PROTEON THERAPEUTICS INC
Form 10-K
March 14, 2016

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, DC 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2015

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: 001-36323

PROTEON THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

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

200 West Street
Waltham, MA

(Address of principal executive offices)

02451

(Zip Code)

(781) 890-0102

(Registrant’s telephone number, including area code)

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes [X] No [ ]

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definitions of “large accelerated filer,” “accelerated filer” and “smaller reporting company” in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer [ ]	Accelerated filer [X]
Non-accelerated filer [ ] (Do not check if a smaller reporting company)	Smaller reporting company [ ]

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

EXPLANATORY NOTE: Under the Jumpstart Our Business Startups Act, the registrant qualifies as an “emerging growth company.” We therefore incorporate the scaled disclosures required of an emerging growth company in this Annual Report on Form 10-K.

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, based on the closing price for such stock as reported on the NASDAQ Global Market on June 30, 2015, the last business day of the registrant’s most recently completed second quarter, was: $294.0 million.

As of March 10, 2016 there were 16,507,894 shares of the registrant’s common stock, par value $0.001 per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2016 Annual Meeting of Stockholders, which is expected to be filed with the Securities and Exchange Commission not later than 120 days after the end of the registrant's fiscal year ended December 31, 2015, are incorporated by reference into Part III of this Annual Report on Form 10-K. With the exception of the portions of the registrant's definitive proxy statement for its 2016 Annual Meeting of Stockholders that are expressly incorporated by reference into this Annual Report on Form 10-K, such proxy statement shall not be deemed filed as part of this Annual Report on Form 10-K.

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PART IV

CAUTIONARY NOTE FORWARD-LOOKING STATEMENTS

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

- the timing of completing enrollment or releasing data or results of our ongoing and planned clinical trials for vonapanitase (formerly PRT-201);
- our estimates regarding the amount of funds we require to complete our two planned Phase 3 clinical trials for vonapanitase;
- whether and when we may submit a Biologics License Application or a supplemental Biologics License Application;
- our search for additional product opportunities;
- the sufficiency of existing facilities to meet our needs;
- whether we will need to conduct any additional studies after our Phase 3 trials;
- our estimates regarding the amount of funds required to fund operations into the fourth quarter of 2017;
- our plans to fund our chemistry, manufacturing and controls;
- our estimates regarding expenses, future revenues, capital requirements, the sufficiency of our current and expected cash resources and our need for additional financing and plans for additional financing;
- our estimate of when we will require additional funding;
- our plans to commercialize and bring vonapanitase to market;
- the timing of, and our ability to, obtain and maintain regulatory approvals for our product candidates, including vonapanitase;
- the timing of a clinical trial of vonapanitase in Europe, results and submission of a Marketing Authorization Application;
- our interpretation of the data from our completed Phase 2 trial for vonapanitase;
- the rate and degree of market acceptance and clinical utility of any approved product candidate and the general market for the prevention of vascular access failure;

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the potential benefits of strategic partnership agreements and our ability to enter into selective strategic partnership arrangements;

- our ability to quickly and efficiently identify and develop additional product candidates;

- our commercialization, marketing, distribution and manufacturing capabilities, strategy and expenses;
- timing to recruit and expand our employee base and sales force, both in and outside the United States;
- plans to initiate Phase 1 or Phase 1/2 trials in symptomatic peripheral artery disease or other indications;
- the reimbursement of vonapanitase;
- our research and development costs;
- our general and administrative costs and salary and personnel costs;
- the costs associated with preparation for commercial operations;
- the costs associated with being a public company;
- our intellectual property position;
- our plans to seek patent protection in available countries;
- our expectations that vonapanitase will qualify for a 12-year period of exclusivity;
- our reliance on third parties as suppliers and manufactures;
- our plans to build out compliance, financial and operating infrastructure after Phase 3 completion;
- our plans to improve existing, and implement new, systems to manage our business;
- future payment of dividends;
- the impact of accounting policies;
- the impact of changes in interest rates;
- exposure to foreign currency exchange risks;
- our purchase of forward foreign currency contracts in the future; and
- the continued adoption of stock trading plans by employees, including executive officers.

All forward-looking statements in this Annual Report on Form 10-K involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, the risk factors set forth below in Part II, Item 1A, Risk Factors, and elsewhere in this Annual Report on Form 10-K. These factors should not be construed as exhaustive and should be read in conjunction with the other cautionary statements that are included in this Annual Report on Form 10-K. 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.

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

NOTE REGARDING STOCK SPLIT

Unless otherwise indicated, all information in this Annual Report on Form 10-K and in our condensed consolidated financial statements gives retrospective effect to 1-for-15.87 reverse stock split of our common stock that was effected on October 6, 2014. All share, share equivalent and per share amounts presented herein have been adjusted to reflect the reverse stock split. The ratios by which shares of preferred stock were converted into shares of common stock upon consummation of our initial public offering have been adjusted to reflect the effects of the reverse stock split.

PART I

Item 1. Business

Unless the context requires otherwise, references in this Annual Report on Form 10-K to "Proteon", "we", "us" and "our" refer to Proteon Therapeutics, Inc.

Overview

We are a late-stage biopharmaceutical company focused on the development of novel, first-in-class pharmaceuticals to address the needs of patients with renal and vascular disease. Our product candidate, vonapanitase (formerly PRT-201), is a recombinant human elastase that we are developing to reduce vascular access failure in patients with chronic kidney disease undergoing or planning for hemodialysis, a lifesaving treatment that cannot be conducted without a functioning vascular access. We believe the data from our completed Phase 2 trial of vonapanitase in patients undergoing creation of an arteriovenous fistula, or AVF, support that a one-time, local application of vonapanitase during AVF surgical creation reduces AVF failure, thereby improving patient outcomes and reducing the burden on patients and the healthcare system. We are not aware of any approved preventative treatments to reduce the failure rate of AVFs. We began enrolling patients in our first Phase 3 clinical trial of vonapanitase, PATENCY-1, during the third quarter of 2014 for patients undergoing creation of a radiocephalic AVF, completed patient enrollment in October 2015 and expect to release top-line data in December 2016. We enrolled the first patient in our second Phase 3 trial, PATENCY-2, in August 2015 and expect to complete enrollment in the first quarter of 2017.

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The need to improve vascular access outcomes is well established in the hemodialysis community. A 2014 publication estimated the total cost of managing hemodialysis vascular access dysfunction in the United States to be approximately $2.9 billion annually. AVFs are the gold standard of vascular access for hemodialysis, given they are associated with fewer complications and reduced rates of hospitalization as compared to other forms of vascular access. We estimate there are approximately 130,000 AVFs created in the United States annually, a procedure in which a surgeon transects a vein and sutures it to the side of a nearby artery, typically in the arm. However, AVFs have a greater than 50% failure rate in their first year after creation, resulting in frequent surgical or interventional procedures and a high rate of abandonment, leading to increased morbidity, mortality and costs of care. Function can usually be restored via additional procedures, either an intervention such as angioplasty, which is dilation of a blood vessel with a balloon, or a surgical revision. These procedures, however, are costly, invasive, painful, associated with a number of complications and often need to be repeated. AVF patients in the United States on average require greater than 1.5 procedures per year, each of which typically costs Medicare between $5,000 and $13,000.

We have demonstrated that vonapanitase generates fragments of elastin, a protein present in blood vessels, and we believe the fragments of elastin inhibit formation of neointimal hyperplasia, which is the growth of tissue inside vessels that narrows AVFs and reduces blood flow. During AVF creation surgery, a surgeon would administer drops of vonapanitase onto the surface of the artery and vein of an AVF for 10 minutes followed by a saline irrigation. We believe that a one-time, local application of vonapanitase to the external surface of the vessels during AVF surgical creation can modify the injury response, or scarring, resulting from surgery and thereby reduce the severity of neointimal hyperplasia and AVF failure following surgery.

In 2012, we completed a multicenter, randomized double-blind, placebo-controlled Phase 2 trial of vonapanitase in 151 patients undergoing surgical creation of an AVF in the wrist, known as radiocephalic AVFs, or upper arm, known as brachiocephalic AVFs. The primary efficacy endpoint was primary unassisted patency, defined as the time from surgical creation of the AVF to occurrence of a thrombosis or an intervention such as angioplasty, to restore or maintain patency, or functionality. Both the 10 microgram and 30 microgram doses of vonapanitase showed a trend toward efficacy on the primary endpoint, although neither dose met the primary endpoint with statistical significance. For all AVFs, median patency, the time at which 50% of patients in a group lost primary unassisted patency, was 224 days in the placebo group and greater than 365 days in each of the vonapanitase treatment groups, indicating that vonapanitase prolonged primary unassisted patency. In the trial, patients treated with vonapanitase reported adverse events comparable to placebo. These events were consistent with the medical events experienced by chronic kidney disease patients undergoing AVF creation surgery.

An analysis of the primary endpoint data revealed an uneven distribution in patency loss events in patients with a brachiocephalic AVF due to central stenosis in the shoulder and chest, remote from the site of an AVF. Central stenoses commonly exist prior to AVF creation and are unmasked following creation of brachiocephalic AVFs, which have higher blood flow than radiocephalic AVFs. These stenoses are unrelated to treatment with vonapanitase. To correct for this uneven distribution, we conducted a non-prespecified analysis of the primary endpoint that excluded patency loss events due to central stenoses. This analysis demonstrated a significant reduction in the risk of primary unassisted patency loss in the 30 microgram vonapanitase dose group (p=0.04) compared to placebo.

The benefit of vonapanitase on primary unassisted patency was most pronounced in the subset of patients undergoing creation of a radiocephalic AVF. The subset analysis of this endpoint for radiocephalic AVF patients receiving the 30 microgram dose, which was not prespecified, showed a significant increase in median primary unassisted patency of >365 days as compared to 125 days in the placebo group. In addition, we observed beneficial drug effects on additional efficacy endpoints, including unassisted maturation, defined as increased vessel diameter and blood flow without the need for an intervention such as angioplasty; rate of procedures to restore or maintain AVF patency; secondary patency, defined as abandonment of the AVF and the need for creation of a new vascular access; use for hemodialysis; and hemodynamically significant stenosis, or narrowing of blood vessels.

In April 2013, we held an end of Phase 2 meeting with the United States Food and Drug Administration, or FDA, during which we confirmed elements of our Phase 3 development plan, including the primary endpoint. We are conducting two 300-patient Phase 3 trials of vonapanitase using a 30 microgram dose, enrolling only patients undergoing a surgical procedure to create a radiocephalic AVF. We began enrolling patients in our first Phase 3 clinical trial of vonapanitase, PATENCY-1, during the third quarter of 2014 for patients undergoing creation of radiocephalic AVFs, completed patient enrollment in October 2015 and expect to release top-line data in December 2016. We enrolled the first patient in our second Phase 3 trial, PATENCY-2, in August 2015 and expect to complete enrollment in the first quarter of 2017. While the FDA offered no assurances that it will not require us to conduct any additional clinical studies, we believe we will not need to conduct any additional clinical studies after our Phase 3 trials. Further, if the results of the first Phase 3 trial are sufficiently compelling, we intend to meet with the FDA to discuss the possibility of submitting a Biologics License Application, or BLA, supported by the single Phase 3 trial and may decide to submit a BLA to the FDA prior to completing the second Phase 3 trial. Vonapanitase has received fast track designation from the FDA which is designed to facilitate the development and expedite the review of drugs and biologics to treat serious conditions and fill an unmet medical need, and orphan drug designation in the United States and European Union, for hemodialysis vascular access indications.

We believe that if our Phase 3 clinical program is successful vonapanitase will potentially become the standard of care for patients with chronic kidney disease, or CKD, who are undergoing surgical creation of a radiocephalic AVF. We retain worldwide commercial rights to vonapanitase. If approved by regulatory authorities, we intend to commercialize this product in the United States ourselves with a specialty hospital sales force, focused primarily on vascular surgeons, and intend to seek one or more collaborators to commercialize the product in additional markets. Our patents include claims covering formulations, methods of manufacturing and use of elastases, providing protection in the United States through mid-2029 and European Union through 2028, with potential extension through 2032 in the United States and in the European Union.

Our Strengths

We believe our company and vonapanitase possess the following attributes that increase the likelihood that we will be successful in developing and commercializing vonapanitase:

- *Entering Phase 3 trials for radiocephalic AVF creation.* We are conducting two Phase 3 clinical trials in radiocephalic AVF creation using a 30 microgram dose of vonapanitase, the population and dose in which, in a non-prespecified analysis, we observed an improvement in primary unassisted patency with vonapanitase in our Phase 2 trial.

- *Phase 3 endpoints same as our Phase 2 trial.* The primary endpoint in our Phase 3 trials, primary unassisted patency, is the same as we used in our Phase 2 trial. In addition, our secondary endpoint (secondary patency) and tertiary endpoints (unassisted maturation, use for hemodialysis and average procedure rates) in our Phase 3 trials were all endpoints in our Phase 2 trial. In April 2013, we held an end of Phase 2 meeting with the FDA during which we confirmed elements of our Phase 3 development plan, including the primary endpoint.

- *Safety profile supports approval.* Based on results from our clinical trials and preclinical studies, we believe vonapanitase, which is administered once and only acts locally, has demonstrated a favorable safety profile. Because vonapanitase is administered in a one-time, local application and is inactivated by antiproteases, substances that inhibit the activity of a protease, in the blood, there is no systemic activity. In clinical trials assessing safety, there were no material increases in adverse events in the vonapanitase treatment groups as compared to placebo and no material findings related to physical examinations or clinical laboratory testing including chemistry, hematology and coagulation panels or antibodies to vonapanitase. At our end of Phase 2 meeting with the FDA, we confirmed that we do not need to conduct any additional preclinical studies to support a BLA filing.

Unmet medical need. While AVFs are considered the most desirable form of vascular access by the medical community, they are also associated with high failure rates, a serious complication for hemodialysis patients that results in substantially higher healthcare costs. A 2014 publication estimated the total cost of managing hemodialysis vascular access dysfunction in the United States to be approximately $2.9 billion annually. We are not aware of any approved preventative treatments to reduce AVF failure rate. Vonapanitase has received fast track designation from the FDA, which is designed to facilitate the development and possibly expedite the review of drugs and biologics to treat serious conditions and fill an unmet medical need. We believe vonapanitase reduces vascular access failure in patients with CKD undergoing hemodialysis and, if approved, could become the standard of care by reducing the cycle of interventions, improving patient outcomes and reducing the overall burden on patients and the healthcare system.

Substantial and readily-addressable market opportunity. If vonapanitase is approved, we intend to commercialize this product in the United States and potentially certain European countries ourselves with a specialty hospital sales force, focused primarily on vascular surgeons, and intend to seek one or more collaborators to commercialize the product in additional markets. We estimate a sales force of approximately 75-100 representatives will enable us to call on the approximately 1,300 hospitals that account for more than 90% of the AVF surgical creations performed in the United States annually. We believe vonapanitase will be supported by key stakeholders, including referring nephrologists, patient advocacy groups, large dialysis organizations and payors. We believe vonapanitase will be reimbursed adequately as costs related to AVF surgical creation, which is typically performed in the hospital outpatient setting, are not included in the End Stage Renal Disease, or ESRD bundle, the single bundled payment from Medicare for a number of the costs of hemodialysis treatments, medications, labs and supplies for patients with end-stage renal disease.

- *Experienced team.* Our executive management team has extensive experience in the renal and vascular disease fields through their substantial involvement in companies such as Abbott, AMAG, GelTex, Genzyme, Glaxo and Merck. Our Chief Executive Officer and Chief Medical Officer were senior executives at GelTex, a biopharmaceutical company, where they played leading roles in the development and commercialization of Renagel, a treatment for hemodialysis patients that led to Genzyme's acquisition of GelTex for more than $1 billion. Our Senior Vice President of Marketing was a senior executive at AMAG Pharmaceuticals, a biopharmaceutical company, where he played a leading role in the commercialization of Feraheme for iron-deficiency anemia in adults with chronic kidney disease.

Our Strategy

Our strategy is to develop and commercialize vonapanitase for patients suffering from renal and vascular diseases, beginning with patients with CKD undergoing surgical creation of a radiocephalic AVF. Key elements of our strategy include our plans to:

- *Complete clinical development of vonapanitase and seek regulatory approval in the United States in its lead indication.* We commenced our first Phase 3 clinical trial of vonapanitase for patients with CKD undergoing creation of a radiocephalic AVF in the third quarter of 2014. Prior to completing enrollment in the first Phase 3 trial, we enrolled the first patient in our second Phase 3 trial in August 2015 and expect to complete enrollment in first quarter of 2017. If the results of the first Phase 3 trial, data expected in December 2016, are sufficiently compelling, we intend to meet with the FDA to discuss the possibility of submitting a BLA supported by the single Phase 3 trial and may decide to submit a BLA to the FDA prior to obtaining data from the second Phase 3 trial.

- *Commercialize vonapanitase directly in the United States.* If vonapanitase is approved by the FDA, we intend to commercialize it ourselves in the United States with a specialty hospital sales force focused primarily on vascular surgeons. There are approximately 2,800 vascular surgeons in the United States. In 2013, according to the U.S. Renal Data System 2015 Annual Data Report, there were approximately 421,000 hemodialysis patients in the United States at the end of the year. Based on various third-party sources, we estimate that approximately 130,000 AVFs are placed annually. We believe a specialty hospital sales force of approximately 75-100 representatives will enable us to call on the approximately 1,300 hospitals that account for more than 90% of the AVF surgical creations performed in the United States annually. We believe that vonapanitase's potential benefits to patients undergoing surgical creation of an AVF will result in its broad adoption.

- *Undertake clinical development of vonapanitase in Europe and establish partnerships for commercialization of vonapanitase in all or parts of Europe.* We are currently evaluating our existing clinical program to support filing in Europe. We may, based on additional data including the data from our Phase 3 clinical trials in the United States and if sufficient funds become available, choose to conduct a clinical trial of vonapanitase in Europe. We estimate that there are approximately 315,000 hemodialysis patients in Europe. Prior to enrolling our first patient in Europe, we plan to formally seek guidance from the European Medicines Agency, or EMA, regarding its requirements for regulatory approval. We expect results from this trial to be available two to three years after the first patient is enrolled. If this European trial successfully meets its primary endpoint and depending on the guidance obtained from the EMA, we would expect to submit a Marketing Authorization Application, or MAA. If vonapanitase is approved by the EMA, we intend to commercialize it in European countries with our own specialty hospital sales force or with a commercial partner, or a combination thereof. Like in the United States, we intend to target both vascular surgeons who create AVFs as well as key referring nephrologists.

- *Pursue additional indications for vonapanitase.* We believe that our Phase 2 clinical data support further development of vonapanitase in brachiocephalic AVF creation. We may, based on additional data including the data from our Phase 3 clinical trials and if sufficient funds become available, study the effects of a 30 microgram dose of vonapanitase versus placebo on brachiocephalic AVFs. If this trial were to successfully meet its primary endpoint, we would expect to submit a supplemental BLA, or sBLA, to the FDA and a supplemental MAA, or sMAA, to the EMA. Further, if sufficient funds become available and after reviewing the results from our Phase 3 clinical trials, we may commence a clinical trial of vonapanitase in patients undergoing placement of an arteriovenous graft, or AVG. We believe vonapanitase's potential to reduce neointimal hyperplasia could offer a significant medical benefit in these patients. Further, we plan to commence three Phase 1 clinical trials of vonapanitase in patients with peripheral artery disease, or PAD. We believe vonapanitase's potential to reduce neointimal hyperplasia and/or dilate blood vessels could offer a significant medical benefit in these patients.

- *Establish partnerships for development and commercialization of vonapanitase in Japan and other Asian countries.* We estimate that in 2013 there were approximately 315,000 patients on hemodialysis in Japan and more than 800,000 throughout all of Asia. Approximately 90% of Japanese hemodialysis patients receive AVFs. We may enter into collaborations for the development and commercialization of vonapanitase in Asia.

- *In-license or acquire additional product opportunities.* We plan to search for additional product opportunities that could be sold and marketed by the specialty hospital sales force required to successfully launch vonapanitase in the United States if it is approved for marketing.

Background on Hemodialysis

Healthy kidneys serve many functions, including removing waste and excess water, helping to control blood pressure and keeping electrolytes, such as sodium and potassium, in balance. Patients with CKD have lost most or all kidney function, most commonly due to diabetes or hypertension. Kidney disease is progressive and once a patient has reached end-stage CKD, the kidneys are no longer able to remove waste and fluids from the body. At this point, some form of renal replacement therapy is required, such as hemodialysis, in which blood is processed by a hemodialysis machine, peritoneal dialysis, a process using a cavity in the abdomen called the peritoneum as a membrane across which fluids are exchanged from the blood, or kidney transplant.

According to the U.S. Renal Data System 2015 Annual Data Report, in 2013 there were approximately 421,000 hemodialysis patients in the United States, and an incremental 103,000 patients initiated hemodialysis in the United States. As reported by Fresenius Medical, a major provider of hemodialysis services and renal care products, in 2013 there were approximately 315,000 hemodialysis patients in Europe, 315,000 hemodialysis patients in Japan and 2.2 million hemodialysis patients worldwide, with an annual worldwide growth rate of 6-7%.

Hemodialysis is the most common form of treatment for end-stage CKD. Hemodialysis is a chronic therapy performed by cannulating, or piercing, a vein with a large bore needle so that blood can be pumped through a hemodialysis machine, which removes waste and excess fluid normally excreted by the kidney. The cleansed blood is then returned to the same vein via a second needle. A hemodialysis session typically lasts three to four hours and is performed three times a week in an outpatient dialysis clinic.

To enable sufficient blood to pass through the hemodialysis machine to complete treatment within four hours, a vein must have blood flow of at least 500 milliliters per minute. The arm is the most convenient location for accessing the blood stream on a recurring basis, but blood flow in the arm is approximately 50 milliliters per minute. Therefore, most hemodialysis patients undergo a surgical procedure in which a surgeon establishes a direct connection between an artery and a vein to create a high flow circuit of sufficient diameter, most often in an arm. The direct artery-vein connection effectively bypasses the capillary circulation in the hand and leads to a process known as maturation, where the internal diameter, or lumen, of the vein and blood flow increase over a period of weeks, resulting in a lumen diameter greater than 4 millimeters and blood flow of 500-2,000 milliliters per minute in successful cases.

The gold standard for vascular access is an AVF, in which a surgeon transects a vein in the arm and sutures it to the side of a nearby artery. AVFs are preferred because they are less prone to patency loss than are AVGs; approximately 50% of AVFs and up to 75% of AVGs will lose primary patency and 20-30% of AVFs and 28-35% of AVGs will lose secondary patency in the first year after surgical placement. As compared to AVGs, AVFs require approximately 40% fewer interventional or surgical procedures and suffer from a rate of vascular access infection that is 54% lower. Patients dialyzing with an AVF have lower rates of thrombosis and hospitalization, longer survival, reduced mortality and lower cost of care. Beyond the substantial medical advantages of an AVF, available data from the U.S. Renal Data System show that patients who dialyze with an AVF cost Medicare approximately $15,000 less annually than patients who dialyze with an AVG and approximately $25,000 less annually than patients who dialyze with a catheter. According to published data, approximately 67% of hemodialysis patients in the United States dialyze with an AVF compared to 67-83% of patients in the major European countries and approximately 90% of patients in Japan.

Based on various third-party sources, we estimate there are approximately 130,000 AVFs created in the United States annually. There are a limited number of potential artery-vein combinations in the arm that can be used to create an AVF, principally the following:

- radiocephalic AVF at the wrist (radial artery sutured to cephalic vein), which we estimate is created in 40% of new AVF creations;
- brachiocephalic AVF at the elbow (brachial artery sutured to cephalic vein), which we estimate is created in 50% of new AVF creations; and
- brachiobasilic AVF in the upper arm (brachial artery sutured to basilic vein), which we estimate is created in 10% of new AVF creations.

The medical community endorses radiocephalic AVFs as the optimal form of vascular access and the recommended first choice for new hemodialysis patients. Creating the vascular access site at the wrist preserves the potential future use of other access further up in the arm, is simpler to create, and is less likely to create heart failure or steal syndrome, where the diversion of flow through the AVF reduces blood to the hand. Radiocephalic AVFs are also less likely to suffer from central stenoses in the shoulder and chest, remote from the site of the AVF. The Kidney Disease Outcome Quality Initiative Guidelines, or KDOQI Guidelines, authored by the National Kidney Foundation, or NKF, specifically recommend starting with a radiocephalic AVF if possible, stating that "starting [closer to the hand] and moving [further up the arm] provides for the possibility of preserving as many potential sites as possible for future access creation." If a radiocephalic AVF must be abandoned, a surgeon can create a new vascular access higher up the arm, most likely a brachiocephalic AVF. However, if a brachiocephalic AVF is placed first, the surgeon cannot later move down that same arm to create a radiocephalic AVF because the cephalic vein has already been transected for use in the brachiocephalic AVF.

Radiocephalic (wrist) AVFs suffer from high rates of patency loss and maturation failure, with up to 70% being subject to primary unassisted patency loss and up to 35% being abandoned within 12 months after their surgical creation. Patency loss in radiocephalic AVFs occurs due to stenosis formation at or near the AVF 75-95% of the time. Some patients never receive a radiocephalic AVF because the surgeon believes the risk of failure is too high for those patients. These patients will typically undergo creation of an AVF higher up on the arm and permanently lose at least one of their access sites. We believe that the number of radiocephalic AVFs created annually may rise if vonapanitase improves outcomes and allows vascular surgeons to create radiocephalic AVFs in sites that they previously considered to pose an unacceptably high risk of failure.

The second choice for vascular access after AVF is an AVG in which a surgeon connects an artery and vein using a synthetic tube. Based on reported data, approximately 19% of hemodialysis patients in the United States dialyze with an AVG, compared to approximately 5-12% of patients in the major European countries and approximately 7% of patients in Japan.

The least desirable type of vascular access is a catheter, a plastic tube that is placed directly through the skin into a vein, typically via an incision in the neck enabling placement of the catheter into a large vein that leads directly to the heart. The catheter connects the patient's vasculature to the hemodialysis machine. Because the catheter penetrates the skin continuously, it is subject to a high risk of infection and increased mortality. One of the primary goals of hemodialysis care is to keep patients off catheters. However, patients most often initiate hemodialysis through a catheter until an AVG or AVF is ready to be used, and are dialyzed temporarily through a catheter when the AVF or AVG they have been using fails and a new one has to be created. Approximately 14% of hemodialysis patients in the United States dialyze with a catheter, compared to 10-28% of patients in the major European countries and 2% of patients in Japan, based on published data.

Established Medical Need

The need to improve vascular access outcomes is well established in the hemodialysis community. The health-related and economic cost of creating and maintaining vascular access for hemodialysis has led to a global effort to address the problem. Over the last 10 years, the NKF has established guidelines in an effort to increase the use of AVFs while reducing the rate of complications, mostly through the identification and promulgation of best practices. The National Institutes of Health, or NIH, joined the effort in 2000 with the creation of a multi-center consortium of medical centers, the Dialysis Access Clinical Trials Consortium to coordinate the testing of new treatments designed to improve AVF and AVG outcomes. The intensity of these efforts increased markedly in 2004, when the Centers for Medicare and Medicaid Services, or CMS, reacting to health and economic data, announced the "Fistula First" initiative to increase the use of AVFs while reducing complications. According to Fistula First, AVFs should be considered for every patient needing hemodialysis because AVFs last longer than AVGs, require fewer surgical and endovascular interventions, are associated with lower rates of infection, hospitalization and death, and are less costly. As a result of these efforts, AVF use has approximately doubled since 2004 to 67% of United States hemodialysis patients.

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A major problem with AVFs and AVGs is patency loss, in which the access experiences either a significant or complete reduction in blood flow, precluding hemodialysis and placing the access at risk of abandonment. However, the increased use of AVFs has led to a concurrent increase in AVF patency loss as AVFs are placed in patients with higher risks of AVF failure, such as the elderly, diabetics or patients with smaller blood vessels. Additionally, physicians have become more aggressive in monitoring and intervening earlier upon AVFs in an attempt to treat patency loss before it results in abandonment of that access site. These factors have resulted in an approximate doubling in the rate of AVF interventions in less than a decade.

We are not aware of any approved preventative measures to reduce the rate of vascular access patency loss, and the clinical implications of patency loss are severe. An episode of patency loss must be addressed urgently to restore blood flow, enable the patient to resume hemodialysis and avoid access abandonment. Treatment of patency loss typically involves an outpatient procedure, either an endovascular intervention, such as balloon angioplasty, stenting or thrombectomy, or a surgical revision.

Procedures to address patency loss are invasive, painful, and associated with a number of complications, and there are a number of problems associated with them, including:

- *The procedures are not always successful in restoring patency.* Procedures to address AVF patency loss are unsuccessful up to 27% of the time. When these procedures are unsuccessful or the physician determines that a procedure to restore patency is futile, the access site must be abandoned, resulting in the urgent need for catheter placement to enable hemodialysis. Recent data indicate that hemodialysis patients who switch from a permanent vascular access to a catheter have a mortality rate that is double those who remain on a permanent access. Access abandonment also results in surgical creation of a new AVF or placement of a new AVG, reducing the number of future access sites available to the patient.

The procedures often fail to provide a durable benefit, resulting in a cycle of interventions for the patient. Recent data indicate that 50% of AVFs that undergo angioplasty to treat patency loss experience another episode of patency loss within 12 months, resulting in the need for additional procedures to restore patency. AVF patients in the United States on average require greater than 1.5 procedures per year, each of which typically costs Medicare between $5,000 and $13,000. A United States hospital recently published data indicating that maintaining a radiocephalic AVF can cost on average more than $17,000 in the first year after surgical creation and in excess of $40,000 for the first and second year after surgical creation. A 2014 publication estimated the total cost of managing vascular access dysfunction in the United States to be approximately $2.9 billion annually.

AVFs and AVGs are also prone to secondary patency loss, in which the access must be abandoned. Patients on hemodialysis must dialyze with a catheter until a new permanent access can be surgically placed and becomes usable for hemodialysis, a process that typically requires a minimum of three months for AVFs. During this time, patients are at a heightened risk of serious infection, hospitalization and death. According to the U.S. Renal Data System, in 2011 hemodialysis patients averaged approximately 11 hospital days per year.

Vonapanitase

Vonapanitase is a recombinant human elastase under development as a treatment to prevent AVF and AVG patency loss. We enrolled the first patient in the first of two Phase 3 trials, PATENCY-1, for vonapanitase in radiocephalic AVF, our lead indication, in the third quarter of 2014, completed patient enrollment in October 2015, and expect to release top-line data in December 2016. In addition, we enrolled the first patient in the second Phase 3 trial, PATENCY-2, in August 2015 and expect to complete enrollment in the first quarter of 2017.

Mechanism of Action

AVF patency loss occurs most commonly due to progressive scarring in the wall of the outflow vein near the lumen, resulting in stenosis of the lumen of the vein and obstruction of blood flow in the AVF. This form of vascular scarring is commonly known as neointimal hyperplasia. When surgeons create an AVF they handle and manipulate blood vessels resulting in mechanical vessel injury. Furthermore, after AVF creation the rapid flow of blood from the artery into the outflow vein results in unnatural physiologic changes and mechanical stresses in the vein wall. The response of the vein to this injury and stress results in activation and recruitment of scar forming cells, which multiply and migrate from the outside wall to the inside wall of the blood vessel and produce a thick layer of tissue, creating a narrowing in the vein lumen and a reduction in AVF blood flow. This blood vessel response to injury occurs during the first two to three weeks following vascular surgery and is shown in the following figure:

Vessel Injury During AVF and AVG Surgical Placement Results in Stenosis Formation

We demonstrated through pre-clinical trials that vonapanitase fragments elastin, a protein present in blood vessel walls. The fragmentation of elastin in the outside wall of the blood vessel is thought to inhibit formation of neointimal hyperplasia thereby reducing the risk of patency loss. Elastase causes localized fragmentation of elastin protein fibers present in blood vessel walls. The elastin fragments generated by elastase are chemoattractants for scar forming cells, meaning that the fragments attract these scar forming cells, inhibiting their migration to the lumen. The cells recognize the elastin fragments via receptors present on the cell surface that bind to specific elastin fragment sub-types. The importance of elastin fragments in vascular biology, including the response to vascular injury has been established in the scientific literature over three decades. Published academic studies conducted in animals provide evidence that fragmentation of elastin in the outer wall of the blood vessels from administration of elastase after vascular injury resulted in a 38-42% reduction in neointimal hyperplasia at 28 days following the surgical procedure. Based on our preclinical *in vivo* and *ex vivo* studies in human vessels, applying vonapanitase to the external surface of the blood vessels generates localized elastin fragments in the outside wall of injured blood vessels. We have established this effect in the doses we plan to advance in our clinical trials. We believe that a one-time, local application of a 30 microgram dose of vonapanitase to the external surface of the vessels during AVF surgical creation can reduce the vascular scarring on the inside of the vessel wall resulting from surgery and thereby reduce the severity of neointimal hyperplasia and the risk of AVF failure. During the AVF creation surgery, the surgeon administers drops of vonapanitase onto the surface of the artery and vein at the AVF for 10 minutes followed by a saline irrigation. We believe the elastin fragments that are generated by vonapanitase attract scar forming cells to the outside wall of the injured vessel, reducing their movement to the inside wall of the vessel, thereby inhibiting lumen stenosis. This mechanism is portrayed in the following figure:

We Believe Vonapanitase Treatment Inhibits Stenosis Formation

This injury response and the role of elastase-generated fragments are operative in other cardiovascular surgeries, such as bypass, and interventional procedures, such as angioplasty.

Clinical Development of Vonapanitase

Our Phase 2 AVF Clinical Trial

In 2012, we completed a multicenter, randomized, double-blind, placebo-controlled Phase 2 trial of vonapanitase in AVF that treated 151 patients with CKD undergoing creation of a radiocephalic AVF (n=67) or brachiocephalic AVF (n=84). Patients were treated with vonapanitase at doses of 10 or 30 micrograms or placebo at the time of AVF creation and were followed for up to 12 months.

Primary endpoint

The primary efficacy endpoint was primary unassisted patency over 12 months. Primary unassisted patency was defined as the time from access creation until the first occurrence of either AVF thrombosis or a procedure, such as balloon angioplasty, to restore or maintain patency.

Both doses of vonapanitase showed a trend toward efficacy, although neither dose met the primary endpoint with statistical significance. Median patency, the time at which 50% of patients in a group lost primary unassisted patency, was 224 days in the placebo group and greater than 365 days in each of the vonapanitase treatment groups indicating patency in the vonapanitase treatment groups was prolonged by vonapanitase. Treatment with vonapanitase at 10 and 30 microgram doses was associated with a reduction of 31% and 33%, respectively, in the risk of primary unassisted patency loss. After adjusting for differences in baseline characteristics associated with the risk of primary unassisted patency loss, treatment with vonapanitase at 10 and 30 microgram doses was associated with a reduction of 24% and 41%, respectively, in the risk of primary unassisted patency loss. The following Kaplan-Meier curves and table display primary unassisted patency for all AVFs.

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Primary Unassisted Patency—All AVFs

The table below shows the primary unassisted patency data in the placebo and vonapanitase treatment groups.

Reduction in Risk of Primary Unassisted Patency Loss vs. Placebo—All AVFs

	Vonapanitase	**Vonapanitase**
	10 microgram dose	**30 microgram dose**
Number of Patients	N=51	N=49
Unadjusted Risk vs. Placebo	-31% (p=0.19)	-33% (p=0.17)
Adjusted Risk(1) vs. Placebo	-24% (p=0.35)	-41% (p=0.10)

Note: Prespecified analysis.

(1) Adjusted for differences in baseline characteristics associated with the risk of primary unassisted patency loss between treatment groups using a prespecified Cox regression analysis.

Ninety-two patients with a patent AVF who completed 12 months of follow-up in the initial trial were followed in a registry to obtain additional data related to the efficacy endpoints. In this follow-up, the vonapanitase 30 mcg benefit on primary unassisted patency persisted out over a median of three years.

Radiocephalic AVFs. The benefit of vonapanitase on primary unassisted patency was more pronounced in the subset of patients undergoing creation of a radiocephalic AVF than in the subset of patients undergoing creation of a brachiocephalic AVF or all patients undergoing creation of an AVF. The subset analysis of this endpoint was not prespecified. The following Kaplan-Meier curves and table summarize the reduction in risk of primary unassisted patency loss in the subset of patients with radiocephalic AVFs. Treatment with vonapanitase at doses of 10 and 30 micrograms was associated with a reduction of 41% and 63%, respectively, in the risk of primary unassisted patency loss. Median patency was 125 days in the placebo group and 377 days in the 30 microgram group (in some cases the 12 month follow up occurred after day 365 due to patient schedules), indicating a significant improvement in primary unassisted patency.

Primary Unassisted Patency—Radiocephalic AVFs

Reduction in Risk of Primary Unassisted Patency Loss vs. Placebo—Radiocephalic AVFs

	Vonapanitase 10 micrograms	**Vonapanitase 30 micrograms**
Number of Patients	N=23	N=20
Unadjusted Risk vs. Placebo	-41% (p=0.18)	-63% (p=0.02)
Adjusted Risk(1) vs. Placebo	-40% (p=0.20)	-61% (p=0.04)

Note: Non-prespecified analysis.

(1) Adjusted for differences in baseline characteristics associated with the risk of primary unassisted patency loss between treatment groups using a prespecified Cox regression analysis.

Brachiocephalic AVFs. The benefit of vonapanitase on primary unassisted patency was less pronounced in the subset of patients undergoing creation of a brachiocephalic AVF. The subset analysis of this endpoint was not prespecified. The less pronounced benefit in brachiocephalic AVFs was in part due to an uneven distribution between brachiocephalic AVF groups in the number of patency loss events occurring in the central veins and cephalic arch, also known as central stenosis, which are remote from the site of the AVF. Patency loss in brachiocephalic AVFs occurs due to central stenosis 50% of the time. Central stenoses commonly exist prior to surgery due to the venous anatomy or scarring from a prior hemodialysis catheter, but are typically unmasked following creation of the higher blood flow brachiocephalic AVFs. Since vonapanitase is active locally at the site where it is applied on the AVF, and because we have demonstrated that vonapanitase is not active remotely, we believe that central stenoses are unrelated to vonapanitase. Therefore, to correct for this uneven distribution, we conducted a non-prespecified analysis of the primary endpoint in brachiocephalic AVFs which excluded patency loss events due to central stenoses. The following table summarizes the risk of primary unassisted patency loss in brachiocephalic AVFs including and then excluding patency loss events related to central stenoses.

Reduction in Risk of Primary Unassisted Patency Loss vs. Placebo—Brachiocephalic AVFs

	Vonapanitase 10 micrograms	**Vonapanitase 30 micrograms**
Number of Patients	N=28	N=29
Unadjusted Risk vs. Placebo	-14% (p=0.72)	+10% (p=0.82)
Unadjusted Risk vs. Placebo Excluding Central Stenoses	-12% (p=0.76)	-26% (p=0.46)

Note: Non-prespecified analysis.

We also conducted a non-prespecified analysis across all patients of the primary endpoint correcting for this uneven distribution in central stenoses. The following Kaplan-Meier curves for primary unassisted patency for all AVFs (excluding central stenoses) and table demonstrate a significant reduction in the risk of primary unassisted patency loss for the 30 microgram dose (p=0.04, for the 30 microgram dose) versus placebo. Treatment with vonapanitase at doses of 10 and 30 micrograms was associated with a reduction of 31% and 48%, respectively, in the risk of primary unassisted patency loss. After adjusting for differences in baseline characteristics associated with the risk of primary unassisted patency loss, treatment with vonapanitase at doses of 10 and 30 micrograms was associated with a reduction of 25% and 52%, respectively, in the risk of primary unassisted patency loss.

Primary Unassisted Patency—All AVFs

(Excluding Central Stenoses)

Reduction in Risk of Primary Unassisted Patency Loss vs. Placebo—All AVFs

(Excluding Central Stenoses)

	Vonapanitase	**Vonapanitase**
	10 micrograms	**30 micrograms**
Number of Patients	N=51	N=49
Unadjusted Risk vs. Placebo	-31% (p=0.20)	-48% (p=0.04)
Adjusted Risk vs. Placebo(1)	-25% (p=0.33)	-52% (p=0.02)

Note: Non-prespecified analysis.

(1) Adjusted for differences in baseline characteristics associated with the risk of primary unassisted patency loss between treatment groups using a prespecified Cox regression analysis.

In a larger trial of brachiocephalic AVFs, we expect that the occurrence of patency loss due to central stenosis would be evenly distributed between treatment groups. In the ongoing Phase 3 clinical trials, we expect that patency loss due to central stenosis will be rare since we intend to enroll radiocephalic AVF patients exclusively, and radiocephalic AVFs rarely suffer from patency loss due to central stenosis because of lower blood flow. In our Phase 2 trial, no radiocephalic AVF in any group lost primary patency due to central stenosis.

Secondary and other endpoints

Vonapanitase showed results consistent with a beneficial effect on multiple secondary efficacy endpoints. The prespecified efficacy endpoints were unassisted maturation, secondary patency, use for hemodialysis and hemodynamically significant lumen stenosis. In addition, we performed a prespecified efficacy analysis of average rate of procedures to restore or maintain AVF patency, a component of our primary endpoint. As with the primary efficacy analyses, we performed a number of prespecified and exploratory analyses of the data from this Phase 2 trial.

- *Unassisted maturation*. Maturation is necessary for use of an AVF for hemodialysis. Unassisted maturation was defined as achieving maturation at three months without an intervention. Maturation was assessed using ultrasound measuring blood flow and lumen vein diameter. All ultrasounds were reviewed by a central reader masked to treatment assignment and AVF outcome. Two well-accepted criteria for measuring maturation were used, as shown in the footnotes in the table below. The 30 microgram dose, which we have included in our Phase 3 trials, showed

improvement in maturation at Month 3, with statistically significant benefit seen in all AVFs combined and patients receiving radiocephalic AVFs (figure below). In the subset of patients with brachiocephalic AVFs, there was a trend toward improvement in unassisted maturation at both the 10 and 30 microgram doses.

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Unassisted Maturation at Three Months—% of Patients (p-Value vs. Placebo)

	Placebo	Vonapanitase 10 micrograms	Vonapanitase 30 micrograms
All AVFs			
Number of Patients	N=39	N=39	N=37
Percentage Mature NKF-KDOQI(1)	46%	64% (p=0.11)	70% (p=0.03)
Percentage Mature Robbin(2)	67%	87% (p=0.03)	92% (p<0.01)
Radiocephalic AVFs			
Number of Patients	N=17	N=19	N=14
Percentage Mature NKF-KDOQI(1)	24%	37% (p=0.48)	57% (p=0.08)
Percentage Mature Robbin(2)	47%	74% (p=0.17)	93% (p<0.01)
Brachiocephalic AVFs			
Number of Patients	N=22	N=20	N=23
Percentage Mature NKF-KDOQI(1)	64%	90% (p=0.07)	78% (p=0.34)
Percentage Mature Robbin(2)	82%	100% (p=0.11)	91% (p=0.41)

Note: Prespecified analysis.

(1) National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) maturation is defined as average vein lumen diameter ≥6 millimeters and an outflow vein blood flow rate ≥600 milliliters/minute.

(2) Robbin maturation is defined as average vein lumen diameter ≥4 millimeters and an outflow vein blood flow rate ≥500 milliliters/minute.

Unassisted Maturation—Radiocephalic AVFs

(1) p-value=0.08 vs. placebo

(2) p-value<0.01 vs. placebo

The average rate of procedures to restore or maintain patency per patient year at risk. Patients undergoing a procedure often require repeated procedures over time because procedures such as balloon angioplasty can restore blood flow acutely but also damage the blood vessel. These data can be expressed as a procedure rate calculated as the number of days in which a procedure to restore or maintain patency was performed per patient divided by the patient's time on the trial. Procedures included thrombectomy, angioplasty, stent deployment and surgical revision. In a

- prespecified analysis, there was a 56% reduction in the rate of procedures in the 30 microgram group versus the placebo group. In the radiocephalic non-prespecified subset there was a 69% reduction in the average rate of procedures in the 30 microgram group versus the placebo group. In the brachiocephalic non-prespecified subset there was a 43% reduction in the average rate of procedure in the 30 microgram group versus the placebo group. Excluding procedures to treat central stenosis, through a non-prespecified analysis, in the brachiocephalic subset there was an 86% reduction in the average rate of procedures in the 30 microgram group versus the placebo group.

Average Procedure Rate to Restore/Maintain Patency (p-Value vs. Placebo)

	Placebo	Vonapanitase 10 micrograms	Vonapanitase 30 micrograms
All AVFs (Prespecified)			
Number of Patients	N=51	N=50	N=48
Procedures per Year	0.9	0.8 (p=0.53)	0.4 (p=0.07)
All AVFs Excluding Central Stenoses (Non-prespecified)			
Number of Patients	N=51	N=50	N=48
Procedures per Year	0.8	0.7 (p=0.44)	0.2 (p<0.01)
Radiocephalic AVFs (Non-prespecified)			
Number of Patients	N=24	N=23	N=20
Procedures per Year	1.0	0.8 (p=0.63)	0.3 (p=0.06)
Brachiocephalic AVFs (Non-prespecified)			
Number of Patients	N=27	N=27	N=28
Procedures per Year	0.7	0.7 (p=0.72)	0.4 (p=0.50)
Brachiocephalic AVFs Excluding Central Stenoses (Non-prespecified)			
Number of Patients	N=27	N=27	N=28
Procedures per Year	0.7	0.7 (p=0.54)	0.1 (p=0.07)

Ninety-two patients with a patent AVF completed 12 months of follow-up in the initial trial were followed in a registry to obtain additional data related to the efficacy endpoints. In this follow up, the vonapanitase 30 mcg benefit on procedure rates persisted out over a median of 3 years in all AVF types as set out in the following table.

Average Procedure Rate to Restore/Maintain Patency Including Registry Data (p-Value vs. Placebo)

	Placebo	Vonapanitase 10 micrograms	Vonapanitase 30 micrograms
All AVFs (Prespecified analysis)			
Number of Patients	N=51	N=50	N=48
Procedures per Year	0.7	0.7 (p=0.93)	0.2 (p=0.03)
Radiocephalic AVFs (Non-prespecified analysis)			
Number of Patients	N=24	N=23	N=20
Procedures per Year	0.9	0.6 (p=0.60)	0.2 (p=0.05)
Brachiocephalic AVFs (Non-prespecified analysis)			
Number of Patients	N=27	N=27	N=28
Procedures per Year	0.6	0.8 (p=0.69)	0.3 (p=0.29)

Secondary patency. Secondary patency loss was defined as abandonment of the AVF, which typically occurs following loss of primary unassisted patency due to thrombosis or failure of a procedure to restore patency and leads to additional surgery to create a new vascular access. We observed no significant differences in the risk of secondary patency loss in the overall AVF population or the non-prespecified subset of patients receiving brachiocephalic AVFs. However, as seen in the Kaplan-Meier curves and table below, a trend toward prolonged secondary patency was seen in patients receiving radiocephalic AVFs. In this non-prespecified subset analysis, treatment with vonapanitase at doses of 10 and 30 micrograms was associated with reductions of 55% and 73%, respectively, in the risk of secondary patency loss.

Secondary Patency—Radiocephalic AVFs

	Vonapanitase	**Vonapanitase**
	10 microgram dose	**30 microgram dose**
Number of Patients	N=23	N=20
Unadjusted Risk vs. Placebo	-55% (p=0.19)	-73% (p=0.08)

Note: Non-prespecified analysis.

Ninety-two patients with a patent AVF completed 12 months of follow-up in the initial trial were followed in a registry to obtain additional data related to the efficacy endpoints. In this follow-up, the vonapanitase 30 mcg benefit on secondary patency in radiocephalic AVFs persisted over a median of three years.

- *Use for hemodialysis*. Use was defined as use of the AVF for hemodialysis at any time without a previous intervention. Although the results were not statistically significant, there was a trend to more patients using the AVF for hemodialysis in the 30 microgram group (69%) compared with the placebo group (53%).

- *Hemodynamically significant lumen stenosis*. Hemodynamically significant lumen stenosis, or narrowing of blood vessels, impairs AVF maturation and contributes to AVF patency loss. Hemodynamically significant lumen stenosis was defined as a 50% or greater stenosis and a significant elevation in peak blood flow velocity across the stenosis detected by ultrasound. Ultrasounds were performed using a standard protocol and reviewed by a central reader masked to treatment assignment and AVF outcome. Although the results were not statistically significant, there was a trend to fewer patients with a hemodynamically significant lumen stenosis in the patients receiving 10 micrograms (30%) and 30 micrograms (39%) of vonapanitase compared with the placebo group (51%) at six weeks. Detecting hemodynamically significant lumen stenosis is technically challenging and often confounded by the performance of procedures, such as angioplasty to treat stenosis prior to the ultrasound examination.

Safety and tolerability

Vonapanitase is administered topically at the vascular access and only acts locally. We have not observed systemic activity or systemic toxicity in our preclinical animal studies, even following single-dose intravenous administration at very high multiples of the Phase 2 clinical trial doses. Safety evaluations in Phase 2 included ascertainment of adverse events, physical examinations, ultrasounds of the AVFs and nearby vessels, vital signs and laboratory studies. No significant safety signals were identified. In the trial, most patients treated with vonapanitase reported adverse events, the most common of which are summarized in the following table, as compared to placebo. These events were generally consistent with the medical events experienced by CKD patients undergoing AVF creation surgery. The most frequent adverse events were AVF incision pain, venous stenosis, procedural pain, AVF thrombosis, steal syndrome and hypoesthesia. Serious adverse events, or SAEs, reported by the investigator as possibly drug-related occurred in two 10 microgram vonapanitase patients (both AVF thrombosis), and two 30 microgram vonapanitase patients (one chest pain and one swelling at the surgical incision). There were no SAEs reported by the investigator as possibly drug-related in the placebo group. There was one SAE reported by the investigator as drug-related in the 10 microgram vonapanitase group (AVF maturation failure), and there were none in the other treatment groups.

Number and Proportion (%) of Patients with

Very Common Adverse Events(1)

N (%)	**Placebo** **N=51**	**Vonapanitase** **10 micrograms** **N=51**	**Vonapanitase** **30 micrograms** **N=49**
Any adverse event	42 (82)	39 (77)	43 (88)
AVF thrombosis	13 (26)	8 (16)	7 (14)
Venous stenosis	10 (20)	7 (14)	8 (16)
Steal syndrome	7 (14)	2 (4)	6 (12)
Hypoesthesia	7 (14)	6 (12)	6 (12)
Procedural pain	6 (12)	11 (22)	11 (22)
AVF incisional pain	5 (10)	9 (18)	9 (18)
AVF site complication	5 (10)	4 (8)	4 (8)
Nausea	5 (10)	1 (2)	2 (4)
Peripheral edema	5 (10)	0 (0)	2 (4)
Arterial stenosis	4 (8)	5 (10)	0 (0)
Paresthesia	1 (2)	1 (2)	5 (10)
Pain in extremity(2)	0 (0)	1 (2)	5 (10)

Note: None of the differences between groups were statistically significant.

(1) Adverse events occurring in at least 10% of placebo or either vonapanitase treatment groups.

(2) All but one unrelated to limb used in AVF surgery.

Phase 1/2 AVF Clinical Trial

We submitted an investigational new drug application, or IND, for vonapanitase as a treatment for patients undergoing AVF creation on April 30, 2008. Our initial clinical trial of vonapanitase was a Phase 1/2, randomized, double-blind, placebo-controlled, dose-escalation safety and exploratory efficacy trial in 66 patients undergoing creation of a radiocephalic or brachiocephalic AVF. Patients were treated with vonapanitase at nine dose levels ranging from 3.3 micrograms to 9 milligrams or placebo at the time of AVF creation and were followed for up to one year. This trial did not meet its primary endpoint, an endpoint we did not pursue in our Phase 2 trial. However, consistent with our mechanism of action that involves partial fragmentation of elastin, doses of vonapanitase at 3.3, 10 and 33 micrograms were associated with a trend toward prolonged primary unassisted patency (secondary endpoint p=0.66 in the All Treated population and p=0.15 in the All Treated Minus 3 population), fewer procedures to restore or maintain patency (collected as supportive data) and less hemodynamically significant lumen stenosis (collected as supportive data) compared with placebo treated patients or patients treated with higher vonapanitase doses. Higher doses showed results similar to placebo and no dose met the primary efficacy endpoint with statistical significance. No dose-related increases in adverse events were observed in the trial. Based on the results of this trial, we selected 10 microgram and 30 microgram doses for further study in the Phase 2 trial.

Our Phase 3 Program

We are conducting two randomized, double-blind Phase 3 trials, with staggered start dates, comparing a 30 microgram dose of vonapanitase to placebo. We began enrolling patients in our first Phase 3 pivotal trial, PATENCY-1, for vonapanitase in patients with CKD undergoing creation of a radiocephalic AVF in the third quarter of 2014 and began enrolling patients in the second Phase 3 trial, PATENCY-2, in August 2015. Each of the trials will enroll patients undergoing a surgical procedure to create a radiocephalic AVF. Each Phase 3 trial will enroll approximately 300 patients, for a total of approximately 600 patients, who will be randomized such that twice as many patients will receive vonapanitase as compared to placebo.

In April 2013, we held an end of Phase 2 meeting with the FDA, during which we confirmed the following key elements of our Phase 3 development plan: (i) the primary efficacy endpoint in our Phase 3 trials, primary unassisted patency, which is the same as our primary endpoint in our Phase 2 trial, is suitable for approval of vonapanitase in the United States; (ii) the secondary efficacy endpoint in our Phase 3 trials, secondary patency, which was a secondary endpoint in our Phase 2 trial, could be acceptable for inclusion in the approved product labeling in the United States if we hit statistical significance on both the primary endpoint and the secondary endpoint, and possibly even if we do not hit statistical significance on the secondary endpoint; (iii) the total number of patients expected to be treated through our Phase 3 trial will provide a sufficient safety database to support a BLA filing; (iv) we do not need to conduct additional preclinical studies prior to conducting our Phase 3 clinical trials or to support a BLA filing; and (v) we have Phase 3-ready active pharmaceutical ingredient, or API, and finished product.

We began enrolling patients in our first Phase 3 trial, PATENCY-1, in the third quarter of 2014. Each patient will be followed for 12 months. We expect that results will be available in December 2016. We began enrolling patients in our second Phase 3 trial, PATENCY-2, in August 2015 and expect to complete full enrollment in the first quarter of 2017.

Our Phase 3 trials will be conducted at sites in the United States with the second trial also including Canadian sites. In addition to collecting data on the primary and secondary endpoints, the Phase 3 clinical trials will collect information related to the endpoints of maturation, use for hemodialysis and the rate of procedures to restore or maintain patency. Patients who consent will be enrolled in a patient registry to obtain long-term follow-up efficacy information.

We have designed each Phase 3 trial to have over 95% power, *i.e.*, there is more than a 95% probability that the study will detect observed clinical effects of vonapanitase if the observed effects are true. In the first Phase 3 trial, 311 patients were randomly allocated by the sites in a 2:1 ratio to either vonapanitase, at 30 micrograms, or to placebo. With a 300 patient sample size (200 vonapanitase and 100 placebo), the study is powered to approximately 96% power to detect an increase in median primary unassisted patency from 5 months to 10 months and 97% power to detect an increase in the proportion of patients with secondary patency at 12 months from 65% to 85%. A 10% drop out rate has been assumed in all of the calculations. The study will follow each patient for a maximum of 12 months. If the results of the first Phase 3 trial are sufficiently compelling, we intend to meet with the FDA to discuss the possibility of submitting a BLA, supported by the single Phase 3 trial in which the single Phase 3 trial would form the primary basis of the demonstration of safety and efficacy, and the Phase 2 trial, including non-prespecified analyses, would provide supportive information. We may decide to submit a BLA to the FDA prior to completing the second Phase 3 trial.

Preclinical Development

We have conducted an extensive preclinical program to evaluate the safety and tolerability of single doses of vonapanitase administered locally in animal models of AVF and AVG placement, by percutaneous and endovascular injection in animal models of peripheral artery disease, or PAD, as well as intravenously. We have conducted preclinical studies in multiple species at doses up to 50 milligrams of vonapanitase, which is over 1,500 times higher than the dose we intend to study in our planned Phase 3 clinical trials. We observed no systemic activity or systemic toxicity for vonapanitase in any of our preclinical studies. We observed no toxicity in any of the doses that we subsequently studied or plan to study in Phase 3 clinical trials in humans. Only local toxicity was observed at surgical sites at high doses (10 and 50 milligrams, which is over 300-1500 times higher than the dose we intend to study in our planned Phase 3 clinical trials). These changes were reversible, with normal wound healing observed at 14 days except at the highest (50 milligrams) dose, in which there were some mild persistent changes in the jugular vein and subcutaneous tissue. Normal wound healing was observed in all the AVF studies in rabbits at doses up to 10 milligrams and in all the AVG studies in dogs and pigs at doses up to 20 milligrams (the highest doses tested).

In our preclinical studies, we observed dose-dependent activity of vonapanitase on elastin removal. Studies have established a correlation with elastin removal and a reduction in neointimal hyperplasia.

Other Programs, Indications and Trials

Other AVF Trials

European clinical program

We are currently evaluating our clinical program to support filing in Europe. We may, based on additional data including the data from our Phase 3 clinical trials in the United States and if sufficient funds become available, choose to conduct a clinical trial of vonapanitase in Europe. Prior to initiating a European clinical trial, we plan to formally seek guidance from the EMA regarding their requirements for regulatory approval.

Brachiocephalic AVF

We believe that our Phase 2 clinical data supports further development of vonapanitase in brachiocephalic AVF creation. We may, based on additional data, including the data from our Phase 3 clinical trials, and if sufficient funds become available, study the effects of a 30 microgram dose of vonapanitase versus placebo on brachiocephalic AVFs. Prior to initiation of this trial, we expect to seek guidance from the FDA regarding trial design.

Arteriovenous Grafts

An arteriovenous graft, or AVG, is a surgical procedure in which a surgeon places a synthetic tube to connect a vein and an artery. We submitted an IND for vonapanitase as a treatment for patients undergoing AVG placement on April 30, 2008. We conducted a Phase 1/2 randomized, double-blind, placebo-controlled, dose-escalation trial in 89 patients undergoing placement of an AVG. Patients were treated with placebo or eight different doses of vonapanitase ranging from 10 micrograms to 9 milligrams at the time of AVG placement and were followed for up to one year. Those patients who had not lost secondary patency were subsequently enrolled in a registry to obtain additional follow-up information on the AVG.

The primary outcome measure was safety. Adverse events were consistent with the medical conditions experienced by patients with CKD undergoing AVG surgery and showed no significant differences between groups. Some of the data showed indications of efficacy, especially in secondary patency, which is an approvable endpoint for hemodialysis access, for the groups treated with vonapanitase at doses of 10 micrograms and 30 micrograms.

After reviewing the results from our first Phase 3 clinical trial, and if sufficient funds become available, we may commence a clinical trial of vonapanitase in patients undergoing placement of an AVG.

Peripheral Artery Disease

In addition to vascular access indications, we are investigating vonapanitase as a treatment for patients with symptomatic peripheral artery disease, or PAD. Patients with lower extremity PAD suffer from stenosis formation in the arteries providing blood to the legs. These patients typically present with exercise-induced leg pain, a condition known as intermittent claudication. Patients with claudication are unable to adequately maintain their activities of daily living because they quickly experience pain that can be resolved only through rest. Severe cases result in critical limb ischemia, or lack of oxygen, and the possibility of amputation. PAD is a global problem affecting a large number of people throughout the industrialized world. Approximately 8 million Americans suffer from PAD.

Patients with early stage PAD typically undergo lifestyle management such as smoking cessation, weight reduction and/or diabetes management, and treatment with oral medications. Approximately 800,000 patients in the United States who do not respond to lifestyle management and have worsening symptoms, undergo an endovascular procedure, typically balloon angioplasty with or without stenting or vein bypass surgery. While these procedures work acutely to restore blood flow, they suffer from poor long-term durability, resulting in the need for repeat procedures.

We believe that vonapanitase may improve the outcomes associated with angioplasty procedures, resulting in prolonged intervention-free patency while reducing the need for implantation of a permanent stent. We submitted an IND for vonapanitase as a treatment for PAD patients on April 9, 2012. Our initial PAD clinical trial was a Phase 1, open-label, dose-escalation safety/technical feasibility trial in 14 patients undergoing balloon angioplasty of the superficial femoral or popliteal artery in the leg. Following successful angioplasty, patients were treated with vonapanitase via an FDA-cleared, drug-delivery catheter that allows vonapanitase to be administered locally in the outer layer of the vessel wall. Patients were followed for up to 12 months. The study met its stated objectives, as data indicated that catheter-based treatment with vonapanitase was generally well-tolerated and technically feasible. We expect to initiate another Phase 1 study of vonapanitase delivered via a drug-delivery catheter in 2016 in up to 40 symptomatic PAD patients undergoing angioplasty of an infrapopliteal artery below the knee. We expect to follow these patients for 12 months.

We believe that vonapanitase may be an alternative to traditional endovascular procedures such as angioplasty, reducing clinical symptoms without the need for an interventional procedure. Vonapanitase may be delivered via a percutaneous approach, in which a physician inserts an image-guided needle through the skin to inject vonapanitase to the artery around the area of blockage. We believe that vonapanitase may dilate the artery, resulting in increased lumen artery diameter, higher blood flow, and an improvement in clinical symptoms. We anticipate initiating in 2016 a Phase 1 study of vonapanitase delivered via a percutaneous approach enrolling up to 30 patients with symptomatic PAD as an alternative to angioplasty.

We believe that vonapanitase may improve the outcomes associated with vein bypass surgery, resulting in prolonged intervention-free patency. During vein bypass surgery, a surgeon places a vein, typically obtained from the patient's leg, as an alternative conduit for blood to flow around the area of blockage restoring direct flow to the lower leg and foot. We believe that vonapanitase, administered to the outside of the vein concurrently with the surgery, may improve the outcomes associated with vein bypass surgery, resulting in prolonged intervention-free patency. We would anticipate initiating in 2017 a Phase 1 trial enrolling approximately 10-20 patients undergoing vein bypass surgery.

Manufacturing and Supply

We depend on third-party contract manufacturers for the production of vonapanitase. Our API is produced at our contract manufacturer, Lonza LTD, or Lonza, which is required to comply with the FDA's Current Good Manufacturing Practice, or cGMP, regulations. Vonapanitase finished product is produced at our contract fill/finisher providers, Jubilant HollisterStier and Patheon Manufacturing Services, LLC (formerly DSM Pharmaceuticals, Inc.), which is required to comply with cGMP regulations.

We used API manufactured at Lonza to create finished product that was used in our Phase 2 AVF clinical trial and is currently being used for our Phase 3 AVF clinical trials. We also plan to manufacture API at Lonza for our commercial launch and future trials.

We modified our finished product at Jubilant HollisterStier for our Phase 3 trials and potential commercial launch in order to facilitate ease of administration and fill and finish at the 30 microgram doses. The modified finished product is reconstituted with sterile water to create a dosing solution containing 30 micrograms of vonapanitase. We demonstrated that the modified finished product had the same elastase activity and the same elastin removal from blood vessels following ex vivo treatments as the previous finished product using synthetic and natural elastin substrates. The modified finished product formulation was similar to the previous finished product formulation in maintaining the health and viability of live cells in culture. These data suggest the modified finished product will have the same efficacy and safety in clinical trials as the previous finished product.

Release and stability testing for API and finished product are performed at PPD, Inc. The tests indicate stability of at least five years for our API and at least two years for our finished product.

In our Phase 1 AVF study, Phase 1 AVG study, and Phase 1 PAD study, vonapanitase finished product at the 5 milligram per vial formulation was used. We plan to use this same 5 milligram formulation of vonapanitase, manufactured at Patheon, in two of our Phase 1 PAD studies. The finished product at Jubilant HollisterStier will be used for a third PAD study.

At our end of Phase 2 meeting, the FDA confirmed that our API and modified finished product are acceptable for Phase 3 clinical trials. We have already manufactured finished product for the AVF Phase 3 clinical trials.

In anticipation of a potential BLA filing, we plan to manufacture a minimum of three batches of API and of finished product as part of process validation and to test these batches for stability with a goal of establishing a commercial shelf-life of at least two years for finished product and a longer expiry for API.

Sales and Marketing

Our commercialization strategy is to develop vonapanitase into a leading therapy worldwide for the treatment of AVFs and in other renal and vascular diseases.

We have not yet established a sales and marketing organization. Our Chief Executive Officer has significant commercial experience in the industry, including commercial launch experience in the renal market. We intend to recruit an in-house specialty hospital sales force in the United States focused on promoting vonapanitase. We plan to target our marketing and sales efforts at those vascular surgeons who create AVFs. There are approximately 2,800 vascular surgeons in the United States. We believe a specialty hospital sales force of approximately 75-100 representatives, supported by reimbursement specialists and a medical affairs team, will enable us to call on the approximately 1,300 hospitals that account for more than 90% of the AVF creations performed in the United States annually.

We believe that vonapanitase will be reimbursed appropriately as costs related to AVF surgical creation, which is typically performed in the hospital outpatient setting, are not included in the ESRD bundle.

If vonapanitase is approved by the EMA, we may commercialize it in European countries with our own specialty hospital sales force or with a commercial partner, or a combination thereof. We believe that the market for vonapanitase in the five largest countries in the European Union represents the bulk of the potential European market and that a launch using a direct sales force may be achievable in these markets. We hope to enter into collaborations for the development and commercialization of vonapanitase in Japan and other Asian countries.

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Intellectual Property

We strive to protect and enhance the proprietary technology, inventions and improvements that are commercially important to our business, including seeking, maintaining and defending patent rights. We also rely on know-how that may be important to the development of our business. We additionally expect to rely on regulatory protection afforded through data exclusivity, market exclusivity and patent term extensions where available.

Our commercial success may depend in part on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business, as well as our ability to defend and enforce our patents and to operate without infringing the valid enforceable patents and proprietary rights of third parties.

Our ability to prevent third parties from making, using, selling, offering to sell or importing competing products to ours, including a competitor to vonapanitase, depends on the scope of our patents. We have several patents and patent applications relating to the vonapanitase formulation and its therapeutic uses, and we possess substantial know-how relating to the development and commercialization of vonapanitase. We cannot be sure that any of our pending patent applications or future patent filings will lead to the issuance of new patents, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be adequate to protect our market.

We plan on pursuing in-licensing opportunities to develop, strengthen and maintain our proprietary position in our field. We expect to use trademark protection for our products as they are marketed.

Patents

We own 21 issued patents and 26 pending patent applications. The patents and applications primarily fall into two families, a first relating to the vonapanitase formulation and its manufacture and use, as well as other formulations of elastases (the "formulation family"), and the second relating to certain therapeutic uses of vonapanitase, and associated systems and kits that include a catheter and are suitable for a subset of those therapeutic uses (the "therapy family"). The formulation family includes two issued United States patent, one issued European patent, additional patents issued in Australia, China, Hong Kong, Japan, Israel, Mexico, and New Zealand, and patent applications pending in several major jurisdictions worldwide, including Japan, China, South Korea, Brazil, Mexico, Russia, India, Europe and the United States. The expected expiration date for any patents that have issued or may issue from the formulation family is December 4, 2028, exclusive of possible patent term extension available for one patent covering vonapanitase under the Hatch-Waxman Amendments or comparable provisions in other jurisdictions, except in the United States where we were awarded a patent term adjustment of 199 days due to United States Patent and Trademark Office, or USPTO delays, taking the expiration date to June 20, 2029. The therapy family includes seven

issued United States patents and two issued European patents, and applications pending in the United States, Europe, Canada and Japan. The expected expiration date for any patents that have issued or may issue from the therapy family patents is September 24, 2020, except in the United States where several patents were awarded a patent term adjustment and the expected expiration date of two therapy family patents related to systems and kits including elastase and a catheter is June 30, 2021, exclusive of possible patent term extension.

Patent Term

The base term of a U.S. patent is 20 years from the filing date of the earliest-filed non-provisional patent application from which the patent claims priority. The term of a U.S. patent can be lengthened by patent term adjustment, which compensates the owner of the patent for administrative delays at the USPTO. In some cases, the term of a U.S. patent is shortened by terminal disclaimer that reduces its term to that of an earlier-expiring patent.

The term of a U.S. patent may be eligible for patent term extension under the Hatch-Waxman Amendment, to account for at least some of the time a product is under development and regulatory review after the patent is granted. With regard to a product for which FDA approval is the first permitted marketing of the active ingredient, the Hatch-Waxman Act allows for extension of protection of one U.S. patent that includes at least one claim covering the composition of matter of an FDA-approved product, an FDA-approved method of treatment using the product, and/or a method of manufacturing the FDA-approved product. The extended protection cannot exceed the shorter of five years beyond the non-extended expiration of the patent or 14 years from the date of the FDA approval of the product. Some foreign jurisdictions, including Europe, have analogous patent extension provisions, which allow for extension of the protection of a patent that covers a drug approved by the applicable foreign regulatory agency. In the future, if and when vonapanitase receives FDA approval, we expect to apply for patent extension to extend the protection of one of our patents covering vonapanitase or its use.

Assignment of Rights and License Agreement

As successor to Proteon Therapeutics, LLC by merger, we acquired all of the assets of the LLC, including all of the intellectual property rights in a patent family entitled "Local, Transcatheter Delivery of Proteases to Reopen Obstructed Biological Conduits" (the "JHU patent family"). This patent family was originally developed by our founder, Dr. F. Nicholas Franano, at The Johns Hopkins University, or Johns Hopkins, and includes United States patent Nos. 7,063,838; 7,153,505; 7,361,335; 7,632,494; 7,883,699; 8,524,226; 8,562,983; and 8,568,716. Johns Hopkins assigned all of the intellectual property rights to Dr. Franano who in turn assigned the rights to the LLC. Under the terms of the assignment of rights and license agreement with Johns Hopkins, Dr. Franano reimbursed certain costs of Johns Hopkins and agreed to pay the future costs and expenses of patent prosecution and maintenance, as well as any costs related to infringement. In addition, under the agreement, Dr. Franano granted to Johns Hopkins rights to practice under the intellectual property rights for non-profit purposes. Our rights are further subject to any rights the United States Government may have in inventions that are the subject matter of the acquired patents under the Bayh Dole Act due to its sponsorship of research that led to certain of such inventions. The agreement does not specify a term and does not include any termination provisions. Dr. Franano agreed that upon commercialization of the assigned invention, he would remit to Johns Hopkins 2.5% of any revenues or fees received from certain net sales of any product covered by the JHU patent family. We assumed, and are the successor to, all of Dr. Franano's payment and other obligations to Johns Hopkins. Seven U.S. patents in the JHU patent family, and their foreign counterparts, described above as the therapy family, relate to certain therapeutic uses of vonapanitase, and the associated systems and kits that include a catheter and are suitable for a subset of those therapeutic uses.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. We face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions.

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

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

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We are not aware of any therapeutic products approved in the United States or Europe for the prevention of vascular access failure. We are aware of other therapies in development by companies including Vascular Therapies and Symic Biomedical. vonapanitase could face competition from companies developing vascular access technologies, including BioConnect Systems, Avenu Medical, Phraxis, CreatiVasc , Laminate Medical Technologies, Stent Tek and TVA Medical. Other potentially competitive products include new synthetic grafts, including those that may be developed by companies that currently compete in the graft market, such as W.L. Gore, C.R. Bard and Maquet, as well as tissue engineered grafts, including those in development by Cytograft and Humacyte. Finally, vonapanitase's commercial success could be adversely affected by the development of technologies to improve the outcomes of interventions to restore patency, including stents, stent grafts and drug-coated balloons.

Government Regulation and Approval

United States—FDA process

In the United States, pharmaceutical products are subject to extensive regulation by the FDA. The Federal Food, Drug, and Cosmetic Act, or FDCA, and other federal and state statutes and regulations, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling, and import and export of pharmaceutical products. Biological products used for the prevention, treatment, or cure of a disease or condition of a human being are subject to regulation under the FDCA, except the section of the FDCA which governs the approval of new drug applications, or NDAs. Biological products, such as vonapanitase, are approved for marketing under provisions of the Public Health Service Act, or PHSA, via a BLA. The application process and requirements for approval of BLAs are very similar to those for NDAs, and biologics are associated with similar approval risks as drugs. Failure to comply with applicable United States requirements may subject a company to a variety of administrative or judicial sanctions, such as FDA refusal to approve pending NDAs or BLAs, warning or untitled letters, clinical holds, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties and criminal prosecution.

Approval process

FDA approval is required before any new unapproved product or a product with certain changes to a previously approved product may be marketed in the United States. FDA approval is required before any new unapproved drug, which includes biologics, or dosage form, including a new use of previously approved products, can be marketed in the United States. The steps required to be completed before a drug or biologic may be marketed in the United States include:

- preclinical laboratory tests, animal studies, and formulation studies, all performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- submission to the FDA of an IND application for human clinical testing, which must become effective before human clinical trials may begin and must be updated annually;
- adequate and well-controlled human clinical trials to establish the safety and efficacy of the drug or biologic for each indication to FDA's satisfaction;
- submission to the FDA of a BLA;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the drug or biologic is produced to assess compliance with cGMP regulations;
- satisfactory completion of FDA clinical site data audits; and
- FDA review and approval of the BLA.

Satisfaction of FDA pre-market approval requirements typically takes many years and the actual time required may vary substantially based upon the type, complexity, and novelty of the product or disease.

Preclinical tests include laboratory evaluation of product chemistry, formulation, and toxicity, as well as animal trials to assess the characteristics and potential safety and efficacy of the product. The conduct of the preclinical tests must comply with federal regulations and requirements, including GLP. The results of preclinical testing are submitted to the FDA as part of an IND along with other information, including information about product chemistry, manufacturing and controls, and a proposed clinical trial protocol. Long term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted.

A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. If the FDA has neither commented on nor questioned the IND within this 30-day period, the clinical trial proposed in the IND may begin. However, the FDA may within the 30-day time period raise concerns or questions relating to one or more proposed clinical trials and place the clinical trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. Accordingly, submission of an IND may or may not result in the FDA allowing clinical trials to commence. A separate submission to an existing IND must also be made for each successive clinical trial conducted during product development.

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Clinical trials involve the administration of the investigational new drug or biologic to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted: (i) in compliance with federal regulations; (ii) in compliance with good clinical practice, or GCP, an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators, and monitors; as well as (iii) under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. Each protocol involving testing on United States patients and subsequent protocol amendments must be submitted to the FDA as part of the IND.

The FDA may order the temporary, or permanent, discontinuation of a clinical trial at any time, or impose other sanctions, if it believes that the clinical trial either is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. The trial protocol and informed consent information for patients in clinical trials, including any changes to the protocols and informed consent forms, must also be submitted to an institutional review board, or IRB, for approval. An IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB's requirements or if the trial poses an unexpected serious harm to subjects, or may impose other conditions.

Clinical trials to support NDAs or BLAs for marketing approval are typically conducted in three sequential phases, but the phases may overlap. In Phase 1, the initial introduction of the drug or biologic into a limited population of healthy human subjects or patients, the product is tested to assess metabolism, pharmacokinetics, pharmacological actions, side effects associated with increasing doses, and, if possible, early evidence on effectiveness. Phase 2 usually involves trials in a limited patient population to evaluate preliminarily the effectiveness of the drug or biologic for a particular indication, dosage tolerance, and optimum dosage, and to identify common adverse effects and safety risks. If a compound demonstrates evidence of effectiveness and an acceptable safety profile in Phase 2 evaluations, Phase 3 trials are undertaken in a larger number of patients, typically at geographically dispersed clinical trial sites, to provide substantial evidence of clinical efficacy, to further test for safety in an expanded and diverse patient population, to permit the FDA to evaluate the overall benefit-risk relationship of the drug or biologic and to provide adequate information for the labeling of the product. In reviewing an NDA or a BLA, the FDA will consider all information submitted in the NDA or BLA, including the results of all clinical trials conducted. In most cases, the FDA requires two adequate and well-controlled Phase 3 clinical trials to demonstrate the efficacy of the drug or biologic. A single Phase 3 trial with other confirmatory evidence such as supportive results from Phase 1 and Phase 2 trials, including non-prespecified analyses, may be sufficient in rare instances where the trial is a large multicenter trial demonstrating internal consistency and a statistically very persuasive finding of a clinically meaningful effect on mortality, irreversible morbidity or prevention of a disease with a potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.

Progress reports detailing the status of the clinical trials must be submitted at least annually to the FDA, and safety reports must be submitted to the FDA and the investigators for serious, related and unexpected side effects. Progress and safety reporting must also be submitted to the applicable IRBs. Marketing application applicants must also report certain investigator financial interests to FDA.

The manufacture of investigational drugs and biologics for the conduct of human clinical trials is subject to cGMP requirements. Investigational drugs, biologics, and active pharmaceutical ingredients imported into the United States are also subject to regulation by the FDA relating to their labeling and distribution. Further, the export of investigational drug products and biologics outside of the United States is subject to regulatory requirements of the receiving country as well as U.S. export requirements under the FDCA.

Sponsors must also develop additional information about the chemistry and physical characteristics of the product and finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality, purity, and potency of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

After completion of the required clinical testing, an NDA or BLA is prepared and submitted to the FDA. FDA approval of the NDA or BLA is required before marketing of the product may begin in the United States. The NDA or BLA must include, among other things, the results of all trials and preclinical testing, and other testing and a compilation of data relating to the product's pharmacology, chemistry, manufacture, and controls, including negative or ambiguous results as well as positive findings. The cost of preparing and submitting an NDA or BLA is substantial. The submission of most NDAs and BLAs is additionally subject to a substantial application user fee, currently $2,374,200, and the manufacturer and/or sponsor under an approved new drug or biologic application are also subject to annual product and establishment user fees, currently $114,450 per product and $585,200 per establishment. These fees are typically increased annually. A waiver or reduction of the application, establishment, and/or product fees may be obtained under certain limited circumstances. For instance, one basis for a waiver of the application user fee is if the applicant employs fewer than 500 employees, including employees of affiliates, the applicant does not have an approved marketing application for a product that has been introduced or delivered for introduction into interstate commerce, and the applicant, including its affiliates, is submitting its first marketing application or the case of orphan designation.

The FDA has 60 days from its receipt of an NDA or BLA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept a BLA for filing. In this event, the BLA must be re-submitted with the additional information. The re-submitted application also is subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of NDAs and BLAs. Under the Prescription Drug User Fee Act, the FDA has a goal of responding to 90% of standard review original BLAs within ten months after the 60-day filing review period, but this timeframe is only a goal and, thus, the review time may be longer or extended. Priority review can be applied to drugs and biologics that the FDA determines are for a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. FDA has the review goal of completing review of 90% of original BLA priority review applications within six months of the 60-day filing review period. The review process for both standard and priority review may be extended by the FDA for three additional months to consider certain late-submitted information, or information intended to clarify information already provided in the submission.

The FDA may also refer applications for novel drug or biologic products, or drug or biologic products that present difficult questions of safety or efficacy, to an advisory committee—typically a panel that includes clinicians and other experts—for review, evaluation, and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. Before approving a drug or biologic for which no active ingredient (including any ester or salt of active ingredients) has previously been approved by the FDA, the FDA must either refer that drug or biologic to an external advisory committee or provide in an action letter, a summary of the reasons why the FDA did not refer the product candidate to an advisory committee.

The FDA reviews a BLA to determine, among other things, whether a product is safe, pure, and potent for its intended use and whether the facility in which it is manufactured, processed, packaged or held, as well as the manufacturing processes and controls, meet standards designed to ensure the product's continued identity, strength, safety, quality, purity, and potency Before approving an NDA or BLA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. Additionally, the FDA will inspect the facility or the facilities at which the drug or biologic is manufactured. FDA will not approve the product unless compliance with cGMP is satisfactory and the NDA or BLA contains data that provide evidence that the drug or biologic is safe and effective in the indication studied.

After the FDA evaluates the NDA or BLA and the manufacturing facilities, it issues either an approval letter or a complete response letter. A complete response letter indicates that the review cycle of the application is complete and the application is not ready for approval. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional clinical data and/or other significant, expensive, and time-consuming requirements related to clinical trials, preclinical studies and/or manufacturing. The FDA has committed to reviewing resubmissions of the NDA or BLA addressing such deficiencies in two or six months depending on the type of information included. Even if such data are submitted, however, the FDA may ultimately decide that the NDA or BLA does not satisfy the criteria for approval.

An approval letter authorizes commercial marketing of the drug or biologic with specific prescribing information for specific indications. If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages, or the indications for use may otherwise be limited, for example to specific patient populations or age groups. Each of these types of limitations could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling, including black box warnings, or may not approve label statements that are necessary for successful commercialization and marketing. As a condition of NDA or BLA approval or following approval, the FDA may require a risk evaluation and mitigation strategy, or REMS, to help ensure that the benefits of the drug or biologic outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The requirement for REMS can materially affect the potential market and profitability of the product. Moreover, product approval may also be conditioned on substantial post-approval testing and surveillance to monitor the product's safety or efficacy. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, require submission and FDA approval of a new NDA or BLA or NDA or BLA supplement before the change can be implemented. An NDA or BLA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA or BLA supplements as it does in reviewing NDAs or BLAs, including user fee requirements for certain submissions.. As with new NDAs, the review process is often significantly extended by the FDA requests for additional information or clarification.

U.S. Patent Term Restoration

Depending upon the timing, duration and specifics of the FDA approval of vonapanitase and any future product candidates, some of our U.S. patents may be eligible for limited patent term extension. The Hatch-Waxman Amendments permit a patent restoration term, often referred to as patent term extension, of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA or BLA plus the time between the submission date of an NDA or BLA and the approval of that application. The period of the patent term restoration may also be reduced to account for time that an applicant did not act with due diligence.0020Only one patent applicable to an approved drug or biologic is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The USPTO, in consultation with the FDA, reviews and approves or denies the application for any patent term extension or restoration. In the future, we intend to apply for extension of patent term for one of our patents covering vonapanitase to add patent life beyond its current expected expiration date.

Post-approval requirements

Once an NDA or BLA is approved, a product will be subject to certain post-approval requirements. For instance, the FDA closely regulates the post-approval marketing and promotion of drugs and biologics, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the internet. Drugs and biologics may be marketed only for the approved indications and in accordance with the provisions of the approved labeling. Failure to comply with these requirements can result in adverse publicity, warning letters, corrective advertising, and potential civil and criminal penalties.

In addition, the distribution of prescription pharmaceutical products, including samples, is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs, biologics and drug and biologic samples at the federal level, and sets minimum standards for the registration and regulation of drug and biologic distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Adverse event reports, deviation reports, and other annual reports are required following FDA approval of an NDA or BLA. The FDA also may require post-marketing testing, known as Phase 4 testing, REMS, and surveillance to monitor the effects of an approved product, or the FDA may place conditions on an approval that could restrict the distribution or use of the product. In addition, quality control, drug and biologic manufacture, packaging, and labeling procedures must continue to conform to cGMPs after approval. Drug and biologic manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies. Registration with the FDA subjects entities to periodic unannounced inspections by the FDA, during which the agency inspects manufacturing facilities to assess compliance with cGMPs. Accordingly, manufacturers must continue to expend time, money, and effort in the areas of production and quality-control to maintain compliance with cGMPs. Regulatory authorities may withdraw product approvals or request product recalls if a company fails to comply with regulatory standards, if it encounters problems following initial marketing, or if previously unrecognized problems are subsequently discovered.

Moreover, the Drug Quality and Security Act imposes obligations on manufacturers of pharmaceutical products related to product tracking and tracing. Among the requirements of this legislation, manufacturers are required to provide certain information regarding the product to individuals and entities to which product ownership is transferred, will be required to label products with a product identifier and are required to keep certain records regarding the product. The transfer of information to subsequent product owners by manufacturers will eventually be required to be done electronically. Manufacturers are also required to verify that purchasers of the manufacturers' products are appropriately licensed. Further, under this legislation, manufacturers have investigation, quarantine, disposition, and FDA and trading partner notification responsibilities related to counterfeit, diverted, stolen and intentionally adulterated products that would result in serious adverse health consequences or death to humans, as well as products that are the subject of fraudulent transactions or which are otherwise unfit for distribution such that they would be reasonably likely to result in serious health consequences or death.

Orphan drug designation

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs or biologics intended to treat a rare disease or condition—generally a disease or condition that affects fewer than 200,000 individuals annually in the United States. Additionally, sponsors must present a plausible hypothesis for clinical superiority to obtain orphan drug designation if there is a product already approved by the FDA that is intended for the same indication and that is considered by the FDA to be the same drug or biologic as the already approved drug or biologic. This hypothesis must be demonstrated to obtain orphan drug exclusivity. Orphan drug designation must be requested before submitting an NDA or BLA. After the FDA grants orphan drug designation, the generic identity of the drug or biologic and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical study costs, tax advantages, and user-fee waivers. The first NDA or BLA applicant to receive FDA approval for a particular drug or biologic to treat a particular disease with FDA orphan drug designation is entitled to a seven-year exclusive marketing period in the United States for that product, for that indication. During the seven-year exclusivity period, the FDA may not approve any other applications to market the same drug or biologic for the same disease, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity, that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of

patients with the rare disease or condition. Orphan drug exclusivity does not prevent the FDA from approving a different drug or biologic for the same disease or condition, or the same drug or biologic for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research, waiver of the NDA or BLA application user fee, and exclusion from price limitations imposed by the 340B drug discount program on sales of covered outpatient drugs to certain categories of hospitals added to the program by the Affordable Care Act.

Fast track designation and accelerated approval

The FDA is required to facilitate the development, and expedite the review, of drugs or biologics that are intended for the treatment of a serious or life-threatening disease or condition and which demonstrate the potential to address unmet medical needs for the condition. Under the fast track program, the sponsor of a new drug or biologic candidate may request that the FDA designate the candidate for a specific indication as a fast track drug or biologic concurrent with, or after, the filing of the IND for the candidate. The FDA determines if the drug or biologic candidate qualifies for fast track designation within 60 days of receipt of the sponsor's request. Under the fast track program, sponsors have more opportunities to interact with FDA, and fast track product candidates may be eligible for priority review, if they meet the priority review criteria. If FDA determines, after preliminary evaluation of clinical data submitted by a sponsor, that a fast track product may be effective, FDA may also permit the sponsor to submit a marketing application on a rolling basis before the full application is complete. This rolling review is available if the applicant provides, and the FDA approves, a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, the FDA's time period goal for reviewing an application does not begin until the last section of the NDA or BLA is submitted. Additionally, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Any product submitted to the FDA for marketing, including under a fast track program, may be eligible for other types of FDA programs intended to expedite development and review, such as accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means the FDA may approve the product based upon a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

In clinical trials, a surrogate endpoint is a measurement of laboratory or clinical signs of a disease or condition that substitutes for a direct measurement of how a patient feels, functions, or survives. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. A drug or biologic candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, will allow the FDA to withdraw the drug or biologic from the market on an expedited basis. All promotional materials for drug or biologic candidates approved under accelerated regulations are subject to prior review by the FDA.

Pediatric information

Under the Pediatric Research Equity Act, or PREA, NDAs or BLAs or supplements to NDAs or BLAs for a new active ingredient, indication, dosage form, dosage regimen or route of administration must contain data to assess the safety and effectiveness of the drug or biologic for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug or biologic is safe and effective. The FDA may grant full or partial waivers, or deferrals, for submission of data. Unless otherwise required by regulation, PREA does not apply to any drug or biologic for an indication for which orphan designation has been granted.

Pediatric exclusivity is another type of exclusivity in the United States. Pediatric exclusivity, if granted, provides an additional six months of exclusivity to be attached to any existing exclusivity or patent protection. This six month exclusivity, which runs from the end of other exclusivity protection or patent delay, may be granted based on the voluntary completion of a pediatric trial that fairly responds to an FDA-issued "Written Request" for such a trial.

Additional controls for biologics

To help reduce the increased risk of the introduction of adventitious agents, the PHSA emphasizes the importance of manufacturing controls for products whose attributes cannot be precisely defined. The PHSA also provides authority to the FDA to immediately suspend licenses in situations where there exists a danger to public health, to prepare or procure products in the event of shortages and critical public health needs, and to authorize the creation and enforcement of regulations to prevent the introduction or spread of communicable diseases in the United States and between states.

After a BLA is approved, the product may also be subject to official lot release as a condition of approval. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing the results of all of the manufacturer's tests performed on the lot. The FDA may also perform certain confirmatory tests on lots of some products before releasing the lots for distribution by the manufacturer.

In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products. As with drugs, after approval of biologics, manufacturers must address any safety issues that arise, are subject to recalls or a halt in manufacturing, and are subject to periodic inspection after approval.

Biosimilars

The Biologics Price Competition and Innovation Act of 2009, or BPCIA, creates an abbreviated approval pathway for biological products shown to be highly similar to or interchangeable with an FDA-licensed reference biological product. Biosimilarity sufficient to reference a prior FDA-approved product requires a high similarity to the reference product notwithstanding minor differences in clinically inactive components, and no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency. Biosimilarity must be shown through analytical studies, animal studies, and at least one clinical trial, absent a waiver by the Secretary of Health and Human Services. There must be no difference between the reference product and a biosimilar in conditions of use, route of administration, dosage form, and strength. A biosimilar product may be deemed interchangeable with a prior approved product if it meets the higher hurdle of demonstrating that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. FDA approved the first biosimilar or interchangeable product under the BPCIA in 2015. Other biosimilar applications are currently under review. Complexities associated with the larger, and often more complex, structures of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation which are still being evaluated by the FDA.

A reference biologic is granted 12 years of exclusivity from the time of first licensure of the reference product, and no application for a biosimilar can be submitted for four years from the date of licensure of the reference product. However, certain changes and supplements to an approved BLA, and subsequent applications filed by the same sponsor, manufacturer, licensor, predecessor in interest, or other related entity do not qualify for the twelve year exclusivity period. The PHSA also includes provisions to protect reference products that have patent protection. The biosimilar product sponsor and reference product sponsor must exchange certain patent and product information for the purpose of determining whether there should be a legal patent challenge. Based on the outcome of negotiations surrounding the exchanged information, the reference product sponsor may bring a patent infringement suit and injunction proceedings against the biosimilar product sponsor. The first biologic product submitted under the abbreviated approval pathway that is determined to be interchangeable with the reference product has exclusivity against a finding of interchangeability for other biologics for the same condition of use for the lesser of (i) one year after first commercial marketing of the first interchangeable biosimilar, (ii) eighteen months after the first interchangeable biosimilar is approved if there is no patent challenge, (iii) eighteen months after resolution of a lawsuit over the patents of the reference biologic in favor of the first interchangeable biosimilar applicant, or (iv) 42 months after the first interchangeable biosimilar's application has been approved if a patent lawsuit is ongoing within the 42-month period.

Disclosure of clinical trial information

Sponsors of clinical trials of FDA-regulated products, including drugs and biologics, are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, trial sites and investigators, and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed until the new product or new indication being studied has been approved. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

European Union—EMA process

In the European Union, medicinal products are authorized following a similar demanding process as that required in the United States and applications are based on the ICH Common Technical Document, an agreed upon format to assemble all quality, safety and efficacy data for preparation of an application of a new drug. Prior to submitting a European Marketing Authorization Application, or MAA, it is necessary to gain approval of a detailed Pediatric Investigation Plan, or PIP, with the European Medicines Agency's Pediatric Committee, or PDCO. After gaining PIP approval, medicines can be authorized in the European Union by using either the centralized authorization procedure or national authorization procedures.

Centralized procedure

Under the centralized procedure, after the EMA issues an opinion, the European Commission issues a single marketing authorization valid across the European Union, as well as Iceland, Liechtenstein and Norway. The centralized procedure is compulsory for human medicines that are: derived from biotechnology processes, such as genetic engineering; contain a new active substance indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions; and officially designated orphan medicines. For medicines that do not fall within these categories, an applicant has the option of submitting an application for a centralized marketing authorization to the EMA, as long as the medicine concerned is a significant therapeutic, scientific or technical innovation, or if its authorization would be in the interest of public health.

National authorization procedures

There are also two other possible routes to authorize medicinal products in several countries, which are available for products that fall outside the scope of the centralized procedure:

- *Decentralized procedure.* Using the decentralized procedure, an applicant may apply for simultaneous authorization in more than one European Union country of a medicinal product that has not yet been authorized in any European Union country and that does not fall within the mandatory scope of the centralized procedure.
- *Mutual recognition procedure.* In the mutual recognition procedure, a medicine is first authorized in one European Union Member State, in accordance with the national procedures of that country. Thereafter, further marketing authorizations can be sought from other European Union countries in a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization.

While we believe that our development program, our Phase 3 trial design, and overall non-clinical and clinical data package could support future regulatory approval of vonapanitase in the European Union, we have not submitted such information to the European Union for their review.

Good manufacturing practices

Like the FDA, the EMA, the competent authorities of the European Union Member States and other regulatory agencies regulate and inspect equipment, facilities and processes used in the manufacturing of pharmaceutical and biologic products prior to approving a product. If, after receiving clearance from regulatory agencies, a company makes a material change in manufacturing equipment, location, or process, additional regulatory review and approval may be required. Once we or our partners commercialize products, we will be required to comply with cGMP, and product-specific regulations enforced by, the European Commission, the EMA and the competent authorities of European Union Member States following product approval. Also like the FDA, the EMA, the competent authorities of the European Union Member States and other regulatory agencies also conduct regular, periodic visits to re-inspect equipment, facilities, and processes following the initial approval of a product. If, as a result of these inspections, it is determined that our or our partners' equipment, facilities, or processes do not comply with applicable regulations and conditions of product approval, regulatory agencies may seek civil, criminal or administrative sanctions and/or remedies against us, including the suspension of our manufacturing operations or the withdrawal of our product from the market.

Data and market exclusivity

Similar to the United States, there is a process for authorization of generic versions of innovator drug products in the European Union. Abridged applications for the authorization of generic versions of drugs authorized by EMA can be submitted to the EMA through a centralized procedure referencing the innovator's data and demonstrating bioequivalence to the reference product, among other things.

New medicinal products in the European Union can receive eight years of data exclusivity coupled with two years of market exclusivity, and a potential one year extension, if the marketing authorizations holder obtains an authorization for one or more new therapeutic indications that demonstrates "significant clinical benefit" in comparison with existing therapies; this system is usually referred to as "8+2+1". We expect to be eligible for at least 10 years of market exclusivity following any approval of vonapanitase.

Abridged applications cannot rely on an innovator's data until after expiry of the eight year data exclusivity term; applications for a generic product can be filed but the product cannot be marketed until the end of the market exclusivity term.

Other international markets—drug approval process

In some international markets (*e.g.*, China or Japan), although data generated in United States or European Union trials may be submitted in support of a marketing authorization application, additional clinical trials conducted in the host territory, or studying people of the ethnicity of the host territory, may be required prior to the filing or approval of marketing applications within the country.

Pricing and reimbursement

In the United States and internationally, sales of products that we market in the future, and our ability to generate revenues on such sales, are dependent, in significant part, on the availability and level of reimbursement from third-party payors such as state and federal governments, managed care providers and private insurance plans. Substantial uncertainty exists as to the reimbursement status of newly approved healthcare products by third-party payors. In the United States no uniform policy of coverage and reimbursement for drug and biologic products exists. Accordingly, decisions regarding the extent of coverage and amount of reimbursement to be provided for any of our products will be made on a payor by payor basis. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our product candidates to each payor separately, with no assurance that coverage and adequate reimbursement will be obtained.

Private insurers, such as health maintenance organizations and managed care providers, have implemented cost-cutting and reimbursement initiatives and likely will continue to do so in the future. These include establishing formularies that govern the drugs and biologics that will be offered and also the out-of-pocket obligations of member patients for such products. Several third-party payors are requiring that drug and biologic companies provide them with predetermined discounts from list prices, are using preferred drug lists (which include biologics) to leverage greater discounts in competitive classes, are disregarding therapeutic differentiators within classes, and are challenging the prices charged for drugs and biologics. It is possible that some third party payors may not consider our technology to be a significant benefit in a clinical and cost effectiveness comparison with other technologies or techniques intended to address the same conditions as our product candidates and reimbursement may not be available to our customers, or may not be sufficient to allow our products to be marketed on a competitive basis. Cost-control initiatives could cause us to discount or rebate a portion of the price we might establish for products, which could result in lower than anticipated product revenues. If the realized prices for our products, if any, decrease or if governmental and other third party payors do not provide adequate coverage or reimbursement, our prospects for revenue and profitability will suffer.

In addition, particularly in the United States and increasingly in other countries, we may be required to provide mandatory discounts and pay fixed rebates to state and federal governments and agencies in connection with purchases of our products that are used or reimbursed by such entities. Rebates also must be paid to the governments of U.S. territories on drugs that are reimbursed by Medicaid in the territories. It is possible that future legislation in the United States and other jurisdictions could be enacted which could potentially impact the reimbursement rates for the products we are developing and may develop in the future and also could further impact the levels of discounts and rebates paid to federal and state government entities. Any legislation that impacts these areas could impact, in a significant way, our ability to generate revenues from sales of products that, if successfully developed, we bring to market. Federal programs also impose penalties on manufacturers of drugs marketed under an NDA and biological products marketed under a BLA in the form of mandatory additional rebates and/or discounts if commercial prices increase at a rate greater than the Consumer Price Index-Urban, and these rebates and/or discounts, which can be substantial, may impact our ability to raise commercial prices. Government authorities and third party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability to sell our product candidates profitably. Biological products approved under BLAs and drugs approved under NDAs are subject to greater discounts and reporting obligations under federal programs than generic drugs approved under Abbreviated New Drug Applications, or ANDAs, although biosimilars are generally treated the same as the reference biologic. The inflation penalty applicable to these products can equal the selling price. It is also not uncommon for market conditions to warrant multiple discounts to different customers on the same unit, such as purchase discounts to institutional care providers and rebates to the health plans that pay them, which reduces the net realization on the original sale.

There is no legislation at the European Union level governing the pricing and reimbursement of medicinal products in the European Union other than in relation to the transparency and timing of national decision making and the availability of appeal. As a result, the competent authorities of each of the 28 European Union Member States have adopted individual strategies regulating the pricing and reimbursement of medicinal products in their territory. These strategies often vary widely in nature, scope and application. However, a major element that they have in common is an increased move towards reduction in the reimbursement price of medicinal products, a reduction in the number and type of products selected for reimbursement and an increased preference for generic products over innovative products. These efforts have mostly been executed through these countries' existing price control methodologies. It is increasingly common in many European Union Member States for Marketing Authorization Holders to be required to demonstrate through health technology assessment the pharmaco-economic superiority of their products as compared to products already subject to pricing and reimbursement in specific countries. In order for drugs to be evaluated positively under such criteria, pharmaceutical companies may need to re-examine, and consider altering, a number of traditional functions relating to the selection, study, and management of drugs, whether currently marketed, under development, or being evaluated as candidates for research and/or development.

Sales and marketing, and other healthcare related activities

Sales, promotion and other activities following product approval are subject to regulation by numerous regulatory authorities in addition to the FDA, including, in the United States, the Centers for Medicare & Medicaid Services, other divisions of the Department of Health and Human Services, the U.S. Department of Justice, and similar foreign, state, and local government authorities.

As described above, the FDA regulates all advertising and promotion activities for products under its jurisdiction both prior to and after approval. A company can make only those claims relating to safety and efficacy that are approved by the FDA in labeling. Physicians may prescribe legally available drugs and biologics for uses that are not described in the product's labeling and that differ from those tested by us and approved by the FDA. These off-label uses are common across medical specialties, and often reflect a physician's belief that the off-label use is the best treatment for the patients. The FDA does not regulate the behavior of physicians in their choice of treatments, but FDA regulations do impose stringent restrictions on manufacturers' communications regarding off-label uses. Failure to comply with applicable FDA requirements may subject a company to adverse publicity, enforcement action by the FDA, corrective advertising, consent decrees and the full range of civil and criminal penalties available to the FDA.

In the United States sales, marketing and scientific/educational programs must also comply with various federal and state laws pertaining to healthcare "fraud and abuse," including anti-kickback laws and false claims laws. Anti-kickback laws make it illegal for a prescription manufacturer to solicit, offer, receive, or pay any remuneration in exchange for, or to induce, the referral of business, including the purchase or prescription of a particular drug or biologic. The term ‘‘remuneration’’ has been broadly interpreted to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, formulary managers, and beneficiaries on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are narrowly drawn. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not meet the requirements of a statutory or regulatory exception or safe harbor. Several courts have interpreted the statute’s intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated. Due to the breadth of the statutory provisions and the absence of guidance in the form of regulations and very few court decisions addressing industry practices, it is possible that our practices might be challenged under anti-kickback or similar laws. Moreover, recent healthcare reform legislation has strengthened these laws. For example, the recently enacted Patient Protection and Affordable Care Act, or ACA, among other things, amends the intent requirement of the federal anti-kickback and criminal healthcare fraud statutes to clarify that a person or entity does not need to have actual knowledge of this statute or specific intent to violate it. In addition, ACA clarifies that the government may assert that a claim that includes items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act.

The civil False Claims Act prohibits anyone from knowingly presenting, or causing to be presented for payment, to third-party payors (including Medicare and Medicaid) claims for reimbursed drugs (including biologics) or services that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services. A claim includes ‘‘any request or demand’’ for money or property presented to the United States government, and may be predicated on false certification of compliance with a statute or regulation that is a condition of payment. The False Claims Act also applies to false submissions that cause the government to be paid less than the amount to which it is entitled, such as a rebate. Intent to deceive is not required to establish liability under the civil False Claims Act. Several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of products for unapproved, and thus non-covered, uses, and for underpaying rebates by concealing their best price. In addition, federal health care programs require drug and biologic manufacturers to report pricing information, which is used to quantify discounts and establish reimbursement rates. Civil False Claims Act actions may be brought by the government or may be brought by private individuals on behalf of the government, called "qui tam" actions. The False Claims Act provides for trebling of actual damages and a penalty for each false claim the manufacturer submitted or caused to be submitted, which, when aggregated, can yield substantial liability,

In addition to the Anti-Kickback Statute and the civil False Claims Act, there are a number of other laws that we may be subject to due to the nature of our business. The criminal False Claims Act prohibits the making or presenting of a claim to the government knowing such claim to be false, fictitious, or fraudulent and, unlike the civil False Claims Act, requires proof of intent to submit a false claim. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, prohibits, among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors, knowingly and willfully embezzling or stealing from a health care benefit program, willfully obstructing a criminal investigation of a health care offense, and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. As discussed above, ACA amended the intent standard for HIPAA’s healthcare fraud provision such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

The civil monetary penalties statute further imposes penalties against any person or entity who, among other things, is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

Section 1927 of the Social Security Act requires that manufacturers of drugs and biological products covered by Medicaid report pricing information to the Centers for Medicare & Medicaid Services, or CMS, on a monthly and quarterly basis, including the best price available to any customer of the manufacturer, with certain exceptions for government programs, and pay prescription rebates to state Medicaid programs based on a statutory formula and derived from reported pricing information. In addition, many states authorize their Medicaid programs to establish Preferred Drug Lists (which include biologics) to leverage supplemental Medicaid rebates. Reporting false pricing information may cause underpayment of rebates or overpayment of pharmacies that are reimbursed by Medicaid on the basis of reported prices and has been the basis of numerous civil, as well as criminal False Claims Act cases against manufacturers.

The Veterans Health Care Act, or VHCA, requires manufacturers of covered drugs and biologics participating in the Medicaid program to report certain non-federal pricing information from which a mandatory purchase discount is derived and to enter into Federal Supply Schedule contracts with the Department of Veterans Affairs through which their covered drugs and biologics must be sold to certain federal agencies at the statutory price. This necessitates compliance with applicable federal procurement laws and regulations and subjects us to contractual remedies as well as administrative, civil, and criminal sanctions. In addition, the VHCA requires manufacturers participating in Medicaid to agree to provide different mandatory discounts to certain Public Health Service grantees and other safety net hospitals and clinics.

The federal and state governments further regulate the payments made to physicians and other health care providers. The ACA created new federal requirements for reporting, by applicable manufacturers of covered drugs and biologics, payments and other transfers of value to physicians and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members.

We may also be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, imposes specified requirements relating to the privacy, security and transmission of individually identifiable health information. Penalties for violating HIPAA include civil penalties, criminal penalties, and imprisonment. Among other things, HITECH, through its implementing regulations, makes HIPAA's privacy and security standards directly applicable to ''business associates,'' defined as a person or organization, other than a member of a covered entity's workforce, that creates, receives, maintains or transmits protected health information on behalf of a covered entity for a function or activity regulated by HIPAA. HITECH also strengthened the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain

circumstances, many of which differ from each other in significant ways and may not have the same requirements, thus complicating compliance efforts.

There further may be state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers, and state laws governing transparency, the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by federal laws, thus complicating compliance efforts.

Our activities relating to our products may be subject to scrutiny under these laws. Violations of fraud and abuse laws may be punishable by criminal and civil sanctions, including fines and civil monetary penalties, the possibility of exclusion from federal healthcare programs (including Medicare and Medicaid) and corporate integrity agreements, which impose, among other things, rigorous operational and monitoring requirements on companies. Similar sanctions and penalties also can be imposed upon executive officers and employees, including criminal sanctions against executive officers under the so-called "responsible corporate officer" doctrine, even in situations where the executive officer did not intend to violate the law and was unaware of any wrongdoing.

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

Depending on the circumstances, failure to comply with these laws can also result in penalties, including criminal, civil and/or administrative criminal penalties, damages, fines, disgorgement, debarment from government contracts and future orders under existing contracts, refusal to allow us to enter into supply contracts, including government contracts, reputational harm, diminished profits and future earnings and the curtailment or restructuring of our operations, any of which could adversely affect our business.

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

Other laws and regulatory processes

We will become subject to a variety of financial disclosure and securities trading regulations as a public company in the United States, including laws relating to the oversight activities of the Securities and Exchange Commission, or SEC and, following the listing of our capital stock on the NASDAQ Global Market, we will be subject to the regulations of the NASDAQ Global Market. In addition, the Financial Accounting Standards Board, or FASB, the SEC and other bodies that have jurisdiction over the form and content of our accounts, our financial statements and other public disclosure are constantly discussing and interpreting proposals and existing pronouncements designed to ensure that companies best display relevant and transparent information relating to their respective businesses.

Our international operations are subject to compliance with the Foreign Corrupt Practices Act, or the FCPA, which prohibits corporations and individuals from paying, offering to pay, or authorizing the payment of anything of value to any foreign government official, government staff member, political party, or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity. The FCPA also obligates companies whose securities are listed in the United States to comply with accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations. We also may be implicated under the FCPA for activities by our partners, collaborators, CROs, vendors or other agents. Activities that violate the FCPA, even if they occur wholly outside the United States, can result in criminal and civil fines, imprisonment, disgorgement, oversight, and debarment from government contracts.

Our present and future business has been and will continue to be subject to various other laws and regulations. Various laws, regulations and recommendations relating to safe working conditions, laboratory practices, the experimental use of animals, and the purchase, storage, movement, import and export and use and disposal of hazardous or potentially hazardous substances used in connection with our research work are or may be applicable to our activities. Certain agreements entered into by us involving exclusive license rights or acquisitions may be subject to national or supranational antitrust regulatory control, the effect of which cannot be predicted. The extent of government regulation, which might result from future legislation or administrative action, cannot accurately be predicted.

Employees

As of March 10, 2016, we had 17 full-time employees and one part-time employee, of whom 11 are in research and development and six are in general and administrative functions. None of our employees is subject to a collective bargaining agreement or represented by a labor or trade union. We believe that our relations with our employees are good.

Corporate Information

We were incorporated under the laws of the State of Delaware in March 2006, and at that time, acquired Proteon Therapeutics, LLC, our predecessor, which was formed in June 2001. Our executive offices are located at 200 West Street, Waltham, Massachusetts 02451, and our telephone number is (781) 890-0102. Our website address is http://www.proteontherapeutics.com. The information on our website, or any website referred to in this Form 10-K, is not incorporated by reference in this Annual Report on Form 10-K or in any other filings we make with the SEC.

Where to Find More Information

We make our public filings with the SEC, including our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and all exhibits and amendments to these reports, available free of charge at our website, http://www.proteontherapeutics.com, as soon as reasonably practicable after we file or furnish such materials with the SEC. Our SEC filings are also at the Public Reference Room of the SEC at 100 F Street, N.E., Washington, D.C. 20549. You may obtain information on the operation of the Public Reference Room by calling 1-800-SEC-0330. In addition, the SEC also maintains an internet site at www.sec.gov that contains reports, proxy statements and other information regarding registrants that file electronically, including Proteon.

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Item 1A. Risk Factors

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

Risks Related to Our Financial Condition and Need for Additional Capital

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

We are a late-stage biotechnology company, and we have not commercialized any products or generated any revenues from the sale of products. We have incurred losses from operations in each year since our inception, and our net losses were $21.4 million and $3.3 million for the years ended December 31, 2015 and 2014, respectively. As of December 31, 2015, we had an accumulated deficit of $131.3 million. We do not expect to generate any product revenues in the foreseeable future. We do not know whether or when we will generate revenue or become profitable.

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

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

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

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

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

Our operations have consumed substantial amounts of cash since inception. As of December 31, 2015, our cash, cash equivalents and available-for-sale investments were $65.3 million. Our research and development expenses were $12.4 million and $6.4 million for the years ended December 31, 2015 and 2014, respectively. We believe that we will continue to expend substantial resources for the foreseeable future developing vonapanitase and any additional product candidates. These expenditures will include costs associated with research and development, potentially acquiring new technologies, potentially obtaining regulatory approvals and manufacturing products, as well as marketing and selling products approved for sale, if any. In addition, other unanticipated costs may arise. Because the outcome of our planned and anticipated clinical trials is highly uncertain, we cannot reasonably estimate the actual amounts necessary to fund and successfully complete the development and commercialization of vonapanitase or any additional product candidates.

We began enrolling patients in our first Phase 3 clinical trial of vonapanitase during the third quarter of 2014 for patients undergoing creation of radiocephalic AVFs, completed patient enrollment in October 2015 and expect to release top-line data in December 2016. We enrolled the first patient in our second Phase 3 AVF trial in August 2015 and expect to complete enrollment in the first quarter of 2017. Based on our current operating plan, and absent any future financings or strategic partnerships, we believe that our existing cash and cash equivalents and available-for-sale investments will be sufficient to fund our projected operating expenses and capital expenditure requirements into the fourth quarter of 2017, allowing us to obtain results from our first Phase 3 clinical trial of vonapanitase in radiocephalic AVFs. This period could be shortened if there are any significant and unexpected increases in spending on development programs or more rapid progress of development programs than anticipated. We do not expect our existing capital resources to be sufficient to enable us to complete our second Phase 3 trial. In addition, we plan to initiate other small Phase 1 or Phase 1/2 trials in additional indications, which would further reduce our capital resources. However, we do not expect to initiate any other Phase 2 or Phase 3 trials prior to receiving and reviewing data from our first Phase 3 AVF clinical trial. Furthermore, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements, or a combination of these approaches. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations.

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

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

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

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

- completing clinical development of vonapanitase for one or more indications and research and preclinical and clinical development of additional product candidates;
- seeking and obtaining regulatory and marketing approvals for vonapanitase if and when we complete clinical trials;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate (in amount and quality) products and services to support clinical development and the market demand for vonapanitase, if approved;
- launching and commercializing vonapanitase if we obtain regulatory and marketing approval, either by collaborating with a partner or, if launched independently, by establishing our own sales, marketing and distribution infrastructure;
- obtaining and maintaining adequate timely coverage and reimbursement from third-party payors for vonapanitase;
- obtaining market acceptance of vonapanitase as a viable treatment option;
- addressing any competing technological and market developments;
- implementing additional internal systems and infrastructure, as needed;
- identifying and validating new product candidates;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter;

- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents and know-how;
- developing vonapanitase such that, if approved, it can be commercialized without infringing the intellectual property rights of third parties; and
- attracting, hiring and retaining qualified personnel.

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

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

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

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

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

We have not previously submitted a Biologics License Application, or BLA, to the FDA, or similar drug or biologic approval filings to comparable foreign authorities, for any product candidate, and we cannot be certain that vonapanitase or any additional product candidates will be successful in clinical trials or receive regulatory approval. In our Phase 2 clinical trial, our primary efficacy endpoint of primary unassisted patency did not show statistically significant benefit for the 30 microgram dose versus placebo. While statistical analyses of the subset of patients with radiocephalic AVFs suggested a clinically significant benefit over placebo for that patient subset, those analyses were not prespecified, and we cannot assure you that these non- prespecified results will be repeated in our Phase 3 trials. Following completion of the Phase 2 clinical trial of vonapanitase, we analyzed the data in a number of ways in addition to the analysis specified in the protocol. For example, we analyzed the data from the subset of patients undergoing creation of a radiocephalic AVF. Analysis of data in a manner or from subsets that were not prespecified in the protocol is typically not sufficient to serve as the basis for regulatory approval and is generally not considered as reliable as analyses which were prespecified in the protocol. Even though our Phase 3 trials will enroll patients undergoing a surgical procedure to create a radiocephalic AVF (*i.e.*, that subset of patients in which vonapanitase showed a greater benefit in our Phase 2 clinical trial), there are risks of failure inherent at any stage of product development, and we may not demonstrate efficacy with regard to the primary endpoint of our ongoing and planned Phase 3 clinical trials, or unexpected adverse events may appear. Further, vonapanitase or any additional product candidates, may not receive regulatory approval even if they are successful in clinical trials. If approved for marketing by applicable regulatory authorities, our ability to generate revenues from vonapanitase will depend on our ability to, among other things:

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

As we continue to develop vonapanitase for other indications, including AVG, brachiocephalic AVF and symptomatic PAD, or develop additional product candidates, we will face similar risks and challenges.

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

Clinical development is expensive, difficult to design and implement, takes many years to complete and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process and vonapanitase is subject to the risks of failure inherent in drug and biological development, including failure to demonstrate efficacy in a pivotal clinical trial or in the patient population we intend to enroll, the occurrence of severe or medically or commercially unacceptable adverse events, failure to comply with protocols or applicable regulatory requirements and determination by the FDA or any comparable foreign regulatory authority that a drug and biological product is not approvable. Trends and results observed in earlier stage clinical trials, particularly trends and results observed through non-prespecified analysis of the data, may not be replicated in later stage clinical trials. For example, as is common with Phase 2 trials, we explored a number of endpoints. We also analyzed the data from our Phase 2 clinical trial of vonapanitase in a number of ways, some of which were not prespecified. Product candidates such as vonapanitase in Phase 3 clinical trials may fail to demonstrate sufficient efficacy despite having progressed through initial clinical trials, even if certain non-prespecified analyses of primary or secondary endpoints in those early trials showed trends toward efficacy or, in some analyses, statistical significance. Companies frequently suffer significant setbacks in late-stage clinical trials due to lack of efficacy, manufacturing or formulation changes or adverse safety profiles, even after earlier clinical trials have shown promising results. During the course of our clinical development, we modified our vonapanitase finished product formulation for our Phase 3 trials and commercial launch in order to facilitate ease of administration and fill and finish of vials at our 30 microgram dose. Our formulation changes could adversely affect results in our clinical trials, requiring us to make further formulation changes. Additional changes could cause us to delay or repeat clinical trials, or could cause FDA to request additional studies or data, and we could incur unexpected costs that would have an adverse effect on our business, operating results and prospects.

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

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

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

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

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

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

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

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

In general, the FDA requires two adequate and well-controlled clinical trials to demonstrate the effectiveness of a product candidate. If the results of our first Phase 3 clinical trial are sufficiently compelling, we intend to meet with the FDA to discuss the possibility of submitting a BLA supported by the single Phase 3 trial and may decide to submit a BLA to the FDA prior to completing the second Phase 3 trial. If we attempt to rely on a single Phase 3 trial to demonstrate the effectiveness of vonapanitase, the usual demonstration of the statistical significance in the primary efficacy endpoint (p=0.05) is unlikely to be sufficient to obtain approval of vonapanitase, and we would likely be required to demonstrate more robust statistical significance. Even with a robust p-value, the FDA may not consider the results of the single Phase 3 trial to be sufficient for BLA filing or approval, and may require that we complete our second Phase 3 trial or that we even conduct additional trials.

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

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

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

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

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

We may face difficulty in enrolling patients for clinical trials.

We may find it difficult to enroll patients in our clinical trials, which could delay or prevent completion of clinical trials of vonapanitase or any additional product candidates. We have never previously limited a trial to patients undergoing a surgical procedure to create a radiocephalic AVF, as we are doing in our ongoing and planned Phase 3 trials. Identifying and qualifying patients to participate in clinical trials of vonapanitase or any additional product candidates are critical to our success. The timing of our clinical trials depends on the speed at which we can recruit patients to participate in testing product candidates. The enrollment timeline for radiocephalic AVF patients is lengthy and there are a limited number of sites from which we can enroll pre-hemodialysis or hemodialysis patients. If patients are unwilling to participate in our trials because of negative publicity from adverse events or for other reasons, including competitive clinical trials for similar patient populations, the timeline for recruiting patients, conducting trials and obtaining regulatory approval of potential products may be delayed or prevented. These delays could result in increased costs, delays in advancing our product development, delays in testing the effectiveness of our technology or termination of the clinical trials altogether. We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics to achieve diversity in a trial, to complete our clinical trials in a timely manner. Patient enrollment is affected by numerous factors including:

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

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

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

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

- trials of vonapanitase or any additional product candidates may produce unfavorable or inconclusive results;
- we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- our third-party contractors, including those manufacturing vonapanitase or any additional product candidates or components or ingredients for commercial use or conducting clinical trials on our behalf, may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner or at all;
- regulators or institutional review boards may not authorize us or our investigators to commence or continue to conduct a clinical trial at a prospective trial site;
- we may have to suspend or terminate clinical trials of vonapanitase or any additional product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of a product candidate;
- regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or their respective standards of conduct, a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of the product candidate or findings of undesirable effects caused by a chemically or mechanistically similar biologic or biologic candidate;

- we may experience delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites and/or Contract Research Organizations;

- we may experience withdrawal of clinical trial sites from our clinical trials as a result of changing standards of care or the ineligibility of a site to participate in our clinical trials, and may further be delayed in trying to add clinical trial sites to our studies;

- we may experience delays in the importation and manufacture of clinical supply;

- patient enrollment in these clinical trials may be slower than we anticipate and is limited to a select number of sites, which could cause significant delays given the prolonged enrollment period;

- participants may drop out of clinical trials of vonapanitase at a higher rate than we anticipate and we may not be able to obtain the follow up data for the 12 month period planned in our Phase 3 trials;

- patients who enroll in a clinical trial may misrepresent their eligibility to do so or may otherwise not comply with the clinical trial protocol, resulting in the need to drop the patients from the clinical trial or increase the needed enrollment size for the clinical trial beyond the 300 proposed for each Phase 3 trial, all of which may extend the clinical trial's duration;

- the FDA or comparable foreign regulatory authorities may disagree with our clinical trial design, implementation, or our interpretation of data from preclinical studies and clinical trials;

- FDA or comparable foreign regulatory authorities may find that our clinical trials were not conducted in accordance with Good Clinical Practices, or GCPs;

- the FDA or comparable foreign regulatory authorities may fail to approve or subsequently find fault with the manufacturing processes or facilities of third-party manufacturers with which we enter into agreements for clinical and commercial supplies;

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

- we may lack adequate funding to continue the clinical trials or to pay FDA's substantial user fees; and

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

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

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

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

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

- restrictions on our ability to conduct clinical trials, including full or partial clinical holds on ongoing or planned trials;
- restrictions on a product's manufacturing processes;
- restrictions on the marketing of a product;
- restrictions on product distribution;
- requirements to conduct post-marketing clinical trials;
- Untitled, Cyber, or Warning Letters from the FDA or similar correspondence from comparable regulatory authorities;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- mandated modifications to promotional materials or require us to provide corrective information to healthcare practitioners;
- requirements to enter into a consent decree, which can include imposition of various fines, reimbursements for inspection costs, required due dates for specific actions and penalties for noncompliance;
- debarring us pursuant to the FDCA, excluding us from participation in federal healthcare programs, requiring a corporate integrity agreement or debarring us from government contracts;
- the imposition of costly new manufacturing requirements or use of alternative suppliers, requiring additional warnings on the label;
- FDA or other regulatory bodies issuing safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings about our products;
- fines, restitution or disgorgement of profits or revenue;

- suspension or withdrawal of regulatory approvals or refusal to approve future or pending applications or supplements;
- refusal to permit the import or export of our products;
- product seizure;
- injunctions; and/or
- imposition of civil or criminal penalties.

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

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

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

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

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

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

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

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

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

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

We have received a fast track product designation for vonapanitase for improving vascular access and decreasing the need for surgery in patients with CKD who are on hemodialysis or being prepared for hemodialysis. As applicable, we may seek fast track, priority review, or other designations for other uses of vonapanitase. A fast track product designation is designed to facilitate the clinical development and expedite the review of drugs and biologics intended to treat a serious condition which demonstrate the potential to address an unmet medical need. Priority review designation is intended to speed the FDA marketing application review timeframe for drugs and biologics that treat a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. For drugs and biologics that have been designated as fast track products, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development. Sponsors of drugs and biologics designated as fast track products therapies may also be able to submit marketing applications on a rolling basis, meaning that the FDA may review portions of a marketing application before the sponsor submits the complete application to the FDA, as long as the sponsor pays the user fee upon submission of the first portion of the marketing application. For products that receive a priority review designation, the FDA's marketing application review goal is shortened to six months, as opposed to ten months under standard review. This review goal is based on the date the FDA accepts the marketing application for review, which typically adds two months to the timeline for review and decision from the date of submission.

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

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

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

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

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

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

Based on additional data including the data from our Phase 3 clinical trials and assuming sufficient funds become available, we plan to commence a clinical trial of vonapanitase in Europe for patients undergoing creation of radiocephalic AVFs. Prior to enrolling our first patient in Europe, we plan to formally seek guidance from the EMA regarding its requirements for regulatory approval. We expect results from this trial to be available two to three years after the first patient is enrolled. If results of this European trial successfully meet its primary endpoint and depending on the guidance obtained from the EMA, we would expect to submit a Marketing Authorization Application, or MAA, following our receipt of the trial results. Obtaining an approval is a lengthy and expensive process and the EMA has its own procedures for approval of product candidates. Even if a product candidate is approved, the EMA may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and Europe also have requirements for approval of product candidates with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of vonapanitase or any additional product candidates in those countries.

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

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

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

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

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

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

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

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

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

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

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

Risks Related to Commercialization of Our Product

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

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

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

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

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

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

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

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

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

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

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

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

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

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

We are not aware of any therapeutic products approved in the United States or Europe for the prevention of vascular access failure. We are aware of therapies in development with companies, including Vascular Therapies and Symic Biomedical. Vonapanitase could face competition from companies developing vascular access technologies, including BioConnect Systems, Avenu Medical, Phraxis, CreatiVasc, Laminate Medical Technologies, Stent Tek and TVA Medical. Other potentially competitive products include new synthetic grafts, including those that may be developed by companies that currently compete in the graft market, such as W.L. Gore, C.R. Bard and Maquet, as well as tissue engineered grafts, including those in development by Cytograft and Humacyte. Finally, vonapanitase’s commercial success could be affected by the development of technologies to improve the outcomes of interventions to restore patency, including stents, stent grafts and drug-coated balloons.

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

The enactment of the Biologics Price Competition and Innovation Act of 2009, or BPCIA, as part of the ACA, created an abbreviated pathway for the approval of biosimilar and interchangeable biological products. The abbreviated regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as “interchangeable” based on its similarity to an existing brand product. Under the BPCIA, an application for a biosimilar product cannot be approved by the FDA until 12 years after the original branded product was approved under a BLA. Certain changes, however, and supplements to an approved BLA, and subsequent applications filed by the same sponsor, manufacturer, licensor, predecessor in interest, or other related entity do not qualify for the 12-year exclusivity period. Moreover, President Obama's proposed budget for fiscal year 2017 proposes cutting this twelve year period of exclusivity down to seven years. President Obama also proposed to prohibit additional periods of exclusivity for brand biologic products due to minor changes in product formulation, a practice often referred to as “evergreening**.”** The Trans-Pacific Partnership international trade agreement further includes exclusivity provisions for biologics that would require member countries not to approve biosimilars before at least 8 years of exclusivity has expired for biologics or, alternatively, five years plus other measures to provide effective market protection. Future proposed budgets, international trade agreements and other arrangements or proposals may also affect periods of exclusivity in the future. .

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The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty. While it is uncertain when such processes intended to implement the BPCIA may be fully adopted by the FDA, any such processes could have a material adverse effect on the future commercial prospects for our biological products.

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

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

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

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

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

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

Risks Related to Dependence on Third Parties

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

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

All entities involved in the preparation of drugs or biologics for clinical trials or commercial sale, including our existing contract manufacturers, are subject to extensive regulation. Ingredients of a finished therapeutic biologic product approved for commercial sale or used in clinical trials must be manufactured in accordance with cGMPs and equivalent foreign standards. These regulations govern manufacturing processes and procedures (including record-keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of product candidate that may not be detectable in final product testing. We or our contract manufacturers must supply all necessary documentation in support of a BLA on a timely basis and must adhere to the FDA’s cGMPs regulations enforced by the FDA through its facilities inspection program. Any failure by our third-party manufacturers to comply with cGMPs, or failure to scale-up manufacturing processes, including any failure to deliver sufficient quantities of product candidates in a timely manner for the process validation required in connection with a BLA filing, could lead to a delay in, or failure to obtain, regulatory approval of the manufacturing facility, vonapanitase or any additional product candidates. For example, on November 27, 2013, our third-party supplier of finished biological product, Jubilant HollisterStier, received a Warning Letter from the FDA alleging that the company was not complying with cGMPs. We received a letter from the FDA on February 13, 2014, stating that the Warning Letter does not impact the batch of finished product we intend to use for our Phase 3 clinical trials. However, this third party or other third parties could encounter similar difficulties that could impede our clinical trials or commercialization.

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

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

If we or any of our third-party manufacturers fail to maintain regulatory compliance, the FDA can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new drug or biologic product or revocation of a pre-existing approval. If any such event occurs, our business, financial condition and results of operations may be materially harmed.

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

Our contract with Lonza for the manufacturing of the API is denominated in Swiss Francs. Therefore, fluctuations in the exchange rate for Swiss Francs may affect our operating results. On January 15, 2015, the Swiss National Bank announced an edit to its policy of fixing the Swiss Franc and Euro exchange rate, which caused volatility in the currency markets for Swiss Francs and an immediate increase in their value, making our contractual payments to Lonza more expensive based on the current exchange rates. In the second quarter of 2015, we entered into forward foreign currency contracts to purchase Swiss Francs to reduce our foreign currency exposure under our contract with Lonza. In the future we may purchase additional forward foreign currency contracts to hedge certain forecasted transactions, including those with Lonza, and reduce exposures to foreign currency fluctuations. Any use of these derivative instruments would be intended to mitigate a portion of the exposure of these risks with the intent to reduce our risk or cost, but generally would not fully offset any change in operating results as a consequence of fluctuations in foreign currencies. Any significant foreign exchange rate fluctuations could adversely affect our financial condition and results of operations and any use of derivative instruments may not offset such fluctuations and could exacerbate their impact on our financial condition and results of operations.

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

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

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

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

We rely on our manufacturers to purchase from third-party suppliers the materials necessary to produce our product candidate, vonapanitase, for our clinical trials, and eventual commercial supply, if we receive regulatory approval. There are a small number of suppliers for certain raw materials that we use to manufacture vonapanitase. These suppliers may not sell these raw materials to our manufacturers at the times we need them or on commercially reasonable terms. We do not have any control over the process or timing of the acquisition of these raw materials by our manufacturers. Moreover, we currently do not have any agreements for the commercial production of these raw materials. Although the API and the finished product for each of our Phase 3 trials has already been manufactured and is held in storage, we will need supply of finished product as part of the process validation and for any stability or other tests in connection with a BLA application and also to conduct additional clinical trials, for example for additional vonapanitase indications. We will further require finished product for commercialization if we receive regulatory approval. Any significant delay in the supply of vonapanitase's ingredients due to the need to replace a third-party manufacturer could considerably delay completion of our clinical trials, product testing and potential regulatory approval of vonapanitase or any additional product candidate, and commercialization as we believe that replacing Lonza as the manufacturer of our API would take one to two years and replacement of any of our other manufactures may take a substantial amount of time. If our manufacturers or we are unable to purchase these raw materials after regulatory approval has been obtained for our product candidate, our ability to commercially launch and/or generate revenues from the sale of any approved product would be impaired. Reliance on third-party manufacturers entails exposure to risks to which we would not be subject if we manufactured the product candidate ourselves, including:

- inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- reduced day-to-day control over the manufacturing process for our product candidates as a result of using third-party manufacturers for all aspects of manufacturing activities;
- reduced control over the protection of our trade secrets and know-how from misappropriation or inadvertent disclosure;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that may be costly or damaging to us or result in delays in the development or commercialization of our product candidates; and
- disruptions to the operations of our third-party manufacturers or suppliers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier.

Any of these events could lead to delays in the development of vonapanitase or any additional product candidates, including delays in our clinical trials, or failure to obtain regulatory approval for our product candidates, or it could impact our ability to successfully commercialize vonapanitase or any additional product candidates. Some of these events could be the basis for FDA or other regulatory action, including Warning Letters, injunction, recall, seizure or total or partial suspension of production. Any of these events could have a material adverse effect on our business.

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

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

We and our CROs are required to comply with the FDA's GCPs for conducting, recording and reporting the results of clinical trials to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. The FDA and comparable foreign regulatory authorities enforce these GCPs through periodic inspections of trial sponsors, principal investigators and clinical trial sites. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our future clinical trials may be deemed unreliable and the FDA, the EMA, or other foreign regulatory authorities may require us to perform additional clinical trials before approving any marketing applications. In addition, we are required to report certain financial interests of our third-party investigators if these relationships exceed certain financial thresholds or meet other criteria. The FDA or comparable foreign regulatory authorities may question the integrity of the data from those clinical trials conducted by principal investigators who previously served or currently serve as scientific advisors or consultants to us from time to time and receive cash compensation in connection with such services.

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

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

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

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

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

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

Risks Related to Our Intellectual Property

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

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

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

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If patent applications we hold with respect to vonapanitase or any additional product candidates fail to issue, if their breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for vonapanitase or any additional product candidates, it could dissuade companies from collaborating with us. As of December 31, 2015 we own 29 issued patents and own 20 pending patent applications, most of which cover aspects of vonapanitase or its use. We cannot offer any assurances about which, if any, of the pending patent applications will issue as patents, the breadth of any such patents or any of our currently issued patents, or whether any issued patents will be challenged by third parties or will be found invalid and unenforceable if challenged. Any successful challenge to these patent applications, or patents that may issue from them, or to currently issued patents owned by us, could deprive us of rights necessary for the successful commercialization of vonapanitase or any other product candidate that we may develop. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file a patent application relating to any particular aspect of a product candidate. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be initiated by these third parties, or by the USPTO itself, to determine who was the first to invent any of the subject matter covered by the patent claims of our patents and patent applications.

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

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

clinical and preclinical data, and then may be able to launch their product earlier than might otherwise be the case.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- that our commercial activities or products will not infringe the patents or proprietary rights of others.

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

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

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

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

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

The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process. There are situations in which noncompliance can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case.

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

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

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

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

Competitors may use our technologies in jurisdictions where we do not pursue and obtain patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. Even if we pursue and obtain issued patents in particular jurisdictions, our patent claims or other intellectual property rights may not be effective or sufficient to prevent third parties from so competing.

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

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

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

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

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

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

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

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

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

As is the case with other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and is therefore costly, time-consuming and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation, the Leahy-Smith America Invents Act, or America Invents Act. The America Invents Act includes a number of significant changes to United States patent law. These include provisions that affect the way patent applications will be prosecuted, provides expanded opportunities for post-grant administrative review of patents before the USPTO, and may also affect patent litigation. It is not yet clear what, if any, impact the America Invents Act will have on the operation of our business. However, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of any patents that may issue from our patent applications, all of which could have a material adverse effect on our business and financial condition.

In addition, recent United States Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. The full impact of these decisions is not yet known. For example, on March 20, 2012 in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, the Court held that several claims drawn to measuring drug metabolite levels from patient samples and correlating them to drug doses were not patent-eligible subject matter. The decision appears to impact diagnostics patents that merely apply a law of nature via a series of routine steps and it has created uncertainty around the ability to obtain patent protection for certain inventions. Additionally, on June 13, 2013 in *Association for Molecular Pathology v. Myriad Genetics, Inc.,* the Court held that claims to isolated genomic DNA are not patent-eligible, but claims to complementary DNA molecules are patent-eligible because they are not a natural product. The effect of the decision on patents for other isolated natural products is uncertain. However, on March 4, 2014, the USPTO issued a memorandum to patent examiners providing guidance for examining claims that recite laws of nature, natural phenomena or natural products under the *Myriad* and *Prometheus* decisions. This guidance did not limit the application of *Myriad* to DNA, but, rather, applied the decision to other natural products.

In addition to increasing uncertainty with regard to our ability to obtain future patents, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on these and other decisions by the United States Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our current or future patents.

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

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

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

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business, provide a barrier to entry against our competitors or potential competitors, or permit us to maintain our competitive advantage. Moreover, if a third party has intellectual property rights that cover the practice of our technology, we may not be able to exercise or extract value from our intellectual property rights fully or at all. The following examples are illustrative:

- we might not have been the first to make the inventions covered by a patent or pending patent application that we own;
- we might not have been the first to file patent applications covering an invention;
- others may independently develop similar or alternative technologies without infringing our intellectual property rights;
- third parties may compete with us in jurisdictions where we do not pursue and obtain patent protection;

- pending patent applications that we own may not lead to issued patents;
- patents that we own may not provide us with any competitive advantages, or may be held invalid or unenforceable;
- third parties may assert an ownership interest in our intellectual property;
- we may not develop or in-license additional proprietary technologies that are patentable; and
- the patents or proprietary rights of others may have an adverse effect on our business.

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

Risks Related to Our Business and Industry

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

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

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

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

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

Future growth will impose significant added responsibilities on members of management, including the need to identify, recruit, maintain and integrate additional employees. In addition, to meet our obligations as a public company, we will need to increase our general and administrative capabilities. Our management, personnel and systems currently in place may not be adequate to support this future growth. Our future financial performance and our ability to commercialize our potential products and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to:

- manage our clinical trials and the regulatory process effectively;
- manage the manufacturing of product candidates and potential products for clinical and commercial use;
- integrate current and additional management, administrative, financial and sales and marketing personnel;
- develop a marketing and sales infrastructure;
- hire new personnel necessary to effectively commercialize vonapanitase and any additional product candidates;
- develop our administrative, accounting and management information systems and controls; and
- hire and train additional qualified personnel.

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

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

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

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

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

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

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For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Large judgments have been awarded in class action lawsuits based on drugs or biologics that had unanticipated adverse effects. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of vonapanitase or any additional product candidates. Regardless of the merits or eventual outcome, liability claims may result in:

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

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

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

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

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

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

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

If supply is interrupted, there could be a significant disruption in our clinical development and commercial supply. If the supply is interrupted after approval of the BLA, an alternative manufacturer would need to be qualified through a BLA supplement which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and would likely result in a delay in our desired clinical and commercial timelines.

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

Our business and operations would suffer in the event of system failures or security breaches.

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

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

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with the regulations of the FDA and foreign regulators, provide accurate information to the FDA and foreign regulators, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, and report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have a Code of Business Conduct and Ethics, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

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

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

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

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

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

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

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- increases in the statutory minimum rebates a manufacturer must pay as a condition to having a drug or biologic available for coverage under the Medicaid program;
- expansion of healthcare fraud and abuse laws, including the federal civil False Claims Act and the federal Anti-Kickback Statute, and the addition of new government investigative powers and enhanced penalties for non-compliance;
- extension of a manufacturer’s Medicaid rebate liability to covered drugs and biologics dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new eligibility categories for certain individuals with income at or below 133% of the federal poverty level beginning in 2014, thereby potentially increasing a manufacturer’s Medicaid rebate liability;

- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements under the federal Open Payments program and its implementing regulations;
- a new requirement to annually report drug and biologic samples that manufacturers and distributors provide to physicians;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and
- a special Medicare Part B payment rate for biosimilars that favors them over the reference biological product.

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

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

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

Risks Related to Our Common Stock

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

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

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

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

Even after we no longer qualify as an EGC, we may still qualify as a "smaller reporting company" which would allow us to take advantage of many of the same exemptions from disclosure requirements, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We cannot predict if investors will find our Common Stock less attractive because we will rely on these exemptions. If some investors find our Common Stock less attractive as a result, there may be a less active trading market for our Common Stock and our stock price may be more volatile.

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

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

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

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

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

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

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

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

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

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

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

We may terminate the Sales Agreement at any time or it will terminate once proceeds of $40 million have been raised. Whether we choose to affect future sales under the At-The-Market program will depend upon a variety of factors, including, among others, market conditions and the trading price of our Common Stock relative to other sources of capital. The issuance from time to time of these new shares of Common Stock through our At-The-Market program or in any other equity offering, or the perception that such sales may occur, could have the effect of depressing the market price of our Common Stock.

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

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

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

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

Raising additional funds through debt or equity financing could be dilutive and may cause the market price of our Common Stock to decline.

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

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

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

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

As of December 31, 2015, our executive officers, directors, current 5% or greater stockholders, and their respective affiliates together beneficially own or control, in aggregate, more than 50% of the shares of our outstanding Common Stock. As a result, these executive officers, directors and principal stockholders, acting together, will have substantial influence over most matters that require approval by our stockholders, including the election of directors, any merger, consolidation or sale of all or substantially all or of our assets or any other significant corporate transaction. Corporate action might be taken even if other stockholders oppose such action. These stockholders may delay or prevent a change of control or otherwise discourage a potential acquirer from attempting to obtain control of our company, even

if such change of control would benefit our other stockholders. This concentration of stock ownership may adversely affect investors' perception of our corporate governance or delay, prevent or cause a change in control of our company, any of which could adversely affect the market price of our Common Stock.

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

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

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

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

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

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

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

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

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

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

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

If a corporation undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, Sections 382 and 383 of the Code, limit the corporation's ability to use carryovers of its pre-change NOLs, credits and certain other tax attributes to reduce its tax liability for periods after the ownership change. We completed an analysis to determine if there were changes in ownership for tax years through 2014, as defined by Section 382 of the Internal Revenue Code that would limit our ability to utilize certain net operating loss and tax credit carryforwards and it was determined there was no change in ownership. We are in the process of completing an analysis to determine if there were changes in ownership for tax years through 2015, as defined by Section 382. To the extent the Company undergoes a change in ownership, as defined by Section 382, utilization of our net operating losses and tax credits carryforwards may become limited. If this were to occur, this could result in increased U.S. federal income tax liability for us if we generate taxable income in a future period. Limitations on the use of NOLs and other tax attributes could also increase our state tax liability. The use of our tax attributes will also be limited to the extent that we do not generate positive taxable income in future tax periods.

We could be subject to securities class action litigation.

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

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

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

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

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

In addition, because we are incorporated in the State of Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us.

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

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

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

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our primary facility is located in Waltham, Massachusetts, where we lease approximately 4,943 square feet of office space. Our lease expires in June 2018. We also have a facility located in Kansas City, Kansas, where we lease approximately 80 square feet of office space. Our lease in Kansas City expires in December 2016. We believe that our existing facilities are sufficient for our current needs and our needs for the foreseeable future.

Item 3. Legal Proceedings

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

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our Common Stock has been publicly traded on the NASDAQ Global Market under the symbol "PRTO" since October 22, 2014. Prior to that time, there was no public market for our Common Stock. The following table sets forth, for the periods indicated, the high and low sales prices for our Common Stock as reported on the NASDAQ Global Market.

	High	Low
Year Ended December 31, 2015		
First quarter	$12.65	$9.88
Second quarter	$18.45	$11.00
Third quarter	$20.00	$11.65
Fourth quarter	$17.76	$12.57
Year Ended December 31, 2014		
Fourth quarter (from and after October 22, 2014)	$12.00	$8.57

On March 10, 2016, the last reported sale price for our Common Stock on the NASDAQ Global Market was $6.24 per share.

Holders

As of March 10, 2016, there were approximately 39 holders of record of our Common Stock. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but

whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividends

We have never declared or paid cash dividends on our Common Stock, and we do not expect to pay any cash dividends on our Common Stock in the foreseeable future. Payment of future dividends, if any, on our Common Stock will be at the discretion of our Board of Directors after taking into account various factors, including our financial condition, operating results, anticipated cash needs, and plans for expansion.

Comparative Stock Performance Graph

The following graph shows a comparison from October 22, 2014, the date on which our Common Stock first began trading on the NASDAQ Global Market, of the cumulative total return on an assumed investment of $100.00 in cash on October 22, 2014, in our Common Stock as compared to the same investment in the NASDAQ Composite Index and the NASDAQ Biotechnology Index, all through December 31, 2015. These returns are based on historical results and are not intended to suggest future performance. Data assumes the reinvestment of dividends. The graph assumes our closing sales price on October 22, 2014 of $10.03 per share as the initial value of our Common Stock and not the initial offering price to the public of $10.00 per share.

The comparisons shown in the graph below are based upon historical data. We caution that the stock price performance shown in the graph below is not necessarily indicative of, nor is it intended to forecast, the potential future performance of our Common Stock. Information used in the graph was obtained from the Nasdaq Stock Market LLC, a source believed to be reliable. The Nasdaq Stock Market LLC is not responsible for any errors or omissions in such information.

COMPARISON OF CUMULATIVE TOTAL RETURN*

Proteon Therapeutics Inc., the NASDAQ Composite Index,

and the NASDAQ Biotechnology Index

* $100 invested on October 22, 2014

Cumulative Total Return Comparison

	10/22/2014	12/31/2014	3/31/2015	6/30/2015	9/30/2015	12/31/2015
Proteon Therapeutics, Inc.	100.00	103.69	115.95	178.07	138.68	154.64
NASDAQ Composite	100.00	108.06	111.82	113.78	105.41	114.25
NASDAQ Pharmaceutical	100.00	104.64	111.83	112.59	102.70	106.34

The performance graph in this Item 5 is not deemed to be "soliciting material" or to be "filed" with the Security and Exchange Commission, or the SEC, for purposes of Section 18 of the Securities and Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liabilities under that Section, and shall not be deemed incorporated by reference into any filing of Proteon Therapeutics, Inc. under the Securities Act of 1933 or the Exchange Act, except to the extent we specifically incorporate it by reference into such a filing.

Securities Authorized for Issuance Under Equity Compensation Plans

The following table contains information about our equity compensation plans as of December 31, 2015.

Plan category	Number of securities to be issued upon exercise of outstanding stock options, warrants and rights	Weighted-average exercise price of outstanding options, warrants and rights	Number of securities remaining available for future issuance under equity compensation plans (excluding securities reflected in column (a))
Equity compensation plans approved by security holders (1)	2,200,369	$ 8.52	516,921
Equity compensation plans not approved by security holders	-	-	-
Total	2,200,369	$ 8.52	516,921

(1) Includes information regarding our Amended and Restated 2006 Equity Incentive Plan.

Stockholders. As of March 10, 2016, we had 39 holders of record of our Common Stock.

Dividends. We have never declared or paid cash dividends on our capital stock, and we have no plan to pay any cash dividends in the foreseeable future. We currently intend to retain any future earnings to finance our operations and future growth.

Purchases of Equity Securities

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

Use of Proceeds from Initial Public Offering

On October 27, 2014, we completed the sale of 6,110,000 shares of Common Stock and, on November 21, 2014, we completed the sale of 916,500 shares of Common Stock upon the exercise of an option by our underwriters to purchase additional shares, in each case at a public offering price of $10 per share for aggregate gross proceeds of $70,265,000. The offer and sale of all of the shares in the Initial Public Offering, or IPO, were registered under the Securities Act of 1933, as amended, or the Securities Act, pursuant to a registration statement on Form S-1, as amended (File No. 333-198777), which was declared effective by the SEC on October 21, 2014. The joint book-running managers for the IPO were Stifel, Nicolaus & Company, Incorporated and JMP Securities LLC. The co-managers for the IPO were Robert W. Baird & Co. Incorporated and Oppenheimer & Co. Inc. Following the sale of the shares in connection with the closing of the IPO, the offering terminated.

We received net proceeds from the IPO, including the exercise of the underwriter's over-allotment, of approximately $62,500,000, after deducting underwriting discounts and commissions of approximately $4,919,000 and offering-related expenses of approximately $2,830,000 payable by us. None of the expenses associated with the IPO were paid to directors, officers, persons owning 10% or more of any class of equity securities, or to their associates, or to our affiliates.

There has been no material change in the planned use of proceeds from our IPO as described in our final prospectus filed with the SEC pursuant to Rule 424(b) of the Securities Act on October 22, 2014. We are holding the balance of the net proceeds from the IPO in investments in U.S. Treasuries, certificates of deposit, corporate bonds and U.S. government-backed and agency securities. As of February 29, 2016, we estimate that we have used approximately $24.7 million of the net proceeds from the IPO to fund the clinical development of vonapanitase and for other general corporate purposes.

Item 6. Selected Financial Data

The selected consolidated statements of operations data for each of the three years ended December 31, 2015, 2014 and 2013, and the selected consolidated balance sheet data at December 31, 2015 and 2014 have been derived from our audited consolidated financial statements included elsewhere in this Annual Report on Form 10-K. The selected consolidated statement of operations data for the year ended December 31, 2012 and the selected consolidated balance sheet data at December 31, 2013 and 2012 have been derived from our audited consolidated financial statements for such years not included in this Annual Report on Form 10-K. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period, and our interim period results are not necessarily indicative of results to be expected in any future period.

The information set forth below should be read in conjunction with the "Management's Discussion and Analysis of Financial Condition and Results of Operations" section of this Annual Report on Form 10-K and with our consolidated financial statements and notes thereto included elsewhere in this Annual Report on Form 10-K. The selected consolidated financial data in this section are not intended to replace the consolidated financial statements and are qualified in their entirety by the consolidated financial statements and related notes included elsewhere in this Annual Report on Form 10-K.

	Proteon Therapeutics, Inc. Year Ended December 31,			
	2015	2014	2013	2012
	(in thousands, except share and per share data)			
Revenue	$-	$2,948	$-	$-
Operating expenses:				
Research and development	12,381	6,432	3,994	5,907
General and administrative	8,489	4,096	3,128	2,089
Total operating expenses	20,870	10,528	7,122	7,996
Loss from operations	(20,870)	(7,580)	(7,122)	(7,996)
Other income (expense):				
Investment income	144	24	4	20
Interest expense	-	(857)	(861)	-
Other (expense) income	(651)	5,071	67	6
Total other (expense) income	(507)	4,238	(790)	26
Net loss	$(21,377)	$(3,342)	$(7,912)	$(7,970)
Unrealized loss on available-for-sale investments	(5)	(6)	(1)	(5)
Comprehensive loss	$(21,382)	$(3,348)	$(7,913)	$(7,975)
Reconciliation of net loss to net loss attributable to common stockholders:				
Net loss	$(21,377)	$(3,342)	$(7,912)	$(7,970)
Accretion of redeemable convertible preferred stock to redemption value	-	(6,353)	(6,119)	(6,133)
Net loss attributable to common stockholders	$(21,377)	$(9,695)	$(14,031)	$(14,103)
Net loss per share attributable to common stockholders - basic and diluted	$(1.30)	$(3.16)	$(59.66)	$(61.16)
Weighted-average common shares outstanding used in net loss per share attributable to common stockholders - basic and diluted	16,464,123	3,064,507	235,184	230,607

Supplemental disclosure of stock-based compensation expense:

Included in operating expenses, above, are the following amounts for non-cash stock based compensation expense:

Research and development	$650	$114	$106	$46
General and administrative	1,514	345	49	64
Total	$2,164	$459	$155	$110

	December 31,			
	2015	2014	2013	2012
	(in thousands)			

Balance Sheet Data:				
Cash, cash equivalents and available-for-sale investments	$65,263	$83,595	$5,152	$7,471
Working capital	62,475	82,263	(4,438)	6,499
Total assets	67,538	84,798	5,659	7,782
Preferred stock	-	-	96,405	90,286
Common stock and additional paid-in-capital	194,667	192,340	-	-
Total stockholders' equity (deficit)	63,405	82,460	(100,514)	(86,656)

Item 7. Management’s Discussion and Analysis of Financial Condition and Results of Operations

MANAGEMENT’S DISCUSSION AND ANALYSIS

OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of our financial condition and results of operations together with the section entitled “Selected Financial Data” and our consolidated financial statements and related notes appearing elsewhere in this Annual Report on Form 10-K.

Our actual results and timing of certain events may differ materially from the results discussed, projected, anticipated, or indicated in any forward-looking statements. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, 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 of this Annual Report on Form 10-K, 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. In addition, even if our results of operations, financial condition and liquidity, and the development of the industry in which we operate are consistent with the forward-looking statements contained in this Annual Report on Form 10-K , they may not be predictive of results or developments in future periods.

Overview

We are a late-stage biopharmaceutical company focused on the development of novel, first-in-class pharmaceuticals to address the medical needs of patients with kidney and vascular disease. Our product candidate, vonapanitase (formerly PRT-201), is a recombinant human elastase that we are developing to improve arteriovenous fistula, or AVF patency in patients with chronic kidney disease undergoing or preparing for hemodialysis, a lifesaving treatment that cannot be conducted without a functioning vascular access. We believe the data from our completed Phase 2 trial of vonapanitase in patients undergoing creation of an arteriovenous fistula, or AVF, support that a one-time, local application of vonapanitase during AVF surgical placement reduces AVF failure, thereby improving patient outcomes and reducing the burden on patients and the healthcare system. We are not aware of any approved preventative treatments to reduce the failure rate of AVFs. We enrolled the first patient in the first of two Phase 3 trials, named PATENCY-1, for vonapanitase in radiocephalic AVFs, our initial indication, in the third quarter of 2014, completed patient enrollment in October 2015 and expect to release top-line data in December 2016. We enrolled the first patient in our second Phase 3 trial, named PATENCY-2, in August 2015 and expect to complete enrollment in the first quarter of 2017.

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

On October 1, 2014, the Board of Directors and on October 3, 2014, the stockholders approved a 1-for-15.87 reverse stock split of our Common Stock and a proportional adjustment to the existing conversion ratios for each series of preferred stock. The effective date of the reverse stock split was October 6, 2014. All share, share equivalent and per share amounts have been adjusted to reflect the reverse stock split. The ratios by which shares of preferred stock were convertible into shares of Common Stock have been adjusted to reflect the effects of the reverse stock split.

As of December 31, 2015, we had received an aggregate of $174.4 million in net proceeds comprised of $94.0 million from the issuance of private equity securities, $7.7 million from the issuance of convertible notes, $10.0 million from business development activities, $0.2 million from government grants and $62.5 million from our IPO.

We have never been profitable and have incurred net losses in each year since inception. As of December 31, 2015, we had an accumulated deficit of $131.3 million and our net loss for the year ended December 31, 2015 was $21.4 million. We expect to incur significant expenses and increasing operating losses for the foreseeable future. We expect our research and development expenses to increase as we continue the clinical trials of, and seek regulatory approval for, vonapanitase. If we obtain regulatory approval for vonapanitase, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. Furthermore, we expect that our general and administrative costs will increase as we grow and operate as a public company. As a result, we will need to generate significant revenue if we are to achieve profitability, and we may never be able to do so.

We believe that our cash and cash equivalents and available-for-sale investments at December 31, 2015 will be sufficient to fund our operating expenses and capital expenditure requirements into the fourth quarter of 2017, thus allowing us to obtain results from our first Phase 3 clinical trial of vonapanitase in radiocephalic AVFs, to enroll patients in our second Phase 3 trial of vonapanitase in radiocephalic AVFs and to fund our chemistry, manufacturing and controls, or CMC, activities.

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

Financial Overview

Revenue

To date, our revenue has been derived from revenue related to the expiration of any rights and obligations under the 2009 agreement with a major pharmaceutical entity and from government grants. In the third quarter of 2014 we recognized $2.9 million of revenue related to the expiration in August 2014 of any rights and obligations related to the 2009 agreement.

Research and Development Expenses

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

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

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

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

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

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

- we commenced our first Phase 3 clinical trial of vonapanitase for patients undergoing creation of a radiocephalic AVF in the third quarter of 2014, completed patient enrollment in October 2015 and expect to release top-line data in December 2016. We enrolled the first patient in our second Phase 3 trial in August 2015 and expect to complete enrollment in the first quarter of 2017. If the results from the first Phase 3 trial are sufficiently compelling, we intend to meet with the FDA to discuss the possibility of submitting a BLA, supported by the single Phase 3 trial and may decide to submit a BLA to the FDA prior to completing the second Phase 3 trial;

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

- we may, based on additional data including the data from our Phase 3 clinical trials and if sufficient funds become available, study the effects of vonapanitase versus placebo on brachiocephalic AVFs and in patients undergoing placement of an arteriovenous graft, or AVG; and

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

General and Administrative Expenses

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

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

Investment Income

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

Interest Expense

Interest expense consists of interest incurred on debt instruments, amortized deferred financing costs and amortized debt discount. The debt discount primarily consists of the fair value of the bifurcated features embedded in the convertible notes issued in September 2013 and converted in May 2014.

Other (Expense) Income, Net

Other (expense) income, net consists of the gain realized by the sale of fixed assets, changes in the fair value of the derivative liability associated with the convertible notes, changes in the fair value of the investors' rights and obligations issued in connection with the Series D redeemable convertible preferred stock, non-cash gains and losses from currency exchange rate fluctuations on transactions or balances denominated in a foreign currency and realized and unrealized gains and losses on the forward foreign currency contracts we entered into in the second quarter of 2015 to purchase Swiss Francs to reduce our foreign currency exposure through 2016. This foreign currency exposure is the result of a contract with the manufacturer of our active pharmaceutical ingredient ("API") which requires us to make payments in Swiss Francs. The derivative liability associated with the convertible notes was extinguished upon the conversion of the notes into Series D redeemable convertible preferred stock in May 2014. The Series D investors' rights and obligations were either exercised or extinguished upon the completion of our IPO in October 2014.

Accretion of Preferred Stock

Subsequent to the May 2014 Series D redeemable convertible preferred stock financing, our shares of preferred stock were redeemable beginning in 2019 at their original issuance price plus any declared or accrued but unpaid dividends upon written election of the preferred stockholders in accordance with the terms of our certificate of incorporation. Accretion of preferred stock reflects the accretion of issuance costs and cumulative dividends on our preferred stock based on their respective redemption values. On October 27, 2014, we closed our IPO and all shares of preferred stock were converted into 8,651,805 shares of our Common Stock. No accretion of preferred stock has been recorded after this date as no shares of preferred stock were outstanding after such date.

Critical Accounting Policies and Significant Judgments and Estimates

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

While our significant accounting policies are described in more detail in the notes to our consolidated financial statements and related notes appearing elsewhere in this Annual Report, we believe the following accounting policies to be most critical to the judgments and estimates used in the preparation of our financial statements.

Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed for us and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our consolidated financial statements based on facts and circumstances known to us at that time. We routinely confirm the accuracy of our estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include fees paid to CROs in connection with clinical trials and vendors related to manufacturing, development and distribution of clinical supplies.

We base our expenses related to clinical trials on our estimates of the services received and efforts expended pursuant to contracts with multiple CROs that conduct and manage clinical trials on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the clinical expense (prepaid expense). Payments under some of these contracts depend on factors such as the successful enrollment of subjects and the completion of clinical trial milestones. In accruing service fees, we estimate the time period over which services will be performed, enrollment of subjects, number of sites activated and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, if our estimates of the status and timing of services performed differs from the actual status and timing of services performed we may report amounts that are too high or too low in any particular period. To date, there have been no material differences from our estimates to the amount actually incurred.

Derivative Financial Instruments

We enter into forward foreign currency contracts to reduce our foreign currency exposure. We record these derivative financial instruments on the consolidated balance sheet at fair value. Although these derivative contracts are intended to economically hedge foreign exchange risk, we have not elected to apply hedge accounting. As such, changes in the fair value of these instruments are recorded directly in earnings as a component of other income (expense) as they occur. We execute derivative instruments with financial institutions that we judge to be credit-worthy, defined as institutions that hold an investment-grade credit rating.

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Stock-Based Compensation

We issue stock-based awards to employees and non-employees, generally in the form of stock options. We account for our stock-based awards in accordance with FASB ASC Topic 718, *Compensation—Stock Compensation*, ("ASC 718"). ASC 718 requires all stock-based payments to employees, including grants of employee stock options and modifications to existing stock options, to be recognized in the consolidated statements of operations and comprehensive loss based on their fair values. We account for stock-based awards to non-employees in accordance with FASB ASC Topic 505-50, *Equity-Based Payments to Non-Employees*, which requires the fair value of the award to be remeasured at fair value as the award vests.

Our stock-based awards are subject to either service or performance-based vesting conditions. Compensation expense related to awards to employees and directors with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards to non-employees with service-based vesting conditions is recognized on the then-current fair value at each financial reporting date prior to the measurement date over the associated service period of the award, which is generally the vesting term, using the accelerated attribution method. Compensation expense related to awards to employees with performance-based vesting conditions is recognized based on the grant date fair value over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable. Compensation expense related to awards to non-employees with performance-based vesting conditions is recognized based on the then-current fair value at each financial reporting date prior to the measurement date over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable.

Described below is the methodology we have utilized in measuring stock-based compensation expense. Following the consummation of our IPO, stock option values have been determined based on the quoted market price of our common stock.

We estimate the fair value of our stock-based awards to employees and non-employees using the Black-Scholes option pricing model, which requires the input of highly subjective assumptions, including (i) the expected volatility of our stock, (ii) the expected term of the award, (iii) the risk-free interest rate and (iv) expected dividends. Due to the lack of a public market for the trading of our common stock and a lack of company specific historical and implied volatility data, we based our estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. For these analyses, we select companies with comparable characteristics to ours including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected life of the stock-based awards. We compute the historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of our stock-based awards. We will continue to apply this process until a sufficient amount of historical information regarding the volatility of our own stock price becomes available. We estimate the expected life of our employee stock options using the "simplified" method, whereby, the expected life equals the average of the vesting term and the original contractual term of the option. The risk-free interest rates for periods within the expected life of the option were based on the U.S. Treasury yield curve in effect during the period the options were granted.

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We are also required to estimate forfeitures at the time of grant, and revise those estimates in subsequent periods if actual forfeitures differ from its estimates. We use historical data to estimate pre-vesting option forfeitures and record stock-based compensation expense only for those awards that are expected to vest. To the extent that actual forfeitures differ from our estimates, the difference is recorded as a cumulative adjustment in the period the estimates were revised. Stock-based compensation expense recognized in the financial statements is based on awards that are ultimately expected to vest.

We have computed the fair value of employee and director stock options at date of grant using the following weighted-average assumptions:

	Year Ended December 31,	
	2015	2014
Weighted average expected volatility	79.80%	79.50%
Expected term (in years)	6.11	6.00
Risk free interest rate	1.76 %	1.88 %
Expected dividend yield	0.00 %	0.00 %

Prior to our IPO, the estimated fair value of our common stock was determined contemporaneously by our Board of Directors based on valuation estimates provided by management and prepared in accordance with the framework of the American Institute of Certified Public Accountants' Technical Practice Aid, Valuation of Privately-Held-Company Equity Securities Issued as Compensation, or AICPA Practice Aid, as well as independent third-party valuations. Our contemporaneous valuations of our common stock were based on a number of objective and subjective factors, including external market conditions affecting the biotechnology industry sector and the prices at which we sold shares of preferred stock, the superior rights and preferences of securities senior to our common stock at the time of each grant and the likelihood of achieving a liquidity event such as an IPO. Consequently, after the IPO the fair value of the shares of common stock underlying the stock options is the closing price on the option grant date.

Results of Operations

Comparison of the Years Ended December 31, 2015 and 2014

The following table summarizes our results of operations for the years ended December 31, 2015 and 2014 (in thousands):

	Years Ended December 31,		Period-to-Period
	2015	2014	Change
Revenue	$-	$2,948	$ (2,948)
Operating expenses:			
Research and development	12,381	6,432	5,949
General and administrative	8,489	4,096	4,393
Total operating expenses	20,870	10,528	10,342
Loss from operations	(20,870)	(7,580)	(13,290)
Other income (expense):			
Investment income	144	24	120
Interest expense	-	(857)	857
Other (expense) income, net	(651)	5,071	(5,722)
Total other (expense) income	(507)	4,238	(4,745)
Net Loss	$(21,377)	$(3,342)	$ (18,035)

Revenue. During the years ended December 31, 2015, our revenue was $2.9 million lower as compared to the year ended December 31, 2014 due to the recognition of $2.9 million of deferred revenue related to the expiration in August 2014 of any rights and obligations under the aforementioned 2009 agreement.

Research and Development Expenses. The following table identifies research and development expenses on both an external and internal basis for the years ended December 31, 2015 and 2014 (in thousands):

	Year Ended December 31,		Period-to-Period
	2015	2014	Change
External PRT-201 research and development expenses	$8,580	$4,096	$ 4,484
Internal research and development expenses	3,801	2,336	1,465
Total research and development expenses	$12,381	$6,432	$ 5,949

During the year ended December 31, 2015, our total research and development expenses increased by $5.9 million compared to the year ended December 31, 2014 primarily due to $4.5 million in increased external expenses. The increase of $4.5 million in external expenses was primarily driven by $3.4 million in increased expenses for our ongoing radiocephalic AVF Phase 3 clinical trials and $1.0 million in increased expenses for our manufacturing pre-validation and other efforts. Our internal research and development expenses increased by $1.4 million in the year ended December 31, 2015 as compared to the year ended December 31, 2014 due primarily to increased personnel costs.

General and Administrative Expenses. During the year ended December 31, 2015, our total general and administrative expenses were $4.4 million higher as compared to the year ended December 31, 2014 primarily due to $2.6 million of additional overhead and personnel costs to support our ongoing corporate activities and $1.8 million in increased expenses associated with being a public company.

Investment Income. During the year ended December 31, 2015, investment income increased by $0.1 million due to the increase in interest income earned on our higher cash, cash equivalents and marketable securities balances during the year ended December 31, 2015 as compared to the year ended December 31, 2014.

Interest Expense. During the year ended December 31, 2015, interest expense was $0.9 million lower as compared to the year ended December 31, 2014 due to the decrease of $0.9 million in interest expense related to our convertible notes which were extinguished in May 2014.

Other (Expense) Income, Net. During the year ended December 31, 2015, other (expense) income, net changed by $5.7 million as compared to the year ended December 31, 2014 primarily due to a decrease of $5.0 million in income related to the change in fair market value of the Series D preferred stock investor rights obligation in 2014 and an increase of $0.7 million expense related to the change in the fair value associated with the forward foreign currency contracts we entered into in second quarter of 2015 and the Swiss Francs denominated currency we held as of the

period end.

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Comparison of the Years Ended December 31, 2014 and 2013

	Years Ended December 31,		Period-to-Period
	2014	2013	Change
Revenue	$2,948	$-	$ 2,948
Operating expenses:			
Research and development	6,432	3,994	2,438
General and administrative	4,096	3,128	968
Total operating expenses	10,528	7,122	3,406
Loss from operations	(7,580)	(7,122)	(458)
Other income (expense):			
Investment income	24	4	20
Interest expense	(857)	(861)	4
Other income, net	5,071	67	5,004
Total other income (expense)	4,238	(790)	5,028
Net Loss	$(3,342)	$(7,912)	$ 4,570

Revenue. Revenue increased by $2.9 million for the year ended December 31, 2014 from the year ended December 31, 2013. This increase was due to the recognition of $2.9 million of deferred revenue related to the expiration in August 2014 of any rights and obligations under the aforementioned 2009 agreement with a major pharmaceutical entity.

Research and Development Expenses. The following table identifies research and development expenses on both an external and internal basis for the years ended December 31, 2014 and 2013:

	Year Ended December 31,		Period-to-Period
	2014	2013	Change
External PRT-201 research and development expenses	$4,096	$1,962	$ 2,134
Internal research and development expenses	2,336	2,032	304
Total research and development expenses	$6,432	$3,994	$ 2,438

During the year ended December 31, 2014, our total research and development expenses increased by $2.4 million compared to the year ended December 31, 2013 primarily due to $2.1 million in increased external expenses. The increase of $2.1 million in external expenses was driven by $2.2 million in increased expenses for our ongoing

radiocephalic AVF Phase 3 clinical trial, $0.1 million in increased external clinical expenses related to preparation for our second radiocephalic AVF Phase 3 clinical trial and $0.2 million in increased expenses for our manufacturing support of the radiocephalic AVF Phase 3 clinical trials offset by $0.4 million in lower external clinical expenses related to our AVF Phase 2 and AVG clinical trials which were completed in 2013. Our internal research and development expenses increased by $0.3 million in the year ended December 31, 2014 as compared to the year ended December 31, 2013 due primarily to personnel costs.

General and Administrative Expenses. During the year ended December 31, 2014, our total general and administrative expenses were $1.0 million higher as compared to the year ended December 31, 2013 primarily due to additional overhead and personnel costs in the year ended December 31, 2014 of $0.7 million to support our on-going corporate activities and $0.3 million in expenses associated with being a public company.

Investment Income. During the year ended December 31, 2014, investment income increased by an immaterial amount.

Interest Expense. During the year ended December 31, 2014, interest expense decreased by an immaterial amount.

Other Income, Net. During the year ended December 31, 2014, other income, net increased by $5.0 million as compared to the year ended December 31, 2013 primarily due to the change in fair value of the investor rights and obligations issued in connection with the Series D preferred stock. The Series D Preferred Stock investor rights were either exercised or extinguished upon the closing of our IPO.

Liquidity and Capital Resources

Overview

Since our inception and through the year ended December 31, 2015, we had received $174.4 million in net proceeds comprised of $94.0 million from the issuance of private equity securities, $7.7 million from the issuance of convertible notes, $10.0 million from business development activities, $0.2 million from government grants and $62.5 million from our IPO. At December 31, 2015, our cash and cash equivalents and available-for-sale investments totaled $65.3 million.

Initial Public Offering

On October 27, 2014, we completed our IPO whereby we sold 7,026,500 shares of Common Stock (including 916,500 shares of Common Stock sold by us pursuant to the full exercise of an overallotment option granted to our underwriters in connection with the IPO) at a price of $10.00 per share. The shares began trading on the NASDAQ Global Market on October 22, 2014. The aggregate net proceeds resulting from the IPO were $62.5 million after

deducting underwriting discounts and commissions and offering-related expenses paid by us.

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Warrants Exercises

Prior to the closing of our IPO, 498,889 shares of our Common Stock were issued upon the exercise of warrants with a weighted-average exercise price of $4.60 per share.

Series D Financing

On May 13, 2014, we received net proceeds of approximately $24.5 million from the issuance of Series D redeemable convertible preferred stock to new and existing investors at a price per share of $0.588656. In aggregate, we issued 52,813,827 shares of Series D redeemable convertible preferred stock including 10,344,201 shares for the conversion of $4.6 million of convertible notes and accrued interest at a conversion price of $0.4414 per share. As provided by the Series D stock purchase agreement, the investors in the Series D redeemable convertible preferred stock had the potential opportunity to invest an additional $20.0 million in Series D redeemable convertible preferred stock at $0.588656 per share. Upon the closing of our IPO, all shares of preferred stock were converted into 8,651,805 shares of our Common Stock and the Series D investors' rights to purchase additional shares of Series D redeemable convertible preferred stock were terminated.

Operating Capital Requirements

We expect to incur increasing operating losses for at least the next several years as we (i) conduct our Phase 3 clinical trials for vonapanitase in radiocephalic AVFs, thereafter seeking marketing approval for vonapanitase in radiocephalic AVFs assuming successful trial outcomes, and (ii) pursue development of vonapanitase for additional indications, including brachiocephalic AVFs and AVGs. We may not be able to complete the development and initiate commercialization of vonapanitase if, among other things, our clinical trials are not successful, and the FDA does not approve vonapanitase or does not approve vonapanitase when we expect.

We believe that our cash and cash equivalents and available-for-sale investments as of December 31, 2015 will be sufficient to fund our operations into the fourth quarter of 2017. We believe that these funds will be sufficient to enable us to obtain results from our first Phase 3 clinical trial of vonapanitase in radiocephalic AVFs, to enroll patients in our second Phase 3 trial of vonapanitase in radiocephalic AVFs, and to fund our CMC activities.

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

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

Cash Flows

The following table summarizes our sources and uses of cash for the years ended December 31, 2015 and 2014 (in thousands):

	Years Ended December 31,	
	2015	2014
Net cash used in operating activities	$(17,566)	$(9,990)
Net cash used in investing activities	(11,331)	(12,483)
Net cash provided by financing activities	163	88,520

Effect of exchange rate changes on cash	(75)	-
Net (decrease) increase in cash and cash equivalents	$(28,809)	$66,047

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Comparison of the Years Ended December 31, 2015 and 2014

Net cash used in operating activities was $17.6 million for the year ended December 31, 2015 compared to $10.0 million for the year ended December 31, 2014. The increase of $7.6 million in cash used in operating activities was driven by an increase in our net loss of $18.0 million and offset by an increase of $10.4 million in non-cash operating expenses as compared to the year ended December 31, 2014.

Net cash used in investing activities was $11.3 million for the year ended December 31, 2015 compared to $12.5 million for the year ended December 31, 2014. The decrease of $1.2 million in cash used by investing activities was primarily driven by an increase in maturities and sale of investments of $55.0 million offset by an increase in the purchases of available-for-sale investments of $53.7 million and an increase in capital equipment purchases of $0.1 million as compared to the year ended December 31, 2015.

Net cash provided by financing activities was $0.2 million during the year ended December 31, 2015 compared to $88.5 million for the year ended December 31, 2014. The decrease in cash provided by financing activities of $88.3 million was primarily driven by the proceeds of our Series D Preferred Stock issuance and our IPO during the year ended December 31, 2014.

The following table summarizes our sources and uses of cash for the years ended December 31, 2014 and 2013:

	Years Ended December 31,	
	2014	2013
Net cash used in operating activities	$(9,990)	$(6,657)
Net cash used in investing activities	(12,483)	2,727
Net cash provided by financing activities	88,520	4,314
Net (decrease) increase in cash and cash equivalents	$66,047	$384

Comparison of the Years Ended December 31, 2014 and 2013

Net cash used in operating activities was $10.0 million for the year ended December 31, 2014 compared to $6.7 million for the year ended December 31, 2013. The increase of $3.3 million in cash used in operating activities was primarily driven by an increase in our operating expenses of $3.4 million and offset by a decrease in working capital balances and a decrease in non-cash operating expenses of $0.1 million as compared to the year ended December 31, 2013.

Net cash used in investing activities was $12.5 million for the year ended December 31, 2014 compared to net cash provided by investing activities of $2.7 million for the year ended December 31, 2013. The increase of $15.2 million in cash used by investing activities was primarily driven by an increase in the purchases of available-for-sale investments of $31.1 million offset by an increase in maturities of investments of $16.0 million as compared to the year ended December 31, 2013.

Net cash provided by financing activities during the year ended December 31, 2014 was $88.5 million and resulted primarily from the proceeds from our Series D Preferred Stock issuance and our IPO. Net cash provided by financing activities during the year ended December 31, 2013 of approximately $4.3 million was attributable to our September 2013 convertible promissory note financing.

Off-Balance Sheet Arrangements

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

Contractual Obligations

The following table summarizes our outstanding contractual obligations as of payment due date by period at December 31, 2015:

	Total	Less than 1 Year	1 to 3 Years	3 to 5 Years	More than 5 Years
Operating leases (1)	$420	$168	$252	-	-

Purchase obligations (2)	1,917	1,917	-	-	-

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

(2) In July 2015, we entered into a manufacturing services agreement with Lonza Ltd ("Lonza") for the processing, development and manufacture of the API in its lead product candidate, vonapanitase. Purchase obligations include a contractual arrangement in the form of purchase orders with Lonza, where there is a fixed non-cancelable payment schedule.

In addition, as of December 31, 2015, we had the following outstanding forward foreign currency contracts that were not designated for hedge accounting and that were used to reduce the exposure to fluctuations in the U.S dollar value of forecasted transactions denominated in Swiss Franc (dollars in thousands):

	Notional Amount	Effective Date	Maturity Date	Number of Instruments
Foreign currency contracts	$ 5,713	June 12, 2015	Various dates through December 15, 2016	4

The contractual obligations tables do not include any potential future royalty payments we may be required to make under our license assignment with Johns Hopkins University, due to the uncertainty of the occurrence of the events requiring payment under that agreement.

JOBS Act

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

Item 7A. Qualitative and Quantitative Disclosures about Market Risk

The market risk inherent in our financial instruments and in our financial position represents the potential loss arising from adverse changes in interest rates. As of December 31, 2015, we had cash equivalents and available-for-sale investments of $65.3 million consisting primarily of investments in U.S. Treasuries and certificates of deposit. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in short-term marketable securities. Our marketable securities are subject to interest rate risk and could fall in value if market interest rates increase. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, an immediate 10% change in interest rates would not have a material effect on the fair market value of our investment portfolio. We have the ability to hold our marketable securities until maturity, and therefore, we would not expect our operating results or cash flows to be

affected to any significant degree by the effect of a change in market interest rates on our investments.

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

Item 8. Financial Statements and Supplementary Data

The consolidated financial statements together with the report of our independent registered public company accounting firm, required to be filed pursuant to this Item 8 are appended to this Annual Report. An index of those consolidated financial statements is found in Item 15.

Item 9. Changes in and Disagreements with Accountants and Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Management's Evaluation of our Disclosure Controls and Procedures

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

As of December 31, 2015, our management, with the participation of our principal executive officer and principal financial officer, evaluated the effectiveness of our disclosure controls and procedures as of the end of the period covered by this Annual Report on Form 10-K. 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 December 31, 2015, our disclosure controls and procedures were effective at the reasonable assurance level.

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

Management's Annual Report on Internal Controls Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over our financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act as the process designed by, or under the supervision of, our Chief Executive Officer, and effected by our Board of Directors, management and other personnel, to provide reasonable assurance regarding the reliability of our financial reporting and the preparation of our financial statements for external purposes in accordance with generally accepted accounting principles, and includes those policies and procedures that:

(1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of assets;

(2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures are being made only in accordance with the authorizations of management and directors; and

(3) provide reasonable assurance regarding the prevention or timely detection of unauthorized acquisition, use or disposition of assets that could have a material effect on our financial statements.

Under the supervision and with the participation of our management, including our Chief Executive Officer, we conducted an evaluation of the effectiveness of our internal control over financial reporting based on the framework provided in *Internal Control—Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission, or COSO. Based on this evaluation, our management concluded that our internal control over financial reporting was effective as of December 31, 2015.

Changes in Internal Control Over Financial Reporting.

During the year ended December 31, 2015, there have been no changes in our internal control over financial reporting, as such term is defined in Rules 13a-15 (f) and 15(d)-15(f) promulgated under the Exchange Act, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this Item is set forth in our Proxy Statement for the 2016 Annual Meeting of Stockholders to be filed with the SEC within 120 days of December 31, 2015, and is incorporated into this Annual Report on Form 10-K by reference.

Item 11. Executive and Director Compensation

The information required by this Item is set forth in our Proxy Statement for the 2016 Annual Meeting of Stockholders to be filed with the SEC within 120 days of December 31, 2015, and is incorporated into this Annual Report on Form 10-K by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters Securities Authorized for Issuance Under Equity Compensation Plans

See “Securities Authorized for Issuance Under Equity Compensation Plans” in Item 5 of this Annual Report on Form 10-K.

The other information required by this Item is set forth in our Proxy Statement for the 2016 Annual Meeting of Stockholders to be filed with the SEC within 120 days of December 31, 2015, and is incorporated into this Annual Report on Form 10-K by reference.

Item 13. Certain Relationships and Related Party Transactions and Director Independence

The information required by this Item is set forth in our Proxy Statement for the 2016 Annual Meeting of Stockholders to be filed with the SEC within 120 days of December 31, 2015, and is incorporated into this Annual Report on Form 10-K by reference.

Item 14. Principal Accounting Fees and Services

The information required by this Item is set forth in our Proxy Statement for the 2016 Annual Meeting of Stockholders to be filed with the SEC within 120 days of December 31, 2015, and is incorporated into this Annual Report on Form 10-K by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a)(1) Financial Statements

The financial statements listed below are filed as part of this Annual Report on Form 10-K.

Report of Independent Registered Public Accounting Firm

Consolidated Balance Sheets at December 31, 2015 and 2014

Consolidated Statements of Operations and Comprehensive Loss for the years ended December 31, 2015, 2014 and 2013

Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit) for the years ended December 31, 2015, 2014 and 2013

Consolidated Statements of Cash Flows for the years ended December 31, 2015, 2014 and 2013

Notes to Consolidated Financial Statements

(a)(2) Financial Statement Schedules

All financial schedules have been omitted because the required information is either presented in the Consolidated Financial Statements or the Notes thereto or is not applicable or required.

(a)(3) Exhibits

The exhibits required by Item 601 of Regulation S-K and Item 15(b) of this Annual Report on Form 10-K are listed in the Exhibit Index immediately preceding the exhibits and are incorporated herein.

(b) Exhibits

The exhibits required by Item 601 of Regulation S-K and Item 15(b) of this Annual Report on Form 10-K are listed in the Exhibit Index immediately preceding the exhibits and are incorporated herein.

Proteon Therapeutics, Inc.

Index to Consolidated Financial Statements	Pages

Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders Proteon Therapeutics, Inc.

We have audited the accompanying consolidated balance sheets of Proteon Therapeutics, Inc. (the Company) as of December 31, 2015 and 2014, and the related consolidated statements of operations and comprehensive loss, redeemable convertible preferred stock and stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 2015. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company's internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Proteon Therapeutics, Inc. at December 31, 2015 and 2014, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2015, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

Boston, Massachusetts

March 14, 2016

Proteon Therapeutics, Inc.

Consolidated Balance Sheets

(in thousands, except share and per share data)

	December 31, 2015	December 31, 2014
Assets		
Current assets:		
Cash and cash equivalents	$40,031	$68,840
Available-for-sale investments	25,232	14,755
Prepaid expenses and other current assets	1,345	1,006
Total current assets	66,608	84,601
Property and equipment, net	224	83
Other non-current assets	706	114
Total assets	$67,538	$84,798
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$1,020	$917
Accrued expenses	2,576	1,421
Other current liabilities	537	-
Total current liabilities	4,133	2,338
Total liabilities	4,133	2,338
Commitments and contingencies (Note 7)	-	-
Stockholders' equity:		
Preferred stock, $0.001 par value per share; 10,000,000 shares authorized, no shares issued and outstanding at December 31, 2015 and 2014	-	-
Common stock, $0.001 par value, 100,000,000 shares authorized at December 31, 2015 and 2014; 16,501,500 and 16,448,455 shares issued and outstanding at December 31, 2015 and 2014, respectively	16	16
Additional paid-in capital	194,651	192,324
Accumulated deficit	(131,251)	(109,874)
Accumulated other comprehensive loss	(11)	(6)
Total stockholders' equity	63,405	82,460
Total liabilities and stockholders' equity	$67,538	$84,798

See accompanying notes to these consolidated financial statements.

Proteon Therapeutics, Inc.

Consolidated Statements of Operations and Comprehensive Loss

(in thousands, except share and per share data)

	Year Ended December 31,		
	2015	2014	2013
Revenue	$-	$2,948	$-
Operating expenses:			
Research and development	12,381	6,432	3,994
General and administrative	8,489	4,096	3,128
Total operating expenses	20,870	10,528	7,122
Loss from operations	(20,870)	(7,580)	(7,122)
Other income (expense):			
Investment income	144	24	4
Interest expense	-	(857)	(861)
Other (expense) income, net	(651)	5,071	67
Total other (expense) income	(507)	4,238	(790)
Net loss	$(21,377)	$(3,342)	$(7,912)
Unrealized loss on available-for-sale investments	(5)	(6)	(1)
Comprehensive loss	$(21,382)	$(3,348)	$(7,913)
Reconciliation of net loss to net loss attributable to common stockholders:			
Net loss	$(21,377)	$(3,342)	$(7,912)
Accretion of redeemable convertible preferred stock to redemption value	-	(6,353)	(6,119)
Net loss attributable to common stockholders	$(21,377)	$(9,695)	$(14,031)
Net loss per share attributable to common stockholders - basic and diluted	$(1.30)	$(3.16)	$(59.66)
Weighted-average common shares outstanding used in net loss per share attributable to common stockholders - basic and diluted	16,464,123	3,064,507	235,184
Supplemental disclosure of stock-based compensation expens**e and loss from currency forward contracts:**			
Included in operating expenses, above, are the following amounts for non-cash stock based compensation expense:			
Research and development	$650	$114	$106
General and administrative	1,514	345	49
Total	$2,164	$459	$155
Included in other expense, above, are the following amounts from forward foreign currency contracts:			
Realized losses from forward foreign currency contracts	$(52)	$-	$-
Unrealized losses from forward foreign currency contracts	(537)	-	-
Total	$(589)	$-	$-

See accompanying notes to these consolidated financial statements.

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Proteon Therapeutics, Inc.

Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)

(in thousands, except share and per share data)

	Series A Redeemable Convertible Preferred Stock		Series A-1 Redeemable Convertible Preferred Stock		Series B Redeemable Convertible Preferred Stock		Series C Redeemable Convertible Preferred Stock		Series Conve Stock
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares
Balance at December 31, 2012	22,638,465	$32,633	10,909,091	$16,526	20,754,461	$24,926	13,202,932	$16,201	-
Accretion of Series A, A-1, B and C redeemable convertible preferred stock to redemption value	-	1,597	-	848	-	2,475	-	1,199	-
Exercise of common stock options	-	-	-	-	-	-	-	-	-
Stock-based compensation expense	-	-	-	-	-	-	-	-	-
Unrealized gain (loss) on short term investments	-	-	-	-	-	-	-	-	-
Net loss	-	-	-	-	-	-	-	-	-
Balance at December 31, 2013	22,638,465	$34,230	10,909,091	$17,374	20,754,461	$27,401	13,202,932	$17,400	-
Issuance of Series D redeemable convertible preferred	-	-	-	-	-	-	-	-	52,81

stock net of $6,639 discount associated with investors rights and obligations and issuance costs of $452									
Accretion of Series A, A-1, B, C and D redeemable convertible preferred stock to redemption value	-	1,304	-	691	-	1,832	-	948	-
Exercise of common stock options	-	-	-	-	-	-	-	-	-
Stock-based compensation expense	-	-	-	-	-	-	-	-	-
Unrealized gain (loss) on short term investments	-	-	-	-	-	-	-	-	-
Exercise of warrants	-	-	-	-	-	-	-	-	-
Conversion of redeemable convertible preferred stock into common stock	(22,638,465)	(35,534)	(10,909,091)	(18,065)	(20,754,461)	(29,233)	(13,202,932)	(18,348)	(52,8
Exercise of investors rights and obligations	-	-	-	-	-	-	-	-	-
Issuance of Common Stock from Initial Public Offering, net of underwriters discounts and issuance costs	-	-	-	-	-	-	-	-	-
Net loss	-	-	-	-	-	-	-	-	-
	-	$-	-	$-	-	$-	-	$-	-

Balance at December 31, 2014									
Exercise of common stock options	-	-	-	-	-	-	-	-	-
Issuance of common stock upon ESPP purchase	-	-	-	-	-	-	-	-	-
Stock-based compensation expense	-	-	-	-	-	-	-	-	-
Unrealized gain on short term investments	-	-	-	-	-	-	-	-	-
Net loss	-	-	-	-	-	-	-	-	-
Balance at December 31, 2015	-	$-	-	$-	-	$-	-	$-	-

See accompanying notes to these consolidated financial statements.

Proteon Therapeutics, Inc.

Condensed Consolidated Statements of Cash Flows

(in thousands)

	Year Ended December 31,		
	2015	2014	2013
Operating activities			
Net loss	$(21,377)	$(3,342)	$(7,912)
Reconciliation of net loss to net cash used in operating activities:			
Depreciation	57	30	27
Amortization of premium/discount on available-for-sale securities	651	30	30
Gain on sale of fixed assets	-	-	(65)
Accretion of discount and debt issuance cost of convertible notes payable	-	742	749
Unrealized loss on forward foreign currency contracts included in net income	537	-	-
Foreign currency remeasurement loss	75	-	-
Stock-based compensation	2,164	459	155
Change in fair value of investor rights/obligation	-	(5,151)	-
Change in fair value of derivative liability	-	81	(2)
Changes in:			
Prepaid expenses and other assets	(899)	(961)	72
Interest receivable	(32)	-	-
Accounts payable and accrued expenses	1,258	955	177
Accrued interest payable	-	115	112
Deferred revenue from sale of acquisition option to acquire company	-	(2,948)	-
Net cash used in operating activities	(17,566)	(9,990)	(6,657)
Investing activities			
Purchases of available-for-sale investments	(88,644)	(34,950)	(3,878)
Proceeds from maturities of available-for-sale investments	75,505	22,518	6,550
Proceeds from sale of available-for-sale investments	2,006	-	-
Purchase of property and equipment	(198)	(51)	(10)
Sale of property and equipment	-	-	65
Net cash (used in) provided by investing activities	(11,331)	(12,483)	2,727
Financing activities			
Proceeds from issuance of Series D preferred stock	-	25,000	-
Issuance costs for preferred stock	-	(452)	-
Proceeds from issuance of common stock under ESPP	75	-	-
Net proceeds from IPO	-	62,485	-
Proceeds from issuance of convertible notes payable	-	-	4,339
Payments for debt issuance costs	-	-	(46)
Exercise of stock options	88	59	21
Exercise of warrants	-	1,428	-
Net cash provided by financing activities	163	88,520	4,314
Effect of exchange rate changes on cash	(75)	-	-
(Decrease) increase in cash and cash equivalents	(28,809)	66,047	384
Cash and cash equivalents, beginning of period	68,840	2,793	2,409

Cash and cash equivalents, end of period	$40,031	$68,840	$2,793
Supplemental disclosure of non-cash investing and financing activities			
Accretion of redeemable convertible preferred stock to redemption value	$-	$6,353	$6,119
Conversion of convertible notes, including accrued interest, into Series D Redeemable Convertible Preferred Stock	$-	$6,089	$-
Fair value of derivative embedded within convertible notes payable	$-	$-	$1,445
Conversion of redeemable convertible preferred stock into common stock	$-	$126,836	$-
Fair value of investors' rights/ obligations reclassified to equity upon IPO	$-	$1,408	$-

See accompanying notes to these consolidated financial statements.

Proteon Therapeutics, Inc.

Notes to Consolidated Financial Statements

(amounts in thousands, except share and per share data)

1. Organization and Operations

The Company

Proteon Therapeutics, Inc. (the "Company") is a late-stage biopharmaceutical company focused on the development of novel, first-in-class pharmaceuticals to address the medical needs of patients with kidney and vascular disease. The Company was formed in June 2001 and incorporated on March 24, 2006. During 2013, the Company formed a wholly-owned subsidiary, organized in the United Kingdom, Proteon Therapeutics Limited. As of December 31, 2015, there has been no activity in this subsidiary other than its formation. During 2014, the Company formed a wholly-owned Massachusetts Securities Corporation subsidiary as a holding company for its available-for-sale investments, Proteon Securities Corp. The Company completed its initial public offering of its common stock, $0.001 par value per share ("Common Stock") on October 27, 2014 (the "IPO"). Since inception, the Company has been primarily involved in research and development activities.

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

As of December 31, 2015, the Company had cash, cash equivalents and available-for-sale investments of $65.3 million. The Company believes that its existing cash, cash equivalents and available-for-sale investments will be sufficient to fund operations and capital expenditures into the fourth quarter of 2017. The Company had an accumulated deficit of $131.3 million as of December 31, 2015.

2. Summary of Significant Accounting Policies

Initial Public Offering

On October 27, 2014, the Company completed the IPO of its Common Stock, pursuant to a registration statement on Form S-1, as amended. An aggregate of 7,026,500 shares of Common Stock registered under the registration statement were sold at a price of $10.00 per share (including 916,500 shares of Common Stock sold by the Company pursuant to the full exercise of an overallotment option granted to the Company's underwriters in connection with the IPO). Net proceeds of the IPO were $62.5 million, after deducting underwriting discounts, commissions and offering-related expenses payable by the Company of approximately $7.8 million. In this transaction, all shares of the Company's redeemable convertible preferred stock (the "Preferred Stock") were automatically converted into an aggregate of 8,651,805 shares of its Common Stock and the Series D redeemable convertible preferred stock (the "Series D Preferred Stock") investors' rights and obligations were either exercised or extinguished.

At-The-Market Equity Offering Program

On November 12, 2015, the Company filed a shelf registration statement on Form S-3 (the "Registration Statement"), and entered into a Sales Agreement with Cowen and Company, LLC (the "Sales Agreement") to establish an at-the-market ("ATM") equity offering program pursuant to which they are able, with the Company's authorization, to offer and sell up to $40 million of the Company's Common Stock at prevailing market prices from time to time. As of December 31, 2015, the Company had not commenced sales under this program. The Registration Statement became effective on January 12, 2016.

Reverse Stock Split

On October 1, 2014, the Board of Directors, and on October 3, 2014, the stockholders, approved a 1-for-15.87 reverse stock split of the Company's Common Stock, resulting in a proportional adjustment to the existing conversion ratios for each series of Preferred Stock. The effective date of the reverse stock split was October 6, 2014. All share, share equivalent and per share amounts have been adjusted to reflect the reverse stock split. The ratios by which shares of Preferred Stock are convertible into shares of Common Stock were also adjusted to reflect the effects of the reverse stock split.

Basis of Presentation and Principles of Consolidation

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

Use of Estimates

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

The Company historically utilized significant estimates and assumptions in determining the fair value of its Common Stock. The Company utilized various valuation methodologies in accordance with the framework of the 2004 and 2013 American Institute of Certified Public Accountants Technical Practice Aids, *Valuation of Privately-Held Company Equity Securities Issued as Compensation*, to estimate the fair value of its Common Stock prior to its IPO. Each valuation methodology included estimates and assumptions that required the Company's judgment.

These estimates and assumptions included a number of objective and subjective factors, including external market conditions affecting the biotechnology industry sector, the prices at which the Company sold shares of Preferred Stock, the superior rights and preferences of securities senior to the Company's Common Stock at the time and the likelihood of achieving a liquidity event, such as an initial public offering or a sale of the Company. Significant changes to the key assumptions used in the valuations could have resulted in different fair values of Common Stock at each valuation date and materially affected the financial statements.

Segment Information

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company and the Company's chief operating decision maker view the Company's operations and manage its business in one operating segment, which is the business of developing and commercializing vonapanitase for the treatment of renal and vascular disease. Currently, the Company operates in only one geographic segment.

Fair Value of Financial Instruments

The Company’s financial instruments consist of cash and cash equivalents, available-for-sale investments, forward foreign currency contracts (see Note 6), accounts payable, accrued liabilities, convertible promissory notes (“Convertible Notes”) and features embedded in the Convertible Notes. The Company is required to disclose information on all assets and liabilities reported at fair value that enables an assessment of the inputs used in determining the reported fair values. FASB ASC Topic 820, *Fair Value Measurement and Disclosures*, established a hierarchy of inputs used in measuring fair value that maximizes the use of observable inputs and minimizes the use of unobservable inputs by requiring that the observable inputs be used when available. Observable inputs are inputs that market participants would use in pricing the financial instrument based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company’s assumptions about the inputs that market participants would use in pricing the financial instrument and are developed based on the best information available under the circumstances. The fair value hierarchy applies only to the valuation inputs used in determining the reported or disclosed fair value of the financial instruments and is not a measure of the investment credit quality. Fair value measurements are classified and disclosed in one of the following three categories:

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

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

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

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

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Financial instruments measured at fair value on a recurring basis include cash equivalents, short-term investments and forward foreign currency contracts (see Note 6). There have been no changes to the valuation methods utilized by the Company during the years ended December 31, 2015 and 2014. The Company evaluates transfers between levels at the end of each reporting period. There were no transfers of financial instruments between levels during the years ended December 31, 2015 and 2014.

Derivative Financial Instruments

The Company enters into forward foreign currency contracts to mitigate its exposure to fluctuations in the exchange rates between the Swiss Franc and the U.S. dollar (see Note 6). The Company records these derivative financial instruments on the consolidated balance sheets at fair value. Although these derivative contracts are intended to economically hedge foreign exchange risk, the Company has not elected to apply hedge accounting. As such, changes in the fair value of these instruments are recorded directly in earnings as a component of other income (expense), as they occur. The Company executes its derivative instruments with financial institutions that the Company judges to be credit-worthy, defined as institutions that hold an investment-grade credit rating.

Recent Accounting Pronouncements

In May 2014, the FASB issued ASU 2014-09, *"Revenue from Contracts with Customers"* ("ASU 2014-09"), a new standard on revenue recognition providing a single, comprehensive revenue recognition model for all contracts with customers. The new revenue standard is based on the principle that revenue should be recognized to depict the transfer of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. The new standard is effective beginning January 1, 2018, with no early adoption permitted. Earlier application is permitted only as of annual reporting periods beginning after December 15, 2016, including interim reporting periods within that reporting period. The amendments may be applied retrospectively to each prior period presented or retrospectively with the cumulative effect recognized as of the date of initial application. The Company is currently evaluating the impact of the new guidance on its condensed consolidated financial statements, if any.

In August 2014, the FASB issued ASU 2014-15, *"Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern"* ("ASU 2014-15"). ASU 2014-15 is authoritative guidance on determining when and how reporting entities must disclose going-concern uncertainties in their financial statements, including requiring management to perform interim and annual assessments of an entity's ability to continue as a going concern within one year of the date of issuance of the entity's financial statements and providing certain disclosures if there is substantial doubt about the entity's ability to continue as a going concern. This guidance will be effective for the Company's fiscal year 2016 and for interim periods beginning in the first quarter of fiscal 2017. The Company is still evaluating the impact of this guidance on its financial statement disclosures. The adoption of this accounting standard may affect the Company's financial statement disclosures in future periods.

In November 2015, the FASB issued ASU No. 2015-17, *Income Taxes (Topic 740): Balance Sheet Classification of Deferred Taxes* ("ASU 2015-17"), which simplifies the presentation of deferred income taxes. ASU 2015-17 requires that deferred tax assets and liabilities be classified as noncurrent in a classified statement of financial position. ASU 2015-17 is effective for financial statements issued for fiscal years beginning after December 15, 2016 (and interim periods within those fiscal years) with early adoption permitted. ASU 2015-17 may be either applied prospectively to all deferred tax assets and liabilities or retrospectively to all periods presented. The Company has elected to early adopt ASU 2015-17 prospectively in the fourth quarter of 2015. As a result, the Company has presented all deferred tax assets and liabilities as noncurrent on the consolidated balance sheet as of December 31, 2015, but have not reclassified current deferred tax assets and liabilities on the consolidated balance sheet as of December 31, 2014. There was no impact on the Company's results of operations as a result of the adoption of ASU 2015-17.

Cash and Cash Equivalents

The Company considers all highly liquid investments with maturities of 90 days or less from the purchase date to be cash equivalents. Cash and cash equivalents are held in depository and money market accounts and are reported at fair value.

Short-Term Investments

The Company classifies its investments as available-for-sale and records such assets at estimated fair value in the consolidated balance sheets, with unrealized gains and losses, if any, reported as a component of other comprehensive income (loss) within the consolidated statements of operations and comprehensive loss and as a separate component of stockholders' equity (deficit). The Company invests its excess cash balances primarily in government debt securities, money market funds and corporate bonds with strong credit ratings and maturities of less than one year. There have been no realized gains and losses for the years ended December 31, 2015, 2014 and 2013.

At each balance sheet date, the Company assesses available-for-sale securities in an unrealized loss position to determine whether the unrealized loss is other-than-temporary. The Company considers factors including: the significance of the decline in value compared to the cost basis, underlying factors contributing to a decline in the prices of securities in a single asset class, the length of time the market value of the security has been less than its cost basis, the security's relative performance versus its peers, sector or asset class, expected market volatility and the market and economy in general. When the Company determines that a decline in the fair value below its cost basis is other-than-temporary, the Company recognizes an impairment loss in the year in which the other-than-temporary decline occurred. There have been no other-than-temporary declines in value of short-term investments for the years ended December 31, 2015, 2014 and 2013, as it is more likely than not the Company will hold the securities until maturity or a recovery of the cost basis.

Concentrations of Credit Risk and Off-Balance Sheet Risk

Financial instruments that potentially subject the Company to concentrations of credit risk are primarily cash, cash equivalents and short-term investments. The Company's cash and cash equivalents are held in accounts with financial institutions that management believes are creditworthy. The Company's investment policy includes guidelines on the quality of the institutions and financial instruments and defines allowable investments that the Company believes minimizes the exposure to concentration of credit risk. These amounts at times may exceed federally insured limits. The Company has not experienced any credit losses in such accounts and does not believe it is exposed to any significant credit risk on these funds. The Company has no financial instruments with off-balance sheet risk of loss.

Deferred Financing Costs

At December 31, 2015, the Company had $0.1 million of deferred offering costs, which primarily consist of direct incremental legal and accounting fees related to the Registration Statement. These costs are recorded as a non-current asset.

Property and Equipment

Property and equipment is stated at cost, less accumulated depreciation. Maintenance and repairs that do not improve or extend the lives of the respective assets are expensed to operations as incurred. Upon disposal, the related cost and accumulated depreciation is removed from the accounts and any resulting gain or loss is included in the results of operations. Depreciation is recorded using the straight-line method over the estimated useful lives of the respective assets, which are as follows:

Asset	Estimated Useful Life
Computer equipment and software (in years)	3
Furniture, fixtures and other (in years)	5
Laboratory equipment (in years)	7

Revenue

In general, the Company recognizes revenue when all of the following criteria are met: persuasive evidence of arrangement exists; delivery has occurred or services have been rendered; the Company's price to the customer is fixed or determinable and collectability is reasonably assured. During 2014, the Company recognized $2.9 million of revenue related to the expiration of residual rights to license the Company’s technology.

Research and Development Costs

Research and development costs are charged to expense as incurred in performing research and development activities. The costs include employee compensation costs, facilities and overhead, clinical study and related clinical manufacturing costs, regulatory and other related costs. Nonrefundable advanced payments for goods or services to be received in the future for use in research and development activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

Stock-Based Compensation Expense

The Company accounts for its stock-based compensation awards to employees and directors in accordance with FASB ASC Topic 718, *Compensation-Stock Compensation* ("ASC 718"). ASC 718 requires all stock-based payments to employees, including grants of employee stock options and restricted stock, to be recognized in the consolidated statements of operations and comprehensive loss based on their grant date fair values. Compensation expense related to awards to employees is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Share-based payments issued to non-employees are recorded at their fair values and are periodically revalued as the equity instruments vest and are recognized as expense over the related service period in accordance with the provisions of ASC 718 and FASB ASC Topic 505, *Equity* and are expensed using an accelerated attribution model.

The Company estimates the fair value of its stock options using the Black-Scholes option pricing model, which requires the input of subjective assumptions, including (a) the expected stock price volatility, (b) the expected term of the award, (c) the risk-free interest rate, (d) expected dividends and (e) the estimated fair value of its Common Stock on the measurement date. Due to the lack of company specific historical and implied volatility data of its Common Stock, the Company has based its estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. When selecting these public companies on which it has based its expected stock price volatility, the Company selected companies with comparable characteristics to it, including enterprise value, risk profiles, position within the industry and with historical share price information sufficient to meet the expected term of the stock based awards. The Company computes historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of the stock-based awards. The Company will continue to apply this process until a sufficient amount of historical information regarding the volatility of its own stock price becomes available. Due to the lack of Company specific historical option activity, the Company has estimated the expected term of its employee stock options using the "simplified" method, whereby, the expected term equals the arithmetic average of the vesting term and the original contractual term of the option. The expected term for non-employee awards is the remaining contractual term of the option. The risk-free interest rates are based on the U.S. Treasury securities with a maturity date commensurate with the expected term of the associated award. The Company has never paid and does not expect to pay dividends in the foreseeable future. Refer to Note 2, "*Use of Estimates*," for a discussion of the Company's estimated fair value of its Common Stock.

The Company is also required to estimate forfeitures at the time of grant and revise those estimates in subsequent periods if actual forfeitures differ from its estimates. The Company uses historical data to estimate forfeitures and records stock-based compensation expense only for those awards that are expected to vest. To the extent that actual forfeitures differ from the Company's estimates, the differences are recorded as a cumulative adjustment in the period the estimates were revised. Stock-based compensation expense recognized in the financial statements is based on awards that are ultimately expected to vest.

Income Taxes

Income taxes are recorded in accordance with FASB ASC Topic 740, *"Income Taxes"* ("ASC 740"), which provides for deferred taxes using an asset and liability approach. Under this method, deferred tax assets and liabilities are determined based on the difference between the financial reporting and tax reporting basis of assets and liabilities and are measured using enacted tax rates and laws that are expected to be in effect when the differences are expected to reverse. Valuation allowances are provided if based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. The Company has evaluated available evidence and concluded that the Company may not realize the benefit of its deferred tax assets; therefore, a valuation allowance has been established for the full amount of the deferred tax assets.

The Company accounts for uncertain tax positions in accordance with the provisions of ASC 740. When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances. As of December 31, 2015 and 2014, the Company did not have any significant uncertain tax positions. The Company's practice is to recognize interest and/or penalties related to income tax matters in income tax expense. See Note 10 for further details.

Net Income (Loss) per Share Attributable to Common Stockholders

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

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

Comprehensive Loss

Comprehensive loss consists of net income or loss and changes in equity during a period from transactions and other events and circumstances generated from non-owner sources. The Company's net loss equals comprehensive loss, net of any changes in the unrealized gains and losses of the Company's short-term investments, held as available-for-sale, for all periods presented.

Subsequent Events

The Company considers events or transactions that occur after the balance sheet date but prior to the date the consolidated financial statements are available to be issued for potential recognition or disclosure in the financial statements. The Company has completed an evaluation of all subsequent events after the consolidated balance sheet date of December 31, 2015 to ensure that this filing includes appropriate disclosure of events both recognized in the consolidated financial statements as of December 31, 2015 and events which occurred subsequently but were not recognized in the consolidated financial statements. See Note 13 for further details concerning events subsequent to the consolidated balance sheet dates.

3. Fair Value Measurements

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

	As of December 31, 2015			
	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)	Total
Assets				
Cash equivalents	$39,233	$ -	$ -	$39,233
Government securities	25,232	-	-	25,232
Total	$64,465	$ -	$ -	$64,465
Liabilities				
Foreign currency forward contracts	$-	$ 537	$ -	$537
Total	$-	$ 537	$ -	$537

	As of December 31, 2014			
	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)	Total
Assets				
Cash equivalents	$68,830	$ -	$ -	$68,830
Government securities	6,508	-	-	6,508

Corporate bonds	-	8,247	-	8,247
Total	$75,338	$ 8,247	$ -	$83,585

As of December 31, 2015 and 2014, the Company’s cash equivalents consist principally of money market funds and government debt securities with original maturities of 90 days or less. Government securities consist principally of government debt securities and money market funds which are classified as available-for-sale. Corporate bonds consist of bonds issued by highly-rated corporate entities which are classified as available-for-sale. Forward foreign currency contracts consist of contracts with credit-worthy financial institutions to buy Swiss Francs with U.S. dollars in the future at agreed upon exchange rates.

Forward foreign currency contracts are stated at fair value and consist of Level 2 financial instruments in the fair value hierarchy. The Company determines the fair value of its forward foreign currency contracts based on pricing from a service provider. The service provider values the instruments based on market prices from a variety of industry-standard independent data providers. Such market prices are based on inputs other than quoted prices included within Level 1 that are observable for the asset, either directly or indirectly (Level 2 inputs). Cash equivalents and government securities are stated at fair value and consist of Level 1 financial instruments in the fair value hierarchy. The Company determined the fair value of its debt security holdings and corporate bonds based on pricing from a service provider. The service provider values the securities based on market prices from a variety of industry-standard independent data providers. These market prices are quoted prices in active markets for identical assets (Level 1 inputs). Corporate bonds are stated at fair value and consist of Level 2 financial instruments in the fair value hierarchy. The Company determines the fair value of its corporate bonds holdings based on pricing from a service provider. The service provider values the securities based on market prices from a variety of industry-standard independent data providers. Such market prices are based on inputs other than quoted prices included within Level 1 that are observable for the asset, either directly or indirectly (Level 2 inputs).

Available-for-sale securities at December 31, 2015 and 2014 consist of the following (in thousands):

	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
December 31, 2015				
Government securities				
(Due within 1 year)	$ 25,243	$ 1	$ (12)	$ 25,232
	$ 25,243	$ 1	$ (12)	$ 25,232
December 31, 2014				
Government securities				
(Due within 1 year)	$ 6,510	$ -	$ (2)	$ 6,508
Corporate bonds				
(Due within 1 year)	8,251	-	(4)	8,247
	$ 14,761	$ -	$ (6)	$ 14,755

4. Property and Equipment, net

Property and equipment, net consists of the following (in thousands):

	As of December 31,	
	2015	2014
Computer equipment and software	$167	$135
Furniture, fixtures, and other	244	84
Laboratory equipment	254	248
	665	467
Accumulated Depreciation	(441)	(384)
Property and equipment, net	$224	$83

Depreciation expense for the years ended December 31, 2015, 2014 and 2013 was $57,000, $30,000, and $27,000, respectively. During 2013, the Company sold fully depreciated fixed assets with an original cost basis of $0.2 million and a net book value of $0, recognizing a gain on sale of $0.1 million. The Company did not sell or dispose of any fixed assets during the years ended December 31, 2015 or 2014.

5. Accrued Expenses

Accrued expenses consist of the following (in thousands):

	As of December 31,	
	2015	2014
Payroll and employee-related costs	$1,058	$641
Contracted service costs	1,040	494
Professional fees and other	478	286
Total	$2,576	$1,421

6. Derivative Financial Instruments

The Company enters into forward foreign currency contracts to mitigate its exposure to fluctuations in the U.S dollar value of forecasted transactions denominated in Swiss Franc. During the year ended December 31, 2015, the Company had forward foreign currency contract activity for which it did not elect hedge accounting for the forward foreign currency contracts outstanding as of December 31, 2015, but may elect to apply hedge accounting in the future. As a result, during the year ended December 31, 2015, the Company experienced unrealized losses within other expense in the consolidated statements of operations from the mark-to-market of outstanding forward foreign currency contracts. The Company expects potential volatility within other income (expense) in future periods for contracts for which the Company does not apply hedge accounting.

As of December 31, 2015, the Company had the following outstanding forward foreign currency contracts that were not designated for hedge accounting and that were used to reduce the exposure to fluctuations in the U.S dollar value of forecasted transactions denominated in Swiss Franc (dollars in thousands):

Notional Amount	Effective Date	Maturity Date	Number of Instruments
$5,713	June 12, 2015	Various dates through December 15, 2016	4

No forward foreign currency contracts were held by the Company prior to May 2015. The table below presents the fair value of the Company's derivative financial instruments as well as their classification on the balance sheet as of December 31, 2015 (in thousands):

	Balance Sheet line item	Gross amounts of recognized liabilities	Gross amount offset in consolidated balance sheet	Net Amount
Forward foreign currency contracts	Other current liabilities	$ 537	$ -	$ 537

7. Commitments and Contingencies

Significant Contracts and Agreements

In February 2002, the Company entered into an agreement to license certain intellectual property with Johns Hopkins University. The agreement calls for payments to be made by the Company upon the commencement of product sales, in the form of a royalty of 2.5% on net sales of the product. As of December 31, 2015 the Company has not commenced product sales and therefore has recognized no royalties on product sales.

In July 2015, the Company entered into a manufacturing services agreement with Lonza Ltd for the processing, development and manufacture of the active pharmaceutical ingredient ("API") in its lead product candidate, vonapanitase. Under the agreement, the Company will execute purchase orders authorizing Lonza to manufacture the batches and will pay for the services and batches in accordance with terms and assumptions in the agreement and to be set forth in a project plan. As of December 31, 2015, the Company has executed one purchase order of $1.9 million for the manufacturing of one batch to commence in July 2016. In addition, management expects to pay $0.3 million to Lonza in the second quarter of 2016 for Lonza's acquisition of raw materials in connection with this purchase order.

Operating Leases

The Company has various non-cancellable operating leases for facilities and office equipment that expire at various dates through 2018. In August 2014, the Company entered into an Amendment (the "Lease Amendment") to the existing Lease Agreement dated July 13, 2009 (the "Lease Agreement"), with Boston Properties Limited Partnership ("Lessor") pursuant to which the Company has agreed to extend the lease for approximately 5,000 square feet of property to be used for office space (the "Leased Property") located at 200 West St., Waltham, Massachusetts. The term of the Lease Amendment commences on January 1, 2015 (the "Commencement Date") and expires in June 2018, approximately three years and six months from the Commencement Date. The Company has the option to extend the term for an additional one-year period upon the Company's written notice to the Lessor at least nine months in advance of the extension. Rental expense for the years ended December 31, 2015, 2014 and 2013 was $0.2 million, $0.2 million and $0.2 million, respectively.

Future minimum payments required under operating leases as of December 31, 2015 are summarized as follows (in thousands):

Year Ending December 31:	Amount
2016	$ 168
2017	168
2018	84
Total minimum lease payments	$ 420

In addition to the base rent, the Company is also responsible for its share of operating expenses and real estate taxes, in accordance with the terms of the lease agreement. As of December 31, 2015, the Company has provided a security deposit in the amount of $14,000 to the lessor.

Restricted cash related to facilities leases

At December 31, 2015 and 2014, the Company had $14,000 and $38,000, respectively, in an outstanding letter of credit to be used as collateral for leased premises. At December 31, 2015 and 2014, the Company pledged an aggregate of $14,000 and $39,000, respectively, to the bank as collateral for the letter of credit, which is included in long-term assets and both short-term deposits and long-term assets, respectively.

8. Common Stock

General

At December 31, 2015, the Company has 100,000,000 shares of Common Stock authorized for issuance, $0.001 par value per share, of which 16,501,500 shares were issued and outstanding. The Common Stock has the following characteristics:

Voting

The holders of shares of Common Stock are entitled to one vote for each share of Common Stock held at all meetings of stockholders and written action in lieu of meetings. There is no cumulative voting.

Dividends

The holders of shares of Common Stock are entitled to receive dividends, if and when declared by the Board of Directors. Cash dividends may not be declared or paid to holders of shares of Common Stock until paid on outstanding Preferred Stock. As of December 31, 2015, no dividends have been declared or paid since the Company's inception.

Liquidation

Upon the dissolution or liquidation or winding up of the affairs of the Company, whether voluntary or involuntary, holders of Common Stock will be entitled to receive all assets of the Company available for distribution to its stockholders equally on a per share basis, subject to any preferential rights of any then outstanding shares of Preferred Stock and after payment or provision for payment of the Company’s debts.

Reserved for Future Issuance

At December 31, 2015, the Company has 100,000,000 shares of Common Stock authorized for issuance, $0.001 par value per share, of which 16,501,500 shares were issued and outstanding. After the 1,768 shares issued in the fourth quarter for the ESPP plan, the Company has the following shares of Common Stock reserved for future issuance:

	December 31, 2015	December 31, 2014
Stock-based compensation awards	2,419,901	1,807,349
Employee Stock Purchase Plan	297,359	140,500
Total	2,717,260	1,947,849

9. Stock-based Compensation

On August 21, 2014, the Company's Board of Directors adopted the 2014 Equity Incentive Plan (the "2014 Plan"), the 2014 Employee Stock Purchase Plan (the "2014 ESPP") and the 2006 Equity Incentive Plan (the "2006 Plan"), as amended and restated (collectively the "Plans"). On October 3, 2014, the stockholders approved these plans.

The Plans provide for the grant of incentive and non-statutory stock options, stock appreciation rights, restricted stock and stock unit awards, performance units, stock grants and qualified performance-based awards. Under the 2006 Plan, no new stock compensation awards will be granted subsequent to the completion of the Company's IPO. The Company initially reserved 704,000 shares of Common Stock for issuance under the 2014 Plan. The 2014 Plan provides that the number of shares reserved and available for issuance under the 2014 Plan will automatically increase each January 1, beginning January 1, 2015 by four percent of the outstanding shares of Common Stock on the immediately preceding December 31 or such lesser number of shares as determined by the Company's Board of Directors prior to each such January 1st.

Terms of the stock awards, including vesting requirements, are determined by the Board of Directors, subject to the provisions of the Plans. Options granted by the Company typically vest over three to four years. Certain awards provide for accelerated vesting if there is a change in control as defined in the Plans. Stock options outstanding under the 2006 Plan are exercisable from the date of grant for a period of ten years. Stock options granted under the 2014 Plan are exercisable only upon vesting. For options granted to date, the exercise price equaled the fair value of the Common Stock as determined by the Board of Directors on the date of grant.

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Stock-based compensation expense

Total stock-based compensation expense is recognized for stock options granted to employees and non-employees and has been reported in the Company's consolidated statements of operations as follows (in thousands):

	Year Ended December 31,		
	2015	2014	2013
Research and development	$650	$114	$106
General and administrative	1,514	345	49
Total	$2,164	$459	$155

The Company estimates the fair value of each employee stock award on the grant date using the Black-Scholes option-pricing model based on the following assumptions regarding the fair value of the underlying Common Stock on each measurement date:

	Year Ended December 31,		
	2015	2014	2013
Weighted average expected volatility	79.8%	79.5%	91.1%
Expected term (in years)	6.11	6.00	5.95
Risk free interest rate	1.76%	1.88%	1.03%
Expected dividend yield	0 %	0 %	0 %

Stock options issued to non-employees are accounted for using the fair value method of accounting; they are periodically revalued as the options vest and are recognized as expense over the related service period. The total expense related to all options granted to non-employees for the years ended December 31, 2015, 2014 and 2013 was $2,000, $4,000 and $32,000, respectively.

Stock Options

The following table summarizes stock option activity for employees and non-employees:

	Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (years)	Aggregate Intrinsic Value
Outstanding at December 31, 2014	1,235,526	$ 4.19	7.1	$ 7,709
Granted	1,010,256	$ 13.52		
Exercised	(45,413)	$ 1.96		
Outstanding at December 31, 2015	2,200,369	$ 8.52	7.8	$ 15,705
Exercisable at December 31, 2015	812,891	$ 3.53	5.3	$ 9,755
Vested or expected to vest at December 31, 2015 (1)	1,991,131	$ 8.16	7.6	$ 14,926

(1) Represents the number of vested options at December 31, 2015 plus the number of unvested options expected to vest based on the unvested options outstanding at December 31, 2015.

During the year ended December 31, 2015, the Company granted stock options to purchase an aggregate of 1,010,256 shares of its Common Stock with a weighted-average exercise price of $13.52 and a weighted-average grant date fair value of $9.34. During the year ended December 31, 2014, the Company granted stock options to purchase an aggregate of 659,865 shares of its Common Stock with a weighted-average grant date fair value of $4.07. During the year ended December 31, 2013, the Company granted stock options to purchase an aggregate of 3,150 shares of its Common Stock with a weighted-average grant date fair value of $16.50.

The total intrinsic value of options exercised in the years ended December 31, 2015 and 2014 was $0.5 million and $0.2 million, respectively. As of December 31, 2015, there was $9.6 million of total unrecognized compensation cost related to employee non-vested stock options. As of December 31, 2015, total compensation cost related to non-employee, non-vested stock options was fully recognized. The total unrecognized compensation cost for employee awards will be adjusted for future forfeitures. The Company expects to recognize its remaining stock-based compensation expense over a weighted-average period of 3.0 years.

Employee Stock Purchase Plan

The 2014 ESPP initially authorized the issuance of up to 140,500 shares of Common Stock. The number of shares increases each January 1, commencing on January 1, 2015 and ending on (and including) January 1, 2024, by an amount equal to the lesser of one percent of the outstanding shares as of the end of the immediately preceding fiscal year, 281,000 shares and any lower amount determined by the Company’s Board of Directors prior to each such January 1st. As of December 31, 2015, as a result of an increase of 164,491 shares on January 1, 2015 of one percent of the outstanding shares as of the end of the fiscal year ending December 31, 2014, the 2014 ESPP authorized the issuance of up to 304,991 shares of Common Stock. The Company’s Board of Directors has determined there was to be no increase on January 1, 2016. The first offering under the 2014 ESPP began on January 1, 2015 and ended on June 30, 2015. The second offering under the 2014 ESPP began on July 1, 2015 and ended on December 31, 2015. During the year ended December 31, 2015, 7,632 shares were issued under the 2014 ESPP resulting in 297,359 shares remaining for future issuance under the plan as of December 31, 2015. The Company incurred $32,000 in stock-based compensation expense related to the 2014 ESPP for the year ended December 31, 2015.

10. Income Taxes

For the years ended December 31, 2015, 2014 and 2013, the Company has not recorded a provision for federal or state income taxes as it has had cumulative net operating losses since inception. The Company's losses before income taxes consist solely of domestic losses.

A reconciliation of income taxes computed using the U.S. federal statutory rate to that reflected in operations follows (in thousands):

	Year Ended December 31,		
	2015	2014	2013
Income tax benefit using U.S. federal statutory rate	$(7,315)	$(1,136)	$(2,690)
Permanent differences	260	124	299
Orphan Drug credit permanent addback	1,310	674	-
State income taxes, net of federal benefit	(808)	(303)	(389)
Tax credits	(4,219)	(2,176)	(7,164)
Expired net operating losses and tax credits	-	312	2,566
Change in valuation allowance	9,782	4,394	7,286
Mark-to-market derivative liability	-	(1,779)	-
Other	990	(110)	92
	$-	$-	$-

The significant components of the Company's deferred tax assets are as follows (in thousands):

	Year Ended December 31,		
	2015	2014	2013
Net operating loss carryforwards	$34,488	$29,217	$26,304
Federal and state tax credits	16,404	12,126	9,941
Deferred revenue	-	-	1,147
Accrued expenses	27	478	332
Patents	443	531	612
Stock-based compensation	596	92	
Other	276	8	300
	52,234	42,452	38,636
Valuation allowance	(52,234)	(42,452)	(38,636)
Net deferred tax asset	$-	$-	$-

In November 2015, the FASB issued ASU No. 2015-17, *Income Taxes (Topic 740): Balance Sheet Classification of Deferred Taxes* (“ASU 2015-17”), which simplifies the presentation of deferred income taxes. ASU 2015-17 requires that deferred tax assets and liabilities be classified as noncurrent in a classified statement of financial position. ASU 2015-17 is effective for financial statements issued for fiscal years beginning after December 15, 2016 (and interim periods within those fiscal years) with early adoption permitted. ASU 2015-17 may be either applied prospectively to all deferred tax assets and liabilities or retrospectively to all periods presented. The Company has elected to early adopt ASU 2015-17 prospectively in the fourth quarter of 2015. As a result, the Company has presented all deferred tax assets and liabilities as noncurrent on the consolidated balance sheet as of December 31, 2015, but have not reclassified current deferred tax assets and liabilities on the consolidated balance sheet as of December 31, 2014.

There was no impact on the Company's results of operations as a result of the adoption of ASU 2015-17.

Management of the Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. Based on the Company's history of operating losses, management of the Company has concluded that it is more likely than not that the benefit of its deferred tax assets will not be realized. Accordingly, the Company has provided a full valuation allowance for deferred tax assets as of December 31, 2015, 2014 and 2013.

The valuation allowance increased approximately $9.8 million during the year ended December 31, 2015, due primarily to the addition of Orphan Drug tax credits and the generation of net operating losses. The valuation allowance increased approximately $3.8 million during the year ended December 31, 2014, due primarily to the addition of Orphan Drug tax credits and the generation of net operating losses. The valuation allowance increased approximately $7.3 million during the year ended December 31, 2013, due primarily to the addition of Orphan Drug tax credits for 2009 through 2012 as well as the generation of net operating losses during the year ended December 31, 2013, both of which have a full valuation allowance.

Subject to the limitations described below, as of December 31, 2015, 2014 and 2013, the Company has net operating loss carryforwards of approximately $94.4 million, $78.1 million and $69.9 million, respectively, to offset future federal taxable income, which will expire at various times between 2026 and 2035. The Company has an additional $0.4 million of net operating losses in 2015 that are attributable to excess stock option deductions which would be recorded as an increase in additional paid-in capital upon reducing cash taxes paid. As of December 31, 2015, 2014 and 2013, the Company has state net operating loss carryforwards of approximately $46.4 million, $55.1 million and $45.4 million, respectively, to offset future state taxable income, which will expire at various times between 2026 and 2035. As of December 31, 2015, 2014 and 2013, the Company has tax credit carryforwards of approximately $16.9 million, $12.5 million and $10.3 million, respectively, to offset future federal and state income taxes, which will expire at various times between 2023 and 2035.

Net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service (the “IRS”) and may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50% as defined under Sections 382 and 383 in the Internal Revenue Code. The Company is in the process of completing an analysis to determine if there were changes in ownership for tax years through 2015, as defined by Section 382. To the extent that the Company undergoes a change in ownership, this could substantially limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. If this were to occur, this could result in increased U.S. federal income tax liability for the Company if it generates taxable income in a future period. Limitations on the use of NOLs and other tax attributes could also increase the state tax liability. The use of tax attributes will also be limited to the extent that the Company does not generate positive taxable income in future tax periods. The amount of the annual limitation is determined based on the Company's value immediately prior to any ownership change.

The Company had no unrecognized tax benefits or related interest and penalties accrued during the years ended December 31, 2015, 2014 and 2013. The Company will recognize interest and penalties related to uncertain tax positions in income tax expense.

The Company is subject to U.S. federal income tax and primarily Massachusetts state income tax. The statute of limitations for assessment by the IRS and state tax authorities is open for tax years ending December 31, 2012 through 2015, although carryforward attributes that were generated prior to tax year 2012 may still be adjusted upon examination by the IRS or state tax authorities if they either have been or will be used in a future period. Currently, no federal or state income tax returns are under examination by the respective taxing authorities.

11. Net Loss per Share Attributable to Common Stockholders

As described in Note 2, Summary of Significant Accounting Policies, the Company computes basic and diluted loss per share using a methodology that gives effect to the impact of outstanding participating securities (the “two-class method”). As the years ended December 31, 2015, 2014 and 2013 resulted in net losses, there is no income allocation required under the two-class method or dilution attributed to weighted-average shares outstanding in the calculation of diluted loss per share.

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

	Year Ended December 31,			
	2015	2014		2013
Convertible preferred stock	-	7,581	(a)	4,254
Common stock warrants	-	660	(a)	660
Outstanding stock options	2,200	1,236		607
Convertible notes	-	243	(a)	243
	2,200	9,720		5,764

(a) These instruments were either exercised or converted to Common Stock during 2014.

12. Quarterly Financial Information (unaudited, in thousands, except share and per share data)

The Company uses the two-class method to calculate net income (loss) per share. During the fourth quarter of the year ended December 31, 2014, the Company recorded net income, although for the full year the Company recorded a net loss. For purposes of calculating basic net income per share for the fourth quarter of 2014, the Company excluded from the numerator $1.3 million of net income attributable to participating securities. The Company calculated diluted net income per share under both the if-converted method and the two-class method noting a greater dilutive effect under the two-class method. For the purposes of calculating diluted net income per share under the two-class method for the fourth quarter of 2014, the Company excluded from the numerator $1.3 million of net income attributable to participating securities and did not assume the conversion of Preferred Stock in the denominator on an as if-converted basis. Shares of Common Stock issuable upon exercise of outstanding stock options and warrants were included in the denominator on an as-if converted basis.

	Three Months Ended			
	March 31, 2015	June 30, 2015	September 30, 2015	December 31, 2015
Revenue	$-	$-	$-	$-
Operating expenses	4,620	4,981	5,082	6,187
Net loss attributable to common stockholders	(4,580)	(5,072)	(5,383)	(6,342)
Net loss per share attributable to common stockholders:				
Basic and Diluted	$(0.28)	$(0.31)	$(0.33)	$(0.38)
Weighted-average common shares outstanding used in net loss per share attributable to common stockholders:				
Basic and Diluted	16,448,688	16,449,937	16,466,945	16,490,430

	Three Months Ended			
	March 31, 2014	June 30, 2014	September 30, 2014	December 31, 2014
Revenue	$-	$-	$2,948	$-
Operating expenses	1,933	2,508	2,814	3,273
Net (loss) income	(2,831)	(2,563)	(5,181)	7,233
Net (loss) income attributable to common stockholders - basic	(4,343)	(4,460)	(7,458)	5,938
Net (loss) income attributable to common stockholders - diluted	(4,343)	(4,460)	(7,458)	5,938
Net (loss) income per share attributable to common stockholders:				
Basic	$(18.09)	$(18.55)	$(31.00)	$0.52
Diluted	$(18.09)	$(18.55)	$(31.00)	$0.48
Weighted-average common shares outstanding used in net (loss) income per share attributable to common stockholders:				
Basic	240,138	240,374	240,610	11,444,807(a)
Diluted	240,138	240,374	240,610	12,295,431(a)

(a) In October 2014, the Company completed its initial public offering of common stock which resulted in net proceeds of approximately $62.5 million from the issuance of 7,026,500 shares of common stock, which includes the sale of 916,500 shares under the underwriter's over allotment option. Immediately prior to the closing of the Company’s IPO, 498,889 shares of Common Stock were issued upon the exercise of warrants with aggregate proceeds of $1.4 million. In connection with the public offering, all of the Company's outstanding redeemable convertible preferred stock was converted to 8,651,805 shares of common stock.

13. Subsequent Events

The Company has evaluated all activity that occurred subsequent to quarter end but prior to issuance of the condensed consolidated financial statements for events or transactions that could require disclosure or that could impact the carrying value of assets or liabilities as of the balance sheet date. In the judgment of management, there were no material events that impacted the unaudited condensed financial statements or disclosures.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) 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.

PROTEON THERAPEUTICS, INC.

By: /s/ Timothy P. Noyes March 14, 2016
Timothy P. Noyes

President, Chief Executive Officer and Director

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed by the following persons on behalf of the registrant in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ Timothy P. Noyes Timothy P. Noyes	President, Chief Executive Officer and Director (Principal Executive Officer)	March 14, 2016
/s/ George A. Eldridge George A. Eldridge	Senior Vice President, Chief Financial Officer, Treasurer and Secretary (Principal Financial and Accounting Officer)	March 14, 2016
/s/ Hubert Birner, Ph.D. Hubert Birner, Ph.D.	Director	March 14, 2016
/s/ Garen Bohlin Garen Bohlin	Director	March 14, 2016
/s/ Scott Canute Scott Canute	Director	March 14, 2016
/s/ John G. Freund, M.D. John G. Freund, M.D.	Director	March 14, 2016

/s/ Tim Haines Tim Haines	Director	March 14, 2016
/s/ Stuart A. Kingsley Stuart A. Kingsley	Director	March 14, 2016
/s/ Dmitry Kobyzev, Ph.D. Dmitry Kobyzev, Ph.D.	Director	March 14, 2016
/s/ Brendan M. O'Leary, Ph.D. Brendan M. O'Leary, Ph.D.	Director	March 14, 2016
/s/ Gregory D. Phelps Gregory D. Phelps	Director	March 14, 2016

EXHIBIT INDEX

Exhibit No.	Description
3.1	Sixth Amended and Restated Certificate of Incorporation of the Company (incorporated by reference to Exhibit 3.1 to the Company's Current Report on Form 8-K filed on October 27, 2014 (File No. 001-36694)).
3.2	Amended and Restated Bylaws of the Company (incorporated by reference to Exhibit 3.2 to the Company's Current Report on Form 8-K filed on October 27, 2014 (File No. 001-36694)).
4.1	Form of Common Stock Certificate (incorporated by reference to Exhibit 4.1 to Amendment No. 1 to the Company's Registration Statement on Form S-1 filed on October 7, 2014 (File No. 333-198777)).
4.2	Fourth Amended and Restated Investors' Rights Agreement, dated May 13, 2014, between the Company and certain investors named therein (incorporated by reference to Exhibit 4.2 to the Company's Registration Statement on Form S-1 filed on September 16, 2014 (File No. 333-198777)).
4.3	Series D Preferred Stock Purchase Agreement, dated May 13, 2014, between the Company and certain investors named therein (incorporated by reference to Exhibit 4.3 to the Company's Registration Statement on Form S-1 filed on September 16, 2014 (File No. 333-198777)).
10.1 †	2006 Equity Incentive Plan, as amended and restated August 21, 2014 (incorporated by reference to Exhibit 10.1 to Amendment No. 1 to the Company's Registration Statement on Form S-1 filed on October 7, 2014 (File No. 333-198777)).
10.2 †	2014 Equity Incentive Plan, Form of Stock Option Agreement and Form of Option Exercise Notice under the Company's 2014 Equity Incentive Plan (incorporated by reference to Exhibit 10.2 to Amendment No. 1 to the Company's Registration Statement on Form S-1 filed on October 7, 2014 (File No. 333-198777)).
10.3 †	Letter Agreement by and between the Company and F. Nicholas Franano, dated August 22, 2014 (incorporated by reference to Exhibit 10.8 to the Company's Registration Statement on Form S-1 filed on September 16, 2014 (File No. 333-198777)).

10.4 ‡	Process Development and Manufacturing Services Agreement by and between the Company and Lonza Ltd., dated September 1, 2009 (as amended by that Amendment No. 1 entered into as of February 21, 2012) (incorporated by reference to Exhibit 10.9 to the Company's Registration Statement on Form S-1 filed on September 16, 2014 (File No. 333-198777)).
10.5	Lease Agreement by and between the Company and Boston Properties Limited Partnership, dated July 13, 2009, as amended by that Amendment No. 1 dated September 14, 2012, as amended by that Amendment No. 2 dated October 17, 2013, as amended by that Amendment No. 3 dated August 4, 2014 (incorporated by reference to Exhibit 10.10 to the Company's Registration Statement on Form S-1 filed on September 16, 2014 (File No. 333-198777)).
10.6	Assignment of Rights/License Agreement, effective as of February 4, 2002, by and between Johns Hopkins University and F. Nicholas Franano (incorporated by reference to Exhibit 10.11 to the Company's Registration Statement on Form S-1 filed on September 16, 2014 (File No. 333-198777)).
10.7	Assignment of Patent made and entered into as of December 30, 2002, by and between F. Nicholas Franano and Proteon Therapeutics, L.L.C (incorporated by reference to Exhibit 10.12 to the Company's Registration Statement on Form S-1 filed on September 16, 2014 (File No. 333-198777)).
10.8	Letter Agreement, dated October 1, 2010, among the National Institutes of Health, F. Nicholas Franano and the Company (incorporated by reference to Exhibit 10.13 to the Company's Registration Statement on Form S-1 filed on September 16, 2014 (File No. 333-198777)).
10.9	Letter Agreement, dated January 12, 2009, by and between F. Nicholas Franano and the Company (as successor-in-interest to Proteon Therapeutics, L.L.C.) (incorporated by reference to Exhibit 10.14 to the Company's Registration Statement on Form S-1 filed on September 16, 2014 (File No. 333-198777)).
10.10	Quitclaim Deed, dated January 17, 2011, by F. Nicholas Franano to the Company (incorporated by reference to Exhibit 10.15 to the Company's Registration Statement on Form S-1 filed on September 16, 2014 (File No. 333-198777)).
10.11 †	Form of Stock Option Grant Notice and Stock Option Agreement under the Company's 2006 Equity Incentive Plan, as amended (incorporated by reference to Exhibit 10.16 to the Company's Registration Statement on Form S-1 filed on September 16, 2014 (File No. 333-198777)).

10.12	†	2014 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.25 to Amendment No. 1 to the Company's Registration Statement on Form S-1 filed on October 7, 2014 (File No. 333-198777)).
10.13	†	Amended and Restated Employment Agreement by and between the Company and Timothy P. Noyes, dated October 1, 2014 (incorporated by reference to Exhibit 10.26 to Amendment No. 1 to the Company's Registration Statement on Form S-1 filed on October 7, 2014 (File No. 333-198777)).
10.14	†	Amended and Restated Employment Agreement by and between the Company and Steven Burke, dated October 1, 2014 (incorporated by reference to Exhibit 10.27 to Amendment No. 1 to the Company's Registration Statement on Form S-1 filed on October 7, 2014 (File No. 333-198777)).
10.15	†	Amended and Restated Employment Agreement by and between the Company and George Eldridge, dated October 1, 2014 (incorporated by reference to Exhibit 10.28 to Amendment No. 1 to the Company's Registration Statement on Form S-1 filed on October 7, 2014 (File No. 333-198777)).
10.16	†	Amended and Restated Employment Agreement by and between the Company and Daniel Gottlieb, dated October 1, 2014 (incorporated by reference to Exhibit 10.29 to Amendment No. 1 to the Company's Registration Statement on Form S-1 filed on October 7, 2014 (File No. 333-198777)).
10.17		Form of Amended and Restated Indemnification Agreement (incorporated by reference to Exhibit 10.30 to Amendment No. 1 to the Company's Registration Statement on Form S-1/A filed on October 7, 2014 (File No. 333-198777)).
10.18	‡	Manufacturing Services Agreement by and between the Company and Lonza Ltd, dated as of June 30, 2015 and signed July 9, 2015 (incorporated by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 filed on November 12, 2015 (File No. 001-36694)).
21.1	*	List of Subsidiaries.
23.1	*	Consent of Ernst & Young LLP, independent registered public accounting firm.
31.1	*	Certification of Principal Executive Officer Required Under Rule 13a-14(a) and 15d-14(a) of the Securities Exchange Act of 1934, as amended.
31.2	*	Certification of Principal Financial Officer Required Under Rule 13a-14(a) and 15d-14(a) of the Securities Exchange Act of 1934, as amended.
32.1	**	Certification of Principal Executive Officer and Principal Financial Officer Required Under Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, and 18 U.S.C. §1350.

101*	Interactive Data Files Pursuant to Rule 405 of Regulation S-T: (i) the Consolidated Balance Sheets as of December 31, 2014 and 2013; (ii) the Consolidated Statements of Operations and Comprehensive Loss for the years ended December 31, 2015, 2014 and 2013; (iii) the Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit) for the years ended December 31, 2015, 2014 and 2013; (iv) the Consolidated Statements of Cash Flows for the years ended December 31, 2015, 2014 and 2013; and (v) the notes to the Consolidated Financial Statements.

*Exhibits filed herewith

** Exhibits furnished herewith.

†Indicates management contract or compensation plan

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