UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 10-Q

(Mark One)

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

For the quarterly period ended June 30, 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: 001-36694

PROTEON THERAPEUTICS, INC.
(Exact name of registrant as specified in its charter)

Delaware	**20-4580525**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

200 West Street
Waltham, MA
(Address of principal executive offices)
02451
(Zip Code)
(781) 890-0102
(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 [X] 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 [X] No [ ]

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definitions of "large accelerated filer," "accelerated filer" and "smaller reporting 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 [X]
Emerging growth company [X]	

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

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

As of July 31, 2018 there were 17,726,713, shares of the registrant's common stock, par value $0.001 per share, outstanding.

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CAUTIONARY NOTE FORWARD-LOOKING STATEMENTS

This Quarterly Report on Form 10-Q contains forward-looking statements, which reflect our current views with respect to, among other things, our operations and financial performance. All statements other than statements of historical facts contained in this Quarterly Report on Form 10-Q are forward-looking statements. You can identify these forward-looking statements by the use of words such as "outlook," "believes," "expects," "potential," "continues," "may," "will," "should," "seeks," "approximately," "predicts," "intends," "plans," "estimates," "anticipates" or the negative version of these words or other comparable words. These forward-looking statements are subject to various risks and uncertainties. Accordingly, there are or will be important factors that could cause actual outcomes or results to differ materially from those indicated in these statements. These forward-looking statements include, but are not limited to, statements about:

- the timing of completing enrollment or releasing data or results of our ongoing and planned clinical trials for vonapanitase (formerly PRT-201);
- our estimates regarding the amount of funds we require to complete our Phase 3 clinical trial for vonapanitase;
- our interpretation of the data from our completed Phase 2 and Phase 3 clinical trials for vonapanitase;
- whether and when we may submit a Biologics License Application, a Marketing Authorization Application or similar drug or biologic regulatory filings;
- whether we will need to conduct any additional studies after our Phase 3 trials;
- our estimates regarding the amount of funds required to fund operations into the fourth quarter of 2019;
- our plans to fund our chemistry, manufacturing and controls;
- our estimates regarding expenses, future revenues, capital requirements, the sufficiency of our current and expected cash resources and our need for additional financing and plans for additional financing;
- our estimate of when we will require additional funding;
- our plans to commercialize and bring vonapanitase to market;
- the timing of, and our ability to obtain and maintain, regulatory approvals for our product candidates, including vonapanitase;
- whether we may conduct a clinical trial of vonapanitase in Europe and the timing of the results;
- the rate and degree of market acceptance and clinical utility of any approved product candidate and the general market for the improvement of vascular access outcomes;
- the potential benefits of strategic partnership agreements and our ability to enter into selective strategic partnership arrangements;
- our ability to quickly and efficiently identify and develop additional product candidates;
- our search for additional product opportunities;
- our commercialization, marketing, distribution and manufacturing capabilities, strategy and expenses;
- timing to recruit and expand our employee base and sales force, both in and outside the United States;

- plans to initiate or continue Phase 1 or Phase 1/2 trials in symptomatic peripheral artery disease or other indications;
- the reimbursement of vonapanitase;
- our research and development costs;
- the sufficiency of existing facilities to meet our needs;
- our estimates regarding general and administrative costs and salary and personnel costs, costs associated with preparation for commercial operations and costs associated with being a public company;
- our intellectual property position;
- our plans to seek patent protection in available countries;
- our expectations that vonapanitase will qualify for a 12-year period of exclusivity and our ability to obtain and maintain other forms of exclusivity relevant to our business;
- our reliance on and the expected performance of our third party suppliers and manufacturers;
- our plans to build out compliance, financial and operating infrastructure after Phase 3 completion;
- our plans to improve existing, and implement new, systems to manage our business;
- future payment of dividends;
- the impact of accounting policies;
- the impact of changes in interest rates;
- exposure to foreign currency exchange risks and our purchase of forward foreign currency contracts in the future; and
- the continued adoption of stock trading plans by employees, including executive officers.

All forward-looking statements in this Quarterly Report on Form 10-Q involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, the risk factors set forth below in Part II, Item 1A, Risk Factors, and elsewhere in this Quarterly Report on Form 10-Q. These factors should not be construed as exhaustive and should be read in conjunction with the other cautionary statements that are included in this Quarterly Report on Form 10-Q. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

This Quarterly Report on Form 10-Q also contains estimates, projections and other information concerning our industry, our business, and the markets for certain medical conditions, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources.

PART I – FINANCIAL INFORMATION

Item 1. Financial Statements

Proteon Therapeutics, Inc.
Condensed Consolidated Balance Sheets
(in thousands, except share and per share data)
(Unaudited)

	June 30, 2018	December 31, 2017
Assets		
Current assets:		
Cash and cash equivalents	$ 12,485	$ 21,170
Available-for-sale investments	13,969	20,971
Prepaid expenses and other current assets	1,057	1,339
Total current assets	27,511	43,480
Property and equipment, net	219	259
Restricted cash	22	22
Other non-current assets	100	218
Total assets	$ 27,852	$ 43,979
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 431	$ 291
Accrued expenses	1,800	8,949
Total current liabilities	2,231	9,240
Total liabilities	2,231	9,240
Commitments and contingencies (Note 4)		
Stockholders' equity:		
Series A convertible preferred stock, par value $0.001 per share, 22,000 shares authorized, issued and outstanding at June 30, 2018 and December 31, 2017, respectively	21,523	21,523
Preferred stock, $0.001 par value per share; 9,978,000 shares authorized, no shares issued and outstanding at June 30, 2018 and December 31, 2017	-	-
Common stock, $0.001 par value, 100,000,000 shares authorized at June 30, 2018 and December 31, 2017; 17,726,713 and 17,674,729 shares issued and outstanding at June 30, 2018 and December 31, 2017, respectively.	18	18
Additional paid-in capital	204,780	202,953
Accumulated deficit	(200,701)	(189,741)
Accumulated other comprehensive income (loss)	1	(14)
Total stockholders' equity	25,621	34,739
Total liabilities and stockholders' equity	$ 27,852	$ 43,979

The accompanying notes are an integral part of these unaudited condensed consolidated financial statements.

Proteon Therapeutics, Inc.
Condensed Consolidated Statements of Operations and Comprehensive Loss
(in thousands, except share and per share data)
(Unaudited)

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Operating expenses:				
Research and development	$ 2,760	$ 3,891	$ 6,831	$ 8,137
General and administrative	2,240	2,095	4,534	4,329
Total operating expenses	5,000	5,986	11,365	12,466
Loss from operations	(5,000)	(5,986)	(11,365)	(12,466)
Other income:				
Investment income	106	46	198	78
Other income, net	15	332	207	282
Total other income	121	378	405	360
Net loss	$ (4,879)	$ (5,608)	$ (10,960)	$ (12,106)
Foreign currency translation adjustment	$ (3)	$ -	$ (1)	$ -
Unrealized gain (loss) on available-for-sale investments	8	(7)	16	(7)
Comprehensive loss	$ (4,874)	$ (5,615)	$ (10,945)	$ (12,113)
Net loss attributable to common stockholders	$ (4,879)	$ (5,608)	$ (10,960)	$ (12,106)
Net loss per share attributable to common stockholders - basic and diluted	$ (0.28)	$ (0.33)	$ (0.62)	$ (0.72)
Weighted-average common shares outstanding used in net loss per share attributable to common stockholders - basic and diluted	17,674,729	17,207,672	17,674,729	16,923,515
Supplemental disclosure of stock-based compensation expense:				
Included in operating expenses, above, are the following amounts for non-cash stock-based compensation expense:				
Research and development	$ 312	$ 308	$ 579	$ 606
General and administrative	610	559	1,164	1,106
Total	$ 922	$ 867	$ 1,743	$ 1,712

The accompanying notes are an integral part of these unaudited condensed consolidated financial statements.

Proteon Therapeutics, Inc.
Condensed Consolidated Statements of Cash Flows
(in thousands)
(Unaudited)

	Six Months Ended June 30,	
	2018	**2017**
Operating activities		
Net loss	$ (10,960)	$ (12,106)
Reconciliation of net loss to net cash used in operating activities:		
Depreciation	61	77
Amortization of premium/discount on available-for-sale securities	(14)	1
Foreign currency remeasurement (loss)/gain	(25)	279
Stock-based compensation	1,743	1,712
Changes in:		
Prepaid expenses and other assets	396	263
Interest receivable	4	(12)
Accounts payable and accrued expenses	(7,009)	(942)
Net cash used in operating activities	(15,804)	(10,728)
Investing activities		
Purchases of available-for-sale investments	(10,957)	(13,360)
Proceeds from maturities of available-for-sale investments	15,990	4,920
Proceeds from sale of available-for-sale investments	1,999	-
Purchase of property and equipment	(21)	(14)
Net cash provided by (used in) investing activities	7,011	(8,454)
Financing activities		
Proceeds from issuance of common stock, net of issuance costs	-	1,287
Proceeds from issuance of common stock under ESPP	84	58
Exercise of stock options	-	109
Net cash provided by financing activities	84	1,454
Effect of exchange rate changes on cash	24	(279)
Decrease in cash, cash equivalents and restricted cash	(8,685)	(18,007)
Cash, cash equivalents and restricted cash, beginning of period	21,192	36,406
Cash, cash equivalents and restricted cash, end of period	$ 12,507	$ 18,399

The accompanying notes are an integral part of these unaudited condensed consolidated financial statements.

1. Organization and Operations

The Company

Proteon Therapeutics, Inc. (the "Company") is a late-stage biopharmaceutical company focused on the development of novel, first-in-class pharmaceuticals to address the medical needs of patients with kidney and vascular disease. The Company was formed in June 2001 and incorporated on March 24, 2006.

The Company devotes substantially all of its efforts to product research and development, initial market development and raising capital. The Company has not generated any product revenue related to its primary business purpose to date and is subject to a number of risks similar to those of other development stage companies, including dependence on key individuals, competition from other companies, the need for development of commercially viable products and the need to obtain adequate additional financing to fund the development of its product candidates. The Company is also subject to a number of risks similar to other companies in the biotechnology industry, including regulatory approval of products, uncertainty of market acceptance of products, competition from therapeutic alternatives and larger companies, compliance with government regulations, protection of proprietary technology, dependence on third parties and product liability.

As of June 30, 2018, the Company had cash, cash equivalents and available-for-sale investments of $26.5 million. The Company believes that its existing cash, cash equivalents and available-for-sale investments will be sufficient to fund operations and capital expenditures into the fourth quarter of 2019. The Company had an accumulated deficit of $200.7 million as of June 30, 2018.

On November 12, 2015, the Company filed a shelf registration statement on Form S-3 (the "Registration Statement"), and entered into a Sales Agreement with Cowen and Company, LLC (the "Sales Agreement") to establish an at-the-market ("ATM") equity offering program pursuant to which they are able, with the Company's authorization, to offer and sell up to $40 million of the Company's Common Stock at prevailing market prices from time to time. The Registration Statement became effective on January 12, 2016. The Company pays Cowen a commission equal to 3% of the gross proceeds of the sales price of all shares sold through it as sales agent under the Sales Agreement. The offering costs are offset against proceeds from the sale of common stock under this agreement. The Company filed a prospectus supplement on March 14, 2018 because the Company is currently subject to General Instruction I.B.6 of Form S-3, which limits the amounts that the Company may sell under the Registration Statement. For the year ended December 31, 2017, the Company sold 896,811 shares of Common Stock under the Sales Agreement for aggregate gross proceeds of $1.4 million offset by total offering costs of $0.1 million. The Company did not sell any shares of Common Stock under the Sales Agreement during the six months ended June 30, 2018.

On June 22, 2017, the Company entered into a Securities Purchase Agreement (the "Purchase Agreement") with a syndicate of current and new institutional investors, led by an affiliate of Deerfield Management Company, L.P., pursuant to which the Company agreed to issue and sell to the investors an aggregate of 22,000 shares of the Company's Series A Convertible Preferred Stock, par value $0.001 per share (the "Series A Preferred"), for a purchase price of $1,000 per share, or an aggregate gross purchase price of $22.0 million, all upon the terms and conditions set forth in the Purchase Agreement (the "Series A Financing"). The Company closed the Series A Financing on August 2, 2017 (see Note 5).

Pursuant to the Series A Financing, on August 2, 2017, the Company entered into a registration rights agreement with the holders of the Series A Preferred (the "Registration Rights Agreement"). On August 3, 2017, in accordance with the Registration Rights Agreement, the Company filed a registration statement on Form S-3 to register the common stock issuable upon conversion of the Preferred Shares. The registration statement became effective on August 21, 2017.

2. Summary of Significant Accounting Policies

Basis of Presentation, Principles of Consolidation and Use of Estimates

The unaudited interim condensed consolidated financial statements of the Company included herein have been prepared, pursuant to the rules and regulations of the Securities and Exchange Commission (the "SEC"). Certain information and footnote disclosures normally included in financial statements prepared in accordance with accounting principles generally accepted in the United States of America have been condensed or omitted from this report, as is permitted by such rules and regulations. Accordingly, these condensed consolidated financial statements should be read in conjunction with the financial statements as of and for the year ended December 31, 2017 and notes thereto, included in the Company's Annual Report on Form 10-K, as filed with the SEC on March 14, 2018.

The unaudited interim condensed consolidated financial statements have been prepared on the same basis as the audited financial statements. In the opinion of the Company's management, the accompanying unaudited interim condensed consolidated financial statements contain all adjustments which are necessary to fairly present the Company's financial position as of June 30, 2018, the results of its operations for the three and six months ended June 30, 2018 and 2017 and its cash flows for the six months ended June 30, 2018 and 2017. Such adjustments are of a normal and recurring nature. The results for the three and six months ended June 30, 2018 are not necessarily indicative of the results for the year ending December 31, 2018, or for any future period.

The unaudited interim condensed consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries. All intercompany balances and transactions have been eliminated in consolidation. These condensed consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP"). Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification ("ASC") and Accounting Standards Update ("ASU") of the Financial Accounting Standards Board ("FASB").

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. On an ongoing basis, the Company's management evaluates its estimates, which include, but are not limited to, estimates related to stock-based compensation expense, clinical trial accruals and reported amounts of revenues and expenses during the reported period. The Company bases its estimates on historical experience and other market-specific or other relevant assumptions that it believes to be reasonable under the circumstances. Actual results may differ from those estimates or assumptions.

Fair Value of Financial Instruments

The Company's financial instruments consist of cash and cash equivalents, available-for-sale investments, accounts payable, and accrued liabilities. The Company is required to disclose information on all assets and liabilities reported at fair value that enables an assessment of the inputs used in determining the reported fair values. FASB ASC Topic 820, *Fair Value Measurement and Disclosures*, established a hierarchy of inputs used in measuring fair value that maximizes the use of observable inputs and minimizes the use of unobservable inputs by requiring that the observable inputs be used when available. Observable inputs are inputs that market participants would use in pricing the financial instrument based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company's assumptions about the inputs that market participants would use in pricing the financial instrument and are developed based on the best information available under the circumstances. The fair value hierarchy applies only to the valuation inputs used in determining the reported or disclosed fair value of the financial instruments and is not a measure of the investment credit quality. Fair value measurements are classified and disclosed in one of the following three categories:

Level 1—Valuations based on unadjusted quoted prices in active markets for identical assets or liabilities that the Company has the ability to access at the measurement date.

Level 2—Valuations based on quoted prices for similar assets or liabilities in markets that are not active or for which all significant inputs are observable, either directly or indirectly.

Level 3—Valuations that require inputs that reflect the Company's own assumptions that are both significant to the fair value measurement and unobservable.

To the extent that valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

Financial instruments measured at fair value on a recurring basis include cash equivalents and available-for-sale investments. There have been no changes to the valuation methods utilized by the Company during the three and six months ended June 30, 2018 and 2017. The Company evaluates transfers between levels at the end of each reporting period. There were no transfers of financial instruments between levels during the three and six months ended June 30, 2018 and 2017.

Net Income (Loss) per Share Attributable to Common Stockholders

Basic net income (loss) per share is calculated by dividing net income (loss) attributable to common stockholders by the weighted-average number of common shares outstanding during the period. Diluted net income per share is calculated by dividing the net income attributable to common stockholders by the weighted-average number of common equivalent shares outstanding for the period, including any dilutive effect from outstanding stock options and warrants using the treasury stock method.

The Company follows the two-class method when computing net income (loss) per share in periods when issued shares that meet the definition of participating securities are outstanding. The two-class method determines net income (loss) per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to common stockholders for the period to be allocated between common and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed. Accordingly, in periods in which the Company reports a net loss attributable to common stockholders when participating securities are outstanding, losses are not allocated to the participating securities. For purposes of calculating diluted net income per share attributable to common shareholders, preferred stock, stock options, warrants and convertible debt are considered common stock equivalents.

Recent Accounting Pronouncements

In May 2014, the FASB issued ASU 2014-09, *Revenue from Contracts with Customers* ("ASU 2014-09"), a new standard on revenue recognition providing a single, comprehensive revenue recognition model for all contracts with customers. The new revenue standard is based on the principle that revenue should be recognized to depict the transfer of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. The new standard was effective beginning January 1, 2018, with early adoption permitted. The Company adopted ASU 2017-09 during the quarter ended March 31, 2018. The adoption did not have a material impact on the condensed consolidated financial statements.

In February 2016, the FASB issued ASU 2016-02, *Leases (Topic 842): Amendments to FASB Codification* ("ASU 2016-02"), which increases transparency and comparability among organizations by recognizing lease assets and lease liabilities on the balance sheet and disclosing key information about leasing arrangements. At the lease commencement date, the lessee must recognize a lease liability and right-of-use asset, which is initially measured at the present value of future lease payments. ASU 2016-02 is effective for public companies for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2018, with early adoption permitted. ASU 2016-02 must be adopted using a modified retrospective transition, and provides for certain practical expedients. Transition will require application of the new guidance at the beginning of the earliest comparative period presented. The Company is currently evaluating the impact of the new guidance on its condensed consolidated financial statements.

In August 2016, the FASB issued ASU 2016-15, *Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments* ("ASU 2016-15"), which provides clarification regarding how certain cash receipts and cash payments are presented and classified in the statement of cash flows. This update addresses eight specific cash flow issues with the objective of reducing the existing diversity in practice. This update is effective for annual and interim periods beginning after December 15, 2017, which required the Company to adopt these provisions in the first quarter of fiscal 2018 using a retrospective approach. The Company adopted ASU 2016-15 during the quarter ended March 31, 2018. The adoption did not have a material impact on the condensed consolidated financial statements.

In May 2017, the FASB issued ASU No. 2017-09, *Compensation - Stock Compensation (Topic 718): Scope of Modification Accounting* ("ASU 2017-09"), which clarifies when changes to the terms or conditions of a share-based payment award must be accounted for as modifications. The new guidance will reduce diversity in practice and result in fewer changes to the terms of an award being accounted for as modifications. Under ASU 2017-09, an entity will not apply modification accounting to a share-based payment award if the award's fair value, vesting conditions and classification as an equity or liability instrument are the same immediately before and after the change. ASU 2017-09 will be applied prospectively to awards modified on or after the adoption date. The guidance is effective for annual periods, and interim periods within those annual periods, beginning after December 15, 2017. The Company adopted ASU 2017-09 during the quarter ended March 31, 2018. The adoption did not have a material impact on the condensed consolidated financial statements.

In November 2016, the FASB issued ASU 2016-18, *Statement of Cash Flows, Restricted Cash* requiring restricted cash and restricted cash equivalents to be included with cash and cash equivalents on the statement of cash flows when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. The guidance is effective for interim and annual periods beginning after December 15, 2017, with early adoption permitted. The Company adopted this standard during the first quarter of 2018. Restricted cash is now included as a component of cash, cash equivalents, and restricted cash on the Company's unaudited condensed consolidated statement of cash flows. Restricted cash is recorded within other non-current assets in the accompanying unaudited condensed consolidated balance sheets. The Company adopted ASU 2016-18 during the quarter ended March 31, 2018. The inclusion of restricted cash increased the beginning balances of the unaudited condensed consolidated statement of cash flows by $22,000 and $14,000 respectively, and the ending balances by $22,000 and $14,000, respectively, for the six months ended June 30, 2018 and 2017.

3. Fair Value Measurements

Below is a summary of assets and liabilities measured at fair value (in thousands):

	As of June 30, 2018			
	Quoted Prices in Active Markets (Level 1)	**Significant Observable Inputs (Level 2)**	**Significant Unobservable Inputs (Level 3)**	**Total**
Assets				
Cash equivalents	$ 10,425	$ -	$ -	$ 10,425
Government securities	13,969	-	-	13,969
Total	$ 24,394	$ -	$ -	$ 24,394

	As of December 31, 2017			
	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)	Total
Assets				
Cash equivalents	$ 11,662	$ -	$ -	$ 11,662
Government securities	20,971	-	-	20,971
Total	$ 32,633	$ -	$ -	$ 32,633

As of June 30, 2018 and December 31, 2017, the Company's cash equivalents consist principally of money market funds and government debt securities with original maturities of 90 days or less. Government securities consist principally of government debt securities and money market funds which are classified as available-for-sale.

Available-for-sale securities at June 30, 2018 and December 31, 2017 consist of the following (in thousands):

	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
June 30, 2018				
Government securities				
(Due within 1 year)	$ 13,973	$ -	$ (4)	$ 13,969
	$ 13,973	$ -	$ (4)	$ 13,969
December 31, 2017				
Government securities				
(Due within 1 year)	$ 20,991	$ -	$ (20)	$ 20,971
	$ 20,991	$ -	$ (20)	$ 20,971

4. Commitments and Contingencies

Future minimum payments required under operating leases as of June 30, 2018 are summarized as follows (in thousands):

Year Ending December 31:	Amount
2018	138
2019	207
Total minimum lease payments	$ 345

In addition to the base rent, the Company is also responsible for its share of operating expenses and real estate taxes, in accordance with the terms of the lease agreement. As of June 30, 2018, the Company has provided a security deposit in the amount of $22,000 to the lessor.

Restricted cash related to facilities leases

As of June 30, 2018 and December 31, 2017, the Company had $22,000 in an outstanding letter of credit to be used as collateral for leased premises. As of June 30, 2018 and December 31, 2017, the Company pledged an aggregate of $22,000 to the bank as collateral for the letter of credit, which is included in other non-current assets.

5. Series A Preferred Financing

On August 2, 2017, the Company issued and sold 22,000 shares of the Company's Series A Convertible Preferred Stock, par value of $0.001 per share (the "Series A Preferred"), for a purchase price of $1,000 per share, or aggregate purchase price and gross proceeds of $22.0 million, all upon the terms and conditions set forth in the Securities Purchase Agreement dated as of June 22, 2017. The Company incurred $0.5 million of issuance costs in connection with the transaction. Each share of Series A Preferred is convertible into approximately 1,005 shares of the Company's Common Stock at a conversion price of $0.9949 per share, in each case subject to adjustment for any stock splits, stock dividends and similar events, provided that any conversion of Series A Preferred by a holder into shares of Common Stock is prohibited if, as a result of such conversion, the holder, together with its affiliates and any other person or entity whose beneficial ownership of the Company's Common Stock would be aggregated with such holder's for purposes of Section 13(d) of the Securities Exchange Act of 1934, as amended (the "Exchange Act") would beneficially own more than 9.985% of the total number of shares of Common Stock issued and outstanding after giving effect to such conversion.

Upon issuance, each share of Series A Preferred included an embedded beneficial conversion feature as the market price of the Company's Common Stock on the date of issuance of the Series A Preferred was $1.30 per share. As a result, the Company recorded the intrinsic value of the beneficial conversion feature of $6.7 million as a discount on the Series A Preferred at issuance. As the Series A Preferred is immediately convertible upon issuance and does not include a stated redemption date, the discount on the Series A Preferred was immediately accreted.

The Company evaluated the Series A Preferred for liability or equity classification in accordance with the provisions of ASC 480, Distinguishing Liabilities from Equity, and determined that equity treatment was appropriate because the Series A Preferred did not meet the definition of the liability instruments defined thereunder for convertible instruments. Specifically, the Series A Preferred are not mandatorily redeemable and do not embody an obligation to buy back the shares outside of the Company's control in a manner that could require the transfer of assets. Additionally, the Company determined that the Series A Preferred would be recorded as permanent equity, not temporary equity, based on the guidance of ASC 480 given that there is no scenario where the holders of equally and more subordinated equity of the entity would not be entitled to also receive the same form of consideration upon the occurrence of the event that gives rise to the redemption.

6. Stock-based Compensation

Stock Options

The following table summarizes stock option activity for employees:

	Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (years)	Aggregate Intrinsic Value
Outstanding at December 31, 2017	2,681,072	$ 7.18	6.8	$ 121
Granted	1,891,600	$ 2.65		
Exercised	-	$ -		
Forfeited	(83,433)	$ 5.82		
Expired	(42,013)	$ 13.30		
Outstanding at June 30, 2018	4,447,226	$ 5.22	7.9	$ 614
Exercisable at June 30, 2018	1,844,871	$ 7.44	6.1	$ 286
Vested or expected to vest at June 30, 2018 (1)	4,447,226	$ 5.22	7.9	$ 614

(1) Represents the number of vested options at June 30, 2018 plus the number of unvested options expected to vest based on the unvested options outstanding at June 30, 2018.

Employee Stock Purchase Plan

The 2014 Employee Stock Purchase Plan (ESPP) initially authorized the issuance of up to 140,500 shares of Common Stock. The number of shares increases each January 1, commencing on January 1, 2015 and ending on (and including) January 1, 2024, by an amount equal to the lesser of one percent of the outstanding shares as of the end of the immediately preceding fiscal year, 281,000 shares and any lower amount determined by the Company's Board of Directors prior to each such January 1st. The Company's Board of Directors determined there was to be no increase on January 1, 2018. As of June 30, 2018, the 2014 ESPP authorized the issuance of up to 304,991 shares of Common Stock. The seventh offering under the 2014 ESPP began on January 1, 2018 and ended on June 30, 2018. 51,984 shares were issued during the three and six months ended June 30, 2018 under the 2014 ESPP. The Company incurred $24,000 and $48,000 in stock-based compensation expense related to the 2014 ESPP for the three and six months ended June 30, 2018, respectively. The Company incurred $52,000 and $0.1 million in stock-based compensation expense related to the 2014 ESPP for the three and six months ended June 30, 2017, respectively.

Common Stock

The Company has the following shares of Common Stock reserved for future issuance:

	June 30, 2018	December 31, 2017
Conversion of Series A Preferred Stock	22,112,775	22,112,775
Stock-based compensation awards	5,163,957	3,572,457
Employee Stock Purchase Plan	140,479	192,463
Total	27,417,211	25,877,695

7. Income Taxes

Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. The Company has evaluated the positive and negative evidence bearing upon the Company's ability to realize the benefit of its deferred tax assets. Based on the Company's history of operating losses, the Company has concluded that it is more likely than not that the benefit of its deferred tax assets will not be realized. Due to the uncertainty surrounding the realization of the favorable tax attributes in future tax returns, the Company has provided a full valuation allowance against its deferred tax assets. There were no significant income tax provisions or benefits for the six months ended June 30, 2018 and 2017.

8. Net Loss per Share Attributable to Common Stockholders

As described in Note 2, Summary of Significant Accounting Policies, the Company computes basic and diluted loss per share using a methodology that gives effect to the impact of outstanding participating securities (the "two-class method"). As the three and six months ended June 30, 2018 and 2017 resulted in net losses, there is no income allocation required under the two-class method or dilution attributed to weighted-average shares outstanding in the calculation of diluted loss per share.

The following Common Stock equivalents, presented on an as converted basis, were excluded from the calculation of net loss per share for the periods presented, due to their anti-dilutive effect:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2018	2017	2018	2017
Outstanding stock options	4,447,226	2,783,570	4,447,226	2,783,570
Convertible preferred stock	22,112,775	-	22,112,775	-
	26,560,001	2,783,570	26,560,001	2,783,570

9. Subsequent Events

The Company has evaluated all activity that occurred subsequent to quarter end but prior to issuance of the unaudited condensed consolidated financial statements for events or transactions that could require disclosure or that could impact the carrying value of assets or liabilities as of the balance sheet date.

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

MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of our financial condition and results of operations together with the unaudited condensed consolidated financial statements and related notes appearing elsewhere in this Quarterly Report on Form 10-Q.

Our actual results and timing of certain events may differ materially from the results discussed, projected, anticipated, or indicated in any forward-looking statements. We caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this Quarterly Report. In addition, even if our results of operations, financial condition and liquidity, and the development of the industry in which we operate are consistent with the forward-looking statements contained in this Quarterly Report, they may not be predictive of results or developments in future periods.

Overview

We are a late-stage biopharmaceutical company focused on the development of novel, first-in-class pharmaceuticals to address the medical needs of patients with kidney and vascular disease. Our product candidate, vonapanitase, is a recombinant human elastase that we are developing to improve vascular access outcomes in patients with chronic kidney disease, or CKD, undergoing or preparing for hemodialysis, a lifesaving treatment that cannot be conducted without a functioning vascular access. We believe the data from our completed Phase 2 and Phase 3 clinical trials of vonapanitase in patients undergoing creation of an arteriovenous fistula support that a one-time, local application of vonapanitase during surgical creation of a radiocephalic fistula for hemodialysis may improve fistula use for hemodialysis and secondary patency (time to fistula abandonment), thereby improving patient outcomes and reducing the burden on patients and the healthcare system. We are currently evaluating vonapanitase in our second Phase 3 trial, PATENCY-2, for vonapanitase in radiocephalic fistulas, our initial indication. Following our review of the complete data sets from our first Phase 3 trial, PATENCY-1 and discussions with the U.S. Food and Drug Administration, or FDA, we amended the protocol for the PATENCY-2 trial in the first quarter of 2017. The protocol amendment reordered the existing endpoints for this ongoing trial, establishing fistula use for hemodialysis and secondary patency as co-primary endpoints. We also increased the planned enrollment for this trial from 300 to 600 patients. The increased sample size provides power to detect the differences observed in the PATENCY-1 trial for fistula use for hemodialysis and secondary patency of 98% and 88%, respectively, with a p-value ≤ 0.05 for each of the co-primary endpoints. We received written confirmation from the FDA that, if PATENCY-2 is successful in showing statistical significance (p-value ≤ 0.05) on each of the co-primary endpoints, the PATENCY-2 trial together with data from previously completed studies would provide the basis for a Biologics License Application, or BLA, submission as a single pivotal study, in which case no additional studies would need to be conducted prior to submitting the BLA. Vonapanitase also received Breakthrough Therapy designation from the FDA in May 2017 for hemodialysis vascular access. The FDA awards Breakthrough Therapy designations to expedite the development and review of investigational drugs that are intended to treat serious or life-threatening conditions when preliminary clinical evidence indicates that the treatment may offer a substantial improvement over currently available therapies on one or more clinically significant endpoints. In March 2018, we completed the enrollment of 603 treated patients in the PATENCY-2 trial at 39 centers in the U.S. and Canada. We expect to report top-line data from the PATENCY-2 trial in March 2019 and, if the PATENCY-2 trial is successful, we expect to submit a BLA to the FDA in 2019. We further expect to submit a Marketing Authorization Application, or MAA, to the European Medicines Agency, or EMA, in 2020 if the PATENCY-2 trial is successful.

We commenced business operations in June 2001 and incorporated in March 2006. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, undertaking preclinical studies and clinical trials of vonapanitase, protecting our intellectual property and providing general and administrative support for these operations. To date, we have not generated any product revenue and have primarily financed our operations through the private placement of our equity securities, business development activities, convertible note financings, and our initial public offering, or IPO, completed in October 2014.

As of June 30, 2018, we had received an aggregate of $197.2 million in net proceeds comprised of $115.5 million from the issuance of private equity securities, $7.7 million from the issuance of convertible notes, $10.0 million from business development activities, $0.2 million from government grants, $62.5 million from our IPO and $1.3 million from the sale of Common Stock under our at-the-market, or ATM, program with Cowen and Company, LLC.

We have never been profitable and have incurred net losses in each year since inception. As of June 30, 2018, we had an accumulated deficit of $200.7 million and our net loss for the three and six months ended June 30, 2018 was $4.9 million and $11.0 million, respectively. We expect to incur significant expenses and increasing operating losses for the foreseeable future. We expect our research and development expenses to increase as we continue the clinical trials of, and seek regulatory approval for, vonapanitase. If we obtain regulatory approval for vonapanitase, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. Furthermore, we expect that our general and administrative costs will increase as we grow and operate as a public company. As a result, we will need to generate significant revenue if we are to achieve profitability, and we may never be able to do so.

We believe that our cash and cash equivalents and available-for-sale investments at June 30, 2018 will be sufficient to fund our operating expenses and capital expenditure requirements into the fourth quarter of 2019. We believe that these funds will be sufficient to enable us to report top line data from the PATENCY-2 trial, our second Phase 3 trial of vonapanitase in radiocephalic fistulas, and to fund our ongoing development and chemistry, manufacturing and controls, or CMC, activities.

We do not expect to generate revenue from product sales unless and until we successfully complete development and obtain regulatory approval for vonapanitase, which we expect will take a number of years and is subject to significant uncertainty. We have no manufacturing facilities and all of our manufacturing activities are contracted out to third parties. Additionally, we currently use third-party clinical research organizations, or CROs, to carry out our clinical development activities and we do not yet have a sales organization. If we obtain regulatory approval for vonapanitase, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. Accordingly, we may seek to further fund our operations through public or private equity or debt financings or other sources, including strategic collaborations. We may, however, be unable to raise additional funds or enter into such other arrangements when needed on favorable terms or at all. Our failure to raise additional capital or enter into such other arrangements as and when needed would have a negative impact on our financial condition and our ability to develop vonapanitase or any additional product candidates, if developed.

Recent Developments

On May 4, 2018, we entered into an amendment (the "Amendment") to our Manufacturing Services Agreement dated as of June 30, 2015 and signed on July 9, 2015 (as previously amended, the "Lonza Agreement") with Lonza Ltd. ("Lonza") for the commercial supply of the active pharmaceutical ingredient in our lead product candidate, vonapanitase. The Amendment extends the term of the Lonza Agreement for a period of seven (7) years from June 30, 2022 until June 30, 2029. The Amendment also allows for termination of the Lonza Agreement by either party upon 36 months' prior written notice to the other party, provided that we shall not exercise this termination right before January 1, 2020 and Lonza shall not exercise this termination right before January 1, 2023. In addition, the Amendment implements a change in the price per batch to be supplied by Lonza pursuant to the Agreement and provides that, contingent upon the approval of the product by the FDA, we are required to place orders for a minimum quantity of batches commencing in calendar year 2022. The parties further agreed to adjust the limitations of liability to cover the proposed manufacturing schedule and to replace the outstanding purchase obligation for one batch scheduled to commence before the end of 2019 with the right to make one batch, at our request, coincident with a pre-approval inspection of Lonza by the FDA.

Financial Overview

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for the development of vonapanitase, which include:

- employee-related expenses, including salaries, benefits, travel and stock-based compensation expense;
- expenses incurred under agreements with clinical research organizations, or CROs and investigative sites that will conduct our clinical trials;
- the cost of acquiring, developing and manufacturing clinical trial materials;
- costs associated with regulatory operations; and
- facilities, depreciation and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance and other supplies.

We expense research and development costs to operations as incurred. We recognize costs for certain development activities, such as clinical trials, based on an evaluation of the progress to completion of specific tasks using data such as patient enrollment, clinical site activations or information provided to us by our vendors.

We cannot determine with certainty the duration and completion costs of the current or future clinical trials or if, when, or to what extent we will generate revenues from the commercialization and sale of vonapanitase. We may never succeed in achieving regulatory approval for vonapanitase. The duration, costs and timing of clinical trials and development of vonapanitase will depend on a variety of factors, which include:

- the scope, rate of progress and expense of our ongoing as well as any additional clinical trials and other research and development activities;
- uncertainties in clinical trial enrollment rate;
- future clinical trial results;
- significant and changing government regulation; and
- the timing and receipt of any regulatory approvals.

A change in any of these factors could mean a significant change in the costs and timing associated with the development of vonapanitase. For example, if the FDA, EMA or another regulatory authority were to require us to conduct clinical trials beyond those that we currently anticipate will be required for the completion of clinical development or if we experience significant delays in enrollment in any of our clinical trials, we could be required to expend significant additional financial resources and time on the completion of clinical development. Our current development activities and future plans include the following:

- We completed enrollment in our second Phase 3 trial, PATENCY-2, and expect to report top-line data in March 2019.
- we may, based on additional data including the data from our ongoing Phase 3 clinical trial and if sufficient funds become available, study the effects of vonapanitase versus placebo on brachiocephalic fistulas and in patients undergoing placement of an arteriovenous graft, or graft;
- we initiated two Phase 1 clinical trials of vonapanitase in patients with peripheral artery disease, or PAD, in the fourth quarter of 2016. These multicenter, dose-escalation trials are designed to evaluate the safety and technical feasibility of a single administration of vonapanitase as a monotherapy and as an adjunct to angioplasty for patients with PAD above the knee and below the knee, respectively. In 2018, we expect to complete the enrollment and treatment of 24 patients in the Phase 1 trial evaluating vonapanitase as an adjunct to angioplasty for PAD below the knee. Based on our current operating plan, we have decided not to begin patient enrollment in the Phase 1 trial evaluating vonapanitase as a monotherapy for PAD. However, if sufficient funds become available, we may increase enrollment in the Phase 1 trial evaluating vonapanitase below the knee and begin patient enrollment in the Phase 1 trial evaluating vonapanitase as a monotherapy above the knee;

- we may, based on additional data including the data from our Phase 3 clinical trials and if sufficient funds become available, choose to conduct a clinical trial of vonapanitase in an additional PAD indication; and

- we expect to continue to manufacture clinical trial materials in support of our clinical trials and to also perform process validation activities in anticipation of a potential BLA submission.

Marketing, General and Administrative Expenses

Marketing, general and administrative expenses consist principally of salaries and related costs for personnel, including stock-based compensation and travel expenses, in executive and other administrative functions. Other marketing, general and administrative expenses also include professional fees for legal, patent review, consulting and accounting services as well as facility related costs. We anticipate increased expenses related to audit, legal, regulatory and tax-related services associated with maintaining compliance with our NASDAQ listing and SEC requirements, director and officer liability insurance premiums and investor relations costs associated with being a public company.

Additionally, if and when we believe a regulatory approval of vonapanitase appears likely, we anticipate that we will increase our salary and personnel costs and other expenses as a result of our preparation for commercial operations.

Investment Income

Investment income consists of interest income earned on our cash, cash equivalents and marketable securities.

Other Income (Expense), Net

Other income (expense), net consists of the gain realized from non-cash gains and losses from currency exchange rate fluctuations on transactions or balances denominated in a foreign currency. This foreign currency exposure is the result of a contract with the manufacturer of active pharmaceutical ingredient, or API for our lead product candidate, vonapanitase, which requires us to make payments in Swiss Francs.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial position and results of operations is based on our financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States of America, or GAAP. The preparation of financial statements in conformity with GAAP requires us to make estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. On an ongoing basis, we evaluate estimates, which include estimates related to clinical trial accruals, stock-based compensation expense, and reported amounts of revenues and expenses during the reported period. We base our estimates on historical experience and other market-specific or other relevant assumptions that we believe to be reasonable under the circumstances. Actual results may differ materially from those estimates or assumptions.

There have been no material changes to our accounting policies from those described in our Annual Report on Form 10-K. It is important that the discussion of our operating results that follows be read in conjunction with the critical accounting policies disclosed in our Annual Report on Form 10-K, as filed with the SEC on March 14, 2018.

Results of Operations

Comparison of the Three Months Ended June 30, 2018 and 2017

The following table summarizes our results of operations for the three months ended June 30, 2018 and 2017 (in thousands):

	Three Months Ended June 30,		
	2018	2017	Period-to-Period Change
Operating expenses:			
Research and development	$ 2,760	$ 3,891	$ (1,131)
General and administrative	2,240	2,095	145
Total operating expenses	5,000	5,986	(986)
Loss from operations	(5,000)	(5,986)	986
Other income:			
Investment income	106	46	60
Other income, net	15	332	(317)
Total other income	121	378	(257)
Net Loss	$ (4,879)	$ (5,608)	$ 729

Research and Development Expenses. The following table identifies research and development expenses on both an external and internal basis for the three months ended June 30, 2018 and 2017 (in thousands):

	Three Months Ended June 30,		
	2018	2017	Period-to-Period Change
External vonapanitase research and development expenses	$ 1,622	$ 2,651	$ (1,029)
Internal research and development expenses	1,138	1,240	(102)
Total research and development expenses	$ 2,760	$ 3,891	$ (1,131)

During the three months ended June 30, 2018, our total research and development expenses decreased by $1.1 million compared to the three months ended June 30, 2017 primarily due to $1.0 million in decreased external research and development expenses. The decrease of $1.0 million in external expenses was primarily driven by $0.5 million in decreased expenses for our manufacturing validation efforts and $0.5 million in decreased expenses for our ongoing clinical trials. Our internal research and development expenses decreased by $0.1 million in the three months ended June 30, 2018 as compared to the three months ended June 30, 2017 due primarily to decreased personnel costs.

Marketing, General and Administrative Expenses. During the three months ended June 30, 2018, our total marketing, general and administrative expenses were $0.1 million higher as compared to the three months ended June 30, 2017 primarily due to increases of $0.1 million in overhead and personnel costs to support our ongoing corporate activities.

Investment Income. During the three months ended June 30, 2018 investment income increased by $0.1 million as compared to the three months ended June 30, 2017 due to an increase in interest income on our cash, cash equivalents, and marketable securities.

Other Income, Net. During the three months ended June 30, 2018, other income, net, decreased by $0.3 million as compared to the three months ended June 30, 2017 primarily due to foreign currency remeasurement gain for cash denominated in Swiss Francs.

Comparison of the Six Months Ended June 30, 2018 and 2017

The following table summarizes our results of operations for the six months ended June 30, 2018 and 2017 (in thousands):

	Six Months Ended June 30,		
	2018	2017	Period-to-Period Change
Operating expenses:			
Research and development	$ 6,831	$ 8,137	$ (1,306)
General and administrative	4,534	4,329	205
Total operating expenses	11,365	12,466	(1,101)
Loss from operations	(11,365)	(12,466)	1,101
Other income:			
Investment income	198	78	120
Other income, net	207	282	(75)
Total other income	405	360	45
Net Loss	$ (10,960)	$ (12,106)	$ 1,146

Research and Development Expenses. The following table identifies research and development expenses on both an external and internal basis for the six months ended June 30, 2018 and 2017 (in thousands):

	Six Months Ended June 30,		
	2018	2017	Period-to-Period Change
External vonapanitase research and development expenses	$ 4,544	$ 5,578	$ (1,034)
Internal research and development expenses	2,287	2,559	(272)
Total research and development expenses	$ 6,831	$ 8,137	$ (1,306)

During the six months ended June 30, 2018, our total research and development expenses decreased by $1.3 million compared to the six months ended June 30, 2017 primarily due to $1.0 million in decreased external research and development expenses. The decrease of $1.0 million in external expenses was primarily driven by $0.6 million in decreased expenses for our ongoing clinical trials and $0.4 million in decreased expenses for our manufacturing validation efforts. Our internal research and development expenses decreased by $0.3 million in the six months ended June 30, 2018 as compared to the six months ended June 30, 2017 due primarily to decreased personnel costs.

Marketing, General and Administrative Expenses. During the six months ended June 30, 2018, our total marketing, general and administrative expenses were $0.2 million higher as compared to the six months ended June 30, 2017 primarily due to increases of $0.3 million in overhead and personnel costs in the six months ended June 30, 2018 to support our ongoing corporate activities offset by decreases of $0.1 million in expenses associated with being a public company.

Investment Income. During the six months ended June 30, 2018 investment income increased by $0.1 million as compared to the six months ended June 30, 2017 due to an increase in interest income on our cash, cash equivalents, and marketable securities.

Other Income, Net. During the six months ended June 30, 2018, other income, net, decreased by $0.1 million as compared to the six months ended June 30, 2017 primarily due to foreign currency remeasurement gain for cash denominated in Swiss Francs.

Liquidity and Capital Resources

Since our inception and through the six months ended June 30, 2018, we had received $197.2 million in net proceeds comprised of $115.5 million from the issuance of private equity securities, $7.7 million from the issuance of convertible notes, $10.0 million from business development activities, $0.2 million from government grants, $62.5 million from our IPO and $1.3 million from the sale of Common Stock under our at-the-market, or ATM, program with Cowen and Company, LLC. As of June 30, 2018, our cash and cash equivalents and available-for-sale investments totaled $26.5 million.

Operating Capital Requirements

We expect to incur increasing operating losses for at least the next several years as we (i) conduct our clinical trials for vonapanitase, thereafter seeking marketing approval for vonapanitase assuming successful trial outcomes, (ii) pursue development of vonapanitase for additional indications, and (iii) prepare for commercial operations. We may not be able to complete the development and initiate commercialization of vonapanitase if, among other things, our clinical trials are not successful, and the FDA does not approve vonapanitase or does not approve vonapanitase when we expect.

We believe that our cash and cash equivalents and available-for-sale investments as of June 30, 2018 will be sufficient to fund our operations into the fourth quarter of 2019. We believe that these funds will be sufficient to enable us to report top line data from our second Phase 3 trial of vonapanitase in radiocephalic fistulas, named PATENCY-2 and to fund our ongoing development and CMC activities through this date.

Our forecast of the period of time through which our financial resources will be adequate to support our operations is a forward-looking statement and involves risks and uncertainties, and actual results could vary as a result of a number of factors. We have based this estimate on assumptions that may prove to be wrong and we could exhaust our available capital resources sooner than we currently expect. Our future funding requirements, both near and long-term, will depend on many factors, including:

- the timing and costs of our Phase 3 clinical trial of vonapanitase in radiocephalic fistulas;
- the timing and costs of developing vonapanitase for additional indications, including PAD;
- the outcome, timing and costs of seeking regulatory approvals;
- the costs of commercialization activities for vonapanitase in radiocephalic fistulas and other indications if we receive marketing approval, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;
- subject to receipt of marketing approval, revenue received from commercial sales of vonapanitase;
- the terms and timing of any future collaborations, licensing, consulting or other arrangements that we may establish;
- the amount and timing of any payments we may be required to make, or that we may receive, in connection with the licensing, filing, prosecution, defense and enforcement of any patents or other intellectual property rights, including royalty payments that we are obligated to pay to Johns Hopkins University pursuant to our assignment agreement related to vonapanitase;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending against intellectual property related claims; and
- the extent to which we in-license or acquire other products and technologies.

Cash Flows

The following table summarizes our sources and uses of cash for the six months ended June 30, 2018 and 2017 (in thousands):

	Six Months Ended June 30,	
	2018	2017
Net cash used in operating activities	$ (15,804)	$ (10,728)
Net cash provided by (used in) investing activities	7,011	(8,454)
Net cash provided by financing activities	84	1,454
Effect of exchange rate changes on cash	24	(279)
Net decrease in cash, cash equivalents, and restricted cash	$ (8,685)	$ (18,007)

Comparison of the Six Months Ended June 30, 2018 and 2017

Net cash used in operating activities was $15.8 million for the six months ended June 30, 2018 compared to $10.7 million for the six months ended June 30, 2017. The increase of $5.1 million in cash used in operating activities was primarily driven by a $6.2 million increase in cash outflows related to changes in the components of working capital, principally related to a decrease in accounts payable and accrued expenses offset by a decrease in our net loss of $1.1 million, as compared to the six months ended June 30, 2017.

Net cash provided by investing activities was $7.0 million for the six months ended June 30, 2018 compared to $8.5 million used in the six months ended June 30, 2017. The change of $15.5 million in cash provided by investing activities was driven by an increase in cash inflows of $13.1 million due to increased proceeds from maturities and sales of available-for-sale investments and a decrease in the cash outflow of $2.4 million in the purchases of available-for-sale investments.

Net cash provided by financing activities for the six months ended June 30, 2018 decreased by $1.4 million compared to the six months ended June 30, 2017 due to there being no issuances of Common Stock or exercises of stock options during the six months ended June 30, 2018, as compared to $1.3 million of proceeds from the issuance of Common Stock, net of issuance costs and $0.1 million of proceeds due to the exercise of stock options during the six months ended June 30, 2017.

Off-Balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under the applicable regulations of the SEC.

Contractual Obligations

The following table summarizes our outstanding contractual obligations as of payment due date by period as of June 30, 2018 (in thousands):

	Total	Less than 1 Year	1 to 3 Years	3 to 5 Years	More than 5 Years
Operating Leases (1)	$ 345	$ 276	$ 69	-	-
Purchase Obligations (2)	CHF -	CHF -	CHF -	-	-

(1) In July 2009 we entered into a multi-year non-cancelable lease for our offices in Waltham, Massachusetts. In October 2011, we amended the lease extending its expiration to December 2014. In August 2014, we amended the lease extending its expiration to June 2018 with one optional one-year extension period. In August 2017, we amended the lease extending its expiration to September 2019 with one optional one-year extension period. The minimum lease payments above do not include common area maintenance charges or real estate taxes.

(2) The near term purchase commitment for Lonza has been removed from the commitments table per the amendment to the manufacturing agreement we signed in May 2018 in which the outstanding purchase obligation for the one batch scheduled to commence before the end of 2019 was replaced with the right to make one batch, at our request, coincident with a pre-approval inspection of Lonza by the FDA.

The contractual obligation table does not include, due to the uncertainty of the occurrence of these events requiring payment under these agreements, any potential future royalty payments we may be required to make under our license assignment with Johns Hopkins University and does not include any potential future payments we may be required to make under our agreement with Lonza, due to the uncertainty of the occurrence of the events requiring payment under those agreements.

JOBS Act

In April 2012, the Jumpstart Our Business Startups Act, or JOBS Act was enacted in the United States. Section 107 of the JOBS Act provides that an "emerging growth company," or EGC, can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act for complying with new or revised accounting standards. Thus, an emerging growth company can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this extended transition period and, as a result, we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-emerging growth public companies.

Item 3. Qualitative and Quantitative Disclosures about Market Risk

The market risk inherent in our financial instruments and in our financial position represents the potential loss arising from adverse changes in interest rates. As of June 30, 2018, we had cash equivalents and available-for-sale investments of $26.5 million consisting primarily of investments in U.S. Treasuries, U.S. government-backed and agency securities, and certificates of deposit. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in short-term marketable securities. Our marketable securities are subject to interest rate risk and could fall in value if market interest rates increase. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, an immediate 10% change in interest rates would not have a material effect on the fair market value of our investment portfolio. We have the ability to hold our marketable securities until maturity, and therefore, we would not expect our operating results or cash flows to be affected to any significant degree by the effect of a change in market interest rates on our investments.

We contract with CROs and contract manufacturers internationally. Transactions with one of our contract manufacturers is settled in Swiss Francs and therefore, while we believe we have some foreign currency exposure, we have entered into forward foreign currency contracts to purchase Swiss Francs to manage this risk. The last outstanding forward foreign currency contract was executed during December 2016.

Item 4. Controls and Procedures

Management's Evaluation of our Disclosure Controls and Procedures

We maintain disclosure controls and procedures (as defined in Rules 13a-15(e) or 15d-15(e) under the Exchange Act) that are designed to ensure that information required to be disclosed in the reports that we file or submit under the Exchange Act is (1) recorded, processed, summarized, and reported within the time periods specified in the SEC's rules and forms and (2) accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate, to allow timely decisions regarding required disclosure.

As of June 30, 2018, our management, with the participation of our principal executive officer and principal financial officer, evaluated the effectiveness of our disclosure controls and procedures as of the end of the period covered by this Quarterly Report. Our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives, and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Our principal executive officer and principal financial officer have concluded based upon the evaluation described above that, as of June 30, 2018, our disclosure controls and procedures were effective at the reasonable assurance level.

We continue to review and document our disclosure controls and procedures, including our internal controls and procedures for financial reporting, and may from time to time make changes aimed at enhancing their effectiveness and to ensure that our systems evolve with our business.

Changes in Internal Control Over Financial Reporting

During the six months ended June 30, 2018, there have been no changes in our internal control over financial reporting, as such term is defined in Rules 13a-15(f) and 15(d)-15(f) promulgated under the Securities Exchange Act of 1934, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II – OTHER INFORMATION

Item 1. Legal Proceedings

From time to time we may become subject to various legal proceedings and claims that arise in the ordinary course of our business activities. Although the results of litigation and claims cannot be predicted with certainty, as of the date of this Quarterly Report on Form 10-Q, we do not believe we are party to any claim or litigation, the outcome of which, if determined adversely to us, would individually or in the aggregate be reasonably expected to have a material adverse effect on our business. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.

Item 1A. Risk Factors

Any investment in our Common Stock involves a high degree of risk. The following risk factors and other information included in this Quarterly Report on Form 10-Q should be carefully considered. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently believe to be immaterial may also adversely affect our business. We refer you to our "Cautionary Note Regarding Forward-Looking Statements," which identifies certain forward-looking statements contained in this report that are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.

Risks Related to Our Financial Condition and Need for Additional Capital

We have a limited operating history and have incurred significant losses since our inception, and we anticipate that we will continue to incur losses for the foreseeable future.

We are a late-stage biotechnology company, and we have not commercialized any products or generated any revenues from the sale of products. We have incurred losses from operations in each year since our inception, and our net losses were $30.0 million and $28.5 million for the years ended December 31, 2017 and 2016, respectively, and $11.0 million and $12.1 million for the six months ended June 30, 2018 and 2017, respectively. As of June 30, 2018, we had an accumulated deficit of $200.7 million. We do not expect to generate any product revenues in the foreseeable future. We do not know whether or when we will generate revenue or become profitable.

We have devoted most of our financial resources to research and development, including our clinical and preclinical development activities. To date, we have financed our operations primarily through the sale of equity securities and, prior to our initial public offering, the sale of convertible debt. Our current product candidate, vonapanitase, is in clinical trials and we have no commercial sales, which, together with our limited operating history, make it difficult to assess our future viability. The amount of our future net losses will depend, in part, on the rate of our future expenditures and our ability to obtain funding through equity or debt financings or strategic collaborations. We have not completed pivotal clinical trials for any product candidate and it will be several years, if ever, before we have vonapanitase or any future product candidates ready for commercialization. Even if we obtain regulatory approval to market vonapanitase or any additional product candidates, our future revenues will depend upon the size of any markets in which vonapanitase or any additional product candidates have received approval, our ability to achieve sufficient market acceptance, reimbursement from third-party payors and other factors.

We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our expenses will increase substantially if and as we:

- continue our clinical development and seek regulatory approval of vonapanitase, particularly with respect to its lead indication for radiocephalic arteriovenous fistulas;
- commercialize vonapanitase directly in the United States;
- undertake clinical development of vonapanitase in Europe and establish partnerships for commercialization of vonapanitase in all or parts of Europe;
- pursue additional indications for vonapanitase including clinical development of vonapanitase for brachiocephalic fistulas, patients requiring placement of an arteriovenous graft, and additional indications for the treatment of patients with symptomatic peripheral artery disease, or PAD;
- in-license or acquire additional product opportunities and make milestone or other payments under any in-license agreements;
- contract for the manufacture of commercial quantities of vonapanitase;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- maintain, protect and expand our intellectual property portfolio;
- attract and retain skilled personnel;
- create additional infrastructure to support our operations as a public company and our product development; and
- experience any delays or encounter issues with any of the above.

The net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance. In any particular quarter or quarters, our operating results could be below the expectations of securities analysts or investors, which could cause our stock price to decline.

We will require substantial additional financing to achieve our goals, and a failure to obtain this necessary capital when needed on acceptable terms, or at all, could force us to delay, limit, reduce or terminate our product development, any commercialization efforts or other operations.

Our operations have consumed substantial amounts of cash since inception. As of June 30, 2018, our cash, cash equivalents and available-for-sale investments were $26.5 million. Our research and development expenses were $6.8 million and $8.1 million for the six months ended June 30, 2018 and 2017, respectively. We believe that we will continue to expend substantial resources for the foreseeable future developing vonapanitase and any additional product candidates. These expenditures will include costs associated with research and development, potentially acquiring new technologies, potentially obtaining regulatory approvals and manufacturing products, as well as marketing and selling products approved for sale, if any. In addition, other unanticipated costs may arise. Because the outcome of our planned and anticipated clinical trials is highly uncertain, we cannot reasonably estimate the actual amounts necessary to fund and successfully complete the development and commercialization of vonapanitase or any additional product candidates.

We began enrolling patients in our first Phase 3 clinical trial of vonapanitase during the third quarter of 2014 for patients undergoing creation of radiocephalic fistulas, completed patient enrollment in October 2015 and released top-line data in December 2016. We enrolled the first patient in our second Phase 3 trial in August 2015, completed enrollment in March 2018 and expect to release top-line data in March 2019. Based on our current operating plan, and absent any future financings or strategic partnerships, we believe that our existing cash, cash equivalents and available-for-sale investments will be sufficient to fund our projected operating expenses and capital expenditure requirements into the fourth quarter of 2019, allowing us to report top-line data from our second Phase 3 trial of vonapanitase in radiocephalic fistulas, named PATENCY-2. Our cash runway could be shortened if there are any significant and unexpected increases in spending on development programs or more rapid progress of development programs than anticipated. In addition, we initiated two Phase 1 clinical trials of vonapanitase in patients with PAD in the fourth quarter of 2016. We plan to complete the enrollment and treatment of 24 patients before the end of 2018 in the Phase 1 trial evaluating vonapanitase as an adjunct to angioplasty for PAD below the knee. We may begin patient enrollment in the Phase 1 trial evaluating vonapanitase as a monotherapy for PAD above the knee if sufficient funds become available. We may also initiate other small Phase 1 or Phase 1/2 trials in additional indications, which would further reduce our capital resources. However, we do not expect to initiate any other Phase 2 or Phase 3 trials prior to receiving and reviewing data from our second Phase 3 clinical trial. Furthermore, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements, or a combination of these approaches. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations.

Additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize vonapanitase or any additional product candidates. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, or at all. We could also be required to seek funds through arrangements with collaborative partners or otherwise at an earlier stage than would otherwise be ideal and we may be required to relinquish rights to vonapanitase or any additional product candidates, or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results and prospects.

If we are unable to obtain funding on a timely basis, we may be required to significantly curtail, delay or discontinue one or more of our research or development programs or the commercialization of any approved products or be unable to expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially adversely affect our business, financial condition and results of operations.

We have never generated any revenue from product sales and may never be profitable.

As a company, we have never obtained regulatory approval for, or commercialized, any product candidate. Our ability to generate substantial revenue and achieve profitability depends on our ability, alone or with strategic collaboration partners, to successfully complete the development of, and obtain the regulatory approvals necessary to commercialize, vonapanitase or any additional product candidates. We do not anticipate generating revenues from product sales for at least the next several years, if ever. If vonapanitase or any additional product candidates fail in clinical trials or do not gain regulatory approval, or if vonapanitase or any additional product candidates, if approved, fail to achieve market acceptance, we may never become profitable. Even if we achieve profitability in the future, we may not be able to sustain profitability in subsequent periods. Our ability to generate future revenues from product sales depends heavily on our success in:

- completing clinical development of vonapanitase for one or more indications and research and preclinical and clinical development of additional product candidates;
- seeking and obtaining regulatory and marketing approvals for vonapanitase if and when we complete clinical trials;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate (in amount and quality) products and services to support clinical development and the market demand for vonapanitase, if approved;
- launching and commercializing vonapanitase if we obtain regulatory and marketing approval, either by collaborating with a partner or, if launched independently, by establishing our own sales, marketing and distribution infrastructure;

- obtaining and maintaining adequate timely coverage and reimbursement from third-party payors for vonapanitase;
- obtaining market acceptance of vonapanitase as a viable treatment option;
- addressing any competing technological and market developments;
- implementing additional internal systems and infrastructure, as needed;
- identifying and validating new product candidates;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents and know-how;
- developing vonapanitase such that, if approved, it can be commercialized without infringing the intellectual property rights of third parties; and
- attracting, hiring and retaining qualified personnel.

Even if vonapanitase or any additional product candidates that we may develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by the United States Food and Drug Administration, or the FDA, the European Medicines Agency, or EMA, or other regulatory agencies, domestic or foreign, to perform clinical trials and other studies in addition to those that we currently anticipate. Even if we are able to generate revenues from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations. Our failure to become and remain profitable would depress the market price of our Common Stock and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

Risks Related to Clinical Development, Regulatory Review and Approval of Our Product

We are substantially dependent on the success of our current product candidate, vonapanitase, and cannot guarantee that this product candidate will successfully complete Phase 3 clinical trials, receive regulatory approval or be successfully commercialized.

We currently have no products approved for commercial distribution. We have invested substantially all of our efforts and financial resources in the development of our current product candidate, vonapanitase. Our business depends entirely on the successful development and commercialization of vonapanitase, in vascular access or additional indications, which may never occur. Our ability to generate revenues in the near term is substantially dependent on our ability to develop, obtain regulatory approval for, and then successfully commercialize vonapanitase. We currently generate no revenues from sales of any products, and we may never be able to develop or commercialize a marketable product.

Vonapanitase will require additional clinical development, regulatory approval, commercial manufacturing arrangements, establishment of a commercial organization, significant marketing efforts and further investment before we generate any revenues from product sales. We are not permitted to market or promote vonapanitase for any indication before we receive regulatory approval from the FDA or comparable foreign regulatory authorities, and we may never receive this regulatory approval for any of our product candidates. If we do not receive FDA approval and successfully commercialize vonapanitase, we will not be able to generate revenue from vonapanitase in the United States in the foreseeable future, or at all. Moreover, any significant delays in obtaining approval for and commercializing vonapanitase will have a substantial adverse impact on our business and financial condition.

We have not previously submitted a Biologics License Application, or BLA, to the FDA, or similar drug or biologic approval filings to comparable foreign authorities, for any product candidate, and we cannot be certain that vonapanitase or any additional product candidates will be successful in clinical trials or receive regulatory approval. In our first Phase 3 clinical trial, our primary efficacy endpoint of primary unassisted patency did not show statistically significant benefit for the 30 microgram dose versus placebo. While analyses of the first Phase 3 trial's other efficacy endpoints, including fistula use for hemodialysis and secondary patency, suggested clinically meaningful improvements over placebo, we cannot assure you that these results will be repeated in our second Phase 3 trial. Following our review of the data from our first Phase 3 clinical trial of vonapanitase and discussions with the FDA, we amended the protocol for our second Phase 3 clinical trial in the first quarter of 2017 to increase the planned enrollment from 300 to 500 patients, which we subsequently increased to 600 patients in the second quarter of 2017. We also re-ordered the endpoints to include co-primary endpoints of fistula use for hemodialysis and secondary patency, each of which are required to show a statistically significant benefit ($p \leq 0.05$) in order to provide the basis for a BLA submission for vonapanitase as a single pivotal trial. Even though our second Phase 3 trial will evaluate co-primary endpoints for vonapanitase that showed improvements in our first Phase 3 clinical trial, there are risks of failure inherent at any stage of product development, and we may not demonstrate efficacy with regard to the co-primary endpoints of our ongoing Phase 3 clinical trial or our reordering of the endpoints could otherwise adversely affect the success of the second Phase 3 trial, or unexpected adverse events may occur. Further, vonapanitase or any additional product candidates may not receive regulatory approval even if they are successful in clinical trials. If approved for marketing by applicable regulatory authorities, our ability to generate revenues from vonapanitase will depend on our ability to, among other things:

- launch vonapanitase commercially, whether alone or in collaboration with others;
- create market demand for vonapanitase through our own marketing and sales organization, and through any other promotional arrangements that we may otherwise establish;
- hire, train and deploy a specialty sales force, focused primarily on vascular surgeons, to commercialize vonapanitase in the United States;
- manufacture vonapanitase in sufficient quantities and at acceptable quality and manufacturing cost to meet commercial demand at launch and thereafter and establish and maintain agreements with wholesalers, distributors and group purchasing organizations on commercially reasonable terms;
- create partnerships with third parties to promote and sell vonapanitase in any foreign markets where we receive marketing approval;
- obtain and maintain patent protection and regulatory exclusivity for vonapanitase;
- achieve appropriate reimbursement for vonapanitase;
- effectively compete with other products should any be successfully developed and approved; and
- maintain a continued acceptable safety profile of vonapanitase following launch.

If we develop vonapanitase for other indications, including arteriovenous grafts, brachiocephalic fistula and symptomatic PAD, or develop additional product candidates, we will face similar risks and challenges.

Clinical development is a lengthy and expensive process with an uncertain outcome due to many factors. Because the results of early clinical trials are not necessarily predictive of future results, vonapanitase may not have favorable results in current or future clinical trials or receive regulatory approval.

Clinical development is expensive, difficult to design and implement, takes many years to complete and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process and vonapanitase is subject to the risks of failure inherent in drug and biological development, including failure to demonstrate efficacy in a pivotal clinical trial or in the patient population we intend to enroll, the occurrence of severe or medically or commercially unacceptable adverse events, failure to comply with protocols or applicable regulatory requirements and determination by the FDA or any comparable foreign regulatory authority that a drug and biological product is not approvable. Results observed in earlier clinical trials may not be replicated in current or future clinical trials. For example, our first Phase 3 clinical trial of vonapanitase failed to meet its primary endpoint of primary unassisted patency, despite encouraging results from our Phase 2 trial. In addition, as is common with clinical trials, we explored a number of endpoints in our Phase 2 clinical trial of vonapanitase. We also analyzed the data from our Phase 2 and Phase 3 clinical trials of vonapanitase in a number of ways. Product candidates such as vonapanitase in Phase 3 clinical trials may fail to demonstrate sufficient efficacy despite having progressed through earlier clinical trials, even if certain analyses of primary, secondary or tertiary endpoints in those early trials showed statistical significance. Companies may suffer significant setbacks in late-stage clinical trials due to lack of efficacy, site or investigator issues, manufacturing or formulation changes or adverse safety profiles, even after earlier clinical trials have shown promising results. During the course of our clinical development, we modified our vonapanitase drug product formulation for our Phase 3 trials and commercial launch in order to facilitate ease of administration and fill and finish of vials at our 30 microgram dose. Our formulation changes could adversely affect results in our clinical trials, requiring us to make further formulation changes. In addition, following our review of the data from our first Phase 3 clinical trial of vonapanitase and discussions with the FDA, we amended the protocol for our second Phase 3 trial to include co-primary endpoints of fistula use for hemodialysis and secondary patency, each of which was studied in earlier clinical trials. Our reordering of the endpoints could adversely affect the success of the second Phase 3 trial. Additional changes or interactions with the FDA could also cause us to delay or repeat clinical trials, or could cause FDA to request additional studies or data, and we could incur unexpected costs that would have an adverse effect on our business, operating results, financial condition and prospects.

The design of a clinical trial can determine whether its results will support approval of a product, and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced or completed. We have limited experience in designing clinical trials and we may be unable to design and execute a clinical trial to support marketing approval. In addition, preclinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for the product candidates. Even if we believe that the results of clinical trials for our product candidates warrant marketing approval, the FDA or comparable foreign regulatory authorities may disagree and may not grant marketing approval of vonapanitase or any additional product candidates.

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the clinical trial visit schedule or protocols, changes in practice patterns outside of the protocols and the rate of dropout among clinical trial participants. Any Phase 3 or other clinical trial that we may conduct may not demonstrate the efficacy and safety necessary to obtain regulatory approval to market vonapanitase or any additional product candidate.

Any delay or failure in our clinical trials would delay our obtaining, or make us unable to obtain, applicable regulatory approvals, which would prevent us from commercializing vonapanitase or any additional product candidates, generating revenues and achieving and sustaining profitability.

If clinical trials of vonapanitase or any additional product candidates fail to demonstrate safety and efficacy to the satisfaction of the FDA and comparable foreign regulators, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of vonapanitase or any additional product candidates.

We are not permitted to commercialize, market, promote or sell any product candidate in the United States without obtaining marketing approval from the FDA. Comparable foreign regulatory authorities, such as the EMA, impose similar restrictions. We may never receive these regulatory approvals. We must have completed extensive preclinical development and clinical trials to demonstrate the safety and efficacy of the product candidate in humans before we will be able to obtain these approvals. Clinical testing is expensive, is difficult to design and implement, can take many years to complete and is inherently uncertain as to outcome.

Any inability to successfully complete clinical development could result in additional costs to us and impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties. If, following submission, our BLA is not accepted for substantive review (i.e., filing) or approved, the FDA may require that we conduct additional clinical or preclinical trials, manufacture additional validation batches or develop additional analytical test methods before it will reconsider our application. If the FDA requires additional studies or data, we would incur increased costs and delays in the marketing approval process, which may require us to expend more resources than we have available. In addition, the FDA may not consider any additional required trials that we perform and complete to be sufficient.

In addition, if (1) we are required to conduct additional clinical trials or other testing of or generate data pertaining to vonapanitase beyond the trials and testing that we contemplate, (2) we are unable to successfully complete clinical trials or other testing of vonapanitase or any additional product candidates, (3) the results of these trials or tests are unfavorable, uncertain or are only modestly favorable, or (4) there are unacceptable safety concerns associated with vonapanitase or any additional product candidates, we, in addition to incurring additional costs, may:

- be delayed in obtaining marketing approval for vonapanitase or any additional product candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as we intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or significant safety warnings, including boxed warnings;
- be subject to additional post-marketing testing or other requirements; or
- be required to remove the product from the market after obtaining marketing approval.

In general, the FDA requires two adequate and well-controlled clinical trials to demonstrate the effectiveness of a product candidate. In December 2016, we announced that our first Phase 3 clinical trial did not meet its primary endpoint of improved primary unassisted patency compared to placebo ($p=0.254$). Based on our interactions with the FDA, we believe that, if the results for each of the co-primary endpoints of our second Phase 3 clinical trial show statistical significance ($p\leq0.05$), our second Phase 3 trial together with data from previously completed studies will provide the basis for a BLA submission for vonapanitase to the FDA. However, even with robust p-values, there is no guarantee that the results of the second Phase 3 trial will be sufficient for a BLA submission, filing or approval, and the FDA, EMA or other foreign regulatory authorities may require that we conduct additional trials.

We may be unable to obtain regulatory approval for vonapanitase or any additional product candidates under applicable regulatory requirements. The denial or delay of any approvals would prevent or delay commercialization and have a material adverse effect on our potential to generate revenue, our business and our results of operations.

Vonapanitase and any additional product candidates are subject to extensive governmental regulations relating to, among other things, research, clinical trials, approval, manufacturing, recordkeeping, labeling, storage, advertising, promotion, distribution, import, export and commercialization. In order to obtain regulatory approval for the commercial sale of any product candidate, we must demonstrate through extensive preclinical studies and clinical trials that the product candidate is safe and effective for use in each target indication. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. Vonapanitase is still in development and is subject to the risks of failure inherent in drug or biologic development. We have not received approval to market any product candidate from regulatory authorities in any jurisdiction. We have only limited experience in conducting and managing the clinical trials, and in submitting and supporting the applications necessary to gain marketing approvals, and we expect to rely on third-parties, including clinical research organizations, or CROs, to assist us in this process. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities and clinical trial sites by, the regulatory authorities. Vonapanitase may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use. We may gain regulatory approval for vonapanitase or any additional product candidates in some but not all of the territories available or some but not all of the target indications, resulting in limited commercial opportunity for the product, or we may never obtain regulatory approval for vonapanitase or any additional product candidates in any jurisdiction.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. The FDA, EMA and other foreign regulatory authorities also have substantial discretion in the drug and biologics approval process. The number and types of preclinical studies and clinical trials that will be required for regulatory approval varies depending on the product candidate, the disease or condition that the product candidate is designed to address, and the regulations applicable to any particular product candidate. Approval policies, regulations or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions, and there may be varying interpretations of data obtained from preclinical studies or clinical trials, either of which may cause delays or limitations in the approval or the decision not to approve an application. Regulatory agencies can delay, limit or deny approval of a product candidate for many reasons, including:

- IRBs, the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials;
- we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that a product candidate is safe and effective for its proposed indications;
- an FDA Advisory Committee or other regulatory authority may recommend against approval or restrictions on approval;
- the results of later-stage clinical trials may not meet the level of statistical or clinical significance required by the FDA or comparable foreign regulatory authorities for approval;
- the results of later-stage clinical trials may not confirm the positive results from earlier preclinical studies or clinical trials;
- we may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- the data collected from clinical trials of vonapanitase or any additional product candidate may not be sufficient to the satisfaction of the FDA or comparable foreign regulatory authorities to support the submission of a BLA, or other comparable submission in foreign jurisdictions or to obtain regulatory approval in the United States or elsewhere;
- our manufacturing processes or facilities may not be adequate to support approval of our product candidates; or
- regulatory agencies may change their approval policies or adopt new regulations in a manner rendering our clinical data insufficient for approval.

It is possible that neither vonapanitase nor any product candidates we may seek to develop in the future will ever obtain the appropriate regulatory approvals necessary for us or any future collaborators to commence product sales. We do not know whether any clinical trials will begin as planned, or will be revised prior to or during the conduct of the study, completed on time or conducted at all. Any delay in obtaining, or failure to obtain, required approvals would materially adversely affect our ability to generate revenue from the particular product candidate, which likely would result in significant harm to our financial position and adversely impact our stock price.

We may face difficulty in enrolling patients for clinical trials.

We may find it difficult to enroll patients in our clinical trials, which could delay or prevent completion of clinical trials of vonapanitase or any additional product candidates. Identifying and qualifying patients to participate in clinical trials of vonapanitase or any additional product candidates are critical to our success. The timing of our clinical trials depends on the speed at which we can recruit patients to participate in testing product candidates. The enrollment timeline for patients can be lengthy and there are a limited number of sites from which we can enroll certain patients. If patients are unwilling to participate in our trials because of negative publicity from adverse events or for other reasons, including the results of completed or competitive clinical trials for similar patient populations, the timeline for recruiting patients, conducting trials and obtaining regulatory approval of potential products may be delayed or prevented. These delays could result in increased costs, delays in advancing our product development, delays in testing the effectiveness of our technology or termination of the clinical trials altogether. We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics to achieve diversity in a trial, to complete our clinical trials in a timely manner. Patient enrollment is affected by numerous factors including:

- severity of the disease under investigation;
- design of the trial protocol;
- size and nature of the patient population;
- eligibility criteria for the trial in question;
- perceived risks and benefits of the product candidate under study;
- proximity and availability of clinical trial sites for prospective patients;
- availability of competing therapies and clinical trials;
- efforts to facilitate timely enrollment in clinical trials;
- our ability to obtain and maintain subject consents;
- the risk that enrolled subjects will drop out or be withdrawn from our studies;
- patient referral practices of physicians;
- ability to monitor patients adequately during and after treatment; and
- the ability of subjects to comply with the clinical trial visit schedule and procedures.

We may not be able to initiate or continue clinical trials if we cannot enroll a sufficient number of eligible patients to participate in the clinical trials required by regulatory agencies. If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit or terminate ongoing or planned clinical trials, any of which would have an adverse effect on our business.

If we experience any of a number of possible unforeseen events in connection with clinical trials of vonapanitase or any additional product candidates, potential marketing approval or commercialization of vonapanitase or any additional product candidates could be delayed or prevented.

If we experience delays in clinical testing, we will be delayed in obtaining regulatory approvals and commercializing our product candidates, our costs may increase and our business may be harmed. We do not know whether any future clinical trials that have not started will begin as planned, whether the design will be revised prior to or during conduct of the study, completed on schedule or conducted at all. Our product development costs may increase if we experience delays in clinical testing or changes to clinical protocols. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which would impair our ability to successfully commercialize our product candidates and may harm our business, results of operations and prospects. We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent marketing approval of vonapanitase or any additional product candidates, including:

- trials of vonapanitase or any additional product candidates may produce unfavorable or inconclusive results;
- we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- our third-party contractors, including those manufacturing vonapanitase or any additional product candidates or components or ingredients for commercial use or conducting clinical trials on our behalf, may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner or at all;
- regulators or institutional review boards, or IRBs, may not authorize us or our investigators to commence or continue to conduct a clinical trial at a prospective trial site;
- we may have to suspend or terminate clinical trials of vonapanitase or any additional product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of a product candidate;
- regulators or IRBs may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or their respective standards of conduct, a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of the product candidate or findings of undesirable effects caused by a chemically or mechanistically similar biologic or biologic candidate;
- we may experience delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites and/or Contract Research Organizations, or CROs;
- we may experience withdrawal of clinical trial sites from our clinical trials as a result of changing standards of care or the ineligibility of a site to participate in our clinical trials, and may further be delayed in trying to add clinical trial sites to our studies;
- we may experience delays in the importation and manufacture of clinical supply;
- patient enrollment in these clinical trials may be slower than we anticipate and is limited to a select number of sites, which could cause significant delays given the prolonged enrollment period;
- participants may drop out of clinical trials of vonapanitase at a higher rate than we anticipate and we may not be able to obtain the follow up data for the 12 month period planned in our Phase 3 trial;
- patients who enroll in a clinical trial may misrepresent their eligibility to do so or may otherwise not comply with the clinical trial protocol, resulting in the need to drop the patients from the clinical trial or increase the needed enrollment size for the clinical trial beyond the current enrollment for the Phase 3 trial, all of which may extend the clinical trial's duration;
- the FDA or comparable foreign regulatory authorities may disagree with our clinical trial design, implementation, or our interpretation of data from preclinical studies and clinical trials;
- FDA or comparable foreign regulatory authorities may find that our clinical trials were not conducted in accordance with Good Clinical Practices, or GCPs;
- the FDA or comparable foreign regulatory authorities may fail to approve or subsequently find fault with the manufacturing processes or facilities of third-party manufacturers with which we enter into agreements for clinical and commercial supplies;

- our finished product that has been manufactured for the vonapanitase Phase 3 trials may be inadequate, or the materials or manufactured product candidates necessary to conduct future clinical trials of vonapanitase or any additional product candidates may be insufficient, inadequate or not available at an acceptable cost, or we may experience interruptions in supply;

- we may lack adequate funding to continue the clinical trials; and

- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient to obtain marketing approval.

Product development costs for us will increase if we experience delays in testing or pursuing marketing approvals, and we may be required to obtain additional funds to complete clinical trials and prepare for possible commercialization of vonapanitase or any additional product candidates. We do not know whether any future clinical trials that have not yet started will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize vonapanitase or any additional product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize vonapanitase or any additional product candidates and may harm our business and results of operations. In addition, many of the factors that cause, or lead to, clinical trial delays may ultimately lead to the denial of marketing approval of vonapanitase or any additional product candidates.

Any product for which we obtain FDA approval will be subject to extensive ongoing regulatory requirements, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.

Any product for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical research, labeling, advertising and promotional activities for the product, will be subject to continual requirements of, and review by, the FDA and comparable regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, tracking, tracing, investigation, notification, and disposition obligations under the Drug Quality and Security Act, registration and listing requirements, current good manufacturing practices, or cGMPs, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. The FDA and comparable foreign regulatory authorities will continue to closely monitor the safety profile of any product even after approval. If the FDA or comparable foreign regulatory authorities become aware of new safety information after approval of any of our product candidates, they may withdraw approval, require labeling changes or establishment of a REMS or similar risk mitigation strategy, impose significant restrictions on a product's indicated uses or marketing, or impose ongoing requirements for potentially costly post-approval studies or post-market surveillance.

Even if regulatory approval of a product is granted, the approval will be subject to limitations on the indicated uses for which the product may be marketed and may be subject to other conditions of approval. We and our contract manufacturers will be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance with cGMPs and other regulatory requirements. In addition, approval may contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the product. Discovery after approval of previously unknown problems with any such products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in actions such as:

- restrictions on our ability to conduct clinical trials, including full or partial clinical holds on ongoing or planned trials;

- restrictions on a product's manufacturing processes or facilities;

- restrictions on the marketing of a product;

- restrictions on product distribution;

- requirements to conduct post-marketing clinical trials;
- Untitled, Cyber, or Warning Letters from the FDA or similar correspondence from comparable regulatory authorities;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- mandated modifications to labeling and promotional materials or requirements to provide corrective information to healthcare practitioners;
- requirements to enter into a consent decree, which can include imposition of various fines, reimbursements for inspection costs, required due dates for specific actions and penalties for noncompliance;
- debarring us pursuant to the Federal Food, Drug, and Cosmetic Act, or FDCA, excluding us from participation in federal healthcare programs, requiring a corporate integrity agreement or debarring us from government contracts;
- the imposition of costly new manufacturing requirements or use of alternative suppliers;
- FDA or other regulatory bodies issuing safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings about our products;
- fines, restitution or disgorgement of profits or revenue;
- suspension or withdrawal of regulatory approvals or refusal to approve future or pending applications or supplements;
- refusal to permit the import or export of our products;
- product seizure;
- injunctions; and/or
- imposition of civil or criminal penalties.

Accordingly, assuming we receive marketing approval for vonapanitase or any additional product candidates, we and our contract manufacturers will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, distribution, product surveillance, post-marketing studies and quality control.

Vonapanitase may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of approved labeling, or result in significant negative consequences following any potential marketing approval.

As with many pharmaceutical and biological products, treatment with vonapanitase or any additional product candidates may produce undesirable side effects or adverse reactions or events. These adverse events may occur despite our belief, based on our preclinical and clinical trials to date, that vonapanitase has a favorable safety profile. For instance, vonapanitase shows a high degree of structural similarity with other human serine proteases, which are proteins that cut other proteins to activate, inactivate or degrade these other proteins, and it is theoretically possible that if anti-vonapanitase antibodies are developed that they could cross-react with one or more of those other proteases because of the structural similarity, and prompt an adverse reaction. However, we have not seen any evidence of such cross-reactivity in our preclinical or clinical trials to date.

Based on our Phase 2 and Phase 3 trials, adverse side effects that could occur with treatment with vonapanitase include fistula surgical incision pain, venous stenosis, procedural pain, fistula thrombosis, steal syndrome and hypoesthesia. If any of these adverse events occur in rates or severity exceeding placebo and unacceptable to regulatory authorities or IRBs, if anti-vonapanitase antibodies develop and are associated with cross-reactivity to other proteases, or unknown serious events emerge, our clinical trials could be suspended or terminated by us, IRBs, or the applicable regulatory authorities, and the FDA, the EMA or other foreign regulatory authorities could order us to cease further development of, or deny approval of, vonapanitase or any additional product candidates for any or all targeted indications. The product-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial. If we elect or are required to delay, suspend or terminate any clinical trial of vonapanitase or any additional product candidates, the commercial prospects of these product candidates will be harmed and our ability to generate product revenues from any of these product candidates will be delayed or eliminated.

In addition, even if we were to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we request, including more limited patient populations, may require that contraindications, warnings or precautions be included in the product labeling, including a boxed warning, may grant approval contingent on the performance of costly post-marketing clinical trials or other post-market requirements, or may approve a product candidate with labeling that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Any of these occurrences may harm our business, financial condition and prospects significantly.

We may not be able to maintain Orphan Drug designation or obtain or maintain orphan drug exclusivity for vonapanitase.

We have obtained Orphan Drug designation from the FDA for vonapanitase. In the United States, under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals annually in the United States for a preventive drug. The first NDA or BLA applicant to receive FDA approval for a particular drug or biologic to treat a particular disease with FDA Orphan Drug designation is entitled to a seven-year exclusive marketing period in the United States for that product, for that indication. During the seven-year exclusivity period, the FDA may not approve any other applications to market the same drug or biologic for the same disease, except in limited circumstances. Orphan drug exclusivity may be lost if the FDA determines, among other reasons, 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.

Even if we obtain orphan drug exclusivity for vonapanitase, that exclusivity may not effectively protect the product from competition because different products can be approved for the same condition. Even after an orphan product is approved, the FDA can subsequently approve a product containing the same principal molecular structural features for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care.

In response to a recent court decision regarding the plain meaning of the exclusivity provision of the Orphan Drug Act and increased scrutiny by legislators, the FDA may undertake a reevaluation of aspects of its orphan drug regulations and policies. We do not know if, when, or how the FDA may change the orphan drug regulations and policies, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be harmed.

A breakthrough therapy, fast track product, priority review, or other designation by the FDA for our product candidates may not lead to faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval.

We have received Breakthrough Therapy and Fast Track product designations for vonapanitase for hemodialysis vascular access indications. As applicable, we may seek Breakthrough Therapy, Fast Track, Priority Review, or other designations for other uses of vonapanitase. Breakthrough Therapy and Fast Track product designations are designed to facilitate the clinical development and expedite the review of drugs and biologics intended to treat a serious or life-threatening condition which demonstrate the potential to address an unmet medical need. Priority Review designation is intended to speed the FDA marketing application review timeframe for drugs and biologics that treat a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. For drugs and biologics that have been designated as Breakthrough Therapy or Fast Track products, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development. Sponsors of drugs and biologics designated as Breakthrough Therapy or Fast Track products may also be able to submit marketing applications on a rolling basis, meaning that the FDA may review portions of a marketing application before the sponsor submits the complete application to the FDA, as long as the sponsor pays the user fee upon submission of the first portion of the marketing application. For products that receive a Priority Review designation, the FDA's marketing application review goal is shortened to six months, as opposed to ten months under standard review. This review goal is based on the date the FDA accepts the marketing application for review (i.e., filing), which typically occurs two months after the date of submission.

Designation as a Breakthrough Therapy, Fast Track product, Priority Review product, or under another program is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a Breakthrough Therapy, Fast Track product, Priority Review product, or other designation, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of any such designation for a product candidate may not result in a faster development process, review or approval compared to drugs and biologics considered for approval under conventional FDA procedures and does not assure ultimate marketing approval by the FDA. In addition, the FDA may later decide that the products no longer meet the conditions for qualification as a Breakthrough Therapy, Fast Track product or under another designation program or decide that the time period for FDA review or approval will not be shortened.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we have focused on developing one product candidate, vonapanitase, and have focused on developing this product candidate for specific indications that we identify as most likely to succeed, in terms of both its regulatory approval and commercialization. As such, we are currently primarily focused on the development of vonapanitase for vascular access, and our Phase 3 trials will be limited to the application of vonapanitase in radiocephalic fistulas.

In the future we intend to pursue additional indications such as the application of vonapanitase in brachiocephalic fistula creation and/or patients undergoing placement of an arteriovenous graft and/or patients with symptomatic PAD. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that may prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

Even if we obtain and maintain approval for vonapanitase or additional product candidates from the FDA, we may never obtain approval for vonapanitase or additional product candidates outside of the United States, which would limit our market opportunities and adversely affect our business.

Even if we obtain approval of a product candidate in the United States from the FDA, such approval does not ensure approval of that product candidate by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. Sales of vonapanitase or any additional product candidates outside of the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval. Even if the FDA grants marketing approval for a product candidate, comparable regulatory authorities of foreign countries must also approve the manufacturing and marketing of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and greater than, those in the United States, including additional preclinical studies or clinical trials. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our products, if approved for sale, is also subject to approval. Moreover, the failure to obtain approval in one jurisdiction may negatively impact our ability to obtain approval in another jurisdiction.

If the PATENCY-2 trial is successful, we would expect to submit a Marketing Authorization Application, or MAA, to the EMA in 2020. However, based on additional data including the data from the PATENCY-2 trial and assuming sufficient funds become available, we may decide to commence a clinical trial of vonapanitase in Europe for patients undergoing creation of radiocephalic fistulas. If we decide to commence a clinical trial of vonapanitase in Europe, we expect results from this trial to be available two to three years after the first patient is enrolled. Obtaining an approval is a lengthy and expensive process and the EMA has its own procedures for approval of product candidates. Even if a product candidate is approved, the EMA may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and Europe also have requirements for approval of product candidates with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of vonapanitase or any additional product candidates in those countries.

Advertising and promotion of any product candidate that obtains approval in the United States will be heavily scrutinized by the FDA, the Department of Justice, the Department of Health and Human Services' Office of Inspector General, state attorneys general, members of Congress and the public.

While the FDA does not restrict physicians from prescribing approved drugs and biologics for uses outside of the products' approved labeling, known as off-label use, pharmaceutical manufacturers are prohibited from promoting and marketing their products for such uses. Violations, including promotion of our products for off-label uses, are subject to enforcement letters, inquiries, investigations, civil and criminal sanctions by the government, corporate integrity agreements, debarment from government contracts, debarment and exclusion from participation in federal healthcare programs. Additionally, comparable foreign regulatory authorities will heavily scrutinize advertising and promotion of any product candidate that obtains approval outside of the United States.

In the United States, engaging in the impermissible promotion of our products for off-label uses can also subject us to false claims litigation under federal and state statutes, which can lead to civil and criminal penalties and fines, debarment from government contracts, exclusion from participation in federal healthcare programs and corporate integrity agreements with governmental authorities that materially restrict the manner in which a company promotes or distributes drug and biologic products. These false claims statutes include the federal civil False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims, or causing to present such false or fraudulent claims, for payment by a federal program such as Medicare or Medicaid. If the government decides to intervene and prevails in the lawsuit, the individual will share in any fines or settlement funds. If the government does not intervene, the individual may proceed on his or her own. Since 2004, these False Claims Act lawsuits against pharmaceutical companies have increased significantly in volume and breadth, leading to several substantial civil and criminal settlements regarding certain sales practices promoting off-label product uses involving fines that are as much as $3.0 billion.

This growth in litigation has increased the risk that a pharmaceutical company will have to defend a false claim action, pay settlement fines or restitution, agree to comply with burdensome reporting and compliance obligations, and be excluded from Medicare, Medicaid and other federal and state healthcare programs. If we do not lawfully promote our approved products, we may become subject to such litigation and, if we do not successfully defend against such actions, those actions may have a material adverse effect on our business, financial condition, results of operations and prospects. The FDA's policies may change and additional government regulations may be enacted that could prevent, limit or delay marketing approval, and the sale and promotion of our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained, which would adversely affect our business, prospects and ability to achieve or sustain profitability.

If we are found in violation of federal or state "fraud and abuse" laws or other healthcare laws and regulations, we may be required to pay a penalty and/or be suspended from participation in federal or state healthcare programs, which may adversely affect our business, financial condition and results of operation.

We may also be subject to various federal and state laws pertaining to healthcare "fraud and abuse," including anti-kickback laws and false claims laws. Anti-kickback laws make it illegal for a prescription drug or biologic manufacturer to solicit, offer, receive or pay any remuneration in exchange for, or to induce, the referral of business, including the purchase or prescription of a particular drug or biologic. Other laws that we may be subject to include the civil False Claims Act, criminal False Claims Act, the HIPAA fraud and abuse provisions, the Civil Monetary Penalties statute, Section 1927 of the Social Security Act, the Veterans Health Care Act, the Foreign Corrupt Practices Act, federal and state statutes and regulations pertaining to payments made to physicians and other health care providers, the HIPAA privacy and security provisions, and other analogous state laws. Due to the breadth of the statutory provisions, it is possible that our practices might be challenged under anti-kickback, healthcare, or other fraud and abuse laws. Moreover, recent healthcare reform legislation has strengthened these laws. For example, the recently enacted Patient Protection and Affordable Care Act, or ACA, among other things, amends the intent requirement of the federal anti-kickback and certain of the criminal healthcare fraud statutes to clarify that a person or entity does not need to have actual knowledge of this statute or specific intent to violate it. In addition, the ACA clarifies that the government may assert that a claim that includes items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act. False claims laws prohibit anyone from knowingly presenting, or causing to be presented for payment, to government third-party payors (including Medicare and Medicaid) claims for reimbursed drugs, or biologics or services that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services. Liability may also arise from false certification of compliance with laws and regulations that are conditions of payment. Our activities relating to the sale and marketing of our products may be subject to scrutiny under these laws. Violations of fraud and abuse laws, and other healthcare statutes are punishable by criminal and civil sanctions, including fines and civil monetary penalties, the possibility of exclusion from federal healthcare programs (including Medicare and Medicaid) and corporate integrity agreements, which impose, among other things, rigorous operational and monitoring requirements on companies. We may further be subject to such other actions as debarment from government contracts and future orders under existing contracts, refusal to allow us to enter into supply contracts, including government contracts, reputational harm, diminished profits and future earnings and the curtailment or restructuring of our operations, any of which could adversely affect our business.

Given the significant penalties and fines that can be imposed on companies and individuals if convicted or found liable, allegations of violations under fraud and abuse laws often result in settlements even if the company or individual being investigated admits no wrongdoing. Settlements often include significant civil sanctions, including fines and civil monetary penalties, and corporate integrity agreements. If the government were to allege or convict us or our executive officers of violating these laws, our business could be harmed. In addition, private individuals have the ability to bring similar actions under the False Claims Act. Our activities could be subject to challenge for the reasons discussed above and due to the broad scope of these laws and the increasing attention being given to them by law enforcement authorities. Further, an increasing number of state laws require manufacturers to make reports to states on pricing and marketing information. Many of these laws contain ambiguities as to what is required to comply with the laws. Given the lack of clarity in laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent state authorities.

Similar rigid restrictions are imposed on the promotion and marketing of medicinal products in the European Union and other countries. Laws (including those governing promotion, marketing and anti-kickback provisions), industry regulations and professional codes of conduct often are strictly enforced. Even in those countries where we are not directly responsible for the promotion and marketing of our products, inappropriate activity by our international distribution partners can have adverse implications for us.

We may not be able to comply with requirements of foreign jurisdictions in conducting trials outside of the United States.

To date, we have not conducted any clinical trials outside of the United States. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country, should we attempt to do so, is subject to numerous risks unique to conducting business in foreign countries, including:

- difficulty in establishing or managing relationships with contract research organizations, or CROs, clinical sites and investigators;
- different standards for the conduct of clinical trials;
- our inability to locate qualified local consultants, physicians and partners;
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment; and
- the acceptability of data obtained from trials conducted outside the United States to the FDA in support of a BLA.

Risks Related to Commercialization of Our Product

If we are unable to establish effective marketing and sales capabilities or enter into agreements with third parties to market and sell our product candidates, if they are approved, we may be unable to generate product revenues.

We currently do not have a commercial infrastructure for the marketing, sale and distribution of biological products. If approved, in order to commercialize our products, we must build our marketing, sales and distribution capabilities or make arrangements with third parties to perform these services. We may not be successful in doing so. If vonapanitase is approved by the FDA, we plan to build a specialty sales force in the United States of approximately 75-100 representatives, supported by reimbursement specialists and a medical affairs team. We may seek to further penetrate the United States market in the future by expanding our sales force or through collaborations with other pharmaceutical or biotechnology companies or third party manufacturing and sales organizations. If approved for marketing outside the United States, we may commercialize outside the United States with our own specialty sales force and/or with a commercial partner.

As a company we have no prior experience in the marketing, sale and distribution of biological products, and there are significant risks involved in the building and managing of a commercial infrastructure. The establishment and development of our own sales force and related compliance plans to market any products we may develop will be expensive and time consuming and could delay any product launch, and we may not be able to successfully develop this capability. We, or our future collaborators, will have to compete with other companies to recruit, hire, train, manage and retain marketing and sales personnel. In the event we are unable to develop a marketing and sales infrastructure, we may not be able to commercialize vonapanitase or any additional product candidates, which would limit our ability to generate product revenues. Our ability to generate product revenues would be impaired by:

- our inability to recruit, train, manage and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to vascular surgeons or persuade adequate numbers of vascular surgeons to use vonapanitase or any additional product candidates;
- our inability to effectively oversee a geographically dispersed sales and marketing team;
- the costs associated with training sales personnel on legal compliance matters and monitoring their actions;
- liability for sales personnel failing to comply with the applicable legal requirements; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

Although our current plan is to hire most of our sales and marketing personnel only if vonapanitase is approved by the FDA, we will incur expenses prior to product launch in recruiting this sales force and developing a marketing and sales infrastructure. If the commercial launch of vonapanitase is delayed as a result of FDA requirements or other reasons, we would incur these expenses prior to being able to realize any revenue from sales of vonapanitase. Even if we are able to effectively hire a sales force and develop a marketing and sales infrastructure, our sales force and marketing teams may not be successful in commercializing vonapanitase or any additional product candidates.

In the event we are unable to hire a sales force or collaborate with a third-party marketing and sales organization to commercialize any approved product candidates outside the United States, our ability to generate product revenues may be limited. To the extent we rely on third parties to commercialize any products for which we obtain regulatory approval, we may receive less revenues than if we commercialized these products ourselves. In addition, we would have less control over the sales efforts of any other third parties involved in our commercialization efforts.

Even if vonapanitase or any additional product candidates receive regulatory approval, they may fail to achieve the broad degree of physician adoption and use necessary for commercial success.

The commercial success of vonapanitase and any product candidates that we may develop will depend upon the degree of market acceptance by physicians, patients, healthcare payors and others in the medical community. Even if the FDA approves vonapanitase or one or more of our future product candidates, physicians and patients may not accept and use them. Acceptance and use of any of our products will depend upon a number of factors including:

- perceptions by members of the healthcare community, including physicians, about the safety and effectiveness of our products, and their advantages as compared to any competitive products;
- the timing of market introduction of the product candidate as well as competitive products;
- the clinical indications for which the product candidate is approved;
- any restrictions on or warnings regarding the use of the products;
- cost-effectiveness of our products relative to any competing products;
- availability of timely coverage and reimbursement for our products from government or other third-party payors; and
- effectiveness of marketing and distribution efforts by us and any our licensees and distributors.

Because we expect sales of vonapanitase, if approved, to generate substantially all of our product revenues for the foreseeable future, the failure of vonapanitase to gain market acceptance would harm our business and would require us to seek additional financing.

Vonapanitase or any additional product candidates, if approved, may face significant competition and our failure to effectively compete may prevent us from achieving significant market penetration and expansion.

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. We face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical, biotechnology and medical device companies, academic institutions, governmental agencies and public and private research institutions. While we believe that vonapanitase's features, safety and efficacy will differentiate it from any competitive products that may become available in the future, we expect to face potential competition from many different sources, including larger and better-funded pharmaceutical, specialty pharmaceutical and biotechnology companies and medical device companies, as well as from academic institutions and governmental agencies and public and private research institutions that may develop potentially competitive products or technologies.

Some of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals, marketing and selling approved products than we do. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

The key competitive factors affecting the success of vonapanitase, if approved, are likely to be its efficacy, safety, convenience, price, and the availability of reimbursement from government and other third-party payors. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, more convenient or less expensive than any products that we may develop. Our competitors may also obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours.

We are not aware of products approved in the United States or Europe that would compete with vonapanitase for the improvement of fistula use for hemodialysis and secondary patency. We are aware of companies with therapies in development including Vascular Therapies, Enceladus Pharmaceuticals, Symic Biomedical, Aplagon, and Athera Biotechnologies. In addition, we are aware of companies with approved catheter-based devices for percutaneous fistula creation, including Becton, Dickinson and Company (as successor to TVA Medical) and Avenu Medical. We are also aware of companies developing other vascular access technologies, including BioConnect Systems, Phraxis, Brookhaven Medical, Fist Assist, Laminate Medical Technologies and Stent Tek. Other technologies in development include new synthetic grafts, including those that may be developed by companies that currently compete in the graft market, such as W.L. Gore, C.R. Bard and Maquet, as well as tissue engineered grafts, including those in development by Cytograft and Humacyte. Finally, vonapanitase's commercial success could be affected by the development of technologies to improve the outcomes of interventions to restore patency, including stents, stent grafts and drug-coated balloons.

Vonapanitase, or any additional product candidates for which we seek approval as biologic products, may face competition sooner than anticipated.

The enactment of the Biologics Price Competition and Innovation Act of 2009, or BPCIA, as part of the ACA, created an abbreviated pathway for the approval of biosimilar and interchangeable biological products. The abbreviated regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as "interchangeable" based on its similarity to an existing brand product. Under the BPCIA, an application for a biosimilar product cannot be approved by the FDA until 12 years after the original branded product was approved under a BLA. Certain changes, however, and supplements to an approved BLA, and subsequent applications filed by the same sponsor, manufacturer, licensor, predecessor in interest, or other related entity do not qualify for the 12-year exclusivity period.

The BPCIA is complex and is still being interpreted and implemented by the FDA. ACA is also facing increased scrutiny by legislators. As a result, the ultimate impact, implementation, meaning and continued effectiveness of BPCIA are subject to uncertainty. While it is uncertain when such processes intended to implement the BPCIA may be fully adopted by the FDA or whether any aspects of BPCIA may change, any such processes or changes could have a material adverse effect on the future commercial prospects for our biological products.

We believe that vonapanitase, or any additional product candidates approved as a biological product under a BLA, should qualify for the BPCIA's 12-year period of exclusivity. However, there is a risk that BPCIA will be repealed or amended, or the FDA will not consider vonapanitase or any additional product candidates to be reference products for competing products, potentially creating the opportunity for generic competition sooner than anticipated.

Additionally, this period of regulatory exclusivity does not preclude submission or regulatory approval of a company's own traditional BLA, as it would an application via the abbreviated pathway. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing. It is possible that payers will give reimbursement preference to biosimilars even over reference biologics absent a determination of interchangeability.

If the government or other third-party payors fail to provide adequate and timely coverage and payment rates for vonapanitase or any additional product candidates or if surgeons or hospitals choose not to use vonapanitase, our revenue and prospects for profitability will be limited.

In both domestic and foreign markets, sales of our future products will depend substantially upon the availability of timely coverage and reimbursement from government and other third-party payors. The majority of incident and prevalent hemodialysis patients have Medicare coverage, while other patients have other third-party payors, including other government health programs such as Medicaid, managed care providers, private health insurers and other organizations. Coverage decisions may depend upon clinical and economic standards that disfavor new drug and biologic products when more established or lower cost therapeutic alternatives are already available or subsequently become available. Vonapanitase or any additional product candidates, if approved, may face competition from other therapies, biologics, and drugs for limited financial resources. We may need to conduct post-marketing studies in order to demonstrate the cost-effectiveness of any future products to the satisfaction of outpatient clinics, hospitals, other target customers and their third-party payors. These post-marketing studies might require us to commit a significant amount of management time and financial and other resources. Our future products might not ultimately be considered cost-effective. Adequate third-party coverage and reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development.

Third-party payors, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. Assuming coverage is approved, the resulting reimbursement payment rates might not be adequate to allow us to establish or maintain a market share sufficient to realize a sufficient return on our investments. If reimbursement is not available, or is available only to limited levels, our product candidates may be competitively disadvantaged, and we, or our collaborators, may not be able to successfully commercialize our product candidates. Alternatively, securing favorable reimbursement terms may require us to compromise pricing and prevent us from realizing an adequate margin over cost. In addition, in the United States, no uniform policy of coverage and reimbursement for drug and biologic products exists among third-party payors. Therefore, coverage and reimbursement for drug and biologic products can differ significantly from payor to payor. Further, we believe that future coverage and reimbursement will likely be subject to increased restrictions both in the United States and in international markets. Third-party coverage and reimbursement for our products or product candidates for which we receive regulatory approval may not be available or adequate in either the United States or international markets, which could have a negative effect on our business, results of operations, financial condition and prospects.

Government programs impose price controls on pharmaceutical and biological products and penalties for increasing commercial prices at rates that exceed the government inflation index, which may limit the commercial price we charge and our realization on sales. Further, the net reimbursement for drug and biologic products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs and biologics from countries where they may be sold at lower prices than in the United States. An inability to promptly obtain coverage and adequate payment rates from both government-funded and private payors for any our product candidates for which we obtain marketing approval could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

Risks Related to Dependence on Third Parties

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

We currently have a relationship with only one supplier, Lonza, for the manufacturing of the API for vonapanitase for clinical testing purposes, and intend to continue to use Lonza as our sole or primary supplier of the API for vonapanitase in the future. We have used two companies, Jubilant HollisterStier and Patheon Manufacturing Services Inc. (formerly DSM Pharmaceuticals), to vial and make our vonapanitase finished product. We also expect to rely upon third parties to produce materials required for the commercial production of vonapanitase or any additional product candidates if we succeed in obtaining the necessary regulatory approvals. This may increase the risk that we will not have sufficient quantities of our product candidates to conduct our clinical trials or such quantities at an acceptable cost, which could result in the delay, prevention, or impairment of clinical development and commercialization of our product candidates.

All entities involved in the preparation of drugs or biologics for clinical trials or commercial sale, including our existing contract manufacturers, are subject to extensive regulation. Ingredients of a finished therapeutic biologic product approved for commercial sale or used in clinical trials must be manufactured in accordance with cGMPs and equivalent foreign standards. 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 product candidate 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 cGMPs regulations enforced by the FDA through its facilities inspection program. Any failure by our third-party manufacturers to comply with cGMPs, or failure to scale-up and validate manufacturing processes, including any failure to deliver sufficient quantities of product candidates in a timely manner for the process validation required in connection with a BLA submission, could lead to a delay in, or failure to obtain, regulatory approval of vonapanitase or any additional product candidates. For example, on November 27, 2013, our third-party supplier of finished biological product, Jubilant HollisterStier, received a Warning Letter from the FDA alleging that the company was not complying with cGMPs. We received a letter from the FDA on February 13, 2014, stating that the Warning Letter does not impact the batch of finished product we are using for our Phase 3 clinical trials. However, if Jubilant HollisterStier or any other third-party supplier does not have an acceptable cGMP compliance status at the time of review by the FDA of any BLA we might submit, approval of the BLA would be delayed. This third party supplier or other third parties could encounter similar difficulties that could impede our clinical trials, approval or commercialization.

Our facilities and quality systems and the facilities and quality systems of some or all of our third-party contractors must also pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of vonapanitase or any additional product candidates. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our product candidate or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities and quality systems do not pass a pre-approval plant inspection from the FDA or a comparable foreign authority, approval of our product candidate by the FDA or the equivalent approvals in other jurisdictions will not be granted until the regulatory authority is satisfied that the facility complies with applicable regulations.

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 trial or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

If we or any of 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 or biologic product or revocation of a pre-existing approval. If any such event occurs, our business, financial condition and results of operations may be materially harmed.

Currency fluctuations in the Swiss Franc and changes in exchange rates could adversely affect our business by increasing our costs and cause our profitability to decline.

Our contract with Lonza for the manufacturing of the API is denominated in Swiss Francs. Therefore, fluctuations in the exchange rate for Swiss Francs may affect our operating results. On January 15, 2015, the Swiss National Bank announced an edit to its policy of fixing the Swiss Franc and Euro exchange rate, which caused volatility in the currency markets for Swiss Francs and an immediate increase in their value, making our contractual payments to Lonza more expensive based on the current exchange rates. In the second quarter of 2015, we entered into forward foreign currency contracts to purchase Swiss Francs to reduce our foreign currency exposure under our contract with Lonza, all of which have been settled and are no longer outstanding. We have purchased Swiss Francs to mitigate our exposure to fluctuations in the U.S. dollar value of forecasted transactions denominated in Swiss Francs. In the future we may purchase additional forward foreign currency contracts to hedge certain forecasted transactions, including those with Lonza, and reduce exposures to foreign currency fluctuations. Any use of these derivative instruments would be intended to mitigate a portion of the exposure of these risks with the intent to reduce our risk or cost, but generally would not fully offset any change in operating results as a consequence of fluctuations in foreign currencies. Any significant foreign exchange rate fluctuations could adversely affect our financial condition and results of operations and any use of derivative instruments may not offset such fluctuations and could exacerbate their impact on our financial condition and results of operations.

We rely on third parties to conduct some or all aspects of our product manufacturing, protocol development, research, and preclinical and clinical testing, and plan to continue to rely on such third parties if we receive marketing approvals. These third parties may not perform satisfactorily.

We do not currently, and do not expect in the future, to independently conduct all aspects of our product manufacturing, protocol development, research and monitoring and management of our clinical programs. Vonapanitase API is produced by our contract manufacturer, Lonza. Vonapanitase finished product is produced by our contract fill/finish provider, Jubilant HollisterStier. Release testing and stability for API and finished product is performed by PPD, Inc. We currently rely, and expect to continue to rely, on third parties with respect to these items for our continued and future clinical studies as well as for commercialization, if we receive regulatory marketing approval. While we will have agreements governing their activities, we will have limited influence over their actual day-to-day performance. Nevertheless, we will be responsible for ensuring that the manufacturing is conducted in accordance with regulatory requirements such as cGMPs. Our reliance on the third parties does not relieve us of our regulatory responsibilities.

Any of these third parties may terminate their engagements with us under the terms of our agreements upon notice to us. If we need to enter into alternative arrangements, our product candidate development and eventual commercialization activities may be delayed. Our reliance on these third parties for research and development activities, and eventual commercial supply, reduces our day-to-day control over these activities but does not relieve us of our responsibility to ensure compliance with all required legal, regulatory and scientific standards and any applicable trial protocols. For example, for vonapanitase or any additional product candidates that we develop and commercialize on our own, we will remain responsible for ensuring that the product is manufactured in accordance with cGMPs, each of our clinical trials is conducted in accordance with GCPs and its protocol and is analyzed in accordance with its statistical analysis plan for the clinical trial.

If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our studies in accordance with regulatory requirements or our protocols, we may be delayed in completing, or unable to complete, the clinical trials required to support future approval of vonapanitase or any additional product candidates, and, if ultimately approved for marketing, may not be able to produce a sufficient amount of commercial supply.

We rely on our manufacturers to purchase from third-party suppliers the materials necessary to produce our product candidate, vonapanitase, for our clinical trials, and eventual commercial supply, if we receive regulatory approval. There are a small number of suppliers for certain raw materials that we use to manufacture vonapanitase. These suppliers may not sell these raw materials to our manufacturers at the times we need them or on commercially reasonable terms. We do not have any control over the process or timing of the acquisition of these raw materials by our manufacturers. Moreover, we currently do not have any agreements for the commercial production of these raw materials. We will need supply of finished product as part of the process validation and for any stability or other tests in connection with a BLA submission and also to conduct additional clinical trials, for example for additional vonapanitase indications. We will further require finished product for commercialization if we receive regulatory approval. Any significant delay in the supply of vonapanitase's ingredients due to the need to replace a third-party manufacturer could considerably delay completion of our clinical trials, product testing and potential regulatory approval of vonapanitase or any additional product candidate, and commercialization as we believe that replacing Lonza as the manufacturer of our API would take one to two years and replacement of any of our other manufacturers may take a substantial amount of time. If our manufacturers or we are unable to purchase these raw materials after regulatory approval has been obtained for our product candidate, our ability to commercially launch and/or generate revenues from the sale of any approved product would be impaired. Reliance on third-party manufacturers entails exposure to risks to which we would not be subject if we manufactured the product candidate ourselves, including:

- inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- reduced day-to-day control over the manufacturing process for our product candidates as a result of using third-party manufacturers for all aspects of manufacturing activities;
- reduced control over the protection of our trade secrets and know-how from misappropriation or inadvertent disclosure;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that may be costly or damaging to us or result in delays in the development or commercialization of our product candidates; 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 delays in the development of vonapanitase or any additional product candidates, including delays in our clinical trials, or failure to obtain regulatory approval for our product candidates, or it could impact our ability to successfully commercialize vonapanitase or any additional product candidates. Some of these events could be the basis for FDA or other regulatory action, including Warning Letters, injunction, recall, seizure or total or partial suspension of production. Any of these events could have a material adverse effect on our business.

We rely on third parties to conduct, supervise and monitor our clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for, or commercialize, vonapanitase or any additional product candidates and our business could be substantially harmed.

We rely on CROs and clinical trial sites to ensure our clinical trials are conducted properly and on time. While we will have agreements governing their activities, we will have limited influence over their actual day-to-day performance. Nevertheless, we will be responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, and legal, regulatory and scientific standards and recognize that our reliance on the CROs does not relieve us of our regulatory responsibilities.

We and our CROs are required to comply with the FDA's GCPs for conducting, recording and reporting the results of clinical trials to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. The FDA and comparable foreign regulatory authorities enforce these GCPs through periodic inspections of trial sponsors, principal investigators and clinical trial sites. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our future clinical trials may be deemed unreliable and the FDA, the EMA, or other foreign regulatory authorities may require us to perform additional clinical trials before approving any marketing applications. In addition, we are required to report certain financial interests of our third-party investigators if these relationships provide for a financial interest in the outcome of the study because of the way the payment was arranged (e.g., a royalty) or because the investigator has a proprietary interest in the product (e.g., a patent) or because the investigator has an equity interest in the sponsor of the covered study exceeding certain financial thresholds. The FDA or comparable foreign regulatory authorities may question the integrity of the data from those clinical trials conducted by principal investigators who previously served or currently serve as scientific advisors or consultants to us from time to time and receive cash compensation in connection with such services.

Upon inspection, the FDA may determine that our clinical trials did not comply with GCPs. In addition, our future clinical trials will require a sufficient number of test subjects to evaluate the safety and efficacy of vonapanitase or any additional product candidates. Accordingly, if our CROs fail to comply with these regulations or fail to recruit a sufficient number of patients, we may be required to repeat such clinical trials, which would delay the regulatory approval process.

Our CROs are not our employees, and we are therefore unable to monitor on a day-to-day basis whether or not they devote sufficient time and resources to our clinical and preclinical programs. These CROs may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other product development activities that could harm our competitive position. If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize, vonapanitase or any additional product candidates. If any such event were to occur, we may be subject to regulatory enforcement actions, our financial results and the commercial prospects for vonapanitase or any additional product candidates would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

If any of our relationships with these third-party CROs terminates, we may not be able to enter into arrangements with alternate CROs or to do so on commercially reasonable terms. Further, switching or adding additional CROs involves additional costs and requires management time and focus. In addition, a transition period may be required when a new CRO commences work. As a result, delays may occur, which could materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

We also rely on other third parties to store and distribute our products for the clinical trials that we conduct. Any performance failure on the part of our distributors could delay clinical development or marketing approval of vonapanitase or any additional product candidates or commercialization of our product, if approved, producing additional losses and depriving us of potential product revenue.

We may seek to form partnerships in the future with respect to vonapanitase or any additional product candidates, and we may not realize the benefits of such partnerships.

We may form partnerships, create joint ventures or collaborations or enter into licensing arrangements with third parties for the development and commercialization of vonapanitase or any additional product candidates. We face significant competition in seeking appropriate strategic partners and the negotiation process is time-consuming and complex. Any delays in entering into new strategic partnership agreements related to our product candidates could delay the development and commercialization of our product candidates and reduce their competitiveness even if they reach the market. Moreover, we may not be successful in our efforts to establish a strategic partnership or other collaborative arrangement for any additional product candidates. For example, potential partners may consider that our research and development pipeline is insufficiently developed to justify a collaborative effort, or that vonapanitase or any additional product candidates and programs do not have the requisite commercial or clinical potential in the target population. Even if we are successful in establishing such a strategic partnership or collaboration, we cannot be certain that, following such a strategic transaction or license, we will be able to progress the development and commercialization of the applicable product candidates as envisioned, or that we will achieve the revenues that would justify such transaction.

Risks Related to Our Intellectual Property

If our efforts to protect our intellectual property related to vonapanitase or any additional product candidates are not adequate, we may not be able to compete effectively in our market.

We rely upon a combination of patents, patent applications, know-how and confidentiality agreements to protect the intellectual property related to our only product candidate, vonapanitase, and will use a similar strategy to protect any additional product candidates. The patent position of biotechnology companies is generally uncertain because it involves complex legal and factual considerations. The standards applied by the United States Patent and Trademark Office, or USPTO, and foreign patent offices in granting patents are not always applied uniformly or predictably. For example, there is no uniform worldwide policy regarding patentable subject matter or the scope of claims allowable in biotechnology patents. The patent applications that we own may fail to result in issued patents with claims that cover vonapanitase or any additional product candidates in the United States or in other countries. There is no assurance that all potentially relevant prior art relating to our patents and patent applications has been found, and prior art that is not before the patent examiners, as well as prior art that is before the patent examiners, could be used by a third party to invalidate a patent or could be relied on to prevent a patent from issuing from a pending patent application. Even if patents do successfully issue and even if these patents cover vonapanitase or any additional product candidates, third parties may challenge their validity, enforceability or scope, which may result in our patents being narrowed or invalidated.

Furthermore, even if they are unchallenged, our patents and patent applications may not adequately provide exclusivity for vonapanitase or any additional product candidates, prevent others from designing around our patents with similar products that are outside the scope of our patents, or prevent others from operating in jurisdictions in which we did not pursue patent protection. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

If patent applications we hold with respect to vonapanitase or any additional product candidates fail to issue, if their breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for vonapanitase or any additional product candidates, it could dissuade companies from collaborating with us. As of June 30, 2018 we own 41 issued patents and own 16 pending patent applications, most of which cover aspects of vonapanitase or its use. We cannot offer any assurances about which, if any, of the pending patent applications will issue as patents, the breadth of any such patents or any of our currently issued patents, or whether any issued patents will be challenged by third parties or will be found invalid and unenforceable if challenged. Any successful challenge to these patent applications, or patents that may issue from them, or to currently issued patents owned by us, could deprive us of rights necessary for the successful commercialization of vonapanitase or any other product candidate that we may develop. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file a patent application relating to any particular aspect of a product candidate. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be initiated by these third parties, or by the USPTO itself, to determine who was the first to invent any of the subject matter covered by the patent claims of our patents and patent applications.

In the United States, for patent applications filed prior to March 16, 2013, assuming the other requirements for patentability are met, the first to invent is entitled to the patent, while outside the United States, the first to file a patent application is entitled to the patent. Certain of our currently pending utility patent applications are examined under the system in place before March 16, 2013. Third parties are allowed to submit prior art prior to the issuance of a patent by the USPTO, and may become involved in reexamination, *inter partes* review or interference proceedings challenging our patent rights. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, which could adversely affect our competitive position with respect to third parties.

In addition, patents have a limited lifespan. In most countries, the statutory term of a patent is 20 years from the earliest domestic priority date claimed. In the United States, for applications filed after June 7, 1995, the statutory term of a patent is 20 years from earliest non-provisional priority date claimed. Various extensions of patent protection may be available in particular countries; however, in all circumstances, the life of a patent, and the protection it affords, has a limited term. If we encounter delays in obtaining regulatory approvals, the period of time during which we could market a product under patent protection could be reduced. We expect to seek extensions of patent protection where these are available in any countries where we are prosecuting patents. Such possible extensions include those permitted under the Drug Price Competition and Patent Term Restoration Act of 1984 in the United States, which permits up to five years' extension of patent protection and no more than fourteen years following product approval for a single patent that covers an FDA-approved drug or biologic that contains an active ingredient or salt or ester of the active ingredient that has not previously been marketed. The scope of protection available during an extension of a patent claiming a product is limited to the approved product itself for approved uses, and the scope of protection available during an extension of a patent claiming a method of using a product is limited to the uses claimed in the patent and approved for the product. The actual length of the extension is calculated by adding one half of the time between the IND effective date and a company's initial submission of a marketing application, plus the entire time between the submission of the marketing application and the FDA's approval of the application. However, the applicable authorities, including the FDA and the USPTO in the United States, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may be able to take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data, and then may be able to launch their product earlier than might otherwise be the case.

Any loss of, or failure to obtain, patent protection could have a material adverse impact on our business. We may be unable to prevent competitors from entering the market with a product that is similar to or the same as our products.

Confidentiality agreements with employees and third parties may not prevent unauthorized disclosure of proprietary information.

We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and know-how by maintaining physical security of our premises and physical and electronic security of our information technology systems. Nonetheless, despite these precautions, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our know-how may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

Enforcing a claim that a third party illegally obtained and is using any of our know-how is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States sometimes are less willing than United States courts to protect know-how. Misappropriation or unauthorized disclosure of our know-how could impair our competitive position and may have a material adverse effect on our business.

We may become involved in lawsuits to protect or enforce our intellectual property, which could be expensive, time consuming and unsuccessful, and which may lead to a finding that our patents are invalid and/or unenforceable.

Competitors may infringe our patents or misappropriate or otherwise violate our intellectual property rights. To counter infringement or unauthorized use, litigation may be necessary to enforce or defend our intellectual property rights, to protect our know-how and/or to determine the validity and scope of our own intellectual property rights. Intellectual property litigation can be expensive and time consuming. Many of our current and potential competitors have the ability to dedicate substantially greater resources to litigate intellectual property rights than we can. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing or misappropriating our intellectual property. Litigation could result in substantial costs and diversion of management resources, which could harm our business and financial results. In addition, in an infringement proceeding, a court may decide that our patents are invalid or unenforceable, and may refuse to stop the other party from using the technology at issue, including on the grounds that our patents are invalid or unenforceable or do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated, held unenforceable or interpreted narrowly. 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.

Third-party claims of intellectual property infringement or misappropriation may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on our ability to develop, manufacture, market and sell vonapanitase or any additional product candidates, and to use proprietary technologies without infringing the patents and proprietary rights of third parties. There is a substantial amount of litigation and adversarial proceedings, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions, reexamination, and *inter partes* review proceedings before the USPTO and corresponding foreign patent offices. Third parties own patent rights both within and outside the United States in the fields in which we are developing and may develop vonapanitase or any additional product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that vonapanitase or any additional product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims that may cover vonapanitase or any additional product candidates and/or the use, manufacture, sale and/or offer for sale of vonapanitase or any additional product candidates. We are aware of European Patent No. EP 1 012 307 B1, or the '307 patent, which claims, among other things, autocatalytically cleavable zymogenic precursor of a serine protease wherein a naturally occurring non-autocatalytic cleavage site is replaced in the zymogenic precursor by an autocatalytic cleavage site. The '307 patent expires on August 12, 2018. We currently estimate that the soonest that we will market vonapanitase is after this date.

In some cases, we may have failed to identify relevant third-party patents or patent applications. For example, applications filed before November 29, 2000, and certain applications filed after that date that will not be filed outside the United States remain confidential until patents issue. Except for the preceding exceptions, patent applications in the United States and elsewhere are generally published but, only after a waiting period of approximately 18 months after the earliest filing. Therefore, patent applications covering vonapanitase or future product candidates could have been filed by others without our knowledge. Additionally, pending patent applications which have been published can, subject to certain limitations, be later amended in a manner that could cover vonapanitase or any additional product candidates and/or the use, manufacture, sale and/or offer for sale of vonapanitase or any additional product candidates.

If any valid and enforceable third-party patents were held by a court of competent jurisdiction to cover vonapanitase or any additional product candidates and/or their use, manufacture, sale, and/or offer for sale, the holders of any of these patents may be able to block our ability to develop and commercialize the applicable product candidate until the patent expired or unless we obtain a license. Licenses may not be available on acceptable terms, if at all. Even if we were able to obtain a license, the rights may be nonexclusive, which could result in our competitors gaining access to the same intellectual property. Ultimately, we could be prevented from commercializing a product, or be forced to cease some aspect of our business operations, if, as a result of actual or threatened patent infringement claims, we are unable to enter into licenses on acceptable terms.

Some of our early research of recombinant expression of vonapanitase, but not the corresponding development work, utilized some technology under license from a third party. The third party may contend that we use the licensed technology for our commercial recombinant expression of vonapanitase. Litigation may be necessary to defend against such a claim. Even if we are successful in defending against such a claim, litigation could result in substantial costs and be a distraction to management. If we are not successful in defending against such a claim, in addition to paying monetary damages, we may have to reconfigure the vonapanitase expression system, which would materially adversely affect our commercial development efforts.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to commercialize vonapanitase or any additional product candidates. We may face a claim of misappropriation if a third party believes that we inappropriately obtained and used trade secrets of that third party. If we are found to have misappropriated a third party's trade secrets, we may be prevented from further using such trade secrets, limiting our ability to develop vonapanitase or any additional product candidates, and we may be required to pay damages.

Defending against claims of patent infringement or misappropriation of trade secrets could be costly and time consuming, regardless of the outcome. Thus, even if we were to ultimately prevail, or to settle at an early stage, any litigation could burden us with substantial unanticipated costs. In addition, litigation or threatened litigation could result in significant demands on the time and attention of our management team, distracting them from the pursuit of other company business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure.

During the course of any patent or other intellectual property litigation, there could be public announcements of the results of hearings, rulings on motions, and other interim proceedings in the litigation. If securities analysts or investors regard these announcements as negative, the perceived value of our products, programs, or intellectual property could be diminished. Accordingly, the market price of our Common Stock may decline.

If we are unable to adequately protect our proprietary technology, or obtain and maintain issued patents which are sufficient to protect our current product candidate, vonapanitase, or any additional product candidates, others could compete against us more directly, which would have a material adverse impact on our business, results of operations, financial condition and prospects.

We strive to protect and enhance the proprietary technologies that we believe are important to our business, including seeking patents intended to cover our products and compositions, their methods of use and any other inventions that are important to the development of our business. We also rely on know-how to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business, defend and enforce our current patents and any future patents that may issue, preserve the confidentiality of our know-how and operate without infringing the valid and enforceable patents and proprietary rights of third parties. We also rely on know-how and in-licensing opportunities to develop, strengthen and maintain the proprietary position of vonapanitase or any additional product candidates.

We cannot provide any assurances that any of our pending patent applications will mature into issued patents and, if they do, that such patents or our currently issued patents will include claims with a scope sufficient to protect vonapanitase or any additional product candidates or otherwise provide any competitive advantage. For example, one of our patents that may provide coverage for vonapanitase only covers particular formulations. As a result, this patent would not prevent third-party competitors from creating, making and marketing alternative formulations that fall outside the scope of our patent claims. There can be no assurance that any such alternative formulations will not be equally effective.

Moreover, other parties have developed technologies that may be related or competitive to our approach, and may have filed or may file patent applications and may have received or may receive patents that may overlap or conflict with our patent applications, either by claiming the same methods or formulations or by claiming subject matter that could dominate our patent position. These third party patent positions may limit or even eliminate our ability to obtain patent protection for certain inventions.

The patent positions of biotechnology and pharmaceutical companies, including our patent position, involve complex legal and factual questions, and, therefore, the issuance, scope, validity and enforceability of any patent claims that we may obtain cannot be predicted with certainty. Patents, if issued, may be challenged, deemed unenforceable, invalidated, or circumvented. United States patents and patent applications may also be subject to interference proceedings, *ex parte* reexamination, or *inter partes* review proceedings, and challenges in district court. Patents may be subjected to opposition, revocation proceedings, or comparable proceedings lodged in various foreign, both national and regional, patent offices. These proceedings could result in either loss of the patent or denial of the patent application or loss or reduction in the scope of one or more of the claims of the patent or patent application. In addition, such proceedings may be costly. Thus, any patents that we may own or exclusively license may not provide any protection against competitors. Furthermore, an adverse decision in an interference proceeding can result in a third party receiving the patent right sought by us, which in turn could affect our ability to develop, market or otherwise commercialize vonapanitase or any additional product candidates.

Furthermore, though a patent is presumed valid and enforceable, its issuance is not conclusive as to its validity or its enforceability and it may not provide us with adequate proprietary protection or competitive advantages against competitors with similar products. Even if a patent issues and is held to be valid and enforceable, competitors may be able to design around our patents, such as using pre-existing or newly developed technology. Other parties may develop and obtain patent protection for more effective technologies, designs or methods. We may not be able to prevent the unauthorized disclosure or use of our technical knowledge or know-how by consultants, vendors, former employees and current employees. The laws of some foreign countries do not protect our proprietary rights to the same extent as the laws of the United States, and we may encounter significant problems in protecting our proprietary rights in these countries. If these developments were to occur, they could have a material adverse effect on our sales.

In addition, proceedings to enforce or defend our patents, if and when issued, could put our patents at risk of being invalidated, held unenforceable, or interpreted narrowly. These proceedings could also provoke third parties to assert claims against us, including that some or all of the claims in one or more of our patents are invalid or otherwise unenforceable. If any of our patents, if and when issued, covering vonapanitase or any additional product candidates, are invalidated or found unenforceable, our financial position and results of operations would be materially and adversely impacted. In addition, if a court found that valid, enforceable patents held by third parties covered vonapanitase, or any additional product candidates, our financial position and results of operations would also be materially and adversely impacted.

The degree of future protection for our proprietary rights is uncertain, and we cannot ensure that:

- any of our patents or pending patent applications, if issued, will include claims having a scope sufficient to protect vonapanitase or any additional product candidates;
- any of our pending patent applications will issue as patents at all;

- we will be able to successfully commercialize product candidates, if approved, before our relevant patents expire;
- we were the first to make the inventions covered by each of our patents and pending patent applications;
- we were the first to file patent applications for these inventions;
- others will not develop similar or alternative technologies that do not infringe our patents;
- others will not use pre-existing technology to effectively compete against us;
- any of our patents will be found ultimately to be valid and enforceable;
- any patents issued to us will provide a basis for an exclusive market for our commercially viable products, will provide us with any competitive advantages or will not be challenged by third parties;
- we will develop additional proprietary technologies or product candidates that are separately patentable; or
- that our commercial activities or products will not infringe the patents or proprietary rights of others.

We rely upon unpatented know-how to maintain our competitive position, which we seek to protect, in part, by confidentiality agreements with our employees and our collaborators and consultants. It is possible that technology relevant to our business will be independently developed by a person that is not a party to such an agreement. Furthermore, if the employees and consultants who are parties to these agreements breach or violate the terms of these agreements, we may not have adequate remedies for any such breach or violation, and our confidential know-how could become known to others through such breaches or violations. Further, our know-how could otherwise become known or be independently discovered by our competitors. Further, the term of confidentiality requirements for current and terminated agreements with some of our consultants, contract manufacturing or research organizations and other third parties is finite.

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

We enter into confidentiality and intellectual property assignment agreements with our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors. These agreements generally provide that inventions conceived by the party in the course of rendering services to us will be our exclusive property. However, these agreements may not be honored and may not effectively assign intellectual property rights to us. For example, even if we have a consulting agreement in place with an academic advisor pursuant to which the academic advisor is required to assign any inventions developed in connection with providing services to us, the academic advisor may not have the right to assign these inventions to us, as it may conflict with his or her obligations to assign all intellectual property to his or her employing institution.

Litigation may be necessary to defend against these and other claims challenging inventorship or ownership of inventions. If we are unsuccessful in defending against any of these 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.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

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.

Issued patents covering vonapanitase or covering any additional product candidates could be found invalid or unenforceable if challenged in court.

If we initiated legal proceedings against a third party to enforce a patent, if and when issued, covering vonapanitase or any additional product candidate, the defendant could counterclaim that the patent covering our product candidate is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge include alleged failures to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for unenforceability assertions include allegations that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. These mechanisms include reexamination and *inter partes* review in the United States and equivalent proceedings in foreign jurisdictions, *e.g.*, opposition proceedings. These proceedings could result in revocation or amendment of our patents in such a way that they no longer cover, for example, vonapanitase or competitive products. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to validity, for example, we cannot be certain that there is no invalidating prior art, including 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 the applicable product candidate. A loss of patent protection would have a material adverse impact on our business.

We will not seek to protect our intellectual property rights in all jurisdictions throughout the world, and we may not be able to adequately enforce our intellectual property rights even in the jurisdictions where we seek protection.

Filing, prosecuting and defending patents on product candidates in all countries and jurisdictions throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States, assuming that rights are obtained in the United States. 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 United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions.

Competitors may use our technologies in jurisdictions where we do not pursue and obtain 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 United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. Even if we pursue and obtain issued patents in particular jurisdictions, our patent claims or other intellectual property rights may not be effective or sufficient to prevent third parties from so competing.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to biotechnology. This could make it difficult for us to stop the infringement of our patents, if obtained, or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. In addition, many countries limit the enforceability of patents against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit. Patent protection must ultimately be sought on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries.

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, could put 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.

Some of our intellectual property may have been discovered through government funded programs and thus may be subject to federal regulations such as government "march-in" rights, certain reporting requirements, and a preference for United States industry. Compliance with these regulations may limit our exclusive rights, subject us to expenditure of resources with respect to reporting requirements, and limit our ability to contract with foreign manufacturers.

Some of our intellectual property rights may have been generated through the use of United States government funding and therefore are subject to certain federal regulations. For example, our patents relating to some therapeutic uses of vonapanitase and associated systems and kits that include a catheter, which we refer to as the "therapy family," arose from research funded by the United States government. As a result, the United States government has certain rights to this intellectual property pursuant to the Bayh-Dole Act of 1980, or Bayh-Dole Act. These United States government rights in certain inventions developed under a government-funded program include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the United States government has the right to require us to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations, also referred to as "march-in rights." The United States government also has the right to take title to these inventions if we, or the applicable licensor, fail to disclose the invention to the government and fail to file an application to register the intellectual property within specified time limits. In addition, the United States government may acquire title to these inventions in any country in which a patent application is not filed within specified time limits. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us or the applicable licensor to expend substantial resources. In addition, the United States government requires that any products embodying the subject invention or produced through the use of the subject invention be manufactured substantially in the United States. The manufacturing preference requirement can be waived if the owner of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for United States manufacturers may limit our ability to contract with foreign product manufacturers for products covered by the applicable intellectual property.

We currently do not plan to apply for additional United States government funding, but if we do, and we discover compounds or drug or biological candidates as a result of such funding, intellectual property rights to these discoveries may be subject to the applicable provisions of the Bayh-Dole Act.

If we do not obtain additional protection under the Hatch-Waxman Amendments and similar foreign legislation by extending the patent protection for vonapanitase, our business may be materially harmed.

Depending upon the timing, duration and specifics of the first FDA marketing approval of vonapanitase and, if applicable, any additional product candidates, a United States patent that we own or license may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit extension of one patent that covers an FDA-approved drug or biologic that contains an active ingredient or salt or ester of the active ingredient that has not previously been marketed for up to five years and no more than fourteen years after product approval for patent term lost during product development and the FDA regulatory review process. The length of the extension is calculated by adding one half of the time between the IND effective date and a company's initial submission of a marketing application, plus the entire time between the submission of the marketing application and the FDA's approval of the application. During this period of extension, the scope of protection is limited to the approved product for approved uses (for patents claiming a product) and any use claimed by the patent and approved for the product (for patents claiming a method of using a product).

Although we plan on seeking patent term restoration for our products, it may not be granted if, for example, we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail 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 restoration or the term of any such patent restoration is less than we request, our competitors may be able to enter the market and compete against us sooner than we anticipate, and our ability to generate revenues could be materially adversely affected.

Changes in United States patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and is therefore costly, time-consuming and inherently uncertain. In addition, the United States has in recent years implemented wide-ranging patent reform legislation, the Leahy-Smith America Invents Act, or America Invents Act. The America Invents Act includes a number of significant changes to United States patent law. These include provisions that affect the way patent applications will be prosecuted, provides expanded opportunities for post-grant administrative review of patents before the USPTO, and may also affect patent litigation. The USPTO developed new regulations and procedures to govern administration of the America Invents Act, and many of the substantive changes to patent law associated with the America Invents Act, in particular the first to file provisions, only became effective on March 16, 2013. A third party that files a patent application in the USPTO after that date but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by the third party. This requires us to be cognizant of the time from invention to filing of a patent application. Thus, for our U.S. patent applications containing a priority claim after March 16, 2013, there is a greater level of uncertainty in the patent law. Moreover, some of the patent applications in our portfolio will be subject to examination under the pre-America Invents Act law and regulations, while other patents applications in our portfolio will be subject to examination under the law and regulations, as amended by the America Invents Act. This introduces additional complexities and costs into the prosecution and management of our portfolio.

In addition, the America Invents Act and recent Supreme Court and U.S. Court of Appeals for the Federal Circuit decisions limit where a patentee may file a patent infringement suit, and the America Invents Act provides opportunities for third parties to challenge any issued patent in the USPTO. These provisions apply to all of our U.S. patents, even those filed before March 16, 2013. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in U.S. federal court necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a federal court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims because it may be easier for them to do so relative to challenging the patent in a federal court action. It is not clear what, if any, impact the America Invents Act will have on the operation of our business. However, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of any patents that may issue from our patent applications, all of which could have a material adverse effect on our business and financial condition.

In addition, recent United States Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. The full impact of these decisions is not yet known. For example, on March 20, 2012 in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, the Court held that several claims drawn to measuring drug metabolite levels from patient samples and correlating them to drug doses were not patent-eligible subject matter. The decision appears to impact diagnostics patents that merely apply a law of nature via a series of routine steps and it has created uncertainty around the ability to obtain patent protection for certain inventions. Additionally, on June 13, 2013 in *Association for Molecular Pathology v. Myriad Genetics, Inc.,* the Court held that claims to isolated genomic DNA are not patent-eligible, but claims to complementary DNA molecules are patent-eligible because they are not a natural product. The effect of the decision on patents for other isolated natural products is uncertain. On June 19, 2014 in *Alice Corporation Pty. Ltd. v. CLS Bank International, et al.,* a case involving patent claims directed to a method for mitigating settlement risk, the Court held that the patent eligibility of claims directed to abstract ideas, products of nature, and laws of nature should be determined using the same framework set forth in Prometheus. The USPTO has issued a series of guidelines setting forth procedures for determining subject matter eligibility of claims directed to abstract ideas, products of nature, and laws of nature in line with the *Prometheus, Myriad and Alice* decisions. This guidance does not limit the application of *Myriad* to DNA, but, rather, applies the decision to other natural products. The USPTO's interpretation of the case law and new guidelines for examination may influence, possibly adversely, prosecution and defense of certain types of claims in our portfolio.

In addition to increasing uncertainty with regard to our ability to obtain future patents, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on these and other decisions by the United States 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 current or future patents.

We may be subject to damages resulting from claims that we or our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

Our employees have been previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors, or at universities or academic medical centers. We also engage advisors and consultants who are concurrently employed at universities or who perform services for other entities. Although we are not aware of any claims currently pending against us, we may be subject to claims that we or our employees, advisors or consultants have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of a former employer or other third party. We may in the future also be subject to claims that an employee, advisor or consultant performed work for us that conflicts with that person's obligations to a third party, such as an employer, and thus, that the third party has an ownership interest in the intellectual property arising out of work performed for us. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management. If we are unsuccessful in defending against such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. A loss of key personnel or their work product could hamper or prevent our ability to commercialize vonapanitase or any additional product candidates, which would materially adversely affect our commercial development efforts.

Numerous factors may limit any potential competitive advantage provided by our intellectual property rights.

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, provide a barrier to entry against our competitors or potential competitors, or permit us to maintain our competitive advantage. Moreover, if a third party has intellectual property rights that cover the practice of our technology, we may not be able to exercise or extract value from our intellectual property rights fully or at all. The following examples are illustrative:

- we might not have been the first to make the inventions covered by a patent or pending patent application that we own;
- we might not have been the first to file patent applications covering an invention;
- others may independently develop similar or alternative technologies without infringing our intellectual property rights;
- third parties may compete with us in jurisdictions where we do not pursue and obtain patent protection;
- pending patent applications that we own may not lead to issued patents;
- patents that we own may not provide us with any competitive advantages, or may be held invalid or unenforceable;
- third parties may assert an ownership interest in our intellectual property;

- we may not develop or in-license additional proprietary technologies that are patentable; and
- the patents or proprietary rights of others may have an adverse effect on our business.

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

Risks Related to Our Business and Industry

If we fail to attract and keep senior management and key scientific personnel, we may be unable to successfully develop our products, conduct our clinical trials and commercialize our product candidates.

Our future growth and success depend on our ability to recruit, retain, manage and motivate our employees. We are highly dependent on our senior management team, in particular, Timothy Noyes, our President and Chief Executive Officer, Steven Burke, our Senior Vice President and Chief Medical Officer, George Eldridge, our Senior Vice President, Chief Financial Officer, Treasurer and Assistant Secretary, Scott Toner, our Senior Vice President of Commercial, and Daniel Gottlieb, our Vice President, Corporate Development, as well as the other principal members of our management and scientific teams. Although we have formal employment agreements with our executive officers, these agreements do not prevent them from terminating their employment with us at any time. The loss of the services of any member of our senior management or scientific team or the inability to hire or retain experienced management personnel could adversely affect our ability to execute our business plan and harm our operating results.

Because of the specialized scientific and managerial nature of our business, we rely heavily on our ability to attract and retain qualified scientific, technical and managerial personnel. We do not currently carry “key person” insurance on the lives of members of executive management. The competition for qualified personnel in the pharmaceutical field is intense. Due to this intense competition, we may be unable to continue to attract and retain qualified personnel necessary for the development of our business or to recruit suitable replacement personnel. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy including, F. Nicholas Franano, our scientific founder. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

We will need to significantly increase the size of our organization, and we may experience difficulties in managing growth.

We are currently a small company and in order to commercialize our potential products, we will need to increase our operations and expand our use of our third-party contractors. We plan to continue to build our compliance, financial and operating infrastructure to ensure the maintenance of a well-managed company including hiring additional staff within our regulatory and clinical groups as we move into later stages of our Phase 3 development. We intend to recruit an in-house commercial organization in the United States focused on promoting vonapanitase, if it is approved. We currently do not have a sales and marketing capability and therefore intend to recruit a specialty sales force of approximately 75-100 representatives in anticipation of vonapanitase's approval. We estimate it will take three to six months to recruit this specialty sales force. We will need to expand our employment base when we are in the full commercial stages of our current potential product's life cycle.

Future growth will impose significant added responsibilities on members of management, including the need to identify, recruit, maintain and integrate additional employees. In addition, to meet our obligations as a public company, we will need to increase our general and administrative capabilities. Our management, personnel and systems currently in place may not be adequate to support this future growth. Our future financial performance and our ability to commercialize our potential products 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 clinical trials and the regulatory process effectively;
- manage the manufacturing of product candidates and potential products for clinical and commercial use;

- integrate current and additional management, administrative, financial and sales and marketing personnel;
- develop a marketing and sales infrastructure;
- hire new personnel necessary to effectively commercialize vonapanitase and any additional product candidates;
- develop our administrative, accounting and management information systems and controls; and
- hire and train additional qualified personnel.

Product candidates that we may acquire or develop in the future may be intended for patient populations that are large. In order to continue development and marketing of these product candidates, if approved, we would need to significantly expand our operations. Our staff, financial resources, systems, procedures or controls may be inadequate to support our operations and our management may be unable to manage successfully future market opportunities or our relationships with customers and other third parties.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

Upon completion of our Initial Public Offering, or IPO, we became subject to the periodic reporting requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, and recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met.

These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements due to error or fraud may occur and not be detected.

If product liability lawsuits are successfully brought against us, our insurance may be inadequate and we may incur substantial liability.

We face an inherent risk of product liability claims as a result of the clinical testing of vonapanitase or any additional product candidates. We will face an even greater risk if we commercially sell vonapanitase or any additional product candidate that we develop. We maintain primary product liability insurance and excess product liability insurance that cover our clinical trials, and we plan to maintain insurance against product liability lawsuits for commercial sale of our potential products. Historically, the potential liability associated with product liability lawsuits for pharmaceutical products has been unpredictable. Although we believe that our current insurance is a reasonable estimate of our potential liability and represents a commercially reasonable balancing of the level of coverage as compared to the cost of the insurance, we may be subject to claims in connection with our clinical trials and, in the future, commercial use of our potential products, for which our insurance coverage may not be adequate, and the cost of any product liability litigation or other proceeding, even if resolved in our favor, could be substantial.

For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical 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, negligence, strict liability or a breach of warranties. Large judgments have been awarded in class action lawsuits based on drugs or biologics that had unanticipated adverse effects. 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 commercialization of vonapanitase or any additional product candidates. Regardless of the merits or eventual outcome, liability claims may result in:

- reduced resources of our management to pursue our business strategy;

- decreased demand for our product candidates or products that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- termination of clinical trial sites or entire trial programs;
- initiation of investigations by regulators;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- significant costs to defend resulting litigation;
- diversion of management and scientific resources from our business operations;
- substantial monetary awards to trial participants or patients;
- loss of revenue; and
- the inability to commercialize any products that we may develop.

We currently have a $5 million product liability insurance coverage in connection with our clinical trials and we will need to increase our insurance coverage if and when we begin selling vonapanitase or any additional product candidates if and when they receive marketing approval. However, the product liability insurance we will need to obtain in connection with the commercial sales of vonapanitase or any additional product candidates if and when they receive regulatory approval may be unavailable in meaningful amounts or at a reasonable cost. In addition, insurance coverage is becoming increasingly expensive. If we are unable to obtain or maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against potential product liability claims, it could prevent or inhibit the development and commercial production and sale of vonapanitase or any additional product candidates if and when they obtain regulatory approval, which could materially adversely affect our business, financial condition, results of operations, cash flows and prospects.

Additionally, we do not carry insurance for all categories of risk that our business may encounter. Some of the policies we currently maintain include general liability, employment practices liability, property, auto, workers' compensation, products liability and directors' and officers' insurance. We do not know, however, if we will be able to maintain insurance with adequate levels of coverage. Any significant uninsured liability may require us to pay substantial amounts, which would materially adversely affect our financial position, cash flows and results of operations.

If we engage in acquisitions in the future, we will incur a variety of costs and we may never realize the anticipated benefits of such acquisitions.

We may attempt to acquire businesses, technologies, services, products or product candidates in the future that we believe are a strategic fit with our business. We have no present agreement regarding any material acquisitions. If we do undertake any acquisitions, however, the process of integrating an acquired business, technology, service, products or product candidates into our business may result in unforeseen operating difficulties and expenditures, including diversion of resources and management's attention from our core business. In addition, we may fail to retain key executives and employees of the companies we acquire, which may reduce the value of the acquisition or give rise to additional integration costs. Future acquisitions could result in additional issuances of equity securities that would dilute the ownership of existing stockholders. Future acquisitions could also result in the incurrence of debt, actual or contingent liabilities or the amortization of expenses related to other intangible assets, any of which could adversely affect our operating results. In addition, we may fail to realize the anticipated benefits of any acquisition.

We currently have our API produced for us by a contract manufacturer exclusively in one manufacturing facility and if this or any future facility, any facility we use for storage of the finished product or our equipment were damaged or destroyed, our ability to continue to operate our business would be materially harmed.

Our executive offices are located in Waltham, Massachusetts, and our API is manufactured at Lonza's facility located in Visp, Switzerland. We expect that Lonza plans to utilize this facility in the future to support commercial production if our product candidate is approved. We have manufactured our entire finished product for the ongoing Phase 3 clinical trial of vonapanitase and currently store the finished product in only one location. Extended delays in our Phase 3 clinical trial causing us to need to manufacture new clinical supply would cause a significant disruption in our operations and cause us to incur unexpected costs to manufacture new finished product. In addition, we have completed three drug substance process validation runs at Lonza's facility in Visp, Switzerland and currently store such material in only one location. We are vulnerable to natural disasters, such as severe storms and other events that could disrupt our operations. We do not carry insurance for natural disasters and we may not carry sufficient business interruption insurance to compensate us for losses that may occur. If the current manufacturing facility or any future facility, stored product or equipment were damaged or destroyed, or if we experience a significant disruption in our operations for any reason, our ability to continue to operate our business would be materially harmed.

If supply is interrupted, there could be a significant disruption in our clinical development and commercial supply. If the supply is interrupted after approval of the BLA, 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 would likely 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 vonapanitase or any additional product candidates, cause us to incur higher costs and prevent 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 business and operations would suffer in the event of system failures or security breaches.

Despite the implementation of security measures, our internal computer systems, and those of our CROs and other third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, cyber attacks, natural disasters, terrorism, war and telecommunication and electrical failures. If issues were to arise and cause interruptions in our operations, it could result in a material disruption of our drug and biologic development programs or could cause loss of critical data or the unauthorized disclosure, access, acquisition, alteration, or use of personal or other confidential information. For example, the loss of clinical trial data from completed or ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security 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 of vonapanitase or any additional product candidates could be delayed. We may also be vulnerable to cyber attacks by hackers, or other malfeasance. This type of breach of our cybersecurity may compromise our confidential information and/or our financial information and detrimentally impact our business or result in significant legal and financial exposure and/or reputational harm.

In addition, while we select third-party vendors and business partners carefully and routinely evaluate the cybersecurity of our CROs and other key vendors, we do not control their actions. Any problems caused by these third parties, including those resulting from cyber attacks and security breaches at a vendor, could result in material delays in our development programs and regulatory approval efforts and adversely affect our business. Moreover, data security incidents and other inappropriate access can be difficult to detect, and any delay in identifying them may lead to increased harm of the type described above.

There are also numerous federal, state, and local laws and regulations in the United States and around the world regarding privacy and the collection, processing, storing, sharing, disclosing, using, cross-border transfer, and protecting of personal information and other data, the scope of which are changing, subject to differing interpretations, and which may be costly to comply with, may result in regulatory fines or penalties, and may be inconsistent between countries and jurisdictions or conflict with other requirements. We strive to comply with all applicable laws, policies, legal obligations, and industry codes of conduct relating to privacy and data protection, to the extent possible. However, it is possible that these obligations may be interpreted and applied in new ways or in a manner that is inconsistent from one jurisdiction to another and may conflict with other rules or our practices or that new regulations could be enacted. Several proposals are pending before federal, state, and foreign legislative and regulatory bodies that could affect our business. Any failure or perceived failure by us to comply with our privacy-related obligations to third parties, or our privacy-related legal obligations, or any compromise of security that results in the unauthorized release or transfer of sensitive information, which could include personally identifiable information or other user data, may result in governmental investigations, enforcement actions, regulatory fines, litigation, or public statements against us by advocacy groups or others, and could cause third parties, including clinical sites, regulators or potential partners, to lose trust in us, which could have an adverse effect on our business.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading, which could significantly harm our business.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with the regulations of the FDA and foreign regulators, provide accurate information to the FDA and foreign regulators, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, and report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, 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. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have a Code of Business Conduct and Ethics, but it is not always possible to identify and deter employee misconduct, 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 comply with these laws or regulations. If any actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

We have broad discretion in our use of our cash and cash equivalents and may not use them effectively.

Our management has broad discretion to use our cash and cash equivalents to fund our operations and could spend these funds in ways that do not improve our results of operations or enhance the value of our Common Stock. The failure of our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our Common Stock to decline and delay the development of our product candidates. Pending their use to fund our operations, we may invest our cash and cash equivalents in a manner that does not produce income or that loses value.

Recent federal legislation may increase the difficulty and cost for us to commercialize vonapanitase and may affect the prices we may obtain, and impair our ability to profitably sell vonapanitase, if approved.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval for vonapanitase, restrict or regulate post-approval activities and affect our ability to profitably sell vonapanitase, if approved. Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We do not know whether additional legislative changes will be enacted, or whether the FDA regulations, targets or interpretations will be changed, or what the impact of such changes on the marketing approvals of vonapanitase, if any, may be. In addition, increased scrutiny by the United States Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

In the United States, the pharmaceutical industry has been significantly affected by legislative initiatives. For example, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug and biologic purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for drugs and biologics. Cost reduction initiatives and other provisions of this legislation could decrease the coverage of, or the reimbursement rate that we receive for, vonapanitase, if approved, and could seriously harm our business. While the MMA applies only to reimbursement of drugs and biologics under the Medicare program, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates, and any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from non-governmental payors.

In March 2010, President Obama signed the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 or, collectively, the ACA, which substantially changes the way healthcare will be financed by both governmental and private insurers, and significantly impacts the pharmaceutical industry. Among the provisions of the ACA of importance to our business, including, without limitation, our ability to commercialize, and the prices we may obtain for, vonapanitase, if approved for sale, are the following:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- increases in the statutory minimum rebates a manufacturer must pay as a condition to having a drug or biologic available for coverage under the Medicaid program;
- expansion of healthcare fraud and abuse laws, including the federal civil False Claims Act and the federal Anti-Kickback Statute, and the addition of new government investigative powers and enhanced penalties for non-compliance;
- extension of a manufacturer's Medicaid rebate liability to covered drugs and biologics dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new eligibility categories for certain individuals with income at or below 133% of the federal poverty level beginning in 2014, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements under the federal Open Payments program and its implementing regulations;
- a new requirement to annually report drug and biologic samples that manufacturers and distributors provide to physicians;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and
- a special Medicare Part B payment rate for biosimilars that favors them over the reference biological product.

Other legislative changes have been proposed and adopted since the ACA was enacted. These changes include aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013. In January 2013 the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. More recently, the Tax Cuts and Jobs Act of 2017 eliminated certain requirements of the ACA, including the individual mandate. The full impact on our business of the ACA and other new laws is uncertain but may result in additional reductions in Medicare and other healthcare funding. In addition, it is unclear whether there will be additional administrative or legislative changes, including modification, repeal, or replacement of all, or certain provisions of, the ACA. Nor is it clear whether other legislative changes will be adopted, if any, or how such changes would affect the demand for vonapanitase, if approved.

We expect that the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and in additional downward pressure on the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our product candidates, if approved.

Moreover, there has recently been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products. Individual states in the United States have become increasingly aggressive in implementing regulations designed to contain pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures. Legally mandated price controls on payment amounts by third-party payors or other restrictions could harm our business, results of operations, financial condition and prospects. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. This could reduce the ultimate demand for our product candidates, if approved, or put pressure on our product pricing, which could negatively affect our business, results of operations, financial condition and prospects.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

Governments outside the United States tend to impose strict price controls, which may adversely affect our revenues, if any.

In international markets, reimbursement and health care payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. In some countries, particularly the countries of 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. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. There can be no assurance that our products will be considered cost-effective by third-party payors, that an adequate level of reimbursement will be available or that the third-party payors' reimbursement policies will not adversely affect our ability to sell our products profitably. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

Risks Related to Our Common Stock

We are an "emerging growth company" and as a result of the reduced disclosure and governance requirements applicable to emerging growth companies, our Common Stock may be less attractive to investors.

We are an "emerging growth company," or EGC, as defined in the JOBS Act, and we intend to take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not EGCs, including: not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We may take advantage of these reporting exemptions until we are no longer an EGC. We will remain an EGC until the earlier of (1) the last day of the fiscal year (a) following the fifth anniversary of the completion of our IPO, (b) in which we have total annual gross revenue of at least $1 billion, or (c) in which we are deemed to be a large accelerated filer, which means the market value of our Common Stock that is held by non-affiliates exceeds $700 million as of the prior June 30th, and (2) the date on which we have issued more than $1 billion in non-convertible debt during the prior three-year period.

We cannot predict whether investors will find our Common Stock less attractive if we 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. In addition, the JOBS Act provides that an EGC can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an EGC to delay the adoption of these accounting standards until they would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not EGCs.

Even after we no longer qualify as an EGC, 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 the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We cannot predict if investors will find our Common Stock less attractive because we will 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.

The market price for our Common Stock may be volatile, which could contribute to the loss of your investment.

Fluctuations in the price of our Common Stock could contribute to the loss of all or part of your investment. Prior to our IPO, there was no public market for our Common Stock. We are now listed on NASDAQ, but we cannot predict the extent to which investor interest in our Company will lead to the development of or sustain an active trading market on NASDAQ or otherwise or how liquid that market might become. If an active trading market for our Common Stock does not develop or is not sustained, the market price and liquidity of our Common Stock will be materially and adversely affected and it may be difficult for stockholders to sell their shares of Common Stock at prices that are attractive to them, or at all. Further, an inactive market may also impair our ability to raise capital by selling shares of our Common Stock.

If an active market for our Common Stock develops and continues, the trading price of our Common Stock is likely to be highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. Any of the factors listed below could have a material adverse effect the price of our Common Stock and stockholders may also be unable to sell their shares of Common Stock at prices that are attractive to them due to fluctuations in the market price of our Common Stock. In such circumstances the trading price of our Common Stock may not recover and may experience a further decline.

Factors affecting the trading price of our Common Stock may include:

- our failure to develop and commercialize vonapanitase or any additional product candidates;
- actual or anticipated fluctuations in our quarterly financial results or the quarterly financial results of companies perceived to be similar to us;
- changes in the market's expectations about our operating results;
- adverse results or delays in preclinical studies or clinical trials;
- our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial;
- adverse regulatory decisions, including failure to receive regulatory approval for vonapanitase or any additional product candidates;
- success of competitive products;
- adverse developments concerning our collaborations and our manufacturers;

- inability to obtain adequate product supply for any product candidate for clinical trials or commercial sale or inability to do so at acceptable prices;
- the termination of a collaboration or the inability to establish additional collaborations;
- unanticipated serious safety concerns related to the use of any of vonapanitase or any additional product candidates;
- our ability to effectively manage our growth;
- the size and growth, if any, of the targeted market;
- our operating results failing to meet the expectation of securities analysts or investors in a particular period or failure of securities analysts to publish reports about us or our business;
- changes in financial estimates and recommendations by securities analysts concerning our company, our market opportunity, or the biotechnology and pharmaceutical industries in general;
- operating and stock price performance of other companies that investors deem comparable to us;
- overall performance of the equity markets;
- announcements by us or our competitors of acquisitions, new product candidates or programs, significant contracts, commercial relationships or capital commitments;
- our ability to successfully market vonapanitase or any additional product candidates;
- changes in laws and regulations affecting our business, including but not limited to clinical trial requirements for approvals;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for vonapanitase or any additional product candidates;
- commencement of, or involvement in, litigation involving our company, our general industry, or both;
- changes in our capital structure, such as future issuances of securities or the incurrence of additional debt;
- the volume of shares of our Common Stock available for public sale;
- additions or departures of key scientific or management personnel;
- any major change in our board or management;
- changes in accounting practices;
- ineffectiveness of our internal control over financial reporting;
- sales of substantial amounts of Common Stock by our directors, executive officers or significant stockholders or the perception that such sales could occur; and
- general economic and political conditions such as recessions, interest rates, fuel prices, international currency fluctuations and acts of war or terrorism.

Broad market and industry factors may materially harm the market price of our Common Stock irrespective of our operating performance. The stock market in general, and NASDAQ and the market for biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of the particular companies affected. The trading prices and valuations of these stocks, and of ours, may not be predictable. A loss of investor confidence in the market for technology or software stocks or the stocks of other companies which investors perceive to be similar to us, the opportunities in the digital simulation market or the stock market in general, could depress our stock price regardless of our business, prospects, financial conditions or results of operations.

Actual or potential sales of our Common Stock by our employees, including our executive officers, pursuant to pre-arranged stock trading plans could cause our stock price to fall or prevent it from increasing for numerous reasons, and actual or potential sales by such persons could be viewed negatively by other investors.

In accordance with the guidelines specified under Rule 10b5-1 of the Exchange Act and our policies regarding stock transactions, a number of our employees, including executive officers, have adopted and may continue to adopt stock trading plans pursuant to which they have arranged to sell shares of our Common Stock from time to time in the future. Generally, sales under such plans by our executive officers and directors require public filings. Actual or potential sales of our Common Stock by such persons could cause the price of our Common Stock to fall or prevent it from increasing for numerous reasons. For example, a substantial number of shares of our Common Stock becoming available (or being perceived to become available) for sale in the public market could cause the market price of our Common Stock to fall or prevent it from increasing. Also, actual or potential sales by such persons could be viewed negatively by other investors.

The issuance of additional sales of our Common Stock, or the perception that such issuances may occur, including through our "At-The-Market" offering, could cause the market price of our Common Stock to fall.

We have entered into a Sales Agreement with Cowen and Company, LLC, or Cowen, for the offer and sale of up to $40 million in aggregate amount of our Common Stock from time to time through Cowen, as our sales agent, pursuant to a Registration Statement on Form S-3 which became effective on January 12, 2016. We filed a prospectus supplement on March 14, 2018 because we are currently subject to General Instruction I.B.6 of Form S-3, which limits the amounts that we may sell under the Registration Statement. Cowen is not required to sell any specific number or dollar amount of shares of our Common Stock but will use its reasonable efforts, as our agent and subject to the terms of the Sales Agreement, to sell that number of shares upon our request. Sales of the shares, if any, may be made by any means permitted by law and deemed to be an "at-the-market" offering as defined in Rule 415 of the Securities Act of 1933, as amended, or the Securities Act, and will generally be made by means of brokers' transactions on the NASDAQ Global Market or otherwise at market prices prevailing at the time of sale, or as otherwise agreed with Cowen.

We may terminate the Sales Agreement at any time or it will terminate once proceeds of $40 million have been raised. For the six month ended June 30, 2018, we did not sell shares of common stock under our At-The-Market, or ATM. Whether we choose to affect future sales under our ATM program will depend upon a variety of factors, including, among others, market conditions and the trading price of our Common Stock relative to other sources of capital. The issuance from time to time of these new shares of Common Stock through our ATM program or in any other equity offering, or the perception that such sales may occur, could have the effect of depressing the market price of our Common Stock.

Our issuance of Common Stock under our "At-The-Market" offering program may be dilutive, and there may be future dilution of our Common Stock.

After giving effect to the issuance of Common Stock under our ATM offering program and the receipt of the expected net proceeds and the use of those proceeds, there may be a dilutive effect on our estimated earnings per share and funds from operations per share in years during which an offering is ongoing. The actual amount of potential dilution cannot be determined at this time and will be based on numerous factors. Additionally, we are not restricted by our organizational documents, contractual arrangements or otherwise from issuing additional Common Stock or preferred stock, including any securities that are convertible into or exchangeable or exercisable for, or that represent the right to receive, Common Stock or preferred stock or any substantially similar securities in the future. The market price of our Common Stock could decline as a result of issuances of a large number of shares of our Common Stock after this offering or the perception that such issuances could occur.

Our management will have broad discretion with respect to the use of the proceeds resulting from the issuance of Common Stock under our "At-The-Market" offering program.

Our management has significant flexibility in applying the net proceeds we expect to receive from the issuance of Common Stock under our ATM program. We intend to use the net proceeds from this offering for general corporate purposes, which may include repaying debt. However, because the net proceeds are not required to be allocated to any specific investment or transaction, investors cannot determine at the time of issuance the value or propriety of our application of the net proceeds, and investors may not agree with our decisions. In addition, our use of the net proceeds from the offering may not yield a significant return or any return at all. The failure by our management to apply these funds effectively could have an adverse effect on our financial condition, results of operations or the trading price of our Common Stock.

The resale of the shares of Common Stock issuable upon the conversion of our Series A Convertible Preferred Stock could adversely affect the prevailing market price of our Common Stock and cause stockholders to experience dilution.

On August 2, 2017, we issued and sold 22,000 shares of our Series A Convertible Preferred Stock, par value $0.001 per share, for a purchase price of $1,000 per share, or an aggregate purchase price of $22.0 million. Each share of Series A Convertible Preferred Stock is convertible into approximately 1,005 shares of our Common Stock at a conversion price of $0.9949 per share, provided that any conversion of Series A Convertible Preferred Stock by a holder into shares of Common Stock is prohibited if, as a result of such conversion, the holder, together with its affiliates and any other person or entity whose beneficial ownership of our Common Stock would be aggregated with such holder's for purposes of Section 13(d) of the Exchange Act, would beneficially own more than 9.985% of the total number of shares of our Common Stock issued and outstanding after giving effect to such conversion (the "Blocker"). Pursuant to the registration statement that we filed with the SEC for the resale by holders of our Series A Preferred Convertible Stock, as selling stockholders, of the aggregate 22,112,775 shares of Common Stock that are issuable upon conversion of the Series A Convertible Preferred Stock, the outstanding shares of Series A Convertible Preferred Stock may, at each holder's election, be converted into our Common Stock, subject to the Blocker. Although we cannot predict if and when the holders of Series A Convertible Preferred Stock may sell such shares in the public market, any converted shares of Common Stock will be available for immediate resale and be able to be freely sold in the open market. The conversion of shares of Series A Convertible Preferred Stock into shares of Common Stock will result in substantial dilution to holders of our Common Stock. Further, the sale of a significant amount of these shares of Common Stock in the open market or the perception that these sales may occur could adversely affect prevailing market prices of our Common Stock, including causing the market price of our Common Stock to decline or become highly volatile.

Raising additional funds through debt or equity financing could be dilutive and may cause the market price of our Common Stock to 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 and debt financings, and potentially through strategic partnerships with third parties. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of those securities could result in substantial dilution for our current stockholders and the terms may include liquidation or other preferences that adversely affect the rights of our current stockholders. Furthermore, the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our Common Stock to decline and existing stockholders may not agree with our financing plans or the terms of such financings. Moreover, the incurrence of debt financing could result in a substantial portion of our operating cash flow being dedicated to the payment of principal and interest on such indebtedness and could impose restrictions on our operations, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. Additional funding may not be available to us on acceptable terms, or at all.

If securities analysts do not publish research or reports about our business or if they downgrade our stock, the price of our Common Stock could decline.

The trading market for our Common Stock will rely in part on the research and reports that industry or financial analysts publish about us, our business, our markets and our competitors. We do not control these analysts. If securities analysts do not cover our Common Stock, the lack of research coverage may adversely affect the market price of our Common Stock. Furthermore, if one or more of the analysts who do cover us downgrade our stock or if those analysts issue other unfavorable commentary about us or our business, our stock price would likely decline. If one or more of these analysts cease coverage of us or fails to regularly publish reports on us, we could lose visibility in the market and interest in our stock could decrease, which in turn could cause our stock price or trading volume to decline and may also impair our ability to expand our business with existing customers and attract new customers.

The concentration of our capital stock ownership with insiders will likely limit your ability to influence corporate matters.

As of June 30, 2018, our executive officers, directors, current 5% or greater stockholders, and their respective affiliates together beneficially own or control, in aggregate, more than 50% of the shares of our outstanding Common Stock. As a result, these executive officers, directors and principal stockholders, acting together, will have substantial influence over most matters that require approval by our stockholders, including the election of directors, any merger, consolidation or sale of all or substantially all or of our assets or any other significant corporate transaction. Corporate action might be taken even if other stockholders oppose such action. These stockholders may delay or prevent a change of control or otherwise discourage a potential acquirer from attempting to obtain control of our company, even if such change of control would benefit our other stockholders. This concentration of stock ownership may adversely affect investors' perception of our corporate governance or delay, prevent or cause a change in control of our company, any of which could adversely affect the market price of our Common Stock.

Future sales and issuances of our Common Stock or rights to purchase Common Stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.

We have filed a registration statement permitting shares of Common Stock issued in the future, pursuant to our employee benefit plans, to be freely resold by plan participants in the public market, subject to applicable lock-up agreements, applicable vesting schedules and, for shares held by directors, executive officers and other affiliates, volume limitations under Rule 144 for shares. Our 2014 Amended and Restated Employee Incentive Plan and 2014 Employee Stock Purchase Plan also contain a provision for the annual increase of the number of shares reserved for issuance under such plan, which shares we also intend to register in the future as such annual increase occurs. If the shares we may issue from time to time under our employee benefit plans are sold, or if it is perceived that they will be sold, by the award recipient in the public market, the trading price of our Common Stock could decline.

We expect that significant additional capital will be needed in the future to continue our planned operations, including conducting clinical trials, commercialization efforts, expanded research and development activities and costs associated with operating a public company. To raise capital, we may sell Common Stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell Common Stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. Such sales may also result in material dilution to our existing stockholders, and new investors could gain rights, preferences and privileges senior to the holders of our Common Stock.

We will incur significant increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives.

As a newly public company, we have incurred and will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act, and rules of the SEC and those of NASDAQ impose various requirements on public companies including requiring establishment and maintenance of effective disclosure and financial controls. Our management and other personnel devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased and will continue to increase our legal and financial compliance costs and will make some activities more time-consuming and costly.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal control over financial reporting and disclosure controls and procedures. In particular, we must perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on the effectiveness of our internal control over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act. In addition, we will be required to have our independent registered public accounting firm attest to the effectiveness of our internal control over financial reporting the later of our second annual report on Form 10-K or the first annual report on Form 10-K following the date on which we are no longer an EGC. Our compliance with Section 404 of the Sarbanes-Oxley Act will require that we incur substantial accounting expense and expend significant management efforts. We currently do not have an internal audit group, and we will need to hire additional accounting and financial staff with appropriate public company experience and technical accounting knowledge. If we are not able to comply with the requirements of Section 404 in a timely manner, or if we or our independent registered public accounting firm identify deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, the market price of our stock could decline and we could be subject to sanctions or investigations by NASDAQ, the SEC or other regulatory authorities, which would require additional financial and management resources.

Our ability to successfully implement our business plan and comply with Section 404 requires us to be able to prepare timely and accurate financial statements. We expect that we will need to continue to improve existing, and implement new operational and financial systems, procedures and controls to manage our business effectively. Any delay in the implementation of, or disruption in the transition to, new or enhanced systems, procedures or controls, may cause our operations to suffer and we may be unable to conclude that our internal control over financial reporting is effective and to obtain an unqualified report on internal controls from our auditors as required under Section 404 of the Sarbanes-Oxley Act. This, in turn, could have an adverse impact on trading prices for our Common Stock, and could adversely affect our ability to access the capital markets.

We do not expect to pay any cash dividends for the foreseeable future.

You should not rely on an investment in our Common Stock to provide dividend income. We do not anticipate that we will pay any cash dividends to holders of our Common Stock in the foreseeable future. Instead, we plan to retain any earnings to maintain and expand our operations. Accordingly, investors must rely on sales of their Common Stock after price appreciation, which may never occur, as the only way to realize any return on their investment. As a result, investors seeking cash dividends should not purchase our Common Stock.

Our ability to use our net operating loss carryovers and certain other tax attributes may be limited.

As described above under "—Risks Related to Our Financial Condition and Need for Additional Capital," we have incurred net losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future. Under the Internal Revenue Code, as amended (the "Code"), a corporation is generally allowed a deduction for net operating losses, or NOLs, carried over from a prior taxable year. Under that provision, we can carry forward our NOLs to offset our future taxable income, if any, until such NOLs are used or expire. The same is true of other unused tax attributes, such as tax credits.

If a corporation undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, Sections 382 and 383 of the Code, limit the corporation's ability to use carryovers of its pre-change NOLs, credits and certain other tax attributes to reduce its tax liability for periods after the ownership change. We completed a preliminary analysis to determine if there were changes in ownership for tax years through 2017, as defined by Section 382 of the Internal Revenue Code that would limit our ability to utilize certain net operating loss and tax credit carryforwards and it was preliminarily determined a change in ownership occurred in 2017. With this change in ownership, as defined by Section 382, we believe utilization of our net operating losses and tax credits carryforwards have become limited. As a result, this could result in increased U.S. federal income tax liability for us if we generate taxable income in a future period. Limitations on the use of NOLs and other tax attributes could also increase our state tax liability. The use of our tax attributes will also be limited to the extent that we do not generate positive taxable income in future tax periods.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology companies, including our company, have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

Provisions in our amended and restated certificate of incorporation, our amended and restated bylaws and Delaware law may have anti- takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management.

Our amended and restated certificate of incorporation, amended and restated bylaws and Delaware law contain provisions that may have the effect of delaying or preventing a change in control of us or changes in our management. Our amended and restated certificate of incorporation and bylaws include provisions that:

- authorize "blank check" preferred stock, which could be issued by our Board of Directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our Common Stock;
- create a classified Board of Directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our Board of Directors;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our Board of Directors;
- provide that our directors may be removed only for cause;
- provide that vacancies on our Board of Directors may be filled only by a majority of directors then in office, even though less than a quorum;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorize our Board of Directors to modify, alter or repeal our amended and restated bylaws; and
- require supermajority votes of the holders of our Common Stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated by laws.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management.

In addition, because we are incorporated in the State of 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.

Any provision of our amended and restated certificate of incorporation or amended and restated bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our Common Stock, and could also affect the price that some investors are willing to pay for our Common Stock.

Our amended and restated certificate of incorporation designates the Court of Chancery of the State of Delaware and federal court within the State of Delaware as the exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated certificate of incorporation provides that, subject to limited exceptions, the Court of Chancery of the State of Delaware and federal court within the State of Delaware will be exclusive forums for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders, (3) any action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law, our amended and restated certificate of incorporation or our amended and restated bylaws, or (4) any other action asserting a claim against us that is governed by the internal affairs doctrine. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our amended and restated certificate of incorporation described above. This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and employees. Alternatively, if a court were to find these provisions of our amended and restated certificate of incorporation inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business and financial condition.

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

Use of Proceeds from Unregistered Securities

None.

Purchase of Equity Securities

We did not purchase any of our registered equity securities during the period covered by this Quarterly Report on Form 10-Q.

Item 5. Other Information

Not applicable.

Item 6. Exhibits

The exhibits filed as part of this Quarterly Report on Form 10-Q are set forth on the Exhibit Index, which Exhibit Index is incorporated herein by reference.

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: August 7, 2018

PROTEON THERAPEUTICS, INC.

By: /s/ Timothy P. Noyes
Timothy P. Noyes
President, Chief Executive Officer and Director
(Principal Executive Officer)

Date: August 7, 2018

By: /s/ George A. Eldridge
George A. Eldridge
Senior Vice President, Chief Financial Officer,
Treasurer and Assistant Secretary
(Principal Financial and Accounting Officer)

EXHIBIT INDEX

Exhibit No.		Description
10.1	*‡	Amendment No. 3 to Manufacturing Services Agreement by and between the Company and Lonza LTD dated as of May 4, 2018.
31.1	*	Certification of Principal Executive Officer Required Under Rule 13a-14(a) and 15d-14(a) of the Securities Exchange Act of 1934, as amended.
31.2	*	Certification of Principal Financial Officer Required Under Rule 13a-14(a) and 15d-14(a) of the Securities Exchange Act of 1934, as amended.
32.1	**	Certification of Principal Executive Officer and Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	*	Interactive Data Files Pursuant to Rule 405 of Regulation S-T: (i) the Condensed Consolidated Balance Sheets as of June 30, 2018 (unaudited) and the Consolidated Balance Sheets as of December 31, 2017; (ii) the Condensed Consolidated Statements of Operations and Comprehensive Loss (unaudited) for the three and six months ended June 30, 2018 and 2017; and (iii) the Condensed Consolidated Statements of Cash Flows (unaudited) for the six months ended June 30, 2018 and 2017; and (iv) the notes to the Condensed Consolidated Financial Statements (unaudited).

*Exhibits filed herewith
** Exhibits furnished herewith.
‡Indicates confidential treatment has been requested with respect to specific portions of this exhibit. Omitted portions have been filed with the Securities and Exchange Commission pursuant to Rule 406 of the Securities Act of 1933, as amended.

Exhibit 10.1

AMENDMENT NO. 3

To

MANUFACTURING SERVICES AGREEMENT

Dated as of 4 May 2018

Between

Proteon Therapeutics, Inc.

And

LONZA LTD

THIS AMENDMENT No. 3 ("Amendment 3") is made effective as of the 4th day of May, 2018 to the Manufacturing Services Agreement, dated 30 June 2015 between Proteon Therapeutics, Inc. (“Proteon” or “Customer”) and Lonza Ltd (“Lonza”), as amended from time to time (the “Agreement”),

BETWEEN:

Proteon Therapeutics Inc., having its address at 200 West Street, Waltham, Massachusetts

and

Lonza Ltd., a Swiss Corporation having a place of business at Münchensteinerstrasse 38, CH-4002 Basel, Switzerland

WHEREAS

A. Proteon and Lonza entered into the Agreement, under which Lonza is required to perform Services relating to the Cell Line and Product described therein, and

B. Parties wish to make several changes to the Agreement.

NOW **THEREFORE THE PARTIES AGREE AS FOLLOWS:**

1. The following terms shall be deleted in their entirety from Clause 1 and replaced with the following:

   “Applicable Laws” means all relevant federal, state and local laws, statutes, rules, and regulations of any Governmental Authority which are applicable to a Party’s activities hereunder, including, without limitation, the applicable regulations and guidelines of any Governmental Authority and all applicable cGMP together with amendments thereto.

   “Batch” means a specific quantity of Product that is intended to have uniform character and quality, within specified limits (including the Specifications), and is derived from a single run of the Manufacturing Process at 1000L nominal volume (approx. 800L working volume). The minimum yield requirements for each Batch (“Minimum Yield”) will be determined by the Parties in good faith after the release of []* Batches (including the Process Validation Batches).

   “Regulatory Authority” means the FDA, EMA, and any similar regulatory authority in the []*. The terms “Regulatory Authority” and “Governmental Authority” shall include any other regulatory authorities or governmental entities as may be agreed upon in writing by the Parties, which agreement shall not be unreasonably withheld or delayed.

   Capitalized terms used but not otherwise defined herein shall have the meanings afforded to them in the Agreement.

2. Clause 6.2 of the Agreement is hereby amended by adding the following after the last sentence:

   “Notwithstanding the forecasting and ordering requirements set forth herein, the Parties agree that, in the event Customer wishes to manufacture one (1) cGMP Batch coincident with a pre-approval inspection of Lonza by the FDA, Lonza will provide Customer with the first available production slot for such Batch upon receipt of written notice from Customer. In addition, Lonza hereby agrees that Proteon’s Affiliates shall have the right, from time to time, to order quantities of a Product hereunder (including one or more Batches of a Campaign), provided that the acceptance of such order shall be subject to Lonza’s discretion, if the order is not in line with the Forecast. Any such Affiliate shall be bound by the terms of this Agreement with respect to any purchase order placed directly with Lonza hereunder and shall be deemed to have all of the rights and obligations of Customer under the Agreement. Proteon shall remain jointly responsible and liable for the performance of the payment obligations related to such order by Proteon's Affiliate in the event that a breach or failure of such a payment obligation relating to such order is not remedied by Proteon's Affiliate within []* after written notice to the Proteon's Affiliate (with a copy to Customer hereunder) from Lonza requiring such breach or failure to be remedied by Proteon's Affiliate, Proteon shall immediately fulfill all outstanding payment obligations.”

* CONFIDENTIAL TREATMENT REQUESTED. OMITTED PORTIONS FILED WITH THE SECURITIES AND EXCHANGE COMMISSION.

3. Clause 7.3.1 of the Agreement is hereby deleted in its entirety and replaced with the following:

"Promptly following Release of Batches, Customer shall inspect such Batches and shall have the right to test such Batches to determine compliance with the Specifications and, if applicable, the Minimum Yield. Customer shall notify Lonza in writing of any rejection of a Batch based on any claim that it fails to meet Specifications or Minimum Yield within thirty (30) days of Release, after which time all unrejected Batches shall be deemed accepted; provided that (a) Lonza provides timely answers to information requests and resolution of issues arising from Customer's review of such Batch (and the thirty (30) day period shall be extended to account for Lonza's failure to provide timely answers to information requests and resolution of such issues); and (b) failure to notify shall not prejudice Customer's right to reject or revoke acceptance of the Batch if the non-conforming condition causing the rejection of such Batch could not have been detected by Customer's inspection undertaken pursuant to this Clause 7.3.1; provided that any such notification shall be provided to Lonza within []* of delivery of the Product. In the event that Customer desires to accept a Batch prior to the end of the thirty (30) day period, Customer will provide written notice of such acceptance to Lonza."

4. The first sentence of Clause 7.3.4 of the Agreement is hereby deleted in its entirety and replaced with the following:

"7.3.4 Lonza shall replace any Batch (except for an Engineering Batch) that failed to meet the Specifications (in each case, a "Failed Batch"). Such replacement shall be made as promptly as practicable, in light of available manufacturing capacity and in any case as soon as reasonably possible after confirmation of a Failed Batch. Where possible, such replacement Batch shall be manufactured with the next scheduled cGMP Batch or Campaign. Customer acknowledges and agrees that its sole remedy with respect to a Failed Batch is as set forth in this Clause 7.3.4, and in furtherance thereof, Customer hereby waives all other remedies at law or in equity regarding the foregoing claims. Lonza shall not be responsible for the cost of Raw Materials or Customer Materials consumed in any Failed Batch except to the extent set forth in this Clause 7.3.4."

5. Clause 8.5.1 of the Agreement shall be deleted entirely and shall be replaced by the following clause:

"8.5.1 Upon reasonable prior written notice, not more than once per calendar year, starting in January []* and on each succeeding anniversary thereafter, Lonza may adjust the Batch Price in accordance with the US Department of Labor's Bureau of Labor Statistics Pharmaceutical Preparations Index, ethical PCU 325414 (or any successor index) ("PPI") percentage change, if any, for the most recent twelve-month period for which figures are available, provided that such adjustment shall not exceed []* of the Batch Price. The new Price reflecting such Batch Price adjustment shall be effective for any Batch for which the Commencement Date is on or after the date of Lonza's notice to Customer of the Price adjustment."

6. Clause 8.5.2 of the Agreement shall be deleted entirely and shall be replaced by the following clause:

"8.5.2 In addition to the above, the Price may be changed once per calendar year, starting in January []* and on each succeeding anniversary thereafter, upon reasonable prior written notice to the Customer (providing reasonable detail and any other documentation reasonably requested by Customer in support thereof), to reflect []* that has a material change of more than []* on Lonza's cost to perform the Services under this Agreement (as calculated on a pro rata basis based on Customer's use of the Facility), provided that such cost changes are not otherwise covered by PPI. In addition, the Parties will work diligently and in good faith to achieve all feasible cost savings with respect to Lonza's processes and materials and pass on at least []* of such savings to Proteon in the form of Batch Price reductions."

* CONFIDENTIAL TREATMENT REQUESTED. OMITTED PORTIONS FILED WITH THE SECURITIES AND EXCHANGE COMMISSION.

7. For purposes of clarity, in accordance with Clause 11.1.1 of the Agreement, Lonza hereby agrees that the Manufacturing Process was used to manufacture and deliver the Process Validation Batches and that, as of the date hereof, no Lonza Information or Lonza Background Intellectual Property has been incorporated into such Manufacturing Process.

8. Clause 12.5 of the Agreement shall be delete entirely and shall be replaced by the following clause:

12.5 LIMITATION OF LIABILITY. (A) EXCEPT FOR BREACH OF CONFIDENTIALITY OBLIGATIONS UNDER CLAUSE 13 AND EXCEPT AS OTHERWISE PROVIDED IN CLAUSE 12.1 WITH RESPECT TO THIRD PARTY CLAIMS, LONZA'S LIABILITY TO THE CUSTOMER UNDER THIS AGREEMENT SHALL IN NO EVENT EXCEED, IN THE AGGREGATE, THE GREATER OF (i) THE TOTAL AMOUNTS PAID BY CUSTOMER AND ITS AFFILIATES TO LONZA UNDER THE PURCHASE ORDER FOR THE CAMPAIGN OR SPECIFIC MANUFACTURING SERVICES GIVING RISE TO SUCH CLAIM AND (ii) THE TOTAL AMOUNTS PAID BY CUSTOMER AND ITS AFFILIATES TO LONZA UNDER THE PROJECT PLAN GIVING RISE TO SUCH CLAIM FOR DAMAGES IN THE TWELVE (12) MONTH PERIOD PRECEDING THE FIRST CLAIM FOR DAMAGES, EXCEPT TO THE EXTENT RESULTING FROM LONZA'S FRAUD, GROSS NEGLIGENCE OR INTENTIONAL MISCONDUCT.

(B) EXCEPT FOR BREACH OF CONFIDENTIALITY OBLIGATIONS UNDER CLAUSE 13 AND EXCEPT AS OTHERWISE PROVIDED IN CLAUSE 12.2 WITH RESPECT TO THIRD PARTY CLAIMS, CUSTOMER'S LIABILITY TO LONZA UNDER THIS AGREEMENT SHALL IN NO EVENT EXCEED, IN THE AGGREGATE, THE GREATER OF (i) THE TOTAL AMOUNTS PAID BY CUSTOMER AND ITS AFFILIATES TO LONZA UNDER THE PURCHASE ORDER FOR THE CAMPAIGN OR SPECIFIC MANUFACTURING SERVICES GIVING RISE TO THE CLAIM AND (ii) THE TOTAL AMOUNTS PAID BY CUSTOMER AND ITS AFFILIATES TO LONZA UNDER THE PROJECT PLAN GIVING RISE TO SUCH CLAIM FOR DAMAGES IN THE TWELVE (12) MONTH PERIOD PRECEDING THE FIRST CLAIM FOR DAMAGES, EXCEPT TO THE EXTENT RESULTING FROM CUSTOMER'S FRAUD, GROSS NEGLIGENCE OR INTENTIONAL MISCONDUCT.

9. Clause 14.1 of the Agreement shall be delete entirely and shall be replaced by the following clause:

"14.1 Term. This Agreement shall commence on the Effective Date and shall have a term ending on June 30, 2029, which is the 14th anniversary of the Effective Date, unless terminated earlier as provided herein or extended by mutual written consent of the Parties (the "Term"). Notwithstanding the foregoing, each Project Plan may have separate term and termination provisions so long as the term of any Project Plan does not extend beyond the Term."

10. Clause 14.2.1 of the Agreement shall be delete entirely and shall be replaced by the following clause:

"14.2.1 by either Party for any reason upon 36 months' prior written notice to the other Party, provided that (i) Customer shall not exercise this termination right before 1 January 2020; and (ii) Lonza shall not exercise this termination right before 1 January 2023;"

11. Parties agree to make the following changes to Project Plan A-1, Exhibit C and Exhibit D.

a. Exhibit C (Estimated Project Plan Timeline)

Subject to Section 6.1 and 6.2 of the Agreement, the following table will be added to Exhibit C of Project Plan A-1 (as amended by Amendment 2, effective as of January 21, 2016), as a non-binding estimate of Customer's commercial requirements for Batches:

[]*

* CONFIDENTIAL TREATMENT REQUESTED. OMITTED PORTIONS FILED WITH THE SECURITIES AND EXCHANGE COMMISSION.

For the sake of clarity, the Parties hereby agree that the Batch scheduled for Q4 2019 is cancelled and no Cancellation Fee related thereto shall be due or payable.

b. Exhibit D (Price and Payment Terms)

Parties hereby agree that the payment schedule set forth in Exhibit D is hereby deleted and the Batch Price of []* per Batch will be replaced by a Batch Price of []* per Batch for all orders placed from and after the date hereof.

12. A new Clause 6.3.1 will be added between Clause 6.3 and Clause 6.4 of the Agreement:

"6.3.1 Minimum Quantity. During the Term of this Agreement and expressly conditioned on the FDA's approval of the Product (including, but not limited to, FDA's approval of Lonza as a supplier of the Product), Customer undertakes to order (by issuing binding purchase orders pursuant to clause 6.2 of this Agreement) from Lonza a minimum of []*, starting in calendar year 2022. For example, the []* forecasted in 2022 would be followed by []* in []*. For the avoidance of doubt, and subject to the first sentence of this Clause 6.3.1, Parties agree that the first binding purchase order for the 2022 []* shall be issued ultimately on or before []*. Unless otherwise agreed to by the Parties in writing, if Customer fails to place a binding purchase order for such []* within the applicable []* period (including any purchase orders placed by an Affiliate of Customer for purposes of this calculation), Customer shall pay the Price for []* not so ordered within []* days following the end of such period and receipt of Lonza's invoice."

13. Remainder of Agreement. All other terms and conditions of the Agreement (as previously amended) shall remain in full force and effect.

14. Entire Agreement. This Amendment 3 and the Agreement supersede all other prior agreements, understandings, representations and warranties, oral or written between the parties hereto in respect of the subject matter hereof.

AS WITNESS the hands of the duly authorized representatives of the parties hereto the day and year first before written.

SIGNED BY:
For and on behalf of
Lonza Ltd

/s/ Bart van Aarnhem

Sr. Legal Counsel

Title

SIGNED BY:
For and on behalf of
Lonza Ltd

/s/ Michael Stanek

General Counsel
Head Legal Team Basel

Title

SIGNED BY:
For and on behalf of
Proteon Therapeutics, Inc.

/s/ Timothy Noyes
Timothy P. Noyes

President and CEO

Title

* CONFIDENTIAL TREATMENT REQUESTED. OMITTED PORTIONS FILED WITH THE SECURITIES AND EXCHANGE COMMISSION.

Exhibit 31.1

CERTIFICATION PURSUANT TO
SECURITIES EXCHANGE ACT RULES 13a-14(a) and 15d-14(a)
AS ADOPTED PURSUANT TO
SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Timothy P. Noyes, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q for the period ended June 30, 2018 of Proteon Therapeutics, 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 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 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.

/s/ Timothy P. Noyes
Timothy P. Noyes
President, Chief Executive Officer and Director
(Principal Executive Officer)

Date: August 7, 2018

Exhibit 31.2

CERTIFICATION PURSUANT TO
SECURITIES EXCHANGE ACT RULES 13a-14(a) and 15d-14(a)
AS ADOPTED PURSUANT TO
SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, George A. Eldridge, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q for the period ended June 30, 2018 of Proteon Therapeutics, 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 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 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.

/s/ George A. Eldridge
George A. Eldridge
Senior Vice President, Chief Financial Officer, Treasurer and Assistant Secretary
(Principal Financial Officer)

Date: August 7, 2018

Exhibit 32.1

CERTIFICATION PURSUANT TO SECTION 1350, AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Quarterly Report of Proteon Therapeutics, Inc. (the "Corporation") on Form 10-Q for the fiscal quarter ended June 30, 2018, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Timothy P. Noyes, as President and Chief Executive Officer of the Corporation, and I, George A. Eldridge, Senior Vice President, Chief Financial Officer, Treasurer and Assistant Secretary of the Corporation, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to my knowledge:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Corporation.

Date: August 7, 2018

By: /s/ Timothy P. Noyes
Timothy P. Noyes
President, Chief Executive Officer and Director
(Principal Executive Officer)

Date: August 7, 2018

By: /s/ George A. Eldridge
George A. Eldridge
Senior Vice President, Chief Financial Officer, Treasurer and Assistant Secretary
(Principal Financial Officer)

A signed original of this written statement required by Section 906 has been provided to the Company and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.