UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 10-Q

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

For the quarterly period ended September 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: 001-37695

Proteostasis Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**20-8436652**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

80 Guest Street, Suite 500
Boston, Massachusetts 02135
(Address of principal executive office) (Zip Code)

Registrant's telephone number, including area code: (617) 225-0096

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

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	☐	Accelerated filer	☒
Non-accelerated filer	☐	Smaller reporting company	☐
Emerging growth company	☒		

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

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

As of November 2, 2018, there were 49,158,422 shares of the registrant's Common Stock, $0.001 par value per share, outstanding.

FORWARD-LOOKING STATEMENTS

This Quarterly Report on Form 10-Q contains forward-looking statements that involve risks and uncertainties. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. All statements other than statements of historical facts contained in this Quarterly Report on Form 10-Q are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "aim," "may," "will," "should," "expects," "intends," "plans," "anticipates," "believes," "estimates," "predicts," "potential," "continue," or the negative of these terms or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- our estimates regarding our clinical trials, including, without limitation, the timing of the initiation of, completion of, enrollment in, and data from our trials;
- our estimates regarding anticipated filing of INDs or amended protocols for nominated drug candidates;
- our estimates regarding expenses, future revenues and capital requirements;
- our ability to obtain and maintain regulatory approval of PTI-428, PTI-801 and PTI-808, and our combination solutions, for any indication, and the labeling under any approval we may obtain;
- our ability to obtain and maintain sanctioning or favorable scoring of our clinical trials or protocols from other third parties, such as the Therapeutics Development Network of the Cystic Fibrosis Foundation or the Clinical Trial Network of the European Cystic Fibrosis Society;
- intense competition in the cystic fibrosis market and the ability of our competitors, many of whom have greater resources than we do, to run clinical trials that may limit the patients available for our trials, and to offer different, better or lower cost therapeutic alternatives than our product candidates;
- anticipated regulatory developments in the United States and foreign countries;
- anticipated developments with respect to, and the commercial availability of, cystic fibrosis transmembrane conductance modulators with which PTI-428 or PTI-801 are intended to be or may in the future be administered, including Vertex's Kalydeco®, Orkambi® and Symdeko®;
- our plans to develop and commercialize PTI-428, PTI-801 and our combination solutions, including expected preclinical and clinical results and timing;
- our ability to obtain and maintain intellectual property protection for our proprietary assets;
- the size and growth of the potential markets for PTI-428, PTI-801 and our combination solutions, and our ability to serve those markets;
- the rate and degree of market acceptance of PTI-428, PTI-801 and our combination solutions for any indication;
- the benefits of FDA designations such as, including, without limitation, Fast Track, Orphan Drug and Breakthrough Therapy;
- our ability to obtain additional financing;
- the loss of key scientific or management personnel; and
- other forward-looking statements discussed elsewhere in this report.

Any forward-looking statements in this report reflect our current views with respect to future events and with respect to our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those described under Part II, Item 1A. Risk Factors and elsewhere in this report. 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 report contains estimates, projections and other information concerning our industry, the general business environment, and the markets for certain diseases, including estimates regarding the potential size of those markets and the estimated 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, circumstances or numbers, including actual disease prevalence rates and market size, may differ materially from the information reflected in this report. Unless otherwise expressly stated, we obtained this industry, business information, market data, prevalence information 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, in some cases applying our own assumptions and analysis that may, in the future, not prove to have been accurate.

Kalydeco, Orkambi and Symdeko are trademarks of Vertex Pharmaceuticals Incorporated.

Proteostasis Therapeutics, Inc.

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PART I — FINANCIAL INFORMATION

PROTEOSTASIS THERAPEUTICS, INC.

CONDENSED BALANCE SHEETS
(In thousands, except share and per share amounts)
(Unaudited)

	September 30, 2018	December 31, 2017
Assets		
Current assets:		
Cash and cash equivalents	$ 19,712	$ 29,724
Short-term investments	26,692	44,738
Restricted cash	—	294
Prepaids and other current assets	1,930	1,377
Total current assets	48,334	76,133
Operating lease, right-of-use asset	14,147	472
Property and equipment, net	648	424
Other assets	6	33
Restricted cash, net of current portion	828	1,656
Total assets	$ 63,963	$ 78,718
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 2,145	$ 2,098
Accrued expenses	8,406	6,120
Deferred revenue	—	1,108
Operating lease liabilities	1,033	559
Total current liabilities	11,584	9,885
Derivative liability	3	25
Operating lease liabilities, net of current portion	13,469	—
Total liabilities	25,056	9,910
Commitments and contingencies		
Stockholders' equity:		
Preferred stock, $0.001 par value; 5,000,000 shares authorized as of September 30, 2018 and December 31, 2017; no shares issued and outstanding as of September 30, 2018 and December 31, 2017	—	—
Common stock, $0.001 par value; 125,000,000 shares authorized as of September 30, 2018 and December 31, 2017; 36,696,948 and 34,416,088 shares issued and outstanding as of September 30, 2018 and December 31, 2017, respectively	37	35
Additional paid-in capital	299,512	285,583
Accumulated other comprehensive loss	(7)	(2)
Accumulated deficit	(260,635)	(216,808)
Total stockholders' equity	38,907	68,808
Total liabilities and stockholders' equity	$ 63,963	$ 78,718

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

PROTEOSTASIS THERAPEUTICS, INC.

CONDENSED STATEMENTS OF OPERATIONS
(In thousands, except share and per share amounts)
(Unaudited)

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Revenue	$ 1,055	$ 1,551	$ 2,840	$ 3,719
Operating expenses:				
Research and development	15,591	12,894	36,595	41,372
General and administrative	4,150	2,741	11,931	8,813
Total operating expenses	19,741	15,635	48,526	50,185
Loss from operations	(18,686)	(14,084)	(45,686)	(46,466)
Interest income	171	155	530	515
Other income (expense), net	87	(25)	224	(57)
Net loss	$ (18,428)	$ (13,954)	$ (44,932)	$ (46,008)
Net loss per share attributable to common stockholders—basic and diluted	$ (0.50)	$ (0.56)	$ (1.26)	$ (1.84)
Weighted average common shares outstanding—basic and diluted	36,694,957	25,093,344	35,734,159	25,051,536

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

PROTEOSTASIS THERAPEUTICS, INC.

CONDENSED STATEMENTS OF COMPREHENSIVE LOSS
(In thousands)
(Unaudited)

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Net loss	$ (18,428)	$ (13,954)	$ (44,932)	$ (46,008)
Other comprehensive loss:				
Unrealized gain (loss) on investments	5	20	(5)	15
Comprehensive loss	$ (18,423)	$ (13,934)	$ (44,937)	$ (45,993)

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

PROTEOSTASIS THERAPEUTICS, INC.
CONDENSED STATEMENTS OF CASH FLOWS
(In thousands)
(Unaudited)

	Nine Months Ended September 30,	
	2018	**2017**
Cash flows from operating activities:		
Net loss	$ (44,932)	$ (46,008)
Adjustments to reconcile net loss to cash used in operating activities:		
Depreciation and amortization	1,428	1,001
Premium (discount) on short-term investments	(205)	42
Stock-based compensation expense	2,697	2,228
Stock issued for consulting services	704	555
Change in fair value of derivative liability	(22)	(88)
Loss on disposal of property and equipment	41	—
Changes in operating assets and liabilities:		
Accounts receivable	—	(411)
Prepaids and other current assets	(553)	2,221
Other assets	27	27
Accounts payable	47	514
Accrued expenses	2,286	1,527
Deferred revenue	(3)	(1,202)
Operating lease liabilities	(1,019)	(963)
Net cash used in operating activities	(39,504)	(40,557)
Cash flows from investing activities:		
Purchases of short-term investments	(30,604)	(23,727)
Proceeds received from maturities of short-term investments	48,850	65,563
Purchases of property and equipment	(406)	(117)
Net cash provided by investing activities	17,840	41,719
Cash flows from financing activities:		
Proceeds from issuance of common stock related to at-the-market offering program, net	10,546	—
Proceeds from exercise of stock options	21	30
Proceeds from issuance of common stock pursuant to employee stock purchase plan	25	43
Deferred offering costs	(62)	—
Net cash provided by financing activities	10,530	73
Net increase (decrease) in cash, cash equivalents and restricted cash	(11,134)	1,235
Cash, cash equivalents and restricted cash at beginning of period	31,674	18,907
Cash, cash equivalents and restricted cash at end of period	$ 20,540	$ 20,142
Supplemental disclosure of non-cash investing and financing activities:		
Addition of operating lease, right-of-use asset	$ 14,962	$ —
Additions to property and equipment included in accounts payable	$ —	$ 12

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

1. Nature of the Business

Proteostasis Therapeutics, Inc. (the "Company") was incorporated in Delaware on December 13, 2006. The Company is a clinical stage biopharmaceutical company developing small molecule therapeutics to treat cystic fibrosis ("CF") and other diseases caused by dysfunctional protein processing. The Company focuses on identifying therapies that restore protein function. CF is a disease caused by defects in the cystic fibrosis transmembrane conductance regulator ("CFTR") protein and insufficient CFTR protein function. The Company's lead product candidates, PTI-428, an amplifier, PTI-801, a third-generation corrector, and PTI-808, a potentiator, as well as a dual combination consisting of PTI-801 and PTI-808, and a triple combination consisting of PTI-428, PT-801, and PTI-808 are in clinical development. The Company's other drug candidates are in the preclinical development and discovery phases.

The Company is subject to risks and uncertainties common to early-stage companies in the biotechnology industry, including, but not limited to, development by competitors of new technological innovations, dependence on key personnel, protection of proprietary technology, compliance with government regulations and ability to secure additional capital to fund operations. Product candidates currently under development will require significant additional research and development efforts, including extensive preclinical and clinical testing and regulatory approval prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel and infrastructure and extensive compliance-reporting capabilities. Even if the Company's product development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

In October 2018, the Company completed a follow-on public offering whereby the Company sold 11,000,000 shares of common stock at a price to the public of $6.75 per share. The aggregate net proceeds received by the Company from the offering were approximately $69.5 million, after deducting underwriting discounts and commissions and estimated offering expenses payable by the Company. On November 6, 2018, the Company issued and sold an additional 1,650,000 shares of its common stock at the offering price of $6.75 per share as a result of the full exercise by the underwriters of their option to purchase additional shares. The net proceeds from this issuance were $10.5 million, after deducting underwriting discounts and commissions.

In March 2018, the Company entered into a sales agreement with Leerink Partners LLC ("Leerink") with respect to an at-the-market ("ATM") offering program under which the Company may issue and sell, from time to time at its sole discretion, shares of its common stock, having an aggregate offering price of up to $50.0 million. Leerink is not required to sell any specific amount but acts as the Company's sales agent on a commercially reasonable efforts basis consistent with its normal trading and sales practices. Common stock will be sold at prevailing market prices at the time of the sale; and as a result, prices may vary. The Company will pay Leerink up to 3% of the gross proceeds from any common stock sold through the sales agreement. In October 2018, the Company sold 1,364,348 shares of its common stock for net proceeds of approximately $11.2 million under the ATM program. As of October 19, 2018, the Company had sold an aggregate of 3,475,166 shares of its common stock for total net proceeds of approximately $21.7 million under the ATM program and $27.6 million of common stock remained available for sale. In connection with its follow-on offering in October 2018, the Company has suspended sales under the ATM program.

In accordance with ASC 205-40, *Going Concern* ("ASC 205-40"), the Company has evaluated whether there are conditions and events, considered in the aggregate, that raise substantial doubt about the Company's ability to continue as a going concern within one year after the date the financial statements are issued. As of September 30, 2018, the Company had an accumulated deficit of $260.6 million. During the nine months ended September 30, 2018, the Company incurred losses of $44.9 million and used $39.5 million of cash in operations. The Company expects to continue to generate operating losses in the foreseeable future. Based upon its current operating plan, the Company expects that its cash, cash equivalents and short-term investments of $46.4 million and the net proceeds from its follow-on offering of approximately $80.0 million, after deducting underwriting discounts and commissions and estimated offering expenses, and net proceeds from the ATM program of approximately $11.2 million during the fourth quarter of 2018 will be sufficient to fund its operating expenses and capital requirements into early 2020. However, additional funding will be necessary to complete the funding of critical path activities anticipated in 2020. In accordance with the requirements of ASC 205-40, the Company determined that there is substantial doubt about the Company's ability to continue as a going concern within 12 months of the issuance date of these financial statements. The financial statements do not include any adjustments that might result from the outcome of this uncertainty. The Company intends to obtain additional funding through public or private financing or collaborative arrangements with strategic partners to increase the funds available to support its operating and capital needs. Although the Company has been successful in raising capital in the past, there is no assurance that it will be successful in obtaining such additional financing on terms acceptable to the Company, if at all, nor is it considered probable under the accounting standards. As such, under the requirements of ASC 205-40, management may not consider the potential for future capital raises or management plans to reduce costs that are not considered probable in its assessment of the Company's ability to meet its obligations for the next 12 months. If the Company is unable to obtain funding, the Company would be forced to delay, reduce or eliminate its research and development programs, product portfolio expansion or commercialization efforts, which could adversely affect its business prospects, or the Company may be unable to continue operations.

2. Summary of Significant Accounting Policies

Unaudited Interim Financial Information

The condensed balance sheet as of December 31, 2017 was derived from audited financial statements but does not include all disclosures required by accounting principles generally accepted in the United States of America ("GAAP"). The accompanying condensed financial statements as of September 30, 2018 and for the three and nine months ended September 30, 2018 are unaudited and have been prepared by the Company, pursuant to the rules and regulations of the Securities and Exchange Commission (the "SEC") for interim financial statements. Certain information and footnote disclosures normally included in financial statements prepared in accordance with GAAP have been condensed or omitted pursuant to such rules and regulations. The Company believes that the disclosures are adequate to make the information presented not misleading. These unaudited condensed financial statements should be read in conjunction with the Company's audited financial statements and the notes thereto for the year ended December 31, 2017 included in the Company's Annual Report on Form 10-K filed with the SEC on March 14, 2018. In the opinion of management, all adjustments, consisting only of normal recurring adjustments as necessary, for the fair statement of the Company's financial position as of September 30, 2018, results of its operations for the three and nine months ended September 30, 2018, and cash flows for the nine months ended September 30, 2018 have been made. The results of operations for the three and nine months ended September 30, 2018 are not necessarily indicative of the results of operations to be expected for the year ending December 31, 2018.

Summary of Significant Accounting Policies

The Company's significant accounting policies, which are disclosed in the audited consolidated financial statements for the year ended December 31, 2017 and the notes thereto are included in the Company's Annual Report on Form 10-K that was filed with the SEC on March 14, 2018. Certain amounts reported in the previous year have been recast as a result of the retrospective adoption of new accounting standards in the first quarter of 2018. Refer to Note 2 - *Recently Issued and Adopted Accounting Pronouncements,* Note 8 - *Collaboration Agreement*, and Note 11 - *Leases,* for further discussion.

Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenue and expenses during the reporting periods. Significant estimates and assumptions reflected in these financial statements include, but are not limited to, revenue recognition, the accrual for research and development expenses and the valuation of common stock, and the derivative liability. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ from those estimates.

Revenue Recognition

Effective January 1, 2018, the Company adopted Accounting Standards Codification ("ASC") Topic 606, *Revenue from Contracts with Customers* ("ASC 606"), using the modified retrospective transition method. Under this method, results for reporting periods beginning after January 1, 2018 are presented under ASC 606, while prior period amounts are not adjusted and continue to be reported in accordance with ASC 605. This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue at a point in time, or over time, as the entity satisfies a performance obligation. The Company only applies the five-step model to contracts when it is probable that it will collect the consideration it is entitled to in exchange for the goods or services it transfers to the customer. At contract inception, once the contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within each contract, determines those that are performance obligations, and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

The Company enters into licensing agreements which are within the scope of ASC 606, under which it may exclusively license rights to research, develop, manufacture and commercialize its product candidates to third parties. The terms of these arrangements typically include payment to the Company of one or more of the following: nonrefundable, upfront license fees; reimbursement of certain costs; customer option exercise fees; development, regulatory and commercial milestone payments; and royalties on net sales of licensed products.

As part of the accounting for these arrangements, the Company must use significant judgment to determine: a) the number of performance obligations based on the determination under step (ii) above; b) the transaction price under step (iii) above; and c) the stand-alone selling price for each performance obligation identified in the contract for the allocation of transaction price in step (iv) above. The Company uses judgment to determine whether milestones or other variable consideration should be included in the transaction price as described further below. The transaction price is allocated to each performance obligation on a relative stand-alone selling price basis, for which the Company recognizes revenue as or when the performance obligations under the contract are satisfied. In developing the stand-alone price for a performance obligation, the Company considers applicable market conditions and relevant entity-specific factors, including factors that were contemplated in negotiating the agreement with the customer and estimated costs. The Company validates the stand-alone selling price for performance obligations by evaluating whether changes in the key assumptions used to determine the stand-alone selling prices will have a significant effect on the allocation of transaction price between multiple performance obligations.

The Company records any amounts received prior to satisfying the revenue recognition criteria as deferred revenue. Amounts recognized as revenue, but not yet received or invoiced are recorded as current assets.

Exclusive Licenses

If the license to the Company's intellectual property is determined to be distinct from the other promises or performance obligations identified in the arrangement, the Company recognizes revenue from nonrefundable, upfront fees allocated to the license when the license is transferred to the customer and the customer is able to use and benefit from the license. In assessing whether a promise or performance obligation is distinct from the other promises, the Company considers factors such as the research, development, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. In addition, the Company considers whether the collaboration partner can benefit from a promise for its intended purpose without the receipt of the remaining promise, whether the value of the promise is dependent on the unsatisfied promise, whether there are other vendors that could provide the remaining promise, and whether it is separately identifiable from the remaining promise. For licenses that are combined with other promises, the Company assesses the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition. The measure of progress, and thereby periods over which revenue should be recognized, are subject to estimates by management and may change over the course of the research and development and licensing agreement. Such a change could have a material impact on the amount of revenue the Company records in future periods.

Research and Development Services

The promises under the Company's collaboration and license agreements generally include research and development services to be performed by the Company on behalf of the collaboration partner. As the provision of research and development services is a part of the Company's central operations, when the Company is principally responsible for the performance of these services under the agreements, the Company recognizes revenue on a gross basis for research and development services in accordance with the ASC 606 framework described above.

Customer Options

If an arrangement is determined to contain customer options that allow the customer to acquire additional goods or services, the goods and services underlying the customer options are not considered to be performance obligations at the outset of the arrangement, as they are contingent upon option exercise. The Company evaluates the customer options for material rights, or options to acquire additional goods or services for free or at a discount. If the customer options are determined to represent a material right, the material right is recognized as a separate performance obligation at the outset of the arrangement. The Company allocates the transaction price to material rights based on the relative standalone selling price, which is determined based on the identified discount and the probability that the customer will exercise the option. Amounts allocated to a material right are not recognized as revenue until, at the earliest, the option is exercised.

Milestone Payments

At the inception of each arrangement that includes development milestone payments, the Company evaluates whether the milestones are considered probable of being achieved and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the control of the Company or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. The Company evaluates factors such as the scientific, clinical, regulatory, commercial, and other risks that must be overcome to achieve the particular milestone in making

this assessment. There is considerable judgment involved in determining whether it is probable that a significant revenue reversal would not occur. At the end of each subsequent reporting period, the Company reevaluates the probability of achievement of all milestones subject to constraint and, if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment.

Royalties

For arrangements that include sales-based royalties, including milestone payments based on a level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, the Company has not recognized any royalty revenue resulting from any of its licensing arrangements.

For a complete discussion of accounting for collaboration revenues, see Note 8 - *Collaboration Agreement*.

Recently Issued and Adopted Accounting Pronouncements

ASU No. 2014-09, *Revenue from Contracts with Customers*

In May 2014, the FASB issued ASU No. 2014-09, which amends the guidance for accounting for revenue from contracts with customers. This ASU supersedes the revenue recognition requirements in ASC Topic 605, *Revenue Recognition* ("ASC 605"), and creates a new topic, ASC 606, *Revenue from Contracts with Customers*. In 2015 and 2016, the FASB issued additional ASUs related to ASC 606 that delayed the effective date of the guidance and clarified various aspects of the new revenue guidance, including principal versus agent considerations, identifying performance obligations, and licensing, and they include other improvements and practical expedients. Companies have the option of applying this new guidance retrospectively to each prior reporting period presented (the full retrospective method) or retrospectively with the cumulative effect of initially applying this update recognized at the date of initial application (the modified retrospective method). The Company only has one contract (see Note 8) within the scope of ASC 606. The Company adopted this new standard on January 1, 2018 using the modified retrospective method for adoption. The Company has elected to use the following practical expedient that is permitted under the rules of the adoption: the Company has not retrospectively restated its contracts that have been amended at each amendment date as is generally required under ASC 606. Instead, upon adoption, the Company reflected the aggregate effect of all modifications that occurred before the beginning of the earliest period presented when identifying the satisfied and unsatisfied performance obligations; determining the transaction price; and allocating the transaction price to the satisfied and unsatisfied performance obligations.

As a result of adopting ASC 606 on January 1, 2018, the Company has recorded a cumulative-effect decrease to opening accumulated deficit of $1.1 million as of January 1, 2018 and a corresponding decrease to deferred revenue. The remaining impacts related to ASC 606 adoption were as follows (in thousands):

	September 30, 2018		
	As Reported under ASC 606	As Determined under ASC 605	Decrease upon Adoption of ASC 606
Balance Sheet:			
Deferred revenue, current	$ —	$ 617	$ (617)
Income Statement:			
Revenue for the three months ended September 30, 2018	1,055	1,751	(696)
Revenue for the nine months ended September 30, 2018	2,840	4,691	(1,851)

The most significant change related to the Company's determination of transaction price at inception and each reporting period as well as the revenue recognition pattern for the Astellas Agreement (as defined below) with Astellas Pharma Inc. as well as treatment of variable consideration in the form of milestone payments. Under ASC 605, the research funding support payments, reimbursement of third-party costs, and milestone payments were being recognized by the Company as revenue on a straight-line basis over the 3½ year research term of the agreement, which commenced in January 2015, with a cumulative catch-up for the elapsed portion of the research term being recognized at the time any such payments are earned. Under ASC 606, the Company is recognizing the revenue allocated to the one performance obligation measuring progress using the proportional performance method. For further discussion of the adoption of this standard, see Note 8.

ASU No. 2016-02, *Leases*

In February 2016, the FASB issued ASU No. 2016-02, *Leases* ("ASU 2016-02"), to enhance the transparency and comparability of financial reporting related to leasing arrangements. Under this new lease standard, leases are required to be recognized on the balance sheet as right-of-use assets and operating lease liabilities. Disclosure requirements have been enhanced with the objective of enabling financial statement users to assess the amount, timing, and uncertainty of cash flows arising from leases.

Due to the Company commencing a new lease in Boston, Massachusetts, in January 2018, the Company elected to early adopt the standard effective January 1, 2018, as permitted by the guidance in order to enhance overall transparency within financial reporting. The Company has implemented the standard using the required modified retrospective approach and has also elected to utilize the package of practical expedients. The expedients used by the Company are as follows: (1) allowing an entity to not reassess the lease classification for any expired or existing leases, (2) allowing an entity to not reassess the treatment of initial direct costs as they related to existing leases, and (3) allowing an entity to not reassess whether expired or existing contracts are or contain leases. The company also elected the practical expedient to use hindsight in determining the appropriate lease term and in assessing impairment of its right-of-use assets. In using the modified retrospective approach, the Company is required to recognize and measure leases existing at, or entered into after, the beginning of the earliest comparative period presented.

During 2017, the Company was deemed the accounting owner of the construction project for the build-to-suit lease in Boston, Massachusetts, because of the Company's involvement in the build-out of the space. Under the new standard, the Company is no longer considered the accounting owner of the leased space due to (1) not having the right to obtain or control the leased premises during the construction period, (2) having no right of payment for the partially constructed assets, and the leased premises are not of a specialized nature and, thus, could be potentially leased to another tenant, and (3) not legally owning or controlling the land on which the property improvements will be constructed. As such, upon transition, the existing construction-in-progress balance within property and equipment, and the corresponding build-to-suit facility lease financing obligation balance within other liabilities, current and non-current, have been derecognized. Prior period results have been restated to this effect through to the earliest period presented. The adoption of this standard has had a material impact on the Company's financial position but did not significantly affect the Company's results of operations. See *Impacts on Previously Reported Results* below.

Impacts to Previously Reported Results

The impact of the adoption of the new leasing standard on the December 31, 2017 balance sheet is as follows (in thousands):

	December 31, 2017		
	As Previously Reported	New Lease Standard Adjustment	As restated
Operating lease right-of-use assets, net	$ —	$ 472	$ 472
Property and equipment, net	16,567	(16,143)	424
Deferred rent, current	87	(87)	—
Operating lease liabilities, current	—	559	559
Other liabilities, current	902	(902)	—
Other liabilities, net of current	15,315	(15,315)	—
Accumulated deficit	(216,882)	74	(216,808)

ASU 2016-15, *Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts*

In August 2016, the FASB issued ASU 2016-15, *Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments*. The new standard clarifies certain aspects of the statement of cash flows, including the classification of debt prepayment or debt extinguishment costs, settlement of zero-coupon debt instruments or other debt instruments with coupon interest rates that are insignificant in relation to the effective interest rate of the borrowing, contingent consideration payments made after a business combination, proceeds from the settlement of insurance claims, proceeds from the settlement of corporate-owned life insurance policies, distributions received from equity method investees and beneficial interests in securitization transactions. The new standard also clarifies that an entity should determine each separately identifiable source or use within the cash receipts and cash payments on the basis of the nature of the underlying cash flows. In situations in which cash receipts and payments have aspects of more than one class of cash flows and cannot be separated by source or use, the appropriate classification should depend on the activity that is likely to be the predominant source or use of cash flows for the item. The new standard was effective for the Company on January 1, 2018. The adoption of this standard did not have a material impact on the Company's financial position or results of operations.

ASU 2016-18, Statement of Cash Flows (Topic 230) – Restricted Cash

In November 2016, the FASB issued ASU 2016-18, *Statement of Cash Flows (Topic 230) - Restricted Cash* ("ASU 2016-18"). ASU 2016-18 requires a statement of cash flows to explain the change during the period in the total of cash, cash equivalents, and amounts generally described as restricted cash or restricted cash equivalents. Amounts generally described as restricted cash and restricted cash equivalents should be included with cash and cash equivalents when reconciling the beginning-of-period and end-of- period total amounts shown on the statement of cash flows. The new standard was effective for the Company on January 1, 2018. This resulted in the $0.8 million and $2.0 million of restricted cash for the nine months ended September 30, 2018 and September 30, 2017, respectively, being displayed within the overall change in the cash balance on the statement of cash flows.

ASU 2017-09*, Compensation – Stock Compensation (Topic 719): Scope of Modification Accounting*

In May 2017, the FASB issued ASU 2017-09, *Compensation – Stock Compensation (Topic 719): Scope of Modification Accounting*. The new standard provides guidance about which changes to the terms or conditions of a share-based payment award require an entity to apply modification accounting in Topic 718. The new standard was effective for the Company on January 1, 2018. The adoption of this standard did not have a material impact on the Company's financial position or results of operations as there were no changes to terms or conditions of share-based payments during the quarter ended September 30, 2018.

Recently Issued Accounting Pronouncements

ASU No. 2018-07, *Improvements to Nonemployee Share-Based Payment Accounting*

In June 2018, the FASB issued ASU No. 2018-07, Improvements to Nonemployee Share-Based Payment Accounting ("ASU 2018-07"). The new standard simplifies the accounting for share-based payments to nonemployees by aligning it with the accounting for share-based payments to employees, with certain exceptions. The new standard will be effective beginning January 1, 2019 and early adoption is permitted. The Company is currently evaluating the impact that the adoption of ASU 2018-07 will have on its results of operations.

ASU No. 2018-13, *Fair Value Measurement (Topic 820): Changes to the Disclosure Requirements for Fair Value Measurement*

In August 2018, the FASB issued ASU No. 2018-13, *Disclosure Framework – Changes to the Disclosure Requirements for Fair Value Measurement* ("ASU 2018-13"). The new standard modifies the disclosure requirements on fair value measure in Topic 820, including removals of existing disclosures, modifications of existing disclosures, and additions of new disclosures. Certain amendments on changes in unrealized gains and losses, the range and weighted average of significant unobservable inputs used to develop Level 3 fair values measurements, and the narrative description of measurement uncertainty should be applied prospectively for only the most recent interim of annual period presented in the initial fiscal year of adoption. All other amendments should be applied retrospectively to all period presented upon their effective date. Early adoption is permitted for any removed or modified disclosure. The new standard is effective beginning after December 15, 2019. The Company is currently evaluating the impact that the adoption of ASU 2018-13 will have on its results of operations.

3. Short-Term Investments

The following table summarizes the Company's short-term investments as of September 30, 2018 and December 31, 2017 (in thousands):

	September 30, 2018			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S government-sponsored enterprise securities	$ 5,235	$ —	$ (2)	$ 5,233
U.S. treasury securities	21,464	—	(5)	21,459
	$ 26,699	$ —	$ (7)	$ 26,692

	December 31, 2017			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S government-sponsored enterprise securities	$ 9,817	$ —	$ (1)	$ 9,816
U.S. treasury securities	34,923	1	(2)	34,922
	$ 44,740	$ 1	$ (3)	$ 44,738

The Company did not have any realized gains or losses on its short-term investments for the three and nine months ended September 30, 2018 and 2017. There were no other-than-temporary impairments recognized for the three and nine months ended September 30, 2018 and 2017.

4. Fair Value of Financial Assets and Liabilities

The following tables present information about the Company's financial assets and liabilities measured at fair value on a recurring basis and indicate the level of the fair value hierarchy utilized to determine such fair values (in thousands):

	Fair Value Measurements as of September 30, 2018 using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash equivalents:				
Money market funds	$ 17,340	$ —	$ —	$ 17,340
Short-term investments:				
U.S. government-sponsored enterprise securities	—	5,233	—	5,233
U.S. treasury securities	—	21,459	—	21,459
	$ 17,340	$ 26,692	$ —	$ 44,032
Liabilities:				
Derivative liability	$ —	$ —	$ 3	$ 3
	$ —	$ —	$ 3	$ 3

	Fair Value Measurements as of December 31, 2017 using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash equivalents:				
Money market funds	$ 13,871	$ —	$ —	$ 13,871
U.S. government-sponsored enterprise securities	—	8,960	—	8,960
U.S. treasury securities	—	3,497	—	3,497
Short-term investments:				
U.S. government-sponsored enterprise securities	—	9,816	—	9,816
U.S. treasury securities	—	34,922	—	34,922
	$ 13,871	$ 57,195	$ —	$ 71,066
Liabilities:				
Derivative liability	$ —	$ —	$ 25	$ 25
	$ —	$ —	$ 25	$ 25

During the periods ended September 30, 2018 and December 31, 2017, there were no transfers between Level 1, Level 2 and Level 3.

Derivative Liability

The derivative liability relates to a cash settlement option associated with the change of control provision in the Company's Cystic Fibrosis Foundation Therapeutics, Inc. ("CFFT") agreement, which meets the definition of a derivative. The fair value of the derivative liability is based on significant inputs not observable in the market, which represents a Level 3 measurement within the fair value hierarchy. The fair value of the derivative instrument was determined using the Monte-Carlo simulation analysis. In determining the fair value of the derivative liability, the inputs impacting fair value include the fair value of the Company's common stock, expected term of the derivative instrument, expected volatility of the common stock price, risk-free interest rate, expected sales-based milestone payments, discount rate, probability of a change of control event, and the probability that the counterparty would elect to accept the alternative cash payment in lieu of its right to the future sales-based milestone payments.

As of September 30, 2018 and December 31, 2017, the Company determined the per share common stock price available based on the closing price of its common stock on the NASDAQ Global Market as of September 28, 2018 and December 29, 2017, respectively. The Company determined the expected term of the instrument to be 1.50 years and 2.00 years as of September 30, 2018 and December 31, 2017, respectively. The Company estimated its expected stock volatility to be 80.0% as of September 30, 2018 and December 31, 2017, respectively, based on the historical volatility of publicly traded peer companies for terms matching the expected term of the instrument for each respective period. The risk-free interest rate was determined to be 2.40% and 1.87% as of September 30, 2018 and December 31, 2017, respectively, by reference to the U.S. Treasury yield curve for terms matching the expected term of the instrument for each respective period.

Changes in the values of the derivative liability are summarized below (in thousands):

	Derivative Liability
Fair value at December 31, 2017	$ 25
Change in fair value	(22)
Fair value at September 30, 2018	$ 3

5. Prepaids and Other Current Assets

Prepaids and other current assets consisted of the following (in thousands):

	September 30, 2018	December 31, 2017
Prepaid clinical, manufacturing and scientific expenses	$ 911	$ 568
Prepaid insurance expenses	347	55
Other prepaid expenses and other current assets	672	754
	$ 1,930	$ 1,377

6. Accrued Expenses

Accrued expenses consisted of the following (in thousands):

	September 30, 2018	December 31, 2017
Accrued payroll and related expenses	$ 2,003	$ 1,542
Accrued research and development expenses	5,510	3,930
Accrued professional fees	647	556
Accrued other	246	92
	$ 8,406	$ 6,120

7. Stock-Based Compensation

2016 Stock Option and Incentive Plan

On February 3, 2016, the Company's stockholders approved the 2016 Stock Option and Incentive Plan (the "2016 Plan"), which became effective on February 9, 2016. The 2016 Plan provides for the grant of incentive stock options, nonqualified stock options, stock appreciation rights, restricted stock units, restricted stock awards and other stock-based awards. The number of shares initially reserved for issuance under the 2016 Plan was 1,581,839 shares. The number of shares of common stock that may be issued under the 2016 Plan will automatically increase on each January 1, beginning on January 1, 2017, by the lesser of 3% of the shares of the Company's common stock outstanding on the immediately preceding December 31 or an amount determined by the Company's board of directors or the compensation committee of the board of directors. The shares of common stock underlying any awards that are forfeited, canceled, repurchased or are otherwise terminated by the Company under the 2016 Plan and the 2008 Equity Incentive Plan, as amended (the "2008 Plan") will be added back to the shares of common stock available for issuance under the 2016 Plan. As of September 30, 2018, the total number of shares reserved under the 2016 Plan and 2008 Plan was 4,343,120 and the Company had 971,898 shares available for future issuance under the 2016 Plan.

2016 Employee Stock Purchase Plan

On February 3, 2016, the Company's stockholders approved the 2016 Employee Stock Purchase Plan (the "2016 ESPP"), which became effective in connection with the completion of the Company's initial public offering. A total of 138,757 shares of common stock were reserved for issuance under this plan. In addition, the number of shares of common stock that may be issued under the 2016 ESPP will automatically increase on each January 1, beginning on January 1, 2017 and ending on January 1, 2026, by the lesser of (i) 138,757 shares of common stock, (ii) 1% of the Company's shares of common stock outstanding on the immediately preceding December 31 and (iii) an amount determined by the Company's board of directors or the compensation committee of the board of directors.

During the nine months ended September 30, 2018, 6,114 shares of common stock were issued pursuant to the 2016 ESPP. As of September 30, 2018, the total number of shares reserved under the 2016 ESPP was 399,328 shares. The Company recognized less than $0.1 million of stock-based compensation during the three and nine months ended September 30, 2018 related to this plan.

Stock Option Grants and Shares to Nonemployees

Prior to 2013, the Company issued options to purchase 203,964 shares of common stock to nonemployees, primarily members of the Company's scientific advisory board, that vest upon the achievement of specified development and clinical milestones. As of September 30, 2018, options for the purchase of 83,250 shares held by nonemployees remained unvested, pending achievement of the specified milestones, and had an aggregate fair value of $0.1 million.

Bonus Restricted Stock Units (RSUs)

On February 1, 2018, the Company's board approved executive bonuses for the year ended December 31, 2017 and elected payment to be made through a grant of an equivalent number of RSUs based on the February 1, 2018 closing share price of the Company's common stock. The requisite service period for the awards is from February 1, 2018 to February 1, 2019 (the vesting period). The Company will recognize employee stock-based compensation expense for the bonus RSU grants on a straight-line basis over the vesting period of the awards. The grants do not meet the criteria for liability classification as there is a fixed number of shares to be issued and there is no variability in the number of shares which have been granted. As of September 30, 2018, 163,425 RSUs had been granted with a total expense of $0.1 million and $0.4 million recognized for the three and nine months ended September 30, 2018.

Stock-Based Compensation

Stock-based compensation expense, including shares issued to a nonemployee for consulting services, was classified in the statements of operations as follows (in thousands):

	For the Three Months Ended September 30,		For the Nine Months Ended September 30,	
	2018	2017	2018	2017
Research and development	$ 419	$ 412	$ 1,195	$ 1,070
General and administrative	606	636	2,206	1,713
	$ 1,025	$ 1,048	$ 3,401	$ 2,783

8. Collaboration Agreement

Astellas

In November 2014, the Company entered into the Collaborative Research, Development, Commercialization and License Agreement (the "Astellas Agreement") with Astellas Pharma Inc. ("Astellas"). The focus of the Astellas Agreement is to identify, develop and commercialize therapeutic candidates relating to the Unfolded Protein Response ("UPR") pathway.

Financial Terms

Under terms of the Astellas Agreement, Astellas purchased from the Company convertible promissory notes totaling $5.0 million with terms consistent with those of other investors that purchased convertible promissory notes issued during 2014. In addition, the Company will be eligible to receive research funding support, based on the establishment of an annual research budget, and future research, development and sales milestone payments of up to $398.5 million, as well as tiered royalty payments ranging in the mid-single-digit to low double-digit percentages of net sales, as defined in the agreement. Under the agreement, the companies will conduct research during the initial research term, which is approximately 3½ years, to identify lead compounds for clinical development. The Company will provide Astellas with a report of the actual expenses incurred within 30 days after the end of the quarter, which Astellas will provide payment to the Company within 30 days of receiving of the report. At the end of the research term, Astellas, in its sole discretion, may designate a development compound and make a milestone payment to the Company. The Company has the right, but not the obligation, to co-develop the compound. If the Company does not exercise its option to co-develop the compound, Astellas will have an exclusive right to the compound and sole right and responsibility for the development of the compound.

Term and Termination

The term of the Astellas Agreement commenced in November 2014 and will continue in full force and effect, unless terminated under the conditions described below, until expiration of all applicable royalty terms with respect to all licensed products in all countries in the territory defined as per the agreement.

The agreement was set to automatically terminate at the end of the 3 ½-year research term, in the second quarter of 2018, if Astellas had not designated at least one development compound, unless mutually agreed to be extended. In April 2018, the Company and Astellas entered into Amendment No. 6 ("Amendment No. 6") to the Astellas Agreement. Amendment No. 6 is effective beginning in April 2018 and extends the research term for the initial project under the Astellas Agreement to December 2018. As of September 30, 2018, all of the Company's performance obligations under the contract have been satisfied. Astellas has the unilateral right to terminate the agreement on a project-by-project basis by providing written notice to the Company. Reciprocal termination rights under the agreement include termination for breach and termination for bankruptcy.

Accounting Analysis

The Company assessed this arrangement in accordance with ASC 606 and concluded that the contract counterparty, Astellas, is a customer. The Company identified the following material promises as of the most recent amendment in April 2018: (1) the research license; (2) the research services to be provided over the research term; and (3) participation in the Joint Research Committee (the "Committee") to be provided over the research term of the agreement. The Company determined that the license and research services were not distinct from one another, as the license has limited value without the performance of the research and development activities. Participation in the Committee to oversee the research activities was determined to be quantitatively and qualitatively immaterial and therefore is excluded from performance obligations. As such, the Company determined that these promises should be combined into a single performance obligation.

The Company evaluated the Astellas option right to designate a development compound, as described above, to determine whether it provides Astellas with a material right. The Company concluded that the option was not issued at a significant and incremental discount and Astellas has only the right to pursue negotiations for additional projects, and therefore does not provide a material right. As such, they are excluded from performance obligations at the inception of the arrangement.

Under the Astellas Agreement, in order to evaluate the appropriate transaction price as of the adoption of ASC 606, the Company determined that the payments received to date for research funding support and reimbursement of third-party costs, the estimated payments that will be received for research funding support and reimbursement of third-party costs over the remaining research term, and the milestone payments received to date represent the transaction price, which was allocated to the single performance obligation. The transaction price as of the adoption of ASC 606 and September 30, 2018 was $13.7 million. The option exercise fee that may be received is excluded from the transaction price until the customer option is exercised. Future potential milestone payments were excluded from the transaction price, as all milestone amounts were fully constrained due to Astellas having only the right to pursue negotiations for additional projects. The Company will reevaluate the transaction price at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur, and, if necessary, adjust its estimate of the transaction price.

Revenue associated with the performance obligation is being recognized as the research and development services were provided using an input method, according to the costs incurred as related to the research and development activities and the costs expected to be incurred in the future to satisfy the performance obligation. The transfer of control occurs over this time period and, in management's judgment, is the best measure of progress towards satisfying the performance obligation. Any amounts received that had not yet been recognized as revenue are recorded in deferred revenue on the Company's condensed balance sheet. As of September 30, 2018, the research and development services related to this performance obligation are complete.

The Company recognized revenue of $1.1 million and $1.6 million for the three months ended September 30, 2018 and 2017, respectively, and $2.8 million and $3.7 million for the nine months ended September 30, 2018 and 2017, respectively. There was $0.1 million recorded as a contract asset under the Astellas Agreement as of September 30, 2018. Amounts recorded as deferred revenue under the Astellas Agreement totaled $1.1 million as of December 31, 2017.

9. Income Taxes

The Company did not record a federal or state income tax benefit for its losses for the three and nine months ended September 30, 2018 and 2017 due to the conclusion that a full valuation allowance is required against the Company's deferred tax assets. All of the Company's losses before income taxes were generated in the United States.

10. Net Loss per Share

Basic and diluted net loss per share attributable to common stockholders was calculated as follows (in thousands, except share and per share amounts):

	For the Three Months Ended September 30,		For the Nine Months Ended September 30,	
	2018	2017	2018	2017
Numerator:				
Net loss	$ (18,428)	$ (13,954)	$ (44,932)	$ (46,008)
Denominator:				
Weighted average number of common shares outstanding—basic	36,694,957	25,093,344	35,734,159	25,051,536
Net loss per share attributable to common stockholders —basic and diluted	$ (0.50)	$ (0.56)	$ (1.26)	$ (1.84)

The following potentially dilutive securities outstanding have been excluded from the computation of diluted weighted-average shares outstanding, because such securities had an antidilutive impact due to the losses reported:

	September 30,	
	2018	2017
Options to purchase common stock	3,207,797	2,946,853
Restricted stock units	163,425	—
Potentially dilutive securities outstanding	3,371,222	2,946,853

11. Leases

The Company has operating leases of office and laboratory space.

In September 2017, the Company entered into a new lease agreement for office and laboratory space in Boston, Massachusetts, which is its new corporate headquarters. The new lease commenced in January 2018 and rent payments began in April 2018. This lease has a ten-year initial term with an option to extend for seven additional years. The Company's prior lease in Cambridge, Massachusetts expired in May 2018.

The lessee has the right to terminate the lease in the event of the inability to use the space due to substantial damage while the lessor has the right to terminate the lease for tenant's default of lease financial obligations. Per the terms of the lease agreement, the Company does not have any residual value guarantees. In calculating the present value of the lease payments, the Company has elected to utilize its incremental borrowing rate based on the original lease term and not the remaining lease term. The Company has elected to account for each lease component and its associated non-lease components as a single lease component and has allocated all of the contract consideration across lease components only. This may result in the initial and subsequent measurement of the balances of the right-of-use asset and lease liability for leases being greater than if the policy election was not applied. The Company's real estate leases in Cambridge and Boston are net leases as their non-lease components (i.e. common area maintenance) are paid separately from rent based on actual costs incurred; therefore, the non-lease components were not included in the right-of-use asset and liability and are reflected as an expense in the period incurred. As of September 30, 2018 and December 31, 2017, assets under operating lease were $14.1 million and $0.5 million, respectively. The elements of lease expense were as follows (in thousands):

	For the Three Months Ended September 30,	
	2018	2017
Lease cost		
Operating lease cost	$ 447	$ 286
Variable lease cost (1)	154	—
Total lease cost	$ 601	$ 286

	For the Nine Months Ended September 30,	
	2018	2017
Lease Cost		
Operating lease cost	$ 1,769	$ 857
Variable lease cost (1)	463	—
Total Lease Cost	$ 2,232	$ 857
Other information		
Operating cash flows used for operating leases	$ 1,220	$ 1,006
Operating lease liabilities arising from obtaining right-of-use assets	$ 14,502	$ —
Weighted-average remaining lease term	9.59 years	0.59 years
Weighted-average discount rate	4.50%	4.06%

(1) The variable lease costs for the three and nine months ended September 30, 2018 include adjustments to the initial direct costs for the Boston lease along with common area maintenance charges.

Future lease payments under noncancelable leases as of September 30, 2018 (in thousands):

Future Operating Lease Payments	
2018	$ 414
2019	1,686
2020	1,733
2021	1,780
2022	1,829
Thereafter	10,637
Total lease payments	18,079
Less: imputed interest	(3,577)
Total operating lease liabilities	$ 14,502

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

The following discussion and analysis of our financial condition and the results of operations should be read in conjunction with our financial statements and related notes thereto included elsewhere in this Quarterly Report on Form 10-Q ("Quarterly Report") and our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2017 (the "Annual Report") filed with the Securities and Exchange Commission on March 14, 2018. Some of the information contained in this discussion and analysis or set forth elsewhere in this Quarterly Report, including information with respect to our plans and strategy for our business, includes forward looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section in our Annual Report and in this Quarterly Report, our actual results could differ materially from the results described, in or implied by, the forward-looking statements contained in the following discussion and analysis.

Overview

We are an innovative, clinical stage biopharmaceutical company committed to the discovery and development of novel therapeutics to treat cystic fibrosis, or CF, and other diseases caused by an imbalance in the proteostasis network, a set of pathways that control protein biosynthesis, folding, trafficking and clearance. We focus on identifying therapies that restore protein function. CF is a disease caused by defects in the function or abundance of cystic fibrosis transmembrane conductance regulator, or CFTR. Our CF focused pipeline consists of novel CFTR modulators including correctors, potentiators and amplifiers. Upon discovery of amplifiers, a novel class of CFTR modulators, we have exploited its novel mechanism of action as a drug screening tool and have subsequently identified correctors and potentiators to be developed as part of combination therapies. Investigational agents representative of all three classes of CFTR modulators are currently in clinical development and include PTI-428, a CFTR amplifier, and PTI-801 a third generation CFTR corrector, and PTI-808, a CFTR potentiator. We believe that both PTI-428 and PTI-801 have potential as add-on therapy to current and future standard-of-care CFTR modulator treatments. Additionally, we are pursuing proprietary dual combination of PTI-801 and PTI-808, and triple combination of PTI-801, PTI-808 and PTI-428 as product opportunities. We are developing and, if approved, intend to commercialize our own therapies, including add-on and combination therapies for CF patients who have at least one F508del mutation, representing the majority of the patient population.

The approval of CFTR modulator-based therapy, consisting of a potentiator and a combination of a potentiator and a corrector, has validated the clinical benefit of a small molecule pharmacological approach to improve CFTR function and has become a standard of care for eligible CF patients. These developments have spurred drug discovery and development initiatives that include a combinational approach of multiple modulators. To our knowledge there are only two pharmaceutical companies currently developing combined uses of three CFTR modulators whose goal is the restoration of CFTR protein activity in CF patients by using one potentiator and two corrector molecules. Correctors, such as lumacaftor or tezacaftor, are believed to improve protein folding and trafficking to enable abnormally folded CFTR protein to achieve a higher level of activity without repairing the actual protein mutation. Potentiators, such as ivacaftor, are believed to increase the opening time of the CFTR protein channel resulting in higher ion flow across the cell membrane.

Unlike other triple combination drug discovery and development approaches for CF that are based on potentiators and correctors, our program includes PTI-428, an amplifier, a novel CFTR modulator with unique and distinguished molecular properties. PTI-428 is an orally bioavailable CFTR modulator belonging to the amplifier class. CFTR modulators are compounds that affect the folding, trafficking, function and clearance of CFTR protein and can be classified according to the ways in which they affect CFTR protein. Amplifiers, which include PTI-428, are CFTR modulators that selectively increase the amount of the newly synthesized unfolded form of CFTR protein, thereby providing additional substrate for other CFTR modulators, such as correctors and potentiators, to act upon. Using industry-standard *in vitro* studies, we have demonstrated that co-administration of PTI-428 with correctors and potentiators significantly improves the *in vitro* CFTR protein activity achieved by these CFTR modulators alone.

Due to the unique ability of amplifiers to selectively increase the amount of the unfolded form of CFTR protein and its synergistic mechanism of action with certain other types of CFTR modulators, we believe that PTI-428 could become the anchor therapeutic agent for combination therapies comprising multiple classes of CFTR modulators for the treatment of CF. A triple combination regimen that includes PTI-428 with PTI-801, a corrector, and PTI-808, a potentiator, has been shown to restore *in vitro* CFTR protein activity to approximately 100% of normal, in patient-derived human bronchial epithelial, or HBE, cells homozygous for F508del.

With the recent advent of CFTR modulators, the CF treatment paradigm is shifting from palliative care, which addresses only the symptoms of CF, to disease-modifying agents that target the genetic cause of the disease or the mutated CFTR protein. We are developing and, if approved, intend to commercialize a proprietary combination therapy for patients with an F508del mutation of the CFTR gene, the most common CFTR gene mutation. In the United States, approximately 86% of all CF patients have an F508del mutation of the CFTR gene, of which approximately 53% are homozygous (having two copies of the F508del mutation), and approximately 47% are heterozygous (having an F508del mutation and one other mutation).

We and others have analyzed published data by Vertex Pharmaceuticals Incorporated, or Vertex, on its CFTR modulators (the potentiator ivacaftor and the correctors lumacaftor, tezacaftor, olacaftor, VX-152, VX-659 and VX-445) and combinations thereof, which showed a strong correlation between the *in vitro* CFTR protein activity and lung function improvement. We have shown *in vitro* that PTI-428 increases the amount of available CFTR protein and, when combined with ivacaftor and either lumacaftor or tezacaftor, nearly doubles the CFTR protein activity in the cell compared to a combination of only ivacaftor and either lumacaftor or tezacaftor. In December 2015, the investigational new drug application, or IND, that we submitted to the U.S. Food and Drug Administration, or FDA, for a Phase 1 clinical trial to evaluate our PTI-428 product candidate became effective. We initiated our first Phase 1 clinical trial in CF patients and healthy volunteers in the first half of 2016. The Phase 1 trial in CF patients included single ascending dose, or SAD, and multiple ascending dose, or MAD, cohorts. The Phase 1 trial in healthy volunteers included SAD and MAD cohorts to assess the safety, pharmacokinetic and exploratory biomarker results. We reported preliminary safety, pharmacokinetic and exploratory biomarker data from SAD and MAD cohorts in the PTI-428 Phase 1 clinical trial in CF subjects receiving PTI-428 or placebo for 7 days in addition to Orkambi® (lumacaftor/ivacaftor) as their background, standard of care therapy, as well as a cohort of CF subjects receiving PTI-428 or placebo for 7 days who were not taking CFTR modulator based therapies.

We have also completed a 28-day Phase 2 clinical trial for PTI-428 in CF patients randomized to receive either PTI-428 or placebo for 28 days in addition to Orkambi as their background, standard of care therapy to evaluate the efficacy, safety, and tolerability of 50 mg of once-a-day PTI-428. In December 2017, we announced the results of this trial.

Our IND for the Phase 1 study of PTI-801, a corrector molecule, was submitted to the FDA in the first quarter of 2017 and is now active. In March 2017, we received Fast Track designation from the FDA for the investigation of PTI-801 for the treatment of CF. We completed dosing of subjects in the SAD and MAD cohorts of the healthy volunteer portion of this study, to assess the safety and PK of PTI-801 and reported initial data on this portion of the study in 2017.

Our IND for the Phase 1 study of PTI-808, a potentiator molecule, was submitted to the FDA in the second quarter of 2017 and is now active. PTI-808 has completed investigation in healthy volunteers in single and multiple dose cohorts. We reported preliminary data from this study in December 2017.

Co-administration of PTI-428, PTI-801 and PTI-808 has been completed in healthy volunteers. We reported preliminary data from this study in December 2017.

In March 2018, the FDA granted Breakthrough Therapy designation for PTI-428 for the treatment of CF in patients homozygous for the F508del mutation who are receiving Orkambi as background therapy. Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s). Also in March 2018, the FDA granted Orphan Drug Designation for PTI-428. The FDA grants Orphan Drug Designation to promote the development of product candidates for rare conditions affecting fewer than 200,000 U.S. patients annually. This designation provides for a seven-year marketing exclusivity period against competition, as well as certain incentives, including federal grants, tax credits and a waiver of certain administrative filing fees.

We have initiated a 14-day once-a-day dosing study with PTI-801 in CF subjects on background Orkambi therapy. In June 2018, we reported preliminary data from the first 48 subjects who completed dosing with either PTI-801 (100 mg, 200 mg and 400 mg) or placebo. Safety and pharmacokinetics results were as expected. At higher doses, PTI-801 demonstrated a statistically significant improvement in sweat chloride and body mass index in the 14-day treatment period. An improvement in ppFEV1 was observed across all dose cohorts, although the change was not statistically significant. Two thirds of subjects in all PTI-801 cohorts were above ppFEV1 baseline by the end of the treatment period and approached baseline by the end of the 7-day follow up period. In hyperglycemic subjects with Cystic Fibrosis Related Diabetes, PTI-801 led to a statistically significant normalization of blood glucose levels at the three dose levels analyzed. Additional data was reported in October 2018. We believe these results support the goal of studying PTI-801 as part of our proprietary double and triple combination therapy regimens.

Combination study protocols for trials in CF patients have been reviewed by key patient advocacy and regulatory authorities in the United States and Europe. In January 2018, we announced that our triple combination clinical study protocol received endorsement and a high strategic fit score from the Therapeutics Development Network (TDN) and the Clinical Trial Network (CTN). Our double combination protocol has also received the endorsement of the TDN. The TDN and CTN are the drug development arms of the Cystic Fibrosis Foundation (CFF) and the European CF Society (ECFS), respectively. In April 2018, the TDN endorsed the study protocol to investigate PTI-428 in CF patients on background Symdeko® therapy.

In April 2018, the FDA granted Fast Track designation for our triple combination program for the treatment of cystic fibrosis. The Company's proprietary triple combination includes the following investigational agents: a cystic fibrosis transmembrane conductance regulator (CFTR) amplifier, a third-generation corrector and a potentiator, known as PTI-428, PTI-801 and PTI-808, respectively. The FDA's Fast Track program is designed to facilitate the development and expedite the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. An investigational drug that receives Fast Track designation is eligible for more frequent communications between the FDA and the company relating to the development plan and clinical trial design and may be eligible for priority review if certain criteria are met.

In October 2018, we announced positive preliminary results from three doublet cohorts of our ongoing Phase 1, randomized, double-blind, placebo-controlled studies of our proprietary combination therapy doublet, PTI-808 and PTI-801, and an enrollment update from the triplet, PTI-808, PTI-801, and PTI-428, in subjects with cystic fibrosis.

These studies were designed to assess the safety, tolerability, and pharmacokinetics (PK) of PTI-801, a third-generation CFTR corrector and PTI-808, a novel CFTR potentiator, compared to placebo over a 14-day dosing period in CF subjects across dose levels of each modulator. Changes in sweat chloride (SC) concentration and in percent predicted FEV1(ppFEV1) were assessed and evaluated as endpoints.

The first dose cohort using the Company's proprietary triplet combination of PTI-801, PTI-808 and PTI-428, a novel CFTR amplifier, is ongoing and we expect preliminary data in the fourth quarter of 2018, with complete data from the doublet and triplet cohorts expected in the first quarter of 2019.

We have exclusive worldwide commercial rights to PTI-428, PTI-801 and PTI-808, as well as our proprietary combinations. We plan to pursue regulatory approval for add-on therapies based on PTI-428 and/or PTI-801 in regions where ivacaftor and lumacaftor (and ivacaftor and tezacaftor, as applicable) are commercially available. Given the well-characterized and clearly identified patient populations with CF in the United States, Canada, Europe and Australia, we plan to independently commercialize our product candidates, including, without limitation, our combination therapy candidates, in those regions. Our commercialization strategy will target key prescribing physicians and advocacy groups, as well as provide patients with support programs, ensure product access and secure reimbursement.

In addition to our wholly owned CF programs, we have partnered with a major pharmaceutical company, Astellas Pharma Inc., or Astellas, on our unfolded protein response, or UPR, program. The UPR program is intended to reduce the accumulation of unfolded proteins in the endoplasmic reticulum, or ER, which is observed in many diseases caused by an imbalance in the proteostasis network and characterized by defects in protein folding, trafficking and clearance, including genetic, neurodegenerative and retinal degenerative diseases. In August 2016, we announced the achievement of a preclinical milestone by demonstrating that selective modulation of the UPR pathway is an effective disease-modifying approach in the treatment of multiple diseases with few or no therapies currently available.

Since our inception in 2006, we have devoted substantially all of our resources to organizing and staffing our company, business planning, raising capital, acquiring and developing product and technology rights, and conducting research and development activities for our product candidates. We do not have any products approved for sale and have not generated any revenue from product sales. We have funded our operations to date with proceeds from the sale of preferred stock, the issuance of convertible promissory notes, proceeds from our initial public offering in February 2016, proceeds from our follow-on public offerings, and to a lesser extent, payments received in connection with collaboration agreements and a research grant, as well as funds from the sale of stock under the at-the-market program described below.

In October 2018, we completed a follow-on public offering whereby we sold 11,000,000 shares of common stock at a price to the public of $6.75 per share. The aggregate net proceeds from the offering were approximately $69.5 million, net of underwriting discounts and commissions and estimated offering expenses. On November 6, 2018, the Company issued and sold an additional 1,650,000 shares of its common stock at the offering price of $6.75 per share as a result of the full exercise by the underwriters of their option to purchase additional shares. The net proceeds from this issuance were $10.5 million, after deducting underwriting discounts and commissions.

In March 2018, we entered into a sales agreement with Leerink Partners LLC ("Leerink") with respect to an at-the-market ("ATM") offering program under which we may offer and sell, from time to time at our sole discretion, shares of our common stock, having an aggregate offering price of up to $50.0 million. Leerink is not required to sell any specific amount but acts as our sales agent on a commercially reasonable efforts basis consistent with its normal trading and sales practices. Common stock will be sold at prevailing market prices at the time of the sale; and as a result, prices may vary. We will pay Leerink up to 3% of the gross proceeds from any common stock sold under the sales agreement. In October 2018, we sold 1,364,348 shares of our common stock for net proceeds of approximately $11.2 million under the ATM program. As of October 19, 2018, we sold an aggregate of 3,475,166 shares of our common stock for total net proceeds of approximately $21.7 million and $27.6 million of common stock remained available for sale under the ATM program. In connection with our follow-on offering in October 2018, we have suspended sales under the ATM program.

Since our inception, we have incurred significant operating losses. Our net losses were $18.4 million and $14.0 million for the three months ended September 30, 2018 and 2017, respectively, and $44.9 million and $46.0 million for the nine months ended September 30, 2018 and 2017, respectively. As of September 30, 2018, we had an accumulated deficit of $260.6 million. We expect to continue to incur significant expenses and increasing operating losses for at least the next several years. We expect our expenses and capital requirements will increase substantially in connection with our ongoing activities, as we:

- expand and/or advance our add-on and proprietary combination therapy candidates, PTI-428, PTI-801 and PTI-808, into Phase 3 clinical trials;
- seek regulatory approval for our product candidates;
- seek support and approval from our collaboration partners, the TDN, the CTN, and other interested parties;
- hire personnel to support our product development, manufacturing, commercialization and administrative efforts; and
- advance the research and development efforts of our CF and other product candidates, including, without limitation, back-up compounds.

We will not generate revenue from product sales unless and until we successfully complete clinical development and obtain regulatory approval for our product candidates. If we obtain regulatory approval for any of our product candidates, we expect to incur significant expenses related to developing our internal commercialization capability to support product sales, marketing and distribution. In addition, we will continue to incur additional costs associated with operating as a public company.

As a result, we will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through the sale of public or private equity, debt financings or other capital sources, including potential collaborations with other companies or other strategic transactions. We may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such agreements as, and when, needed, we may have to significantly delay, scale back or discontinue the development and commercialization of one or more of our product candidates.

We expect that our cash, cash equivalents and short-term investments of $46.4 million as of September 30, 2018, together with net proceeds of approximately $80.0 million, after deducting underwriting discounts and commissions and estimated offering expenses, from our follow-on offering and the net proceeds of approximately $11.2 million from sales under our ATM program during the fourth quarter of 2018 will enable us to fund our operating expenses and capital requirements, based upon our current operating plan, into early 2020. However, additional funding will be necessary to complete the funding of critical path activities anticipated in 2020. In accordance with the requirements of ASC 205-40, we determined that there is substantial doubt about the Company's ability to continue as a going concern within 12 months of the issuance date of these financial statements. The financial statements do not include any adjustments that might result from the outcome of this uncertainty. We intend to obtain additional funding through public or private financing or collaborative arrangements with strategic partners to increase the funds available to support its operating and capital needs. Although we have been successful in raising capital in the past, there is no assurance that we will be successful in obtaining such additional financing on terms acceptable to us, if at all, nor is it considered probable under the accounting standards. As such, under the requirements of ASC 205-40, we may not consider the potential for future capital raises or management plans to reduce costs that are not considered probable in its assessment of our ability to meet our obligations for the next 12 months. If we are unable to obtain funding, we would be forced to delay, reduce or eliminate its research and development programs, product portfolio expansion or commercialization efforts, which could adversely affect our business prospects, or we may be unable to continue operations. See "Liquidity and Capital Resources."

Components of our Results of Operations

Revenue

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from the sale of products in the foreseeable future. All of our revenue during the three and nine months ended September 30, 2018 and 2017 was derived from our collaboration agreement with Astellas.

We adopted Accounting Standards Codification Topic 606, Revenue from Contracts with Customers, or ASC 606, on January 1, 2018. Under ASC 606, we are recognizing revenue over the expected research and development period using the proportional performance method.

Operating Expenses

Research and Development Expenses

Research and development expenses, which include costs of research services incurred in connection with our collaboration agreements and research grant, consist primarily of costs incurred in connection with the discovery and development of our product candidates, which include:

- employee-related expenses, including salaries, related benefits, travel and stock-based compensation expense for employees engaged in research and development functions;
- expenses incurred in connection with the preclinical and clinical development of our product candidates and under agreements with contract research organizations, or CROs and contract manufacturing organizations, or CMOs;
- facilities, depreciation and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance and supplies; and
- payments made under third-party licensing agreements.

We expense research and development costs as incurred. We recognize external development costs based on an evaluation of the progress to completion of specific tasks using information provided to us by our service providers.

Our direct research and development expenses are tracked on a program-by-program basis and consist primarily of external costs, such as fees paid to consultants, central laboratories, contractors, CROs, and CMOs in connection with our clinical trials and preclinical development activities. We do not allocate employee costs, costs associated with our platform technology and facility expenses, including depreciation or other indirect costs, to specific product development programs because these costs are deployed across multiple product development programs and, as such, are not separately classified. We use internal resources to manage our preclinical development activities and perform data analysis for such activities. These employees work across multiple development programs and, therefore, we do not track their costs by program.

The table below summarizes our research and development expenses incurred by program (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
CF	$ 10,455	$ 7,484	$ 22,892	$ 24,858
UPR	875	529	1,553	1,119
Unallocated expenses:				
Personnel related (including stock-based compensation)	2,475	3,270	7,563	9,969
Facility related	609	659	1,891	2,272
Other	1,177	952	2,696	3,154
Total research and development expenses	$ 15,591	$ 12,894	$ 36,595	$ 41,372

We expect that our expenses will increase substantially in connection with our ongoing clinical trials, preclinical development, and commercialization activities. At this time, we cannot reasonably estimate the costs for completing the clinical development of PTI-428, PTI-801 or PTI-808 or our proprietary combination therapies for the treatment of CF or the cost associated with the development of any of our other product candidates.

The successful development and commercialization of our product candidates is highly uncertain. This is due to the numerous risks and uncertainties associated with product development and commercialization, including the uncertainty of:

- the scope, progress, outcome and costs of our preclinical development activities, clinical trials and other research and development activities;
- establishing an appropriate safety profile with IND-enabling studies;
- successful patient enrollment in, and the initiation and completion of, clinical trials;
- the cooperation and approval we receive from third parties including clinical investigators, CROs, the TDN and CTN;
- the timing, receipt and terms of any marketing approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;

- obtaining, maintaining, defending and enforcing patent claims and other intellectual property rights;
- significant and changing government regulation;
- launching commercial sales of our product candidates, if and when approved, whether alone or in collaboration with others; and
- maintaining a continued acceptable safety profile of the product candidates following approval.

Any changes in the outcome of any of these variables, or others identified within this filing, with respect to the development of our product candidates in preclinical and clinical development could mean a significant change in the costs and timing associated with the development of these product candidates. For example, if the FDA or another regulatory authority were to delay our planned start of clinical trials or require us to conduct clinical trials or other testing beyond those that we currently expect or if we experience significant delays in enrollment in any of our planned clinical trials, we could be required to expend significant additional financial resources and time on the completion of clinical development of that product candidate.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and related costs, including stock-based compensation, for personnel in executive, finance and administrative functions. General and administrative expenses also include direct and allocated facility-related costs as well as professional fees for legal, consulting, accounting and audit services.

Other Income (Expense), Net

Interest Income. Interest income consists of interest earned on cash equivalents and short-term investments held by us during the reporting periods.

Other Income (Expense), Net. Other income (expense), net, primarily consists of the amortization of premium on our short-term investments and the gains or losses associated with the changes in the fair values of our derivative liability. The derivative liability relates to a cash settlement option associated with the change of control provision in our CFFT collaboration agreement, which meets the definition of a derivative. Therefore, we have classified this derivative as a liability that we remeasure to fair value at each reporting period, and we record the changes in the fair value of the derivative liability as a component of other income (expense), net.

Critical Accounting Policies and Significant Judgments and Estimates

Our financial statements are prepared in accordance with generally accepted accounting principles in the United States, or GAAP. The preparation of our financial statements and related disclosures requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenue, costs and expenses, and the disclosure of contingent assets and liabilities in our financial statements. We base our estimates on historical experience, known trends and events and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. We evaluate our estimates and assumptions on an ongoing basis.

Our actual results may differ from these estimates under different assumptions or conditions. During the nine months ended September 30, 2018, there were no material changes to our critical accounting policies, except for our revenue recognition policy as a result of the adoption of ASC 606 and our lease policy as a result of the adoption of ASC 842, which are discussed in detail in Note 2*, Summary of Significant Accounting Policies*. Our critical accounting policies are described under the heading, "Management's Discussion and Analysis of Financial Condition and Results of Operations— Critical Accounting Policies and Significant Judgments and Estimates," in our Annual Report on Form 10-K filed with the Securities and Exchange Commission, or SEC, on March 14, 2018 and the notes to the financial statements appearing elsewhere in this Quarterly Report on Form 10-Q. We believe that of our critical accounting policies, the following accounting policies involve the most judgment and complexity:

- revenue recognition;
- accrued research and development expenses;
- stock-based compensation; and
- valuation of derivative liability.

Accordingly, we believe the policies set forth above are critical to fully understanding and evaluating our financial condition and results of operations. If actual results or events differ materially from the estimates, judgments and assumptions used by us in applying these policies, our reported financial condition and results of operations could be materially affected.

Results of Operations

Comparison of Three Months Ended September 30, 2018 and 2017

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

	Three Months Ended September 30,		Increase
	2018	2017	(Decrease)
Revenue	$ 1,055	$ 1,551	$ (496)
Operating expenses:			
Research and development	15,591	12,894	2,697
General and administrative	4,150	2,741	1,409
Total operating expenses	19,741	15,635	4,106
Loss from operations	(18,686)	(14,084)	(4,602)
Interest income	171	155	16
Other income (expense), net	87	(25)	112
Net loss	$ (18,428)	$ (13,954)	$ (4,474)

Revenue

Revenue was $1.1 million for the three months ended September 30, 2018, compared to $1.6 million for the three months ended September 30, 2017, all of which was derived from our collaboration agreement with Astellas. The decrease of $0.5 million is primarily the result of the adoption of ASC 606 on January 1, 2018. The total impact to revenue for the three months ended September 30, 2018 as a result of the adoption of ASC 606 was a decrease of $0.7 million. Total revenue recorded in the three months ended September 30, 2018 under ASC 606 was $1.1 million, as compared to $1.8 million that would have been recorded under ASC 605.

Research and Development Expenses

Research and development expenses were $15.6 million for the three months ended September 30, 2018, compared to $12.9 million for the three months ended September 30, 2017. The increase of $2.7 million was primarily due to increases of approximately $3.1 million in clinical related research activities and $0.4 million in professional fees, partially offset by a decrease in employee-related costs of approximately $0.8 million. The decrease in employee-related expenses was due to a decrease in research headcount in October 2017.

General and Administrative Expenses

General and administrative expenses were $4.2 million for the three months ended September 30, 2018, compared to $2.7 million for the three months ended September 30, 2017. The increase of $1.5 million in general and administrative expenses was primarily due to increases of $0.6 million in facility costs, $0.5 million in professional fees, and $0.3 million in employee-related expenses.

Interest Income

Interest income was $0.2 million for the three months ended September 30, 2018 and 2017 and consists of interest earned on short-term investments.

Other Income (Expense), Net

Other expenses were less than $0.1 million for the three months ended September 30, 2018 and 2017.

Comparison of Nine Months Ended September 30, 2018 and 2017

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

	Nine Months Ended September 30,		Increase (Decrease)
	2018	2017	
Revenue	$ 2,840	$ 3,719	$ (879)
Operating expenses:			
Research and development	36,595	41,372	(4,777)
General and administrative	11,931	8,813	3,118
Total operating expenses	48,526	50,185	(1,659)
Loss from operations	(45,686)	(46,466)	780
Interest income	530	515	15
Other income (expense), net	224	(57)	281
Net loss	$ (44,932)	$ (46,008)	$ 1,076

Revenue

Revenue was $2.8 million for the nine months ended September 30, 2018, compared to $3.7 million for the nine months ended September 30, 2017, all of which was derived from our collaboration agreement with Astellas. The decrease of $0.9 million is primarily the result of the adoption of ASC 606 on January 1, 2018. The total impact to revenue for the nine months ended September 30, 2018 as a result of the adoption of ASC 606 was a decrease of $1.9 million. Total revenue recorded in the nine months ended September 30, 2018 under ASC 606 was $2.8 million, as compared to $4.7 million that would have been recorded under ASC 605.

Research and Development Expenses

Research and development expenses were $36.6 million for the nine months ended September 30, 2018, compared to $41.4 million for the nine months ended September 30, 2017. The decrease of $4.8 million was primarily due to a decrease of approximately $2.4 million in employee-related expenses, $1.6 million in clinical related research activities, and $0.5 million in facility costs. The decrease in employee-related expenses was due to a decrease in research headcount in October 2017.

General and Administrative Expenses

General and administrative expenses were $11.9 million for the nine months ended September 30, 2018, compared to $8.8 million for the nine months ended September 30, 2017. The increase of $3.1 million in general and administrative expenses was primarily due to increases of $1.7 million in employee-related expenses, $0.8 million in facility costs, and $0.7 million in professional fees.

Interest Income

Interest income was $0.5 million for the nine months ended September 30, 2018 and 2017 and consists of interest earned on short-term investments.

Other Income (Expense), Net

Other income was $0.2 million for the nine months ended September 30, 2018 compared to other expense of less than $0.1 million for the nine months ended September 30, 2017. The increase of $0.3 million was primarily due to an increase in investment amortization of $0.4 million.

Liquidity and Capital Resources

Since our inception, we have incurred significant operating losses. We have generated limited revenue to date from our collaboration agreements and research grant. We have not yet commercialized any of our product candidates, which are in various phases of preclinical development and clinical trials; and we do not expect to generate revenue from sales of any product for several years, if at all. We have funded our operations to date with proceeds received from our initial public offering and subsequent follow-on offerings, the sale of preferred stock, the issuance of convertible promissory notes and, to a lesser extent, payments received in connection with collaboration agreements and a research grant, as well as sales of stock under our ATM program with Leerink acting as our sales agent.

As of September 30, 2018, we had cash, cash equivalents and short-term investments of $46.4 million. We expect that our cash, cash equivalents and short-term investments as of September 30, 2018 together with net proceeds of approximately $80.0 million, after deducting underwriting discounts and commissions and estimated offering expenses, from our follow-on offering and the net proceeds of approximately $11.2 million from sales under our ATM program during the fourth quarter of 2018 will enable us to fund our operating expenses and capital requirements, into early 2020. However, additional funding will be necessary to complete the funding of critical path activities anticipated in 2020. As of September 30, 2018, we have assessed this risk and, in accordance with the requirements of ASC 205-40, determined that there is substantial doubt about our ability to continue as a going concern within 12 months of the issuance date of these condensed financial statements. The financial statements do not include any adjustments that might result from the outcome of this uncertainty.

Although we have been successful in raising capital in the past, there is no assurance that we will be successful in obtaining such additional financing on terms acceptable to us, if at all. As such, under the requirement of ASC 205-40, management may not consider the potential for future capital raises or management plans to reduce costs that are not considered probable in its assessment of our ability to meet our obligations for the next 12 months. If we are unable to obtain funding, we could be forced to delay, reduce or eliminate some or all of our research and development programs, product portfolio expansion or commercialization efforts, which would adversely affect our business prospects, or we may be unable to continue operations.

Cash Flows

The following table summarizes our sources and uses of cash for each of the periods presented (in thousands):

	Nine Months Ended September 30,	
	2018	2017
Cash used in operating activities	$ (39,504)	$ (40,557)
Cash provided by investing activities	17,840	41,719
Cash provided by financing activities	10,530	73
Net increase (decrease) in cash and cash equivalents	$ (11,134)	$ 1,235

Operating Activities. Net cash used in operating activities was $39.5 million during the nine months ended September 30, 2018, primarily driven by our net loss of $44.9 million, and offset by changes in our operating assets and liabilities of $0.8 million and non-cash charges of $4.6 million. Our net loss was primarily attributed to our research and development activities associated with the advancement of our preclinical studies and clinical trials.

Net cash used in operating activities was $40.6 million during the nine months ended September 30, 2017, primarily driven by our net loss of $46.0 million, partially offset by changes in our operating assets and liabilities of $1.7 million and non-cash charges of $3.7 million. Our net loss was primarily attributed to our research and development activities associated with the advancement of our preclinical studies and clinical trials.

Investing Activities. During the nine months ended September 30, 2018, net cash provided by investing activities was $17.8 million, primarily consisting of proceeds received from maturities of short-term investments and offset by additional purchases of short-term investments.

During the nine months ended September 30, 2017, net cash provided by investing activities was $41.7 million, primarily consisting of proceeds received from maturities of short-term investments and offset by additional purchases of short-term investments.

Financing Activities. During the nine months ended September 30, 2018, net cash provided by financing activities was $10.5 million, primarily resulting from $10.5 million of net proceeds from the issuance of 2,110,818 shares of common stock related to sales under our ATM program.

During the nine months ended September 30, 2017, net cash provided by financing activities was less than $0.1 million, primarily resulting from the exercise of stock options.

Operating Capital Requirements

We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we advance the preclinical activities and clinical trials of our product candidates in development.

Our expenses will also increase as we:

- pursue the clinical development of our most advanced product candidates, including PTI-428 and PTI-801, as well as our combination therapies;
- seek the support and approval from our collaboration partners, the TDN and other interested parties;
- continue the research and development of our other product candidates;
- seek to identify and develop additional product candidates;
- seek marketing approvals for any of our product candidates that successfully complete clinical development;
- develop and expand our sales, marketing and distribution capabilities for our product candidates for which we obtain marketing approval;
- scale up our manufacturing processes and capabilities to support our ongoing preclinical activities and clinical trials of our product candidates and commercialization of any of our product candidates for which we obtain marketing approval;
- maintain, expand and protect our intellectual property portfolio;
- expand our operational, financial and management systems and increase personnel, including personnel to support our clinical development, manufacturing and commercialization efforts and our operations as a public company; and
- increase our product liability and clinical trial insurance coverage as we initiate additional clinical trials, expand our existing clinical trials and launch commercialization efforts.

Because of the numerous risks and uncertainties associated with research, development and commercialization of pharmaceutical drugs, we are unable to estimate the exact amount of our working capital requirements. Our future funding requirements will depend on many factors, including:

- the number and characteristics of the product candidates we pursue;
- the scope, progress, results and costs of researching and developing our product candidates, and conducting preclinical studies and clinical trials;
- the timing of, and the costs involved in, obtaining regulatory approvals for our product candidates;
- the timing of, and costs involved in, manufacturing our drug candidates and any drugs we successfully commercialize;
- our ability to establish and maintain strategic collaborations, licensing or other arrangements and the financial terms of such agreements;
- delays that may be caused by changing regulatory requirements;
- cost and timing of hiring new employees to support our continued growth;
- the costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing patent claims, including litigation costs and the outcome of such litigation; and
- the timing, receipt and amount of sales of, or milestone payments related to or royalties on, our current or future product candidates, if any.

Until such time, if ever, as we can generate product revenue sufficient to achieve profitability, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaboration agreements, other third-party funding, strategic alliances, licensing arrangements or marketing and distribution arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through other third-party funding, collaborations agreements, strategic alliances, licensing arrangements or marketing and distribution arrangements, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves.

Based upon our current operating plan, we believe our existing cash, cash equivalents and short-term investments together with net proceeds from our follow-on offering and the net proceeds from sales under our ATM program during the fourth quarter of 2018 will enable us to fund our operating expenses and capital expenditure requirements into early 2020. However, additional funding will be necessary to complete the funding of critical path activities anticipated in 2020.

Contractual Obligations and Commitments

In September 2017, we entered into a lease agreement for our new headquarters, consisting of approximately 30,000 square feet of laboratory and office space located in Boston, Massachusetts. The lease commencement date was in January 2018. The lease term will expire in April 2028. We are entitled to one seven-year option to extend. Annual rent under the lease, exclusive of operating expenses and real estate taxes, will be approximately $1.7 million in the first year, with annual increases of 2.75% each year thereafter. We were entitled to an improvement allowance of approximately $4.8 million for certain permitted costs related to the design and construction of our improvements to the premises. The lease contains customary provisions allowing the landlord to terminate the lease if we fail to remedy a breach of any of its obligations within specified time periods, or upon bankruptcy or insolvency of the Company.

We formerly leased office and laboratory space in Cambridge, Massachusetts, pursuant to an operating lease that, as amended, expired in May 2018. We recorded rent expense of $0.9 million and $0.4 million during the three months ended September 30, 2018 and 2017, and $2.1 million and $1.3 million during the nine months ended September 30, 2018 and 2017, respectively.

The following table summarizes our contractual obligations as of September 30, 2018 and the effects that such obligations are expected to have on our liquidity and cash flows in future periods (in thousands):

	Total	Less Than 1 Year	1 to 3 Years	3 to 5 Years	More than 5 Years
Operating lease commitments (1)	$ 18,079	$ 1,675	$ 3,489	$ 3,684	$ 9,231
Consulting agreement (2)	630	630	—	—	—
Total	$ 18,709	$ 2,305	$ 3,489	$ 3,684	$ 9,231

(1) Amounts in the table reflect payments due for our new lease of office and laboratory space in Boston, Massachusetts for which rent commenced in April 2018 and which expires in April 2028.

(2) In May 2016, we entered into an agreement with Dr. Stelios Papadopoulos to provide consulting and advisory services as and when requested. We will pay a quarterly retainer of $0.2 million to Dr. Papadopoulos over a three-year term for a total of $2.5 million. The quarterly retainer may be settled in cash, common stock of the Company or a combination thereof, at our discretion.

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 in the rules and regulations of the Securities and Exchange Commission.

Item 3. Quantitative and Qualitative Disclosures About Market Risks

Interest Rate Fluctuation Risk

Our cash, cash equivalents and short-term investments as of September 30, 2018, consisted of money market funds, government-sponsored enterprise securities and U.S. treasury securities. The primary objectives of our investment activities are to preserve principal, provide liquidity and maximize income without significantly increasing risk. Our primary exposure to market risk is interest income sensitivity, which is affected by changes in the general level of U.S. interest rates. However, because of the nature of the instruments in our portfolio, a sudden change in market interest rates would not be expected to have a material impact on our financial condition and/or results of operation.

Item 4. Management's Evaluation of our Disclosure Controls and Procedures.

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in the reports that we file or submit under the Securities and Exchange Act of 1934 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 President and Chief Executive Officer, who is our principal executive officer, and our Interim VP of Finance, who is our principal financial officer, as appropriate, to allow timely decisions regarding required disclosure.

As of September 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 defined in Rules 13a-15(e) and 15d-15(e) under the Securities and Exchange Act of 1934). 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 September 30, 2018, our disclosure controls and procedures were effective at the reasonable assurance level.

There were no changes in our internal control over financial reporting during the three months ended September 30, 2018 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

In the ordinary course of business, we are from time to time involved in lawsuits, claims, investigations, proceedings, and threats of litigation relating to intellectual property, commercial arrangements, employment and other matters. While the outcome of these proceedings and claims cannot be predicted with certainty, as of September 30, 2018, we were not party to any material pending legal proceedings, and we are not aware of any claims or actions pending or threatened against us that would have a material adverse impact on our financial position, results of operations or cash flows.

Item 1A. Risk Factors

Investing in our common stock involves a high degree of risk. You should carefully consider the following risks and uncertainties, together with all of the other information in this Quarterly Report on Form 10-Q, or this report, including our financial statements and related notes, before investing in our common stock. Any of the risks we describe below could adversely affect our business, financial condition or results of operations. The market price of our common stock could decline if one or more of these risks or uncertainties actually occur, causing you to lose all or part of your investment. Additional risks that we currently do not know about, or that we currently believe to be immaterial, may also impair our business. Certain statements below are forward-looking statements. See "Forward-Looking Statements" in this report.

Risks Relating to Our Business

We have incurred significant losses since our inception. We anticipate that we will continue to incur significant losses for the foreseeable future, and we may never achieve or maintain profitability.

We are a drug research and development company focused primarily on developing our lead product candidates, PTI-428, PTI-801 and PTI-808 for the treatment of CF, as add-ons to existing standard of care therapies and/or as part of our proprietary combination therapy candidates. We have incurred significant net losses in each year since our inception, including net losses of $25.0 million, $37.2 million and $59.4 million for the years ended December 31, 2015, 2016 and 2017, respectively, and $18.4 million and $44.9 million for the three and nine months ended September 30, 2018. As of September 30, 2018, we had an accumulated deficit of $260.6 million.

To date, we have financed our operations primarily through the sale of equity securities and debt financings. We have devoted most of our financial resources to research and development, including our preclinical and clinical development activities. We have not completed the development of any of our product candidates. We expect to continue to incur significant and increasing losses and negative cash flows for the foreseeable future. The size of our losses will depend, in part, on the rate of future expenditures and our ability to generate revenues. In particular, we expect to incur substantial and increased expenses as we:

- continue the clinical development of our lead product candidates, PTI-428, PTI-801 and PTI-808, including, without limitation, as part of our proprietary combination therapy candidates, for the treatment of CF;
- seek to obtain regulatory approvals for PTI-428, PTI-801, and our proprietary combination therapy candidates, and our other product candidates;
- seek cooperation and support from third parties, including clinical investigators, industry experts, therapeutic development networks of patient advocacy groups and clinical research organizations, as we enroll patients in our clinical trials;
- conduct our ongoing clinical trials and prepare for additional clinical trials and potential commercialization of PTI-428, PTI-801, and potential combination therapies, and our other product candidates;
- scale up contracted manufacturing processes and quantities to conduct our ongoing clinical trials and prepare for additional clinical trials and the commercialization of PTI-428, PTI-801, and potential combination therapies, and our other product candidates for any indications for which we receive regulatory approval;
- establish outsourcing of the commercial manufacturing of PTI-428, PTI-801, PTI-808 and our other product candidates for any indications for which we may receive regulatory approval;
- establish an infrastructure for the sales, marketing and distribution of PTI-428, PTI-801, potential combination therapies, and our other product candidates for any indications for which we may receive regulatory approval;
- continue to advance our combination therapies as potential treatments for CF in clinical trials;

- prepare for Phase 3 trials, including, without limitation, trial design, conducting additional pre-clinical studies, manufacturing Phase 3 drug substance and drug product, producing Phase 2 data and other necessary work to support commencement of Phase 3 trials;
- expand our research and development activities and advance the discovery and development programs for other product candidates, including, without limitation, preclinical laboratory, animal and other testing and reports and the preparation of investigational new drug filings in the United States, and the equivalent in non-U.S. jurisdictions where we may seek to conduct clinical trials;
- maintain, expand and protect our intellectual property portfolio;
- continue our research and development efforts and seek to discover additional product candidates, including back-up candidates to existing product candidates; and
- add clinical, regulatory, operational, financial and management information systems and personnel, including personnel to support our clinical development and commercialization efforts and operations as a public company.

To become and remain profitable, we must succeed in developing and eventually commercializing products with significant market potential. This will require us to be successful in a range of challenging activities, including discovering product candidates, completing preclinical testing and clinical trials of our product candidates, obtaining and maintaining regulatory approval for these product candidates, and manufacturing, marketing and selling those products. We are in the early stages of these activities.

None of our product candidates has been approved or commercialized. We may never succeed in obtaining regulatory approval for or commercializing any of our product candidates. If our product candidates are not approved or commercialized, if any products that do receive regulatory approvals later show unanticipated properties (for example, unexpected safety issues), or if revenues from any products that do receive regulatory approvals are insufficient, we will not achieve profitability and our business may fail.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company 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 cause you to lose all or part of your investment.

Our ability to generate future revenues from product sales is uncertain and depends upon our ability to successfully develop, obtain regulatory approval for and commercialize our product candidates, as well as the receipt and/or maintenance of regulatory approval of products and product candidates under development by third parties that our product candidates will or may in the future depend on.

Our ability to generate revenue and achieve profitability depends on our ability, alone or with collaborators, to successfully complete the development of, obtain the necessary regulatory approvals for, and commercialize, a product candidate or candidates. Our several development programs are currently focused on demonstrating their respective clinical benefit for CF patients. If either PTI-428 or PTI-801 is approved, it may be approved for co-administration with ivacaftor and lumacaftor (and/or ivacaftor and tezacaftor). We do not anticipate generating revenues from sales of PTI-428, PTI-801, and our proprietary combination therapy candidates, or any other product candidate for the foreseeable future, if ever. Our ability to generate future revenues from product sales depends heavily on:

- Vertex's continued compliance with regulatory requirements, the continued commercial availability of ivacaftor and lumacaftor (and ivacaftor and tezacaftor), the reimbursement of their cost to CF patients by insurers and their overall success in the market;
- the successful regulatory approval and commercial launch of CFTR modulators other than ivacaftor and lumacaftor (and ivacaftor and tezacaftor) that we desire to test for administration with PTI-428, PTI-801 and/or our other product candidates;
- obtaining favorable results for and advancing the development of PTI-428, PTI-801, PTI-808, our proprietary combination therapy candidates, and our other product candidates, including successfully enrolling patients in and completing our ongoing clinical trials and initiating and completing additional clinical trials;
- obtaining regulatory approval in the United States of PTI-428, PTI-801, our proprietary combination therapy candidates, and our other product candidates for CF and equivalent foreign regulatory approvals;
- launching and commercializing PTI-428, PTI-801, our proprietary combination therapy candidates, and our other product candidates, including building a production infrastructure and a sales force, and collaborating with third parties;

- achieving broad market acceptance of PTI-428, PTI-801, our proprietary combination therapy candidates, and our other product candidates in the medical community and with third-party payors; and
- generating and advancing through clinical development, a pipeline of product candidates in addition to PTI-428, PTI-801, PTI-808, our proprietary combination therapy candidates, and next-generation CFTR modulators.

Conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the data necessary to obtain regulatory approval and achieve product sales. Our anticipated development costs would likely increase if we do not obtain favorable results or if development of any product candidate is delayed. In particular, if we are required by the U.S. Food and Drug Administration, or FDA, and comparable regulatory authorities in other countries to perform studies or trials in addition to those that we currently expect to undertake, we would likely incur higher costs and it will likely take more time than we anticipate. Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to predict the timing or amount of any increase in our anticipated development costs.

In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products that we do not expect to be commercially available for several years, if at all. Even if one or more of our product candidates is approved for commercial sale, we anticipate incurring significant costs in connection with commercialization. As a result, we cannot assure you that we will be able to generate revenues from sales of any approved product candidates, or that we will achieve or maintain profitability even if we do generate sales.

We will require additional capital to fund our operations, including if our operating plan changes. If we fail to obtain additional capital, we would be forced to delay, reduce or eliminate one or more of our product research and development programs, seek corporate partners for the development of our product development programs or relinquish or license on unfavorable terms our rights to technologies or product candidates.

Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is a time-consuming, expensive and uncertain process that takes years to complete. We expect our research and development expenses to substantially increase in connection with our ongoing activities, particularly as we advance our clinical programs for PTI-428, PTI-801, PTI-808, our proprietary combination therapy candidates, and our other product candidates.

Based upon our current operating plan, we believe that our existing cash, cash equivalents and short-term investments of $46.4 million as of September 30, 2018, together with the net proceeds of approximately $80.0 million, after deducting underwriting discounts and commissions and estimated offering expenses, from our follow-on offering and approximately $11.2 million in net proceeds from sales under our ATM program during the fourth quarter of 2018 will enable us to fund our operating expenses and capital expenditure requirements into early 2020. However, additional funding will be necessary to complete the funding of critical path activities anticipated in 2020. As of September 30, 2018, management has further assessed this risk and, in accordance with the requirements of ASC 205-40, determined that there is substantial doubt about our ability to continue as a going concern within 12 months of the issuance date of the financial statements in this Quarterly Report on Form 10-Q. Although we have been successful in raising capital in the past, there is no assurance that we will be successful in obtaining additional financing on terms acceptable to us, if at all, nor is it considered probable under the accounting standards. As such, under the requirements of ASC 205-40, management may not consider the potential for future capital raises or management plans to reduce costs that are not considered probable in their assessment of our ability to meet our obligations for the next 12 months. If we are unable to obtain funding, we would be forced to delay, reduce or eliminate one or more of our research and development programs, product portfolio expansion or commercialization efforts, which would adversely affect our business prospects, or we may be unable to continue operations.

In addition, should our operating plan change, we will be required to reassess our operating capital needs and there can be no assurance that we will have the cash resources to fund any changed operating plan or that additional funding will be available on terms acceptable to us, if at all. Changing circumstances including those beyond our control may cause us to consume capital more rapidly than we currently anticipate, and we may need additional funds sooner than planned. For example, our clinical trials may encounter technical, enrollment or other difficulties that could increase our development costs more than we expect, or the FDA may require us or we may choose to perform studies or trials in addition to those that we currently anticipate. We may need to raise additional funds to support our ongoing programs for PTI-428, PTI-801 and PTI-808, our proprietary combination therapy candidates, and other clinical candidates, through regulatory approval and commercialization, or if we need or opt to seek to obtain regulatory approval for PTI-428 and/or PTI-801 for administration with drugs other than ivacaftor and lumacaftor, such as ivacaftor and tezacaftor.

Securing additional financing may divert our management from our day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates, including PTI-428, PTI-801 and PTI-808, and our proprietary combination therapy candidates. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. If we are unable to raise additional capital when required or on acceptable terms, we may be required to:

- significantly delay, scale back or discontinue the research, development or commercialization of our product candidates, including PTI-428, PTI-801 and PTI-808, our proprietary combination therapy candidates, and our other research or pre-clinical activities;
- seek corporate partners for PTI-428, PTI-801, PTI-808, our proprietary combination therapy candidates, or any of our other product candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available; or
- relinquish, or license on unfavorable terms, our rights to technologies or product candidates that we otherwise would seek to develop or commercialize ourselves.

If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we will be prevented from pursuing our development and commercialization efforts, which will have a material adverse effect on our business, operating results and prospects and on our ability to develop our product candidates. In addition, if we are unable to raise capital, we will also need to implement cost reductions, and any failure to effectively do so will harm our business, results of operations and prospects.

Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates on terms unfavorable to us.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs primarily through the sale of equity securities, debt financings and government and foundation grants. We may also seek to raise capital through third-party collaborations, strategic alliances and similar arrangements. We currently do not have any committed external source of funds.

In order to raise additional funds to support our operations, we may sell additional equity or debt securities, enter into collaborations, strategic alliances, or licensing arrangements or other marketing or distribution arrangements. For example, we have two effective universal shelf registration statements on Form S-3 pursuant to which we registered for sale up to $125.0 million and $100.0 million, respectively, of any combination of our common stock, preferred stock, debt securities, warrants, rights, purchase contracts and/or units from time to time and at prices and on terms that we may determine, including up to $50.0 million of our common stock available for issuance pursuant to an at-the-market offering program sales agreement that we entered into with Leerink Partners LLC (“Leerink”) in March 2018. As of November 2, 2018, an aggregate of approximately $82.4 million of securities remain available for issuance under the two shelf registration statements, including up to approximately $27.6 million of our common stock that we may offer and sell, from time to time, at our discretion, through Leerink as our sales agent under the at-the-market offering program sales agreement. To the extent that we raise additional capital through the sale of equity or debt securities, the ownership interest of existing stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of common stockholders. For example, our board of directors has the right to issue previously-authorized shares of preferred stock with such preferences without stockholder approval. Debt financing, if available, may involve the right to convert any such debt into equity on favorable conversion terms, which conversion would dilute existing stockholders’ ownership interest. Any such debt financing would also likely include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures, and declaring dividends, and will impose 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.

If we raise additional funds through collaborations, strategic alliances, or licensing arrangements or other marketing or distribution arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates, or grant licenses on terms that may not be favorable to us. If we are unable to expand our operations or otherwise capitalize on our business opportunities, our business, financial condition and results of operations could be materially adversely affected. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or commercialization efforts, or grant others rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

We have a limited operating history, which may make it difficult to evaluate the success of our business to date and to assess our future viability.

We were formed and began operations in December 2006. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, acquiring and developing product and technology rights and conducting research and development activities for our product candidates. We have not obtained regulatory approval for any of our product candidates. Consequently, any predictions about our future success, performance or viability may not be as accurate as they could be if we had a longer operating history, more experience with clinical development or approved products on the market.

We might not be able to utilize all or a significant portion of our net operating loss carryforwards and research and development tax credit carryforwards.

As of December 31, 2017, we had federal and state net operating loss carryforwards of $196.9 million and $182.1 million, respectively, which begin to expire in 2026 and 2030, respectively. As of December 31, 2017, we also had federal and state research and development tax credit carryforwards of $6.8 million and $3.1 million, respectively, which begin to expire in 2027 and 2026, respectively. These net operating loss and tax credit carryforwards could expire unused and be unavailable to offset future income tax liabilities. In addition, under Section 382 of the Internal Revenue Code of 1986, as amended, and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50% change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income may be limited. We have not determined if we have experienced Section 382 ownership changes in the past and if a portion of our net operating loss and tax credit carryforwards are subject to an annual limitation under Section 382. In addition, we may experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If we determine that an ownership change has occurred and our ability to use our historical net operating loss and tax credit carryforwards is materially limited, it would harm our future operating results by effectively increasing our future tax obligations. We have a full valuation allowance against our net deferred tax assets.

In addition, under the Tax Cuts and Jobs Act (the Tax Act), the amount of post 2017 NOLs that we are permitted to deduct in any taxable year is limited to 80% of our taxable income in such year, where taxable income is determined without regard to the NOL deduction itself. The Tax Act generally eliminates the ability to carry back any NOL to prior taxable years, while allowing post 2017 unused NOLs to be carried forward indefinitely. There is a risk that due to changes under the Tax Act, regulatory changes or other unforeseen reasons, our existing NOLs could expire or otherwise be unavailable to offset future income tax liabilities.

Risks Relating to the Development and Regulatory Approval of Our Product Candidates

We depend substantially on the success of our lead product candidate, PTI-428, which is currently in clinical development and is a new class of CFTR modulator. We cannot be certain that we will be able to successfully complete the clinical development of, obtain regulatory approval for, or successfully commercialize PTI-428.

We currently have no products on the market, and our most advanced product candidate, PTI-428, is currently in clinical development. Our other product candidates – PTI-801 and PTI-808 – are at an even earlier stage of clinical development, and we are early in our clinical development of our proprietary combination therapy candidates.

Our business depends substantially on the successful clinical development, regulatory approval and commercialization of PTI-428, a new class of CFTR modulator known as amplifier, and it will require substantial additional clinical development and regulatory approval efforts before we are permitted to commence its commercialization, if ever. The clinical trials and manufacturing and marketing of PTI-428 and any other product candidates will be subject to extensive and rigorous review and regulation by numerous government authorities in the United States, the European Union and other jurisdictions where we intend to test and, if approved, market our product candidates. Before obtaining regulatory approvals for the commercial sale of any product candidate, we must demonstrate through preclinical testing and clinical trials that the product candidate is safe and effective for use in each target indication, and potentially in specific patient populations, including the pediatric population. This process can take many years and may include post-marketing studies and surveillance, which would require the expenditure of substantial resources beyond the proceeds we have currently raised. Of the large number of drugs in development for approval in the United States and the European Union, only a small percentage successfully complete the FDA or European Medicines Agency, or EMA, regulatory approval processes, as applicable, and are commercialized. Accordingly, even if we are able to obtain the requisite financing to continue to fund our research, development and clinical programs, we cannot assure you that PTI-428 or any of our other product candidates will be successfully developed or commercialized.

We are pursuing a development path for PTI-428 to be administered with other CFTR modulators, as an add-on to existing or future standard of care therapies and/or as part of a proprietary triple combination together with PTI-801 and PTI-808. The success of PTI-428 is therefore dependent on the success of our other proprietary agents (alone or in combination with each other), the success of possible future standard of care therapies, and/or continued market acceptance of existing standard of care therapies. If these agents or standard of care therapies are not successful and available in the market, as the case may be, the development of PTI-428 will be hindered, delayed or not possible to complete or achieve.

In March 2018, the FDA granted Breakthrough Therapy designation for PTI-428 for the treatment of CF in homozygous patients for the F508del mutation who are receiving Orkambi® as background therapy. We may not achieve expedited clinical development or review as a result of the Breakthrough Therapy designation, the FDA may rescind such designation if our development program does not continue to meet the criteria for Breakthrough Therapy designation, and Breakthrough Therapy designation does not change the standards of approval for investigational new drugs.

We also depend on the success of our product candidate PTI-801, which is currently in early clinical development. We cannot be certain that we will be able to successfully complete the clinical development of, obtain regulatory approval for, or successfully commercialize PTI-801.

Our business depends on the successful clinical development, regulatory approval and commercialization of PTI-801, a class of CFTR modulator known as a corrector, and it will require substantial additional clinical development and regulatory approval efforts before we are permitted to commence its commercialization, if ever. The clinical trials and manufacturing and marketing of PTI-801 and any other product candidates will be subject to extensive and rigorous review and regulation by numerous government authorities in the United States, the European Union and other jurisdictions where we intend to test and, if approved, market our product candidates. Before obtaining regulatory approvals for the commercial sale of any product candidate, we must demonstrate through preclinical testing and clinical trials that the product candidate is safe and effective for use in each target indication, and potentially in specific patient populations, including the pediatric population. This process can take many years and may include post-marketing studies and surveillance, which would require the expenditure of substantial resources beyond the proceeds we have currently raised. Of the large number of drugs in development for approval in the United States and the European Union, only a small percentage successfully complete the FDA or European Medicines Agency, or EMA, regulatory approval processes, as applicable, and are commercialized. Accordingly, even if we are able to obtain the requisite financing to continue to fund our research, development and clinical programs, we cannot assure you that PTI-801 or any of our other product candidates will be successfully developed or commercialized.

We are pursuing a development path for PTI-801 to be administered with other CFTR modulators, as an add-on to existing or future standard of care therapies and/or as part of a proprietary double or triple combination together with PTI-808, or with PTI-428 and PTI-808. The success of PTI-801 is therefore dependent on the success of our other proprietary agents (alone or in combination with each other), the success of possible future standard of care therapies, and/or continued market acceptance of existing standard of care therapies. If these agents or standard of care therapies are not successful and available in the market, as the case may be, the development of PTI-801 will be hindered, delayed or not possible to complete or achieve.

We also depend on the success of our proprietary combination therapies, including a double and a triple combination, which are currently in early clinical development. We cannot be certain that we will be able to successfully complete the clinical development of, obtain regulatory approval for, or successfully commercialize these combinations. Combination therapies involve additional complexity and risk that could delay or cause our programs to stall or fail; development of such programs may be more costly, may take longer to achieve regulatory approval and may be associated with unanticipated adverse events.

Our business depends on the successful clinical development, regulatory approval and commercialization of combination therapies, including potential proprietary double and triple combinations that will require substantial additional clinical development and regulatory approval efforts before we are permitted to commence commercialization, if ever. The clinical trials and manufacturing and marketing of these combinations will be subject to extensive and rigorous review and regulation by numerous government authorities in the United States, the European Union and other jurisdictions where we intend to test and, if approved, market them. Before obtaining regulatory approvals for the commercial sale of any product candidate, we must demonstrate through preclinical testing and clinical trials that the product candidate is safe and effective for use in each target indication, and potentially in specific patient populations, including the pediatric population. This process can take many years and may include post-marketing studies and surveillance, which would require the expenditure of substantial resources beyond the proceeds we have currently raised. Of the large number of drugs in development for approval in the United States and the European Union, only a small percentage successfully complete the FDA or European Medicines Agency, or EMA, regulatory approval processes, as applicable, and are commercialized. Accordingly, even if we are able to obtain the requisite financing to continue to fund our research, development and clinical programs, we cannot assure you that our proprietary combination therapies or any of our other product candidates will be successfully developed or commercialized.

Clinical development and commercialization of combination therapies, such as our potential proprietary double and triple combinations, and our PTI-428 and PTI-801 candidates being tested in the clinic with patients taking background standard of care therapies, involve additional complexity and risk, including without limitation, those involving pre-clinical studies, drug-drug interactions, dose selection, unanticipated adverse events, clinical design and approvals of regulatory bodies and therapeutic development networks of patient advocacy groups. For example, if we or regulatory bodies identify concerns in pre-clinical combination toxicology studies, we may need to run additional studies before commencing or continuing clinical development. Combination therapy clinical development may also involve more restrictive inclusion criteria based on the profiles of multiple investigational products, which could delay enrollment. We have limited experience developing and commercializing combination therapies and are competing with industry players with greater resources than us. If we are unable to manage the additional complexities and risks of the development and commercialization of combination therapies, our proposed combination program could be delayed, halted or otherwise fail to receive approval.

The regulatory approval processes of the FDA and comparable foreign regulatory authorities are lengthy, time-consuming and inherently unpredictable. Agency requirements that differ from our assumptions or change can result in delays in starting, conducting and finishing clinical trials that are needed before we can apply for the next phase of development and, if successful, marketing approvals. If we are ultimately unable to obtain regulatory approval for PTI-428, PTI-801, PTI-808, our potential combination therapies, or our other product candidates, our business will be substantially harmed.

We are not permitted to market PTI-428, PTI-801, PTI-808, our potential combination therapies, or any of our other product candidates in the United States or the European Union until we receive approval of a New Drug Application, or NDA, from the FDA or a Marketing Authorization Application, or MAA, from the European Commission, respectively. Prior to submitting an NDA to the FDA or an MAA to the EMA for approval of any of our product candidates for a specific indication, we will need to complete preclinical and toxicology studies, as well as Phase 1, Phase 2 and Phase 3 clinical trials.

Successfully initiating and completing our clinical program and obtaining approval of an NDA or an MAA is a complex, lengthy, expensive and uncertain process, and the FDA, the EMA or other comparable foreign regulatory authorities may delay, limit or deny approval of any of our candidates for many reasons, including, among others:

- we may not be able to demonstrate that our product candidates are safe and effective to the satisfaction of the FDA or the EMA;
- the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA or the EMA for marketing approval;
- the FDA or the EMA may disagree with the number, design, size, conduct or implementation of our clinical trials or the requirements for or adequacy of the information and data needed to support the next phase of development (including, without limitation, Phase 3) for one or more of our product candidates, such as PTI-428, PTI-801 or our combination therapy candidates;
- the FDA or the EMA may require that we conduct additional clinical trials or cohorts or run cohorts sequentially, all of which could delay our trial completion timelines;
- the FDA or the EMA may not approve the formulation, labeling or specifications of PTI-428, PTI-801, PTI-808, or our other product candidates;
- the clinical research organizations, or CROs, that we retain to conduct our clinical trials may take actions outside of our control that materially adversely impact our clinical trials;
- the FDA or the EMA may find the data from preclinical studies and clinical trials insufficient to demonstrate that PTI-428, PTI-801, PTI-808, our potential combination therapies, and/or our other product candidates' clinical and other benefits outweigh their safety or other risks, including, without limitation, the potential for drug-drug interaction;
- the FDA or the EMA may disagree with our interpretation of data from our preclinical studies and clinical trials, including our characterization of observed toxicities;
- the FDA or the EMA may not accept data generated at our clinical trial sites;
- if our NDAs or MAAs, if and when submitted, are reviewed by the FDA or the EMA, as applicable, the regulatory agency may have difficulties scheduling the necessary review meetings in a timely manner, may recommend against approval of our application or may recommend that the FDA or the EMA, as applicable, require, as a condition of approval, additional preclinical studies or clinical trials, limitations on approved labeling or distribution and use restrictions;
- the FDA may require development of a Risk Evaluation and Mitigation Strategy as a condition of approval or post-approval, and the EMA may grant only conditional approval or impose specific obligations as a condition for marketing authorization, or may require us to conduct post-authorization safety studies;
- the FDA or the EMA may find deficiencies with or not approve the manufacturing processes or facilities of third-party manufacturers with which we contract; or
- the FDA or the EMA may change their approval policies or adopt new regulations.

Any of these factors, many of which are beyond our control, could jeopardize our ability to obtain regulatory approval for and successfully market PTI-428, PTI-801, PTI-808, our potential combination therapies, or any of our other product candidates. Any such setback in our pursuit of regulatory approval would have a material adverse effect on our business and prospects.

In addition to the United States and the European Union, we intend to market our product candidates, if approved, in other international markets. Such marketing will require separate regulatory approvals in each market and compliance with numerous and varying regulatory requirements. The approval procedures vary from country-to-country and may require additional testing. Moreover, the time required to obtain approval may differ from that required to obtain FDA or EMA approval. In addition, in many countries, a product candidate must be approved for reimbursement before it can be approved for sale in that country. Approval by the FDA or the EMA does not ensure approval 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 or the EMA. The regulatory approval process in other international markets may include all of the risks associated with obtaining FDA or EMA approval.

Our lead product candidates, PTI-428 and PTI-801, are designed to be administered with other CF therapies. Developing product candidates for administration with other therapies may lead to unforeseen side effects or failures in our clinical trials that could delay or prevent their regulatory approval or limit the commercial profile of an approved label. Such other therapies could also be removed from or supplanted in the market and result in significant negative consequences.

We are studying our lead product candidates PTI-428 and PTI-801 in clinical trials as a combination therapy with therapies that are approved and commercially available to the patients we plan to enroll in such clinical trials. We are also exploring proprietary combination therapies consisting of combinations of PTI-801 and PTI-808, as a double combination, and PTI-428, PTI-801 and PTI-808, as a triple combination. We anticipate that if one or more of our product candidates is approved for marketing, it will be approved to be administered only with other therapies. Our development programs and planned studies carry all the risks inherent in drug development activities, including the risk that they will fail to demonstrate meaningful efficacy or acceptable safety. In addition, our development programs are subject to additional regulatory, commercial, manufacturing and other risks because of the use of other therapies in combination with our product candidates. For example, the other therapies may lead to toxicities that are improperly attributed to our product candidates or the combination of our product candidates with other therapies may result in toxicities that the product candidate or other therapy does not produce when used alone. As these other therapies are not owned by us, we have less access to and information about them than if they were proprietary agents, which limits our understanding of these products. The other therapies we are using in combination may be removed from the market, or we may not be able to secure adequate quantities of such materials for which we have no guaranteed supply contract, and thus be unavailable for testing or commercial use with any of our approved products. The other therapies we may use in combination with our product candidates may be supplanted in the market by newer, safer and/or more efficacious products or combinations of products. For example, we have or are currently testing PTI-428 and PTI-801 in clinical trials where we provide our investigational product to CF patients stable on background therapy of ivacaftor and lumacaftor. The manufacturer of this background therapy has recently received marketing approval from the FDA to market ivacaftor and tezacaftor as Symdeko®, and is conducting testing of Symdeko's components together with additional corrector modulators as part of triple combinations, any of which, if approved, could supplant the existing therapy. Symdeko could supplant Orkambi as, or become its own independent, standard of care. Testing product candidates in combination with other therapies may increase the risk of significant adverse effects or test failures, or impact from drug-drug interactions. The timing, outcome and cost of developing products to be used in combination with other therapies is difficult to predict and dependent on a number of factors that are outside our reasonable control. If we experience safety or toxicity issues in our clinical trials or with any approved products, we may not receive approval to market any products, which could prevent us from ever generating revenues or achieving profitability.

If the data from our existing, ongoing and planned preclinical studies and clinical trials of PTI-428 and PTI-801 each as a combination therapy administered with ivacaftor and lumacaftor and/or as a combination therapy administered with ivacaftor and tezacaftor, and/or as part of a proprietary combination therapy, in each case regarding the safety or efficacy of these combinations are not favorable, the FDA and comparable foreign regulatory authorities may not approve these combination therapies and we may be forced to delay or terminate the development of any of these combination therapies, which would materially harm our business. Further, even if we gain marketing approvals for any of these combination therapies from the FDA and comparable foreign regulatory authorities in a timely manner, we cannot be certain that they will be commercially successful. If the results of the anticipated or actual timing of marketing approvals for these combination therapies, or the market acceptance of these combination therapies, if approved, including treatment reimbursement levels agreed to by third-party payors, do not meet the expectations of investors or public market analysts, the market price of our common stock would likely decline. Currently, some jurisdictions outside of the United States do not provide reimbursement for all or some of the standard of care therapies included in some of our combination therapies. Government and other third-party payors seek to contain costs of health care through legislative and other means. If they fail to provide coverage and adequate reimbursement rates for these products, it could increase the cost of our trials in such jurisdictions and decrease the possible market for any approved combination therapy that includes these co-administered drugs.

Failures or delays in the commencement, progress or completion of our clinical trials of our product candidates, including PTI-428, PTI-801 and PTI-808, and our proprietary combination therapy candidates, including due to competition from competing trials for CF patients, amended or additional trials or cohorts, lack of sufficient approvals including from the FDA, local regulatory and ethics bodies and those of therapeutic development networks of patient advocacy groups, or trial holds or stoppage due to interim results or safety concerns, could result in increased costs to us and could delay, prevent or limit our ability to generate clinical trial data, advance our product candidates in the clinic, submit an NDA (or foreign equivalent) for any of our product candidates for U.S. or foreign marketing approval, derive revenue and continue our business.

Successful completion of the clinical trials for PTI-428, PTI-801, PTI-808, our proprietary combination therapy candidates, and our other candidates is a prerequisite to submitting an NDA to the FDA or a MAA to the EMA and, consequently, the ultimate approval and commercial marketing of PTI-428, PTI-801, PTI-808, our proprietary combination therapy candidates, and our other candidates in the United States and the European Union. Similar prerequisites apply in other foreign jurisdictions and for all of our product candidates in any jurisdiction. Clinical trials are expensive, difficult to design and implement, can take many years to complete and are uncertain as to outcome. A product candidate can unexpectedly fail at any stage of clinical development. The historical failure rate for product candidates is high due to scientific feasibility, safety, tolerability, toxicology, efficacy, changing standards of medical care and other variables. If the FDA requires us to complete, or we choose to implement, amended or additional studies beyond what we currently expect or assume, or to run additional cohorts or conduct cohorts sequentially, we may be delayed in completing our clinical trials and our expenses will increase. Conducting our trials in Europe and other ex-U.S. jurisdictions has and will continue to require IND-equivalent submissions to, and the approval of, local regulatory and ethics bodies, and we cannot assure you we will receive these approvals, or receive them in a timely manner. If therapeutic development networks of CF patient advocacy groups in the United States and/or other jurisdictions such as Europe do not timely sanction or highly rate or score our trials, or prioritize trials of other sponsors over our trials, we may not be able to enroll sufficient patients to conduct our trials at their member sites, or it may take longer to conduct these trials and we may need to look to other jurisdictions where we can more efficiently run our trials. Many CF clinical trial sites place importance on the review, ranking and sanctioning of therapeutic development networks of CF patient advocacy groups. In the U.S., we believe many sites consider sanctioning from the Protocol Review Committee, or PRC, of the Therapeutic Development Network of the U.S.-based Cystic Fibrosis Foundation, or the TDN, when deciding whether and when to participate in a trial or which trials to prioritize. For example, the TDN deferred sanctioning of PTI-428, which we believe contributed to a delay in our now completed PTI-428 Phase 2 trial. There is also a large number of CF programs in clinical development at this time, including numerous corrector and combination trials from Vertex, including, without limitation, Vertex's Phase 3 triple combination studies with CF patients on Symdeko therapy taking an additional Vertex investigational corrector, and other companies with greater resources and experience than us. We face intense competition for eligible CF patients, which has and could continue to hamper our recruitment efforts. We do not know whether all of our clinical trials will begin or be completed on schedule, if at all, as the commencement and completion of clinical trials can be delayed or prevented for a number of reasons, including, among others:

- delays in reaching or failing to reach agreement on acceptable terms with prospective CROs and trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- inadequate quantity or quality of or access to a product candidate or other materials, such as combination therapies for co-administration in our trials that are marketed by other firms, necessary to conduct clinical trials;
- difficulties obtaining institutional review board, or IRB, or ethics committee approval to conduct a clinical trial at a prospective site or sites;
- challenges in recruiting and enrolling patients to participate in clinical trials, including the size and nature of the patient population, the proximity of patients to clinical sites (including, without limitation, if U.S. trial sites include international subjects coming to the U.S. on a visa), eligibility criteria for the clinical trial, screen failures, the nature of the clinical trial protocol (including, without limitation, patient factors such as the time commitment involved in the required number of trial-related visits and procedures and the inability to take certain existing therapies during the trial), risks included in the signed informed consent and any new or amended consents required by each study participant, the availability of approved effective treatments for the relevant disease and competition from other clinical trial programs for similar indications;
- unfavorable review of or a decision to defer sanctioning or not to sanction one or more of our clinical trials by the TDN, or the CTN, each of which may not sanction our trials for conduct at prospective trial sites, may change or alter any approval it may grant, or may provide a ranking or revised ranking of an amended protocol that adversely impacts recruitment in our clinical trials compared with other investigational new drugs in CF; while the TDN approved and favorably ranked our triple combination (for PTI-428, PTI-801 and PTI-808), double combination (for PTI-801 and PTI-808), PTI-801 protocols as well as our PTI-428 and PTI-801 trials in patients on background Symdeko, we cannot assure you that it will sanction any of our other trials; the CTN has approved and favorably ranked the protocols for our PTI-428, PTI-801 and triple combination trials and we are actively working to continue to expand into Europe with its member sites, subject to regulatory and ethics approvals in local jurisdictions, but we cannot assure you that such expansion will be successful;

- severe or unexpected drug-related side effects experienced by patients in our clinical trials or by individuals using drugs similar to our product candidates;
- reports from preclinical or clinical testing of other similar therapies that raise safety or efficacy concerns; or
- difficulties retaining and/or obtaining data from patients who have enrolled in a clinical trial but may be prone to withdraw due to lack of efficacy, side effects, personal issues, loss of interest, difficulty travelling to the trial site or returning for required check-ins, or other factors, some of which are out of our control.

There are an unprecedented number of CF clinical trials ongoing in the United States and in other countries. As a result of this and other factors described above, the activation of clinical trial sites for our ongoing trials, and securing our target subject enrollment for these clinical trials, has been delayed from what we had originally planned. If we are unable to increase our enrollment, we will not have a substantially complete data set for these trials by our target dates.

We expanded our clinical trial protocols for PTI-428, PTI-801 and PTI-808 to include CF patients. These expansions required protocol amendments to our INDs that are in effect with the FDA, which are subject to FDA comment. We are required to receive IRB approval for these amended protocols but there is no guarantee that IRBs of our existing and prospective clinical trial sites will approve these expansions. Any failure or delay in obtaining necessary permissions from the relevant IRBs to expand our trials may delay their completion and our overall development plan.

Clinical trials may also be delayed or terminated as a result of ambiguous or negative interim results. In addition, a clinical trial may be suspended, placed on clinical hold or terminated by us, the FDA, other regulatory authorities or the IRBs at the sites where the IRBs are overseeing a clinical trial, or a data safety monitoring board, or DSMB, may recommend that the sponsor suspend or terminate a trial, due to a number of factors, including, among others:

- failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols;
- inspection of the clinical trial operations or trial sites by the FDA, the EMA or other regulatory authorities that reveals deficiencies or violations that require us to undertake corrective action, including the imposition of a clinical hold;
- unforeseen safety issues, including any that could be identified in our ongoing toxicology studies, adverse side effects or lack of effectiveness, including as part of ambiguous or negative interim results;
- changes in government regulations or administrative actions;
- problems with clinical supply materials; and
- lack of adequate funding to continue the clinical trial.

Positive results from preclinical or in vitro and in vivo testing of PTI-428, PTI-801, PTI-808, our proprietary combination therapy candidates, or our other candidates are not necessarily predictive of the results of our ongoing and future clinical trials of these candidates. If we cannot achieve positive results in our clinical trials for PTI-428, PTI-801, PTI-808, our proprietary combination therapy candidates, or our other candidates, we may be unable to successfully develop, obtain regulatory approval for and commercialize PTI-428, PTI-801, PTI-808, our proprietary combination therapy candidates, or our other candidates.

Positive results from our preclinical testing of PTI-428, PTI-801, PTI-808, our proprietary combination therapy candidates, and our other candidates in vitro and in vivo may not necessarily be predictive of the results from our clinical trials in humans (including, without limitation, as part of any predicted correlation between in vitro CFTR protein activity as measured by an Ussing Chamber Assay and lung function improvement measured by FEV_1 improvement in clinical trials). Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical trials after achieving positive results in preclinical in vitro and in vivo studies, and we, or the third parties whose drug candidates we expect to be co-administered with PTI-428 and PTI-801, may face similar setbacks. For example, CFTR mRNA levels in target tissues of rats and monkeys exposed to PTI-428 were observed to increase proportionally with exposure to PTI-428. Additionally, preliminary exploratory biomarker nasal CFTR mRNA and protein data from the SAD and MAD cohorts in our Phase 1 clinical trial for PTI-428 in healthy volunteers confirm target engagement. However, later clinical trials may not show that this biomarker is predictive of clinical efficacy or we may not be able to successfully obtain sufficient biomarker data to analyze. Preclinical and clinical data are often susceptible to varying interpretations and analyses, and the FDA or other regulatory agencies may require changes to our protocols or other aspects of our clinical trials or require additional studies. Additionally, many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials nonetheless failed to obtain FDA or EMA approval. If we fail to produce positive results in our clinical trials of one or more of our product candidates, the development timeline and regulatory approval and commercialization prospects for those product candidates, and, correspondingly, our business and financial prospects, would be materially adversely affected. These risks could also impair our ability to successfully commence, progress or complete studies of our proprietary combination therapy candidates.

Even if we obtain positive clinical results for PTI-428 or PTI-801 or our proprietary combination therapy candidates in early-stage clinical trials (including, without limitation, those involving a relatively short duration in a small number of subjects, with the publication of interim, initial, preliminary or final results), those positive results may not be repeated in later-stage clinical trials.

Before obtaining regulatory approval for the sale of our product candidates, including PTI-428, PTI-801, and any proprietary combination therapy candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Successful completion of such clinical trials is a prerequisite to submitting an NDA to the FDA and, consequently, the ultimate approval and commercial marketing of PTI-428 and PTI-801 and any proprietary combination therapy candidates in the United States. Similar requirements apply in the European Union and other foreign jurisdictions. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and preliminary, initial or interim results of a clinical trial do not necessarily predict final results. Our current CF trials involve relatively short duration in a small number of patients, resulting in limited data sets. From time to time, we may publish or report interim, initial or preliminary data from our clinical trials. Interim, initial or preliminary data from clinical trials that we may conduct may not be indicative of the final results of the trial and are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Interim, initial or preliminary data also remain subject to audit and verification procedures that may result in the final data being materially different from the interim, initial or preliminary data. We may also experience delays in analyzing or an inability to analyze samples, including, without limitation, biomarker data, due to insufficient sample size, errors in collection procedures at one or more sites, or other factors. As a result, interim, initial or preliminary data should be viewed with caution until the final data are available.

Negative or inconclusive results of our clinical trials of PTI-428 or PTI-801, any proprietary combination therapy candidates, or any other clinical trials we conduct, could mandate repeated or additional clinical studies. We do not know whether our clinical trials of any product candidate will demonstrate adequate efficacy and safety to result in regulatory approval to market such product candidate. Even if early-stage clinical results are favorable, if later-stage clinical trials (including, without limitation, those for longer duration with greater numbers of patients) do not produce favorable results, our ability to obtain regulatory approval for our product candidates, including PTI-428 and PTI-801, and any proprietary combination therapy candidates, may be adversely impacted.

Our product candidates may cause adverse effects or have other properties that could delay or prevent their regulatory approval or limit the scope of any approved label or market acceptance.

Undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in the denial of regulatory approval by the FDA or other comparable foreign regulatory authorities. It is possible that, during the course of the development of PTI-428, PTI-801, our proprietary combination therapy candidates, or our other product candidates, results of our studies and clinical trials could reveal an unacceptable severity and prevalence of side effects and/or drug-drug interactions. For example, in preclinical testing of PTI-428 we observed reduced platelet counts in the animals we tested following administration at doses in excess of the doses we expect to administer in our clinical trials. As a result of this or any other side effects, our clinical trials could be suspended or terminated and the FDA or comparable foreign regulatory authorities could order us to cease further development, or deny approval, of our product candidates for any or all targeted indications. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims or result in delays in the trials due to requirements to provide new informed consents to patients to disclose new or changed risks or side effects. Even if approved for marketing, our product candidates could face label restrictions based on the above factors or others.

Additionally, if one or more of our product candidates receive marketing approval, and we or others later identify undesirable side effects caused by such products, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw approvals of such product or impose restrictions on its distribution in a form of a modified Risk Evaluation and Mitigation Strategy;
- regulatory authorities may require additional labeling, such as warnings or contraindications;
- we may be required to change the way the product is administered or to conduct additional clinical studies;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could delay or prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, results of operations and prospects.

If we cannot demonstrate an acceptable safety and toxicity profile for our product candidates in our clinical studies, we will not be able to continue our clinical trials or obtain approval for our product candidates.

In order to obtain approval of a product candidate, we must demonstrate safety in various nonclinical and clinical tests. At the time of initiating human clinical trials, we may not have conducted or may not conduct the types of nonclinical testing ultimately required by regulatory authorities, or future nonclinical tests may indicate that our product candidates are not safe for use. Nonclinical testing and clinical testing are both expensive and time-consuming and have uncertain outcomes. For example, results of an earlier laboratory study of PTI-130, a former amplifier candidate, in non-rodent species suggested potential hematologic and reproductive toxicology issues that we believe are specific to the non-rodent species. We cannot predict whether future safety and toxicology studies may produce these same problems or cause other undesirable effects. We also observed certain undesired hematological (including reduced platelet count) side effects in animals dosed at levels of PTI-428 that are higher than those intended for our clinical studies. We plan to complete additional toxicity studies of reproductive toxicity, carcinogenicity and long-term side effects prior to or concurrent with any Phase 3 clinical trials of our product candidates, and we cannot exclude the possible occurrence of these or other side effects in future nonclinical or clinical studies. In addition, success in initial tests does not ensure that later testing will be successful. We may experience numerous unforeseen events during, or as a result of, the testing process, which could delay or prevent our ability to develop or commercialize our product candidates, including:

- our preclinical and nonclinical testing may produce inconclusive or negative safety results, which may require us to conduct additional nonclinical testing or to abandon product candidates;
- our product candidates may have unfavorable pharmacology or toxicity characteristics or suggest possible drug-drug interaction;
- our product candidates may cause undesirable side effects; and
- the FDA or other regulatory authorities may determine that additional safety testing is required.

Any such events would increase our costs and could delay or prevent our ability to commercialize our product candidates, which could adversely impact our business, financial condition and results of operations.

PTI-428 is based on a novel technology, which may raise development issues we may not be able to resolve, regulatory issues that could delay or prevent approval, or personnel issues that may keep us from being able to develop our product candidates.

Our product candidate PTI-428 is based on our novel amplifier technology. We are not aware of other drugs that work in a manner that we believe our amplifier technology does. We cannot assure you that development problems related to our novel technology will not arise in the future that could cause significant delays or that we are not able to resolve.

Clinical development and regulatory approval of novel product candidates such as ours can be more expensive and take longer than other, more well-known or extensively studied pharmaceutical product candidates due to our, investigators' and regulatory agencies' lack of experience with them. These factors also apply to patient advocacy groups and sanctioning by their affiliated therapeutic development center arms, such as the TDN. To our knowledge, there are no other amplifiers in clinical development and none have been approved to date. The novelty of our technology may lengthen the clinical development timeline and regulatory review process, require us to conduct additional studies or clinical trials, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our product candidates or lead to significant post-approval limitations or restrictions. For example, the FDA could require additional studies or characterization that may be difficult or impossible to perform.

In addition, if we are unable to hire and retain the necessary personnel, the rate and success at which we can develop and commercialize product candidates will be limited. Any such events would increase our costs and could delay or prevent our ability to commercialize our product candidates, which could adversely impact our business, financial condition and results of operations.

Even if we meet safety and efficacy endpoints in clinical trials, we cannot predict whether or when we will obtain regulatory approval to commercialize our product candidates and we cannot, therefore, predict the timing of any future revenue from PTI-428, PTI-801, our proprietary combination therapy candidates or any of our other product candidates.

We cannot commercialize our product candidates, including PTI-428, PTI-801, and our proprietary combination therapy candidates, until the appropriate regulatory authorities, such as the FDA, have reviewed and approved the product candidate. The regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval for PTI-428, PTI-801, proprietary combination therapy candidates, or our other product candidates at all. Additional delays may result if PTI-428, PTI-801, proprietary combination therapy candidates, or any other product candidate is brought before an FDA advisory committee or an analogous foreign body, which could recommend restrictions on approval or recommend non-approval of the product candidate. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or

administrative action, or changes in regulatory agency policy during the period of product development, clinical studies and the review process. As a result, we cannot predict when, if at all, we will receive any future revenue from commercialization of any of our product candidates, including PTI-428, PTI-801, and proprietary combination therapy candidates.

Even if we obtain regulatory approval for PTI-428, PTI-801, our proprietary combination therapy candidates and/or our other product candidates, we will still face extensive regulatory requirements and our products may face future development and regulatory difficulties.

Even if we obtain regulatory approval in the United States, the FDA may still impose significant restrictions on the indicated uses or marketing of our product candidates, including PTI-428 and PTI-801 and our proprietary combination therapy candidates, or impose ongoing requirements for potentially costly post-approval studies or post-market surveillance, including Phase 4 clinical trials. For example, the labeling, if approved for our product candidates, including PTI-428 and PTI-801 and our proprietary combination therapy candidates, will likely include restrictions on use due to the specific patient population and manner of use in which the drug was evaluated and the safety and efficacy data obtained in those evaluations.

PTI-428, PTI-801, our proprietary combination therapy candidates and our other product candidates will also be subject to additional ongoing FDA requirements governing the labeling, packaging, storage, distribution, safety surveillance, advertising, promotion, record-keeping and reporting of safety and other post-market information. The holder of an approved NDA is obligated to monitor and report adverse events and any failure of a product to meet the specifications described in the NDA. The holder of an approved NDA must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

In addition, manufacturers of drug products and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with current good manufacturing practice, or cGMP, requirements and adherence to commitments made in the NDA. If we, or a regulatory agency, discover previously unknown problems with a product, such as quality issues or adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions relative to that product or the manufacturing facility, including requesting a recall or requiring withdrawal of the product from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following approval of our product candidate, a regulatory agency may:

- issue an untitled or warning letter asserting that we are in violation of the law;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending NDA or supplements to an NDA submitted by us; or
- request a recall and/or seize product.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize PTI-428, PTI-801, our proprietary combination therapy candidates and our other product candidates and inhibit our ability to generate revenues.

Even if we obtain FDA approval for PTI-428, PTI-801, our proprietary combination therapy candidates or any of our other product candidates in the United States, we may never obtain approval for or commercialize PTI-428, PTI-801, our proprietary combination therapy candidates or any of our other product candidates outside of the United States, which would limit our ability to realize their full market potential.

In order to market any products outside of the United States, we must establish and comply with numerous and varying regulatory requirements on a country-by-country basis regarding safety and efficacy. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions. In addition, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not guarantee regulatory approval in any other country. Approval processes vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking foreign regulatory approval could result in difficulties and costs for us and require additional preclinical studies or clinical trials which could be costly and time consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our product candidates in those countries. We do not have any product

candidates approved for sale in any jurisdiction, including international markets, and we do not have experience in obtaining regulatory approval in international markets. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, or if regulatory approvals in international markets are delayed, our target market will be reduced and our ability to realize the full market potential of our product candidates will be unrealized.

If we are not able to obtain orphan product status for PTI-801, PTI-808 or other current product candidates (or maintain orphan drug designation for PTI-428) or obtain such status for future product candidates for which we seek this status, we will not be able to claim the tax credits for our clinical trials of such products provided by this status or potentially take advantage of other benefits of orphan drug status.

Regulatory authorities in some jurisdictions, including the United States and the European Union, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product as an orphan drug if it is a drug intended to treat a rare disease or condition, which is generally defined as a disease or condition that fewer than 200,000 individuals in the United States have been diagnosed as having at the time of the submission of the request for orphan drug designation. Under Regulation No. (EC) 141/2000 on Orphan Medicinal Products, a medicinal product may be designated as an orphan medicinal product if, among other things, it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 people in the European Union when the application is made. Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of market exclusivity. This exclusivity precludes the EMA or the FDA, as applicable, from approving another marketing application for the same or, in the European Union, a similar drug for the same indication for that time period, unless, among other things, the later product is clinically superior. The exclusivity period is seven years in the United States and ten years in the European Union following marketing approval. The EU exclusivity period can be reduced to six years if a drug no longer meets the criteria for orphan drug designation, for example if the drug is sufficiently profitable so that market exclusivity is no longer justified.

In the United States, orphan drug exclusivity may be lost if the FDA withdraws or revokes the orphan-drug designation as permitted by law, we withdraw the marketing application for the drug, we consent to another's marketing application for approval of the same use or indication as the designated orphan drug, or we fail to assure a sufficient quantity of the drug as required by law. Similarly, in the European Union, exclusivity may be lost if we request the removal of the orphan-drug designation or the drug no longer meets any of the criteria that made it eligible for orphan-drug status at the outset. Even after an orphan drug is approved, the same or, in the European Union, a similar drug can subsequently be approved for the same condition if the competent regulatory agency concludes that the later drug is clinically superior to the original orphan drug by providing a significant therapeutic advantage over and above that drug.

If we do not obtain orphan drug exclusivity or if our competitors obtain orphan drug exclusivity for other rare diseases or conditions we are targeting before we do, we may be delayed in obtaining marketing authorization or we may lose out on the potential benefits of market exclusivity associated with the orphan drug designation. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the NDA application user fee. If we do not obtain orphan designation for PTI-801 or our other product candidates (and maintain such designation as to PTI-428), we will lose out on such benefits associated with orphan designation.

Use of social media platforms presents new risks.

Social media increasingly is being used to communicate about our product candidates and the diseases our therapies are designed to treat. We believe that members of the CF community may be more active on social media as compared to other patient populations. Social media practices in the pharmaceutical and biotechnology industries are evolving, which creates uncertainty and risk of noncompliance with regulations applicable to our business. For example, patients may use social media platforms to comment on the effectiveness of, or adverse experiences with, a drug candidate, which could result in reporting obligations. In addition, there is a risk of inappropriate disclosure of sensitive information or negative or inaccurate posts or comments about us on any social networking website. If any of these events were to occur or we otherwise fail to comply with applicable regulations, we could incur liability, face restrictive regulatory actions or incur other harm to our business.

Risks Relating to Our Dependence on Third Parties

If third parties on which we depend to conduct our preclinical studies or any ongoing or future clinical trials do not perform as contractually required, fail to satisfy regulatory or legal requirements or miss expected deadlines, our development program could be delayed with materially adverse effects on our business and prospects.

We rely on clinical research organizations, clinical data management organizations and consultants, collectively referred to as CROs, to design, conduct, supervise and monitor preclinical and clinical studies of our product candidates and plan to do the same for our ongoing and future clinical trials for PTI-428, PTI-801, PTI-808, proprietary combination therapy candidates and any other clinical trials. We and our CROs are required to comply with various regulations, including Good Clinical Practice, or GCP, requirements, which are enforced by the FDA, and guidelines of the Competent Authorities of the Member States of the European Economic Area, and comparable foreign regulatory authorities to ensure that the health, safety and rights of patients are protected in clinical development and clinical trials, and that trial data integrity is assured. Regulatory authorities ensure compliance with these requirements through periodic inspections of trial sponsors, principal investigators and trial sites, as well as third party contractors. If we or any of our CROs fail to comply with applicable requirements, or the CRO does not perform its contractually required obligations (or makes errors or mistakes), the clinical data, including, without limitation, biomarker data, generated in our clinical trials may not be collected or may be collected but be deemed unreliable, and the FDA, the EMA or other comparable foreign regulatory authorities may require us (or we may choose ourselves) to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with such requirements. In addition, our clinical trials must be conducted with products produced under cGMP requirements, which mandate the methods, facilities and controls used in manufacturing, processing and packaging of a drug product to ensure its safety and identity. Failure to comply with these regulations may require us to delay or repeat preclinical and clinical trials, which would delay the regulatory approval process.

Our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our ongoing clinical and preclinical programs. We generally represent a small percentage of these firms' overall business, which could limit our ability to receive priority allocation of their resources. If CROs do not successfully carry out their contractual duties or obligations or 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, regulatory requirements or for 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 our product candidates. As a result, our operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed.

We also rely on clinical investigators and clinical research organizations, as well as therapeutics development arms of patient advocacy groups, such as the TDN and CTN, to assist in the design and review of our clinical trials, including supporting the enrollment of qualified patients. If these third parties do not approve or sanction our trial protocols to facilitate enrollment, our ability to conduct clinical trials may be impeded. Because we have relied on third parties, our internal capacity to perform these functions is limited. Outsourcing these functions involves risk that third parties may not perform to our standards, may not produce results in a timely manner or may fail to perform at all. In addition, the use of third-party service providers requires us to disclose our proprietary information to these parties, which could increase the risk that this information will be misappropriated or inadvertently be made publicly-available. We currently have a small number of employees, which limits the internal resources we have available to identify and monitor our third-party providers. To the extent we are unable to identify and successfully manage the performance of third-party service providers in the future, our business may be adversely affected. Though we carefully manage our relationships with our CROs, and other third parties, there can be no assurance that we will not encounter similar 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.

If we cannot contract with acceptable third parties on commercially reasonable terms, or at all, or if these third parties do not carry out their contractual duties, satisfy legal and regulatory requirements for the conduct of preclinical studies or clinical trials or meet expected deadlines, our clinical development programs could be delayed and otherwise adversely affected. In all events, we are responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. The FDA and the EMA require clinical trials to be conducted in accordance with GCP, including for conducting, recording and reporting the results of preclinical studies and clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. Any such event could have a material adverse effect on our business, financial condition, results of operations and prospects.

We rely on third-party manufacturers and suppliers and we intend to rely on third parties to produce preclinical, clinical and commercial supplies of PTI-428, PTI-801, PTI-808 and any future product candidates. These third parties may not perform as contractually required or expected and issues may arise that could delay the commencement or completion of clinical trials.

We rely on third parties to supply the materials and components for our research and development, preclinical and clinical trial supplies. We do not own manufacturing facilities or supply sources for such components and materials. There can be no assurance that our supply of research and development, preclinical and clinical development drugs and other materials will not be limited, interrupted, restricted in certain geographic regions or of satisfactory quality or continue to be available at acceptable prices. Any replacement of these third parties could require significant effort and expertise because there may be a limited number of qualified replacements.

The manufacturing process for a product candidate is subject to FDA, EMA and other foreign regulatory authority review. Suppliers and manufacturers must meet applicable manufacturing requirements and undergo rigorous facility and process validation tests required by regulatory authorities to comply with regulatory standards such as cGMP. In the event that any of our suppliers or manufacturers fails to comply with such requirements or to perform its obligations to us in relation to quality, timing or otherwise, or if our supply of components or other materials becomes limited or interrupted for other reasons, our regulatory filings may be delayed, our preclinical studies or clinical trials may be delayed or suspended, and we may be forced to manufacture the materials ourselves, for which we currently do not have the capabilities or resources, or enter into an agreement with another third party, which we may not be able to do on reasonable terms, if at all. In some cases, the technical skills or technology required to manufacture our product candidates may be unique or proprietary to the original manufacturer and we may have difficulty, or there may be contractual restrictions prohibiting us from, transferring such skills or technology to another third party and a feasible alternative may not exist; even if it exists, it may be cost-prohibitive and time-prohibitive to engage in technology transfer to switch vendors for drug substance and/or product candidate manufacturing. These factors would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third party manufacture our drug substance and/or product candidates. If we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. The delays associated with the verification of a new manufacturer could negatively affect our ability to develop product candidates in a timely manner or within budget. Drug formulation is an inherently uncertain process with numerous steps, some of which may need to be repeated, to ensure quality, accuracy and yield; unexpected variances may occur, which could delay our manufacturing efforts and delay commencement or completion of pre-clinical studies and/or clinical trials.

We expect to continue to rely on third-party manufacturers if we receive regulatory approval for any product candidate. To the extent that we have existing, or enter into future, manufacturing arrangements with third parties, we will depend on these third parties to perform their obligations in a timely manner consistent with contractual and regulatory requirements, including those related to quality control and assurance. If we are unable to obtain or maintain third-party manufacturing for product candidates, or to do so on commercially reasonable terms, we may not be able to develop and commercialize our product candidates successfully. Our or a third party's failure to execute on our manufacturing requirements could adversely affect our business in a number of ways, including:

- preventing us from initiating or continuing preclinical studies or clinical trials of product candidates under development;
- delaying our trials and/or delaying submissions of regulatory applications or receipt of regulatory approvals for product candidates;
- preventing a collaborator from cooperating with us;
- subjecting our product candidates to additional inspections by regulatory authorities;
- requiring us to cease distribution or to recall batches of our product candidates; and
- in the event of approval to market and commercialize a product candidate, preventing us from meeting commercial demands for our products.

If a current or future collaborative partner terminates or fails to perform its obligations under an agreement with us, or if research does not produce viable lead candidates or meet specified criteria during the applicable research term, the development and commercialization of the product candidates could be delayed or terminated.

We are currently party to a collaborative arrangement with Astellas. If our collaborative partner does not devote sufficient time and resources to a collaboration arrangement with us, we may not realize the potential commercial benefits of the arrangement, and our results of operations may be materially adversely affected.

Much of the potential revenue from our collaboration consists of contingent payments, such as payments for achieving scientific or regulatory milestones or royalties payable on sales of drugs. The milestone and royalty revenue that we may receive under collaborations will depend upon our collaborators' ability to successfully develop, introduce, market and sell new products. Our collaboration partners may fail to develop or effectively commercialize their products using our products or technologies or otherwise discontinue their research activities because they:

- exercise their unilateral right to terminate the collaboration agreement, which, for example, our former collaboration partner, Biogen, did in December 2016, including, without limitation, if research does not produce a viable lead candidate or meet specified criteria during the applicable research term;
- decide not to devote the necessary resources due to internal constraints, such as limited personnel with the requisite expertise, limited cash resources or specialized equipment limitations, or the belief that other drug development programs may have a higher likelihood of obtaining marketing approval or may potentially generate a greater return on investment;
- decide to pursue other technologies or develop other product candidates, either on their own or in collaboration with others, including our competitors, to treat the same diseases targeted by our own collaborative programs;
- do not have sufficient resources necessary to carry the product candidate through clinical development, marketing approval and commercialization; or
- cannot obtain the necessary marketing approvals.

Competition may negatively impact a partner's focus on and commitment to our relationship and, as a result, could delay or otherwise negatively affect the commercialization of our products, which would have a material adverse effect on our operating results and financial condition. Terminated collaborations include the risk that the former partner maintains rights to exploit certain co-developed technology, and the risk that, to the extent the program is desired to continue, funding formerly provided by the partner will need to come from alternative sources such as us or a new partner and such funding may not be available on terms acceptable to us, if at all. These factors can cause a delay or abandonment of technology programs and could negatively affect commercialization of our products, which would have a material adverse effect on our operating results and financial condition.

We face a number of challenges in seeking future collaborations. Collaborations are complex and any potential discussions may not result in a definitive agreement for many reasons. For example, whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration, and the proposed collaborator's evaluation of a number of factors, such as the design or results of our clinical trials, the potential market for our product candidates, the costs and complexities of manufacturing and delivering our product candidates to patients, the potential of competing products, the existence of uncertainty with respect to ownership or the coverage of our intellectual property, and industry and market conditions generally. If we determine that additional collaborations for our product candidates are necessary and are unable to enter into such collaborations on acceptable terms, we might elect to delay or scale back the development or commercialization of our product candidates in order to preserve our financial resources or to allow us adequate time to develop the required physical resources and systems and expertise ourselves.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner, or at all. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. If a current or future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program could be delayed, diminished or terminated.

Risks Relating to Commercialization of Our Product Candidates

The commercial success of PTI-428, PTI-801, any proprietary combination therapy candidates and our other product candidates will depend upon the acceptance of those products, if approved, by the medical community, including physicians, patients and health care payors.

Even if PTI-428, PTI-801, any proprietary combination therapy candidates or our other product candidates are approved for sale, they may not achieve sufficient market acceptance by physicians, patients, healthcare payors and others in the medical community. If these product candidates, if approved, do not achieve an adequate level of acceptance, we may not generate significant product revenues and we may not become profitable. The degree of market acceptance of any of our product candidates, including PTI-428 and PTI-801 and any proprietary combination therapy candidates, will depend on a number of factors, including:

- demonstration of safety and efficacy in our clinical trials and in any post-marketing studies;
- the relative convenience, ease of administration and acceptance by physicians, patients and health care payors;
- the prevalence and severity of any adverse effects;
- limitations or warnings contained in the FDA-approved label for the relevant product candidate;
- availability of alternative treatments;
- pricing and cost-effectiveness;
- the effectiveness of our or any future collaborators' sales and marketing strategies; and
- our ability to obtain and maintain healthcare payor approval or reimbursement, which may vary from country to country and within a country.

If any of our product candidates, including PTI-428 and PTI-801 and any proprietary combination therapy candidates, is approved but does not achieve an adequate level of acceptance by physicians, patients and health care payors, we may not generate sufficient revenue and we may not become or remain profitable.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to sell and market our product candidates, we may not be successful in commercializing our product candidates if and when they are approved.

We do not have a sales or marketing infrastructure, and we have limited experience in the sales, marketing or distribution of pharmaceutical products. Our commercialization strategy will target key prescribing physicians and advocacy groups, as well as provide patients with support programs, and seek to ensure product access and secure reimbursement. Outside of the United States, Canada, Europe and Australia, we may seek a partner to commercialize our products. In the future, we may choose to build a focused sales and marketing infrastructure to market or co-promote our product candidates if and when they are approved, which would be expensive and time-consuming. Alternatively, we may elect to outsource these functions to third parties. Either approach carries significant risks. For example, recruiting and training a sales force is expensive and time-consuming and, if done improperly, could delay a product launch and result in limited sales. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our product candidates on our own include:

- inability to recruit, manage and retain adequate numbers of effective sales and marketing personnel;
- the inability of marketing personnel to develop effective marketing materials;
- the inability of sales personnel to obtain access to or persuade adequate numbers of physicians to prescribe any future products;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

We may also not be successful in entering into additional arrangements with third parties to sell and market our product candidates or doing so on terms that are favorable to us. Even if we do enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenues or the profitability of these product candidates are likely to be lower than if we were to market and sell our products ourselves. In addition, we likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

If our competitors develop technologies or product candidates more rapidly than we do or their technologies are more effective, our ability to develop and successfully commercialize our products may be adversely affected. Competitive products for treatment of CF may reduce or eliminate the commercial opportunity for our product candidates.

The clinical and commercial landscape for CF is highly competitive and subject to rapid and significant technological change. New data from clinical-stage products continue to emerge. It is possible that these data may alter the current standard of care, completely precluding us from further developing PTI-428, PTI-801, our proprietary combination therapy candidates or our other product candidates for CF. Further, it is possible that we may advance our clinical trials only to find that data from competing products make it impossible for us to complete enrollment in these trials, resulting in our inability to file for marketing approval with regulatory agencies. Even if PTI-428, PTI-801, proprietary combination therapy candidates or our other product candidates are approved for marketing, they may have limited sales due to particularly intense competition in the CF market.

Competitive therapeutic treatments include those that are currently in development and any new treatments that enter the market. We believe that a significant number of products are currently under development, and may become commercially available in the future, for the treatment of conditions for which we may try to develop product candidates. Our potential competitors include large pharmaceutical and biotechnology companies, specialty pha rmaceutical and generic drug companies, academic institutions, government agencies and research institutions. Examples include Vertex, AbbVie Inc., Galapagos NV, ProQR Therapeutics N.V., Flatley Discovery Lab, LLC, F. Hoffmann-LaRoche Ltd., Novartis AG, Gilead Sciences, Inc., Laurent Pharmaceuticals Inc., Pfizer Inc., AstraZeneca, Translate Bio Inc., Sanofi Genzyme, Bayer AG, Corbus Pharmaceuticals Holdings, Inc., Eloxx Pharmaceuticals, Verona Pharma plc, Spyryx Biosciences Inc., Talee Bio, and several other companies.

Although PTI-428 and PTI-801 are being developed as individual therapies to be administered with ivacaftor and lumacaftor, Vertex or other competitors could develop other drugs or combinations that may obviate the applicability of PTI-428 and PTI-801. Changes in standard of care or use patterns could also make our combination therapy obsolete. For example, Vertex has developed tezacaftor and ivacaftor as a combination therapy on its own and was recently granted marketing approval for this combination under the name Symdeko. While we are conducting studies of PTI-428 and PTI-801, each to be administered with ivacaftor and tezacaftor, Vertex is also in clinical development and is in Phase 3 for several combinations of ivacaftor and tezacaftor as part of potential triple combination therapies that add an additional Vertex corrector to that combination. If PTI-428 or PTI-801 is approved for marketing as a combination therapy to be administered with ivacaftor and lumacaftor but use of another therapy becomes more prevalent than ivacaftor and lumacaftor, the availability of ivacaftor and lumacaftor may be limited, sales of PTI-428 or PTI-801 could be negatively impacted and our financial results and stock price would be adversely affected. Additionally, if one or more of Vertex's triple combinations is approved for marketing and becomes prevalent, the availability of ivacaftor and tezacaftor alone may be limited, sales of our products, if approved, could be negatively impacted and our financial results and stock price would be adversely affected.

Many of our competitors have greater financial, technical, manufacturing, clinical development, marketing, sales and supply resources, technical and human resources or experience than us and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of product candidates and the commercialization of those products. Accordingly, our competitors may be more successful than we may be in obtaining FDA and other regulatory approvals for therapies and achieving widespread market acceptance. Our competitors' products may be more effective, or more effectively marketed and sold, than any product candidate we may commercialize and may render our therapies obsolete or non-competitive before we can recover development and commercialization expenses.

If we successfully obtain approval for any product candidate, we will face competition based on many different factors, including the efficacy, safety and tolerability of our products, the ease with which our products can be administered, the extent to which physicians and patients accept combination therapies and, for PTI-428, new classes of modulators, the timing and scope of regulatory approvals for these products, the availability and cost of manufacturing, marketing and sales capabilities, price, reimbursement coverage and patent position. Competing products could present superior treatment alternatives, including being more effective, safer, or less expensive, or could be marketed and sold more effectively than any products we may develop. Competitive products may make any products we develop, or products with which we are approved for use in combination, obsolete or noncompetitive before we recover the expense of developing and commercializing our product candidates. Such competitors could also recruit our employees, which could negatively impact our level of expertise and our ability to execute our business plan. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a small number of competitors.

We also compete with other clinical-stage companies and institutions for clinical trial participants, which could reduce our ability to recruit participants for our clinical trials. For example, actual or perceived risks of our product candidates, such as PTI-428, PTI 801, or our proprietary combination therapy candidates, or actual or perceived benefits of product candidates of our competitors, may negatively affect potential clinical trial participants or patients when deciding whether to participate in our clinical trials, and could result in patients seeking alternative clinical trials or commercial therapies from our competitors. Delay in recruiting clinical trial participants could adversely affect our ability to bring a product to market. Further, research and discoveries by others may result in breakthroughs that render our product candidates obsolete even before they begin to generate any revenue.

In addition, our competitors may obtain patent protection or FDA approval and commercialize products more rapidly than we do, which may impact future sales of any of our product candidates that receive marketing approval. If the FDA approves the commercial sale of any of our product candidates, we will also be competing with respect to marketing capabilities and manufacturing efficiency, areas in which we have limited or no experience. We expect competition among products will be based on product efficacy and safety, the timing and scope of regulatory approvals, availability of supply, marketing and sales capabilities, product price, reimbursement coverage by government and private third-party payors, and patent position. Our profitability and financial position will suffer if we cannot compete effectively in the marketplace, even if our products receive regulatory approval.

Payor approval and reimbursement may not be available for PTI-428, PTI-801, any proprietary combination therapy candidates and our other product candidates, or third party therapies taken with our drugs, which could make it difficult or impossible for us to sell our products profitably.

Market acceptance and sales of PTI-428 or PTI-801, any proprietary combination therapy candidates, or any other product candidates that we develop, will depend in part on the extent to which reimbursement for these products and related third party treatments will be available from government health administration authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers, health maintenance organizations and pharmacy benefit management organizations, decide which medications they will pay for, at what tier level and establish reimbursement levels. A primary trend in the United States healthcare industry and elsewhere is cost containment. Government authorities and these third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that reimbursement will be available for any product that we commercialize and, if reimbursement is available, what the level of reimbursement will be. Even if we are successful in gaining reimbursement in one country, that does not mean we will achieve reimbursement at the same levels or at all in any other country. Reimbursement may impact the demand for, or the price of, any product for which we obtain marketing approval. Obtaining reimbursement for our products may be particularly difficult because of the higher prices often associated with products administered under the supervision of a physician. Reimbursement levels may be impacted by factors including, without limitation, the perceived safety and efficacy of our products relative to the cost (and relative to the perceived safety and efficacy and cost for available competitive products), the views of independent research organizations on drug pricing and the political climate, many of which factors we cannot control. Also, reimbursement amounts may reduce the demand for, or the price of, our products. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize PTI-428, PTI-801, any proprietary combination therapy candidates, or any other product candidates that we develop. We will also be required to establish systems and programs that assist patients in determining the reimbursement level and in some instances establishing patient economic support programs to alleviate the economic burden of co-pays and/or co-insurance. These patient support programs are complex, costly and require knowledge and expertise that we currently do not possess.

There have been a number of legislative and regulatory proposals to change the healthcare system in the United States and in some foreign jurisdictions that could affect our ability to sell any future products profitably. These legislative and regulatory changes may negatively impact the reimbursement for any future products, following approval. The availability of generic treatments may also substantially reduce the likelihood of reimbursement for any future products, including PTI-428 and PTI-801 or any proprietary combination therapy candidates. The application of user fees to generic drug products will likely expedite the approval of additional

generic drug treatments. We expect to experience pricing pressures in connection with the sale of PTI-428, PTI-801, any proprietary combination therapy candidates, and any other product candidate that we develop, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes.

In addition, there may be significant delays in obtaining reimbursement for approved products, and coverage may be more limited than the purposes for which the product is approved by the FDA or regulatory authorities in other countries. Moreover, eligibility for reimbursement does not imply that any product will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim payments for new products, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Payment rates may vary according to the use of the product and the clinical setting in which it is used, may be based on payments allowed for lower cost products that are already reimbursed, and may be incorporated into existing payments for other services. Net prices for products may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of products from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies, however reimbursement and levels of reimbursement may also vary within a country based on the individual decisions of private payors.

Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any of our product candidates, including PTI-428 and PTI-801 and any proprietary combination therapy candidates, could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

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.

The success of our business depends primarily on our ability to identify, develop and commercialize product candidates. Because we have limited financial and managerial resources, we focus on research programs and product candidates for the indications that take advantage of our deep expertise and knowledge and that we believe are the most scientifically and commercially promising. Our resource allocation decisions may cause us to fail to capitalize on viable scientific or commercial products or profitable market opportunities. In addition, we may spend valuable time and managerial and financial resources on research programs and product candidates for specific indications that ultimately do not yield any scientifically or commercially viable products. If we do not accurately evaluate the scientific and 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 situations where it would have been more advantageous for us to retain sole rights to development and commercialization.

Risks Relating to Regulation of Our Industry

We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws and health information privacy and security laws. Some of these laws were recently amended, and their interpretation following such amendments remains unclear. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

If we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our operations may be directly, or indirectly through our customers, subject to various federal and state fraud and abuse laws, including, without limitation, the federal anti-kickback statute. These laws may impact, among other things, our proposed sales, marketing and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal anti-kickback statute which prohibits, among other things, persons or entities from knowingly and willfully soliciting, offering, receiving or paying any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, lease, order or recommendation of, any good, facility, item or service, for which payment may be made, in whole or in part, under federal healthcare programs such as Medicare and Medicaid;
- the federal false claims laws and civil monetary penalties, including civil whistleblower or qui tam actions, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, to the federal government, claims for payment or approval that are false or fraudulent or from knowingly making a false statement to improperly avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA) which, among other things, imposes criminal liability for knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or to obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly or willfully falsifying, concealing, or covering up by any trick or device a material fact or making

any materially false statement using or making any false or fraudulent document, in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, and as amended by the final HIPAA omnibus rule, Modifications to the HIPAA Privacy, Security, Enforcement, and Breach Notification Rules Under HITECH and the Genetic Information Nondiscrimination Act; Other Modifications to HIPAA, published in January 2013, which imposes certain obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information without appropriate authorization by entities subject to the rule, such as health plans, clearinghouses and healthcare providers;
- the Federal Food, Drug, and Cosmetic Act, or FDCA, which prohibits, among other things, the distribution of adulterated or misbranded drugs or medical devices;
- the federal Physician Payments Sunshine Act, enacted as part of the Patient Protection and Affordable Care Act and the Health Care and Education Reconciliation Act of 2010, collectively referred to herein as the Affordable Care Act, or the ACA, and its implementing regulations, which requires certain manufacturers of drugs, devices, biologicals and medical supplies to report to the Centers for Medicare and Medicaid Services information related to payments and other transfers of value made to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in civil monetary penalties of up to an aggregate of $150,000 per year (or up to an aggregate of $1 million per year for "knowing failures"), for all payments, transfers of value, or ownership or investment interests that are not reported; and
- analogous state laws and regulations, including: state anti-kickback and false claims laws, which may apply to our business practices, including but not limited to, research, distribution, sales and marketing arrangements and claims involving healthcare items or services reimbursed by state governmental and non-governmental third-party payors, including private insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government; and state laws and regulations that require manufacturers to file reports relating to pricing and marketing information, which requires tracking gifts and other remuneration and items of value provided to healthcare professionals and entities.

Further, the ACA, among other things, amends the intent requirement of the federal anti-kickback and criminal health care fraud statutes. A person or entity can now be found guilty of fraud or false claims under ACA without actual knowledge of the statute or specific intent to violate it. In addition, ACA provides that the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the false claims statutes. Possible sanctions for violation of these anti-kickback laws include monetary fines, civil and criminal penalties, exclusion from Medicare, Medicaid and other government programs and forfeiture of amounts collected in violation of such prohibitions. Any violations of these laws, or any action against us for violation of these laws, even if we successfully defend against it, could result in a material adverse effect on our reputation, business, results of operations and financial condition.

In addition, regulators globally are also imposing greater monetary fines for privacy violations. For example, in 2016, the E.U. adopted a new regulation governing data practices and privacy called the General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR applies to any company established in the E.U. as well as to those outside the E.U. if they collect and use personal data in connection with the offering goods or services to individuals in the E.U. or the monitoring of their behavior. The GDPR enhances data protection obligations for processors and controllers of personal data, including, for example, expanded disclosures about how personal information is to be used, limitations on retention of information, mandatory data breach notification requirements and onerous new obligations on services providers. Non-compliance with the GDPR may result in monetary penalties of up to €20 million or 4% of worldwide revenue, whichever is higher. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of personal data, such as healthcare data or other sensitive information, could greatly increase our cost of providing our products and services or even prevent us from offering certain services in jurisdictions that we operate in.

In addition, there has been a trend of increased state regulation of payments made to physicians for marketing. Some states, such as California, Massachusetts and Vermont, mandate implementation of corporate compliance programs, along with the tracking and reporting of gifts, compensation, and other remuneration to physicians.

The scope and enforcement of these laws is uncertain and subject to change in the current environment of health care reform, especially in light of the lack of applicable precedent and regulations. Such changes are impossible to predict. It is possible that some of our business activities could be subject to challenge by federal or state regulatory authorities under one or more of these laws. Any such challenge could have a material adverse effect on our reputation, business, results of operations, and financial condition. Any

state or federal regulatory review of us, regardless of the outcome, would be costly and time-consuming, and could have a material adverse effect on our business, financial condition and results of operations.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have a material adverse effect on our business.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, provide accurate information to the FDA, comply with manufacturing standards we have established, comply with federal and state health-care fraud and abuse laws and regulations, 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, 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 adopted 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 misconduct may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

Health care reform measures could adversely affect our business.

In the United States and foreign jurisdictions, there have been a number of legislative and regulatory changes to the healthcare system that could affect our future results of operations. In particular, there have been and continue to be a number of initiatives at the U.S. federal and state levels that seek to reduce healthcare costs. The ACA, which includes measures to significantly change the way health care is financed by both governmental and private insurers, was enacted in March 2010. Among the provisions of the ACA of greatest importance to the pharmaceutical and biotechnology industry are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic products, apportioned among these entities according to their market share in certain government healthcare programs;
- new requirements to report certain financial arrangements with physicians and teaching hospitals, including reporting any “transfer of value” made or distributed to physicians and teaching hospitals and reporting any ownership interests held by physicians and their immediate family members;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- creation of the Independent Payment Advisory Board which, beginning in 2014, has authority to recommend certain changes to the Medicare program that could result in reduced payments for prescription drugs, which recommendations can have the effect of law even without congressional action; and
- establishment of a Center for Medicare Innovation at the Centers for Medicare & Medicaid Services to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

At this time, the full effect that the ACA would have on our business remains unclear. As a result of the 2016 election in the United States, there is great political uncertainty concerning the fate of the ACA and other healthcare laws. Legislation has been drafted to repeal and replace parts of the ACA, but it is uncertain when a bill would be passed and what any replacement law would encompass. We cannot predict any initiatives that may be adopted in the future.

Individual states have become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access, and marketing cost disclosure and transparency measures, and designed to encourage importation from other countries and bulk purchasing. 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 ultimate demand for our products or put pressure on our product pricing, which could negatively affect our business, results of operations, financial condition and prospects.

In addition, given recent federal and state government initiatives directed at lowering the total cost of healthcare, Congress and state legislatures will likely continue to focus on healthcare reform, the cost of prescription drugs and biologics and the reform of the Medicare and Medicaid programs. While we cannot predict the full outcome of any such legislation, it may result in decreased reimbursement for drugs and biologics, which may further exacerbate industry-wide pressure to reduce prescription drug prices. This could harm our ability to generate revenues. Increases in importation or re-importation of pharmaceutical products from foreign countries into the United States could put competitive pressure on our ability to profitably price our products, which, in turn, could adversely affect our business, results of operations, financial condition and prospects. We might elect not to seek approval for or market our products in foreign jurisdictions in order to minimize the risk of re-importation, which could also reduce the revenue we generate from our product sales. It is also possible that other legislative proposals having similar effects will be adopted.

Furthermore, regulatory authorities' assessment of the data and results required to demonstrate safety and efficacy can change over time and can be affected by many factors, such as the emergence of new information, including on other products, changing policies and agency funding, staffing and leadership. We cannot be sure whether future changes to the regulatory environment will be favorable or unfavorable to our business prospects. For example, average review times at the FDA for marketing approval applications can be affected by a variety of factors, including budget and funding levels and statutory, regulatory and policy changes.

The Referendum of the United Kingdom's Membership of the European Union creates uncertainty and could negatively impact our business.

We conduct trials in the United Kingdom, or the U.K., and, if approved, expect to market our products in the U.K. On June 23, 2016, the U.K., held a referendum in which voters approved an exit from the European Union, or the E.U., commonly referred to as "Brexit." As a result of the referendum, the British government is negotiating the terms of the U.K.'s withdrawal from the E.U. A withdrawal could, among other outcomes, disrupt the free movement of goods, services and people between the U.K. and the E.U., undermine bilateral cooperation in key policy areas and significantly disrupt trade between the U.K. and the E.U. In addition, Brexit could lead to legal uncertainty and potentially divergent national laws and regulations as the U.K. determines which E.U. laws to replace or replicate. Given the lack of comparable precedent, it is unclear what financial, trade, regulatory and legal implications the withdrawal of the U.K. from the E.U. would have and how such withdrawal would affect us.

The announcement of Brexit caused significant volatility in global stock markets and currency exchange rate fluctuations that resulted in the strengthening of the U.S. dollar against foreign currencies in which we could, if we ever commercialize a product, conduct business. The announcement of Brexit and the withdrawal of the U.K. from the E.U. may also create global economic uncertainty, which may cause third-party payors, including governmental organizations, to closely monitor their costs and reduce their spending budgets. Any of these effects of Brexit, among others, could adversely affect our business, financial condition and operating results, particularly if we receive approval to commercialize a product.

Risks Relating to Protecting Our Intellectual Property

It is difficult and expensive to protect our intellectual property rights and we cannot ensure that they will prevent third parties from competing against us. If we are unable to adequately protect our proprietary technology, or obtain and maintain issued patents that are sufficient to protect our 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.

Our success will depend, in part, on our ability to obtain and maintain intellectual property rights, both in the United States and other countries, successfully defend this intellectual property against third-party challenges and successfully enforce this intellectual property to prevent third-party infringement. We rely upon a combination of patents, trade secret protection and confidentiality agreements.

Our ability to protect any of our product candidates and technologies from unauthorized or infringing use by third parties depends in substantial part on our ability to obtain and maintain valid and enforceable patents in both the United States and other countries. Patent matters in the biotechnology and pharmaceutical industries can be highly uncertain and involve complex legal and factual questions. Changes in the patent laws, their implementing regulations or their interpretations may diminish the value of our patent rights.

There can be no assurance that we will discover or develop patentable products or processes or that patents will issue from any pending patent applications owned or licensed by us, or if issued, the breadth of such patent coverage. We currently have no issued patents covering any of our product candidates, including PTI-428, PTI-801, PTI-808 and our combination therapies, or our technologies, and many of our patent applications related to our CF program are in the earliest stages, including several provisional patent applications, although we do have three (3) issued patents covering early CFTR modulator compounds not currently in development. We cannot provide any assurances that any of our pending patent applications will lead to issued patents and, if they do, that such patents will include claims with a scope sufficient to protect our product candidates or otherwise provide any competitive advantage. Even if issued, we cannot guarantee that claims of issued patents owned or licensed to us are or will be held valid or enforceable by the courts or, even if unchallenged, will provide us with exclusivity or commercial value for our product candidates or

technology or any significant protection against competitive products or prevent others from designing around our claims. Further, if we encounter delays in regulatory approvals, the period of time during which we could market our product candidates under patent protection could be reduced. Our patent rights also depend on our compliance with technology and patent licenses upon which our patent rights are based and upon the validity of assignments of patent rights from consultants and other inventors that were, or are, not employed by us.

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. U.S. patents and patent applications may also be subject to derivation or adversarial proceedings, *ex parte* reexamination, or *inter partes* review proceedings, supplemental examination and challenges in district court. Patents may be subjected to opposition, post-grant review, 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, should they issue, that we may own or exclusively license may not provide any protection against competitors.

Patent applications are generally maintained in confidence until publication. In the United States, for example, patent applications are maintained in secrecy for up to 18 months after their filing. Similarly, publication of discoveries in scientific or patent literature often lags behind actual discoveries. Consequently, we cannot be certain that we were the first to file patent applications on our product candidates. There is also no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found, which could be used by a third party to challenge validity of our patents, should they issue, or prevent a patent from issuing from a pending patent application.

In addition, even if patents do successfully issue, third parties may challenge any such patent we own or license through adversarial proceedings in the issuing offices, which could result in the invalidation or unenforceability of some or all of the relevant patent claims. If a third party asserts a substantial new question of patentability against any claim of a U.S. patent we own or license, the U.S. Patent and Trademark Office, or USPTO, may grant a request for reexamination, which may result in a loss of scope of some claims or a loss of the entire patent. The adoption of the Leahy-Smith America Invents Act, or the Leahy-Smith Act, on September 16, 2011, established additional opportunities for third parties to invalidate U.S. patent claims, including *inter partes* review and post-grant review, on the basis of a lower legal standards than reexamination and additional grounds.

We will incur significant ongoing expenses in maintaining our patent portfolio. Should we lack the funds to maintain our patent portfolio or to enforce our rights against infringers, we could be adversely impacted. Moreover, the failure of any patents that may issue to us or our licensors to adequately protect our product candidates or technology could have an adverse impact on our business.

We will not be able to seek and obtain protection for our intellectual property 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 all of our product candidates throughout the world would be prohibitively expensive. Competitors may manufacture and sell our potential products in those foreign countries where we do not file for and obtain patent protection or where patent protection may be unavailable, not obtainable or ultimately not enforceable. Our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets and, further, may be able to export otherwise infringing products to territories where we have patent protection but where enforcement is not as strong as that in the United States. These products may compete with our products in jurisdictions where we do not have any issued patents and our patent claims or other intellectual property rights may not be effective or sufficient to prevent them from so competing.

The statutory deadlines for pursuing patent protection in individual foreign jurisdictions are based on the priority date of each of our patent applications. For PTI-428, PTI-801 and PTI-808, all of the statutory deadlines have passed. For certain patent applications related to our CFTR modulators, their use, and related technology, the relevant statutory deadlines have not yet expired. Thus, for each of these patent families, particularly those that we believe provide coverage for these product candidates, we will need to decide whether and where to pursue protection outside the United States by the relevant deadlines, and we will only have the opportunity to obtain patent protection in those jurisdictions where we file for protection, and prosecute and obtain issued claims.

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 scope and available coverage thus may vary significantly. Outside of the United States, patents we own or license, if issued, may become subject to patent opposition in the European Patent Office or similar proceedings, which may result in loss of scope of some claims or loss of the entire patent. Participation in adversarial proceedings is very complex and expensive, and may divert our management's attention from our core business and may result in unfavorable outcomes that could adversely affect our ability to prevent third parties from competing with us.

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. For example, an April 2014 report from the Office of the United States Trade Representative identified a number of countries, including India and China, where challenges to the procurement and enforcement of patent rights have been reported. Several countries, including India and China, have been listed in the report every year since 1989. If we encounter difficulties in protecting our intellectual property rights in foreign jurisdictions, our business prospects could be substantially harmed.

Proceedings to enforce our patent rights, if obtained, 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.

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

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

- Others may be able to make compounds that are similar to our product candidates but that are not covered by the claims of any patents, should they issue, that we own or have exclusively licensed.
- We or our licensors or strategic collaborators might not have been the first to make the inventions covered by any issued patent or pending patent application that we own or have exclusively licensed.
- We or our licensors or strategic collaborators might not have been the first to file patent applications covering certain of our inventions.
- Others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights.
- Our pending patent applications may not lead to issued patents.
- Patents, should they issue, that we own or that we have exclusively licensed, if any, may not provide us with any competitive advantages, or may be held invalid or unenforceable, as a result of legal challenges by our competitors.
- Our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets.
- We may not develop additional proprietary technologies that are patentable.
- The patents of others may have an adverse effect on our business.

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

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

The Leahy-Smith Act includes a number of significant changes to United States patent law. These include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business, our current and pending patent portfolio and future intellectual property strategy. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

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.

Periodic maintenance fees on any issued patent are due to be paid to the USPTO, the European Patent Office and other foreign patent agencies in several stages over the lifetime of the patent. The USPTO and various foreign national or international patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of patent rights include, but are not limited to, failure to file non-provisional applications claiming priority to our provisional applications by the statutory deadlines, failure to timely file national and regional stage patent applications based on an international patent application, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we or our licensors fail to maintain the patents and patent applications covering our product candidates, our competitors might be able to enter the market, which would have a material adverse effect on our business.

The patent protection and patent prosecution for some of our product candidates is dependent or may be dependent in the future on third parties.

While we normally seek and gain the right to fully prosecute the patents relating to our product candidates, there may be times when platform technology patents or product-specific patents that relate to our product candidates are controlled by our licensors or collaboration partners. In addition, our licensors and/or licensees and/or collaboration partners may have back-up rights to prosecute patent applications in the event that we do not do so or choose not to do so, and our licensees and/or collaboration partners may have the right to assume patent prosecution rights after certain milestones are reached. If any of our licensing partners fails to appropriately prosecute and maintain patent protection for patents covering any of our product candidates, our ability to develop and commercialize those product candidates may be adversely affected and we may not be able to prevent competitors from making, using and selling competing products.

We have entered into and may in the future enter into licenses to licensed intellectual property. If we were to lose our rights to licensed intellectual property, we may not be able to continue developing or commercializing a product candidate, if approved, that relied on such licensed intellectual property.

We are currently a party to and may in the future be party to license agreements under which we are or will be granted rights to intellectual property that are important to our business. Certain of our existing and terminated license agreements impose, and we expect that future license agreements will impose on us, various diligence obligations, payment of milestones and/or royalties and other obligations, including, without limitation, patent prosecution, research and development and efforts to meet milestones under mutually-agreed development plans. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to continue to use the rights granted under the license, or develop or market products covered by the license. Our business could suffer, for example, if any current or future licenses terminate, if the licensors fail to abide by the terms of the license, if the licensed patents or other rights are found to be invalid or unenforceable, or if we are unable to enter into necessary licenses on acceptable terms.

We may need to obtain licenses from third parties to advance our research or allow commercialization of our product candidates, and we cannot provide any assurances that third-party patents do not exist that might be enforced against our current product candidates or future products in the absence of such a license. We may fail to obtain any of these licenses on commercially reasonable terms, if at all. Even if we are able to obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. In that event, we may be required to expend significant time and resources to develop or license replacement technology. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could materially harm our business, and the third parties owning such intellectual property rights could seek either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation.

Licensing of intellectual property involves complex legal, business and scientific issues. Disputes may arise between us and our licensors regarding intellectual property subject to a license agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- our right to sublicense patent and other rights to third parties under collaborative development relationships;
- our diligence obligations with respect to the use of the licensed technology in relation to our development and commercialization of our product candidates, and what activities satisfy those diligence obligations; and
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners.

If disputes over intellectual property that we license now or in the future prevent or impair our ability to maintain our licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

We may be subject to litigation alleging that we are infringing the intellectual property rights of third parties or litigation or other adversarial proceedings seeking to invalidate our patents or other proprietary rights, and we may need to resort to litigation to protect or enforce our patents or other proprietary rights, all of which will be costly to defend, uncertain in its outcome and may prevent or delay development and commercialization efforts or otherwise harm our business.

Our success also will depend, in part, on our refraining from infringing patents or otherwise violating intellectual property owned or controlled by others. Numerous patents and pending applications are owned by third parties in the fields in which we are developing product candidates, both in the United States and elsewhere. It is difficult for industry participants, including us, to identify all third-party patent rights that may be relevant to our product candidates and technologies because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty in assessing the meaning and scope of patent claims. Moreover, because some patent applications are maintained in secrecy until the patents publish, we cannot be certain that third parties have not filed patent applications that cover our products and technologies. We may fail to identify relevant patents or patent applications or may identify pending patent applications of potential interest but incorrectly predict the likelihood that such patent applications may issue with claims of relevance to our technology. In addition, we may be unaware of one or more issued patents that would be infringed by the manufacture, sale, importation or use of a current or future product candidate, or we may incorrectly conclude that a third-party patent is invalid, unenforceable or not infringed by our activities. Additionally, pending patent applications can, subject to certain limitations, be later amended in a manner that could cover our technologies, our future products or the manufacture or use of our future products. Pharmaceutical companies, biotechnology companies, universities, research institutions and others may have filed patent applications or have received, or may obtain, issued patents in the United States or elsewhere relating to aspects of our technology, including our products, processes for testing, manufacture, formulation or methods of use, including combination therapy. It is uncertain whether the issuance of any third-party patents will require us to alter our product candidates or processes, obtain licenses, or cease certain activities.

If patents issued to third parties contain blocking, dominating or conflicting claims we may choose to or, if such claims are ultimately determined to be valid, be required to obtain licenses to these patents or to develop or obtain alternative non-infringing technology and cease practicing those activities, including, potentially, the manufacture or marketing of any products deemed to infringe those patents. If any licenses are required, there can be no assurance that we will be able to obtain any such licenses on commercially favorable terms, if at all, and if these licenses are not obtained, we might be prevented from pursuing the development and commercialization of certain of our potential products entirely or for certain indications. Even if a license can be obtained on acceptable terms, the rights may be non-exclusive, which could give our competitors access to the same technology or intellectual property rights licensed to us. Our failure to obtain a license to any technology that we may require to commercialize our products on favorable terms may have a material adverse impact on our business, financial condition and results of operations.

We may be exposed to, or threatened with, future litigation by third parties, including our competitors, having patent or other intellectual property rights alleging that our technologies, including our products, processes for manufacture or methods of use, including combination therapy, or other proprietary technologies infringe, either literally or under the doctrine of equivalents, their intellectual property rights. Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful infringement or other intellectual property claim against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our affected products, which may be impossible or require substantial time and monetary expenditure. We cannot predict whether any such license would be available at all or whether it would be available on commercially reasonable terms. Parties making successful claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates. We cannot provide any assurances that third-party patents do not exist which might be enforced against our products or product candidates, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties. Any of those occurrences would have a material adverse impact on our business.

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 or any other patent litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock.

We may be involved in lawsuits to protect or enforce our intellectual property, which could be time consuming, expensive and unsuccessful, and issued patents covering our product candidates could be found invalid or unenforceable if challenged in court.

Competitors may infringe our patents or the patents of our licensors, assuming patents issue from patent applications we own or license. Litigation, which could result in substantial costs to us (even if determined in our favor), may also be necessary to enforce any patents issued or licensed to us. The cost to us in initiating any litigation or other proceeding relating to patent or other proprietary rights, even if resolved in our favor, could be substantial, and litigation would divert our management's attention. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could delay our research and development efforts and limit our ability to continue our operations. In addition, in an infringement proceeding, a court may decide that a patent of ours or our licensors is not valid, is unenforceable and/or is not infringed, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question.

If we were to initiate legal proceedings against a third party to enforce a patent covering one of our product candidates or our technology, the defendant could counterclaim that our patent is invalid or unenforceable. In patent litigation in the United States and in most European countries, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, for example, lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. The outcome following legal assertions of invalidity and unenforceability during patent litigation is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on one or more of our products or certain aspects of our platform technology. Such a loss of patent protection could have a material adverse impact on our business. Patents and other intellectual property rights also will not protect our technology if competitors design around our protected technology without legally infringing our patents or other intellectual property rights.

An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing. Any of these outcomes would not only have an adverse effect on our patent portfolio but may also have an adverse effect on our business if we are unable to prevent the competitive activities of third parties.

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 or any other patent litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock.

If we are not able to adequately prevent disclosure of trade secrets and other proprietary information, the value of our technology and products could be significantly diminished.

We rely on trade secrets to protect technology especially where patent protection is not believed to be appropriate or obtainable or where patents have not issued. We attempt to protect our proprietary technology and processes, in part, with confidentiality agreements and assignment of invention agreements with our employees and confidentiality agreements with our consultants and certain contractors. There can be no assurance that these agreements will not be breached, that we would have adequate remedies for any breach, or that our trade secrets will not otherwise become known or be independently discovered by competitors. We may fail in certain circumstances to obtain the necessary confidentiality agreements, or their scope or term may not be sufficiently broad to protect our interests.

If our trade secrets or other intellectual property become known to our competitors, it could result in a material adverse effect on our business, financial condition and results of operations. To the extent that we or our consultants or research collaborators use intellectual property owned by others in work for us, disputes may also arise as to the rights to related or resulting know-how and inventions.

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 advisors, and sponsored researchers. 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. Moreover, we may not obtain these agreements in all circumstances.

Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

We may be subject to claims that we or our employees or consultants have wrongfully used or disclosed alleged trade secrets of our employees' or consultants' former employers or their clients. These claims may be costly to defend and if we do not successfully do so, we may be required to pay monetary damages and may lose valuable intellectual property rights or personnel.

Many of our employees and consultants were previously or concurrently employed at universities or biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, we may be subject to claims that these employees, consultants or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their employers. Litigation may be necessary to defend against these claims. If we fail in defending such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. A loss of key research personnel or their work product could compromise our ability to commercialize, or prevent us from commercializing, our product candidates, which could severely harm our business. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management.

Risks Relating to Our Business Operations and Industry

Our future success depends on our ability to retain executives and to attract, retain and motivate key personnel in a competitive environment for skilled biotechnology personnel.

Because of the specialized scientific nature of our business and the unique properties of our technology, our success is highly dependent upon our ability to attract and retain qualified scientific and technical personnel, consultants and advisors. We are dependent on the principal members of our scientific and management staff, particularly Ms. Meenu Chhabra, Ms. Shelia Wilson, and Drs. Po-Shun Lee, Geoffrey Gilmartin, Benito Munoz and Marija Zecevic, who have extensive knowledge of and experience developing our technology. The loss of any of their services might significantly delay or prevent the achievement of our research, development and business objectives.

We will need to recruit a significant number of additional personnel in order to achieve our operating goals. In order to pursue our product development and marketing and sales plans, we will need to hire additional qualified scientific personnel to perform research and development, and preclinical studies, as well as personnel with expertise in clinical operations, clinical testing, government regulation, compliance, manufacturing, marketing and sales, which may strain our existing managerial, operational, regulatory compliance, financial and other resources. We also rely on consultants and advisors to assist in formulating our research and development strategy and adhering to complex regulatory requirements. We face strong competition for qualified individuals from numerous pharmaceutical and biotechnology companies, universities and other research institutions, many of which have greater financial and other resources than us. There can be no assurance that we will be able to attract and retain such individuals on acceptable terms, if at all. Additionally, our facilities are located in Massachusetts, which may make attracting and retaining qualified scientific and technical personnel from outside of Massachusetts difficult. The failure to attract and retain qualified personnel, consultants and advisors could have a material adverse effect on our business, financial condition and results of operations.

As our product candidates advance through clinical trials we may experience difficulties in managing our growth and expanding our operations, including, without limitation, managing international clinical trials.

We have limited experience in drug development. As our product candidates advance through preclinical studies and clinical trials, we will need to expand our development, regulatory and manufacturing capabilities or contract with other organizations to provide these capabilities for us. In the future, we expect to have to manage additional relationships with collaborators or partners, suppliers and other organizations, including, without limitation, international clinical trials. Our ability to manage our operations and future growth will require us to continue to improve our operational, financial and management controls, reporting systems and procedures. We may not be able to implement improvements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls.

We are exposed to potential product liability or similar claims, and insurance against these claims may not be sufficient to cover our liabilities, or may not be available to us at a reasonable rate in the future or at all.

Our business exposes us to potential liability risks that are inherent in the testing, manufacturing and marketing of human therapeutic products. Clinical trials involve the testing of product candidates on human subjects or volunteers under a research plan, and carry a risk of liability for personal injury or death to patients due to unforeseen adverse side effects, improper administration of the product candidate, or other factors. Many of these patients are already seriously ill and are therefore particularly vulnerable to further illness or death. Our trials may include third party drugs taken with ours that could injure trial subjects for whose damages we would be liable and, even if we were not, we nevertheless may not be able to show or prove that our product was not a cause of the injury.

We carry clinical trial liability insurance. However, there can be no assurance that we will be able to obtain the amount of insurance necessary to cover potential claims or liabilities. We could be materially and adversely affected if we were required to pay damages or incur defense costs in connection with a claim outside the scope of indemnity or insurance coverage, if the indemnity is not performed or enforced in accordance with its terms, or if our liability exceeds the amount of applicable insurance. In addition, there can be no assurance that insurance, if obtained, will continue to be available on terms acceptable to us. Similar risks would exist upon the commercialization or marketing of any products by us or our collaborators.

Regardless of their merit or eventual outcome, product liability claims may result in:

- decreased demand for our product;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial volunteers or subjects;
- costs of litigation;
- distraction of management; and
- substantial monetary awards to plaintiffs.

Should any of these events occur, it could have a material adverse effect on our business and financial condition.

We may become involved in securities class action litigation that could divert management's attention and adversely affect our business and could subject us to significant liabilities.

The stock markets have from time to time experienced significant price and volume fluctuations that have affected the market prices for the common stock of pharmaceutical and biotechnology companies. These broad market fluctuations as well a broad range of other factors, including the realization of any of the risks described in this "Risk Factors" section of this report, may cause the market price of our common stock to decline. 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 and pharmaceutical companies generally experience significant stock price volatility. We may become involved in this type of litigation in the future. Litigation often is expensive and diverts management's attention and resources, which could adversely affect our business. Any adverse determination in any such litigation or any amounts paid to settle any such actual or threatened litigation could require that we make significant payments.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, to provide accurate information to the FDA, to comply with manufacturing standards we have established, to comply with federal and state healthcare fraud and abuse laws and regulations, to report financial information or data accurately or to 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, 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. 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 be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

We must comply with environmental laws and regulations, and failure to comply with these laws and regulations could expose us to significant liabilities.

We use hazardous chemicals and biological materials in certain aspects of our business and are subject to a variety of U.S. federal, state and local laws and regulations governing the use, generation, manufacture, distribution, storage, handling, treatment and disposal of these materials. Although we believe our safety procedures for handling and disposing of these materials and waste products comply with these laws and regulations, we cannot eliminate the risk of accidental injury or contamination from the use, manufacture, distribution, storage, handling, treatment or disposal of hazardous materials. In the event of contamination or injury, or failure to comply with environmental, occupational health and safety and export control laws and regulations, we could be held liable for any resulting damages and any such liability could exceed our assets and resources, including any available insurance.

Risks Relating to Our Common Stock

Our stock price will likely continue to be volatile and an active, liquid and orderly trading market may not develop for our common stock. As a result you may not be able to resell your shares at or above your purchase price.

The market price of our common stock may fluctuate substantially as a result of many factors, some of which are beyond our control. These fluctuations could cause you to lose all or part of the value of your investment in our common stock. Factors that could cause fluctuations in the market price of our common stock include the following:

- the development status of our product candidates and when our products receive regulatory approval or are granted special regulatory designations, or lose such designations;
- the results, and the timing of results, of our preclinical studies and clinical trials, including, without limitation, the publication or delay in publication of preliminary, interim or final results, adverse events, side effects, safety or efficacy data or other information;
- the support and approval, if any, that we receive from our collaboration partners, the TDN and other interested parties;
- performance of third parties on whom we rely to conduct pre-clinical studies, manage our clinical trials, and manufacture our products, product components and product candidates, including their ability to comply with regulatory requirements;

- the success of, and fluctuation in, the sales of our product candidates, if approved;
- our execution of our sales and marketing, manufacturing and other aspects of our business plan;
- results of operations that vary from those of our competitors and the expectations of securities analysts and investors;
- changes in expectations as to our future financial performance, including financial estimates by securities analysts and investors;
- changes in expectations as to our future pre-clinical or clinical results or prospects, including those of securities analysts and investors;
- our announcement of significant licensing or collaboration arrangements, or the termination of such arrangements;
- our announcement of significant contracts, acquisitions, or capital commitments;
- announcements by our competitors of competing products, clinical data, or other initiatives, including, without limitation, those that lead to the development of a new standard of care;
- announcements by third parties of significant claims or proceedings against us;
- regulatory and reimbursement developments in the United States and abroad;
- future sales of our common stock or debt securities;
- additions or departures of key personnel; and
- general domestic and international economic conditions unrelated to our performance.

In addition, the stock market in general has experienced significant price and volume fluctuations that have often been unrelated or disproportionate to operating performance of individual companies. These broad market factors may adversely affect the market price of our common stock, regardless of our operating performance. In the past, following periods of volatility in the market price of a company's securities, securities class action litigation has often been instituted. A securities class action suit against us could result in significant liabilities and, regardless of the outcome, could result in substantial costs and the diversion of our management's attention and resources.

Prior to our initial public offering in February 2016, there was no public market for shares of our common stock. The listing of our common stock on The NASDAQ Global Market does not assure that a meaningful, consistent and liquid trading market exists. Although our common stock is listed on The NASDAQ Global Market, trading volume in our common stock has been limited and an active trading market for our shares may never develop or be sustained. If an active market for our common stock does not develop, you may be unable to sell your shares when you wish to sell them or at a price that you consider attractive or satisfactory. The lack of an active market may also adversely affect our ability to raise capital by selling securities in the future, or impair our ability to license or acquire other product candidates, businesses or technologies using our shares as consideration.

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 and pharmaceutical companies 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.

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

The trading market for our common stock will depend in part on the research and reports that securities or industry analysts or investors publish about us or our business. We do not have any control over these analysts or investors. If one or more of the analysts who covers us downgrades our stock or analysts or investors publish inaccurate or unfavorable research about our business, our stock price would likely decline. If one or more of these analysts ceases coverage of us or fails to publish reports on us regularly, demand for our stock could decrease, which could cause our stock price and trading volume to decline.

Our principal stockholders have and will have a controlling influence over our business affairs and may make business decisions with which you disagree and which may adversely affect the value of your investment.

Our executive officers, directors and principal stockholders and their affiliates beneficially own or control, directly or indirectly, a majority of the outstanding shares of our common stock. As a result, if some of these persons or entities act together, they will have the ability to exercise significant influence over matters submitted to our stockholders for approval, including the election and removal of directors, amendments to our certificate of incorporation and by-laws and the approval of any business combination. These actions may be taken even if they are opposed by other stockholders. This concentration of ownership may also have the effect of delaying or preventing a change of control of our company or discouraging others from making tender offers for shares of our common stock, which could prevent our stockholders from receiving a premium for their shares. Some of these persons or entities who make up our principal stockholders may have interests different from yours.

Future sales, or the expectation of future sales, of a substantial number of our common shares could depress the trading price of our common stock.

If we or our stockholders sell substantial amounts of shares of our common stock in the public market or if the market anticipates that these sales could occur, the market price of shares of our common stock could decline. These sales may make it more difficult for us to sell equity or equity-related securities in the future at a time and price that we deem appropriate, or to use equity as consideration for future acquisitions. Stock sales by us could include private placements of stock and/or public offerings, including without limitation underwritten offerings and sales under our at-the-market common stock sales program with Leerink acting as our sales agent.

Pursuant to our 2016 Stock Option and Incentive Plan, or the 2016 Plan, our board is authorized to grant stock options and other equity-based awards to our employees, directors and consultants. The number of shares available for future grant under the 2016 Plan automatically increases each year by up to 3% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our board of directors or compensation committee to take action to reduce the size of the increase in any given year. Currently, we plan to register the increased number of shares available for issuance under the 2016 Plan each year. If our board of directors or compensation committee elects to increase the number of shares available for future grant by the maximum amount each year, our stockholders may experience additional dilution, which could cause our stock price to fall.

A significant portion of our total outstanding shares may be sold into the market. This could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. If our stockholders sell, or the market believes that our stockholders intend to sell, substantial amounts of our common stock in the public market, the market price of our common stock could decline significantly.

The holders of a significant portion of shares of our common stock, or their transferees, have rights, subject to some conditions, to require us to file one or more registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. If we were to register the resale of these shares, they could be freely sold in the public market. If these additional shares are sold, or if it is believed that they will be sold, in the public market, the trading price of our common stock could decline.

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 Securities Exchange Act of 1934, as amended, and our policies regarding stock transactions, our employees and executive officers may 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.

We have broad discretion in the use of our cash and cash equivalents and may not use them effectively or may use them in a way with respect to which stockholders do not approve.

Our management will have broad discretion in the use of our cash and could spend it in ways that do not improve our results of operations or enhance the value of shares of our common stock. The failure by our management to utilize our cash effectively could result in financial losses that could have a material adverse effect on our business, cause the market price of shares of our common stock to decline and delay the development of our product candidates. We may invest our cash in a manner that does not produce income or that loses value. If we do not invest our cash in ways that enhance stockholder value, we may fail to achieve expected financial results, which could cause the price of shares of our common stock to decline.

As an "emerging growth company," we are allowed to postpone the date by which we must comply with certain laws and regulations intended to protect investors and to reduce the amount of information we provide in our reports filed with the Securities and Exchange Commission, or SEC. This reduced disclosure could make our common stock less attractive to investors.

The JOBS Act is intended to reduce the regulatory burden on "emerging growth companies." As defined in the JOBS Act, a public company whose initial public offering of common equity securities occurred after December 8, 2011 and whose annual gross revenues are less than $1.07 billion will, in general, qualify as an "emerging growth company" until the earliest of:

- the last day of its fiscal year following the fifth anniversary of the date of its initial public offering of common equity securities;
- the last day of its fiscal year in which it has annual gross revenue of $1.07 billion or more;
- the date on which it has, during the previous three-year period, issued more than $1.0 billion in non-convertible debt; and
- the date on which it is deemed to be a "large accelerated filer," which will occur at such time as the company (1) has an aggregate worldwide market value of common equity securities held by non-affiliates of $700.0 million or more as of the last business day of its most recently completed second fiscal quarter, (2) has been required to file annual and quarterly reports under the Securities Exchange Act of 1934, as amended, or the Exchange Act, for a period of at least 12 months and (3) has filed at least one annual report pursuant to the Exchange Act.

Under this definition, we are an "emerging growth company" and could remain an "emerging growth company" for more than five years. For so long as we are an "emerging growth company," we will, among other things:

- not be required to comply with the auditor attestation requirements of section 404(b) of Sarbanes-Oxley;
- not be required to hold a nonbinding advisory stockholder vote on executive compensation pursuant to Section 14A(a) of the Exchange Act;
- not be required to seek stockholder approval of any golden parachute payments not previously approved pursuant to Section 14A(b) of the Exchange Act;
- be exempt from any rule adopted by the Public Company Accounting Oversight Board, requiring mandatory audit firm rotation or a supplemental auditor discussion and analysis; and
- be subject to reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements.

In addition, Section 107 of the JOBS Act provides that an emerging growth company can use the extended transition period provided in Section 7(a)(2)(B) of the Securities Act for complying with new or revised accounting standards. This permits an emerging growth company to 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 other companies. Section 107 of the JOBS Act provides that our decision to opt out of the extended transition period for complying with new or revised accounting standards is irrevocable.

In this report and our other periodic reports we have not included all of the executive compensation related information that would be required if we were not an emerging growth company. We cannot predict whether investors will find our common stock less attractive for relying 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.

As a public reporting company, we are and will be subject to rules and regulations established from time to time by the SEC and the Public Company Accounting Oversight Board, or PCAOB, regarding our internal control over financial reporting. We may not complete improvements to our internal control over financial reporting in a timely manner, or these internal controls may not be determined to be effective, which may adversely affect investor confidence in our company and, as a result, the market price of our common stock could decline and you could lose all or part of your investment.

We are a public reporting company subject to the rules and regulations established from time to time by the SEC and the PCAOB. These rules and regulations require, among other things, that we establish and periodically evaluate procedures with respect to our internal controls over financial reporting. Reporting obligations as a public company are likely to place a considerable strain on our financial and management systems, processes and controls, as well as on our personnel.

In addition, as a public company we are required to document and test our internal controls over financial reporting pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, so that our management can certify as to the effectiveness of our internal controls over financial reporting, which will require us to continue to document and make changes to our internal controls over financial reporting. Likewise, our independent registered public accounting firm will be required to provide an attestation report on the effectiveness of our internal control over financial reporting at such time as we cease to be an "emerging growth company," as defined in the JOBS Act, although, as described in the preceding risk factor, we could potentially qualify as an "emerging growth company" for more than five years. At such time, our independent registered public accounting firm may issue a report that is adverse in the event it is not satisfied with the level at which our controls are documented, designed or operating.

If our senior management is unable to conclude that we have effective internal control over financial reporting, or to certify the effectiveness of such controls, or if our independent registered public accounting firm cannot render an unqualified opinion on management's assessment and the effectiveness of our internal control over financial reporting once we cease to be an emerging growth company, or if material weaknesses in our internal controls are identified, we could be subject to regulatory scrutiny and a loss of public confidence, which could have a material adverse effect on our business and our stock price. In addition, if we do not maintain adequate financial and management personnel, processes and controls, we may not be able to manage our business effectively or accurately report our financial performance on a timely basis, which could cause a decline in our common stock price and adversely affect our results of operations and financial condition.

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

We are subject to the periodic reporting requirements of the Exchange Act. Our disclosure controls and procedures are designed to reasonably ensure 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 as well as 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 and will be 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.

Operating as a public company has significantly increased our costs and requires our management to devote substantial time to compliance efforts.

As a public company, we are incurring and will continue to incur significant legal, accounting, insurance and other expenses that we did not incur as a private company. The Dodd-Frank Act and the Sarbanes-Oxley Act, as well as related rules implemented by the SEC and The NASDAQ Stock Market, have required changes in corporate governance practices of public companies. In addition, rules that the SEC is implementing or is required to implement pursuant to the Dodd-Frank Act are expected to require additional changes. We expect that compliance with these and other similar laws, rules and regulations, including compliance with Section 404 of the Sarbanes-Oxley Act, will substantially increase our expenses, including our legal and accounting costs, and make some activities more time-consuming and costly. We also expect these laws, rules and regulations to make it more expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage, which may make it more difficult for us to attract and retain qualified persons to serve on our board of directors or as officers. We expect that we will need to hire additional accounting, finance and other personnel in connection with our efforts to comply with the requirements of being a public company, and our management and other personnel will need to devote a substantial amount of time towards maintaining compliance with these requirements. These requirements will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. Although the JOBS Act may for a limited period of time somewhat lessen the cost of complying with these additional regulatory and other requirements, we nonetheless expect a continued increase in legal, accounting, insurance and certain other expenses in the future, which will negatively impact our business, results of operations and financial condition.

Anti-takeover provisions in our charter documents could discourage, delay or prevent a change in control of our company and may affect the trading price of our common stock.

Our amended and restated certificate of incorporation and amended and restated by-laws and the Delaware General Corporation Law contain provisions that may enable our board of directors to resist a change in control of our company even if a change in control were to be considered favorable by you and other stockholders. These provisions:

- provide that directors can be removed only for cause, and then only by a supermajority stockholder vote;
- establish advance notice requirements for nominating directors and proposing matters to be voted on by stockholders at stockholder meetings;
- require majority stockholder voting to effect certain amendments to our certificate of incorporation and by-laws;
- 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;
- 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 by-laws, subject to any limitations set forth therein;
- require supermajority votes of the holders of our common stock to amend specified provisions of our amended and restated certificate of incorporation; and
- require supermajority votes of the holders of our common stock to amend our amended and restated by-laws, unless such amendments have been recommended to the stockholders, in which case only a majority vote is necessary.

In addition, we are subject to the provisions of Section 203 of the Delaware General Corporation Law. In general, Section 203 prohibits a publicly-held Delaware corporation from engaging in a "business combination" with an "interested stockholder" for a three-year period following the time that this stockholder becomes an interested stockholder, unless the business combination is approved in a prescribed manner. A "business combination" includes, among other things, a merger, asset or stock sale or other transaction resulting in a financial benefit to the interested stockholder. An "interested stockholder" is a person who, together with affiliates and associates, owns, or did own within three years prior to the determination of interested stockholder status, 15% or more of the corporation's voting stock.

A Delaware corporation may "opt out" of these provisions with an express provision in its original certificate of incorporation or an express provision in its certificate of incorporation or by-laws resulting from a stockholders' amendment approved by at least a majority of the outstanding voting shares. We have not opted out of these provisions. As a result, mergers or other takeover or change in control attempts of us may be discouraged or prevented.

We do not expect to pay any dividends on our common stock for the foreseeable future.

We currently expect to retain all future earnings, if any, for future operations, expansion and repayment of debt and have no current plans to pay any cash dividends to holders of our common stock for the foreseeable future. Any decision to declare and pay dividends in the future will be made at the discretion of our board of directors and will depend on, among other things, our results of operations, financial condition, cash requirements, contractual restrictions and other factors that our board of directors may deem relevant. As a result, you may not receive any return on an investment in our common stock unless you sell our common stock for a price greater than that which you paid for it.

Our by-laws provide that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers, employees or stockholders.

Our by-laws provide that the Court of Chancery of the State of Delaware is the sole and exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a breach of fiduciary duty, any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our certificate of incorporation or our by-laws, or any action asserting a claim against us that is governed by the internal affairs doctrine. The 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, other employees or stockholders (including beneficial owners), which may discourage such lawsuits against us and our directors, officers, other employees or stockholders (including beneficial owners). Alternatively, if a court were to find the choice of forum provision contained in our by-laws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business and financial condition.

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

Not applicable.

Item 3. Defaults Upon Senior Securities

Not applicable.

Item 4. Mine Safety Disclosures

Not applicable.

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 is incorporated herein by reference.

Exhibit No.	Exhibit Description	Incorporated by Reference			
		Form	File No.	Exhibit No.	Filing Date
3.1	Fifth Amended and Restated Certificate of Incorporation of the Company.	S-1/A	333-208735	3.2	February 1, 2016
3.2	Second Amended and Restated By-laws of the Company.	S-1/A	333-208735	3.4	February 1, 2016
4.1	Specimen Common Stock Certificate.	S-1/A	333-208735	4.1	February 1, 2016
4.2	Third Amended and Restated Stockholders' Agreement of the Company.	S-1/A	333-208735	4.2	February 1, 2016
4.3	Form of Preferred Stock Warrant.	S-1	333-208735	4.3	December 23, 2015
10.5	Offer Letter, dated August 3, 2018, by and between the Company and Sandra Zimmerman	10-Q	001-37695	10.5	August 8, 2018
31.1	Certification of Principal Executive Officer pursuant to Exchange Act rules 13a-14 or 15d-14.				Filed herewith
31.2	Certification of Principal Financial Officer pursuant to Exchange Act rules 13a-14 or 15d-14.				Filed herewith
32.1	Certification of Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. Section 1350.				Furnished herewith
101.INS	XBRL Instance Document.				Filed herewith
101.SCH	XBRL Taxonomy Extension Schema Document.				Filed herewith
101.CAL	XBRL Taxonomy Extension Calculation Document.				Filed herewith
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document.				Filed herewith
101.LAB	XBRL Taxonomy Extension Labels Linkbase Document.				Filed herewith
101.PRE	XBRL Taxonomy Extension Presentation Link Document.				Filed herewith

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.

PROTEOSTASIS THERAPEUTICS, INC.

Date: November 6, 2018

By: /s/ Meenu Chhabra
Meenu Chhabra
President and Chief Executive Officer
(Principal Executive Officer)

Date: November 6, 2018

By: /s/ Sandra Zimmerman
Sandra Zimmerman
Interim VP of Finance
(Principal Financial Officer)

Exhibit 31.1

Certification

I, Meenu Chhabra, certify that:

1. I have reviewed this quarterly report on Form 10-Q for the period ended September 30, 2018 of Proteostasis 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(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

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

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

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

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

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

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

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

Date: November 6, 2018

/s/ Meenu Chhabra
Meenu Chhabra
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

Certification

I, Sandra Zimmerman, certify that:

1. I have reviewed this quarterly report on Form 10-Q for the period ended September 30, 2018 of Proteostasis 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(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

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

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

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

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

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

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

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

Date: November 6, 2018

/s/ Sandra Zimmerman
Sandra Zimmerman
Interim VP of Finance
(Principal Financial Officer)

Exhibit 32.1

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

In connection with the quarterly report on Form 10-Q of Proteostasis Therapeutics, Inc. (the "Company") for the period ended September 30, 2018, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Meenu Chhabra, President and Chief Executive Officer (Principal Executive Officer) hereby certify, pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, 18 U.S.C. Section 1350, that to my knowledge:

1) the Report which this statement accompanies fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Date: November 6, 2018

/s/ Meenu Chhabra
Meenu Chhabra
President and Chief Executive Officer
(Principal Executive Officer)

In connection with the quarterly report on Form 10-Q of Proteostasis Therapeutics, Inc. (the "Company") for the period ended September 30, 2018, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Sandra Zimmerman, Interim VP of Finance (Principal Financial Officer) hereby certify, pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, 18 U.S.C. Section 1350, that to my knowledge:

(1) the Report which this statement accompanies fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Date: November 6, 2018

/s/ Sandra Zimmerman
Sandra Zimmerman
Interim VP of Finance
(Principal Financial Officer)