UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 10-Q

(Mark One)

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

For the quarterly period ended March 31, 2018

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.)**

1035 O'Brien Drive,
Menlo Park, CA
(Address of principal executive offices)

94025
(Zip Code)

(650) 272-6269
(Registrant's telephone number, including area code)

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted 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 and post such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or 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. (Check one):

Large accelerated filer	☐	Accelerated filer	☒
Non-accelerated filer	☐ (Do not check if a smaller reporting company)	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 ☒

As of April 30, 2018 there were 62,271,901 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 except share and per share data)

	March 31, 2018	December 31, 2017
	(Unaudited)	
Assets		
Current assets:		
Cash and cash equivalents	$ 152,716	$ 70,519
Short-term investments	94,321	119,966
Prepaid expenses and other current assets	2,161	3,256
Total current assets	249,198	193,741
Property and equipment, net	2,820	3,024
Deposit and other long-term assets	140	140
Intangible asset	5,000	5,000
Total assets	$ 257,158	$ 201,905
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 685	$ 1,731
Accrued expenses and other current liabilities	7,205	6,964
Deferred rent, current portion	138	129
Deferred revenue, current portion	1,246	1,850
Total current liabilities	9,274	10,674
Deferred rent, net of current portion	187	222
Deferred revenue, net of current portion	–	5,250
Deferred tax liability	1,250	1,250
Other noncurrent liabilities	404	481
Total liabilities	11,115	17,877
Commitments and contingencies (Note 6)		
Stockholders' equity:		
Preferred stock, $0.0001 par value, 5,000,000 shares authorized; no shares issued and outstanding	—	—
Common stock, $0.0001 par value, 300,000,000 shares authorized at March 31, 2018 and December 31, 2017; 62,232,372 and 49,015,339 shares issued and outstanding at March 31, 2018 and December 31, 2017, respectively	7	5
Additional paid-in capital	512,173	439,048
Accumulated other comprehensive loss	(1,021)	(963)
Accumulated deficit	(265,116)	(254,062)
Total stockholders' equity	246,043	184,028
Total liabilities and stockholders' equity	$ 257,158	$ 201,905

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)

	Three Months Ended March 31,	
	2018	2017
	(Unaudited)	
Collaboration and license revenue	$ 216	$ 462
Operating expenses:		
Research and development	12,794	9,061
General and administrative	5,368	7,989
Total operating expenses	18,162	17,050
Operating loss	(17,946)	(16,588)
Other income:		
Other income, net	746	489
Total other income, net	746	489
Net loss	$ (17,200)	$ (16,099)
Other comprehensive loss:		
Net unrealized (loss) gain on marketable securities	17	(88)
Foreign currency translation adjustment	(75)	(118)
Comprehensive loss	$ (17,258)	$ (16,305)
Net loss per share attributable to common stockholders-basic and diluted	$ (0.30)	$ (0.38)
Weighted-average common shares outstanding-basic and diluted	57,420	42,144

See accompanying notes to condensed consolidated financial statements

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

	Three Months Ended March 31,	
	2018	2017
	(Unaudited)	
Cash flows from operating activities:		
Net loss	$ (17,200)	$ (16,099)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	459	516
Stock-based compensation expense	3,429	1,896
Other	183	89
Changes in operating assets and liabilities:		
Accounts receivable, net	—	886
Prepaid expenses and other current assets	818	(462)
Accounts payable	(1,046)	1,610
Accrued expenses and other current liabilities	107	229
Deferred revenue	292	(462)
Deferred rent	(26)	(20)
Net cash used in operating activities	(12,984)	(11,817)
Cash flows from investing activities:		
Purchases of marketable securities	(30,374)	(138,591)
Maturities of marketable securities	55,973	—
Purchases of property and equipment	(216)	(263)
Net cash provided by (used in) investing activities	25,383	(138,854)
Cash flows from financing activities:		
Proceeds from offerings of common stock, net of issuance costs	70,191	—
Proceeds from issuance of common stock pursuant to option exercises	308	187
Taxes paid related to net share settlement of restricted stock units	(801)	—
Proceeds from a financing arrangement	100	—
Net cash provided by financing activities	69,798	187
Effect of foreign currency exchange rate on cash and cash equivalents	-	(117)
Net increase (decrease) in cash and cash equivalents	82,197	(150,601)
Cash and cash equivalents at beginning of period	70,519	222,170
Cash and cash equivalents at end of period	$ 152,716	$ 71,569
Supplemental schedule of noncash investing and financing information		
Fixed assets in accounts payable, accrued expenses and other current liabilities	$ 153	$ 413

See accompanying notes to condensed consolidated financial statements.

Notes to Condensed Consolidated Financial Statements
(Unaudited)

1. Organization and Basis of Presentation

Adverum Biotechnologies, Inc. (the "Company") was incorporated in Delaware on July 17, 2006 as Avalanche Biotechnologies, Inc. and changed its name to Adverum Biotechnologies, Inc. on May 11, 2016. The Company is headquartered in Menlo Park, California. The Company is a gene therapy company advancing novel medicines that has the potential to offer life-changing benefits to patients living with serious rare and ocular diseases. Since the Company's inception, it has devoted its efforts principally to performing research and development activities, including conducting preclinical studies and, early clinical trials, filing patent applications, obtaining regulatory agreements, 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 $265.1 million as of March 31, 2018. 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 through at least the end of 2019.

Follow-on Offerings— In February 2018, the Company completed an underwritten public offering for the sale of 10,222,235 shares of its common stock and raised total net proceeds of $64.5 million, after discounts and other issuance costs.

In August 2017, the Company entered into an at-the-market sales agreement with an agent for the sales of its common stock at market price (the "2017 stock offering agreement"). In January 2018, the Company issued and sold a total of 1,419,893 shares of its common stock at market prices under the 2017 stock offering agreement and raised total net proceeds of $5.7 million, after issuance costs. No additional shares were issued and sold under the 2017 stock offering agreement during the three months ended March 31, 2018.

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 months ended March 31, 2018, 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, 2017 is derived from the audited consolidated financial statements at that date but does not include all of the information required by U.S. GAAP for complete consolidated financial statements.

The accompanying unaudited condensed consolidated financial statements and related financial information should be read in conjunction with the audited consolidated financial statements and the related notes thereto included in the Company's Annual Report on Form 10-K for the year ended December 31, 2017 filed with the SEC.

2. Summary of Significant Accounting Policies

Use of Estimates— The accompanying consolidated financial statements have been prepared in accordance with U.S. GAAP. The preparation of the 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 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.

Accounting Standard Updates Recently Adopted

Accounting Standard Update ("ASU") No. 2014-09, Revenue from Contracts with Customers (Topic 606), which supersedes the revenue recognition requirements in ASC 605, Revenue Recognition. Effective January 1, 2018, the Company adopted the new revenue standards under Topic 606 using the modified retrospective approach. Results for reporting periods beginning after January 1, 2018 are presented under Topic 606, while prior period results are not adjusted and continue to be reported in accordance with the revenue standards under Topic 605. Under ASC 606, the Company recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the Company expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that the Company determines are within the scope of ASC 606, the Company performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the Company satisfies a performance obligation. At contract inception, once the contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within each contract and determines those that are performance obligations. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

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

Upon the adoption of Topic 606, the Company recorded a net decrease of $6.1 million to its deferred revenue and opening accumulated deficit as of January 1, 2018 for the cumulative effect of the adoption. The effect of the adoption is summarized for the Company's license and collaboration agreements as follows:

Collaboration Agreement with Regeneron— Under Topic 606, the transaction price at contract inception is $8.0 million related to the non-refundable upfront payment for license and research services. The arrangement also provides for additional payments to the Company when certain development and regulatory milestones are achieved. Since these milestone payments are not within the control of the Company and are not considered probable of being achieved until the events occur, the Company did not include them in the transaction price at contract inception. The transaction price of $8.0 million at contract inception was allocated to two performance obligations. The Company's deferred revenue associated with its Regeneron collaboration agreement as of December 31, 2017 under Topic 605 was $6.5 million. As a result of adopting Topic 606, the Company recorded $6.5 million reduction to its deferred revenue and opening accumulated deficit during the three months ended March 31, 2018 as the performance obligations associated with the Regeneron deferred revenue were satisfied as of January 1, 2018. There was no outstanding deferred revenue associated with Regeneron as of March 31, 2018.

Collaboration Agreement with Editas— Under Topic 606, the transaction price at contract inception is $1.0 million related to the non-refundable upfront payment for license and research services. The arrangement provides for additional payments to the Company when certain development and regulatory milestones are achieved. Since these milestone payments are not within the control of the Company and are not considered probable of being achieved until the events occur, the Company did not include them in the transaction price at contract inception. The transaction price of $1.0 million was allocated to a single performance obligation. The Company's deferred revenue associated with its Editas collaboration agreement as of December 31, 2017 under Topic 605 was $0.5 million. As a result of adopting Topic 606, the Company recorded an increase of $0.4 million to its deferred revenue and opening accumulated deficit during the three months ended March 31, 2018 due to differences in the timing of recognition under Topic 606.

Under Topic 605, the Company's revenue for the three months March 31, 2018 would have been $0.5 million.

Recently-Issued and Not Yet Adopted Accounting Pronouncements

In February 2016, the Financial Accounting Standards Board ("FASB") issued ASU No. 2016-2, Leases, which amends the current guidance on leasing activities to provide more transparency and comparability, and requires that all leases be recognized by lessees on their balance sheet as a right-of-use asset and corresponding lease liability, which are currently accounted for as operating leases. The new standard is effective for fiscal years and interim periods within those fiscal years beginning after December 15, 2018, with early adoption permitted. This ASU will be effective for the Company in the first quarter of 2019 and must be adopted using a modified retrospective transition approach. The Company is currently evaluating the impact of the adoption of this standard on its consolidated financial statements and related disclosures.

3. Fair Value Measurements and Fair Value of Financial Instruments

The authoritative guidance on the fair value hierarchy for disclosure of fair value measurements is as follows:

Level 1: Quoted prices in active markets for identical assets or liabilities.

Level 2: Observable inputs other than Level 1 prices, such as quoted prices for similar assets or liabilities, quoted prices in markets that are not active, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

Level 3: Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

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 as of March 31, 2018:

	March 31, 2018			
	Amortized Cost Basis	Unrealized Gains	Unrealized Loses	Estimated Fair Value
	(In thousands)			
Level 1:				
Money market funds	$ 59	$ —	$ —	$ 59
Level 2:				
U.S. government and agency securities	38,278	—	(135)	38,143
Commercial paper	159,844	—	—	159,844
Corporate bonds	32,797	—	(30)	32,767
Certificates of deposit	7,836	—	—	7,836
Total cash equivalents and short-term investments	238,814	—	(165)	238,649
Less: cash equivalents	(144,329)	—	1	(144,328)
Total short-term investments	$ 94,485	$ —	$ (164)	$ 94,321

The following is a summary of the Company's cash equivalents and short-term investments as of December 31, 2017:

	December 31, 2017			
	Amortized Cost Basis	Unrealized Gains	Unrealized Loses	Estimated Fair Value
	(In thousands)			
Level 1:				
Money market funds	$ 65	$ —	$ —	$ 65
Level 2:				
U.S. government and agency securities	58,351	—	(145)	58,206
Commercial paper	71,427	—	—	71,427
Corporate bonds	38,354	1	(38)	38,317
Certificates of deposit	9,731	—	—	9,731
Total cash equivalents and short-term investments	177,928	1	(183)	177,746
Less: cash equivalents	(57,780)	—	—	(57,780)
Total short-term investments	$ 120,148	$ 1	$ (183)	$ 119,966

As of March 31, 2018 and December 31, 2017, the fair value of the Company's financing liability related to The Alpha-1 Project, Inc. (the "TAP financing"), which is classified within Level 3 in the fair value hierarchy, was $0.2 million. The Company elected the fair value option to account for this financing arrangement. The fair value of the financing arrangement was determined based on the expected value approach and is classified as Level 3 within the fair value hierarchy. The key unobservable inputs in the valuation model include timing of milestones, probability of achievement of development and commercial milestones, and a discount factor.

There were no transfers within the hierarchy during the three months ended March 31, 2018.

The Company's marketable securities as of March 31, 2018 mature within one year. Management regularly reviews all of the Company's investments for other-than-temporary declines in estimated fair value. Management's review includes the consideration of the cause of the impairment, including the creditworthiness of the security issuers, the number of securities in an unrealized loss position, the severity and duration of the unrealized losses, whether management has the intent to sell the securities and whether it is more likely than not that the Company will be required to sell the securities before the recovery of their amortized cost basis. Management determined that the gross unrealized losses of $0.2 million on the Company's marketable securities as of March 31, 2018 were temporary in nature. Therefore, none of the Company's marketable securities were other-than-temporarily impaired as of March 31, 2018.

4. Significant Agreements

Editas— In January 2018, the Company entered into an agreement to amend its collaboration, option and license agreement with Editas. The Company originally entered into an agreement with Editas in August 2016 pursuant to which the Company and Editas collaborate on certain studies using AAV vectors in connection with Editas' genome editing technology and the Company grants to Editas an exclusive option to obtain certain exclusive rights to use the Company's proprietary vectors in up to five ophthalmic indications. In January 2018, the Company and Editas extended the research collaboration, option and license agreement. In consideration for extending the agreement, Editas made a one-time, non-refundable cash payment of $0.5 million to the Company in February 2018.

Under the terms of the agreement, as amended, Editas may exercise the option with respect to a designated initial indication until September 30, 2018. With respect to the four other indications, Editas may exercise the option until the fourth anniversary of the effective date, provided that the option will expire on the third anniversary of the effective date if Editas has not exercised the option with respect to the initial indication or any other indication by such date. Upon Editas' timely exercise of the option with respect to the designated initial indication, Editas will pay the Company a $1.3 million fee. For the first additional indication for which Editas timely exercises its option, Editas will pay the Company a $1.5 million fee. Upon each subsequent exercise of the option, Editas will pay the Company a $1.0 million fee per Indication. If Editas elects to develop a product using certain of the Company's proprietary vectors, the Company will be eligible to receive up to $15.5 million in development and commercialization milestone payments for such product, and tiered royalties between the mid-single digits and low teens on net sales of such product, subject to certain adjustments.

Unless earlier terminated, the agreement will be in effect until the later of the expiration of the option exercise period or the expiration of the royalty term of the last product. At any time after the option is first exercised, Editas may terminate the agreement for convenience in its entirety or on an indication-by indication or country-by-country basis, upon prior written notice to the Company. The Company may also terminate the agreement if Editas challenges the Company's patents relating to its proprietary vectors and does not withdraw such challenge within a defined period of time. In addition, either party may terminate the agreement with written notice upon a bankruptcy of the other party or upon an uncured material breach by the other party.

Under Topic 606, the transaction price is $1.5 million related to the $1.0 million non-refundable upfront payment for license and research services at contract inception and the one-time, non-refundable cash payment of $0.5 million made by Editas in February 2018 in consideration for extending the agreement. The arrangement provides for additional payments to the Company when certain development and regulatory milestones are achieved. Since these milestone payments are not within the control of the Company and are not considered probable of being achieved until the events occur, the Company did not include them in the transaction price. The transaction price of $1.5 million was allocated to a single performance obligation, research and development.

During the three months ended March 31, 2018, the Company recognized revenue of $0.2 million associated with Editas. The Company's deferred revenue balance of $1.2 million as of March 31, 2018 was associated with Editas and is expected to be recognized over a period of six months as the research and development services are performed.

5. Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consist of the following:

	March 31, 2018	December 31, 2017
	(In thousands)	
Employee compensation	$ 1,769	$ 2,259
Accrued preclinical costs	1,337	1,255
Accrued professional services	2,696	2,295
Accrued clinical and process development costs	826	910
Other	577	245
Total accrued expenses and other current liabilities	$ 7,205	$ 6,964

6. Commitments and Contingencies

Guarantees and Indemnifications

In the normal course of business, the Company enters into contracts and agreements that contain a variety of representations and warranties and provide for indemnification for certain liabilities. The exposure under these agreements is unknown because it involves claims that may be made against the Company in the future but have not yet been made. Other than the obligations connected with the shareholder litigation described below, the Company has not paid any claims or been required to defend any action related to its indemnification obligations. However, the Company may record charges in the future as a result of these indemnification obligations. The Company also has indemnification obligations to its past and current directors and executive officers for specified events or occurrences, subject to some limits, while they were or are serving at the Company's request in such capacities. Other than the obligations connected with the shareholder litigation described below, there have been no claims to date and the Company has not recorded any liabilities for these agreements as of March 31, 2018.

Legal Proceedings

From time to time, the Company may become involved in litigation and other legal actions. The Company estimates the range of liability related to any pending litigation where the amount and range of loss can be estimated. The Company records its best estimate of a loss when the loss is considered probable. Where a liability is probable and there is a range of estimated loss with no best estimate in the range, the Company records a charge equal to at least the minimum estimated liability for a loss contingency when both of the following conditions are met: (i) information available prior to issuance of the financial statements indicates that it is probable that a liability had been incurred at the date of the financial statements and (ii) the range of loss can be reasonably estimated.

In July 2015, three securities class action lawsuits were filed against the Company and certain of its officers in the United States District Court for the Northern District of California ("U.S. District Court"), each on behalf of a purported class of investors who acquired the Company's publicly traded securities between July 31, 2014 and June 15, 2015. The lawsuits asserted claims under the Securities Exchange Act of 1934, as amended (the "Exchange Act") and Securities Act of 1933, as amended (the "Securities Act") and alleged that the defendants 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 product candidate which is no longer being developed, and the prospects of AVA-101. The complaints sought unspecified damages, attorneys' fees and other costs.

In December 2015, a putative securities class action lawsuit was filed against the Company, the Company's board of directors, underwriters of the Company's January 13, 2015, follow-on public stock offering, and two of the Company's institutional stockholders, in the Superior Court of the State of California for the County of San Mateo ("San Mateo Superior Court"). The complaint alleged that, in connection with the Company's follow-on stock offering, the defendants violated the Securities Act by allegedly making materially false and misleading statements and by allegedly omitting material information related to the Phase 2a clinical trial for AVA- 101 and the prospects of AVA-101. The complaint also sought unspecified damages, attorneys' fees and other costs.

On March 16, 2017, the Company agreed to settle the actions and the settlements are now final. The total settlement amount paid was $13.0 million, of which $1.0 million was contributed by the Company to cover its indemnification obligations to the underwriters. The Company's insurers paid the remainder. The Company and the defendants have denied and continue to deny the claims alleged in the actions, and the settlement does not assign or reflect any admission of fault, wrongdoing or liability as to any defendant. Notice of the settlement was provided to shareholders in the fall of 2017, and no shareholder objected to the settlement. On January 19, 2018, the San Mateo Superior Court entered a judgment and order finally approving the settlement. And on February 5, 2018, the U.S. District Court entered an order dismissing the consolidated federal action with prejudice. The Company recorded $1.0 million as general and administrative expense during the three months ended March 31, 2017, when the amount and time of settlement became estimable and probable.

7. Equity Incentive Awards

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

	Number of Options (in thousands)	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Life (in years)	Aggregate Intrinsic Value (in thousands)
Balance at December 31, 2017	6,695	$ 4.51		
Options granted	1,364	6.40		
Options exercised	(1,362)	0.23		
Options cancelled	(14)	37.42		
Balance at March 31, 2018	6,683	$ 5.70	8.2	$ 13,710
Exercisable as of March 31, 2018	2,324	$ 7.44	7.0	$ 5,497

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	Weighted-Average Remaining Contractual Term (in years)
Outstanding at December 31, 2017	2,515	$ 3.24	1.6
Granted	672	6.19	
Vested and released	(329)	3.19	
Forfeited	(181)	4.49	
Outstanding at March 31, 2018	2,677	$ 3.90	1.8

Stock-Based Compensation Expense

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

	Three Months Ended March 31,	
	2018	2017
	(In thousands)	
Research and development	$ 2,378	$ 1,242
General and administrative	1,051	654
Total stock-based compensation expense	$ 3,429	$ 1,896

8. Net Loss per Share

Basic net loss per share is calculated by dividing the net loss by the weighted-average number of shares of common stock outstanding for the period. Diluted net loss per share is computed by giving effect to all potential dilutive common stock equivalents outstanding for the period using the treasury stock method. Outstanding stock options, RSUs, 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 Company excluded approximately 9.5 million and 9.9 million shares of potentially dilutive securities as of March 31, 2018 and 2017, respectively, from the computations of diluted weighted-shares outstanding because their effect would be anti-dilutive.

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

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, 2017, 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 6, 2018. 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). These forward-looking statements are subject to risks and uncertainties, including those discussed in the section titled "Risk Factors," set forth in Part II – Other Information, Item 1A below and elsewhere in this report that could cause actual results to differ materially from historical results or anticipated results.

Overview

Adverum is a clinical-stage gene therapy company targeting unmet medical needs in serious rare and ocular diseases. Leveraging our next-generation adeno-associated virus ("AAV")-based directed evolution platform, we generate gene therapy product candidates designed to provide durable efficacy by inducing sustained expression of a therapeutic protein. Our core capabilities include clinical development, novel vector discovery and in-house manufacturing expertise, specifically in process development, assay development, and current Good Manufacturing Practices ("cGMP") quality control. Our leadership team has significant drug development and gene therapy expertise.

We are advancing our robust pipeline of gene therapy candidates designed to treat rare diseases alpha-1 antitrypsin ("A1AT") deficiency and hereditary angioedema ("HAE") as well as in wet age-related macular degeneration ("wAMD").

For the treatment of A1AT deficiency, we are advancing our gene therapy product candidate ADVM-043, AAVrh.10-A1AT, in an ongoing Phase 1/2 clinical trial (the "ADVANCE trial"). The ADVANCE trial is a multi-center, open-label, dose-escalation study. The study will include up to 20 patients across four planned dosing cohorts of up to five patients each. Cohort 1, two patients were dosed and were evaluated following a single intravenous (administration of ADVM-043 at a dose of ~1E12 vg/kg (8E13 total vg). Based on a review of the preliminary safety data, in February 2018 the independent data monitoring committee ("DMC") recommended proceeding to Cohort 2. In Cohort 2, we dosed the first patient in late April 2018 with a dose of ~5E12 vg/kg (4E14 total vg) of ADVM-043 and we continue to enroll patients. Per protocol, patients being treated with standard-of-care weekly IV infusions of A1AT protein are required to wash out for at least two months prior to receiving ADVM-043. The primary endpoint in the ADVANCE trial is safety and tolerability, and secondary endpoints include changes in plasma concentrations of both total and M-specific A1AT levels. We expect to report preliminary data from this trial in the second half of 2018. We plan to use this data to inform next steps, including potential further dose escalation. Further details about the study can be found at ClinicalTrials.gov under trial identifier number NCT02168686.

ADVM-043 is designed as a potential single-administration treatment to induce stable, long-term A1AT protein levels, or expression. In a preclinical proof-of-concept study, ADVM-043 demonstrated robust protein expression above therapeutic levels in mice following either IV or intrapleural ("IP") administration. In another study in non-human primates, evidence of stable long-term expression of hA1AT was observed out to one year following IP administration of ADVM-043.

For treatment of the rare disease HAE, we are advancing our gene therapy product candidate ADVM-053, AAVrh.10-C1EI. ADVM-053 is designed as a potential single-administration treatment to provide sustained levels of the C1 esterase inhibitor ("C1EI") protein to eliminate protein concentration variability and prevent breakthrough angioedema attacks. In preclinical studies, a single IV administration of ADVM-053 increased C1EI protein expression above therapeutic levels and decreased vascular permeability in a mouse model of HAE. We plan to submit an Investigational New Drug ("IND") application for ADVM-053 for HAE with the U.S. Food and Drug Administration ("FDA") in the second half of 2018.

For wAMD, we are advancing our gene therapy product candidate ADVM-022, AAV.7m8-aflibercept. ADVM-022 utilizes a proprietary vector capsid (AAV.7m8) carrying an aflibercept coding sequence under the control of a proprietary expression cassette and is administered as a single intravitreal injection. VEGF overexpression can lead to wAMD progression and vision loss. Treatment with ADVM-022 is designed to minimize the burden of frequent anti-VEGF injections, the current standard-of-care treatment for wAMD. We plan to submit an IND Application for ADVM-022 in subjects with wAMD with the FDA in the second half of 2018.

In May 2018, we announced long-term preclinical efficacy data on ADVM-022 in non-human primate models of wAMD. In this preclinical study, the efficacy of ADVM-022 at 13 months post-administration was consistent with earlier reported data, demonstrating that single intravitreal injection of ADVM-022 was found to be safe and statistically significant ($p<0.0001$) in preventing the development of Grade IV lesions compared to the untreated vehicle control group. ADVM-022 induced long-term efficacy that was comparable to aflibercept, an anti-Vascular Endothelial Growth Factor ("VEGF") standard-of-care therapy. ADVM-022 was well-tolerated, with no serious adverse events. These data will be presented in a poster session on May 17, 2018 at the American Society of Gene & Cell Therapy 21st Annual Meeting.

Our earlier-stage research programs include gene therapy product candidates targeting cardiomyopathy associated with Friedreich's ataxia ("FA") and severe allergy.

Our partnered programs include vectors we are developing under collaboration agreements. Under an agreement with Editas Medicine, Inc. ("Editas") we are leveraging our AAV-vectors for use with Editas' leading Clustered Regularly Interspaced Short Palindromic Repeats ("CRISPR")-based genome editing technologies to treat up to five inherited retinal diseases. Our agreement with Regeneron Pharmaceuticals, Inc. ("Regeneron") provides for development of up to eight distinct ocular therapeutic targets, four of which are already identified, including AVA-311 for the treatment of juvenile X-Linked Retinoschisis ("XLRS").

Financial Overview

Summary

We have not generated positive cash flow or net income from operations since our inception and, as of March 31, 2018, we had an accumulated deficit of $265.1 million. We expect to incur substantial expenses and increasing losses from operations in the foreseeable future as we continue our research and development efforts, advance our product candidates through preclinical and clinical development, manufacture clinical study materials, seek regulatory approval, and prepare for and, if approved, proceed to commercialization. We are at an early stage of development and may never be successful in developing or commercializing our product candidates.

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

We entered into our collaboration and license arrangements with Regeneron in May 2014 and Editas in August 2016, which are revenue-generating arrangements. We have no clinical or commercial manufacturing facilities, and all of our clinical manufacturing activities are contracted out to third parties. Additionally, we use third-party clinical research organizations ("CROs") to carry out our clinical development and we do not have a sales organization.

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

As of March 31, 2018, we had $247.0 million in cash, cash equivalents and short-term investments. We believe that we have sufficient funds to continue our operations through at least the end of 2019.

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

In August 2017, we entered into an at-the-market sales agreement with an agent for the sales of our common stock at market price (the "2017 stock offering agreement"). Under the terms and conditions of the 2017 stock offering agreement, we may offer to sell our common stock for an aggregate offering price of up to $50.0 million through the agent from time to time. In January 2018, we sold a total of 1,419,893 shares of our common stock at market prices under the 2017 stock offering agreement and raised total net proceeds of $5.7 million, after issuance costs. No additional shares were issued and sold under the 2017 stock offering agreement during the three months ended March 31, 2018. We have sold a total of 6,550,232 shares of our common stock at market prices pursuant to the 2017 stock offering agreement and raised total net proceeds of $22.5 million, after issuance costs.

Revenue

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

Effective January 1, 2018, we adopted accounting Standard Update ("ASU") No. 2014-09, Revenue from Contracts with Customers (Topic 606) using the modified retrospective approach. Our collaboration agreements with Regeneron and Editas were impacted by the adoption of the new revenue standards under Topic 606. Results for reporting periods beginning after January 1, 2018 are presented under Topic 606, while prior period results are not adjusted and continue to be reported in accordance with the revenue standards under Topic 605.

Upon adoption of Topic 606, we recorded a net decrease of $6.1 million to our deferred revenue and opening accumulated deficit as of January 1, 2018 for the cumulative effect of the adoption. The effect of the adoption is summarized for our license and collaboration agreements as follows:

Collaboration Agreement with Regeneron— Under Topic 606, the transaction price at contract inception is $8.0 million related to the non-refundable upfront payment for license and research services. The arrangement also provides for additional payments to us when certain development and regulatory milestones are achieved. Since these milestone payments are not within our control and are not considered probable of being achieved until the events occur, we did not include them in the transaction price at contract inception. The transaction price of $8.0 million at contract inception was allocated to two performance obligations. Our deferred revenue associated with Regeneron collaboration agreement as of December 31, 2017 under Topic 605 was $6.5 million. As a result of adopting Topic 606, we recorded $6.5 million reduction to our deferred revenue and opening accumulated deficit during the three months ended March 31, 2018 as the performance obligations associated with the Regeneron deferred revenue were satisfied as of January 1, 2018.

Collaboration Agreement with Editas— Under Topic 606, the transaction price is $1.5 million related to the $1.0 million non-refundable upfront payment for license and research services at contract inception and the one-time, non-refundable cash payment of $0.5 million made by Editas in February 2018 in consideration for extending the agreement. The arrangement provides for additional payments to us when certain development and regulatory milestones are achieved. Since these milestone payments are not within our control and are not considered probable of being achieved until the events occur, we did not include them in the transaction price. The transaction price of $1.5 million was allocated to a single performance obligation, research and development. Our deferred revenue associated with Editas collaboration agreement as of December 31, 2017 under Topic 605 was $0.5 million. As a result of adopting Topic 606, we recorded an increase of $0.4 million to our deferred revenue and opening accumulated deficit during the three months ended March 31, 2018 due to differences in the timing of recognition under Topic 606.

During the three months ended March 31, 2018, we recognized revenue of $0.2 million associated with Editas. Our deferred revenue balance of $1.2 million as of March 31, 2018 was associated with Editas and is expected to be recognized over a period of six months as the research and development services are performed.

Under Topic 605, our revenue for the three months March 31, 2018 would have been $0.5 million.

Research and Development Expenses

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

Research and development costs are expensed as incurred. Advance payments for goods or services for future research and development activities are deferred and expensed as the goods are delivered or the related services are performed.

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

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

We received refundable tax credits from the Australian and French tax authorities in connection with certain research costs incurred by our subsidiary conducting research in Australia and France. These refunds do not depend on our taxable income or tax position and therefore we do not account for them under an income tax accounting model. We recognize such refunds as government grants in the period when qualified expenses are incurred as a reduction of research expenses. We have recorded the reimbursement from the Australian and French tax authorities as a reduction of research and development expense in the consolidated statements of operations and comprehensive loss for the applicable period. During the years ended December 31, 2017, 2016 and 2015, tax credits received were immaterial.

General and Administrative Expenses

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

investment in conjunction with our ongoing consideration of our pipeline of product candidates. We anticipate increased expenses related to audit, legal and regulatory functions, as well as director and officer insurance premiums and investor relations costs associated with being a public reporting company.

Other Income (Expense), Net

Other income (expense), net primarily consists of interest income on our cash equivalents and 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. generally accepted accounting principles ("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. Our significant accounting policies are more fully described in Note 2 to our audited consolidated financial statements contained in our Annual Report on Form 10-K (Annual Report) as filed with the SEC, on March 6, 2018.

Results of Operations

Comparison of the Three Months Ended March 31, 2018 and 2017

	Three Months Ended March 31,		
	2018	2017	Change
	(In thousands)		
Collaboration and license revenue	$ 216	$ 462	$ (246)
Operating expenses:			
Research and development	12,794	9,061	3,733
General and administrative	5,368	7,989	(2,621)
Total operating expenses	18,162	17,050	1,112
Operating loss	(17,946)	(16,588)	(1,358)
Other income, net	746	489	257
Net loss	$ (17,200)	$ (16,099)	$ (1,101)

Revenue

Our revenue for the three months ended March 31, 2018 was related to research services provided to Editas under our collaboration agreement with Editas while our revenue for the three months ended March 31, 2017 was related to license and research services under our collaboration agreements with Regeneron and Editas. Our collaboration revenue for the three months ended March 31, 2018 was recognized under Topic 606, which we adopted effective January 1, 2018. We recognized our collaboration revenue for the three months ended March 31, 2017 under Topic 605. Under Topic 605, our revenue for the three months March 31, 2018 would have been $0.5 million

Research and Development Expense

Research and development expense increased to $12.8 million for the three months ended March 31, 2018, from $9.1 million for the three months ended March 31, 2017. This increase was primarily due to an overall increase in research and development activity, including $2.0 million of higher compensation and benefits, including $1.1 million of higher stock-based compensation expense, and $1.5 million of higher material production related to our wAMD and HAE programs to support our plans to advance these programs to clinical 1/2. Higher stock-based compensation expense was primarily due to a higher stock-based compensation charge related to a non-employee stock award, which is calculated based on the then-current fair value at each measurement date using accelerated attribution method, or commonly referred to as mark-to-market method.

For the periods presented, our research and development activities are primarily for our A1AT deficiency, wAMD and HAE programs and earlier-stage research programs. We expect that research and development expenses will increase in future periods as we continue to invest in our three lead gene therapy programs and earlier-stage research programs.

General and Administrative Expense

General and administrative expense decreased to $5.4 million for the three months ended March 31, 2018, from $8.0 million for the three months ended March 31, 2017. The decrease in general and administrative expense was primarily due to one-time charges related to the termination costs associated with our master services agreement with Cornell and the settlements of litigation during the three months ended March 31, 2017.

We expect general and administrative expenses to increase in future periods to support continued research and development initiatives of our product candidates. We will continue to assess such expenses as we advance our three lead gene therapy programs and earlier-stage research programs.

Other Income, Net

The increase in other income, net was primarily due to higher interest income from our investments in marketable securities and gain on marketable securities as we invested in higher yield securities, as well as we invested the net proceeds the sales of our common stock pursuant to the 2017 stock offering agreement and from our February 2018 underwritten public offering of our common stock in marketable securities.

Liquidity and Capital Resources and Plan of Operations

We have not generated positive cash flow or net income from operations since our inception and as of March 31, 2018, we had an accumulated deficit of $265.1 million. As of March 31, 2018, we had $247.0 million in cash, cash equivalents and short-term investments compared to $190.5 million as of December 31, 2017. We believe that our existing cash and cash equivalents as of March 31, 2018 will be sufficient to fund our operations through at least the end of 2019.

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

In August 2017, we entered into the 2017 stock offering agreement. Under the terms and conditions of the 2017 stock offering agreement, we may offer to sell our common stock for an aggregate offering price of up to $50.0 million through the agent from time to time. In January 2018, we sold a total of 1,419,893 shares of our common stock at market prices under the 2017 stock offering agreement and raised total net proceeds of $5.7 million, after issuance costs. No additional shares were issued and sold under the 2017 stock offering agreement during the three months ended March 31, 2018. We have sold a total of 6,550,232 million shares of our common stock at market prices pursuant to the 2017 stock offering agreement and raised total net proceeds of $22.5 million, after issuance costs.

We expect to incur substantial expenditures in the foreseeable future for the development and potential commercialization of our product candidates and ongoing internal research and development programs. At this time, we cannot reasonably estimate the nature, timing or aggregate amount of such costs. 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 Food and Drug Administration (FDA) and other regulatory authorities, including the potential for the FDA and other regulatory authorities to require that we perform more studies than those that we currently expect;
- the ability of our product candidates to progress through clinical development activities successfully;
- our need to expand our research and development activities;
- the rate of progress and cost of our commercialization of our products;
- the cost of preparing to manufacture our products on a larger scale;
- the costs of commercialization activities including product sales, marketing, manufacturing and distribution;
- the degree and rate of market acceptance of any products launched by us or future partners;
- the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights;
- our need to implement additional infrastructure and internal systems;
- our ability to hire additional personnel;

- our ability to enter into additional collaboration, licensing, commercialization or other arrangements and the terms and timing of such arrangements, and;
- the emergence of competing technologies or other adverse market developments.

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

Cash Flows

	Three Months Ended March 31,	
	2018	2017
	(in thousands)	
Net cash used in operating activities	$ (12,984)	$ (11,817)
Net cash provided by (used in) investing activities	25,383	(138,854)
Net cash provided by financing activities	69,798	187
Effect of foreign currency exchange rate	—	(117)
Net increase in cash and cash equivalents	$ 82,197	$ (150,601)

Cash Used in Operating Activities

During the three months ended March 31, 2018, net cash used in operating activities was primarily as a result of the net loss of $17.2 million, partially offset by $4.1 million of non-cash charges mainly related to stock-based compensation expense and depreciation and amortization expense and $0.1 million of net increase in operating assets and liabilities.

During the three months ended March 31, 2017, net cash used in operating activities was primarily as a result of the net loss of $16.1 million, partially offset by $2.5 million of non-cash charges related to stock-based compensation expense and depreciation and amortization expense and $1.8 million of net increase in operating assets and liabilities.

Ca***sh Provided by (Used in) Investing Activities***

Net cash provided by investing activities for the three months ended March 31, 2018 consisted of $56.0 million maturities of marketable securities, partially offset by $30.4 million of purchases of marketable securities and $0.2 million of purchases of property and equipment.

Net cash used investing activities for the three months ended March 31, 2017, was primarily due to purchases of marketable securities.

Purchases of property and equipment primarily consisted of the acquisition of laboratory equipment to support our research and development activities.

Cash Provided by Financing Activities

The net cash provided by financing activities for three months ended March 31, 2018 consisted of $70.2 million of the net proceeds from the sales of our common stock, $0.3 million of the proceeds from the exercises of stock options and $0.1 million of the proceeds from our financing arrangement with the Alpha-1 Project, Inc., partially offset by $0.8 million in taxes paid relating to net share settlement of restricted stock units.

The net cash provided by financing activities for three months ended March 31, 2017 of $0.2 million was the proceeds from the exercises of stock options.

Contractual Obligations and Commitments

We have lease obligations consisting of an operating lease for our operating facility that expires in 2020. Additionally, we have contractual obligations to vendors.

Our contractual obligations and commitments have not changed materially from those described in our Annual Report on Form 10-K for the year ended December 31, 2017.

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

There were not material changes to our exposure to market risk during the three months ended March 31, 2018. For additional information regarding market risk, refer to the *Qualitative and Quantitative Disclosures About Market Risk* section of our Annual Report on Form 10-K.

Item 4. Controls and Procedures

Evaluation of disclosure controls and procedures. Management, including Leone Patterson, our Chief Financial Officer and Interim President and Chief Executive Officer, who is currently serving as both our principal executive officer and our principal financial officer, evaluated the effectiveness of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, as of March 31, 2018. 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. This type of evaluation is done quarterly so that our conclusions concerning the effectiveness of these controls can be reported in our periodic reports filed with the SEC. The overall goals of these evaluation activities are to monitor our disclosure controls and procedures and to make modifications as necessary. We intend to maintain these disclosure controls and procedures, modifying them as circumstances warrant.

Based on that evaluation, Ms. Patterson concluded that, as of March 31, 2018, 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 v principal executive officer and our principal 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 March 31, 2018 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Inherent Limitations on Controls and Procedures

Our management, including the Principal Executive Officer and the Principal Financial Officer, does not expect that our disclosure controls and procedures and our internal controls will prevent all error and all fraud. A control system, no matter how well designed and operated, can only provide reasonable assurances that the objectives of the control system are met. The design of a control system reflects resource constraints; the benefits of controls must be considered relative to their costs. Because there are inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within Adverum have been or will be detected. As these inherent limitations are known features of the financial reporting process, it is possible to design into the process safeguards to reduce, though not eliminate, these risks. These inherent limitations include the realities that judgments in decision-making can be faulty and that breakdowns occur because of simple error or mistake. Controls can be circumvented by the individual acts of some persons, by collusion of two or more people, or by management override of the control. The design of any system of controls is based in part upon certain assumptions about the likelihood of future events. While our disclosure controls and procedures are designed to provide reasonable assurance of achieving their objectives, there can be no assurance that any design will succeed in achieving its stated goals under all future conditions. Over time, controls may become inadequate because of changes in conditions or deterioration in the degree of compliance with the policies or procedures. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

We intend to review and evaluate the design and effectiveness of our disclosure controls and procedures on an ongoing basis, to improve our controls and procedures over time and to correct any deficiencies that we may discover in the future. While our Principal Executive Officer and Principal Financial Officer have concluded that, as of March 31, 2018, the design of our disclosure controls and procedures, as defined in Rule 13a-15(e) under the Exchange Act, was effective, future events affecting our business may cause us to significantly modify our disclosure controls and procedures.

PART II – OTHER INFORMATION

Item 1. Legal Proceedings

In July 2015, three securities class action lawsuits were filed against us and certain of our officers in the United States District Court for the Northern District of California ("U.S. District Court"), each on behalf of a purported class of investors who acquired our publicly traded securities between July 31, 2014 and June 15, 2015. The lawsuits asserted claims under the Securities Exchange Act of 1934, as amended (the "Exchange Act") and Securities Act of 1933, as amended (the "Securities Act") and alleged that the defendants 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 product candidate which is no longer being developed, and the prospects of AVA-101. The complaints sought unspecified damages, attorneys' fees and other costs. In December 2015, a putative securities class action lawsuit was filed against us, our board of directors, underwriters of our January 13, 2015, follow-on public stock offering, and two of our institutional stockholders, in the Superior Court of the State of California for the County of San Mateo ("San Mateo Superior Court"). The complaint alleged that, in connection with our follow-on stock offering, the defendants violated the Securities Act by allegedly making materially false and misleading statements and by allegedly omitting material information related to the Phase 2a clinical trial for AVA- 101 and the prospects of AVA-101. The complaint also sought unspecified damages, attorneys' fees and other costs.

On March 16, 2017, we agreed to settle the actions and the settlements are now final. The total settlement amount paid was $13.0 million, of which $1.0 million was contributed by us to cover our indemnification obligations to the underwriters. Our insurers paid the remainder. We and the defendants have denied and continue to deny the claims alleged in the actions, and the settlement does not assign or reflect any admission of fault, wrongdoing or liability as to any defendant. Notice of the settlement was provided to shareholders in the fall of 2017, and no shareholder objected to the settlement. On January 19, 2018, the San Mateo Superior Court entered a judgment and order finally approving the settlement. And on February 5, 2018, the U.S. District Court entered an order dismissing the consolidated federal action with prejudice.

Item 1A. Risk Factors

Risks facing our business have not changed substantively from those discussed in our Annual Report on Form 10-K for the year ended December 31, 2017, except for those risk factors below designated by an asterisk (*). 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 the Company. Risks and uncertainties not currently known to us or that we currently deem to be immaterial also may materially adversely affect our business, financial condition, results of operations and prospects.

Risks Related to Our Financial Position and Need for Capital

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

We have incurred significant operating losses since we were founded in 2006 and expect to incur significant losses for the foreseeable future as we continue development of our product candidates. As of March 31, 2018, we had an accumulated deficit of $265.1 million. Losses have resulted principally from costs incurred in our clinical trials for our prior wAMD product candidate, AVA-101, research and development programs and from our general and administrative expenses. In the future, we intend to continue to conduct research and development, clinical testing, 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 and cash equivalents will be sufficient to fund our lead gene therapy programs through at least the end of 2019. If this expectation proves to be wrong, we may be forced to delay, limit or terminate certain of our development efforts.

As of March 31, 2018, our cash, cash equivalents and short-term investments were approximately $247.0 million. We currently expect this cash, cash equivalents and short-term investments to fund our planned operations through at least the end of 2019. 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 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 lead 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 of our product candidates would cause an increase in our spending levels, as would other corporate activities. The amount and timing of any expenditure needed to implement our development and commercialization programs will depend on numerous factors, including:

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

We 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 ADVM-043, ADVM-053, and ADVM-022, our lead product candidates. If we are unable to develop, obtain regulatory approval for, or successfully commercialize, any or all of our lead product candidates, our business will be materially harmed.

Our lead product candidates are in the early stages of development and will require substantial clinical development and testing, manufacturing process improvement and validation, bridging studies and regulatory approval prior to commercialization. We are conducting the ADVANCE trial in patients with A1AT deficiency and we are continuing pre-clinical development of our other lead product candidates to support planned IND application submissions in the second half of 2018. It is critical to our business to successfully develop and ultimately obtain regulatory approval for one or more of these lead 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 lead product candidates;
- receipt of marketing approvals for any future products for which we complete clinical trials, including securing regulatory exclusivity to the extent available;
- establishing commercial manufacturing capabilities, for example, by engaging third-party manufacturers that can provide products and services to support clinical development and the market demand for our product candidates, if approved;
- successfully launching 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 regulation 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.

Moreover, 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 lead 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 decide to invest in the continued development and potential commercialization of any or all of our lead product candidates and we or any of our future development partners are unable to develop, or obtain regulatory approval for, or, if approved, successfully commercialize, such 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 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 products 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 product candidates such as ours can be more expensive and take longer than for other product candidates, which are better known or more extensively studied to date. As an example, the FDA has only recently approved the first gene therapy product, LUXTURNA™ (voretigene neparvovec-rzyl) for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy.

Regulatory requirements governing gene and cell therapy products have changed and may continue to change in the future. Gene therapy clinical trials may be subject to review by the NIH Office of Science Policy's Recombinant DNA Advisory Committee ("RAC"). Although the FDA decides whether individual gene therapy protocols may proceed, the RAC public review process, if warranted, can impede the initiation of a clinical trial, even if the FDA has reviewed the trial and approved its initiation. Conversely, the FDA can put an IND on clinical hold even if the RAC has provided a favorable review or an exemption from in-depth, public review. Clinical trial sites in the U.S. that receive NIH funding for research involving recombinant or synthetic nucleic acid molecules are required to follow RAC recommendations, or risk losing NIH funding for such research or risk needing NIH pre-approval before conducting such research.

Conversely, the FDA can put an IND on clinical hold even if the RAC has provided a favorable review or an exemption from in-depth review of the proposed gene transfer protocol. Also, before a clinical study can begin, that clinical site's institutional review board ("IRB") and its Institutional Biosafety Committee will have to review the proposed clinical trial to assess appropriateness to conduct the clinical study at that site. In addition, adverse developments in clinical trials of gene therapy products conducted by others may cause the FDA or other oversight bodies to change the requirements for human research on or for approval of any of our product candidates.

These regulatory review committees and advisory groups and the new guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these treatment candidates or lead to significant post-approval limitations or restrictions. As we advance our product candidates, we may be required to consult with these 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 in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue to maintain our business.

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

The success of our business depends primarily upon our ability to identify, develop and commercialize products based on our platform. Our research programs, including those subject to our collaborations with Regeneron and Editas, may fail to identify other potential product candidates for clinical development for a number of reasons. Our research methodology may be unsuccessful in identifying potential product candidates or our potential product candidates may be shown to 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 ultimately prove to be unsuccessful.

Except for our recently-initiated ADVANCE Phase 1/2 trial, we have not tested any of our internally-developed viral vectors or product candidates in clinical trials.

Drug development has inherent risk. Except for our ADVANCE Phase 1/2 trial, which was initiated in December 2017, we have not conducted human clinical trials to evaluate any of our current product candidates, and we may experience unexpected results in the future. We or any of our future development partners will be required to demonstrate through adequate and well-controlled clinical trials that our product candidates containing our proprietary vectors are safe and effective, with a favorable benefit-risk profile, for use in their target indications before we can seek regulatory approvals for their 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.

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 proprietary vectors are not shown to be safe and effective, we may not realize the value of our investment in our technology. In addition, success in pre-clinical studies or in early clinical trials does not mean that later clinical trials will be successful, because product candidates in later-stage clinical trials may fail to demonstrate sufficient safety or efficacy despite having progressed through pre-clinical and initial clinical testing. Furthermore, any future trials will need to demonstrate sufficient safety and efficacy for approval by regulatory authorities in larger patient populations. 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 BLA to the FDA and even fewer are approved for commercialization.

We cannot guarantee that results from any clinical trials that we plan will be successful, and any safety 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 more patient data become available.

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. As a result, preliminary and interim data should be viewed with caution until the final data from a locked database are available. Material adverse changes in the final data compared to the interim data could significantly harm our business, prospects, financial condition and results of operations.

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 clinical development, manufacturing, 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;
- such 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 or facilities of third-party manufacturers 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 subjects in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

We initiated the ADVANCE Phase 1/2 trial in patients with A1AT deficiency in December 2017. Identifying and qualifying subjects to participate in the ADVANCE trial and future planned clinical trials for ADVM-053 and ADVM-022 will be critical to our success. The timing of future clinical trials will depend on the speed at which we can recruit subjects to participate in future testing of these product candidates.

Subject enrollment, a significant factor in the timing of clinical trials, is affected by many factors including the size and nature of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the trial, the design of the clinical trial, competing clinical trials and clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating. We will be required to identify and enroll a sufficient number of subjects with the relevant disease we are targeting for the ADVANCE Phase 1/2 trial and any future clinical trials for our product candidates. Potential subjects may not be adequately diagnosed or identified with the diseases which we are targeting or may not meet the entry criteria for our trials. We also may encounter difficulties in identifying and enrolling subjects 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 subjects, or those with required or desired characteristics to achieve diversity in a study.

In particular, ADVM-043 and ADVM-053 are designed to treat rare genetic disorders with limited patient pools from which to draw for clinical trials. ADVM-043 is focused on the treatment of patients with A1AT deficiency. It is estimated that A1AT deficiency affects approximately 100,000 individuals in the U.S.

ADVM-053 is focused on the treatment of patients with HAE. The prevalence of HAE is estimated to be between 1 in 10,000 to 1 in 50,000, impacting approximately 8,000 individuals in the United States. Enrollment of eligible subjects with orphan diseases like A1AT and HAE may be limited or slower than we anticipate, in light of the small subject populations involved. We plan to seek initial marketing approval of these product candidates in the U.S. and Europe and we may not be able to initiate clinical trials if we cannot enroll a sufficient number of eligible subjects 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 subjects 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 subjects, 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. For example, generalized public backlash developed against gene therapy following the death in September 1999 of an 18-year-old who had volunteered for a gene therapy experiment at the University of Pennsylvania. Researchers at the university had infused the volunteer's liver with a gene aimed at reversing a rare metabolic disease of the liver. The procedure triggered an extreme immune-system reaction that caused multiple-organ failure in a very short time, leading to the first death to occur as a direct result of a gene therapy experiment. In addition, in 2003, 20 subjects treated for X-linked severe combined immunodeficiency in two gene therapy studies using a murine gamma-retroviral vector showed correction of the disease, but the studies were terminated after five subjects developed leukemia (four of whom were subsequently cured). The cause of these adverse events was shown to be insertional oncogenesis, which is the process whereby the corrected gene inserts near a gene that is important in a critical cellular process like growth or division, and this insertion results in the development of a cancer (often leukemia). Using molecular diagnostic techniques, it was determined that clones from these subjects showed retrovirus insertion in proximity to the promoter of the LMO2 proto-oncogene. Earlier generation retroviruses like the one used in these two trials have been shown to preferentially integrate in regulatory regions of genes that control cell growth. Although none of our current product candidates utilize the gamma-retroviruses used in the 2003 studies, and our vectors are designed not to integrate into the patient's genome, our product candidates do use a viral vector delivery system. 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.

We believe we have appropriately accounted for the above factors in our trials when determining expected clinical trial timelines, but we cannot assure you that our assumptions are correct or that we will not experience delays in enrollment, which would result in the delay of completion of such trials beyond our expected timelines.

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, subjects may experience changes in their health, including illnesses, injuries and discomforts. Often, it is not possible to determine whether or not the product candidate being studied caused these conditions. Various illnesses, injuries, and discomforts 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, discomforts 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, 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.

Our product candidates built on AAV vectors have similar risks to other gene therapy vectors, including inflammation, cytotoxic T-cell response, anti-AAV antibodies and immune response to the transgene product, such as T-cell responses and/or auto-antibodies against the expressed protein. Recent studies by third parties have also found that intravenous delivery of certain AAV vectors at very high doses may result in toxicity and prompted the recommendation that studies involving high doses of AAV vectors should be monitored carefully for such toxicity. In addition, patients given infusions of any protein may develop severe hypersensitivity reactions or infusion reactions. 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. 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.

Risks Related to Our Reliance on Third Parties

We will rely on third parties to conduct our planned clinical trials. If these third parties do not meet our deadlines or otherwise 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 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 by such third parties and may occur at times substantially different from our estimates. Specifically, we use clinical research organizations ("CROs") to conduct our clinical trials and we rely on medical institutions, clinical investigators, CROs and consultants to conduct our trials in accordance with our clinical protocols and regulatory

requirements. Our CROs, investigators and other third parties play a significant role in the conduct of these trials and subsequent collection and analysis of data.

There is no guarantee that any CROs, investigators or other third parties on which we rely for administration and conduct of our clinical trials will devote adequate time and resources to such trials or perform as contractually required. If any of these third parties fails to meet expected deadlines, fails to adhere to our clinical protocols, fails to meet regulatory requirements, or otherwise performs in a substandard manner, our clinical trials may be extended, delayed or terminated. If any of our clinical trial sites terminates for any reason, we may experience the loss of follow-up information on subjects enrolled in our ongoing clinical trials unless we are able to transfer those subjects to another qualified clinical trial site. In addition, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and may receive cash or equity compensation in connection with such services. If these relationships and any related compensation result in perceived or actual conflicts of interest, or the FDA concludes that the financial relationship may have affected the interpretation of the study, the integrity of the data generated at the applicable clinical trial site may be questioned and the utility of the clinical trial itself may be jeopardized, which could result in the delay or rejection of any BLA we submit to the FDA. Any such delay or rejection could prevent us from commercializing our product candidates.

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

We do not expect to independently conduct all aspects of our vector production, product manufacturing, protocol development, research and preclinical and clinical testing. We currently rely, and expect to continue to rely, on third parties with respect to these items.

Any of these third parties may not be successful at manufacturing our vector products 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 research and development activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations and study protocols. If any of these third parties on which we rely do not perform satisfactorily, we will remain responsible for ensuring that each of our IND-enabling studies and clinical trials are conducted in accordance with the study plan and protocols.

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. For example, on December 6, 2016, we delivered a notice to the appropriate persons at Cornell University of our intent to terminate our Amended and Restated Master Services Agreement for breach as a result of Cornell University's failure to deliver suitable materials for use in our clinical trials of ADVM-043. If third parties breach their contractual obligations to us, we may not be able to complete, or may be delayed in 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 also 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 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 bankruptcy of the manufacturer or supplier.

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

We and our contract manufacturers are subject to significant regulation with respect to manufacturing our products. The manufacturing facilities on which we rely may not continue to meet regulatory requirements and may have limited capacity.

We currently have relationships with limited number of suppliers for the manufacturing of our vector product candidates. Our suppliers may require licenses to manufacture 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 manufacturer for our product candidates, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in late-stage clinical trials must be manufactured in accordance with the FDA's current Good Manufacturing Practices ("cGMP"). 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 current Good Laboratory Practice regulations and cGMP regulations enforced by the FDA through its facilities inspection program. Our contract manufacturers have not produced a commercially-approved AAV product and therefore have not obtained the requisite FDA approvals to do so. 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. 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. If the facility does not pass a pre-approval plant inspection, FDA approval of the products will not be granted.

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

Additionally, if supply from an approved manufacturer is interrupted, there could be a significant disruption in commercial supply. An alternative manufacturer would need to be qualified through a BLA supplement which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers 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 products 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, which increases the possibility that a competitor will discover them or that our 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 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 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. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's independent discovery of our trade secrets or other unauthorized use or disclosure 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 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 or trade secret information from any such publication. 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, independent development 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 termination or 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 body 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 for a number of reasons, including delays related to:

- the FDA failing to grant permission to proceed or placing the clinical trial on hold;
- subjects failing to enroll or remain in our trial at the rate we expect;
- subjects 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;
- subjects 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, 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 entire trial 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 subjects, 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 reexamination, which may impact the costs, timing or successful completion of a clinical trial. If we experience delays in completion of our clinical trials, or if we, the FDA or other regulatory authorities, the IRB, other reviewing entities, or any of our clinical trial sites suspend or terminate any of our clinical trials, the commercial prospects for a product candidate may be harmed and our ability to generate product revenue will be delayed. In addition, many of the factors that cause, or lead to, termination or suspension of, or a delay in the commencement or completion of, clinical trials 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, 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 products may be delayed 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, 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.

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

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

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

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

- issue warning letters or untitled letters;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve pending applications or supplements or applications filed by us;
- 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 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 continuing 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 obtain 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 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 wAMD, A1AT deficiency, HAE or other conditions for which our products 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 the treatment of wAMD 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 wAMD, a disease we believe to be the most common cause of vision loss in adults over the age of 50 in developed countries. If the size of the market for wAMD is smaller than we anticipate, we may not be able to achieve profitability and growth. Our projections of the number of people who have wAMD, as well as the subset of people with these diseases who have the potential to benefit from treatment with wAMD, 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, and we cannot accurately predict the number of patients for whom treatment might be possible. Additionally, the potentially addressable patient population may be limited or may not be amenable to treatment with our product candidates, and new patients may become increasingly difficult to identify or gain access to, which would adversely affect our results of operations and our business.

Because the target patient populations of ADVM-043 and ADVM-053 are relatively small, we must be able to successfully identify patients and achieve a significant market share to maintain profitability and growth. If the market opportunities for these product candidates are smaller than we believe they are, our future revenue may be adversely affected, and our business may suffer.

ADVM-043 and ADVM-053 are designed to treat rare genetic diseases. ADVM-043 is designed to treat A1AT deficiency, which impacts approximately 100,000 individuals in the U.S. ADVM-053 is designed to treat HAE, which impacts approximately 8,000 individuals in the U.S. Our estimates of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with these product candidates, may prove to be incorrect. The number of patients in the U.S. and elsewhere, or the portion of those patients who are amenable to treatment with these products, may turn out to be lower than expected or new patients may become increasingly difficult to identify or gain access to, all of which would adversely affect our results of operations and our business. Further, even if we obtain significant market share for our product candidates, because the potential target populations are very small, we may never achieve profitability despite obtaining such significant market share.

Additionally, because the target patient populations for these product candidates are 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 these product candidates will be adversely affected. The manner and level at which reimbursement is provided for services related to these product candidates (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 these products.

We may be unable to obtain orphan drug designation or exclusivity for ADVM-043, ADVM-053 or certain of our other product candidates. If our competitors are able to obtain orphan drug exclusivity for products that constitute the same drug and treat the same indications as our product candidates, we may not be able to have competing products approved by the applicable regulatory authority for a significant period of time.

Regulatory authorities in some jurisdictions, including the U.S. and the European Union, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is defined under the Food, Drug and Cosmetic Act as having a patient population of fewer than 200,000 individuals in the U.S., or a patient population greater than 200,000 in the U.S. where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the U.S. In the European Union, following the opinion of the EMA's Committee for Orphan Medicinal Products, the European Commission grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the European Union. Additionally, orphan designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biologic product.

Generally, if a product candidate with an orphan drug designation receives the first marketing approval for the indication for which it was designated, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the European Commission from approving another marketing application for a product that constitutes the same drug treating the same indication during the marketing exclusivity period, except in limited circumstances. If another sponsor receives such approval before we do (regardless of our orphan drug designation), we will be precluded from receiving marketing approval for our product for the applicable exclusivity period. The applicable period is seven years in the U.S. and 10 years in the European Union. The exclusivity period in the U.S. can be extended by six months if the BLA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The exclusivity period in the European Union can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be revoked if any regulatory agency determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

We intend to request orphan drug designation for ADVM-043, ADVM-053 or any of our other product candidates that we believe could qualify, but there can be no assurances that the FDA or the European Commission will grant any of such requests. Additionally, the designation of any of our product candidates as an orphan product does not guarantee that any regulatory agency will accelerate regulatory review of, or ultimately approve, that product candidate, nor does it limit the ability of any regulatory agency to grant orphan drug designation to product candidates of other companies that treat the same indications as our product candidates prior to our product candidates receiving exclusive marketing approval.

If we are unable to obtain orphan drug exclusivity for the product candidates for which it is available, we may be unable to prevent competitors from marketing competing products in certain territories. Even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs can be approved for the same condition. In the U.S., even after an orphan drug is approved, the FDA may subsequently approve another drug for the same condition if the FDA concludes that the latter drug is not the same drug as the first or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care as compared to the first. In the European Union, marketing authorization may be granted to a similar medicinal product for the same orphan indication if:

- the second applicant can establish in its application that its medicinal product, although similar to the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior;
- the holder of the marketing authorization for the original orphan medicinal product consents to a second orphan medicinal product application; or
- the holder of the marketing authorization for the original orphan medicinal product cannot supply sufficient quantities of orphan medicinal product.

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;
- cost-effective; and
- neither experimental nor investigational.

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 gene therapy products have been approved over the past year by the FDA. Although the U.S. Center for Medicare & Medicaid Services ("CMS") subsequently 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, collectively referred to as 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.

Some of the provisions of the Affordable Care Act have yet to be implemented, and there have been judicial and Congressional challenges to certain aspects of the Affordable Care Act. Since January 2017, President Trump has signed two Executive Orders and other directives designed to delay, circumvent or loosen the implementation of certain provisions requirements mandated by 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 repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." Additionally, on January 23, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain Affordable Care Act-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. Congress may consider other legislation to repeal or replace elements of the Affordable Care Act.

Other legislative changes have also been proposed and adopted in the U.S. since the Affordable Care Act was enacted. 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 will stay in effect through 2024 unless additional Congressional action is taken.

These cost reduction initiatives could decrease the coverage and reimbursement that we receive for any approved products, and could seriously harm our business. We expect that additional healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal, state and foreign governments will pay for healthcare products and services, which could result in reduced demand for our products, 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 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, 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 have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

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

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

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

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

We are subject to many manufacturing risks, any of which could substantially increase our costs and limit supply of our products. The process of manufacturing our products is complex, highly regulated and subject to several risks, including:

- The manufacturing 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 products or in the manufacturing facility in which our products 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 products 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 products 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 products. This may lead to significant delays in the availability of products 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 products 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 to assure that the process works, and the product or product candidate is made strictly and consistently in compliance with the process.
- Problems with the manufacturing process, even minor deviations from the normal process, 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 products may result in shipment delays, inventory shortages, lot failures, product withdrawals or recalls, or other interruptions in the supply of our products. We may also have to take inventory write-offs and incur other charges and expenses for products that fail to meet specifications, undertake costly remediation efforts, or seek more costly manufacturing alternatives. We may encounter problems

achieving adequate or clinical-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 potential milestone payments.

We have entered into development or other strategic collaborations with major biotechnology or pharmaceutical companies. For example, our research collaboration and license agreement with Regeneron, which was announced in May 2014, covers up to eight distinct therapeutic targets, in which we could earn up to $80.0 million in development and regulatory milestones for product candidates directed toward each therapeutic target, for a combined total of up to $640.0 million in potential milestone payments for product candidates directed toward all eight therapeutic targets, and low- to mid-single digit royalties on worldwide net sales of collaboration product candidates. For any two therapeutic targets, we have an option to share up to 35% of the worldwide product candidate development costs and profits. Additionally, in August 2016, we entered into a collaboration, option, and license agreement with Editas Medicine, pursuant to which we and Editas will collaborate on certain studies using AAV vectors in connection with Editas' genome editing technology, and we will grant to Editas an exclusive option to obtain certain exclusive rights to use our proprietary vectors in up to five ophthalmic indications. If Editas elects to develop a product using certain of our proprietary vectors, we will be eligible to receive up to $5.5 million in development milestone payments and $10.0 million in commercialization milestone payments for such product, and tiered royalties between the mid-single digits and low teens on net sales of such product, subject to certain adjustments.

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. Furthermore, our strategic partners have negotiated for certain rights to control decisions regarding the development and commercialization of our product candidates, if approved, and may not conduct those activities in the same manner as we would.

Moreover, if we fail to maintain development or other strategic collaborations related to our product candidates that we may choose to enter into:

- the development of certain of our current or future product candidates may be terminated or delayed;
- our cash expenditures related to development of certain of our current or future product candidates would increase significantly, and we may need to seek additional financing;
- we may be required to hire additional employees or otherwise develop expertise, such as sales and marketing expertise, for which we have not budgeted; and
- we will bear all of the risk related to the development of any such product candidates.

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 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 subjects for clinical trials, and in identifying and in-licensing new product candidates. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

New developments, including the development of other biotechnology and vectorology technologies and methods of treating disease, occur in the pharmaceutical, biotechnology and gene therapy industries at a rapid pace. Developments by competitors may render our product candidates obsolete or noncompetitive. Competition in drug development is intense. 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, EYLEA® is currently available in the U.S. for treatment of wAMD and macular edema following central retinal vein occlusion ("CRVO"), and in the United Kingdom, Germany, Switzerland, Australia, Japan, and certain other countries for the treatment of wAMD. Additionally, marketing approval has been obtained in the EU for EYLEA® for the treatment of visual impairment due to macular edema secondary to CRVO. 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 immune modulating therapies that may be safer or more effective than our product candidates, including ADVM-022. For example, if we continue clinical development of, and seek to commercialize, ADVM-022, it will compete with a variety of therapies currently marketed and in development for wAMD, using therapeutic modalities such as biologics, small molecules and gene therapy. Lucentis®, EYLEA® and Avastin® 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 wAMD. There are several other companies with marketed products or products in development for the treatment of wAMD, including Alcon; Allegro Ophthalmics, LLC; Allergan; Apellis Pharmaceuticals; Graybug Vision, Inc.; Bayer, Hoffmann-La Roche Ltd.; Genentech, Inc.; Iconic Therapeutics, Inc.; Novartis; Ophthotech Corporation; Opthea Ltd.; OxfordBioMedica; PanOptica, Inc; Regeneron Pharmaceuticals, Inc.; REGENXBIO, Inc; Santen Pharmaceutical Co., Ltd.; SciFluor Life Sciences, LLC; and Valeant Pharmaceuticals North America LLC.

For the treatment of A1AT deficiency and HAE, we know of a number of products currently in development that aim to reduce the frequency of injection, improve the route of administration, and deliver better efficacy compared to the standard-of-care treatments available today. There are several companies with products for A1AT deficiency in clinical development, including Kamada Ltd. For the treatment of HAE, there are several companies with products in clinical development, including CSL Behring, Biocryst Pharmaceuticals Inc., Ionis Pharmaceuticals, Inc., and Shire.

We have no sales, marketing or distribution capabilities, and we may 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 may 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 foreign jurisdictions, we will be subject to rules and regulations in those jurisdictions relating to our product candidates. In

some foreign 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. For example, in 2003, trials using early versions of murine gamma-retroviral vectors, which integrate with, and thereby alter, the host cell's DNA, have led to several well-publicized adverse events, including reported cases of leukemia. Although none of our current product candidates utilize murine gamma-retroviral vectors, our product candidates use a viral delivery system. Adverse events in our clinical trials, even if not ultimately attributable to our product candidates, and the 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. Although none of our current product candidates utilize the gamma-retroviruses used in the 2003 studies, and our vectors are designed not to integrate into the patient's genome, our product candidates do use a viral vector delivery system. The risk of cancer remains a concern for gene therapy and we cannot assure that it will not occur in any of our 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 potential product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates. If any such adverse events 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. In particular, our Chief Executive Officer and Chief Medical Officer have recently left our company, and our success is dependent on our ability to identify, hire and retain a new Chief Executive Officer and Chief Medical Officer. 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, including a new Chief Executive Officer and Chief Medical Officer, 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. In addition, the fact that our current Chief Executive Officer and Chief Medical Officer are serving on an interim basis, and are serving in dual roles that may result in significant time constraints and burdens on performing each such role (for example, our interim Chief Executive Officer is also our Chief Financial Officer), any difficulties we may have in hiring a new Chief Executive Officer or Chief Medical Officer, and the hiring of a new Chief Executive Officer or Chief Medical Officer, may be disruptive to our business and personnel.

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

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

We had 77 full-time employees as of March 31, 2018. 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 so accomplish could prevent us from successfully growing our company.

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

In addition to FDA restrictions on the marketing of pharmaceutical products, several other types of state and federal healthcare fraud and abuse laws have been applied in recent years to restrict certain marketing practices in the pharmaceutical industry. These laws include anti-kickback, false claims, physician payment transparency and privacy and security laws and regulations. Because of the breadth of these laws and the narrowness of the 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 exemptions and regulatory safe harbors protecting certain common activities from prosecution, the exemptions 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 exemption 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 statute governing healthcare fraud statutes. 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 and the civil monetary penalty law, including the False Claims Act, prohibits knowingly presenting or causing the presentation of a false, fictitious, or fraudulent claim for payment to the U.S. government. Actions under the False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Violations of the False Claims Act can result in significant monetary penalties and treble damages. The federal government is using the False Claims Act, and the accompanying threat of significant liability, in its investigation and prosecution of pharmaceutical and biotechnology companies throughout the country, for example, in connection with the promotion of products for unapproved uses and other sales and marketing practices. The government has obtained multi-million and multi-billion dollar settlements under the False Claims Act in addition to individual criminal convictions under applicable criminal statutes. Given the significant size of actual and potential settlements, it is expected that the government will continue to devote substantial resources to investigating healthcare providers' and manufacturers' compliance with applicable fraud and abuse laws.

In addition, there has been a recent trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The Affordable Care Act, among other things, imposes new reporting requirements on drug manufacturers, under the federal Physician Payments Sunshine Act, for payments made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in

civil monetary penalties of up to an aggregate of $0.2 million per year (or up to an aggregate of $1.0 million per year for "knowing failures"), for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. Certain states also mandate implementation of commercial compliance programs, impose restrictions on drug manufacturer marketing practices and/or require the tracking and reporting of gifts, compensation and other remuneration to physicians.

The need to build and maintain a robust compliance program with different compliance and/or reporting requirements increases the possibility that a healthcare company may violate one or more of the requirements. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs, imprisonment, and additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, any of which could adversely affect our ability to operate our business and our financial results.

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

Among other matters, Trade Laws prohibit companies and their employees, agents, clinical research organizations, 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 certain health plans, healthcare clearinghouses and 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 is scheduled to go into effect in May 2018 and introduces 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. 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 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 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 other 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 products. 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 our products and delay in approval or clearance of future 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 the 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, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or manmade disasters or business interruptions, for which we are predominantly self-insured. We rely on third-party manufacturers to produce our product candidates. Our ability to obtain clinical supplies of our product candidates could be disrupted if the operations of these suppliers are affected by a man-made or natural disaster or other business interruption. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses.

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

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

ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

Risks Relating to Our Intellectual Property

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

We currently are heavily reliant upon licenses of certain patent rights and proprietary technology from third parties that are important or necessary to the development of our technology and products, including technology related to our manufacturing process and our gene therapy product candidates. These and other licenses may not provide adequate rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and products in the future, or may contain other limitations on our ability to use such intellectual property or technology. As a result, our ability to develop or commercialize our processes and product candidates may be limited by the terms of such agreements. 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.

Licenses to additional third-party technology that may be required for our development programs may not be available in the future or may not be available on commercially reasonable terms, which could 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.

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.

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 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;
- 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 potential 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.

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

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

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

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

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

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

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

If we or any of our future development partners were to initiate legal proceedings against a third party to enforce a patent directed at one of our product candidates, or one of our future product candidates, the defendant could counterclaim that our patent is invalid

and/or unenforceable in whole or in part. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge include an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could include an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO or made a false or misleading statement during prosecution. Third parties may also raise similar claims before the USPTO, even outside the context of litigation. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on such product candidate. Such a loss of patent protection would have a material adverse impact on our business.

Interference proceedings provoked by third parties or brought by us or declared by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our research and development programs, license necessary technology from third parties, or enter into development or manufacturing partnerships that would help us bring our product candidates to market.

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

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

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

On September 16, 2011, the Leahy-Smith America Invents Act ("Leahy-Smith Act"), was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. In particular, under the Leahy-Smith Act, the U.S. transitioned in March 2013 to a "first to file" system in which the first inventor to file a patent application will be entitled to the patent. Third parties are allowed to submit prior art before the issuance of a patent by the USPTO, and we may become involved in post-grant proceedings including opposition, derivation, reexamination, *inter partes* review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope or enforceability of, or invalidate, our patent rights, which could adversely affect our competitive position.

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

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

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

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

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

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

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

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

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

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

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

We may also be subject to claims that former employees, collaborators or other third parties have an ownership interest in our patents or other intellectual property. We 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 extension and data exclusivity for 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;
- 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.

Known third party patent rights could delay or otherwise adversely affect our planned development and sale of several of our lead programs.

We are aware of patent rights held by third parties that could be construed to cover certain aspects of our lead product candidates. 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 each case, we expect the relevant patent to expire before we commercially introduce such product candidate. 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 lead 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. generally accepted accounting principles ("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. When we cease to be an "emerging growth company," which will occur no later than December 31, 2019, unless we have become a smaller reporting company, our independent registered public accounting firm will also be required to attest to the effectiveness of our internal control over financial reporting, and the related report will also be required to be included in our annual reports filed with the SEC. However, for so long as we remain an emerging growth company, we intend to take advantage of an exemption available to companies meeting these criteria from these auditor attestation requirements. Sarbanes-Oxley Section 404 compliance requirements are complex and require significant documentation, testing, and possible remediation. If we (or our auditors if they are required to assess and attest to the effectiveness of our internal control over financial reporting) 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, 2017, we cannot assure you that there will not be material weaknesses in our internal control over financial reporting 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 plans regarding further development of ADVM-043, ADVM-053, or ADVM-022;
- our ability to enroll and dose patients in any clinical trials that we plan in the future;
- our ability to obtain regulatory approvals for our product candidates and delays or failure to obtain such approvals;
- results of any clinical trials, and the results of trials of our competitors or those of other companies in our market sector;
- 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;
- 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 and certain of our former officers have been named defendants in purported securities class action lawsuits. These, and any additional securities litigation, could result in substantial losses and may divert management's time and attention from our business.

On June 15, 2015, we announced the top-line results of our Phase 2a clinical trial for AVA-101. In July 2015, three purported securities class action lawsuits were commenced in the U.S. District Court for the Northern District of California, naming as defendants us and certain of our former officers. These lawsuits assert that the defendants violated the Securities Exchange Act of 1934, as amended ("Exchange Act"), and the Securities Act of 1933, as amended ("Securities Act"), and allege that the defendants made materially false and misleading statements and omitted allegedly material information related to, among other things, the Phase 2a clinical trial for AVA-101 and the prospects of AVA-101. The plaintiffs seek unspecified damages, attorneys' fees and other costs, each on behalf of a purported class of persons and entities who purchased or otherwise acquired our publicly traded securities between July 31, 2014 and June 15, 2015. It is possible that additional suits will be filed with respect to these same matters and also naming us and/or our officers and directors as defendants.

In addition, in December 2015, a putative securities class action lawsuit was filed against us, our board of directors, underwriters of our January 13, 2015, follow-on public stock offering, and two of our institutional stockholders, in the Superior Court of the State of California for the County of San Mateo. The complaint alleges that, in connection with our follow-on stock offering, the defendants violated the Securities Act by allegedly making materially false and misleading statements and by allegedly omitting material information related to the Phase 2a clinical trial for AVA-101 and the prospects of AVA-101. The complaint seeks unspecified compensatory and rescissory damages, attorneys' fees and other costs.

In March 2017, we reached an agreement to settle the asserted actions. The proposed aggregate amount of the settlement is $13.0 million, of which $1.0 million would be contributed by us to cover our indemnification obligations to the underwriters, and the remainder would be contributed by our insurers. Notice of the settlement was provided to stockholders in the fall of 2017, and no stockholder objected to the settlement. In January 2018, the San Mateo Superior Court entered a judgment and order finally approving the settlement and, in February 2018, the U.S. District Court dismissed the consolidated federal action with prejudice. If the settlement does not become effective and litigation resumes, following an appeal or otherwise, adverse outcomes in the actions could result in

substantial damages. We and the defendants have denied and continue to deny each and all of the claims alleged in the actions, and the settlement does not assign or reflect any admission of fault, wrongdoing or liability as to any defendant. If final court approval is not obtained with respect to the settlement or the settlement otherwise does not become effective and litigation resumes, adverse outcomes in the actions could result in substantial damages.

The current securities litigation and any future litigation of this type could result in diversion of management's attention and resources, which could adversely impact our business. Monitoring and defending against legal actions is 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;
- any intellectual property infringement lawsuit 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, or additional shares under our at-the-market sales agreement, 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. We filed a universal shelf registration statement on Form S-3 with the SEC, which was declared effective on August 22, 2017, pursuant to which we registered for sale up to $150.0 million 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, including up to $50.0 million of our common stock available for issuance pursuant to our sales agreement with Cowen. Pursuant to the sales agreement, we may offer and sell, from time to time at our discretion, shares of our common stock having an aggregate offering price of up to $50.0 million through Cowen as our sales agent. Under the sales agreement, Cowen may sell the shares by any method permitted by law deemed to be an "at the market" offering as defined in Rule 415 of the Securities Act. We may seek to raise additional capital at any time. In January 2018, we issued and sold a total of 1,419,893 shares of our common stock at market prices under the 2017 stock offering agreement and raised total net proceeds of $5.7 million. We have sold a total of 6,550,232 shares of our common stock at market prices pursuant to the 2017 stock offering agreement and raised total net proceeds of $22.5 million. Further, pursuant to the aforementioned universal shelf registration statement, in February 2018, we completed the issuance of 10,222,235 shares of our common stock at $6.75 per share in an underwritten public offering for net proceeds to us of $64.5 million. 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. For example, in May 2016, we issued 14,087,246 shares of our common stock to Annapurna's shareholders as consideration for all of the outstanding shares of Annapurna. If we issue common stock or securities convertible into common stock, our common stockholders would experience additional dilution and, as a result, our stock price may decline.

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

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

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

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

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

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

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

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

We are an emerging growth company, as defined in the JOBS Act. For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404 of Sarbanes-Oxley, reduced disclosure obligations regarding executive compensation and our periodic reports and proxy statements and exemptions from the requirements of holding nonbinding advisory votes on executive compensation and stockholder approval of any golden parachute payments not previously approved. We could be an emerging growth company until the last day of the fiscal year 2019, although circumstances could cause us to lose that status earlier, including if we become a large accelerated filer (in which case we will cease to be an emerging company as of the date we become a large accelerated filer, which, generally, would occur if, at the end of a fiscal year, among other things, the market value of our common stock that is held by non-affiliates exceeds $700.0 million as of the last business day of our most recently completed second fiscal quarter), if we have total annual gross revenue of $1.0 billion or more during any fiscal year (in which cases we would no longer be an emerging growth company as of December 31 of such fiscal year), or if we issue more than $1.0 billion in non-convertible debt during any three year period before that time (in which case we would cease to be an emerging growth company immediately). Even after we no longer qualify as an emerging growth company, we may still qualify as a "smaller reporting company," which would allow us to take advantage of many of the same exemptions from disclosure requirements including not being required to comply with the auditor attestation requirements of Section 404 of Sarbanes-Oxley and reduced disclosure obligations regarding executive compensation and our periodic reports and proxy statements. 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.

We have incurred and will continue to incur significant increased costs as a result of operating as a public company, and our management devotes substantial time to new compliance initiatives.

As a public company, we have incurred and will continue to incur significant legal, accounting and other expenses. We are subject to the reporting requirements of the Exchange Act, which require, among other things, that we file with the SEC annual, quarterly and current reports with respect to our business, results of operations and financial condition. In addition, Sarbanes-Oxley, as well as rules adopted by the SEC and The Nasdaq Global Market that implement provisions of Sarbanes-Oxley, impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. Further, pursuant to the Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010, the SEC adopted additional rules and regulations in these areas, such as mandatory "say on pay" voting requirements that will apply to us when we cease to be an emerging growth company. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate.

The rules and regulations applicable to public companies have substantially increased our legal and financial compliance costs and make some activities more time-consuming and costly. To the extent these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition and results of operations and prospects. The increased costs will decrease our net income or increase our net loss, and may require us to reduce costs in other areas of our business or increase the prices of our products or services. For example, we expect these rules and regulations to make it more difficult and more expensive for us to obtain director and officer liability insurance, and we may be required to incur substantial costs to maintain the same or similar coverage. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers.

If securities or industry analysts do not publish research or reports or publish unfavorable research or reports about our business, our stock price and trading volume could decline.

The trading market for our common stock will depend in part on the research and reports that securities or industry analysts publish about us, our business, our market or our competitors. If one or more of the analysts who covers us downgrades our stock, our stock price would likely decline. If one or more of these analysts ceases to cover us or fails to regularly publish reports on us, interest in our stock could decrease, which could cause our stock price or trading volume to decline.

The recently passed comprehensive tax reform bill could adversely affect our business, results of operations and financial condition.

On December 22, 2017, new legislation was signed into law that significantly revises the Internal Revenue Code of 1986, as amended (the "Code"). The newly enacted federal income tax law, among other things, contains significant changes to corporate taxation, including adoption of a flat 21% corporate tax rate, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction of net operating losses generated in tax years beginning after December 31, 2017 to 80% of taxable income and elimination of carrybacks of such net operating losses, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, current inclusion in U.S. federal taxable income of certain earnings of controlled foreign corporations for tax years beginning after January 1, 2018, mandatory capitalization of research and development expenses beginning in 2022, immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits (including reducing the business tax credit for certain clinical testing expenses incurred in the testing of certain drugs for rare diseases or conditions generally referred to as "orphan drugs"). Notwithstanding the reduction in the corporate income tax rate, the overall impact of the new federal tax law is uncertain, and our business, results of operations and financial condition could be adversely affected. In addition, it is uncertain if and to what extent various states will conform to the newly enacted federal tax law. The impact of this tax reform on holders of our common stock is also uncertain and could be adverse. Investors should consult with their legal and tax advisors with respect to this legislation and the potential tax consequences of investing in or holding our common stock.

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. As of December 31, 2017, we had U.S. federal net operating loss ("NOL") carryforwards of approximately $53.2 million to offset future federal income. NOLs expire at various years beginning with 2036. As of December 31, 2017, we also had U.S. state NOL carryforwards of approximately $37.8 million to offset future state income. U.S. State NOLs expire at various years beginning with 2036. At December 31, 2017, we also had approximately $44.1 million of foreign net operating loss carryforwards which may be available to offset future foreign income; these carryforwards do not expire.

Under the newly enacted federal income tax law, 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. It is uncertain if and to what extent various states will

conform to the newly enacted federal tax law. 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 for both federal and state purposes were severely limited and therefore we removed a significant amount of NOLs 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 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

Unregistered Sales of Equity Securities

None.

Use of Proceeds

On August 5, 2014, we closed our IPO and issued 6,900,000 shares of our common stock at an initial offering price of $17.00 per share. The offer and sale of all of the shares in the IPO were registered under the Securities Act pursuant to a registration statement on Form S-1, as amended (File Nos. 333-197133 and 333-197739), which was declared effective by the SEC on July 30, 2014. The joint book-running managers for the IPO were Jefferies LLC, Cowen and Company, LLC and Piper Jaffray & Co. The aggregate offering price to the public for the shares sold in the IPO was $117.3 million. We received net proceeds from the IPO of approximately $106.5 million, after deducting underwriting discounts and commissions of approximately $8.2 million and expenses of approximately $2.6 million payable by us. None of the expenses associated with the IPO were paid to directors, officers, persons owning 10% or more of any class of equity securities, or to their associates, or to our affiliates.

We have discontinued development of AVA-101, and so we will not use approximately $20.0 million of our net proceeds from the IPO to fund Phase 3 research and development startup activities for our AVA-101 study, as we had described in our final prospectus filed with the SEC on July 31, 2014 pursuant to Rule 424(b) of the Securities Act. Instead, we have reallocated such proceeds to fund research and development expenses for additional preclinical studies relating to our wAMD gene therapies, ADVM-022 and ADVM-032 and for ADVM-043 for A1AT deficiency and for ADVM-053 for HAE.

Item 3. Defaults Upon Senior Securities

None.

Item 4. Mine Safety Disclosures

Not applicable.

Item 5. Other Information

None.

Item 6. Exhibits

EXHIBIT INDEX

EXHIBIT NUMBER	EXHIBIT DESCRIPTION	INCORPORATED BY REFERENCE				PROVIDED HEREWITH
		FILE NUMBER	FORM	DATE	EXHIBIT NUMBER	
3.1	Amended and Restated Certificate of Incorporation.	001-36579	10-K	March 9, 2017	3.1	
3.2	Amended and Restated Bylaws.	001-36579	8-K	May 12, 2016	3.2	
4.1	Reference is made to Exhibits 3.1 through 3.2.					
4.2	Form of Common Stock Certificate.	333-197133	S-1/A	July 25, 2014	4.1	

10.1	Change in Compensation Arrangement with Chief Executive Officer	001-36579	8-K	February 22, 2017	Item 5.02	
10.2†	Amendment to Collaboration, Option and License Agreement, dated January 25, 2018	001-36579	10-K		10.10	
12.1	Statement of Computation of Ratio of Earnings to Fixed Charges					X
31.1	Certification of Principal Executive Officer, as required by Rule 13a-14(a) or Rule 15d-14(a).					X
31.2	Certification of Chief Financial Officer, as required by Rule 13a-14(a) or Rule 15d-14(a).					X
32.1*	Certification pursuant to 18 U.S.C. section 1350, as adopted pursuant to section 906 of the Sarbanes-Oxley Act of 2002.					X
101.SCH	XBRL Taxonomy Extension Schema Document.					X
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document.					X
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document.					X
101.LAB	XBRL Taxonomy Extension Label Linkbase Document.					X
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document.					X

† Portions of this exhibit (indicated by asterisks) have been omitted pursuant to a request for confidential treatment and this exhibit has been filed separately with the SEC.

* The certification attached as Exhibit 32.1 that accompanies this Quarterly Report on Form 10-Q is not deemed filed with the SEC and is not to be incorporated by reference into any filing of Adverum Biotechnologies, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date of this Form 10-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: May 9, 2018

ADVERUM BIOTECHNOLOGIES, INC.

By: /s/ Leone Patterson

Leone Patterson
Chief Financial Officer and Interim President and Chief Executive Officer
(Principal Executive and Financial Officer)

Exhibit 12.1

Adverum Biotechnologies, Inc.
Deficiency of earnings
March 31, 2018

	Three Months Ended March 31, 2018	Year Ended December 31, 2017	2016	2015	2014
			(In thousands)		
Fixed charges:					
Interest expense on indebtedness	$ 7	$ 27	$ 25	$ 14	$ 0
Interest expense on portion of rent expense representative of interest	$ 32	126	122	92	18
Total fixed charges	$ 38	$ 152	$ 147	$ 106	$ 18
Preferred stock deemed dividend	$ 0	$ 0	$ 0	$ 0	$ 3,230
Total fixed charges and preferred dividend	$ 38	$ 152	$ 147	$ 106	$ 3,248
Net loss	(17,200)	(56,147)	(114,522)	(47,453)	(25,404)
Fixed charges per above	38	152	147	106	18
Total earnings (loss)	(17,162)	(55,995)	(114,375)	(47,347)	(25,386)
Ratio of earnings to fixed charges	N/A	N/A	N/A	N/A	N/A
Deficiency of earnings available to cover fixed charges	(17,200)	(56,147)	(114,522)	(47,453)	(28,634)

Exhibit 31.1

CERTIFICATION OF THE PRINCIPAL EXECUTIVE OFFICER

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

I, Leone Patterson, certify that:

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

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

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

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

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

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

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

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

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

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

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

Date: May 9, 2018

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

Exhibit 31.2

CERTIFICATION OF THE PRINCIPAL FINANCIAL OFFICER

PURSUANT TO SECTION 302 OF

THE SARBANES-OXLEY ACT OF 2002

I, Leone Patterson, certify that:

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

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

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

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

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

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

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

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

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

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

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

Date: May 9, 2018

By: /s/Leone Patterson
Name: Leone Patterson
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 three months ended March 31, 2018 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Leone Patterson, both in her capacity as Interim President and Chief Executive Officer, and as Chief Financial Officer, of Adverum Biotechnologies, Inc., hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to the best of her knowledge, the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of Adverum Biotechnologies, Inc.

Date: May 9, 2018

By: /s/Leone Patterson
Leone Patterson
Interim President and Chief Executive Officer, Chief Financial Officer
(Principal Executive and Financial Officer)