be derived principally from or corroborated by observable market data such as pricing for similar securities, recently executed transactions, cash flow models with yield curves, and benchmark securities. In addition, Level 2 financial instruments are valued using comparisons to like-kind financial instruments and models that use readily observable market data as their basis. U.S. government and agency securities, commercial paper, corporate bond and certificates of deposit are valued primarily using market prices of comparable securities, bid/ask quotes, interest rate yields and prepayment spreads and are included in Level 2. In certain cases, where there is limited activity or less transparency around inputs to valuation, securities are classified as Level 3 within the valuation hierarchy.

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

	September 30, 2020			
	Amortized Cost Basis	Unrealized Gains	Unrealized Losses	Estimated Fair Value
	(In thousands)			
Level 1:				
Money market funds	$ 727	$ —	$ —	$ 727
Level 2:				
U.S. government and agency securities	394,905	144	(18)	395,031
Commercial paper	53,729	13	(1)	53,741
Total cash equivalents and short-term investments	449,361	157	(19)	449,499
Less: cash equivalents	(67,735)	—	2	(67,733)
Total short-term investments	$ 381,626	$ 157	$ (17)	$ 381,766

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

As of September 30, 2020, $61.4 million of marketable securities had remaining maturities between one and two years. The remainder of the marketable securities have a remaining maturity of less than one year. As the Company may sell these securities at any time for use in current operations even if the securities have not yet reached maturity, all marketable securities are classified as current assets in the Company's consolidated balance sheet. Management regularly reviews all of the Company's investments for other-than-temporary declines in estimated fair value. Management determined that the gross unrealized losses on the Company's marketable securities as of September 30, 2020 were temporary in nature and none were in continuous loss position for 12 months or more. Therefore, none of the Company's marketable securities were other-than-temporarily impaired as of September 30, 2020.

4. Balance Sheet Components

Property and Equipment, Net

Property and equipment, net consists of the following:

	September 30, 2020	December 31, 2019
	(In thousands)	
Computer equipment and software	$ 924	$ 752
Laboratory equipment	9,147	6,291
Furniture and fixtures	1,263	678
Leasehold improvements	25,304	1,602
Construction in progress	137	23,553
Total property and equipment	36,775	32,876
Less accumulated depreciation and amortization	(9,480)	(7,992)
Property and equipment, net	$ 27,295	$ 24,884

Depreciation and amortization expense related to property and equipment for the three months ended September 30, 2020 and 2019 was $1.2 million, and $0.4 million, respectively, and for the nine months ended September 30, 2020 and 2019 was $3.1 million and $1.2 million, respectively.

Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consist of the following:

	September 30, 2020	December 31, 2019
	(In thousands)	
Employee compensation	$ 4,858	$ 4,055
Accrued preclinical, clinical and process development costs	2,298	1,973
Accrued professional services	943	2,607
Other	543	2,636
Total accrued expenses and other current liabilities	$ 8,642	$ 11,271

5. 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, 2019	8,995	$ 7.19
Options granted	3,920	18.84
Options exercised	(2,036)	6.22
Options forfeited	(617)	10.20
Balance at September 30, 2020	10,262	$ 11.65
Exercisable as of September 30, 2020	3,486	$ 7.95

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, 2019	1,121	$ 4.59
Granted	104	15.75
Vested and released	(572)	4.53
Forfeited	(95)	7.12
Outstanding at September 30, 2020	558	$ 6.33

Stock-Based Compensation Expense

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2020	2019	2020	2019
	(In thousands)			
Research and development	$ 2,051	$ 1,352	$ 4,967	$ 2,829
General and administrative	3,969	1,309	9,247	4,220
Total stock-based compensation expense	$ 6,020	$ 2,661	$ 14,214	$ 7,049

6. 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, rights under the employee stock purchase plan ("ESPP") and warrants are considered to be common stock equivalents and are only included in the calculation of diluted net loss per share when their effect is dilutive.

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:

	September 30, 2020	September 30, 2019
	(In thousands)	
Stock options	10,262	8,655
Restricted stock units	558	1,137
ESPP	66	96
Warrants to purchase common stock	40	90
	10,926	9,978

7. Related Party Transactions

In our February 2020 underwritten public offering of common stock, James Scopa, a member of our Board, and Anne Kenner, as Trustees for the James P. Scopa and Anne E. Kenner Family Trust (the "Trust") purchased on behalf of the Trust 10,000 shares of our common stock at a price of $13.75 per share, the public offering price in our February 2020 underwritten public offering of common stock, for an aggregate purchase price of $0.1 million, payable in cash.

In our August 2020 underwritten public offering of common stock, our CEO and one other executive officer purchased an aggregate of 15,384 shares of our common stock at a price of $13.00 per share, the public offering price in our August 2020 underwritten public offering of common stock, for an aggregate purchase price of $0.2 million, payable in cash.

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, 2019, 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 12, 2020. 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. In particular, we encourage you to review the risk factor related to the impact of the coronavirus pandemic titled "The coronavirus ("COVID-19") pandemic has impacted our business practices and the effects of its continued impact on our business, results of operations, and financial condition will depend on future developments, which cannot be predicted."

Overview

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

Our lead product candidate ADVM-022 is a single intravitreal ("IVT") injection gene therapy designed to deliver long-term durability with robust treatment response, reduce the treatment burden of frequent anti-vascular endothelial growth factor ("anti-VEGF") injections, and improve real-world vision outcomes for patients. ADVM-022 is being developed for the treatment of patients with chronic retinal diseases who respond to standard-of-care anti-VEGF therapy, including wet age-related macular degeneration ("wet AMD") and diabetic macular edema ("DME"). ADVM-022 utilizes a proprietary vector capsid, AAV.7m8, carrying an aflibercept coding sequence under the control of a proprietary expression cassette.

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

We are conducting the OPTIC trial, designed as a multi-center, open-label, Phase 1, dose-ranging safety trial of ADVM-022 in patients with wet AMD who have demonstrated responsiveness to anti-VEGF treatment. Patients in OPTIC are treatment experienced, and previously required frequent anti-VEGF injections to control their wet AMD and to maintain functional vision. Patients received a high dose (6 x 10^11 vg/eye) of ADVM-022 in Cohort 1 (n=6) and Cohort 4 (n=9), and patients received a low dose (2 x 10^11 vg/eye) of ADVM-022 in Cohort 2 (n=6) and Cohort 3 (n=9).

In OPTIC, ADVM-022 continues to show robust treatment response from both high and low doses. As reported in our most recent presentation of OPTIC data in early August 2020, we have observed long-term durability beyond 15 months from a single IVT injection of ADVM-022 with zero anti-VEGF rescue injections in Cohort 1 (high dose). ADVM-022 continues to be well tolerated across all four cohorts. In addition, we have seen encouraging early safety data with prophylactic steroid eye drops from Cohort 4 (high dose) consistent with Cohort 3 (low dose). In November 2020, we plan to present additional clinical data from all four cohorts. As we continue to follow patients in OPTIC, we plan to present additional clinical data from this trial in 2021.

Based on the promising data observed thus far from OPTIC, we plan to initiate a pivotal trial for ADVM-022 in wet AMD in mid-2021. As we advance ADVM-022 for two large ocular disease indications, we are initiating process scale-up from 200L to 1000L scale to support the future commercial product launch of ADVM-022. In addition, we are beginning to plan for in-house manufacturing capabilities with the initiation of site selection.

Diabetes impacts over 30 million people in the United States, over 400 million people globally and is increasing in prevalence. Approximately 5% of adults with type II diabetes are impacted by DME, a vision-threatening complication of diabetic retinopathy ("DR") and the leading cause of vision loss in patients with DR. Based on the promising safety and efficacy data from the OPTIC trial for ADVM-022 in patients with wet AMD, we are advancing our novel gene therapy for patients with DME. We are conducting the INFINITY Phase 2 trial, a multi-center, randomized, double-masked, active comparator-controlled study evaluating a single IVT injection of ADVM-022 in patients with DME.

In the INFINITY trial, we are randomizing patients and plan to enroll approximately 33 patients. The INFINITY trial is designed to demonstrate superior control of disease activity following a single IVT injection of ADVM-022 compared to a single aflibercept injection, as measured by time to worsening of DME disease activity in the study eye. Additional objectives include assessments of treatment burden, visual acuity, retinal anatomy and safety outcomes. Participants in this double-masked trial are being randomized to one of three arms for their study eye treatment: Arm 1 will receive high dose (6 x 10^11 vg/eye) of ADVM-022, Arm 2 will receive low dose (2 x 10^11 vg/eye) of ADVM-022, and Arm 3 will receive aflibercept at a dose of 2 mg. As we advance the INFINITY trial, we plan to present clinical data from this trial in the second half of 2021.

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

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

Impact of COVID-19

Our results of operations and financial condition for the three and nine months ended September 30, 2020 were not significantly impacted by the COVID-19 pandemic. However, the full extent to which the COVID-19 pandemic will directly or indirectly impact these areas in the future is unknown at this time and will depend on future developments that are unpredictable. We are actively monitoring and managing our response and assessing actual and potential impacts to these areas. Please refer to the "Risk Factors" section for further discussion of the risks we face as a result of the COVID-19 pandemic.

Impact on Operations

We are continuously evaluating and addressing potential impacts of the COVID-19 pandemic on our operations. To date, we have experienced limited impact due to COVID-19 on our operations. Our offices, laboratories, clinical trial sites, contract research organizations ("CROs"), contract manufacturing organizations, and other collaborators and partners are located in jurisdictions where quarantines, executive orders, shelter-in-place orders, guidelines, and other similar orders and restrictions intended to control the spread of the disease have been put in place by governmental authorities.

We are committed to the health and safety of our employees and their families and doing our part to slow the community spread of COVID-19. In mid-March, we implemented a number of actions, including a work-from-home policy for employees whose jobs do not require them to be onsite, allowing for flexible work schedules, restricting in-person meetings, and limiting onsite activities to only the most time-critical or necessary operational activities. We have maintained certain essential in-person laboratory functions in order to advance key research and development initiatives, supported by the implementation of updated onsite procedures. We believe these measures and others have allowed us to mitigate, but not eliminate, the effects and risks on our on-site operations posed by the COVID-19 pandemic.

Impact on Clinical Trials

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

Impact on Supply Chain and Manufacturing

While we have not yet experienced significant disruptions to our supply chain and manufacturing as a result of the COVID-19 pandemic, we cannot be certain that this trend will continue. Based on current information, we believe that our partners in our supply chain have been and will continue to serve us continuously during the COVID-19 pandemic. However, certain of these partners have prioritized and allocated more resources and capacity to supply drug product or raw materials to other companies engaged in the study of potential treatments or vaccinations for COVID-19, which could result in supply interruptions. We have sufficient drug supply for our ongoing current clinical trials; however, to mitigate against future potential delays in product supply, we are currently implementing additional measures to address these risks, including securing additional supplies and manufacturing capacity reserve, which have resulted in additional expenses and may result in other additional expenses in the future.

Financial Overview

Summary

We have not generated positive cash flow or net income from operations since our inception and, as of September 30, 2020, we had an accumulated deficit of $464.9 million. We expect to incur substantial expenses and increasing losses from operations in the foreseeable future as we continue our research and development efforts, advance our product candidates through preclinical and clinical development, manufacture clinical study materials, seek regulatory approval, and prepare for and, if approved, proceed to commercialization. We are at an early stage of development and may never be successful in developing or commercializing our product candidates.

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

We 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 CROs to carry out our clinical development and we do not have a sales organization.

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

As of September 30, 2020, we had $454.5 million in cash, cash equivalents and short-term investments. We believe that we have sufficient cash to fund operations into mid-2022.

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

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

General and Administrative Expenses

General and administrative expenses 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 anticipate 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 consists of interest income on our cash equivalents and short-term investments in marketable securities.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of financial condition and results of operations are based upon 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 judgments that affect the reported amounts of assets, liabilities, revenues and expenses. On an on-going basis, we evaluate our critical accounting policies and estimates. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable in the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions and conditions. There have been no material changes to our critical accounting policies from those described in our Annual Report on Form 10-K as filed with the SEC on March 12, 2020.

Results of Operations

Comparison of the Three and Nine Months Ended September 30, 2020 and 2019

	Three Months Ended September 30,			Nine Months Ended September 30,		
	2020	2019	Change	2020	2019	Change
	(In thousands)					
Collaboration and license revenue	$ —	$ 250	$ (250)	$ —	$ 250	$ (250)
Operating expenses:						
Research and development	16,653	9,944	6,709	50,581	29,045	21,536
General and administrative	11,351	7,389	3,962	30,989	20,097	10,892
Total operating expenses	28,004	17,333	10,671	81,570	49,142	32,428
Operating loss	(28,004)	(17,083)	(10,921)	(81,570)	(48,892)	(32,678)
Other income, net	235	965	(730)	1,695	3,331	(1,636)
Net loss	$ (27,769)	$ (16,118)	$ (11,651)	$ (79,875)	$ (45,561)	$ (34,314)

Revenue

Our revenue for the three and nine months ended September 30, 2019 was related to a milestone payment under our license agreement with GenSight.

Research and Development Expense

Research and development expense increased $6.7 million to $16.7 million for the three months ended September 30, 2020 from $9.9 million for the three months ended September 30, 2019. This overall increase was primarily related to a $2.2 million increase in personnel-associated costs including higher stock-based compensation expense, salaries and bonus mainly driven by headcount increase, a $2.0 million increase in production costs related to product candidate ADVM-022 and earlier-stage research programs, a $0.9 million increase in laboratory costs, a $0.7 million increase in expenses for consultants and contractors, and a $0.6 million increase in clinical trial. Stock-based compensation included in research and development expenses was $2.1 million for the third quarter of 2020, compared to $1.4 million for the third quarter of 2019.

Research and development expense increased $21.5 million to $50.6 million for the nine months ended September 30, 2020 from $29.0 million for the nine months ended September 30, 2019. This overall increase was primarily related to a $9.4 million increase in production costs related to product candidate ADVM-022 and earlier-stage research programs, a $6.0 million increase in personnel-associated costs including higher stock-based compensation expense, salaries and bonus mainly driven by headcount increase, a $1.8 million increase in laboratory costs, a $1.3 million increase in expenses for consultants, contractors, and other outside services, a $1.1 million increase in facilities costs as we moved into the new facilities during the first quarter of 2020, and a $0.7 million increase in clinical trial. Stock-based compensation expense included in research and development expenses was $5.0 million for the nine months ended September 30, 2020, compared to $2.8 million for the nine months ended September 30, 2019.

For the periods presented, our research and development activities were attributable to our wet AMD, DME, rare disease programs and earlier-stage research programs. We expect that research and development expenses will increase in future periods as we continue to invest in advancing our gene therapy product candidate ADVM-022 and earlier-stage research programs.

General and Administrative Expense

General and administrative expense increased $4.0 million to $11.4 million for the three months ended September 30, 2020 from $7.4 million for the three months ended September 30, 2019, primarily related to an increase of $3.5 million in personnel-associated costs including higher stock-based compensation expense, salaries and bonus mainly driven by headcount increase. The overall increase was also caused by increases of $0.7 million in depreciation expense as we moved into the new facilities during the first quarter of 2020 and $0.3 million in insurance and license fees, partially offset by a $0.5 million decrease in expenses for consultants and contractors. Stock-based compensation expense included in general and administrative expenses was $4.0 million for the third quarter of 2020, compared to $1.3 million for the third quarter of 2019.

General and administrative expense increased $10.9 million to $31.0 million for the nine months ended September 30, 2020 from $20.1 million for the nine months ended September 30, 2019, primarily related to an increase of $7.5 million in personnel-associated costs including higher stock-based compensation expense, salaries and bonuses mainly driven by headcount increase. The overall increase was also caused by increases of $1.7 million in depreciation expense as we moved into the new facilities during the first quarter of 2020, $0.9 million in fees for audit, tax, patent and other professional services, and $0.7 million in insurance and license fees. Stock-based compensation expense included in general and administrative expenses was $9.2 million for the nine months ended September 30, 2020, compared to $4.2 million for the nine months ended September 30, 2019.

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

Other Income, Net

The decreases of $0.7 million and $1.6 million in other income, net, for the three and nine months ended September 30, 2020 as compared to 2019, respectively, were primarily due to a lower yield from our short term investments.

Liquidity and Capital Resources

We have not generated positive cash flow or net income from operations since our inception and as of September 30, 2020, we had an accumulated deficit of $464.9 million. As of September 30, 2020, we had $454.5 million in cash, cash equivalents and short-term investments compared to $166.0 million as of December 31, 2019. We believe that our existing cash and cash equivalents and short-term investments as of September 30, 2020 will be sufficient to fund our operations into mid-2022.

In August 2020, we sold an aggregate of 16,675,000 shares of our common stock for $203.4 million in net proceeds after deducting underwriting discounts and commissions and estimated offering expenses.

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

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

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

- the initiation, progress, timing, costs and results of preclinical studies and any clinical trials for our product candidates;
- the outcome, timing of and costs involved in, seeking and obtaining approvals from the FDA and other regulatory authorities, including the potential for the FDA and other regulatory authorities to require that we perform more studies than those that we currently expect;
- the ability of our product candidates to progress through clinical development activities successfully;
- our need to expand our research and development activities;
- the rate of progress and cost of our commercialization of our products;
- the cost of preparing to manufacture our products on a larger scale;
- the costs of commercialization activities including product sales, marketing, manufacturing and distribution;
- the degree and rate of market acceptance of any products launched by us or future partners;
- the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights;
- our need to implement additional infrastructure and internal systems;
- our ability to hire additional personnel;
- our ability to enter into additional collaboration, licensing, commercialization or other arrangements and the terms and timing of such arrangements;
- the emergence of competing technologies or other adverse market developments; and
- the effects of the COVID-19 pandemic on our business, results of operations, and financial condition.

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

Cash Flows

	Nine Months Ended September 30,	
	2020	2019
	(in thousands)	
Net cash used in operating activities	$ (57,067)	$ (34,335)
Net cash used in investing activities	(291,743)	(48,863)
Net cash provided by financing activities	355,609	1,420
Net increase (decrease) in cash and cash equivalents and restricted cash	$ 6,799	$ (81,778)

Cash Used in Operating Activities

During the nine months ended September 30, 2020, net cash used in operating activities was $57.1 million, primarily as a result of net loss of $79.9 million due to the continued activities developing our product candidates, partially offset by $16.5 million of non-cash charges mainly related to $14.2 million of stock-based compensation expense and $3.1 million of depreciation and amortization expenses, and $6.3 million of net increase in operating assets and liabilities, which fluctuate due to timing of expenses and payments.

During the nine months ended September 30, 2019, net cash used in operating activities was $34.3 million, primarily as a result of net loss of $45.6 million due to the continued activities developing our product candidates, partially offset by $9.1 million of non-cash charges primarily related to $7.0 million of stock-based compensation expense and $1.2 million depreciation and amortization expenses, and $2.1 million of net decrease in operating assets and liabilities, which fluctuate due to timing of expenses and payments.

Cash Used in Investing Activities

Net cash used in investing activities for the nine months ended September 30, 2020 consisted of $281.3 million of net purchases of marketable securities and $10.4 million of purchases of property and equipment primarily related to the new facility.

Net cash used in investing activities for the nine months ended September 30, 2019 consisted of $38.0 million of net purchases of marketable securities and $10.9 million of purchases of property and equipment. Purchases of property and equipment primarily consisted of the leasehold improvements related to the new facility.

Cash Provided by Financing Activities

Net cash provided by financing activities for nine months ended September 30, 2020 consisted of $344.5 million of net proceeds from the sale of our common stock, $12.7 million of net proceeds from the exercise of stock options, and $0.5 million in proceeds from employee stock purchase plan, partially offset by $2.0 million in taxes paid relating to net share settlement of restricted stock units and repayment of loans.

Net cash provided by financing activities for nine months ended September 30, 2019 consisted primarily of $2.6 million of the net proceeds from the exercises of stock options, and $0.2 million proceeds from employee stock purchases, partially offset by $1.4 million in taxes paid relating to net share settlement of restricted stock units and repayment of loans.

Off-Balance Sheet Arrangements

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

Item 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 September 30, 2020. 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 September 30, 2020, our disclosure controls and procedures were effective to provide reasonable assurance that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is (i) recorded, processed, summarized and reported as and when required and (ii) accumulated and communicated to our management, including the Chief Executive Officer and our Chief Financial Officer, as appropriate to allow timely discussion regarding required disclosure.

Changes in internal control over financial reporting. There have been no changes in our internal control over financial reporting during the three months ended September 30, 2020 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

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.

PART II – OTHER INFORMATION

Item 1. Legal Proceedings

Not applicable.

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

Risks Related to Our Financial Position and Need for Capital

We have incurred significant operating losses since inception, and we expect to incur significant losses for the foreseeable future. We may never become profitable or, if achieved, be able to sustain profitability.

We have incurred significant operating losses since we were founded in 2006 and expect to incur significant losses for the foreseeable future as we continue development of our product candidates. Losses have resulted principally from costs incurred in our research and development programs and from our general and administrative expenses. In the future, we intend to continue to conduct research and development, regulatory compliance activities and, if any of our product candidates is approved, sales and marketing activities that, together with anticipated general and administrative expenses, will likely result in us incurring significant losses for the next several years.

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

We expect that our cash, cash equivalents, and short-term investments will be sufficient to fund our lead gene therapy programs into mid-2022. 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 mid-2022. However, this estimate is based on a number of assumptions that may prove to be wrong, including our expectations about the timing of planned clinical trials and expected investments into our manufacturing capabilities, and changing circumstances beyond our control may cause capital to be consumed more rapidly than currently anticipated. As a result, our operating plan may change, and we may need to seek additional funds sooner than planned, through collaboration agreements and public or private financings. If we run low on capital before we are able to achieve meaningful clinical data for some or all of our product candidates, we may be unable to successfully raise additional funds, and, consequentially, may need to significantly curtail some or all of our development activities.

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

We will require substantial future capital in order to complete the preclinical and clinical development for our product candidates and potentially to commercialize these product candidates. Any future clinical trials or expansion of ongoing clinical trials of our product candidates would cause an increase in our spending levels, as would other corporate activities such as building a manufacturing facility to supply 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, expansion costs, results of and timing of any future preclinical studies and clinical trials of any of our product candidates which we are pursuing or may choose to pursue in the future;
- the need for, and the progress, costs and results of, any additional clinical trials or nonclinical studies of our product candidates we may initiate based on the results of any clinical trials that we may plan or discussions with the FDA, including any additional clinical trials or nonclinical studies the FDA or other regulatory agencies may require evaluating the safety of our product candidates;
- the costs of obtaining, maintaining and enforcing our patents and other intellectual property rights;

- the costs and timing of obtaining or maintaining manufacturing for our product candidates, including commercial manufacturing;
- the costs and timing of establishing sales and marketing capabilities and enhanced internal controls over financial reporting;
- the terms and timing of establishing collaborations, license agreements and other partnerships;
- costs associated with any new product candidates that we may develop, in-license or acquire;
- the effect of competing technological and market developments;
- our ability to establish and maintain partnering arrangements for development; and
- the costs associated with being a public company.

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

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

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

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

Risks Related to the Discovery and Development of Our Product Candidates

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

Our product candidates are in the early stages of development and will require substantial preclinical and/or clinical development and testing, manufacturing process improvement and validation, bridging studies and regulatory approval prior to commercialization. It is critical to our business to successfully develop and ultimately obtain regulatory approval for one or more of these product candidates. Our ability to commercialize our product candidates effectively will depend on several factors, including the following:

- successful completion of preclinical studies and clinical trials, including the ability to demonstrate safety and efficacy of our product candidates;
- receipt of marketing approvals for any future products for which we complete clinical trials, including securing regulatory exclusivity to the extent available;
- establishing commercial manufacturing capabilities, for example, by engaging third-party manufacturers or developing our own manufacturing capabilities that can provide products and services to support clinical development and the market demand for our product candidates, if approved;
- successful launch and commercial sales of the product, whether alone or in collaboration with potential partners;
- acceptance of the product as a viable treatment option by patients, the medical community and third-party payers;
- establishing market share while competing with other therapies;
- a continued acceptable safety profile of our products following regulatory approval;
- maintaining compliance with post-approval regulations and other requirements; and
- qualifying for, identifying, registering, maintaining, enforcing and defending intellectual property rights and claims covering our product candidates.

If we or our collaborators do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to commercialize our product candidates, which would materially and adversely affect our business, financial condition, results of operations and prospects.

Of the large number of biologics and drugs in development in the pharmaceutical industry, only a small percentage result in the submission of a biologics license application (“BLA”) to the FDA and even fewer are approved for commercialization. Furthermore, even if we do receive regulatory approval to market any of our product candidates, any such approval may be subject to limitations on the indicated uses for which we may market the product, or limitations related to its distribution. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development programs, there can be

no assurance that any of our product candidates will be successfully developed or commercialized. If we or any of our future development partners are unable to develop, or obtain regulatory approval, or, if approved, successfully commercialize, any of our product candidates, we may not be able to generate sufficient revenue to continue our business.

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

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

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

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

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

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

The success of our business depends primarily upon our ability to identify, develop and commercialize products based on our platform 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 would have a material adverse effect on our business, financial condition, results of operations, and prospects and could potentially cause us to cease operations. Research programs to identify new product candidates require substantial technical, financial and human resources. We may focus our efforts and resources on potential programs or product candidates that may ultimately prove to be unsuccessful.

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

Drug development has inherent risk. Few of our product candidates and proprietary viral vectors have been evaluated in clinical trials in patients. Our lead product candidate, ADVM-022 for the treatment of wet age-related macular degeneration ("wet AMD") and DME, uses a proprietary vector, AAV.7m8, which has undergone limited human testing, and may experience unexpected results in clinical trials in the future. We, or any licensee or development partner, will be required to demonstrate through adequate and well-controlled clinical trials that our product candidate or another party’s product candidate containing one of our proprietary viral vectors are safe and effective for use in their target indications before seeking regulatory approvals for commercial sale. Drug development is a long, expensive and uncertain process, and delay or failure can occur at any stage

of development, including after commencement of any of our clinical trials or any clinical trials using our proprietary viral vectors. Any such delay or failure could significantly harm our business prospects, financial condition and results of operations.

The results of preclinical studies and early clinical trials are not always predictive of future results. Any product candidate we or any of our future development partners advance into clinical trials may not have favorable results in later clinical trials, if any, or receive regulatory approval.

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

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

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

From time to time, we may announce or publish preliminary or interim data from our clinical trials. Preliminary and interim results of a clinical trial are not necessarily predictive of final results. Preliminary and interim data are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues or further patient follow up occurs and more patient data become available. For example, although we have periodically announced interim data from patients in our OPTIC trial, which showed all ADVM-022 related adverse events ("AEs") as mild to moderate, there is no guarantee that in the future, we will not have more severe drug- or treatment-related adverse events, including serious adverse events ("SAEs") or drug-limiting toxicities ("DLTs") in patients treated with ADVM-022. In addition, in certain clinical trials, such as our OPTIC trial, individual cohorts of patients are enrolled with different dosages and other treatment conditions under our protocol. These different dosages and other treatment conditions may affect clinical outcomes, including safety profiles or efficacy, such as the number of rescue injections required, in each of the cohorts. As a result, preliminary and interim data should be viewed with caution and not relied upon until the final data from a locked database for the entire clinical trial are available. Material changes in the final data compared to preliminary or interim data could significantly harm our business prospects.

Our product candidates are subject to extensive regulation, compliance with which is costly and time consuming, and such regulation may cause unanticipated delays or prevent the receipt of the required approvals to commercialize our product candidates.

The preclinical and clinical development, manufacturing, analytical testing, labeling, storage, record-keeping, advertising, promotion, import, export, marketing and distribution of our product candidates are subject to extensive regulation by the FDA and by comparable regulatory authorities in foreign markets. In the U.S., we are not permitted to market our product candidates until we receive regulatory approval from the FDA. The process of obtaining regulatory approval is expensive, often takes many years and can vary substantially based upon the type, complexity and novelty of the products involved, as well as the

target indications and patient population. Approval policies or regulations may change, and the regulatory authorities have substantial discretion in the drug approval process, including the ability to delay, limit or deny approval of a product candidate for many reasons. Despite the time and expense invested in clinical development of product candidates, regulatory approval is never guaranteed.

The FDA or comparable foreign regulatory authorities can delay, limit or deny approval of a product candidate for many reasons, including:

- such authorities may disagree with the design or implementation of our or any of our future development partners' clinical trials;
- we or any of our future development partners may be unable to demonstrate to the satisfaction of the FDA or other regulatory authorities that a product candidate is safe and effective for any indication;
- the FDA or other regulatory authorities may not accept clinical data from trials which are conducted at multinational clinical facilities or in countries where the standard of care is potentially different from that of the U.S.;
- the results of clinical trials may not demonstrate the safety or efficacy required by such authorities for approval; we or any of our future development partners may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- such authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- approval may be granted only for indications that are significantly more limited than what we apply for and/or with other significant restrictions on distribution and use;
- such authorities may find deficiencies in the manufacturing processes, analytical testing, or facilities of third-party manufacturers or testing laboratories with which we or any of our future development partners contract for clinical and commercial supplies; or
- the approval policies or regulations of such authorities may significantly change in a manner rendering our or any of our future development partners' clinical data insufficient for approval.

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

If we encounter difficulties enrolling patients in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

Identifying and qualifying patients to participate in the INFINITY trial for ADVM-022 for the treatment of DME and any future planned clinical trials will be critical to our success. The timing of current and future clinical trials will depend on the speed at which we can recruit patients to participate in future testing of these product candidates.

Patient enrollment, a significant factor in the timing of clinical trials, is affected by many factors including the size and nature of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the trial, the design of the clinical trial, competing clinical trials, 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 during a pandemic. We will be required to identify and enroll a sufficient number of patients with DME for the INFINITY trial, and we will be required to identify and enroll a sufficient number of patients for any future clinical trials for our product candidates. Potential patients may not be adequately diagnosed or identified with the diseases which we are targeting or may not meet the entry criteria for our trials. Additionally, some patients may have neutralizing antibodies at titer levels that would prevent them from being enrolled in a clinical trial for any of our product candidates, or may meet other exclusion criteria. The incidence of neutralizing antibodies in the population of patients, particularly for rare diseases, is unknown, and may be higher than we expect. As a consequence, enrollment in our clinical trials may be limited or slowed. We also may encounter difficulties in identifying and enrolling patients with a stage of disease appropriate for such future clinical trials. We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics to achieve diversity in a trial.

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

We plan to seek initial marketing approval of these product candidates in the U.S. and/or Europe and we may not be able to successfully conduct clinical trials if we cannot enroll a sufficient number of eligible patients to participate in the clinical trials

required by the FDA or the EMA or other regulatory agencies. In addition, the process of finding and diagnosing patients may prove costly.

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

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

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

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

During the conduct of preclinical studies and clinical trials, animal models and patients may experience changes in their health, including illnesses, injuries and discomforts. Often, it is not possible to determine whether or not the product candidate being studied caused these conditions. In addition, patients may not comply with the requirements of the study, such as missing physician visits or not taking eye drops as prescribed, which may result in changes to their health or vision that are then attributed to the product candidate. Various illnesses, injuries, and discomfort may be reported from time-to-time in clinical trials of our product candidates. It is possible that as we test our product candidates in larger, longer and more extensive clinical programs, or as use of these product candidates becomes more widespread if they receive regulatory approval, illnesses, injuries, discomfort and other adverse events that were observed in earlier trials, as well as conditions that did not occur or went undetected in previous trials, will be reported by patients. Many times, side effects are only detectable after investigational products are tested in large-scale, Phase 3 clinical trials or later stage clinical trials, or, in some cases, after they are made available to patients on a commercial scale after approval. If additional clinical experience indicates that one or more of our product candidates has side effects or causes serious or life-threatening side effects, the development of one or more of our product candidates may fail or be delayed, or, if one or more of our product candidates has received regulatory approval, such approval may be revoked, which would severely harm our business prospects, financial condition and results of operations.

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

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

Our product candidates built on AAV vectors have similar risks to other gene therapy vectors, including inflammation, cytotoxic T-cell responses, anti-AAV antibodies and immune response to the transgene product, such as T-cell responses and/or

antibodies against the expressed protein. For example, based on our current clinical experience, ocular inflammation is a known side effect of ADVM-022 administration, but the duration of inflammation caused by ADVM-022, our ability to manage that inflammation using steroids or other anti-inflammatory treatments, and any potential clinical sequelae of that inflammation and treatments used to manage inflammation are not fully understood. If we are unable to manage this inflammation appropriately, the FDA or other regulatory authorities may not approve ADVM-022. Even if we achieve marketing approval, doctors may not prescribe, and patients may not use ADVM-022 or our other product candidates if they deem the levels or risk of inflammation to be unacceptable. Further, patients treated with ADVM-022 could develop antibodies against AAV.7m8 capsid and/or aflibercept protein. These antibodies could preclude these patients from receiving other AAV-based gene therapies and/or recombinant aflibercept protein in the future. Studies have also found that intravenous delivery of certain AAV vectors at very high doses may result in adverse events and have prompted the recommendation that studies involving high doses of AAV vectors should be monitored carefully for such adverse events. In addition, patients given infusions of any protein may develop severe hypersensitivity reactions, infusion reactions, or serious side effects including transaminitis. With respect to our product candidates that are being or may be studied in diseases of the eye, there are additional potential serious complications related to intravitreal injection, such as retinal detachment, endophthalmitis, ocular inflammation, cataract formation, glaucoma, hypotony, damage to the retina or cornea, and bleeding in the eye. Serious complications or serious, unexpected side effects in connection with the use of our product candidates could materially harm our business prospects, financial condition and results of operations.

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

Risks Related to Our Reliance on Third Parties

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

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

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

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

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

We do not expect to independently conduct all aspects of our vector production, product manufacturing, product testing, protocol development, protocol performance, and research. We currently rely, and expect to continue to rely, on third parties with respect to these items. We may not be able to enter into agreements with these third parties and if we do enter into

agreements with these third parties, any of these third parties may not be successful at fulfilling their contractual obligations or may choose to terminate their engagements with us at any time. If we need to enter into alternative arrangements, it could delay our product development activities. Our reliance on these third parties for vector production, process development, assay development, product manufacturing, product testing, protocol development, protocol performance, and research activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations. If any of these third parties on which we rely do not perform satisfactorily, we will remain responsible for ensuring that:

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

These third parties may not successfully carry out their contractual duties, meet expected deadlines or conduct our studies in accordance with regulatory requirements or our stated study plans and protocols. If third parties breach their contractual obligations to us, we may not be able to start or complete, or may be delayed in starting or completing, the preclinical studies and clinical trials required to support future IND submissions, development work, and approval of our product candidates.

Reliance on third-party manufacturers entails risks to which we would not be subject to if we manufactured the product candidates ourselves, including:

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

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

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

We currently have relationships with a limited number of suppliers for the manufacturing and testing of our vector product candidates. Our suppliers may require licenses to manufacture or test such components if such processes are not owned by the suppliers or in the public domain and we may be unable to transfer or sublicense the intellectual property rights we may have with respect to such activities, and may be unable to acquire such rights, to the extent that we do not already have them.

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

We or our contract manufacturers must supply all necessary documentation in support of a BLA on a timely basis and must adhere to the FDA's cGMP regulations enforced by the FDA through its facilities inspection program as well as other regulations enforced by other regulatory authorities. Our contract manufacturers have not produced a commercially-approved AAV product and therefore have not yet demonstrated compliance with cGMP regulations to the satisfaction of the FDA or other regulatory authority. Our facilities and quality systems and the facilities and quality systems of some or all of our third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. If the facility does not pass a pre-approval plant inspection, FDA or other regulatory approval of the products will not be granted. In addition, the regulatory authorities may, at any time, audit or inspect our manufacturing facilities or those of our third-party contractors involved with the preparation of our product candidates or our other potential products or the associated quality systems for compliance with the

regulations applicable to the activities being conducted. Should the FDA or other regulatory authority determine that the facility is not in compliance with applicable regulations, the manufacture and release of our product candidates may not be possible, and our business could be harmed.

Changes in laws and governmental policies may have an effect on regulations. For example, on January 31, 2020, the United Kingdom (UK) withdrew from the European Union (EU), commonly referred to as Brexit. Under the withdrawal agreement agreed between the UK and the EU, the UK will be subject to a transition period until December 31, 2020 (the "Transition Period") during which EU rules will continue to apply. During the Transition Period, negotiations between the UK and the EU are expected to continue in relation to the future customs and trading relationship between the UK and the EU following the expiration of the Transition Period. Under the formal withdrawal arrangements between the UK and the EU, the parties had until June 30, 2020 to agree to extend the Transition Period if required. No such extension was agreed prior to such date. No agreement has yet been reached between the UK and the EU and it may be the case that no formal customs and trading agreement will be reached prior to the expiration of the Transition Period on December 31, 2020. We and our contract vendors currently rely on other contractors based in the UK. After the Transition Period, if the implementation of new governmental policies associated with Brexit occurs, these governmental policies may affect our UK-based contractors' ability to comply with applicable regulations, including existing EU regulations. If they are unable to return to compliance, or if an acceptable substitute vendor cannot be identified, it may negatively impact our business. Further, to the extent that our UK-based contractors have supply relationships with vendors in the EU, these contractors may experience difficulties, delay or increased costs in receiving materials from their vendors in the EU, which could have a material adverse effect on our UK-based contractors' ability to provide the services or materials to us.

The regulatory authorities also may, at any time, following approval of a product for sale, audit our manufacturing facilities or those of our third-party contractors. If any such inspection or audit identifies a failure to comply with applicable regulations or if we become aware of a violation of our product specifications or applicable regulations, independent of an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time-consuming for us or a third party to implement and which may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a facility. Such violations could also result in civil and/or criminal penalties. Any such remedial measures or other civil and/or criminal penalties imposed upon us or third parties with whom we contract could materially harm our business.

If we or our third-party contractors fail to maintain regulatory compliance, the FDA can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new biologic product, revocation of a pre-existing approval, injunction, seizure of product, or other civil or criminal penalties or closing one or more manufacturing or testing facilities. As a result, our business, financial condition and results of operations may be materially harmed.

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

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

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

Because we rely on third parties to research and develop and to manufacture our product candidates, we must, at times, share confidential information, including trade secrets, with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements containing confidentiality provisions with our advisors, employees, third-party contractors and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, including our trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are purposefully or inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Public disclosure of our confidential information also prevents us from

seeking patent protection for that or related discoveries. Given that our proprietary position is based, in part, on our know-how and trade secrets, the unauthorized use or disclosure of our trade secrets would impair our competitive position and may have a material adverse effect on our business, financial conditions, results of operations and prospects.

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

Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of our agreements with third parties, or publication of information by any of our third-party collaborators. A competitor's discovery of our trade secrets could impair our competitive position and have an adverse impact on our business, financial condition, results of operations and prospects.

Risks Related to Commercialization of Our Product Candidates

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

Before we can initiate clinical trials in the U.S. for our product candidates, we need to submit the results of preclinical testing to the FDA, along with other information including information about product candidate chemistry, manufacturing and controls and our proposed clinical trial protocol, as part of an IND. We may rely in part on preclinical, clinical and quality data generated by CROs and other third parties for regulatory submissions for our product candidates. If these third parties do not provide timely data for our product candidates, it will delay our plans for our IND submissions and clinical trials. If those third parties do not make this data available to us, we will likely have to develop all necessary preclinical and clinical data on our own, which will lead to significant delays and increase development costs of the product candidate. In addition, the FDA may require us to conduct additional preclinical testing for any product candidate before it allows us to initiate clinical testing under any IND, which may lead to additional delays and increase the costs of our preclinical development. Delays with any regulatory authority or agency may significantly affect our product development timeline. Delays in the commencement or completion of any clinical trials that we plan for our product candidates could significantly affect our product development costs. We do not know whether any trials that we plan will begin on time or be completed on schedule, if at all. The commencement and completion of clinical trials can be delayed or terminated for a number of reasons, including delays or terminations related to:

- the FDA failing to grant permission to proceed or placing the clinical trial on hold;
- patients failing to enroll or remain in our trial at the rate we expect;
- patients choosing an alternative treatment for the indication for which we are developing our product candidates, or participating in competing clinical trials;
- lack of adequate funding to continue the clinical trial;
- patients experiencing severe or unexpected drug-related adverse effects;
- a facility manufacturing any of our product candidates or any of their components being ordered by the FDA or other government or regulatory authorities to temporarily or permanently shut down due to violations of cGMP or other applicable requirements, or infections or cross-contaminations of product candidates in the manufacturing process;
- any changes to our manufacturing process that may be necessary or desired;
- third-party clinical investigators losing the licenses or permits necessary to perform our clinical trials, lacking the ability or resources to appropriately handle our product candidates, not performing our clinical trials on our anticipated schedule or consistent with the clinical trial protocol, Good Clinical Practice or regulatory requirements, or other third parties not performing data collection or analysis in a timely and accurate manner;
- inspections of clinical trial sites by the FDA or the finding of regulatory violations by the FDA or an IRB that require us to undertake corrective action, result in suspension or termination of one or more sites or the imposition of a clinical hold on the IND or that prohibit us from using some or all of the data in support of our marketing applications;
- third-party contractors becoming debarred or suspended or otherwise penalized by the FDA or other government or regulatory authorities for violations of regulatory requirements, in which case we may need to find a substitute contractor, and we may not be able to use some or all of the data produced by such contractors in support of our marketing applications; or

- one or more IRBs refusing to approve, suspending or terminating the trial at an investigational site, precluding enrollment of additional patients, or withdrawing its approval of the trial.

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

If we do not achieve our projected development goals in the time frames we announce and expect, the commercialization of our product candidates, if approved, may be delayed and the credibility of our management team may be adversely affected and, as a result, our stock price may decline.

From time to time, we estimate the timing of the accomplishment of various scientific, clinical, regulatory and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of, or the availability of data from, scientific studies and clinical trials and the submission of regulatory filings. From time to time, we may publicly announce the expected timing of some of these milestones. All of these milestones will be based on a variety of assumptions. The actual timing of these milestones can vary dramatically compared to our estimates, in some cases for reasons beyond our control. If we do not meet these milestones as publicly announced, the commercialization of our products may be delayed and the credibility of our management team may be adversely affected and, as a result, our stock price may decline.

Final marketing approval for our product candidates by the FDA or other regulatory authorities for commercial use may be delayed, limited or denied, any of which would adversely affect our ability to generate operating revenue.

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

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

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

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

- issue warning letters or untitled letters;

- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve pending applications or supplements or applications filed by us;
- institute import holds;
- suspend or impose restrictions on operations, including costly new manufacturing requirements; or
- seize or detain products, refuse to permit the import or export of product or request us to initiate a product recall.

The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and generate revenue. The FDA has the authority to require a Risk Evaluation and Mitigation Strategy ("REMS") plan as part of a BLA or after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug, such as limiting prescribing to certain physicians or medical centers that have undergone specialized training, limiting treatment to patients who meet certain safe-use criteria and requiring treated patients to enroll in a registry.

In addition, if any of our product candidates is approved, our product labeling, advertising and promotion would be subject to regulatory requirements and ongoing regulatory review. The FDA strictly regulates the promotional claims that may be made about prescription products. In particular, a product may not be promoted for uses that are not approved by the FDA as reflected in the product's approved labeling. If we receive marketing approval for a product candidate, physicians may nevertheless prescribe it to their patients in a manner that is inconsistent with the approved label. If we are found to have promoted such off-label uses, we may become subject to significant liability. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant sanctions. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into consent decrees or be subject to permanent injunctions under which specified promotional conduct is changed or curtailed.

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

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

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

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

If the market for our product candidate, if approved, in the treatment of wet AMD or DME, or any other indication we seek to treat is smaller than we believe it is, our future revenue may be adversely affected, and our business may suffer.

We are advancing the development of ADVM-022 for the treatment of wet AMD, a disease we believe to be the most common cause of vision loss in adults over the age of 50 in developed countries. We are also advancing the development of ADVM-022 for the treatment of DME. If the size of the market for wet AMD, DME, or any other indication we seek to treat is smaller than

we anticipate (including in our rare disease programs), we may not be able to achieve profitability and growth. Our projections of the number of people who have wet AMD, DME and other indications, as well as the subset of people with the disease who have the potential to benefit from treatment with ADVM-022 or other future product candidates, are based on estimates. These estimates have been derived from a variety of sources, including the scientific literature, surveys of clinics, patient foundations and market research and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower than expected.

The effort to identify patients with diseases we seek to treat is in early stages as we conduct the OPTIC trial of ADVM-022 for the treatment of wet AMD and enroll patients in the INFINITY trial of ADVM-022 for the treatment of DME, and we cannot accurately predict the number of patients for whom treatment might be possible. For example, some patients with wet AMD have neutralizing antibodies at titer levels that may prevent them from benefiting from ADVM-022. If this patient population is larger than we estimate, the market for ADVM-022 may be smaller than we anticipate, and our future revenue may be adversely affected. In addition, we expect prophylactic steroid treatment will be required to manage inflammation associated with treatment with ADVM-022, and certain patients cannot be treated with prophylactic steroids. If this proportion of patient population is larger than we estimate, the market for ADVM-022 may be smaller than we anticipate. Additionally, the potentially addressable patient population may be limited or may not be amenable to treatment with our product candidates for other reasons, and new patients may become increasingly difficult to identify or gain access to, which would adversely affect our results of operations and our business.

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

Additionally, because the target patient population for any of our rare disease programs is relatively small, the pricing and reimbursement of these product candidates, if approved, must be adequate to support commercial infrastructure. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell any of our product candidates targeting such rare disease will be adversely affected. The manner and level at which reimbursement is provided for services related to this product candidate (e.g., for administration of such product to patients) is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell our product candidates targeting such rare disease.

Coverage and reimbursement may be limited or unavailable in certain market segments for our product candidates, which could make it difficult for us to sell our product candidates profitably.

Market acceptance and sales of our product candidates will depend significantly on the availability of adequate coverage and reimbursement from third-party payers for any of our product candidates and may be affected by existing and future health care reform measures. Government authorities and third-party payers, such as private health insurers and health maintenance organizations, decide which drugs they will pay for and establish reimbursement levels.

Reimbursement by a third-party payer may depend upon a number of factors including the third-party payer's determination that use of a product candidate is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient; and
- cost-effective.

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

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

As a result of legislative proposals and the trend toward managed health care in the U.S., third-party payers are increasingly attempting to contain health care costs by limiting both coverage and the level of reimbursement of new drugs. By way of example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or 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.

There remain executive, judicial and Congressional challenges to certain aspects of the Affordable Care Act. Since January 2017, President Trump has signed Executive Orders and other directives designed to eliminate, circumvent or loosen the implementation of certain provisions of the Affordable Care Act or otherwise circumvent some of the requirements for health insurance mandated by the Affordable Care Act. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the Affordable Care Act. While Congress has not passed repeal legislation, the Tax Cuts and Jobs Act of 2017 includes a provision that repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." Additionally, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the Affordable Care Act's mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminates the health insurer tax. Moreover, the Bipartisan Budget Act of 2018, or the BBA, among other things, amended the Affordable Care Act, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare Part D drug plans, commonly referred to as the "donut hole." Further, in December 2018, CMS published a final rule permitting further collections and payments to and from certain Affordable Care Act-qualified health plans ("QHPs") and health insurance issuers under the Affordable Care Act adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. On April 27, 2020, the United States Supreme Court reversed a Federal Circuit decision that previously upheld Congress' denial of $12 billion in "risk corridor" funding. In December 2018, a federal district court judge in Texas found the Affordable Care Act's individual mandate to be unconstitutional and therefore the entire law to be invalid. In December 2019, the Fifth Circuit affirmed the ruling regarding the individual mandate but remanded the case to the district court for additional analysis of the question of severability and whether other portions of the law remain valid. On March 2, 2020, the United States Supreme Court granted the petitions for writs of certiorari to review this case. It is unclear how such litigation and other efforts to repeal and replace the Affordable Care Act will impact the Affordable Care Act and our business.

Other legislative changes have also been proposed and adopted in the U.S. since the Affordable Care Act was enacted. On August 2, 2011, the Budget Control Act of 2011 created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This included aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013 and due to subsequent legislative changes to the statute, including the BBA, will stay in effect through 2030 unless additional Congressional action is taken. The Coronavirus Aid, Relief and Economic Security Act, or CARES Act, which was signed into law in March 2020 and is designed to provide financial support and resources to individuals and businesses affected by the COVID-19 pandemic, suspended the 2% Medicare sequester from May 1, 2020 through December 31, 2020, and extended the sequester by one year, through 2030.

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

Recently there has been heightened governmental scrutiny over pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. At the federal level, the Trump administration's budget proposal for fiscal year 2021 includes a $135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and increase patient access to lower-cost generic and biosimilar drugs. On March 10, 2020, the Trump administration sent "principles" for drug pricing to Congress, calling for legislation that would, among other things, cap Medicare Part D beneficiary out-of-pocket pharmacy expenses, provide an option to cap Medicare Part D beneficiary monthly out-of-pocket expenses, and place limits on pharmaceutical price increases. Further, the Trump administration previously released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contained proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. The U.S. Department of Health and Human Services solicited feedback on some of these measures and has implemented others under its existing authority. On July 24, 2020, the Trump administration announced four executive orders related to prescription drug pricing that attempt to implement several of the administration's proposals. Although a number of these and other measures may require additional authorization to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

The continuing efforts of the government, insurance companies, managed care organizations and other payers of healthcare services to contain or reduce costs of health care may adversely affect:

- the demand for any product candidates for which we may obtain regulatory approval;
- our ability to set a price that we believe is fair for our product candidates;
- our ability to generate revenue and achieve or maintain profitability;
- the level of taxes that we are required to pay; and
- the availability of capital.

It is possible that additional governmental action is taken in response to the COVID-19 pandemic. For example, on August 6, 2020, the Trump administration issued another executive order that instructs the federal government to develop a list of "essential" medicines and then buy them and other medical supplies from U.S. manufacturers instead of from companies around the world, including China.

Due to the novel nature of our technology and the potential for our product candidates to offer therapeutic benefit in a single administration, we face uncertainty related to pricing and reimbursement for these product candidates.

Our product candidates are designed to provide potential therapeutic benefit after a single administration and, therefore, the pricing and reimbursement of our product candidates, if approved, must be adequate to support commercial infrastructure. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell our product candidates will be adversely affected. The manner and level at which reimbursement is provided for services related to our product candidates (e.g., for administration of our product to patients) is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell our product candidates.

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

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

- The manufacturing and distribution of biologics is extremely susceptible to product loss due to contamination, equipment failure, improper installation or operation of equipment or vendor or operator error. Even minor deviations from normal manufacturing processes could result in reduced production yields, product defects, and other supply disruptions. If microbial, viral, or other contaminations are discovered in our product candidates or in the manufacturing facility in which our product candidates are made, such manufacturing facility may need to be closed for an extended period of time to investigate and remedy the contamination.

- The manufacturing facilities in which our product candidates are made could be adversely affected by equipment failures, labor shortages, contaminants, raw materials shortages, natural disasters, power failures, and numerous other factors.
- We and our contract manufacturers must comply with the FDA's cGMP regulations and guidelines. We and our contract manufacturers may encounter difficulties in achieving quality control and quality assurance and may experience shortages in qualified personnel. We and our contract manufacturers are subject to inspections by the FDA and comparable agencies in other jurisdictions to confirm compliance with applicable regulatory requirements. Any failure to follow cGMP or other regulatory requirements or any delay, interruption, or other issues that arise in the manufacture, fill-finish, packaging or storage of our product candidates as a result of a failure of our facilities, or the facilities or operations of third parties, to comply with regulatory requirements or pass any regulatory authority inspection could significantly impair our ability to develop and commercialize our product candidates. This may lead to significant delays in the availability of sufficient supply of the product candidate substance for our clinical trials or the termination or hold on a clinical trial, or the delay or prevention of a filing or approval of marketing applications for our product candidates.
- Significant noncompliance could also result in the imposition of sanctions, including fines, injunctions, civil penalties, failure of regulatory authorities to grant marketing approvals for our product candidates, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of products, operating restrictions, and criminal prosecutions, any of which could be costly and damage our reputation. If we are not able to maintain regulatory compliance, we may not be permitted to market our product candidates, if approved, and/or may be subject to product recalls, seizures, injunctions or criminal prosecution.
- Our product candidates are biologics and require processing steps that are more complex than those required for most chemical pharmaceuticals. Moreover, unlike chemical pharmaceuticals, the physical and chemical properties of a biologic such as our product candidates generally cannot be adequately characterized prior to manufacturing the final product. As a result, an assay of the finished product is not sufficient to ensure that the product will perform in the intended manner. Accordingly, we expect to employ multiple steps to attempt to control our manufacturing process and assure that the product or product candidate is made strictly and consistently in compliance with the process.
- We have to develop the manufacturing process for late stage clinical product, and our current process has not been fully characterized and therefore is open to potential variations that could lead to defective product substance that does not meet specification.
- Problems with the manufacturing, storage or distribution of our product candidates, including even minor deviations from our established parameters, could result in product defects or manufacturing failures that result in lot failures, product recalls, product liability claims and insufficient inventory.
- Some of the raw materials required in our manufacturing process are derived from biological sources. Such raw materials are difficult to procure and may also be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our product candidates could adversely impact or disrupt commercialization.
- Any adverse developments affecting manufacturing operations for our product candidates may result in shipment delays, inventory shortages, lot failures, product withdrawals or recalls, or other interruptions in the supply of our product candidates. We may also have to take inventory write-offs and incur other charges and expenses for product substance that fails to meet specifications, undertake costly remediation efforts, or seek more costly manufacturing alternatives. We may encounter problems manufacturing sufficient research-, clinical-, or commercial-grade materials that meet FDA, EMA or other applicable standards or specifications with consistent and acceptable production yields and costs.

We may not be successful in establishing and maintaining development or other strategic collaborations, which could adversely affect our ability to develop and commercialize product candidates and receive milestone and/or royalty payments.

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

We may form strategic alliances in the future, and we may not realize the benefits of such alliances.

We may form strategic alliances, create joint ventures or collaborations, or enter into licensing arrangements with third parties that we believe will complement or augment our existing business, including for the continued development or commercialization of our product candidates. These relationships or those like them may require us to incur non-recurring and other charges, increase our near-and long-term expenditures, issue securities that dilute our existing stockholders, or disrupt our management and business. In addition, we face significant competition in seeking appropriate strategic partners and the negotiation process is time-consuming and complex. Moreover, we may not be successful in our efforts to establish a strategic partnership or other alternative arrangements for our product candidates because third parties may view the risk of failure in future clinical trials as too significant, or the commercial opportunity for our product candidate as too limited. We cannot be certain that, following a strategic transaction or license, we will achieve the revenue or specific net income that justifies such transaction. Even if we are successful in our efforts to establish development partnerships, the terms that we agree upon may not be favorable to us, and we may not be able to maintain such development partnerships if, for example, development or approval of a product candidate is delayed or sales of an approved product candidate are disappointing. Any delay in entering into development partnership agreements related to our product candidates could delay the development and commercialization of our product candidates and reduce their competitiveness if they reach the market.

If our competitors develop treatments for the target indications of our product candidates that are approved, marketed more successfully, or demonstrated to be safer or more effective or easier to administer than our product candidates, our commercial opportunity will be reduced or eliminated.

We operate in highly competitive segments of the biopharmaceutical markets. We face competition from many different sources, including larger and better-funded pharmaceutical, specialty pharmaceutical, biotechnology, and gene therapy companies, as well as from academic institutions, government agencies and private and public research institutions. Our product candidates, if successfully developed and approved, will compete with established therapies as well as with new treatments that may be introduced by our competitors. There are a variety of drug candidates and gene therapies in development or being commercialized by our competitors for the indications that we intend to test. Many of our competitors have significantly greater financial, product candidate development, manufacturing, and marketing resources than we do. Large pharmaceutical and biotechnology companies have extensive experience in clinical testing and obtaining regulatory approval for drugs. In addition, universities and private and public research institutes may be active in our target disease areas, and some could be in direct competition with us. We also may compete with these organizations to recruit management, scientists, and clinical development personnel. We will also face competition from these third parties in establishing clinical trial sites, registering patients for clinical trials, and in identifying and in-licensing new product candidates. For example, REGENXBIO is developing RGX-314, an AAV-based gene therapy delivering a gene encoding a therapeutic antibody fragment similar to ranibizumab (Lucentis®) for the treatment of wAMD and diabetic retinopathy, which competes for the same patients, study site resources, and personnel as ADVM-022. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

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

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

Our potential competitors in these diseases may be developing novel therapies that may be safer or more effective or easier to administer than our product candidates. For example, if we continue clinical development of, and seek to commercialize, ADVM-022 for the treatment of wet AMD and DME, it will compete with a variety of therapies currently marketed and in development for wet AMD, using therapeutic modalities such as biologics, small molecules, long acting delivery devices, and gene therapy. Lucentis and EYLEA are anti-VEGF therapies that are well established and widely accepted by physicians, patients and third-party payers as the standard of care for the treatment of wet AMD. There are several other companies with marketed products or products in development for the treatment of wet AMD, including Bayer, Graybug Vision, Hoffmann-La Roche Ltd., Kodiak Sciences, Novartis, Regeneron and REGENXBIO.

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

We have no internal sales, marketing, or distribution capabilities. If any of our product candidates ultimately receive regulatory approval, we may not be able to effectively market and distribute the product candidate. We would have to invest significant amounts of financial and management resources to develop internal sales, distribution and marketing capabilities, some of which will be committed prior to any confirmation that any of our product candidates will be approved, if at all. We may not be able to hire consultants or external service providers to assist us in sales, marketing and distribution functions on acceptable financial terms or at all. Even if we determine to perform sales, marketing and distribution functions ourselves, we could face a number of additional related risks, including:

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

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

We intend to seek approval to market our product candidates in both the U.S. and in foreign jurisdictions. If we obtain approval in one or more jurisdictions, we will be subject to rules and regulations in those jurisdictions relating to our product candidates. In some countries, particularly in the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product candidate. If reimbursement of our future products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, we may be unable to achieve or sustain profitability.

Risks Related to Our Business Operations

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

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

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

Adverse events in trials or studies conducted by us or other parties, in particular involving the same or similar AAV serotypes to the ones we are using, even if not ultimately attributable to our product candidates or to an AAV serotype that we employ, and resulting publicity, could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates. Similarly, our lead product candidate, ADVM-022 expresses the aflibercept protein, which is also the active ingredient in Eylea. If safety or efficacy issues occur relating to Eylea, even if not ultimately attributable to aflibercept, this may negatively impact our product candidate. If any such adverse events or issues occur, development and commercialization of our product candidates or advancement of any potential clinical trials could be halted or delayed, which would have a material adverse effect on our business and operations.

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

We are dependent on the principal members of our management, clinical and scientific staff. The loss of service of any of our management or clinical or scientific staff could harm our business. In addition, we are dependent on our continued ability to attract, retain and motivate highly qualified additional management, clinical and scientific personnel. If we are not able to retain our management, and to attract, on acceptable terms, additional qualified personnel necessary for the continued development of our business, we may not be able to sustain our operations or grow. Although we have executed employment agreements with each member of our current executive management team, these agreements are terminable at will with or without notice and, therefore, we may not be able to retain their services as expected.

We may not be able to attract or retain qualified management, scientific and clinical personnel in the future due to the intense competition for qualified personnel among biotechnology, pharmaceutical and other businesses, particularly in the San Francisco Bay Area. Our industry has experienced a high rate of turnover of management and scientific personnel in recent years. If we are not able to attract, retain and motivate necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our development objectives, our ability to raise additional capital and our ability to implement our business strategy.

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

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

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

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

In addition to FDA restrictions on the marketing of pharmaceutical products, several other types of state and federal healthcare fraud and abuse laws restrict certain practices, including research and marketing, in the pharmaceutical industry. These laws include anti-kickback, false claims, physician payment transparency and privacy and security laws and regulations. Because of the breadth of these laws and the narrowness of their exceptions and safe harbors, it is possible that some of our business activities could be subject to challenge under one or more of these laws.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce, or in return for, purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. Remuneration has been broadly defined to include anything of value, including cash, improper discounts, and free or reduced-price items and services. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formula managers on the other. Although there are several statutory exceptions and regulatory safe harbors protecting certain common activities from prosecution, the exceptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exception or safe harbor. Many states have similar laws that apply to their state health care programs as well as private payers.

The federal Health Insurance Portability and Accountability Act of 1996 ("HIPAA") created new federal criminal statutes that prohibit among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payers; knowingly and willfully embezzling or stealing from a healthcare benefit program; willfully obstructing a criminal investigation of a healthcare offense; and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. The Affordable Care Act, among other things, amended the intent requirement of the federal Anti-Kickback Statute and certain criminal statutes governing healthcare fraud. A person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it. In addition, the Affordable Care Act provided that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

Additionally, federal false claims laws, including the False Claims Act, and the civil monetary penalty law prohibit knowingly presenting or causing the presentation of a false, fictitious, or fraudulent claim for payment to the U.S. government. Actions under the False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Violations of the False Claims Act can result in significant monetary penalties and treble damages. The federal government is using the False Claims Act, and the accompanying threat of significant liability, in its investigation and prosecution of pharmaceutical and biotechnology companies throughout the country, for example, in connection with the promotion of products for unapproved uses and other sales and marketing practices. The government has obtained multi-million and multi-billion dollar settlements under the False Claims Act in addition to individual criminal convictions under applicable criminal statutes. Given the significant size of actual and potential settlements, it is expected that the government will continue to devote substantial resources to investigating healthcare providers' and manufacturers' compliance with applicable fraud and abuse laws.

In addition, there has been a recent trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The Affordable Care Act, among other things, imposed new reporting requirements on drug manufacturers, under the federal Physician Payments Sunshine Act, for payments made by them to physicians, as defined by such law, and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report such information regarding their relationships with physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists and certified nurse midwives during the previous year. 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, impose restrictions on drug manufacturer marketing practices, require the tracking and reporting of gifts, compensation and other remuneration to physicians and/or require the registration of pharmaceutical sales representatives.

We will need to build and maintain a robust compliance program with different compliance and/or reporting requirements. We cannot ensure that our compliance controls, policies and procedures will be sufficient to protect against acts of our employees, vendors, or other third parties that may violate such laws. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to significant penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs, imprisonment, and additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, any of which could adversely affect our ability to operate our business and our financial results.

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

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

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

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

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

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

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

We and our development partners, third-party manufacturer and suppliers use biological materials and use or may use hazardous materials, and any claims relating to improper handling, storage or disposal of these materials could be time consuming or costly.

We and our development partners, third-party manufacturer and suppliers use or may use hazardous materials, including chemicals and biological agents and compounds that could be dangerous to human health and safety or the environment. Our operations and the operations of our third-party manufacturers and suppliers also produce hazardous waste products. Federal, state and local laws and regulations govern the use, generation, manufacture, storage, handling and disposal of these materials and wastes. Compliance with applicable environmental laws and regulations may be expensive, and current or future environmental laws and regulations may impair our product development efforts. In addition, we cannot entirely eliminate the risk of accidental injury or contamination from these materials or wastes. We do not carry specific biological or hazardous waste insurance coverage, and our property, casualty and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or contamination. Accordingly, in the event of contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We face an inherent risk of product liability as a result of the clinical testing of our product candidates and will face an even greater risk if we commercialize our product candidates. For example, we may be sued if our product candidates allegedly caused or cause injury or are found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product candidate, negligence, strict liability, and a breach of warranties.

Claims could also be asserted under state consumer protection acts.

If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit or cease the commercialization of our product candidates.

Even a successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our product candidates;
- injury to our reputation;
- withdrawal of clinical trial participants;
- costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;

- loss of revenue;
- the inability to commercialize our product candidates; and
- a decline in our stock price.

We currently hold $5.0 million in product liability insurance, which may not adequately cover all liabilities that we may incur. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of our product candidates. Although we plan to maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. Our insurance policies will also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We may have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

We and any of our future development partners will be required to report to regulatory authorities if any of our approved products cause or contribute to adverse medical events, and any failure to do so would result in sanctions that would materially harm our business.

If we and any of our future development partners or CROs are successful in commercializing our products, the FDA and foreign regulatory authorities would require that we and any of our future development partners report certain information about adverse medical events if those products may have caused or contributed to those adverse events. The timing of our obligation to report would be triggered by the date we become aware of the adverse event as well as the nature of the event. We and any of our future development partners may fail to report adverse events we become aware of within the prescribed timeframe. We and any of our future development partners may also fail to appreciate that we have become aware of a reportable adverse event, especially if it is not reported to us as an adverse event or if it is an adverse event that is unexpected or removed in time from the use of our product candidates. If we and any of our future development partners fail to comply with our or their reporting obligations, the FDA or a foreign regulatory authority could take action, including criminal prosecution, the imposition of civil monetary penalties, seizure of the product and delay in approval or clearance of other products.

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

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

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

Business disruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, fires, disease epidemics and other natural or manmade disasters or business interruptions, for which we are predominantly self-insured. In addition, we rely on third-party research facilities, manufacturers and other service providers from other countries and from different parts of the U.S. to provide services and resources necessary to support our research and development plans, to produce our product candidates, and support our clinical trials. Our ability to obtain this necessary support or supplies could be disrupted if the operations of these suppliers or service providers, or national and international supply chains are affected by a man-made or natural disaster or other business interruption, including national or international health concerns. The occurrence of any of these business disruptions, including of our own operations, could seriously harm our operations and financial condition and increase our costs and expenses.

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

The COVID-19 pandemic has caused us to modify our business practices (including adhering to "shelter-in-place" orders, limiting employee travel, and cancelling physical participation in meetings, events and conferences), and we may take further actions that may be required by government authorities or that we determine are in the best interests of our employees, customers and business partners. We are uncertain that such measures will be sufficient to mitigate the risks posed by the virus or otherwise be satisfactory to government authorities and how long we will be required to continue these measures.

Operating under the "shelter-in-place" orders has made it more challenging and time-consuming for us to conduct certain of our operations. The effects of operating under the "shelter-in-place" orders may continue to negatively impact productivity, disrupt our operations and negatively impact our business and financial condition, the magnitude of which will depend, in part, on the length and severity of the restrictions and other limitations on our ability to conduct our business in the ordinary course. For example, restrictions on our financial functions' access to our facilities led to a delay in our ability to prepare, complete and file our Quarterly Report on Form 10-Q for the first quarter of 2020. Separately, an increased reliance by us and the companies with which we do business on information technology systems may increase cyber security risk, create data accessibility issues, increase the risk for communication disruptions, or otherwise disrupt or delay normal business operations.

The COVID-19 pandemic may also affect our current and planned trials and development programs, possibly affecting our timelines for commercialization. Shelter-in-place or equivalent orders and the current general reluctance of people to make in-person visits to healthcare providers for treatment of non-life-threatening ailments may make initiating clinical trial sites, identifying potential patients and enrolling them in our clinical trials, retaining any such patients, ensuring that such patients comply with treatment protocols, and collecting sufficient trial data to progress our clinical programs more difficult. For example, patient concerns related to COVID-19 caused some of our OPTIC trial patients to miss scheduled appointments for fear of contracting the virus which, if this were to be repeated over longer periods of time, could impact our ability to collect data we need.

In addition, due to the limited ability to access our facilities and our reliance on outside vendors who may be similarly affected, our development programs may not proceed along the timelines we previously anticipated. We rely on third-party research facilities, manufacturers, suppliers and other service providers from other countries and from different parts of the U.S. to provide services and resources necessary to support our research and development plans, to produce our product candidates, and support our clinical trials. Our ability to obtain this necessary support or supplies could be disrupted, or the cost of this support or these supplies could increase, if the operations of these suppliers or service providers, or national and international supply chains, including of transportation carriers and transportation hubs, are affected by the COVID-19 pandemic. In addition, if our relationships with our service providers, suppliers or other vendors are terminated or scaled back as a result of the COVID-19 pandemic or other health epidemics, we may not be able to enter into arrangements with alternative service providers, suppliers or other vendors or do so on commercially reasonable terms or in a timely or cost-effective manner. Further, we may be subject to the inability or unwillingness of clinical investigators or patients to follow our research protocols as a result of the recent COVID-19 pandemic. As a result, delays could occur which could adversely impact our ability to meet our desired clinical development and any future commercialization timelines. The COVID-19 pandemic may also affect the operations of the FDA or other health authorities, which could result in delays of reviews and approvals, including with respect to our product candidates.

The spread of COVID-19, which has caused a broad impact globally, may materially affect us economically. While the potential economic impact brought by, and the duration of, COVID-19 may be difficult to assess or predict, the widespread pandemic could result in significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity. In addition, a recession or market correction resulting from the spread of COVID-19 could materially affect our business and the value of our common stock.

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

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

Our employees, independent contractors, principal investigators, CROs, consultants and vendors may engage in misconduct or other improper activities, including noncompliance with our code of conduct or regulatory standards and requirements.

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

Risks Relating to Our Intellectual Property

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

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

We anticipate that licenses to additional third-party technology will be required 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

If we or any of our future development partners were to initiate 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 United States, 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.

Our registered or unregistered trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively, and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could materially and adversely impact our business, financial condition, results of operations, or prospects.

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

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

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

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

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

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

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

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

- others may be able to make gene therapies that are similar to our product candidates but that are not covered by the claims of any patents that we own or have exclusively licensed;
- we or our licensors or future collaborators might not have been the first to make the inventions covered by the issued patent or pending patent application that we own or have exclusively licensed;
- we or our licensors or future collaborators might not have been the first to file patent applications covering certain of our inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- any patent applications that we have filed or may file in the future may not lead to issued patents;
- any of the issued patents that we own or have exclusively licensed may be held invalid or unenforceable, as a result of legal challenges by our competitors;
- any of the issued patents that we have filed or may file in the future may expire before or shortly after commercialization of the covered product;
- our competitors might conduct research and development activities in countries where, or for products for which, we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable; and
- the patents of others may have an adverse effect on our business.

Should any of these events occur, they could significantly harm our business, financial condition, results of operations and prospects.

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

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

Risks Related to Our Common Stock

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

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002 ("Sarbanes-Oxley"), our management is required to report upon the effectiveness of our internal control over financial reporting. Our independent registered public accounting firm is also required to attest to the effectiveness of our internal control over financial reporting, and the related report is required to be included in our annual reports filed with the SEC. Sarbanes-Oxley Section 404 compliance requirements are complex and require significant documentation, testing, and possible remediation. If we or our auditors are unable to conclude that our internal control over financial reporting is effective, investors may lose confidence in our financial reporting, and the trading price of our common stock may decline.

Although we have determined that our internal control over financial reporting was effective as of December 31, 2019, we cannot assure that there will not be material weaknesses in our internal control over financial reporting for this period, following completion of our independent registered public accounting firm's review of our internal control over financial reporting, or in the future. Any failure to maintain internal control over financial reporting could severely inhibit our ability to accurately report our financial condition, results of operations, or cash flows. If we are unable to conclude that our internal control over financial reporting is effective, or if our independent registered public accounting firm determines we have a material weakness in our internal control over financial reporting, we could lose investor confidence in the accuracy and completeness of our financial reports, the market price of our common stock could decline, and we could be subject to sanctions or investigations by The Nasdaq Stock Market, the SEC or other regulatory authorities. Failure to implement and maintain effective internal control over financial reporting, including failure to remediate any material weaknesses we or our auditors identify, could also restrict our future access to the capital markets.

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

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

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

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

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

In the past, we and certain of our former officers were involved in purported securities class action lawsuits, which have since been settled. The purported securities class action lawsuits asserted that the defendants violated the Exchange Act and the Securities Act of 1933, as amended (the "Securities Act"), and alleged that the defendants who are no longer at Adverum made materially false and misleading statements and omitted allegedly material information related to, among other things, the Phase 2a clinical trial for AVA-101, a program which was discontinued in 2015, and the prospects of AVA-101. We settled these lawsuits for $13.0 million, of which $1.0 million we contributed to cover our indemnification obligations to the underwriters, and the remainder was contributed by our insurers. Any future litigation of this type could result in payment of damages or settlement fees and diversion of management's attention and resources, any of which could adversely impact our business. Monitoring and defending against legal actions are time-consuming for our management and detracts from our ability to focus fully on our business activities.

Our quarterly operating results may fluctuate significantly.

We expect our operating results to be subject to quarterly fluctuations. Our net loss and other operating results will be affected by numerous factors, including:

- variations in the level of expenses related to our clinical trial and development programs;
- addition or termination of clinical trials or addition of cohorts to clinical trials;
- any intellectual property infringement lawsuit or other litigation in which we may become involved;
- regulatory developments affecting our product candidates;
- our execution of any collaborative, licensing or similar arrangements and the timing of payments we may make or receive under these arrangements;
- nature and terms of stock-based compensation grants; and
- derivative instruments recorded at fair value.

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

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

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, licensing, collaboration or similar arrangements, grants and debt financings. We do not have any committed external source of funds. As a result, we may from time to time issue additional shares of common stock or securities convertible into or exercisable for shares of our common stock. On August 8, 2019, we filed a universal shelf registration statement on Form S-3 with the SEC that automatically became effective, pursuant to which we registered for sale an undetermined amount of any combination of our common stock, preferred stock, debt securities, warrants, and/or units from time to time and at prices and on terms that we may determine, so long as we continue to satisfy the requirements of a "well-known seasoned issuer" under SEC rules. In February 2020 we sold an aggregate of 10,925,000 shares of our common stock for $140.8 million of net proceeds after deducting underwriting discounts and commissions and estimated offering expenses. In August 2020 we sold an aggregate of 16,675,000 shares of our common stock for $203.4 million of net proceeds after deducting underwriting discounts and commissions and estimated offering expenses. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a holder of our common stock. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends or other distributions. Furthermore, we may issue common stock as consideration in acquisitions. If we issue common stock or securities convertible into common stock, our common stockholders would experience additional dilution and, as a result, our stock price may decline.

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

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

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

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

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

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.

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

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

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

We are a smaller reporting company. For as long as we continue to be a smaller reporting company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not smaller reporting companies, including reduced disclosure obligations regarding executive compensation. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

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

Legislation enacted on December 22, 2017, known as the Tax Cuts & Jobs Act ("TCJA"), significantly revises the Internal Revenue Code of 1986, as amended. The TCJA, as modified by tax provisions in the CARES Act, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, in each case for tax years beginning after 2020, one-time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, creation of a base erosion and anti-abuse tax and modification or repeal of many business deductions and credits. Several aspects of the TCJA remain unclear and may not be clarified for some time. Future guidance from the Internal Revenue Service and other tax authorities with respect to the TCJA may affect us, and certain aspects of the TCJA could be repealed or modified in future legislation, as they were by the CARES Act. Notwithstanding the reduction in the corporate income tax rate, it is possible that the TCJA, the CARES Act, or regulations or interpretations under them, or any other future changes in tax laws, could adversely affect our business and financial condition, and such effect could be material.

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

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

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

As a result, the amount of the NOLs and research and credit carryforwards presented in our financial statements could be limited and may expire unutilized.

Item 2. Unregistered Sales of Equity Securities and Use of Proceeds

None

Item 3. Defaults Upon Senior Securities

None.

Item 4. Mine Safety Disclosures

Not applicable.

Item 5. Other Information

Not applicable

Item 6. Exhibits

EXHIBIT INDEX

EXHIBIT NUMBER	EXHIBIT DESCRIPTION	INCORPORATED BY REFERENCE				PROVIDED HEREWITH
		FILE NUMBER	FORM	DATE	EXHIBIT OR ITEM NUMBER	
3.1	Amended and Restated Certificate of Incorporation.	001-36579	10-K	March 9, 2017	3.1	
3.2	Amended and Restated Bylaws.	001-36579	8-K	June 29, 2020	3.1	
4.1	Reference is made to Exhibits 3.1 through 3.2.					
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 September 30, 2020, 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.

Date: November 5, 2020

ADVERUM BIOTECHNOLOGIES, INC.

By: /s/ Laurent Fischer
Laurent Fischer
Chief Executive Officer
(Principal Executive Officer)

Date: November 5, 2020

By: /s/ Thomas Leung
Thomas Leung
Chief Financial Officer
(Principal Financial and 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: November 5, 2020

By: /s/Laurent Fischer

Name: Laurent Fischer

Title: *Chief Executive Officer*
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION OF THE PRINCIPAL FINANCIAL AND ACCOUNTING OFFICER

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

I, Thomas Leung, certify that:

1. I have reviewed this Form 10-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: November 5, 2020

By: /s/Thomas Leung

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

Exhibit 32.1

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

In connection with the Quarterly Report on Form 10-Q of Adverum Biotechnologies, Inc. for the fiscal quarter ended September 30, 2020 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: November 5, 2020

By: /s/Laurent Fischer
Laurent Fischer
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 September 30, 2020 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Thomas Leung, in his 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 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: November 5, 2020

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