PROTEON THERAPEUTICS INC
Form 10-K
March 14, 2018

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2017

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 001-36289

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	**02451**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: **(781) 890-0102**

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Name of each exchange on which registered**
Common Stock, $0.001 par value	**NASDAQ Global Market**

Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. o Yes x No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. o Yes x No

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. x Yes o No

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate website, 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). x Yes o No

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Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. o

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

Large accelerated filer o	Accelerated filer o
Non-accelerated filer x (Do not check if a smaller reporting company)	Smaller reporting company o Emerging growth company x

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

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

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, 2017, the last business day of the registrant's most recently completed second quarter, was: $16.3 million.

As of March 9, 2018 there were 17,674,729 shares of the registrant's common stock, par value $0.001 per share, outstanding.

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DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2018 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, 2017, 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 2018 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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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 Phase 3 clinical trial for vonapanitase;
- our interpretation of the data from our completed Phase 2 and Phase 3 clinical trials for vonapanitase;
- whether and when we may submit a Biologics License Application or a supplemental Biologics License Application;
- whether we will need to conduct any additional studies after our Phase 3 trials;
- our estimates regarding the amount of funds required to fund operations into the fourth quarter of 2019;
- our plans to fund our chemistry, manufacturing and controls;
- our estimates regarding expenses, future revenues, capital requirements, the sufficiency of our current and expected cash resources and our need for additional financing and plans for additional financing;
- our estimate of when we will require additional funding;
- our plans to commercialize and bring vonapanitase to market;
- the timing of, and our ability to obtain and maintain, regulatory approvals for our product candidates, including vonapanitase;
- the timing of, and whether we will conduct, a clinical trial of vonapanitase in Europe, results and submission of a Marketing Authorization Application;
- 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;
- the potential benefits of strategic partnership agreements and our ability to enter into selective strategic partnership arrangements;

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

All forward-looking statements in this 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.

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.

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, is a recombinant human elastase that we are developing to improve vascular access outcomes in patients with chronic kidney disease, or CKD, undergoing or planning for hemodialysis, a lifesaving treatment that cannot be conducted without a functioning vascular access. We believe data from our completed Phase 2 and Phase 3 clinical trials of vonapanitase support that a one-time, local application of investigational vonapanitase during surgical creation of a radiocephalic fistula for hemodialysis may improve fistula use for hemodialysis and secondary patency (time to fistula abandonment), thereby improving patient outcomes and reducing the burden on patients and the healthcare system.

Arteriovenous fistulas 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 fistulas 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. Radiocephalic fistulas created in the forearm are the preferred form of arteriovenous fistula because they preserve the maximum number of future sites for vascular accesses (i.e., the potential use of other vascular access sites further up in the arm) and are associated with the lowest rate of serious complications such as steal syndrome (hand ischemia).

However, radiocephalic fistulas suffer from a high rate of failure, typically due to insufficient blood flow, precluding hemodialysis. Recent data demonstrate that within one year of surgical creation of a radiocephalic fistula:

- Up to 55% will fail to become usable for hemodialysis because the fistula either has inadequate blood flow or cannot be successfully cannulated;
- Up to 40% will be abandoned (secondary patency loss); and
- Up to 70% will experience either a thrombosis or undergo a corrective procedure to restore or maintain blood flow (primary patency loss).

The need to improve vascular access outcomes for patients is well established in the hemodialysis community. Achieving a usable fistula for vascular access and maintaining the patency (blood flow) of such fistula enables the hemodialysis patient to avoid use of a dialysis catheter, the worst form of vascular access because of the increased risk of serious infection, hospitalization and death. Patients with a usable fistula also avoid the need for additional surgical procedures to create new forms of vascular access. Finally, as each patient has only a limited number of vascular access sites, fistula abandonment increases the risk that the patient may exhaust all permanent access sites and be subjected to chronic use of a dialysis catheter.

Vascular access failure also results in substantially higher healthcare costs. A recent study indicated that the total cost to Medicare for managing hemodialysis vascular access was more than $2.8 billion in 2013. This amount excludes costs of managing vascular access in predialysis patients and dialysis patients covered by Medicare Advantage HMOs or other non-Medicare payers, as well as patient co-pays and deductibles. It was also reported that fistulas that fail to become usable resulted in incremental costs to Medicare of up to $24,000 in the first year and $11,000 in the second year following fistula creation.

Because the clinical implications of fistula non-use and abandonment are severe, health care providers are aggressive in monitoring and intervening upon fistulas in an attempt to increase fistula use and reduce the rate of fistula abandonment. In less than a decade, the rate of procedures has approximately doubled. The function of usable fistulas can usually be restored via corrective 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 invasive, painful and associated with a number of complications. These procedures are also costly and often need to be repeated. Fistula 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 $15,000.

We have demonstrated in nonclinical studies that vonapanitase fragments elastin fibers in blood vessels. Elastin fragmentation generates peptides in the adventitia that are recognized by cells possessing elastin receptors, including cells involved in vascular remodeling and the formation of neointimal hyperplasia. The generation of peptides in the adventitia may stimulate cells that restructure the vessel wall, promoting outward vascular remodeling, a process necessary for a fistula to become usable. In experimental models, fragmentation of elastin has been shown to be an early and essential event in outward vascular remodeling. The peptides are also chemo-attractants, which may reduce cell migration to the vessel lumen, inhibiting neointimal hyperplasia, which is the growth of tissue inside vessels that narrows fistulas and reduces blood flow. Vonapanitase has also been shown to lead to vessel dilation when administered at a sufficient concentration. During fistula creation surgery, a surgeon would administer drops of vonapanitase onto the surface of the artery and vein of a fistula for 10 minutes followed by a saline irrigation. Based on clinical and nonclinical studies, we believe that a one-time, local application of investigational vonapanitase to the external surface of the vessels during fistula surgical creation may enhance outward vascular remodeling and inhibit neointimal hyperplasia, thereby reducing the risk of fistula failure.

PATENCY-1, the first of two multicenter, randomized, double-blind, placebo-controlled Phase 3 clinical trials, evaluated the safety and efficacy of a single dose of investigational vonapanitase in patients with CKD who underwent surgical creation of a radiocephalic arteriovenous fistula for hemodialysis. We reported top-line data from the PATENCY-1 trial in December 2016. While this trial did not meet the primary endpoint of improving primary unassisted patency, we are encouraged that vonapanitase demonstrated clinically meaningful improvements in other efficacy endpoints, including:

- 45% relative increase (20% absolute increase) in the proportion of patients who had a fistula that was used for hemodialysis (p=0.006);
- 34% reduction in the risk of secondary patency loss (fistula abandonment) over 12 months (p=0.048); and
- 56% relative increase (14% absolute increase) in the proportion of patients who had a fistula that was used for hemodialysis without prior corrective procedures such as angioplasty (p=0.035).

Reported adverse events were also comparable between the vonapanitase and placebo arms of the study. These events were consistent with the medical events experienced by patients with CKD undergoing surgical creation of a

radiocephalic fistula.

Our ongoing Phase 3 clinical trial, PATENCY-2, is the second Phase 3 trial of investigational vonapanitase in patients with CKD undergoing surgical creation of a radiocephalic fistula for hemodialysis. After announcing top-line results from the PATENCY-1 trial in December 2016, we had discussions with the U.S. Food and Drug Administration, or FDA, regarding changes to the PATENCY-2 trial. Following our review of the complete data sets from the PATENCY-1 trial and discussions with the FDA, we amended the protocol for the PATENCY-2 trial. The protocol amendment reordered the endpoints for this ongoing trial, establishing fistula use for hemodialysis and secondary patency as co-primary endpoints. The protocol amendment also increased the planned enrollment for this trial from 300 to 500 patients, which we subsequently increased to 600 patients. The increased sample size for the PATENCY-2 trial provides power to detect the differences observed in the PATENCY-1 trial for fistula use for hemodialysis and secondary patency of 98% and 88%, respectively, with a p-value ≤0.05 for each of the co-primary endpoints. In connection with these changes, we received written confirmation from the FDA that, if PATENCY-2 is successful in showing statistical significance ($p \leq 0.05$) on each of the co-primary endpoints, the PATENCY-2 trial together with data from previously completed studies would provide the basis for a Biologics License Application, or BLA, submission as a single pivotal study, in which case no additional studies would need to be conducted prior to submitting the BLA. We completed enrollment in the PATENCY-2 trial in March 2018 and expect to report top-line data in March 2019. If the PATENCY-2 trial is successful, we expect to submit a BLA in 2019.

Vonapanitase received Breakthrough Therapy designation from the FDA in May 2017 for hemodialysis vascular access indications. The FDA awards Breakthrough Therapy designations to expedite the development and review of investigational drugs that are intended to treat serious or life-threatening conditions when preliminary clinical evidence indicates that the treatment may offer a substantial improvement over currently available therapies on one or more clinically significant endpoints. Vonapanitase previously received Fast Track designation from the FDA which is also designed to facilitate the development and expedite the review of drugs and biologics to treat serious conditions and address an unmet medical need. We also received orphan drug designations for vonapanitase in the United States and European Union for hemodialysis vascular access indications.

We believe that, if our ongoing Phase 3 clinical trial is successful and vonapanitase is approved, vonapanitase will potentially become the standard of care for patients with CKD undergoing surgical creation of a radiocephalic fistula. 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 sales force, focused primarily on vascular surgeons. We also intend to seek one or more collaborators to commercialize the product in additional markets, including Europe and China. Our patents include claims covering formulations, methods of manufacturing and use of elastases, providing protection in the United States into 2030 and European Union through 2028, with potential extension into 2033 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:

- *Completed enrollment in pivotal Phase 3 trial.* We completed enrollment in the PATENCY-2 trial in March 2018 and expect to report top-line data in March 2019. Previously, we made important changes to the protocol for the PATENCY-2 trial based on the results of our first Phase 3 trial, PATENCY-1. The protocol amendment for the PATENCY-2 trial reordered the existing endpoints, establishing co-primary endpoints of fistula use for hemodialysis and secondary patency (time to fistula abandonment), each of which demonstrated improvements in the PATENCY-1 trial. We also increased the planned enrollment for the PATENCY-2 trial from 300 to 600 patients. The increased sample size for the PATENCY-2 trial provides power to detect the differences observed in the PATENCY-1 trial for fistula use for hemodialysis and secondary patency of 98% and 88%, respectively, with a p-value ≤ 0.05 for each of the co-primary endpoints. We have also received written confirmation from the FDA that, if PATENCY-2 is successful in showing statistical significance ($p \leq 0.05$) on each of the co-primary endpoints, the PATENCY-2 trial together with data from previously completed studies would provide the basis for a BLA submission. If the PATENCY-2 trial is successful, we expect to submit a BLA in 2019.

- *Safety profile supports approval*. Based on results from our clinical trials and preclinical studies, we believe investigational vonapanitase, which is administered once and only acts locally, has demonstrated a favorable safety profile. Vonapanitase is applied to the outside of blood vessels for ten minutes and then washed away, which limits the potential for any absorption into the body and systemic activity. Any vonapanitase that might enter the bloodstream would be inactivated by anti-proteases, substances in the blood that inhibit the activity of vonapanitase. In clinical trials, 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 antibodies to vonapanitase. At our end of Phase 2 meeting with the FDA in 2013, we confirmed that we do not need to conduct any additional preclinical studies to support a BLA submission.

- *Expedited programs to address unmet medical need*. Vonapanitase has received Breakthrough Therapy and Fast Track designations from the FDA, which are designed to expedite the development and review of drugs and biologics to treat serious or life-threatening conditions and fill an unmet medical need. While radiocephalic fistulas are considered the preferred form of vascular access by the medical community, they are associated with high failure

rates, most critically fistula non-use and abandonment. Achieving a usable fistula and maintaining patency (blood flow) enables the patient to avoid the temporary or permanent use of a dialysis catheter, the worst form of vascular access because of the increased risk of serious infection, hospitalization and death. Patients with a usable fistula also avoid the adverse effects of under-dialysis and the need for additional surgical procedures to create new fistulas. We are not aware of any products approved in the United States or Europe that would compete with vonapanitase for the improvement of fistula use for hemodialysis and secondary patency.

Substantial and readily-addressable market opportunity. If vonapanitase is approved, we intend to commercialize this product in the United States ourselves with a specialty sales force, focused primarily on vascular surgeons. We also intend to seek one or more collaborators to commercialize the product in markets outside of the United States, including Europe and China. In the United Sates, 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 fistula surgical creations performed annually. We believe vonapanitase will be supported by key stakeholders, including referring nephrologists, patient advocacy groups, large dialysis organizations and payors. We also believe that, if our ongoing Phase 3 clinical trial is successful and vonapanitase is approved, it will potentially become the standard of care for patients with CKD undergoing surgical creation of a radiocephalic fistula by increasing the use of fistulas for hemodialysis and reducing the rate of fistula abandonment and, in doing so, reduce the overall burden on patients and the healthcare system. We also believe vonapanitase will be reimbursed adequately by Medicare, Medicaid and other public and commercial payors. Costs related to fistula 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. Vascular access failure results in substantially higher healthcare costs. A recent study indicated that the total cost to Medicare for managing hemodialysis vascular access was more than $2.8 billion in 2013, which excludes costs of managing vascular access in predialysis patients and dialysis patients covered by Medicare Advantage HMOs or other non-Medicare payers as well as patient co-pays and deductibles. It was also reported that fistulas that fail to become usable resulted in incremental costs to Medicare of up to $24,000 in the first year and $11,000 in the second year following fistula creation.

- *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 Commercial 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 CKD.

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 fistula. 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 completed enrollment in the PATENCY-2 trial, our second Phase 3 trial for patients with CKD, in March 2018 and expect to report top-line data in March 2019. If PATENCY-2 is successful, we expect to submit a BLA for vonapanitase to the FDA in 2019.

- *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 sales force focused primarily on vascular surgeons. Based on various third-party sources, we estimate that approximately 130,000 arteriovenous fistulas are created annually. We believe a specialty 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 fistula surgical creations performed in the United States annually. We believe that, if our current Phase 3 clinical trial is successful and vonapanitase is approved, it will potentially become the standard of care for patients with CKD undergoing surgical creation of a radiocephalic fistula.

- *Establish partnerships for the development and commercialization of vonapanitase in all or parts of Europe and other countries outside of the United States*. 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 undertake clinical development of vonapanitase in Europe. We estimate that there are approximately 315,000 hemodialysis patients in Europe. We plan to formally seek guidance from the European Medicines Agency, or EMA, in 2018 regarding its requirements for regulatory approval. If we decide to conduct a clinical trial of vonapanitase in Europe or if such a clinical trial is necessary for regulatory approval, we expect results from this trial to be available two to three years after the first patient is enrolled. Depending on the guidance obtained from the EMA and additional clinical data including data from the PATENCY-2 trial, we would expect to submit a Marketing Authorization Application, or MAA. We intend to seek one or more collaborators to develop and commercialize the product in European countries. In addition, we may enter into collaborations for the development and commercialization of vonapanitase in other countries outside of the United States with large populations of hemodialysis patients, such as China and Japan. We estimate that there are approximately 385,000 patients on hemodialysis in China, 320,000 patients on hemodialysis in Japan and more than

2,600,000 hemodialysis patients worldwide, with an annual worldwide growth rate of 6-7%. Approximately 90% of hemodialysis patients in China and Japan dialyze using an arteriovenous fistula.

Pursue additional vascular access indications for vonapanitase. We believe that our clinical data support further development of vonapanitase in brachiocephalic fistula 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 fistulas. If this trial were to successfully meet its primary endpoint, we would expect to submit a supplemental BLA to the FDA and a supplemental MAA to the EMA. Further, if sufficient funds become available and after reviewing the results from our ongoing Phase 3 clinical trial, we may commence a clinical trial of vonapanitase in patients undergoing placement of an arteriovenous graft. We believe vonapanitase could offer a significant medical benefit in these patients.

- *Pursue indications for vonapanitase in 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. In 2016, we initiated a Phase 1, multicenter, dose-escalation trial designed to evaluate the safety and technical feasibility of a single administration of vonapanitase as an adjunct to angioplasty for patients with PAD below the knee. We expect to complete the enrollment and treatment of 24 patients in this study before the end of 2018. We may, if sufficient funds become available, increase enrollment in the Phase 1 trial evaluating vonapanitase below the knee and/or begin patient enrollment in a Phase 1, multicenter, dose-escalation trial evaluating vonapanitase as a monotherapy for PAD above the knee.

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

Background on Hemodialysis

Healthy kidneys serve many functions, including eliminating metabolic waste products and excess water, helping to control blood pressure, and keeping electrolytes such as sodium and potassium in balance. Patients with CKD have lost 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 perform their normal functions. 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.

Hemodialysis is the most common form of treatment for end-stage CKD. According to the U.S. Renal Data System 2017 Annual Data Report, in 2015 there were approximately 444,000 hemodialysis patients in the United States with approximately 109,000 new incident patients having started hemodialysis during the year, reflecting an annual U.S. growth rate of approximately 3%. We believe that there are approximately 330,000 hemodialysis patients in Europe, 385,000 hemodialysis patients in China, 320,000 hemodialysis patients in Japan and 2.6 million hemodialysis patients worldwide, with an annual worldwide growth rate of 6-7%.

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 metabolic waste and excess water 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, referred to as a fistula, to create a high flow circuit of sufficient diameter, most often in an arm. The fistula 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.

Arteriovenous fistulas are the gold standard for vascular access. Arteriovenous fistulas are preferred because they are associated with fewer complications and reduced rates of hospitalization as compared to other forms of vascular access. As compared to grafts, fistulas require approximately 40% fewer interventional or surgical procedures and suffer from a rate of vascular access infection that is 54% lower. Patients dialyzing with a fistula have lower rates of thrombosis and hospitalization, longer survival, reduced mortality and lower cost of care. Beyond the substantial medical advantages of a fistula, available data from the U.S. Renal Data System show that patients who dialyze with a fistula cost Medicare approximately $15,000 less annually than patients who dialyze with a graft and approximately $25,000 less annually than patients who dialyze with a catheter. According to published data, approximately 68% of hemodialysis patients in the United States dialyze with a fistula compared to 67-83% of patients in the major European countries and approximately 90% of patients in China and Japan.

Based on various third-party sources, we estimate there were approximately 130,000 fistulas 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 a fistula, principally the following:

- radiocephalic fistulas at the forearm (radial artery connected to cephalic vein), which we estimate are created in 35 - 40% of new fistula creations;

- brachiocephalic fistulas at the elbow (brachial artery sutured to cephalic vein), which we estimate are created in 50 - 55% of new fistula creations; and

- brachiobasilic fistulas in the upper arm (brachial artery sutured to basilic vein), which we estimate are created in 10% of new fistula creations.

The medical community endorses radiocephalic fistulas as the optimal form of vascular access and the recommended first choice for new hemodialysis patients. Creating the vascular access site at the forearm preserves the potential future use of other accesses further up in the arm, is simpler to create, and is less likely to create heart failure due to very high blood flow or steal syndrome, where the diversion of flow through the fistulas reduces blood to the hand. Radiocephalic fistulas are also less likely to suffer from symptomatic central stenoses in the shoulder and chest, remote from the site of the fistula. The Kidney Disease Outcome Quality Initiative Guidelines, or KDOQI Guidelines, authored by the National Kidney Foundation, or NKF, specifically recommend starting with a radiocephalic fistulas 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 fistula must be abandoned, a surgeon can create a new vascular access higher up the arm, most likely a brachiocephalic fistula. However, if a brachiocephalic fistula is created first, the surgeon cannot later move down that same arm to create a radiocephalic fistula because the cephalic vein has already been transected for use in the brachiocephalic fistula.

While radiocephalic fistulas are considered the most desirable form of vascular access, radiocephalic fistulas suffer from high rates of patency loss and non-use for hemodialysis. Up to 40% of radiocephalic fistulas are abandoned within 12 months after their surgical creation. Additionally, up to 55% of radiocephalic fistulas fail to become usable for hemodialysis. Some patients never receive a radiocephalic fistula because the surgeon believes the risk of failure is too high for those patients. These patients who tend to be older and sicker will undergo creation of a fistula higher up on the arm and permanently lose at least one of their access sites. We believe that the number of radiocephalic fistulas created annually may rise if vonapanitase improves outcomes and allows vascular surgeons to create radiocephalic fistulas in patients that they previously considered to be at an unacceptably high risk of failure.

The second choice for vascular access after a fistula is an arteriovenous graft in which a surgeon connects an artery and vein using a synthetic tube. Approximately 20% of hemodialysis patients in the United States dialyze with a graft, compared to approximately 5-12% of patients in the major European countries and approximately 2% and 7% of patients in China and Japan, respectively.

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, in the United States approximately 80% of patients initiate hemodialysis through a catheter until a fistula or graft is ready to be used, and are dialyzed through a catheter when the fistula or graft does not become usable for hemodialysis or must be abandoned and a new one has to be created. Approximately 12% of hemodialysis patients in the United States dialyze with a permanent catheter,

compared to 10-28% of patients in the major European countries and approximately 10% and 2% of patients in China and 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 costs of creating vascular accesses and addressing access dysfunction and associated complications have led to a global effort to address the problem. Over the last twenty years, the NKF has established guidelines in an effort to increase the use of fistulas 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 fistula and graft 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 fistulas while reducing complications. According to Fistula First, fistulas should be considered for every patient needing hemodialysis because, compared to other forms of vascular access, fistulas last longer, 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, fistula use has approximately doubled since 2004 to 68% of United States hemodialysis patients.

Although arteriovenous fistulas are the preferred form of vascular access, they suffer from a high rate of failure, typically due to insufficient blood flow, precluding hemodialysis. The increased use of fistulas has also led to a concurrent increase in the number of fistulas created in patients with higher risks of dysfunction. Manifestations of fistula failure can include the following:

- failure of the fistula to become usable for hemodialysis, in which the fistula either has inadequate blood flow or cannot be successfully cannulated;

- loss of primary patency, in which the fistula experiences a thrombosis or requires a corrective procedure to restore blood flow; or

- loss of secondary patency, in which the fistula is abandoned.

We are not aware of products approved in the United States or Europe that would compete with vonapanitase for the improvement of fistula use for hemodialysis and secondary patency.

For patients on hemodialysis, fistula non-use or abandonment is associated with a number of poor outcomes, many of which are associated with prolonged catheter exposure. Patients whose fistula fails to become usable or is abandoned are often subjected to the following:

- Interrupted and missed dialysis sessions, which are associated with an increased risk of morbidity and mortality.

- Surgical placement of a new permanent access, often in the same arm but in a more proximal location, which is associated with increased complications such as steal syndrome (hand ischemia). A recent study indicated that subsequent accesses are at a greater risk of infectious and noninfectious complications compared to an initial access.

- New vascular accesses may also require additional corrective procedures to promote use of the fistula or maintain its function.

- Some patients may be considered poor candidates for a new fistula, resulting in placement of an arteriovenous graft, which are associated with higher rate of infection, thrombosis and patency loss compared to a fistula.

- Until a new permanent access is available for use, a process that typically requires a minimum of three months for fistulas in patients on hemodialysis, patients must dialyze with a catheter. If the new access fails to become usable, catheter exposure will be further lengthened. A recent study indicated that patients whose fistula fails to become usable are subjected to more than twice the time of catheter exposure in the first year after surgical creation of the fistula.

- Finally, some patients may be forced to dialyze with a catheter chronically, either because the patient has depleted all of his or her vascular access options or the patient refuses to undergo an additional surgical procedure to create a permanent access.

One of the primary goals of the Fistula First campaign is to reduce the use of catheters, which is considered the worst form of vascular access. As a foreign body, a catheter may incite chronic inflammation resulting in malnutrition, anemia and cardiovascular disease. Catheters are also subject to low blood flow, predisposing patients to

underdialysis. In addition, patients dialyzing with a catheter are at heightened risk of hospitalization compared to patients dialyzing with a fistula. Patients dialyzing with a catheter average 18 hospital days per patient-year, which is approximately twice the rate of patients dialyzing with a fistula. Catheter exposure results in a substantially higher rate of infections, especially catheter-related bacteremia, due to the challenges of inserting and maintaining a foreign body through the skin. Infection is the second leading cause of death in hemodialysis patients, and catheter use is independently associated with increased risk of infectious, cardiovascular, and all-cause mortality compared to fistula use.

Among pre-dialysis patients, fistula failure can result in the patient initiating hemodialysis using a catheter instead of a fistula, which has been shown to be associated with increased risk of subsequent fistula failure and hospitalization. Patients who initiate hemodialysis on a catheter have two times the rate of admissions for infection in the first month of hemodialysis and a higher risk of all-cause hospitalization compared to patients initiating with a fistula. A recent study indicated an incremental cost increase of $30,000 in the first year of hemodialysis for patients initiating hemodialysis on a catheter.

Because the clinical implications of fistula non-use and abandonment are severe, health care providers are aggressive in monitoring and intervening upon fistulas in an attempt to increase fistula use and reduce the rate of fistula abandonment. In less than a decade, the rate of procedures has approximately doubled. Such procedures include balloon angioplasty and surgical revision, which are invasive, painful and associated with a number of complications. The procedures also often fail to provide a durable benefit, resulting in a cycle of interventions for the patient. Recent data indicate that 50% of fistulas 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. Additionally, the procedures are not always successful in restoring patency, with up to 27% of the procedures failing to restore function, resulting in fistula abandonment. Patients in the United States using a fistula on average require more than 1.5 procedures per year, each of which typically costs Medicare between $5,000 and $15,000. A United States hospital published data in 2014 indicating that maintaining function in a radiocephalic fistula 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. In addition, a recent study indicated that the total cost to Medicare for managing hemodialysis vascular access was more than $2.8 billion in 2013. This amount excludes costs of managing vascular access in predialysis patients and dialysis patients covered by Medicare Advantage HMOs or other non-Medicare payers, as well as patient co-pays and deductibles. It was also reported that fistulas that fail to become usable resulted in incremental costs to Medicare of up to $24,000 in the first year and $11,000 in the second year following fistula creation.

Vonapanitase

Vonapanitase is a recombinant human elastase under development as a treatment to improve vascular access outcomes in patients with CKD undergoing or planning for hemodialysis, a lifesaving treatment that cannot be conducted without a functioning vascular access. We have completed four multicenter, randomized, double-blind, placebo-controlled studies evaluating vonapanitase compared to placebo in patients with CKD, including the first of two Phase 3 clinical trials, PATENCY-1. We also completed patient enrollment in our second Phase 3 clinical trial, PATENCY-2, in March 2018 and expect to release top-line data in March 2019. Vonapanitase received Breakthrough Therapy designation from the FDA in May 2017 for hemodialysis vascular access. The FDA awards Breakthrough Therapy designations to expedite the development and review of investigational drugs that are intended to treat serious or life-threatening conditions when preliminary clinical evidence indicates that the treatment may offer a substantial improvement over currently available therapies on one or more clinically significant endpoints. Vonapanitase previously received Fast Track designation from the FDA which is also designed to facilitate the development and expedite the review of drugs and biologics to treat serious conditions and address an unmet medical need. We also received orphan drug designations for vonapanitase in the United States and European Union for hemodialysis vascular access indications.

Mechanism of Action

Based on clinical and nonclinical studies, we believe that a one-time, local application of investigational vonapanitase to the external surface of the blood vessels during fistula surgical creation may enhance outward vascular remodeling and inhibit neointimal hyperplasia, thereby reducing the risk of fistula failure.

We believe there are two primary causes of fistula failure:

- *Failure due to insufficient outward vascular remodeling*. For a fistula to become usable for dialysis, the outflow vein must outwardly remodel, experiencing an increase in diameter and blood flow. This process, known as vascular remodeling, involves proliferation of cells in the vessel wall, secretion of proteases that degrade extracellular matrix, and synthesis of new extracellular matrix by these cells. Fistulas that fail to outwardly remodel do not experience a sufficient increase in blood flow to enable successful dialysis.
- *Failure due to neointimal hyperplasia*. Fistulas may also fail to become usable for dialysis or may experience patency loss due to neointimal hyperplasia, which is scarring of the interior wall of the outflow vein near the lumen, resulting in stenosis of the vein lumen and obstruction of blood flow in the fistula. Neointimal hyperplasia typically occurs in response to vessel injury, such as following fistula creation or due to hemodynamic stress caused by the rapid flow of blood from the artery into the outflow vein. Fistulas also often undergo additional corrective procedures to restore blood flow, which expose the fistula to further mechanical injury. The response of the vein to these injuries results in activation and recruitment of scar forming cells, which multiply and migrate from the outside to the inside wall of the blood vessel and produce a layer of tissue, creating a narrowing in the vein lumen and reducing fistula blood flow. Fistulas that experience neointimal hyperplasia may not have sufficient blood flow to enable successful dialysis.

We demonstrated through nonclinical studies that vonapanitase, at the concentrations being studied in arteriovenous fistulas, causes partial fragmentation of elastin fibers, primarily in the adventitial layer of the vessel wall. Elastin fragmentation generates peptides in the adventitia that are recognized by cells possessing elastin receptors, including cells involved in vascular remodeling and the formation of neointimal hyperplasia. The generation of peptides in the adventitia may stimulate cells that restructure the vessel wall, promoting outward vascular remodeling, a process necessary for a fistula to become usable. In experimental models, fragmentation of elastin is an early and essential event in outward vascular remodeling. The peptides are also chemo-attractants, which may reduce cell migration to the vessel lumen, focusing the healing response to vessel injury to the adventitial layer and inhibiting neointimal hyperplasia. In animal models of vascular injury, the porcine homologue of vonapanitase applied to the adventitial surface of veins and arteries fragmented elastin and directed the migration of proliferating cells away from the vessel lumen, significantly reducing neointimal hyperplasia. Vonapanitase has also been shown to lead to vessel dilation when administered at a sufficient concentration.

Clinical Development of Vonapanitase

Our First Phase 3 Clinical Trial, PATENCY-1

In December 2016, we announced that the PATENCY-1 trial did not meet its primary endpoint of improved primary unassisted patency compared to placebo (p=0.254). Primary unassisted patency was defined as the length of time from fistula surgical creation to the first occurrence of a fistula thrombosis or corrective procedure to restore or maintain patency (blood flow). While not statistically significant, vonapanitase treated patients demonstrated a 17% reduction in the risk of primary unassisted patency loss over one year. At the end of one year, 42% of vonapanitase-treated patients maintained primary unassisted patency, compared to 31% of placebo-treated patients. Median patency, the time at which 50% of patients in a group lost primary unassisted patency, was 171 days in the placebo group and 214 days in the vonapanitase treatment group based on the Kaplan-Meier estimates.

Kaplan-Meyer curves for primary unassisted patency in PATENCY-1:

Secondary patency, the secondary endpoint in the PATENCY-1 trial, was defined as the length of time from surgical creation until fistula abandonment. Results suggested that vonapanitase may have improved secondary patency compared to placebo, as vonapanitase-treated patients demonstrated a 34% reduction in the risk of secondary patency loss (p=0.048). At the end of one year, 74% of vonapanitase-treated patients maintained secondary patency, compared to 61% of placebo-treated patients.

Kaplan-Meyer curves for secondary patency in PATENCY-1:

Results also suggested that vonapanitase may have improved fistula use for hemodialysis, one of the PATENCY-1 trial's tertiary endpoints. 39% of vonapanitase-treated patients achieved unassisted use of their fistula for hemodialysis, compared to 25% of placebo-treated patients (p=0.035). 64% of vonapanitase-treated patients used their fistula for dialysis (unassisted or assisted), compared to 44% of placebo-treated patients (p=0.006). Use for hemodialysis was defined as use of the fistula for hemodialysis for at least 90 days or, if hemodialysis was not initiated at least 90 days prior to the patient's last visit, for at least 30 days prior to the patient's last visit and in use at the patient's last visit. Unassisted use was defined as use without prior loss of primary unassisted patency.

Results from the PATENCY-1 trial's other tertiary endpoints include the following:

- *Unassisted and Assisted Maturation*. 63% of vonapanitase-treated patients achieved unassisted maturation, compared to 53% of placebo-treated patients (p=0.109). Unassisted maturation by ultrasound criteria was defined as achieving a vein diameter ≥4 millimeters and blood flow ≥500 milliliters per minute by three months without loss of primary patency. 66% of vonapanitase-treated patients achieved maturation without regard for prior procedures (i.e., unassisted or assisted) compared to 58% of placebo-treated patients (p=0.170).

- *Rate of Procedures*. Over one year, the rate per patient per year of procedures to restore or maintain patency was 1.10 in vonapanitase-treated patients compared to 1.48 in placebo-treated patients (p=0.479). Such procedures included thrombectomy, angioplasty, stent deployment and surgical revision. The rate per patient per year of all procedures was 1.54 in vonapanitase-treated patients compared to 2.07 in placebo-treated patients (p=0.149).

We are continuing to follow patients who completed 12 months of follow-up in the initial trial with a patent fistula and consented to be enrolled in a patient registry to obtain long-term follow-up efficacy information.

Safety Data

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 3 clinical trial doses. Safety evaluations in Phase 2 and Phase 3 clinical trials included ascertainment of adverse events, physical examinations, ultrasounds of the fistulas and nearby vessels, vital signs and laboratory studies. In the PATENCY-1 trial, no significant safety signals were identified, and no patients were considered positive for anti-drug antibodies. Most patients reported adverse events, the most common of which are summarized in the table set forth below, as compared to placebo. These events were generally consistent with the medical events experienced by CKD patients undergoing fistula creation surgery.

Proportions of Patients in PATENCY-1
Experiencing Most Common Adverse Events

Adverse Events	**Vonapanitase N=209**	**Placebo N=102**
Vascular stenosis	38.3%	40.2%
Fistula thrombosis	19.6%	26.5%

Hypoaesthesia (numbness)	5.3%	4.9%
Procedural pain	4.8%	5.9%

Note: Includes any adverse event that occurred in at least 5% of patients in either treatment group.

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The percentages of serious adverse events, or SAEs, was also similar between the treatment groups in the PATENCY-1 trial (placebo 14.7%, vonapanitase 13.9%). Individual SAEs were never reported by more than one (1%) placebo patient or two (1%) vonapanitase patients with the exception of pneumonia reported by three (2.9%) placebo patients and myocardial infarction reported by two (2.0%) placebo patients. No SAEs were related to study drug with the exception of one (0.5%) arteriovenous fistula thrombosis in a vonapanitase patient. The percentages of severe SAEs were similar between treatment groups (placebo 4.9%, vonapanitase 4.8%) as were the percentages with life-threatening SAEs (placebo 4.9%, vonapanitase 3.3%). Life-threatening SAEs included acute myocardial infarctions, one cardiac arrest, and two pneumonias in the placebo group and single occurrences of coronary artery disease, cardiac arrest, pulseless electrical activity, death, injury, hypoxic-ischemic encephalopathy, and shock in the vonapanitase group. Four (3.9%) placebo patients and seven (3.3%) vonapanitase patients died during the study. All 11 deaths were considered unrelated to study drug.

Our Ongoing Phase 3 Clinical Trial, PATENCY-2

Our ongoing Phase 3 clinical trial, PATENCY-2, is the second of two randomized, double-blind Phase 3 trials, comparing a 30 microgram dose of investigational vonapanitase to placebo. As in PATENCY-1, PATENCY-2 enrolled patients with CKD undergoing surgical creation of a radiocephalic fistula for hemodialysis. Patients were randomized 2:1, vonapanitase to placebo, and are being followed for a period of 12 months. In March 2018, we completed enrollment of a total of 603 treated patients at 39 centers in the U.S. and Canada. We expect to report top-line data in March 2019.

Following our review of the complete data sets from the PATENCY-1 trial and discussions with the FDA, we amended the protocol for the PATENCY-2 trial. The protocol amendment reordered the existing endpoints for the study, establishing fistula use for hemodialysis and secondary patency (time to fistula abandonment) as co-primary endpoints, each of which demonstrated improvements in the PATENCY-1 trial. Other efficacy endpoints in the amended protocol include unassisted fistula use for hemodialysis, primary unassisted patency, unassisted fistula maturation by ultrasound criteria, fistula maturation by ultrasound criteria, the rate of procedures performed to the fistula, and the rate of procedures to restore or maintain fistula patency. We also increased the planned enrollment for this study from 300 to 600 patients. The increased sample size for the PATENCY-2 trial provides power to detect the differences observed in the PATENCY-1 trial for fistula use for hemodialysis and secondary patency of 98% and 88%, respectively, with a p-value ≤0.05 for each of the co-primary endpoints. We received written confirmation from the FDA that, if PATENCY-2 is successful in showing statistical significance (p-value≤0.05) on each of the co-primary endpoints, the PATENCY-2 trial together with data from previously completed studies would provide the basis for a BLA submission as a single pivotal study, in which case no additional studies would need to be conducted prior to submitting the BLA.

Our Phase 2 Fistula Clinical Trial

In 2012, we completed a multicenter, randomized double-blind, placebo-controlled Phase 2 trial of vonapanitase in 151 patients undergoing surgical creation of a radiocephalic fistula (n=67) or brachiocephalic fistula (n=84). Patients were treated with vonapanitase at doses of 10 or 30 micrograms or placebo at the time of fistula creation and were followed for up to 12 months. The primary efficacy endpoint was primary unassisted patency, defined as the time from surgical creation of the fistula to occurrence of a thrombosis or a procedure, such as angioplasty, to restore or maintain patency. In the primary analysis for all fistulas, the risk of primary patency loss was not significantly reduced versus placebo for vonapanitase at doses of 10 micrograms (HR, 0.69; 95% CI, 0.39-1.22) or 30 micrograms (HR, 0.67; 95% CI, 0.38-1.19). Median patency, based on the Kaplan-Meier estimates, 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. Ninety-two patients with a patent fistula 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 microgram benefit on primary unassisted patency persisted out over a median of three years.

An analysis of the primary endpoint data revealed an uneven distribution in patency loss events in patients with a brachiocephalic fistula due to central stenosis in the shoulder and chest, remote from the site of a fistula. Central stenoses commonly exist prior to fistula creation and are unmasked following creation of brachiocephalic fistulas, which have higher blood flow than radiocephalic fistulas. 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 (HR 0.52; 95% CI, 0.28-0.97; P=0.04) compared to placebo.

The benefit of vonapanitase in the Phase 2 trial on primary unassisted patency was most pronounced in the subset of patients undergoing creation of a radiocephalic fistula. The risk of primary patency loss was significantly reduced by vonapanitase at doses of 30 micrograms versus placebo (HR, 0.37; 95% CI, 0.15-.91; p=0.02). The subset analysis of this endpoint for radiocephalic fistula patients receiving the 30 microgram dose, which was not pre-specified, showed a significant increase in median primary unassisted patency of more than 365 days as compared to 125 days in the placebo group. The apparent benefit of the vonapanitase 30 microgram dose on primary unassisted patency persisted for these patients in the two-year registry period.

As with the primary efficacy analyses, we performed a number of prespecified and exploratory analyses of the data on additional efficacy endpoints, including secondary patency loss and unassisted use for hemodialysis. We observed no significant differences in the risk of secondary patency loss, which was defined as abandonment of the fistula, in the overall fistula population in the Phase 2 trial. However, a trend toward prolonged secondary patency was seen in patients receiving radiocephalic fistulas. In this non-prespecified subset analysis, treatment with vonapanitase at doses of 30 micrograms was associated with a reduction of 73% in the risk of secondary patency loss. However, this reduction in the risk of secondary patency loss was not statistically significant (HR, 0.27; 95% CI, 0.006-1.29; p=0.08). Additionally, in a recent publication of three-year follow-up data from the Phase 2 trial, a trend toward increased fistula use for hemodialysis was seen in the patients receiving radiocephalic fistulas when applying the definition of use for hemodialysis from the Phase 3 clinical trials of vonapanitase. While the differences observed in this prospective analysis were not statistically significant, 80% of patients receiving radiocephalic fistulas in the vonapanitase 30 microgram group used their fistula for hemodialysis compared with 56% in the placebo group (p=0.14).

In the Phase 2 trial, patients treated with vonapanitase reported adverse events comparable to placebo. These events were consistent with the medical events experienced by patients with CKD undergoing fistula creation surgery. Based on the results of this Phase 2 trial and our end of Phase 2 meeting with the FDA in April 2013, we selected the 30 microgram dose for further study in the Phase 3 trials.

Our Phase 1/2 Fistula Clinical Trial

We submitted an investigational new drug application, or IND, for vonapanitase as a treatment for patients undergoing fistula 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 fistula. Patients were treated with vonapanitase at nine dose levels ranging from 3.3 micrograms to 9 milligrams or placebo at the time of fistula 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 and Phase 3 trials. However, 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.

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 fistula and arteriovenous graft creation, by percutaneous and

endovascular injection in animal models of 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 used in our 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 our Phase 3 clinical trial 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 are studying in our Phase 3 clinical trial). 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 fistula studies in rabbits at doses up to 10 milligrams and in all the arteriovenous graft studies in dogs and pigs at doses up to 20 milligrams (the highest doses tested).

Other Programs, Indications and Trials

Other Fistula 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 Fistula

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

Arteriovenous Grafts

An arteriovenous graft is a synthetic tube to connect a vein and an artery placed in a surgical procedure. In 2012, we completed a Phase 1/2 randomized, double-blind, placebo-controlled, dose-escalation trial in 89 patients undergoing placement of an arteriovenous graft. Patients were treated with placebo or eight different doses of vonapanitase ranging from 10 micrograms to 9 milligrams at the time of graft 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 arteriovenous graft.

The primary outcome measure was safety. Adverse events were consistent with the medical conditions experienced by patients with CKD undergoing graft 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 second Phase 3 clinical trial, and if sufficient funds become available, we may commence a clinical trial of vonapanitase in patients undergoing placement of an arteriovenous graft.

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 arteries in the leg above the knee. 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. In the fourth quarter of 2016, we initiated another Phase 1 study of vonapanitase delivered via a drug-delivery catheter in symptomatic PAD patients undergoing angioplasty of an artery below the knee. We expect to complete the enrollment and treatment of 24 patients before the end of 2018 in this Phase 1 study and to follow each of these patients for period of up to seven months.

We also believe that vonapanitase may be an alternative to traditional angioplasty. Vonapanitase may be delivered via a percutaneous approach, in which a physician inserts a 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. In the fourth quarter of 2016 we initiated a Phase 1 study of vonapanitase delivered as a monotherapy in patients with a clinical diagnosis of PAD due to an atherosclerotic lesion in an artery above the knee. Based on our current operating plan, we have decided not to begin patient enrollment at this time.

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.

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 drug product that was used in our Phase 3 fistula clinical trials. We also plan to manufacture API at Lonza for our commercial launch and future fistula trials. We also have a separate 5 milligram formulation that was used in our completed Phase 1 fistula study, Phase 2 fistula study, Phase 1 arteriovenous graft study, and Phase 1 PAD study. We plan to use this 5 milligram formulation in our Phase 1 PAD studies.

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 using synthetic and natural elastin substrates and the same elastin removal from blood vessels following ex vivo treatments as the previous finished product. 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 drug 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 drug product.

In anticipation of a potential BLA submission, we plan to manufacture a minimum of three batches of API and of drug 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 fistulas in patients with CKD undergoing or planning for hemodialysis and to improve vascular access outcomes in patients with other vascular diseases. If the PATENCY-2 trial is successful, we expect to be able to submit a BLA in 2019.

We have not yet established a commercial infrastructure, however, our Chief Executive Officer and other members of our executive management team have significant commercial experience in the industry, including commercial launch experience in the renal market. We intend to recruit an in-house specialty sales force in the United States focused on promoting vonapanitase. We plan to target our marketing and sales efforts at vascular surgeons who create fistulas. There are approximately 2,800 vascular surgeons in the United States. We believe a 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 fistula creations performed in the United States annually.

We believe that vonapanitase will be reimbursed appropriately by Medicare, Medicaid and private payers. Costs related to fistula 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 expect to commercialize vonapanitase in Europe with one or more commercial partners. We also may enter into collaborations for the development and commercialization of vonapanitase in China, Japan and other countries outside of the United States.

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 for our products. We expect to use trademark protection for our products as they are marketed.

Patents

As of December 31, 2017, we own 37 issued patents and 20 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 patents, two issued European patents, additional patents issued in Australia, China, Hong Kong, India, Israel, Japan, Mexico, New Zealand, Russia, South Korea and Taiwan, and patent applications pending in several major jurisdictions worldwide, including Japan, China, South Korea, Brazil, Mexico, 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 our two formulation family patents were awarded patent term adjustments of 199 and 668 days, respectively, due to United States Patent and Trademark Office, or USPTO delays taking their expiration dates to June 20, 2029 and October 3, 2030, respectively. The therapy family includes eight issued United States patents, three issued European patents, one issued Canadian patent, one issued Hong Kong patent, and an application pending in the United States. 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.

We are not aware of products approved in the United States or Europe that would compete with vonapanitase for the improvement of fistula use for hemodialysis and secondary patency. We are aware of other therapies in development by companies including Vascular Therapies, Enceladus Pharmaceuticals, Symic Biomedical, Aplagon and Athera Biotechnologies. We are also aware of companies developing vascular access technologies, including BioConnect Systems, Avenu Medical, Phraxis, Brookhaven Medical, Fist Assist, Laminate Medical Technologies, Stent Tek and TVA Medical. Other technologies in development include new synthetic grafts, including those that may be developed by companies that currently compete in the graft market, such as W.L. Gore, C.R. Bard and Maquet, as well as tissue engineered grafts, including those in development by Cytograft and Humacyte. Finally, vonapanitase’s commercial success could be 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.

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.

In addition, the manufacturer of an investigational drug in a Phase 2 or Phase 3 clinical trial for a serious or life-threatening disease is required to make available, such as by posting on its website, its policy on evaluating and responding to requests for expanded access to such investigational drug.

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. NDA or BLA 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 $2,421,495 for Fiscal Year 2018, and the applicant under an approved new drug or biologic application is also subject to an annual program fee, currently exceeding $300,000 per product for Fiscal Year 2018. Beginning in Fiscal Year 2018, this annual program fee replaces the annual product and establishment fees. These fees are typically increased annually. A waiver or reduction of the application, establishment and/or program 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 NDA or BLA for filing. In this event, the NDA or 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 an NDA or 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. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling, including boxed warnings. 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. Only 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 for a preventive drug. 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.

Expedited development and review programs

The FDA maintains several programs intended to facilitate and expedite development and review of new drugs and biologics to address unmet medical needs in the treatment of serious or life- threatening diseases or conditions. These programs include Fast Track designation, Breakthrough Therapy designation, Priority Review designation and

Accelerated Approval, and the purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures.

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.

In addition, a new drug or biologic may be eligible for Breakthrough Therapy designation if it is intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Breakthrough Therapy designation provides all the features of Fast Track designation in addition to intensive guidance on an efficient drug development program and FDA organizational commitment to expedited development, including involvement of senior managers and experienced review staff in a cross-disciplinary review, where appropriate.

Any product submitted to the FDA for marketing, including a product with Fast Track or Breakthrough Therapy designation, may be eligible for other types of FDA programs intended to expedite development and review, such as Priority Review and Accelerated Approval. Any application for a product that treats a serious or life-threatening condition is eligible for Priority Review if the product would provide safe and effective therapy where no available therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products, among other things. The FDA aims to review applications for new products designated for Priority Review within six months, compared to ten months under standard review. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate such review. Additionally, a drug or biological product that treats a serious or life-threatening illness and that generally provides 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.

Fast Track designation, Breakthrough Therapy designation, Priority Review designation and Accelerated Approval do not change the standards for approval but may expedite the development or review process. We have received Breakthrough Therapy and Fast Track designations for vonapanitase.

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 except a product with a new active ingredient that is molecularly targeted cancer product intended for the treatment of an adult cancer and directed at a molecular target determined by FDA to be substantially relevant to the growth or progression of a pediatric cancer that is subject to an NDA or BLA submitted on or after August 18, 2020.

Pediatric exclusivity is another type of exclusivity in the United States. For biological products, pediatric exclusivity, if granted, provides an additional six months of exclusivity to be attached to any existing non-patent exclusivity. This

six month exclusivity, which runs from the end of other exclusivity protection, 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. To date, FDA has approved a handful of biosimilar products and no interchangeable products have been approved by the FDA under the BPCIA. 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 may 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. This patent exchange process – and whether or not it is mandatory – is currently before the Supreme Court of the United States. 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 in certain circumstances for up to two years after the date of completion of the trial. 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.

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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, healthcare reform legislation has strengthened these laws. For example, the 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 many of which differ from each other in significant ways and often are not preempted by federal laws, thus complicating compliance efforts. There are also an increasing number of state laws with requirements for manufacturers and/or marketers of pharmaceutical products. Some states require the reporting of expenses relating to the marketing and promotion of drug products and the reporting of gifts and payments to individual healthcare practitioners in these states. Other states prohibit various marketing-related activities, such as the provision of certain kinds of gifts or meals. Still other states require the reporting of certain pricing information, including information pertaining to and justification of price increases, or prohibit prescription drug price gouging. In addition, states such as California, Connecticut, Nevada, and Massachusetts require pharmaceutical companies to implement compliance programs and/or marketing codes. Many of these laws contain ambiguities as to what is required to comply with the laws.

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 are 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, 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.

Research and Development

Our total research and development expenses were $21.6 million and $18.9 million, during the years ended December 31, 2017 and 2016, respectively. See Part II—Item 7—"Management's Discussion and Analysis of Financial Condition and Results of Operations" of this Annual Report on Form 10-K for additional detail regarding our research and development activities."

Employees

As of March 9, 2018, we had 16 full-time employees, of whom 9 are in research and development and seven 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.

We also make available free of charge through our website http://www.proteontherapeutics.com certain of our corporate governance policies, including the charters for the audit, compensation and nominating and corporate governance committees of the Board and our code of business conduct and ethics, corporate governance guidelines and whistleblower policy. We will also provide to any person without charge, upon request, a copy of any of the foregoing materials. Any such request must be made in writing to us at: Proteon Therapeutics, Inc., 200 West Street, Waltham, Massachusetts 02451.

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 $30.0 million and $28.5 million for the years ended December 31, 2017 and 2016, respectively. As of December

31, 2017, we had an accumulated deficit of $189.7 million. We do not expect to generate any product revenues in the foreseeable future. We do not know whether or when we will generate revenue or become profitable.

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

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

- continue our clinical development and seek regulatory approval of vonapanitase, particularly with respect to its lead indication for radiocephalic arteriovenous fistulas;
- commercialize vonapanitase directly in the United States;
- undertake clinical development of vonapanitase in Europe and establish partnerships for commercialization of vonapanitase in all or parts of Europe;
- pursue additional indications for vonapanitase including clinical development of vonapanitase for brachiocephalic fistulas, patients requiring placement of an arteriovenous graft, and additional indications for the treatment of patients with symptomatic peripheral artery disease, or PAD;

- in-license or acquire additional product opportunities and make milestone or other payments under any in-license agreements;
- contract for the manufacture of commercial quantities of vonapanitase;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- maintain, protect and expand our intellectual property portfolio;
- attract and retain skilled personnel;
- create additional infrastructure to support our operations as a public company and our product development; and
- experience any delays or encounter issues with any of the above.

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

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

Our operations have consumed substantial amounts of cash since inception. As of December 31, 2017, our cash, cash equivalents and available-for-sale investments were $42.1 million. Our research and development expenses were $21.7 million and $18.9 million for the years ended December 31, 2017 and 2016, respectively. We believe that we will continue to expend substantial resources for the foreseeable future developing vonapanitase and any additional product candidates. These expenditures will include costs associated with research and development, potentially acquiring new technologies, potentially obtaining regulatory approvals and manufacturing products, as well as marketing and selling products approved for sale, if any. In addition, other unanticipated costs may arise. Because the outcome of our planned and anticipated clinical trials is highly uncertain, we cannot reasonably estimate the actual amounts necessary to fund and successfully complete the development and commercialization of vonapanitase or any additional product candidates.

We began enrolling patients in our first Phase 3 clinical trial of vonapanitase during the third quarter of 2014 for patients undergoing creation of radiocephalic fistulas, completed patient enrollment in October 2015 and released top-line data in December 2016. We enrolled the first patient in our second Phase 3 trial in August 2015, completed enrollment in March 2018 and expect to release top-line data in March 2019. Based on our current operating plan, and absent any future financings or strategic partnerships, we believe that our existing cash, cash equivalents and available-for-sale investments will be sufficient to fund our projected operating expenses and capital expenditure requirements into the fourth quarter of 2019, allowing us to report top-line data from our second Phase 3 trial of vonapanitase in radiocephalic fistulas, named PATENCY-2. Our cash runway could be shortened if there are any significant and unexpected increases in spending on development programs or more rapid progress of development programs than anticipated. In addition, we initiated two Phase 1 clinical trials of vonapanitase in patients with PAD in the fourth quarter of 2016. We plan to complete the enrollment and treatment of 24 patients before the end of 2018 in the Phase 1 trial evaluating vonapanitase as an adjunct to angioplasty for PAD below the knee. We may begin patient

enrollment in the Phase 1 trial evaluating vonapanitase as a monotherapy for PAD above the knee if sufficient funds become available. We may also initiate other small Phase 1 or Phase 1/2 trials in additional indications, which would further reduce our capital resources. However, we do not expect to initiate any other Phase 2 or Phase 3 trials prior to receiving and reviewing data from our second Phase 3 clinical trial. Furthermore, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements, or a combination of these approaches. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations.

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

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

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

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

- completing clinical development of vonapanitase for one or more indications and research and preclinical and clinical development of additional product candidates;
- seeking and obtaining regulatory and marketing approvals for vonapanitase if and when we complete clinical trials;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate (in amount and quality) products and services to support clinical development and the market demand for vonapanitase, if approved;
- launching and commercializing vonapanitase if we obtain regulatory and marketing approval, either by collaborating with a partner or, if launched independently, by establishing our own sales, marketing and distribution infrastructure;
- obtaining and maintaining adequate timely coverage and reimbursement from third-party payors for vonapanitase;
- obtaining market acceptance of vonapanitase as a viable treatment option;
- addressing any competing technological and market developments;
- implementing additional internal systems and infrastructure, as needed;
- identifying and validating new product candidates;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents and know-how;
- developing vonapanitase such that, if approved, it can be commercialized without infringing the intellectual property rights of third parties; and
- attracting, hiring and retaining qualified personnel.

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

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

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

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

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

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

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

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

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

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

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

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the clinical trial visit schedule

or protocols, changes in practice patterns outside of the protocols and the rate of dropout among clinical trial participants. Any Phase 3 or other clinical trial that we may conduct may not demonstrate the efficacy and safety necessary to obtain regulatory approval to market vonapanitase or any additional product candidate.

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

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

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

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

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

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

In general, the FDA requires two adequate and well-controlled clinical trials to demonstrate the effectiveness of a product candidate. In December 2016, we announced that our first Phase 3 clinical trial did not meet its primary endpoint of improved primary unassisted patency compared to placebo (p=0.254). Based on our interactions with the FDA, we believe that, if the results for each of the co-primary endpoints of our second Phase 3 clinical trial show statistical significance ($p \leq 0.05$), our second Phase 3 trial together with data from previously completed studies will provide the basis for a BLA submission for vonapanitase to the FDA. However, even with robust p-values, there is no guarantee that the results of the second Phase 3 trial will be sufficient for a BLA submission, filing or approval, and the FDA may require that we conduct additional trials.

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

Vonapanitase and any additional product candidates are subject to extensive governmental regulations relating to, among other things, research, clinical trials, approval, manufacturing, recordkeeping, labeling, storage, advertising, promotion, distribution, import, export and commercialization. In order to obtain regulatory approval for the commercial sale of any product candidate, we must demonstrate through extensive preclinical studies and clinical

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

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. The FDA 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;
- an FDA Advisory Committee or other regulatory authority may recommend against approval or restrictions on approval;
- the results of later-stage clinical trials may not meet the level of statistical or clinical significance required by the FDA or comparable foreign regulatory authorities for approval;
- the results of later-stage clinical trials may not confirm the positive results from earlier preclinical studies or clinical trials;
- we may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- the data collected from clinical trials of vonapanitase or any additional product candidate may not be sufficient to the satisfaction of the FDA or comparable foreign regulatory authorities to support the submission of a BLA, or other comparable submission in foreign jurisdictions or to obtain regulatory approval in the United States or elsewhere;
- our manufacturing processes or facilities may not be adequate to support approval of our product candidates; or
- regulatory agencies may change their approval policies or adopt new regulations in a manner rendering our clinical data insufficient for approval.

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

We may face difficulty in enrolling patients for clinical trials.

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

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

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

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

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

- trials of vonapanitase or any additional product candidates may produce unfavorable or inconclusive results;
- we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- our third-party contractors, including those manufacturing vonapanitase or any additional product candidates or components or ingredients for commercial use or conducting clinical trials on our behalf, may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner or at all;
- regulators or institutional review boards, or IRBs, may not authorize us or our investigators to commence or continue to conduct a clinical trial at a prospective trial site;
- we may have to suspend or terminate clinical trials of vonapanitase or any additional product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of a product candidate;
- regulators or IRBs may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or their respective standards of conduct, a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of the product candidate or findings of undesirable effects caused by a chemically or mechanistically similar biologic or biologic candidate;
- we may experience delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites and/or Contract Research Organizations, or CROs;
- we may experience withdrawal of clinical trial sites from our clinical trials as a result of changing standards of care or the ineligibility of a site to participate in our clinical trials, and may further be delayed in trying to add clinical trial sites to our studies;
- we may experience delays in the importation and manufacture of clinical supply;

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

- participants may drop out of clinical trials of vonapanitase at a higher rate than we anticipate and we may not be able to obtain the follow up data for the 12 month period planned in our Phase 3 trial;
- patients who enroll in a clinical trial may misrepresent their eligibility to do so or may otherwise not comply with the clinical trial protocol, resulting in the need to drop the patients from the clinical trial or increase the needed enrollment size for the clinical trial beyond the current enrollment for the Phase 3 trial, all of which may extend the clinical trial's duration;
- the FDA or comparable foreign regulatory authorities may disagree with our clinical trial design, implementation, or our interpretation of data from preclinical studies and clinical trials;
- FDA or comparable foreign regulatory authorities may find that our clinical trials were not conducted in accordance with Good Clinical Practices, or GCPs;

- the FDA or comparable foreign regulatory authorities may fail to approve or subsequently find fault with the manufacturing processes or facilities of third-party manufacturers with which we enter into agreements for clinical and commercial supplies;
- our finished product that has been manufactured for the vonapanitase Phase 3 trials may be inadequate, or the materials or manufactured product candidates necessary to conduct future clinical trials of vonapanitase or any additional product candidates may be insufficient, inadequate or not available at an acceptable cost, or we may experience interruptions in supply;
- we may lack adequate funding to continue the clinical trials; and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient to obtain marketing approval.

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

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

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

Even if regulatory approval of a product is granted, the approval will be subject to limitations on the indicated uses for which the product may be marketed and may be subject to other conditions of approval. We and our contract manufacturers will be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance

with cGMPs and other regulatory requirements. In addition, approval may contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the product. Discovery after approval of previously unknown problems with any such products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in actions such as:

- restrictions on our ability to conduct clinical trials, including full or partial clinical holds on ongoing or planned trials;
- restrictions on a product's manufacturing processes or facilities;
- restrictions on the marketing of a product;
- restrictions on product distribution;
- requirements to conduct post-marketing clinical trials;
- Untitled, Cyber, or Warning Letters from the FDA or similar correspondence from comparable regulatory authorities;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- mandated modifications to labeling and promotional materials or requirements to provide corrective information to healthcare practitioners;

- requirements to enter into a consent decree, which can include imposition of various fines, reimbursements for inspection costs, required due dates for specific actions and penalties for noncompliance;
- debarring us pursuant to the Federal Food, Drug, and Cosmetic Act, or FDCA, excluding us from participation in federal healthcare programs, requiring a corporate integrity agreement or debarring us from government contracts;
- the imposition of costly new manufacturing requirements or use of alternative suppliers;
- FDA or other regulatory bodies issuing safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings about our products;
- fines, restitution or disgorgement of profits or revenue;
- suspension or withdrawal of regulatory approvals or refusal to approve future or pending applications or supplements;
- refusal to permit the import or export of our products;
- product seizure;
- injunctions; and/or
- imposition of civil or criminal penalties.

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

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

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

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

generate product revenues from any of these product candidates will be delayed or eliminated.

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

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

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

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

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

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

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

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

time period for FDA review or approval will not be shortened.

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

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

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

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

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

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 fistulas. Prior to enrolling our first patient in Europe, we plan to formally seek guidance from the EMA regarding its requirements for regulatory approval. If a clinical trial of vonapanitase in Europe is necessary 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. Obtaining an approval is a lengthy and expensive process and the EMA has its own procedures for approval of product candidates. Even if a product candidate is approved, the EMA may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and Europe also have requirements for approval of product candidates with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of vonapanitase or any additional product candidates in those countries.

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

While the FDA does not restrict physicians from prescribing approved drugs and biologics for uses outside of the products' approved labeling, known as off-label use, pharmaceutical manufacturers are prohibited from promoting and marketing their products for such uses. Violations, including promotion of our products for off-label uses, are subject to enforcement letters, inquiries, investigations, civil and criminal sanctions by the government, corporate integrity

agreements, debarment from government contracts, debarment and exclusion from participation in federal healthcare programs. Additionally, comparable foreign regulatory authorities will heavily scrutinize advertising and promotion of any product candidate that obtains approval outside of the United States.

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

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

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

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

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

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

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

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

- difficulty in establishing or managing relationships with contract research organizations, or CROs, clinical sites and investigators;
- different standards for the conduct of clinical trials;

- our inability to locate qualified local consultants, physicians and partners;
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment; and
- the acceptability of data obtained from trials conducted outside the United States to the FDA in support of a BLA.

Risks Related to Commercialization of Our Product

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

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

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

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

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

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

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

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

- perceptions by members of the healthcare community, including physicians, about the safety and effectiveness of our products, and their advantages as compared to any competitive products;

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

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

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

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

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

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

We are not aware of products approved in the United States or Europe that would compete with vonapanitase for the improvement of fistula use for hemodialysis and secondary patency. We are aware of companies with therapies in

development including Vascular Therapies, Enceladus Pharmaceuticals, Symic Biomedical, Aplagon, and Athera Biotechnologies, as well as companies developing vascular access technologies, including BioConnect Systems, Avenu Medical, Phraxis, Brookhaven Medical, Fist Assist, Laminate Medical Technologies, Stent Tek and TVA Medical. Other technologies in development include new synthetic grafts, including those that may be developed by companies that currently compete in the graft market, such as W.L. Gore, C.R. Bard and Maquet, as well as tissue engineered grafts, including those in development by Cytograft and Humacyte. Finally, vonapanitase's commercial success could be affected by the development of technologies to improve the outcomes of interventions to restore patency, including stents, stent grafts and drug-coated balloons.

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

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

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

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

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

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

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

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

candidates for which we receive regulatory approval may not be available or adequate in either the United States or international markets, which could have a negative effect on our business, results of operations, financial condition and prospects.

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

Risks Related to Dependence on Third Parties

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

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

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

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

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

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

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

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

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

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

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

with cGMPs, each of our clinical trials is conducted in accordance with GCPs and its protocol and is analyzed in accordance with its statistical analysis plan for the clinical trial.

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

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

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

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

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

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

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

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

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

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

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

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

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

Risks Related to Our Intellectual Property

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

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

parties may challenge their validity, enforceability or scope, which may result in our patents being narrowed or invalidated.

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

If patent applications we hold with respect to vonapanitase or any additional product candidates fail to issue, if their breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for vonapanitase or any additional product candidates, it could dissuade companies from collaborating with us. As of December 31, 2017 we own 37 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. Certain of our currently pending utility patent applications are examined under the system in place before March 16, 2013. Third parties are allowed to submit prior art prior to the issuance of a patent by the USPTO, and may become involved in reexamination, *inter partes* review or interference proceedings challenging our patent rights. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, which could adversely affect our competitive position with respect to third parties.

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

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

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

We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and know-how by maintaining physical security of our premises and physical and electronic security of our information technology systems. Nonetheless, despite these precautions, agreements or

security measures may be breached, and we may not have adequate remedies for any breach. In addition, our know-how may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

We enter into confidentiality and intellectual property assignment agreements with our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors. These agreements generally provide that

inventions conceived by the party in the course of rendering services to us will be our exclusive property. However, these agreements may not be honored and may not effectively assign intellectual property rights to us. For example, even if we have a consulting agreement in place with an academic advisor pursuant to which the academic advisor is required to assign any inventions developed in connection with providing services to us, the academic advisor may not have the right to assign these inventions to us, as it may conflict with his or her obligations to assign all intellectual property to his or her employing institution.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

claiming a method of using a product).

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

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

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

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

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

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

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

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

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

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

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

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

Risks Related to Our Business and Industry

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

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

Because of the specialized scientific and managerial nature of our business, we rely heavily on our ability to attract and retain qualified scientific, technical and managerial personnel. We do not currently carry “key person” insurance on the lives of members of executive management. The competition for qualified personnel in the pharmaceutical field is

intense. Due to this intense competition, we may be unable to continue to attract and retain qualified personnel necessary for the development of our business or to recruit suitable replacement personnel. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy including, F. Nicholas Franano, our scientific founder. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

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

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

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

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

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

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

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

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

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

We face an inherent risk of product liability claims as a result of the clinical testing of vonapanitase or any additional product candidates. We will face an even greater risk if we commercially sell vonapanitase or any additional product candidate that we develop. We maintain primary product liability insurance and excess product liability insurance that cover our clinical trials, and we plan to maintain insurance against product liability lawsuits for commercial sale of our potential products. Historically, the potential liability associated with product liability lawsuits for pharmaceutical

products has been unpredictable. Although we believe that our current insurance is a reasonable estimate of our potential liability and represents a commercially reasonable balancing of the level of coverage as compared to the cost of the insurance, we may be subject to claims in connection with our clinical trials and, in the future, commercial use of our potential products, for which our insurance coverage may not be adequate, and the cost of any product liability litigation or other proceeding, even if resolved in our favor, could be substantial.

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

·reduced resources of our management to pursue our business strategy;
·decreased demand for our product candidates or products that we may develop;
·injury to our reputation and significant negative media attention;
·withdrawal of clinical trial participants;
·termination of clinical trial sites or entire trial programs;
·initiation of investigations by regulators;
·product recalls, withdrawals or labeling, marketing or promotional restrictions;

·significant costs to defend resulting litigation;
·diversion of management and scientific resources from our business operations;
·substantial monetary awards to trial participants or patients;
·loss of revenue; and
·the inability to commercialize any products that we may develop.

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

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

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

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

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

Our executive offices are located in Waltham, Massachusetts, and our API is manufactured at Lonza's facility located in Visp, Switzerland. We expect that Lonza plans to utilize this facility in the future to support commercial production if our product candidate is approved. We have manufactured our entire finished product for the ongoing Phase 3 clinical trial of vonapanitase and currently store the finished product in only one location. Extended delays in our Phase 3 clinical trial causing us to need to manufacture new clinical supply would cause a significant disruption in our operations and cause us to incur unexpected costs to manufacture new finished product. 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. In addition, we have initiated three drug substance process validation runs at Lonza's facility in Visp, Switzerland and currently store such material in only one location.

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

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

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

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

In addition, while we select third-party vendors carefully and routinely evaluate the cybersecurity of our CROs and other key vendors, we do not control their actions. Any problems caused by these third parties, including those resulting from cyber attacks and security breaches at a vendor, could result in material delays in our development programs and regulatory approval efforts and adversely affect our business.

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

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

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

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

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

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

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

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

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

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- increases in the statutory minimum rebates a manufacturer must pay as a condition to having a drug or biologic available for coverage under the Medicaid program;
- expansion of healthcare fraud and abuse laws, including the federal civil False Claims Act and the federal Anti-Kickback Statute, and the addition of new government investigative powers and enhanced penalties for non-compliance;
- extension of a manufacturer's Medicaid rebate liability to covered drugs and biologics dispensed to individuals who are enrolled in Medicaid managed care organizations;
-

expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new eligibility categories for certain individuals with income at or below 133% of the federal poverty level beginning in 2014, thereby potentially increasing a manufacturer's Medicaid rebate liability;

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

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

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

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

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

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

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

Risks Related to Our Common Stock

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

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

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

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

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

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

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

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

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

·our failure to develop and commercialize vonapanitase or any additional product candidates;

- actual or anticipated fluctuations in our quarterly financial results or the quarterly financial results of companies perceived to be similar to us;
- changes in the market's expectations about our operating results;
- adverse results or delays in preclinical studies or clinical trials;
- our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial;
- adverse regulatory decisions, including failure to receive regulatory approval for vonapanitase or any additional product candidates;
- success of competitive products;
- adverse developments concerning our collaborations and our manufacturers;
- inability to obtain adequate product supply for any product candidate for clinical trials or commercial sale or inability to do so at acceptable prices;
- the termination of a collaboration or the inability to establish additional collaborations;
- unanticipated serious safety concerns related to the use of any of vonapanitase or any additional product candidates;
- our ability to effectively manage our growth;
- the size and growth, if any, of the targeted market;
- our operating results failing to meet the expectation of securities analysts or investors in a particular period or failure of securities analysts to publish reports about us or our business;
- changes in financial estimates and recommendations by securities analysts concerning our company, our market opportunity, or the biotechnology and pharmaceutical industries in general;
- operating and stock price performance of other companies that investors deem comparable to us;
- overall performance of the equity markets;
- announcements by us or our competitors of acquisitions, new product candidates or programs, significant contracts, commercial relationships or capital commitments;
- our ability to successfully market vonapanitase or any additional product candidates;
- changes in laws and regulations affecting our business, including but not limited to clinical trial requirements for approvals;

- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for vonapanitase or any additional product candidates;
- commencement of, or involvement in, litigation involving our company, our general industry, or both;
- changes in our capital structure, such as future issuances of securities or the incurrence of additional debt;
- the volume of shares of our Common Stock available for public sale;
- additions or departures of key scientific or management personnel;
- any major change in our board or management;
- changes in accounting practices;
- ineffectiveness of our internal control over financial reporting;
- sales of substantial amounts of Common Stock by our directors, executive officers or significant stockholders or the perception that such sales could occur; and
- general economic and political conditions such as recessions, interest rates, fuel prices, international currency fluctuations and acts of war or terrorism.

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

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

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

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

We have entered into a Sales Agreement with Cowen and Company, LLC, or Cowen, for the offer and sale of up to $40 million in aggregate amount of our Common Stock from time to time through Cowen, as our sales agent, pursuant to a Registration Statement on Form S-3 which became effective on January 12, 2016. We filed a prospectus supplement on March 16, 2017 because we are currently subject to General Instruction I.B.6 of Form S-3, which limits the amounts that we may sell under the Registration Statement. Cowen is not required to sell any specific number or dollar amount of shares of our Common Stock but will use its reasonable efforts, as our agent and subject to the terms of the Sales Agreement, to sell that number of shares upon our request. Sales of the shares, if any, may be made by any means permitted by law and deemed to be an “at-the-market” offering as defined in Rule 415 of the Securities Act of 1933, as amended, or the Securities Act, and will generally be made by means of brokers' transactions on the NASDAQ Global Market or otherwise at market prices prevailing at the time of sale, or as otherwise agreed with Cowen.

We may terminate the Sales Agreement at any time or it will terminate once proceeds of $40 million have been raised. For the years ended December 31, 2017, we sold 896,811 shares of common stock under our At-The-Market, or ATM, program for aggregate net proceeds of $1.3 million. Whether we choose to affect future sales under our ATM program will depend upon a variety of factors, including, among others, market conditions and the trading price of our Common Stock relative to other sources of capital. The issuance from time to time of these new shares of Common Stock through our ATM program or in any other equity offering, or the perception that such sales may occur, could have the effect of depressing the market price of our Common Stock.

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

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

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

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

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

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

result in substantial dilution to holders of our Common Stock. Further, the sale of a significant amount of these shares of Common Stock in the open market or the perception that these sales may occur could adversely affect prevailing market prices of our Common Stock, including causing the market price of our Common Stock to decline or become highly volatile.

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

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

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

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

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

As of December 31, 2017, our executive officers, directors, current 5% or greater stockholders, and their respective affiliates together beneficially own or control, in aggregate, more than 50% of the shares of our outstanding Common Stock. As a result, these executive officers, directors and principal stockholders, acting together, will have substantial influence over most matters that require approval by our stockholders, including the election of directors, any merger, consolidation or sale of all or substantially all or of our assets or any other significant corporate transaction. Corporate action might be taken even if other stockholders oppose such action. These stockholders may delay or prevent a change of control or otherwise discourage a potential acquirer from attempting to obtain control of our company, even if such change of control would benefit our other stockholders. This concentration of stock ownership may adversely affect investors' perception of our corporate governance or delay, prevent or cause a change in control of our company, any of which could adversely affect the market price of our Common Stock.

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

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

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

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

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

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

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

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

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

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

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

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

We could be subject to securities class action litigation.

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

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

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

- authorize "blank check" preferred stock, which could be issued by our Board of Directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our Common Stock;
- create a classified Board of Directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our Board of Directors;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our Board of Directors;
- provide that our directors may be removed only for cause;

- provide that vacancies on our Board of Directors may be filled only by a majority of directors then in office, even though less than a quorum;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorize our Board of Directors to modify, alter or repeal our amended and restated bylaws; and
- require supermajority votes of the holders of our Common Stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated by laws.

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

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

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

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

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

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our primary facility is located in Waltham, Massachusetts, where we lease approximately 7,495 square feet of office space. Our lease expires in September 2019. We also have a facility located in Kansas City, Kansas, where we lease approximately 80 square feet of office space. 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, 2017		
First quarter	$2.20	$1.40
Second quarter	$1.95	$1.10
Third quarter	$2.20	$1.25
Fourth quarter	$2.75	$1.60
Year Ended December 31, 2016		
First quarter	$15.00	$5.10
Second quarter	$11.63	$4.90
Third quarter	$10.70	$7.00
Fourth quarter	$11.45	$1.75

On March 9, 2018, the last reported sale price for our Common Stock on the NASDAQ Global Market was $2.30 per share.

Holders

As of March 9, 2018, there were approximately 29 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, 2017. 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	3/31/2016	6/30/2016	9/30/2016	12/31/2016	3/31/2017
Proteon Therapeutics, Inc.	100.00	103.69	115.95	178.07	138.68	154.64	77.17	80.06	93.02	18.94	17.45
NASDAQ Composite	100.00	108.06	111.82	113.78	105.41	114.25	111.11	110.49	121.20	122.82	134.88
NASDAQ Pharmaceutical	100.00	104.64	111.83	112.59	102.70	106.34	96.94	103.87	100.40	94.57	99.94

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

Information about securities authorized for issuance under our equity compensation plans is set forth in our Proxy Statement for the 2018 Annual Meeting of Stockholders to be filed with the SEC within 120 days of December 31, 2017, and is incorporated into this Annual Report on Form 10-K by reference.

Recent Sales of Unregistered Securities

On June 22, 2017, the Company entered into a Securities Purchase Agreement (the "Purchase Agreement") with a syndicate of current and new institutional investors, led by an affiliate of Deerfield Management Company, L.P., pursuant to which the Company agreed to issue and sell to the investors an aggregate of 22,000 shares of the Company's Series A Convertible Preferred Stock, par value $0.001 per share (the "Preferred Shares"), for a purchase price of $1,000 per share, or an aggregate gross purchase price of $22.0 million, all upon the terms and conditions set forth in the Purchase Agreement. The Company closed the transaction on August 2, 2017. The offer and sale of the Preferred Shares was not registered under the Securities Act, in reliance on the exemption from registration provided by Section 4(a)(2) of the Securities Act and/or Rule 506 of Regulation D promulgated thereunder. Each of the Investors has represented to the Company that they qualify as an "accredited investor" as that term is defined in Rule 501 under the Securities Act.

Issuer 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.

Item 6. Selected Financial Data

The selected consolidated statements of operations data for each of the three years ended December 31, 2017, 2016 and 2015, and the selected consolidated balance sheet data at December 31, 2017 and 2016 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, 2014 and 2013 and the selected consolidated balance sheet data at December 31, 2015, 2014 and 2013 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,				
	2017	2016	2015	2014	2013
	(in thousands, except share and per share data)				
Revenue	$-	$-	$-	$2,948	$-
Operating expenses:					
Research and development	21,686	18,869	12,381	6,432	3,994
General and administrative	8,676	9,836	8,489	4,096	3,128
Total operating expenses	30,362	28,705	20,870	10,528	7,122
Loss from operations	(30,362)	(28,705)	(20,870)	(7,580)	(7,122)
Other income (expense):					
Investment income	259	193	144	24	4
Other income (expense)	139	(14)	(651)	5,071	67
Total other income (expense)	398	179	(507)	4,238	(790)
Net loss	$(29,964)	$(28,526)	$(21,377)	$(3,342)	$(7,912)
Foreign currency translation adjustment	$6	$-	$-	$-	$-

Unrealized (loss) gain on available-for-sale investments	(20)	11	(5)	(6)	(1)
Comprehensive loss	$(29,978)	$(28,515)	$(21,382)	$(3,348)	$(7,913)
Reconciliation of net loss to net loss attributable to common stockholders:					
Net loss	$(29,964)	$(28,526)	$(21,377)	$(3,342)	$(7,912)
Accretion of redeemable convertible preferred stock to redemption value	-	-	-	(6,353)	(6,119)
Accretion of convertible preferred stock to redemption value	(6,747)	-	-	-	-
Net loss attributable to common stockholders	$(36,711)	$(28,526)	$(21,377)	$(9,695)	$(14,031)
Net loss per share attributable to common stockholders - basic and diluted	$(2.13)	$(1.72)	$(1.30)	$(3.16)	$(59.66)
Weighted-average common shares outstanding used in net loss per share attributable to common stockholders - basic and diluted	17,274,326	16,561,799	16,464,123	3,064,507	235,184

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	$1,109	$1,114	$650	$114	$106
General and administrative	2,118	2,229	1,514	345	49
Total	$3,227	$3,343	$2,164	$459	$155

	December 31,				
	2017	2016	2015	2014	2013
	(in thousands)				
Balance Sheet Data:					
Cash, cash equivalents and available-for-sale investments	$42,141	$41,317	$83,595	$5,152	$7,471
Working capital	34,240	37,676	82,263	(4,438)	6,499
Total assets	43,979	43,520	84,798	5,659	7,782
Convertible preferred stock	21,523	-	-	-	-
Preferred stock	-	-	-	96,405	90,286
Common stock and additional paid-in-capital	202,971	198,218	192,340	-	-
Total stockholders' equity (deficit)	34,739	38,441	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, is a recombinant human elastase that we are developing to improve vascular access outcomes in patients with chronic

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

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

As of December 31, 2017, we had received an aggregate of $197.2 million in net proceeds comprised of $115.5 million from the issuance of private equity securities, $7.7 million from the issuance of convertible notes, $10.0 million from business development activities, $0.2 million from government grants, $62.5 million from our IPO and $1.3 million from the sale of common stock under our at-the-market, or ATM, program with Cowen and Company, LLC.

We have never been profitable and have incurred net losses in each year since inception. As of December 31, 2017, we had an accumulated deficit of $189.7 million and our net loss for the year ended December 31, 2017 was $30.0 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, 2017 will be sufficient to fund our operating expenses and capital expenditure requirements into the fourth quarter of 2019. We believe that these funds will be sufficient to enable us to report top line data from the PATENCY-2 trial, our second Phase 3 trial of vonapanitase in radiocephalic fistulas, and to fund our ongoing development and chemistry, manufacturing and controls, or CMC, activities.

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

Recent Developments

On June 22, 2017, we entered into a Securities Purchase Agreement (the “Purchase Agreement”) with a syndicate of current and new institutional investors (collectively, the “Investors”), led by an affiliate of Deerfield Management Company, L.P., pursuant to which the Company agreed to issue and sell to the Investors an aggregate of 22,000 shares (the “Preferred Shares”) of the Company’s Series A Convertible Preferred Stock, par value $0.001 per share (the

"Transaction"), for a purchase price of $1,000 per share, or an aggregate purchase price of $22.0 million, all upon the terms and conditions set forth in the Purchase Agreement. We also entered into certain Voting Agreements and the Fifth Amended and Restated Investors' Rights Agreement in connection on June 22, 2017. We closed the Transaction on August 2, 2017.

The rights, preferences and privileges of the Series A Preferred Stock are set forth in a Certificate of Designation of Preferences, Rights and Limitations of Series A Convertible Preferred Stock that we filed on August 1, 2017, with the Secretary of State of the State of Delaware. The holders of a majority of the outstanding shares of Series A Convertible Preferred Stock are entitled to elect one (1) member of the Company's Board of Directors (the "Series A Director"). Jonathan Leff was elected as the Series A Director on August 2, 2017.

In addition, on August 2, 2017, we entered into a registration rights agreement with the Investors (the "Registration Rights Agreement"). On August 3, 2017, in accordance with the Registration Rights Agreement, we filed a registration statement on Form S-3 to register the resale of the common stock issuable upon conversion of the Preferred Shares.

Financial Overview

Research and Development Expenses

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

- employee-related expenses, including salaries, benefits, travel and stock-based compensation expense;

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

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

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

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

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

- We completed enrollment in our second Phase 3 trial, PATENCY-2, and expect to report top-line data in March 2019.
- we may, based on additional data including the data from our ongoing Phase 3 clinical trial and if sufficient funds become available, choose to conduct a clinical trial of vonapanitase in Europe;

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

- we initiated two Phase 1 clinical trials of vonapanitase in patients with peripheral artery disease (PAD) in the fourth quarter of 2016. These multicenter, dose-escalation trials are designed to evaluate the safety and technical feasibility of a single administration of vonapanitase as a monotherapy and as an adjunct to angioplasty for patients with PAD above the knee and below the knee, respectively. In 2018, we expect to complete the enrollment and treatment of 24 patients in the Phase 1 trial evaluating vonapanitase as an adjunct to angioplasty for PAD below the knee. Based on our current operating plan, we have decided not to begin patient enrollment in the Phase 1 trial evaluating vonapanitase as a monotherapy for PAD. However, if sufficient funds become available, we may increase enrollment in the Phase 1 trial evaluating vonapanitase below the knee and begin patient enrollment in the Phase 1 trial evaluating vonapanitase as a monotherapy above the knee;

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

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

Marketing, General and Administrative Expenses

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

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

Investment Income

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

Other Income (Expense), Net

Other income (expense), net consists of the gain realized from non-cash gains and losses from currency exchange rate fluctuations on transactions or balances denominated in a foreign currency 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 active pharmaceutical ingredient ("API") for our lead product candidate, vonapanitase, which requires us to make payments in Swiss Francs. The last outstanding forward foreign currency contract was executed during December 2016.

Derivative Financial Instruments

We purchase Swiss Francs or have entered into forward foreign currency contracts to reduce our foreign currency exposure in making contractual payments under our Lonza agreement. 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 the Swiss Francs we hold or in these derivative 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.

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.

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.

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,	
	2017	2016
Weighted average expected volatility	94.5%	84.4%
Expected term (in years)	6.06	6.05
Risk free interest rate	2.09%	1.45%
Expected dividend yield	0 %	0 %

Results of Operations

Comparison of the Years Ended December 31, 2017 and 2016

The following table summarizes our results of operations for the years ended December 31, 2017 and 2016 (in thousands):

	Years Ended December 31,		
	2017	2016	Period-to-Period Change
Operating expenses:			
Research and development	$21,686	$18,869	$ 2,817
General and administrative	8,676	9,836	(1,160)
Total operating expenses	30,362	28,705	1,657
Loss from operations	(30,362)	(28,705)	(1,657)
Other income (expense):			
Investment income	259	193	66
Other income (expense), net	139	(14)	153
Total other income	398	179	219
Net loss	$(29,964)	$(28,526)	$ (1,438)

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, 2017 and 2016 (in thousands):

	Year Ended December 31,		
	2017	2016	Period-to-Period Change
External vonapanitase research and development expenses	$16,955	$13,669	$ 3,286
Internal research and development expenses	4,731	5,200	(469)
Total research and development expenses	$21,686	$18,869	$ 2,817

During the year ended December 31, 2017, our total research and development expenses increased by $2.8 million compared to the year ended December 31, 2016 primarily due to $3.3 million in increased external expenses. The increase of $3.3 million in external expenses was primarily driven by $4.1 million in increased expenses for our manufacturing pre-validation and offset by $0.8 million in decreased expenses for our ongoing clinical trials. Our

internal research and development expenses decreased by $0.5 million in the year ended December 31, 2017 as compared to the year ended December 31, 2016 due primarily to decreased personnel costs.

Marketing, General and Administrative Expenses. During the year ended December 31, 2017, our total marketing, general and administrative expenses were $1.2 million lower as compared to the year ended December 31, 2016 primarily due to reductions in overhead and personnel costs in the year ended December 31, 2017 of $1.2 million to support our ongoing corporate activities.

Investment Income. During the year ended December 31, 2017, investment income increased by $0.1 million primarily due to an increase in interest income of $0.1 million.

Other Expense, Net. During the year ended December 31, 2017, other expense, increased by $0.2 million as compared to the year ended December 31, 2016 primarily due to foreign currency remeasurement gain for cash denominated in Swiss Francs and the change in the fair value associated with the forward foreign currency contracts we entered into in the second quarter of 2015. As of December 31, 2016, all forward foreign currency contracts had been settled and are no longer outstanding.

Comparison of the Years Ended December 31, 2016 and 2015

The following table summarizes our results of operations for the years ended December 31, 2016 and 2015 (in thousands):

	Years Ended December 31,		
	2016	2015	Period-to-Period Change
Operating expenses:			
Research and development	$18,869	$12,381	$ 6,488
General and administrative	9,836	8,489	1,347
Total operating expenses	28,705	20,870	7,835
Loss from operations	(28,705)	(20,870)	(7,835)
Other income (expense):			
Investment income	193	144	49
Other expense, net	(14)	(651)	637
Total other income (expense)	179	(507)	686
Net loss	$(28,526)	$(21,377)	$ (7,149)

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, 2016 and 2015 (in thousands):

	Year Ended December 31,		
	2016	2015	Period-to-Period Change
External vonapanitase research and development expenses	$13,669	$8,580	$ 5,089
Internal research and development expenses	5,200	3,801	1,399
Total research and development expenses	$18,869	$12,381	$ 6,488

During the year ended December 31, 2016, our total research and development expenses increased by $6.5 million compared to the year ended December 31, 2015 primarily due to $5.1 million in increased external expenses. The increase of $5.1 million in external expenses was primarily driven by $3.9 million in increased expenses for our manufacturing pre-validation and $1.2 million in increased expenses for our ongoing clinical trials. Our internal research and development expenses increased by $1.4 million in the year ended December 31, 2016 as compared to the year ended December 31, 2015 due primarily to increased personnel costs.

Marketing, General and Administrative Expenses. During the year ended December 31, 2016, our total marketing, general and administrative expenses were $1.3 million higher as compared to the year ended December 31, 2015 primarily due to additional overhead and personnel costs in the year ended December 31, 2016 of $1.6 million to support our ongoing corporate activities and offset by $0.3 million in lower expenses associated with being a public company.

Investment Income. During the year ended December 31, 2016, investment income increased by an immaterial amount.

Other Expense, Net. During the year ended December 31, 2016, other expense, net changed by $0.6 million as compared to the year ended December 31, 2015 due to the change in the fair value associated with the forward foreign currency contracts we entered into in the second quarter of 2015 and the Swiss Francs denominated currency we held as of the period end.

Liquidity and Capital Resources

Overview

Since our inception and through the year ended December 31, 2017, we had received $197.2 million in net proceeds comprised of $115.5 million from the issuance of private equity securities, $7.7 million from the issuance of convertible notes, $10.0 million from business development activities, $0.2 million from government grants, $62.5 million from our IPO and $1.3 million from the sale of common stock under our at-the-market, or ATM, program with Cowen and Company, LLC. At December 31, 2017, our cash and cash equivalents and available-for-sale investments totaled $42.1 million.

Series A Preferred Financing

On August 2, 2017 we received net proceeds of approximately $21.5 million from the issuance of Series A convertible preferred stock to new and existing investors at a price per share of $1,000. In aggregate, we issued 22,000 shares of Series A convertible preferred stock, each share of which is convertible into approximately 1,005 shares of our Common Stock at a conversion price of $0.9949 per share.

Operating Capital Requirements

We expect to incur increasing operating losses for at least the next several years as we (i) conduct our clinical trials for vonapanitase, thereafter seeking marketing approval for vonapanitase assuming successful trial outcomes, and (ii) pursue development of vonapanitase for additional indications, including brachiocephalic arteriovenous fistulas and grafts. 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, 2017 will be sufficient to fund our operations into the fourth quarter of 2019. We believe that these funds will be sufficient to enable us to report top line data from our second Phase 3 trial of vonapanitase in radiocephalic fistulas, named PATENCY-2 and to fund our ongoing development and CMC activities through this date.

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

- the timing and costs of our Phase 3 clinical trial of vonapanitase in radiocephalic fistulas;
- the timing and costs of developing vonapanitase for additional indications, including PAD;
- the outcome, timing and costs of seeking regulatory approvals;
- the costs of commercialization activities for vonapanitase in radiocephalic fistulas and other indications if we receive marketing approval, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;

- subject to receipt of marketing approval, revenue received from commercial sales of vonapanitase;
- the terms and timing of any future collaborations, licensing, consulting or other arrangements that we may establish;
- the amount and timing of any payments we may be required to make, or that we may receive, in connection with the licensing, filing, prosecution, defense and enforcement of any patents or other intellectual property rights, including royalty payments that we are obligated to pay to Johns Hopkins University pursuant to our assignment agreement related to vonapanitase;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending against intellectual property related claims; and
- the extent to which we in-license or acquire other products and technologies.

Cash Flows

The following table summarizes our sources and uses of cash for the years ended December 31, 2017 and 2016 (in thousands):

	Years Ended December 31,	
	2017	2016
Net cash used in operating activities	$(22,352)	$(23,687)
Net cash (used in) provided by investing activities	(16,099)	19,916
Net cash provided by financing activities	23,049	208
Effect of exchange rate changes on cash	180	(76)
Net decrease in cash and cash equivalents	$(15,222)	$(3,639)

Comparison of the Years Ended December 31, 2017 and 2016

Net cash used in operating activities was $22.4 million for the year ended December 31, 2017 compared to $23.7 million for the year ended December 31, 2016. The decrease of $1.3 million in cash used in operating activities was primarily driven by a $2.7 million decrease in cash inflows related to changes in the components of working capital offset by an increase in our net loss of $1.4 million, as compared to the year ended December 31, 2016.

Net cash used in investing activities was $16.1 million for the year ended December 31, 2017 compared to $19.9 million provided in the year ended December 31, 2016. The change of $36.0 million in cash used in investing activities was primarily driven by a decrease in cash inflows of $43.0 million due to decreased proceeds from maturities and sale of investments offset by a decrease in cash outflows of $6.8 million due to decreased purchases of available-for-sale investments and a decrease in cash outflows of $0.2 million due to decreased capital equipment purchases as compared to the year ended December 31, 2016.

Net cash provided by financing activities for the year ended December 31, 2017 increased by $22.8 million compared to the year ended December 31, 2016 due to net proceeds of $21.5 million from our preferred equity financing in August 2017 and $1.3 million from the sale of Common Stock under our ATM program.

The following table summarizes our sources and uses of cash for the years ended December 31, 2016 and 2015 (in thousands):

	Years Ended December 31,	
	2016	2015
Net cash used in operating activities	$(23,687)	$(17,566)
Net cash provided by (used in) investing activities	19,916	(11,331)
Net cash provided by financing activities	208	163
Effect of exchange rate changes on cash	(76)	(75)
Net decrease in cash and cash equivalents	$(3,639)	$(28,809)

Comparison of the Years Ended December 31, 2016 and 2015

Net cash used in operating activities was $23.7 million for the year ended December 31, 2016 compared to $17.6 million for the year ended December 31, 2015. The increase of $6.1 million in cash used in operating activities was primarily driven by an increase in our net loss of $7.1 million offset by a $1.0 million increase in cash inflows related

to changes in the components of working capital, as compared to the year ended December 31, 2015.

Net cash provided by investing activities was $19.9 million for the year ended December 31, 2016 compared to $11.3 million used in the year ended December 31, 2015. The change of $31.2 million in cash provided by investing activities was primarily driven by a decrease in cash outflows of $48.9 million due to decreased purchases of available-for-sale investments of $48.9 million offset by a decrease in cash inflows of $17.6 million due to decreased proceeds from maturities and sale of investments and an increase in cash outflows of $0.1 million due to increased capital equipment purchases as compared to the year ended December 31, 2015.

Net cash provided by financing activities for the year ended December 31, 2016 increased by approximately $0.1 million compared to the year ended December 31, 2015 due to an increase in the proceeds from stock option exercises.

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, 2017:

	Total	Less than 1 Year	1 to 3 Years	3 to 5 Years	More than 5 Years
Operating Leases (1)	$ 477	270	207	-	-
Purchase Obligations (2)	CHF7,600	5,700	1,900	-	-

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

(2) In July 2015, we entered into a manufacturing services agreement with Lonza Ltd ("Lonza") for the processing, development and manufacturing of the active pharmaceutical ingredient, or API, in our lead product candidate, vonapanitase. Purchase obligations include contractual arrangements in the form of purchase orders with Lonza, where there is a fixed non-cancelable payment schedule. We have one purchase obligation of 7.6 million Swiss Francs for work performed during 2017 and 2018 totaling 5.7 million Swiss Francs and for work to be performed by the end of 2019 totaling 1.9 million Swiss Francs.

The contractual obligation table does 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, 2017, we had cash equivalents and available-for-sale investments of $42.1 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. The last outstanding forward foreign currency contract was executed during December 2016.

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 and incorporated by reference herein. 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, 2017, 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, 2017, our disclosure controls and procedures were effective at the reasonable assurance level.

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

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, 2017.

Changes in Internal Control Over Financial Reporting.

During the year ended December 31, 2017, 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.

This Annual Report on Form 10-K does not include an attestation report of the Company's registered public accounting firm regarding internal control over financial reporting. Management's report was not subject to attestation by the Company's registered public accounting firm pursuant to rules of the SEC and the JOBS Act that permit emerging growth companies like us to provide only management's report in this Annual Report on Form 10-K.

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 2018 Annual Meeting of Stockholders to be filed with the SEC within 120 days of December 31, 2017, 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 2018 Annual Meeting of Stockholders to be filed with the SEC within 120 days of December 31, 2017, 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 2018 Annual Meeting of Stockholders to be filed with the SEC within 120 days of December 31, 2017, 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 2018 Annual Meeting of Stockholders to be filed with the SEC within 120 days of December 31, 2017, 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 2018 Annual Meeting of Stockholders to be filed with the SEC within 120 days of December 31, 2017, and is incorporated into this Annual Report on Form 10-K by reference.

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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, 2017 and 2016

Consolidated Statements of Operations and Comprehensive Loss for the years ended December 31, 2017, 2016 and 2015

Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity for the years ended December 31, 2017, 2016 and 2015

Consolidated Statements of Cash Flows for the years ended December 31, 2017, 2016 and 2015

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.

Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of Proteon Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Proteon Therapeutics, Inc. (the Company) as of December 31, 2017 and 2016, the related consolidated statements of operations and comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2017, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2017 and 2016, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2017, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting 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.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as

evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2008.

Boston, Massachusetts

March 14, 2018

Proteon Therapeutics, Inc.

Consolidated Balance Sheets

(in thousands, except share and per share data)

	December 31, 2017	December 31, 2016
Assets		
Current assets:		
Cash and cash equivalents	$21,170	$36,392
Available-for-sale investments	20,971	4,925
Prepaid expenses and other current assets	1,339	1,438
Total current assets	43,480	42,755
Property and equipment, net	259	372
Other non-current assets	240	393
Total assets	$43,979	$43,520
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$291	$556
Accrued expenses	8,949	4,523
Total current liabilities	9,240	5,079
Total liabilities	9,240	5,079
Commitments and contingencies (Note 7)		
Stockholders' equity:		
Series A convertible preferred stock, par value $0.001 per share, 22,000 and zero shares authorized, issued and outstanding at December 31, 2017 and 2016, respectively	21,523	-
Preferred stock, $0.001 par value per share; 10,000,000 shares authorized, no shares issued and outstanding at December 31, 2017 and 2016	-	-
Common stock, $0.001 par value, 100,000,000 shares authorized at December 31, 2017 and 2016; 17,674,729 and 16,603,559 shares issued and outstanding at December 31, 2017 and 2016, respectively	18	17
Additional paid-in capital	202,953	198,201
Accumulated deficit	(189,741)	(159,777)
Accumulated other comprehensive loss	(14)	-
Total stockholders' equity	34,739	38,441
Total liabilities and stockholders' equity	$43,979	$43,520

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,		
	2017	2016	2015
Operating expenses:			
Research and development	$21,686	$18,869	$12,381
General and administrative	8,676	9,836	8,489
Total operating expenses	30,362	28,705	20,870
Loss from operations	(30,362)	(28,705)	(20,870)
Other income (expense):			
Investment income	259	193	144
Other income (expense), net	139	(14)	(651)
Total other income (expense)	398	179	(507)
Net loss	$(29,964)	$(28,526)	$(21,377)
Foreign currency translation adjustment	$6	$-	$-
Unrealized (loss) gain on available-for-sale investments	(20)	11	(5)
Comprehensive loss	$(29,978)	$(28,515)	$(21,382)
Reconciliation of net loss to net loss attributable to common stockholders:			
Net loss	$(29,964)	$(28,526)	$(21,377)
Accretion of convertible preferred stock to redemption value	(6,747)	-	-
Net loss attributable to common stockholders	$(36,711)	$(28,526)	$(21,377)
Net loss per share attributable to common stockholders - basic and diluted	$(2.13)	$(1.72)	$(1.30)
Weighted-average common shares outstanding used in net loss per share attributable to common stockholders - basic and diluted	17,274,326	16,561,799	16,464,123
Supplemental disclosure of stock-based compensation expense 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	$1,109	$1,114	$650
General and administrative	2,118	2,229	1,514
Total	$3,227	$3,343	$2,164
Included in other expense, above, are the following amounts from forward foreign currency contracts:			
Realized losses from forward foreign currency contracts	$-	$(61)	$(52)
Unrealized gains (losses) from forward foreign currency contracts	-	127	(537)
Total	$-	$66	$(589)

See accompanying notes to these consolidated financial statements.

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Proteon Therapeutics, Inc.

Statements of Stockholders' Equity

(in thousands, except share and per share data)

	Series A Convertible Preferred Stock		Common Stock					
	Shares	Amount	Shares	$0.001 Par Value	Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive (Loss) Income	Total Stockholders' Equity
Balance at December 31, 2014	-	$-	16,448,455	$ 16	$192,324	$(109,874)	$ (6)	$ 82,460
Exercise of common stock options	-	-	45,413	-	88	-	-	88
Issuance of common stock upon ESPP purchase	-	-	7,632	-	75	-	-	75
Stock-based compensation expense	-	-	-	-	2,164	-	-	2,164
Unrealized gain (loss) on short term investments	-	-	-	-	-	-	(5)	(5)
Net loss	-	-	-	-	-	(21,377)	-	(21,377)
Balance at December 31, 2015	-	$-	16,501,500	$ 16	$194,651	$(131,251)	$ (11)	$ 63,405
Exercise of common stock options	-	-	97,521	1	196	-	-	197
Issuance of common stock upon ESPP purchase	-	-	4,538	-	11	-	-	11
Stock-based compensation expense	-	-	-	-	3,343	-	-	3,343
Unrealized gain on short term investments	-	-	-	-	-	-	11	11
Net loss	-	-	-	-	-	(28,526)	-	(28,526)
Balance at December 31, 2016	-	$-	16,603,559	$ 17	$198,201	$(159,777)	$ -	$ 38,441
Issuance of Series A Convertible Preferred Stock, net of issuance costs	22,000	14,776	-	-	6,747	-	-	21,523
Accretion of Series A Convertible Preferred Stock		6,747			(6,747)	-	-	-

Exercise of common stock options	-	-	74,001	-	108	-	-	108
Issuance of common stock upon ESPP purchase	-	-	100,358	-	130	-	-	130
Issuance of common stock, net of issuance costs			896,811	1	1,287			1,288
Stock-based compensation expense	-	-			3,227	-	-	3,227
Other comprehensive loss	-	-	-	-	-	-	(14)	(14)
Net loss	-	-	-	-	-	(29,964)	-	(29,964)
Balance at December 31, 2017	22,000	$21,523	17,674,729	$ 18	$202,953	$(189,741)	$ (14)	$ 34,739

See accompanying notes to these consolidated financial statements.

Proteon Therapeutics, Inc.

Consolidated Statements of Cash Flows

(in thousands)

	Year Ended December 31,		
	2017	2016	2015
Operating activities			
Net loss	$(29,964)	$(28,526)	$(21,377)
Reconciliation of net loss to net cash used in operating activities:			
Depreciation	148	123	57
Amortization of premium/discount on available-for-sale securities	(2)	131	651
Unrealized (gain) loss on forward foreign currency contracts included in net income	-	(127)	537
Foreign currency remeasurement (gain)/loss	(173)	76	75
Stock-based compensation	3,227	3,343	2,164
Changes in:			
Prepaid expenses and other assets	297	246	(899)
Interest receivable	(46)	(26)	(32)
Accounts payable and accrued expenses	4,161	1,073	1,258
Net cash used in operating activities	(22,352)	(23,687)	(17,566)
Investing activities			
Purchases of available-for-sale investments	(32,942)	(39,756)	(88,644)
Proceeds from maturities of available-for-sale investments	16,878	59,943	75,505
Proceeds from sale of available-for-sale investments	-	-	2,006
Purchase of property and equipment	(35)	(271)	(198)
Net cash (used in) provided by investing activities	(16,099)	19,916	(11,331)
Financing activities			
Proceeds from issuance of common stock, net of issuance costs	1,288	-	-
Proceeds from the issuance of Series A Convertible Preferred Stock, net of issuance costs	21,523	-	-
Proceeds from issuance of common stock under ESPP	130	11	75
Exercise of stock options	108	197	88
Net cash provided by financing activities	23,049	208	163
Effect of exchange rate changes on cash	180	(76)	(75)
Decrease in cash and cash equivalents	(15,222)	(3,639)	(28,809)
Cash and cash equivalents, beginning of period	36,392	40,031	68,840
Cash and cash equivalents, end of period	$21,170	$36,392	$40,031
Supplemental disclosure of non-cash investing and financing activities			
Accretion of convertible preferred stock	$6,747	$-	$-

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.

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

As of December 31, 2017, the Company had cash, cash equivalents and available-for-sale investments of $42.1 million. The Company believes that its existing cash, cash equivalents and available-for-sale investments will be sufficient to fund operations and capital expenditures into the fourth quarter of 2019. The Company had an accumulated deficit of $189.7 million as of December 31, 2017.

2. Summary of Significant Accounting Policies

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. The Registration Statement became effective on January 12, 2016. The Company pays Cowen a commission equal to 3% of the gross proceeds of the sales price of all shares sold through it as sales agent under the Sales Agreement. The offering costs are offset against proceeds from the sale of common stock under this agreement. The Company filed a prospectus supplement on March 16, 2017 because the Company is currently subject to General Instruction I.B.6 of Form S-3, which limits the amounts that the Company may sell under the Registration Statement. For the year ended December 31, 2017, the Company sold 896,811 shares of Common Stock under the Sales Agreement for aggregate gross proceeds of $1.4 million, respectively. For the year ending December 31, 2017, total offering costs of $0.1 million were offset against the proceeds from the sale of common stock.

Series A Preferred Financing

On June 22, 2017, the Company entered into a Securities Purchase Agreement (the "Purchase Agreement") with a syndicate of current and new institutional investors, led by an affiliate of Deerfield Management Company, L.P., pursuant to which the Company agreed to issue and sell to the investors an aggregate of 22,000 shares of the Company's Series A Convertible Preferred Stock, par value $0.001 per share (the "Transaction"), for a purchase price of $1,000 per share, or an aggregate gross purchase price of $22.0 million, all upon the terms and conditions set forth in the Purchase Agreement. The Company closed this Transaction on August 2, 2017 (see Note 8).

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

Basis of Presentation, Principles of Consolidation and Use of Estimates

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

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. On an ongoing basis, the Company's management evaluates its estimates, which include, but are not limited to, estimates related to stock-based compensation expense, clinical trial accruals and reported amounts of 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.

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

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

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

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

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

Financial instruments measured at fair value on a recurring basis include cash equivalents, available-for-sale investments and forward foreign currency contracts (see Note 3). There have been no changes to the valuation methods utilized by the Company during the years ended December 31, 2017 and 2016. 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, 2017 and 2016.

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 4). 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 does not expect this guidance to have a material impact on its condensed consolidated financial statements, if any.

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

In March 2016, the FASB issued ASU 2016-09, *Compensation - Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting* ("ASU 2016-09"), which simplifies various aspects of the accounting for share-based payments, including accounting for income taxes, earnings per share, and forfeitures. ASU 2016-09 is effective for annual periods beginning after December 15, 2016, and interim periods within those annual periods with early adoption permitted. The Company adopted ASU 2016-09 during the quarter ended March 31, 2017. As a result of adoption, the deferred tax assets associated with net operating losses increased by $0.6 million. These amounts were offset by a corresponding increase in the valuation allowance. In addition, the Company has elected to recognize the effect of forfeitures in compensation cost when they occur rather than estimate forfeitures in advance. The Company will reverse any previously recognized compensation cost for an award in the period that the award is forfeited. The adoption had an immaterial impact on the condensed consolidated financial statements.

In August 2016, the FASB issued ASU 2016-15, *Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments* ("ASU 2016-15"), which provides clarification regarding how certain cash receipts and cash payment are presented and classified in the statement of cash flows. This update addresses eight specific cash flow issues with the objective of reducing the existing diversity in practice. This update is effective for annual and interim periods beginning after December 15, 2017, which will require the Company to adopt these provisions in the first quarter of fiscal 2019 using a retrospective approach. Early adoption is permitted. The Company does not expect the adoption of this guidance to have a material impact on its consolidated financial statements.

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

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 and money market funds 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, 2017, 2016 and 2015.

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, 2017, 2016 and 2015, 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.

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

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.

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, 2017 and 2016, 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 11 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, and foreign currency translation 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, 2017 to ensure that this filing includes appropriate disclosure of events both recognized in the consolidated financial statements as of December 31, 2017 and events which occurred subsequently but were not recognized in the consolidated financial statements.

3. Fair Value Measurements

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

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

	As of December 31, 2016			
	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)	Total
Assets				
Cash equivalents	$28,876	$ -	$ -	$28,876
Government securities	4,925	-	-	4,925
Total	$33,801	$ -	$ -	$33,801

As of December 31, 2017, and 2016, the Company's cash equivalents consist principally of money market funds and government debt securities with original maturities of 90 days or less. Government securities consist principally of government debt securities and money market funds which are classified as available-for-sale.

Available-for-sale securities at December 31, 2017 and 2016 consist of the following (in thousands):

	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
December 31, 2017				
Government securities				
(Due within 1 year)	$20,991	$ -	$ (20)	$20,971
	$20,991	$ -	$ (20)	$20,971

December 31, 2016

Government securities				
(Due within 1 year)	$4,924	$ 1	$ -	$4,925
	$4,924	$ 1	$ -	$4,925

4. Derivative Financial Instruments

Beginning in May 2015 and through 2016, the Company purchased Swiss Francs and entered into a series of forward foreign currency contracts to mitigate its exposure to fluctuations in the U.S. dollar value of forecasted transactions denominated in Swiss Franc. The latter are considered derivative financial instruments that the Company records on the consolidated balance sheet at fair value. The Company elected not to apply hedge accounting to these instruments. As a result, during the year ended December 31, 2016, the Company experienced unrealized gains within other income (expense), net, in the consolidated statements of operations from the mark-to-market of outstanding forward foreign currency contracts. As of December 31, 2016, all forward foreign currency contracts had been settled and are no longer outstanding.

5. Property and Equipment, net

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

	As of December 31,	
	2017	2016
Computer equipment and software	$192	$141
Furniture, fixtures, and other	302	318
Laboratory equipment	477	478
	971	937
Accumulated depreciation	(712)	(565)
Property and equipment, net	$259	$372

Depreciation expense for the years ended December 31, 2017, 2016 and 2015 was $0.1 million, $0.1 million, and $0.1 million, respectively.

6. Accrued Expenses

Accrued expenses consist of the following (in thousands):

	As of December 31,	
	2017	2016
Payroll and employee-related costs	$1,318	$1,139
Contracted service costs	7,218	2,891
Professional fees and other	413	493
Total	$8,949	$4,523

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, 2017 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, or ("Lonza") for the processing, development and manufacturing of the active pharmaceutical ingredient ("API") in its lead product candidate, vonapanitase. Under the agreement, the Company will issue purchase orders authorizing Lonza to manufacture API 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, 2017, the Company has issued a purchase order for 7.6 million Swiss Francs, approximately $7.8 million at current exchange rates, for the manufacturing of three batches that commenced in July 2017 and one batch to commence by the end of 2019. As of December 31, 2017, nearly all of the services related to the three batches that commenced in July 2017 have been rendered under this purchase order.

Operating Leases

The Company has various non-cancellable operating leases for facilities and office equipment that expire at various dates through 2019. In August 2017, 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 (i) extend the term of the lease for a period of fifteen (15) months from June 30, 2018 until September 30, 2019 and (ii) increase the Company's office space under the Lease Agreement by 2,552 square feet of additional property for a total of approximately 7,500 square feet of property (the "Leased Property"). The Leased Property is located at 200 West St., Waltham, Massachusetts. In addition, the Company has the option to extend the term of the Lease Agreement for an additional one-year period upon the Company's written notice to the Lessor at least six months prior to the expiration of the term. Rental expense for each of the years ended December 31, 2017, 2016 and 2015 was $0.2 million.

Future minimum payments required under operating leases as of December 31, 2017 are summarized as follows (in thousands):

Year Ending December 31:	Amount
2018	$ 270
2019	207
Total minimum lease payments	$ 477

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, 2017, the Company has provided a security deposit in the amount of $22,000 to the lessor.

Restricted cash related to facilities leases

At December 31, 2017 and 2016, the Company had $22,000 and $14,000, respectively, in an outstanding letter of credit to be used as collateral for leased premises. At December 31, 2017 and 2016, the Company pledged an aggregate of $22,000 and $14,000, respectively, to the bank as collateral for the letter of credit, which is included in other non-current assets.

8.Series A Preferred Financing

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

Upon issuance, each share of Series A Preferred included an embedded beneficial conversion feature as the market price of the Company's Common Stock on the date of issuance of the Series A Preferred was $1.30 per share. As a result, the Company recorded the intrinsic value of the beneficial conversion feature of $6.7 million as a discount on

the Series A Preferred at issuance. As the Series A Preferred is immediately convertible upon issuance and does not include a stated redemption date, the discount on the Series A Preferred was immediately accreted.

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

Dividends

Holders of the Series A Preferred Stock are entitled to receive dividends, if and when declared by the Board of Directors.

Liquidation Preference

Holders of the Series A Preferred Stock have preference in the event of a liquidation or dissolution of the Company equal to $0.001 per share, plus any declared dividends.

Thereafter, the Holders of the shares of Series A Preferred Stock shall share ratably in any distributions and payments of any remaining assets of the Company, on an as converted basis, with the holders of Common Stock.

Voting Rights

Except for matters with specific voting rights as provided in the Series A Preferred Stock Purchase Agreement, the Holders of shares of Series A Preferred Stock have no voting rights.

9. Common Stock

General

At December 31, 2017, the Company has 100,000,000 shares of Common Stock authorized for issuance, $0.001 par value per share, of which 17,674,729 shares were issued and outstanding.

Reserved for Future Issuance

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

	December 31, 2017	December 31, 2016
Conversion of Series A Preferred Stock	22,112,775	-
Stock-based compensation awards	3,572,457	2,982,470
Employee Stock Purchase Plan	192,463	292,821
Total	25,877,695	3,275,291

10. 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"). On October 3, 2014, the stockholders approved these plans. The stockholders also approved an amendment to the 2014 Plan on July 31, 2017.

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.

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,		
	2017	2016	2015
Research and development	$1,109	$1,114	$650
General and administrative	2,118	2,229	1,514
Total	$3,227	$3,343	$2,164

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,		
	2017	2016	2015
Weighted average expected volatility	94.5%	84.4%	79.8%
Expected term (in years)	6.06	6.05	6.11
Risk free interest rate	2.09%	1.45%	1.76%
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, 2017, 2016 and 2015 was $0, $0 and $2,000, 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, 2016	2,166,254	$ 8.55	7.1	$ 124
Granted	719,337	$ 1.99		
Exercised	(74,001)	$ 1.45		
Forfeited	(30,272)	$ 10.69		
Expired	(100,246)	$ 2.60		

Outstanding at December 31, 2017	2,681,072	$ 7.18	6.8	$ 121
Exercisable at December 31, 2017	1,495,789	$ 8.18	5.9	$ 85
Vested or expected to vest at December 31, 2017 (1)	2,681,072	$ 7.18	6.8	$ 121

(1) Represents the number of vested options at December 31, 2017 plus the number of unvested options expected to vest based on the unvested options outstanding at December 31, 2017.

During the year ended December 31, 2017, the Company granted stock options to purchase an aggregate of 719,337 shares of its Common Stock with a weighted-average grant date fair value of $1.99. During the year ended December 31, 2016, the Company granted stock options to purchase an aggregate of 132,495 shares of its Common Stock with a weighted-average exercise price of $7.11 and a weighted-average grant date fair value of $5.08. 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 grant date fair value of $9.34

The total intrinsic value of options exercised in the years ended December 31, 2017 and 2016 was $27,000 and $0.6 million, respectively. As of December 31, 2017, there was $4.2 million of total unrecognized compensation cost related to employee non-vested stock options. 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 1.95 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, 2017, 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, 2018. The sixth offering under the 2014 ESPP began on July 1, 2017 and ended on December 31, 2017. During the years ended December 31, 2017 and 2016, 100,358 and 4,538 shares, respectively, were issued under the 2014 ESPP resulting in 192,463 shares remaining for future issuance under the plan as of December 31, 2017. The Company incurred $0.1 million and $0.1 million in stock-based compensation expense related to the 2014 ESPP for the years ended December 31, 2017 and 2016, respectively.

11. Income Taxes

The components of income from operations before income taxes are as follows (in thousands):

	Year Ended December 31,		
	2017	2016	2015
Domestic	$(24,803)	$(15,860)	$(21,377)
Foreign	(5,161)	(12,666)	-
Loss before income taxes	$(29,964)	$(28,526)	$(21,377)

For the years ended December 31, 2017, 2016, 2015, the Company has not recorded a provision for federal or state income taxes as it has had net operating losses since inception.

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

	Year Ended December 31,		
	2017	2016	2015
Income tax benefit using U.S. federal statutory rate	$(10,186)	$(9,696)	$(7,315)
Permanent differences	4	430	260
Stock Compensation - Perm Items	689	-	-
R&D Credit -Perm Items	1,751	1,437	1,310

State income taxes, net of federal benefit	(853)	(498)	(808)
Tax credits	(5,495)	(4,846)	(4,219)
Change in valuation allowance	(54,319)	8,804	9,782
Foreign rate differential	1,752	4,304	-
Rate change	2,202	-	-
382 Limitation	64,975	-	-
Other	(520)	65	990
	$-	$-	$-

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

	Year Ended December 31,		
	2017	2015	2014
Net operating loss carryforwards	$2,651	$42,156	$34,488
Federal and state tax credits	2,244	21,223	16,404
Accrued expenses	399	544	27
Patents	191	360	443
Stock-based compensation	1,262	1,353	596
Other	202	320	276
	6,949	65,956	52,234
Valuation allowance	(6,949)	(65,956)	(52,234)
Net deferred tax asset	$-	$-	$-

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, 2017, 2016, and 2015.

On December 22, 2017, the President of the United States signed into law the Tax Cuts and Jobs Act (“TCJA”) tax reform legislation. This legislation makes significant changes in U.S. tax law including a reduction in the corporate tax rates, changes to net operating loss carryforwards and carrybacks, and a repeal of the corporate alternative minimum tax. The legislation reduced the U.S. corporate tax rate from the current rate of 34% to 21%. As a result of the enacted law, the Company was required to revalue deferred tax assets and liabilities at the enacted rate. This revaluation resulted in a decrease in net deferred tax asset of $2.2 million and a corresponding reduction in the valuation allowance against these assets. There is no impact to income tax expense. The other provisions of the Tax Cuts and Jobs Act did not have a material impact on the 2017 consolidated financial statements. Our preliminary estimate of the TCJA and the remeasurement of our deferred tax assets and liabilities is subject to the finalization of management’s analysis related to certain matters, such as developing interpretations of the provisions of the TCJA, changes to certain estimates and the filing of our tax returns. U.S. Treasury regulations, administrative interpretations or court decisions interpreting the TCJA may require further adjustments and changes in our estimates. The final determination of the TCJA and the remeasurement of our deferred assets and liabilities will be completed as additional information becomes available, but no later than one year from the enactment of the TCJA

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 (“§382 limitation”). This could substantially limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the Company's value immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. On August 2, 2017, the Company completed a financing transaction for $22.0 million. As a result of this transaction, the company performed a study to review the application of IRC §382 and §383 to the Company. It was determined there was an ownership change as of the date of this financing and the Company’s NOLs generated prior to August 2, 2017 would be fully limited. Therefore, the NOLs and credits generated prior to August 2, 2017 have been written down to zero. This represents a decrease in Federal NOLs of approximately $107.3 million ($34.1 million tax affected) and a decrease in federal credits of $23.8 million. State NOLs and credits were also fully limited as a result of this ownership change. The state NOLs were reduced by approximately $5.0 million and credits were reduced by $2.1 million.

As a result of current year activity, the valuation allowance increased by approximately $13.1 million during the year ended December 31, 2017. This was due primarily to the addition of Orphan Drug Tax credits and the generation of net operating losses. However, this increase was offset by a reduction of $65.0 million due the §382 limitation and a reduction of $2.2 million due to the change in tax rate. Therefore, there was an overall decrease to the valuation allowance of $54.1 million. The valuation allowance increased by approximately $8.8 million during the year ended December 31, 2016, due primarily to the addition of Orphan Drug Tax credits and the generation of net operating losses. The valuation allowance increased by 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.

Subject to the limitations described above, as of December 31, 2017, 2016, and 2015, the Company has net operating loss carryforwards of approximately $10.6 million, $101.4 million, and $94.2 million, respectively, to offset future federal taxable income, which will expire during 2037. As of December 31, 2017, 2016, and 2015, the Company has state net operating loss carryforwards of approximately $6.8 million, $53.0 million, and $46.4 million, respectively, to offset future state taxable income, which will expire at various times between 2032 and 2037. As of December 31, 2017, 2016 and 2015, the Company has tax credit carryforwards of approximately $2.3 million, $21.8 million and $16.9 million, respectively, to offset future federal and state income taxes, which will expire at various times between 2022 and 2037.

The Company had no unrecognized tax benefits or related interest and penalties accrued during the years ended December 31, 2017, 2016, and 2015. 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, 2014 through 2017, although carryforward attributes that were generated prior to tax year 2014 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.

The Company has adopted ASU 2016-09, Improvements to Employee Share-Based Payment Accounting, for the quarter ended March 31, 2017. As a result of adoption, the deferred tax assets associated with net operating losses were increased by $0.6 million. These amounts were offset by a corresponding increase in the valuation allowance.

12. 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, 2017, 2016 and 2015 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:

	Year Ended December 31,		
	2017	2016	2015
Outstanding stock options	2,681,072	2,166,254	2,200,369
Convertible preferred stock	22,112,775	-	-
	24,793,847	2,166,254	2,200,369

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

The following table contains selected quarterly financial information from 2017 and 2016. The Company believes that the following information reflects all normal recurring adjustments necessary for a fair statement of the information for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period.

	Three Months Ended			
	March 31, 2017	June 30, 2017	September 30, 2017	December 31, 2017
Operating expenses	$6,480	$5,986	$12,306	$5,590
Net loss attributable to common stockholders	(6,498)	(5,608)	(19,054)	(5,551)
Net loss per share attributable to common stockholders:				
Basic and Diluted	$(0.39)	$(0.33)	$(1.08)	$(0.33)
Weighted-average common shares outstanding used in net loss per share attributable to common stockholders:				

Basic and Diluted	16,636,201	17,207,672	17,619,418(a)	17,619,418

	Three Months Ended			
	March 31, 2016	June 30, 2016	September 30, 2016	December 31, 2016
Operating expenses	$6,819	$7,854	$7,166	$6,866
Net loss attributable to common stockholders	(6,552)	(7,905)	(7,107)	(6,962)
Net loss per share attributable to common stockholders:				
Basic and Diluted	$(0.40)	$(0.48)	$(0.43)	$(0.42)
Weighted-average common shares outstanding used in net loss per share attributable to common stockholders:				
Basic and Diluted	16,507,586	16,561,239	16,582,276	16,595,502

(a) Adjusted to correct an immaterial error in the weighted-average share calculation in the Company's Form 10-Q as of September 30, 2017.

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, 2018
Timothy P. Noyes

President and Chief Executive Officer

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, 2018
/s/ George A. Eldridge George A. Eldridge	Senior Vice President, Chief Financial Officer, Treasurer and Secretary *(Principal Financial and Accounting Officer)*	March 14, 2018
/s/ Paul J. Hastings Paul J. Hastings	Chairman and Director	March 14, 2018

/s/ Hubert Birner Hubert Birner, Ph.D.	Director	March 14, 2018
/s/ Garen Bohlin Garen Bohlin	Director	March 14, 2018
/s/ Scott A. Canute Scott Canute	Director	March 14, 2018
/s/ John G. Freund, M.D. John G. Freund, M.D.	Director	March 14, 2018
/s/ Tim Haines Tim Haines	Director	March 14, 2018
/s/ Stuart A. Kingsley Stuart A. Kingsley	Director	March 14, 2018
/s/ Jonathan Leff Jonathan Leff	Director	March 14, 2018

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).
3.2	Certificate of Designation of Preferences, Rights and Limitations of Series A Convertible Preferred Stock, dated August 1, 2017 (incorporated by reference to Exhibit 3.1 of Current Report on Form 8-K, filed on August 3, 2017).
3.3	Second Amended and Restated By-laws of Proteon Therapeutics, Inc. (incorporated by reference to Exhibit 3.2 of Current Report on Form 8-K, filed on August 3, 2017).
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).
4.2	Fifth Amended and Restated Investors' Rights Agreement, dated June 22, 2017, by and among Proteon Therapeutics, Inc. and the stockholders party thereto (incorporated by reference to Exhibit 4.18 of Current Report on Form 8-K, filed on June 23, 2017).
4.3	Registration Rights Agreement, dated as of August 2, 2017 by and between Proteon Therapeutics, Inc. and the Investors party thereto (incorporated by reference to Exhibit 4.1 of Current Report on Form 8-K, filed on August 3, 2017).
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 †	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).
10.3	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).
10.4	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).
10.5	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).

10.6	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).
10.7	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).

10.8		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).
10.9	†	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).
10.10	†	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).
10.11	†	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).
10.12	†	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).
10.13	†	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).
10.14	†	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).
10.15		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).
10.16		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).
10.17	‡	Amendment to Manufacturing Services Agreement by and between the Company and Lonza LTD entered into on January 21, 2016 (incorporated by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q for the quarter ended March 31, 2016 filed on May 9, 2016).
10.18	†	Amendment No. 1 to Employment Agreement by and between the Company and George Eldridge dated as of March 15, 2017 (incorporated by reference to Exhibit 10.19 to the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2016 filed on March 16, 2017).
10.19		Securities Purchase Agreement, dated as of June 23, 2017, by and among the Company and the purchasers party thereto (incorporated by reference to Exhibit 10.20 of Current Report on Form 8-K, filed on June 23, 2017).
10.20	†	Amended and Restated 2014 Equity Incentive Plan of Proteon Therapeutics, Inc. (incorporated by reference to Exhibit 10.1 of Current Report on Form 8-K, filed on August 3, 2017).

10.21		Fourth Amendment to Lease by and between Proteon Therapeutics, Inc. and Boston Properties Limited Partnership, dated August 17, 2009 (incorporated by reference to Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q for the quarter ended September 30, 2017 filed on November 7, 2017).
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	***	Principal Executive Officer Certification and Principal Financial Officer Certification Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	*	Interactive Data Files Pursuant to Rule 405 of Regulation S-T: (i) the Consolidated Balance Sheets as of December 31, 2017 and 2016; (ii) the Consolidated Statements of Operations and Comprehensive Loss for the years ended December 31, 2017, 2016, and 2015; (iii) the Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity for the years ended December 31, 2017, 2016, and 2015; (iv) the Consolidated Statements of Cash Flows for the years ended December 31, 2017, 2016, and 2015; and (v) the notes to the Consolidated Financial Statements.

*Exhibits filed herewith

** Exhibits furnished herewith.

*** This exhibit shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 or otherwise subject to the liabilities of the Section, nor shall it be deemed incorporated by reference in any filings under the Security Act of 1933 or the Securities Exchange Act of 1934, whether made before or after the date hereof and irrespective of any general incorporation language in any filing.

†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.