PROTEOSTASIS THERAPEUTICS, INC.

FORM 8-K
(Current report filing)

Filed 03/30/17 for the Period Ending 03/08/17

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BOSTON, MA, 02135

Telephone 617-225-0096
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Symbol PTI
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Industry Biotechnology & Medical Research
Sector Healthcare
UNITED STATES SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of The Securities Exchange Act of 1934

Date of Report (Date of Earliest Event Reported): March 8, 2017

Proteostasis Therapeutics, Inc.
(Exact name of registrant as specified in its charter)

DELAWARE 001-37695 20-8436652
(State or other jurisdiction (Commission (I.R.S. Employer
of incorporation) File Number) Identification No.)

200 Technology Square, 4th Floor
Cambridge, MA 02139
(Address of principal executive offices)

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

Not Applicable
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))
Item 5.02. Departure of Directors or Certain Officers; Election of Directors; Appointment of Certain Officers; Compensatory Arrangements of Certain Officers.

On March 8, 2017, the Board of Directors of Proteostasis Therapeutics, Inc., or the Company, elected Brett Hagen, the Company’s Vice President of Finance, Controller, Assistant Treasurer and Principal Accounting Officer, to the additional position of Principal Financial Officer. The Company announced this election on the date hereof, by press release.

Mr. Hagen, age 43, has been serving as the Company’s Controller since May 2016, Principal Accounting Officer since August 2016, Assistant Treasurer since October 2016, Vice President of Finance since February 2017, and Principal Financial Officer since March 2017. Previously, Mr. Hagen served as the controller for BIND Therapeutics, Inc. (NASDAQ: BIND), Vice President, Finance/Segment Controller of Boston Private Financial Holdings (NASDAQ: BPFH), Manager of SEC Financial Reporting and Technical Account of The Princeton Review, Controller of BioProcessors Corporation and held a number of positions at PricewaterhouseCoopers LLP. He received a B.A. from the University of Minnesota, a Master in Accountancy from Wright State University and a M.S. in Finance from Suffolk University.

Item 7.01 Regulation FD Disclosure.

On March 30, 2017, the Company issued a press release announcing its financial results for the quarter and fiscal year ended December 31, 2016, and corporate updates. A copy of the press release is furnished hereto as Exhibit 99.1.

Spokespersons of the Company plan to present the information in the presentation slides furnished hereto as Exhibit 99.2.

The furnishing of the attached presentation slides is not an admission as to the materiality of any information therein. The information contained in the slides is summary information that is intended to be considered in the context of more complete information included in the Company’s filings with the SEC and other public announcements that the Company has made and may make from time to time by press release or otherwise. The Company undertakes no duty or obligation to update or revise the information contained in this report, although it may do so from time to time as its management believes is appropriate. Any such updating may be made through the filing of other reports or documents with the SEC, through press releases or through other public disclosures. For important information about forward looking statements, see the slide titled “Safe Harbor and Disclaimer” in Exhibit 99.2 attached hereto.

The information in this Item 7.01 of this Current Report on Form 8-K and Exhibits 99.1 and 99.2 attached hereto shall not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liabilities of that section or Sections 11 and 12(a)(2) of the Securities Act of 1933, as amended. The information contained in this Item 7.01 and in the press release attached as Exhibit 99.1 and the presentation slides attached as Exhibit 99.2 to this Current Report shall not be incorporated by reference into any filing with the SEC made by the Company, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

<table>
<thead>
<tr>
<th>Exhibit No.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>99.1</td>
<td>Press release dated March 30, 2017, furnished herewith</td>
</tr>
<tr>
<td>99.2</td>
<td>Presentation slides, furnished herewith</td>
</tr>
</tbody>
</table>
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 hereunto duly authorized.

Date: March 30, 2017

PROTEOSTASIS THERAPEUTICS, INC.

By: /s/ Meenu Chhabra
    Meenu Chhabra
    President and Chief Executive Officer
<table>
<thead>
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Proteostasis Therapeutics Reports Fourth Quarter and Year-End 2016 Financial Results and Provides Corporate Update

PTI-801 Receives FDA Fast Track Designation; Phase 1 Study Underway

IND Submission for PTI-808 Planned for 2Q17

Phase 1 Study of PTI-428 Updated and Ongoing; Results Expected 2Q17

CAMBRIDGE, Mass. – March 30, 2017 – Proteostasis Therapeutics, Inc. (NASDAQ:PTI), a biopharmaceutical company developing small molecule therapeutics to treat diseases caused by dysfunctional protein processing such as cystic fibrosis (CF), today announced financial results for the fourth quarter and year ended December 31, 2016 and provided a corporate update.

“Today, CFTR modulator triple combinations represent the greatest promise for delivering maximum efficacy for the vast majority of CF patients and have become the central focus in a rapidly evolving clinical landscape,” said Meenu Chhabra, president and chief executive officer of Proteostasis Therapeutics. “Preclinical data suggest that Proteostasis’ proprietary triple combination solution of an amplifier (PTI-428), a corrector (PTI-801) and a potentiator (PTI-808) has the potential to demonstrate best-in-class efficacy because it is the only triple combination that addresses separate aspects of CFTR dysfunction in an entirely orthogonal manner from protein synthesis to processing to function. To realize this potential in an increasingly crowded clinical environment, we are pivoting our PTI-428 program to ex-U.S. clinical sites, initiating the clinical development of PTI-801 in regions where Orkambi is approved and expect to file an IND for PTI-808 in the second quarter. Our goal is to establish efficacy for PTI-428 and PTI-801 in an Orkambi population, and thus start the proof of concept study for our triple combination by the end of the year.”

Corporate Updates

PTI-428 – Fast Track-Designated CFTR Amplifier

To date, Proteostasis has reported preliminary safety, pharmacokinetic and exploratory biomarker data from both single and multiple ascending dose cohorts in its healthy volunteer trial of PTI-428. The drug was well tolerated and no drug-related SAEs were identified. Subjects who achieved a threshold concentration approximating EC$_{70}$ had a two-fold increase in cystic fibrosis transmembrane conductance regulator (CFTR) mRNA and protein which returned to baseline in the follow-up period.

Based on this nasal biomarker data, preclinical studies, and study precedent for other CFTR modulator programs, the Company now aims to report preliminary data in the second quarter from at least 8 CF subjects from a cohort of stable Orkambi patients dosed with PTI-428 for 7 days followed by a 7-day follow-up period. After wash-out, these subjects will then be eligible to enroll in a 28-day dosing cohort. Initial data will include safety and pharmacokinetics (PK) as well as changes in CFTR mRNA, protein, sweat chloride and lung function as measured by forced expiratory volume in 1 second, or FEV1. Data from the 28-day dosing cohort is expected in the second half of 2017.
The delay in study timeline from first quarter to second quarter stems from a highly competitive clinical development environment in the U.S., including several recent CF study starts for investigational agents that, unlike PTI-428, have received Therapeutics Development Network (TDN) endorsement and ranking. The Company believes the TDN, the development arm of the Cystic Fibrosis Foundation Therapeutics, Inc., can play a key role in helping access U.S. study participants. The Company has an active IND with the U.S. Food and Drug Administration (FDA) for PTI-428 and, following deferred endorsement, continues discussions with the TDN on its review of PTI-428.

To ensure the continued, rapid development of PTI-428, the Company expects to focus substantial resources toward European clinical development. To this end, the Company has sought and received endorsement and prioritization in Europe by the Clinical Trial Network (CTN), which is the development network of the European Cystic Fibrosis Society. In addition, PTI-428 has been reviewed and approved for clinical study by the Medicines and Healthcare products Regulatory Agency (UK) and Health Canada.

PTI-801, PTI-808 and PTI-NC-733 – Second Generation Fast Track-Designated CFTR Corrector, Potentiator and Triple Combination Therapy

In the first quarter of 2017, Proteostasis filed an IND for its proprietary corrector, PTI-801, and is currently initiating a Phase 1 healthy volunteer study to assess its safety and PK. The Company also announced today that PTI-801 has received fast track designation from the FDA for the treatment of CF. Fast Track designation is designed to facilitate development and expedite review of new therapies that address unmet medical needs of patients with serious conditions. The designation offers various benefits, including more frequent interaction with the FDA, eligibility for Accelerated Approval or Priority Review, if relevant criteria are met, and the opportunity to submit a new drug application (NDA) on a rolling basis.

The Company plans for the Phase 1 trial, which will also investigate PTI-801 in CF patients, to run in U.S. and European sites and is working with both the TDN and CTN to review the study protocol for sanctioning. Subject to favorable results from the healthy volunteer arm, the Company expects data from patients stable on Orkambi who have been dosed with PTI-801 for 14 days in the second half of 2017.

Subject to filing an IND for PTI-808 in the second quarter of 2017, and positive results from its PTI-428 and PTI-801 programs, the Company aims to initiate a trial for our third CFTR modulator by the end of 2017. The PTI-808 Phase 1 study is expected to include SAD and MAD cohorts in healthy volunteers as well as co-administration of PTI-428 and PTI-801 and ascending doses of PTI-808, for the proprietary triple combination therapy PTI-NC-733 in CF patients homozygous for F508del who are not receiving Orkambi. The Company believes that PTI-NC-733 could represent a new standalone therapy for CF.
Personnel Updates

On March 8, 2017, the Board elected Brett Hagen, the Company’s Vice President of Finance, Controller, Assistant Treasurer and Principal Accounting Officer, to the additional position of Principal Financial Officer. Mr. Hagen, age 43, has been serving as our Controller since May 2016, Principal Accounting Officer since August 2016, Assistant Treasurer since October 2016, Vice President of Finance since February 2017 and Principal Financial Officer since March 2017. Previously, Mr. Hagen served as the controller for BIND Therapeutics, Inc. (NASDAQ: BIND), Vice President, Finance/Segment Controller of Boston Private Financial Holdings (NASDAQ: BPFH), Manager of SEC Financial Reporting and Technical Account of The Princeton Review, Controller of BioProcessors Corporation and held a number of positions at PricewaterhouseCoopers LLP. He received a B.A. from University of Minnesota, a Master in Accountancy from Wright State University and a M.S. in Finance from Suffolk University.

Fourth Quarter & Year End 2016 Financial Results

Proteostasis reported a net loss of approximately $37.2 million for the full year ended December 31, 2016, as compared to a net loss of $25.0 million for the prior year ended December 31, 2015. The Company reported a net loss of $9.4 million for the three months ended December 31, 2016, as compared to a net loss of $5.6 million for the three months ended December 31, 2015.

Research and development expenses were $34.0 million for the full year ended December 31, 2016, as compared to $22.5 million for the prior year ended December 31, 2015. Research and development expenses for the three months ended December 31, 2016 were $10.5 million, as compared to $5.8 million for the same period in the prior year. The increase was due to costs incurred in advancing the preclinical development and clinical trials of our CF program, including support for our Phase 1 clinical trials of PTI-428, which commenced during the first quarter of 2016.

General and administrative expenses for the full year ended December 31, 2016 were $11.9 million, as compared to $6.3 million for the prior year. General and administrative expenses for the three months ended December 31, 2016 were $3.2 million, as compared to $1.8 million for the same period in the prior year. The increase in G&A expense in these periods was due primarily to an increase in professional fees and personnel related costs.

Proteostasis ended the fourth quarter of 2016 with $85.5 million in cash, cash equivalents and investments.

Based on the Company’s current operating plan, the Company expects its cash, cash equivalents and short-term investments will be sufficient to fund its operating expenses and capital expenditures requirements through the second quarter of 2018.

About Proteostasis Therapeutics, Inc.

Proteostasis Therapeutics, Inc. is a biopharmaceutical company dedicated to the discovery of groundbreaking therapies to treat diseases caused by dysfunctional protein processing, such as cystic fibrosis (CF). Headquartered in Cambridge, MA, the Proteostasis Therapeutics team focuses on identifying therapies that modulate the proteostasis imbalance in cells and restore protein function. Proteostasis
Therapeutics is currently enrolling eligible adults with CF to participate in its Phase 1 clinical trials of PTI-428. In addition to its multiple programs in cystic fibrosis, Proteostasis Therapeutics has formed a collaboration with Astellas Pharma, Inc. to research and identify therapies targeting the Unfolded Protein Response (UPR) pathway. For more information, visit www.proteostasis.com.

Safe Harbor

To the extent that statements in this release are not historical facts, they are forward-looking statements reflecting the current beliefs and expectations of management made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Words such as “aim,” “may,” “will,” “expect,” “anticipate,” “estimate,” “intend,” and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) are intended to identify forward-looking statements. Examples of forward-looking statements made in this release include, without limitation, statements regarding the expected timing of the initiation of, patient enrollment in, data from, and our completion of, our clinical studies and cohorts for PTI-428, PTI-801, PTI-808 and our triple combination therapy candidate, PTI-NC-733, the timing of our expected IND filing for PTI-808, our cash forecast, and discussions with and endorsement by therapeutic development arms of CF patient advocacy groups. Forward-looking statements made in this release involve substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by the forward-looking statements, and we therefore cannot assure you that our plans, intentions, expectations or strategies will be attained or achieved. Such risks and uncertainties include, without limitation, uncertainties inherent in the execution and completion of clinical trials (including, without limitation, the possibility FDA requires us to run additional cohorts sequentially), in the enrollment of CF patients in our clinical trials, in the timing of availability of trial data, in the actions of regulatory agencies, in endorsement, if any, by therapeutic development arms of CF patient advocacy groups, and those set forth in our Annual Report on Form 10-K for the year ended December 31, 2016, and our other SEC filings. We assume no obligation to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise.
## PROTEOSTASIS THERAPEUTICS, INC.

### BALANCE SHEETS

(In thousands, except share and per share amounts)

<table>
<thead>
<tr>
<th>Assets</th>
<th>December 31, 2016</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current assets:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cash and cash equivalents</td>
<td>$18,613</td>
<td>$13,844</td>
</tr>
<tr>
<td>Short-term investments</td>
<td>66,897</td>
<td>—</td>
</tr>
<tr>
<td>Accounts receivable</td>
<td>668</td>
<td>918</td>
</tr>
<tr>
<td>Prepaids and other current assets</td>
<td>4,059</td>
<td>180</td>
</tr>
<tr>
<td>Total current assets</td>
<td>90,237</td>
<td>14,942</td>
</tr>
<tr>
<td>Property and equipment, net</td>
<td>541</td>
<td>566</td>
</tr>
<tr>
<td>Deferred offering costs</td>
<td>—</td>
<td>2,744</td>
</tr>
<tr>
<td>Other assets</td>
<td>68</td>
<td>144</td>
</tr>
<tr>
<td>Restricted cash</td>
<td>294</td>
<td>294</td>
</tr>
<tr>
<td>Total assets</td>
<td>$91,140</td>
<td>$18,690</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liabilities, Convertible Preferred Stock and Stockholders’ Equity</th>
<th>2016</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current liabilities:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accounts payable</td>
<td>$2,021</td>
<td>$3,330</td>
</tr>
<tr>
<td>Accrued expenses</td>
<td>4,328</td>
<td>2,248</td>
</tr>
<tr>
<td>Deferred revenue</td>
<td>2,204</td>
<td>4,076</td>
</tr>
<tr>
<td>Deferred rent</td>
<td>201</td>
<td>182</td>
</tr>
<tr>
<td>Total current liabilities</td>
<td>8,754</td>
<td>9,836</td>
</tr>
<tr>
<td>Deferred revenue, net of current portion</td>
<td>752</td>
<td>4,265</td>
</tr>
<tr>
<td>Deferred rent, net of current portion</td>
<td>87</td>
<td>287</td>
</tr>
<tr>
<td>Preferred stock warrant liability</td>
<td>—</td>
<td>110</td>
</tr>
<tr>
<td>Derivative liability</td>
<td>91</td>
<td>2</td>
</tr>
<tr>
<td>Total liabilities</td>
<td>9,684</td>
<td>14,500</td>
</tr>
</tbody>
</table>

**Convertible preferred stock (Series A and B), $0.001 par value; 0 and 110,057,398 shares authorized as of December 31, 2016 and 2015, respectively; 0 and 104,854,769 shares issued and outstanding as of December 31, 2016 and 2015, respectively; aggregate liquidation preference of $0 and $149,392, respectively, as of December 31, 2016 and 2015**

<table>
<thead>
<tr>
<th>Commitments and contingencies (Note 16)</th>
<th>2016</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total stockholders’ equity (deficit)</td>
<td>$81,456</td>
<td>($108,102)</td>
</tr>
<tr>
<td>Total liabilities, convertible preferred stock and stockholders’ equity (deficit)</td>
<td>$91,140</td>
<td>$18,690</td>
</tr>
</tbody>
</table>
## PROTEOSTASIS THERAPEUTICS, INC.

### STATEMENTS OF OPERATIONS

(In thousands, except share and per share amounts)

<table>
<thead>
<tr>
<th></th>
<th>Three Months Ended December 31</th>
<th>Year Ended December 31</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2016</td>
<td>2015</td>
</tr>
<tr>
<td>Revenue</td>
<td>$4,060</td>
<td>$1,234</td>
</tr>
<tr>
<td>Operating expenses:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research and development</td>
<td>10,461</td>
<td>5,787</td>
</tr>
<tr>
<td>General and administrative</td>
<td>3,198</td>
<td>1,769</td>
</tr>
<tr>
<td>Total operating expenses</td>
<td>13,659</td>
<td>7,556</td>
</tr>
<tr>
<td>Loss from operations</td>
<td>(9,599)</td>
<td>(6,322)</td>
</tr>
<tr>
<td>Interest income</td>
<td>190</td>
<td>—</td>
</tr>
<tr>
<td>Interest expense</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Other income (expense), net</td>
<td>(8)</td>
<td>691</td>
</tr>
<tr>
<td>Net loss</td>
<td>(9,417)</td>
<td>(5,631)</td>
</tr>
<tr>
<td>Modification of Series A preferred stock</td>
<td>—</td>
<td>743</td>
</tr>
<tr>
<td>Modification of Series B preferred stock</td>
<td>—</td>
<td>(26)</td>
</tr>
<tr>
<td>Accruing dividends on Series A preferred stock</td>
<td>—</td>
<td>(3,026)</td>
</tr>
<tr>
<td>Net loss attributable to common stockholders</td>
<td>$ (9,417)</td>
<td>$ (7,940)</td>
</tr>
<tr>
<td>Net loss per share attributable to common stockholders—basic and diluted</td>
<td>$ (0.38)</td>
<td>$ (13.95)</td>
</tr>
<tr>
<td>Weighted average common shares outstanding—basic and diluted</td>
<td>24,975,010</td>
<td>569,026</td>
</tr>
</tbody>
</table>

### CONTACTS:

**Investors:**
David Pitts
Argot Partners
212.600.1902
david@argotpartners.com

**Media:**
Eliza Schleifstein
Argot Partners
973.361.1546
eliza@argotpartners.com
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This presentation also contains estimates and other statistical data made by independent parties and by us relating to, among other items, disease incidence, market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. Projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of risk and uncertainty. New risks emerge from time to time, and neither we nor any other person makes any representation as to the accuracy or completeness of such data or undertakes any obligation to update such date after the date of this presentation. By attending or receiving this presentation you acknowledge you are solely responsible for your own assessment of the market and our market position and that you will conduct your own analysis and are solely responsible for forming your own view of the potential future performance of our business. The trademarks included in this presentation are the property of the owners thereof and are used for reference purposes only. Such use should not be construed as an endorsement of the Company or its securities.
Investment Highlights

- Proprietary platform to develop novel therapeutics for diseases caused by dysfunctional protein processing
- Initial focus on increasing CFTR activity in patients with CF
- Developing a novel class of CFTR modulators (amplifiers) that increase CFTR protein levels
  - Significantly increase the activity of correctors and potentiators in standard HBE cell assays shown to be predictive of clinical efficacy
  - No safety or tolerability issues noted in initial Phase I studies to date
- Developing proprietary triple combination therapy including PTI-428 for the treatment of CF - cellular assays suggest full restoration of CFTR activity
- Additional upside from Astellas collaboration for other protein processing diseases
- Q4 16 Ending cash of $85.5M after successful follow-on financing
Key Updates Q1 2017

- PTI-428 CFTR Amplifier Advancing to Safety, Biomarker and Efficacy Data in CF
  - Completed dosing of SAD and MAD healthy volunteers
  - Completed dosing of SAD in CF subjects not on Orkambi or Kalydeco
  - Demonstrated dose proportional increase in exposure across all dose levels
  - Dosing of CF subjects who are stable on Orkambi is underway
  - Showed comparable PK in healthy volunteers and CF subjects
  - No safety concerns observed to date

- PTI-801 CFTR Corrector Advancing to First in Human Study
  - IND on file and active
  - Healthy volunteer screening activities underway
  - Preliminary efficacy data in Orkambi subjects expected in 2H’17

- PTI-808 Novel Potentiator Progressing to IND
  - IND submission planned for Q2 2017
  - Healthy volunteer study planning to start in Q3 and CF studies planned for Q4
### Cystic Fibrosis
- **PTI-428 (Amplifier)**
- **PTI-801 (Corrector)**
- **PTI-808 (Potentiator)**

### Protein Conformational Diseases
- **UPR* Modulators**

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Preclinical Development</th>
<th>Clinical Development</th>
<th>Collaborators</th>
<th>Highlights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Fibrosis</td>
<td>PTI-428 (Amplifier)</td>
<td></td>
<td></td>
<td>PTI-NC-733 is comprised of PTI-428 + PTI-801 + PTI-808</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>PTI-801 (Corrector)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>PTI-808 (Potentiator)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein Conformational Diseases</td>
<td><em><em>UPR</em> Modulators</em>*</td>
<td></td>
<td></td>
<td>Eligible to receive up to $400M in milestones via Astellas collaboration</td>
</tr>
</tbody>
</table>

* UPR: Unfolded Protein Response
PTI-428 Amplifier May Serve as the Lynchpin of CFTR Modulator Combination Therapy Approaches

Amplifiers act early in CFTR biosynthesis and are designed to increase the amount of protein available for later acting modulators, such as correctors and potentiators.
Significant Unrealized Efficacy in CF Patients

Approximate % CF Population (U.S. & Canada)

- 5% Gating Mutation
- 10% Conductance & Synthesis Mutations
- 47% F508del Homozygotes
- 39% F508del Heterozygotes
- 12% Stop Codon Mutation

% Predicted FEV₁, Absolute Improvement

Unrealized Efficacy

Kalydeco
Orkambi
PTI-428 and PTI-NC-733 May Provide Optimal Risk Benefit Profile for the Majority of the CF Population

Approximate % CF Population (U.S. & Canada)

- Gating Mutation
- Conductance & Synthesis Mutations
- Processing Mutation
- Stop Codon Mutation

% Predicted FEV1: Absolute Improvement

- Target for PTI-NC-733
- Predicted PTI-428 + Orkambi or Kalydeco
- Kalydeco
- Orkambi

NB: PTI-428, PTI-NC-733 projection of FEV1, values based on actual in vitro efficacy data
PTI, Vertex And Galapagos In the Hunt for a Triple Combo Pill

<table>
<thead>
<tr>
<th></th>
<th>1H 2016</th>
<th>2H 2016</th>
<th>1H 2017</th>
<th>2H 2017</th>
<th>1H 2018</th>
<th>2H 2018</th>
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<tbody>
<tr>
<td><strong>PTI</strong></td>
<td></td>
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<tr>
<td><strong>Galapagos</strong></td>
<td>GLPG1837 corr. P1 results</td>
<td>GLPG1837 and 7451 pot. P2 results</td>
<td>Dual combo P1 results</td>
<td>Triple combo P1 results</td>
<td>Triple combo P1 results</td>
<td></td>
</tr>
<tr>
<td><strong>ProQR</strong></td>
<td>QR-010 P1 results</td>
<td>QR-410 P1 PREC results</td>
<td>QR-410 P1b results</td>
<td>QR-410 P2 results</td>
<td>QR-210 P2 results</td>
<td></td>
</tr>
<tr>
<td><strong>Vertex</strong></td>
<td>Triple combo P1 results</td>
<td>VX-661 P3 results</td>
<td>VX-440/661/iva P3 results</td>
<td>VX-440/641/iva P2 results</td>
<td>VX-661 (oncology approval)</td>
<td></td>
</tr>
</tbody>
</table>

- **Publicly disclosed guidance**
- **Failed or to be abandoned**
- **Triple combo data**
In Vitro Efficacy Data of Vertex CFTR Modulators Seem to Predict Clinical Efficacy

NB: PTI-428, PTI-801, PTI-808, (PTI-NC-733) projection of percent predicted FEV₁ values based on actual in vitro efficacy data.

NB: PTI-428, PTI-801, PTI-808, (PTI-NC-733) projection of percent predicted FEV₁ values based on actual in vitro efficacy data.
Measurement of CFTR Protein Activity In Vitro is Highly Correlated with Clinical Efficacy

- **Severity of CF progression is measured by FEV₁ (forced expiratory volume in one second) in patients**

- **CFTR modulators are evaluated in Ussing Chamber Assay**
  - In vitro CFTR protein activity is measured in human bronchial epithelial (HBE) cells derived from the lungs of CF patients
  - Ussing Chamber Assay invented in 1946 and well-established in CF basic research

- **Potentiators and correctors show a strong correlation between their effect in vitro measured by the Ussing Chamber Assay and lung function improvement**

- **In vitro activity of CFTR protein expressed as 50% of normal CFTR function correlates with an absolute FEV₁ improvement of approximately 10% observed in clinical trials**

- FEV₁ is industry-standard efficacy endpoint in CF clinical trials
- Rate of FEV₁ decline correlates with life expectancy and is predictive of mortality

- Rate of FEV₁ decline correlates with life expectancy and is predictive of mortality
Amplifiers are designed to improve the efficiency of CFTR translation by enhancing successful signal-sequence targeting to the ER membrane. This slows CFTR mRNA degradation and tips the balance back in favor of CFTR protein biosynthesis.

SRP, signal recognition particle.
PTI-428 Has Been Shown to Increase CFTR Activity in HBE Cells Across All CF Mutation Classes

- HBE cells derived from the lungs of CF patients can be cultured and tested for CFTR function measured by chloride current in an Ussing Chamber Assay
- Experimental approach well validated by CF research community and industry, including Vertex Pharmaceuticals
- *In vitro* studies currently demonstrate that PTI-428 increases the amount of unfolded CFTR protein
- Additional substrate for correctors and potentiators to act upon leads to improved CFTR protein activity

<table>
<thead>
<tr>
<th>CFTR Genotype</th>
<th>Genotype Class</th>
<th>CFTR activity increased by PTI-428</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild type</td>
<td>Wild-Type</td>
<td>✔️</td>
</tr>
<tr>
<td>F508del/F508del</td>
<td>II/II</td>
<td>✔️</td>
</tr>
<tr>
<td>G542X/F508del</td>
<td>I/II</td>
<td>✔️</td>
</tr>
<tr>
<td>R117H/F508del</td>
<td>IV/II</td>
<td>✔️</td>
</tr>
<tr>
<td>G551D/F508del</td>
<td>III/II</td>
<td>✔️</td>
</tr>
<tr>
<td>G542X/G542X</td>
<td>I/I</td>
<td>✔️</td>
</tr>
<tr>
<td>3849 + 10kbC&gt;T/N1303K</td>
<td>V/II</td>
<td>✔️</td>
</tr>
</tbody>
</table>
PTI-428 Has Been Shown to Increase the Efficacy of CFTR Modulators in Genotypes with at Least One F508del Allele

<table>
<thead>
<tr>
<th>Class</th>
<th>I: Stop Codon Mutation</th>
<th>II: Processing Mutation</th>
<th>III: Gating Mutation</th>
<th>IV: Conductance Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defect</td>
<td>Protein translation prematurely stopped</td>
<td>Misfolded protein fails to reach surface</td>
<td>Abnormal regulation of ion flow</td>
<td>Faulty channel conductance slows ion flow</td>
</tr>
<tr>
<td>HBE Genotype Tested</td>
<td>G542X/F508del</td>
<td>F508del/F508del</td>
<td>G551D/F508del</td>
<td>R117H/F508del</td>
</tr>
<tr>
<td>Class</td>
<td>I/II</td>
<td>II/II</td>
<td>III/II</td>
<td>IV/II</td>
</tr>
</tbody>
</table>

**In vitro increase in ion flow from PTI-428 combinations**

- G542X/F508del: 140% compared to lumacaftor/ivacaftor
- F508del/F508del: 134% compared to lumacaftor/ivacaftor
- G551D/F508del: 130% compared to ivacaftor/VX-661
- R117H/F508del: 150% compared to ivacaftor

*PTI-428 added to indicated compound(s)
PTI-428 has shown to improve the effect of additional CF disease modifying drugs such as stop codon read-through compounds *in vitro* suggesting possible therapeutic applications in Class I and Class V CFTR genotypes.
PTI-428 Upregulates Synthesis and Function of CFTR in Normal Cells

- The activity of PTI-428 can also be seen on normal CFTR in HBEs and leads to:
  - Increased amount of normal CFTR mRNA
  - Increased CFTR chloride transport activity as measured in Ussing Chamber Assay
- Correctors do not modulate normal CFTR function
- PTI-428 increases normal CFTR mRNA both in vitro and in human subjects
Amplifiers are the only known CFTR modulators that lead to an increase in immature CFTR protein that results in an increase in mRNA. Thus, a clinical biomarker was designed to detect an increase in CFTR mRNA and protein.

Nasal brush biomarker is noninvasive technique to sample the respiratory epithelium.
Persistent Increase in CFTR mRNA Observed in Nasal Epithelium After 90 Days of Dosing with PTI-428

- 90 days of consecutive oral once a day dosing
- Dose levels are 0, 2.5 mg/kg, 5 mg/kg, 10 mg/kg
- 32 monkeys total (16 male and 16 female monkeys); 8 per group
- Necropsy at 24 hours post last dose
- Changes in CFTR mRNA 24hr post dosing
PTI-428 Phase 1 Trials Update

**PTI-428-01 CF Patients**

- Dosing in SAD completed
- Safety Review Committee has not identified any safety concerns based on reviews of adverse events, vital signs, ECG, chemistry and hematology lab values
- 14 sites currently active in sites across North America and Canada; on-boarding European sites
- Preliminary data, including lung function, from a 14-day MAD cohort from at least 8 CF subjects receiving PTI-428 or placebo for 7 days on top of Orkambi expected in the second quarter of 2017
- Patients from MAD cohort to be eligible to enroll in longer duration study after a wash-out

**PTI-428-02 Healthy Volunteers**

- SAD and MAD arms completed up to 300 mg and 150 mg, respectively
- Safety Review Committee has not identified any safety concerns based on reviews of adverse events, vital signs, ECG, chemistry and hematology lab values
- Exploratory biomarker nasal CFTR mRNA and protein data confirms approximately a 2-fold increase in CFTR mRNA and protein observed in subjects where PTI-428 achieved a threshold concentration
- Preliminary PK data show dose-proportionality and support once daily dosing
Pharmacokinetic Data from Healthy Volunteers and CF Subjects in SAD Cohorts Shows Dose Proportionality

- $T_\frac{1}{2} \sim 14-15$ hours
Timing of Nasal CFTR mRNA Response Mirrored PK Profile in 100 mg SAD

- An increase in mRNA up to 1.5x considered within the noise of the assay
Pharmacokinetic Data from Healthy Volunteers MAD Cohorts Shows Dose Proportionality

PTI-428 Concentration vs Time in PTI-428-02 Study

Day=7

Concentration (ng/mL)

Time (h)
- PTI-428 was tested in MAD study at three dose levels; daily dosing over 7 days and 7 days of follow up
- 150 mg cohort suggests a sustained effect on CFTR mRNA levels measured in the target tissue (nasal epithelia)
- Target effect of approximately 2x increase over baseline level was achieved with the 150 mg daily dose over 7 days
- CFTR mRNA level returned towards baseline level by the end of the 7 day follow up period
PTI-428 Demonstrates Linear Dose Proportionality in Healthy Volunteers

- PTI-428 pharmacokinetic profile confirms linear dose proportionality across all doses tested in healthy volunteers.
- Single 100 mg dose achieves a plasma concentration level (Cmax) that exceeds EC50 (approximately EC70).
- Highest dose tested (300 mg) exceeds EC90.
- Linear dose proportionality is preserved in multiple daily dosing cohorts (20 mg, 50 mg and 150 mg).
- CFTR mRNA quantification in target tissue (nasal epithelia) confirms a positive relationship between biological effect and drug exposure.
- Target efficacy of approximately 2 fold increase in CFTR mRNA can be achieved with doses between 50 mg and 150 mg.

**Cmax at Day 1 (SAD)**

- R² = 0.97

**Activity vs Exposure (MAD)**

- Relative CFTR mRNA
- Cmax at Steady State (μM)
- R² = 0.9807

**Target biological activity**
**Estimated Efficacious Dose is Approximately 50 – 100 mg Once Daily**

- When taken with food, PTI-428 shows an increased exposure
- Projected exposure values estimate that at least an EC$_{50}$ (1.48 µM) may be achieved with a 50 mg dose level and at least an EC$_{90}$ (4.28 µM) may be achieved with a 100 mg dose level in CF subjects taking PTI-428 with food

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose (mg)</th>
<th>Maximum CFTR mRNA Increase at Steady State</th>
<th>Steady State $C_{\text{max}}$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual values (fasted healthy volunteer subjects)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAD</td>
<td>20</td>
<td>1.44</td>
<td>0.62</td>
</tr>
<tr>
<td>MAD</td>
<td>50</td>
<td>1.57</td>
<td>1.65</td>
</tr>
<tr>
<td>MAD</td>
<td>150</td>
<td>2.52</td>
<td>8.00</td>
</tr>
<tr>
<td>Projected values (fed healthy volunteer and CF subjects)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td>50</td>
<td>1.89</td>
<td>2.70</td>
</tr>
<tr>
<td>CF patients</td>
<td>50</td>
<td>1.86</td>
<td>2.58</td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td>100</td>
<td>2.28</td>
<td>5.39</td>
</tr>
<tr>
<td>CF patients</td>
<td>100</td>
<td>2.26</td>
<td>5.17</td>
</tr>
</tbody>
</table>
PTI-801 IND Submitted and Active, PTI-808 IND Expected Q2 17

**PTI-801** (corrector)
- Linear PK profile established in dog and rat
- GLP tox studies complete
- Estimated safety margin >20x
- DDI potential low based on *in vitro* profiling

**PTI-808** (potentiator)
- Linear PK profile established in dog and rat
- GLP tox studies complete
- Estimated safety margin >20x
- DDI potential comparable to ivacaftor based on *in vitro* profiling

Initial feasibility study supports co-formulation of PTI-428, PTI-801 and PTI-808
PTI Corrector Chemistry Progress

- *In vitro* PTI correctors are synergistic with tezacaftor and ivacaftor and PTI believes can be developed as add-on to this combination upon its approval.
- F508del/G542X compound heterozygote («Het/Min») HBE cell CFTR activity can be restored.
- Nomination of PTI-801 as candidate includes efficacy, potency and ADME/PK properties.

PTI-801

*Triple combinations of the PTI corrector on top of tezacaftor and ivacaftor.*
In Vitro PTI’s Amplifier and Corrector Synergize with Known CFTR Modulators in Heterozygote (F508del/G542X) Patient Cells

- PTI amplifier/corrector combination is superior to both luma/iva and teza/iva
- PTI doublet (corrector/potentiatior) is complementary to teza/iva, the combination achieves highest rescue reported to date in HBE heterozygote cells («het/min»)
- PTI believes PTI-428 and PTI-801 can be developed as add ons to both luma/iva and teza/iva
- PTI triple combination provides full restoration of CFTR activity in F508del heterozygotes («het/min»)
Unique Features of PTI CF Product Candidates Allow for Differentiated Clinical Development Strategy

Limited availability and eligibility of CF patients for investigational clinical trials can negatively impact study duration and costs.

Differentiated profile of PTI drug candidates allows for a unique clinical development strategy that could circumvent potential pitfalls faced by other investigational drugs.

- Approximately 1 out of 2 CF patients are eligible for approved disease modifying drugs (Orkambi, Kalydeco) in the US and thus not likely to participate in clinical trials that require treatment suspension.
- Approximately 1 out of 6 patients are being targeted by currently ongoing clinical studies in the US.

- **PTI-428**
  - Phase 1 study will be performed in CF patients on as-come basis regardless of CFTR genotype.
  - Studies will be conducted in patients already on standard of care and all patients will receive marketed drugs.

- **PTI-NC-733 (PTI-428/PTI-801/PTI-808)**
  - The combination of the corrector and potentiator in PTI-NC-733 has demonstrated superior *in vitro* efficacy compared to the combination of lumacaftor and ivacaftor.
- Based on *in vitro* studies, PTI-801, a novel corrector, is synergistic with ORKMABI® (lumacaftor/ivacaftor) and tezacaftor/ivacaftor and PTI believes can be developed as add on to these combinations upon its approval.

- Active IND under FDA

- Phase 1 study in healthy volunteers initiated in Q1 2017

- Topline efficacy data in CF subjects actively taking Orkambi expected in 2H 2017
PTI-NC-733 Proof-of-Concept Study Targeted to Start 2H 2017 and Topline Data Expected in 1H 2018

<table>
<thead>
<tr>
<th>2017</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Q2</td>
</tr>
<tr>
<td>PTI-428</td>
<td>PTI-428</td>
</tr>
<tr>
<td>PTI-808</td>
<td>PTI-NC-733</td>
</tr>
</tbody>
</table>

Parallel trials testing safety of single drug candidates PTI-801 and PTI-808

Parallel testing of combination regimens in dose-ranging and proof-of-concept* studies

- PTI-801 and Orkambi in F508del homozygous CF patients
- PTI-NC-733 in CF patients with at least one F508del allele

* Pending positive Phase 1 data
Key Upcoming Milestones

☑ Q1 2017: PTI-801 IND Submission
- Q2 2017: PTI-428 preliminary data as measured by FEV₁
- Q2 2017: PTI-808 IND submission
- 2H 2017: PTI-801 Phase 1 topline data
- 2H 2017: PTI-808 Phase 1 initiation
- 2H 2017: PTI-801, PTI-808 and PTI-NC-733 Phase 2 initiation*
- 1H 2018: PTI-801, 808 and PTI-NC-733 Phase 2 Topline data

* If PTI-428 Phase 1 trial is successful