Mast Therapeutics, Inc.
Form 10-K
March 14, 2016

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2015

or

¨TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission File No. 001-32157

Mast Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware (State or other jurisdiction of incorporation or organization)	84-1318182 (I.R.S. Employer Identification No.)
3611 Valley Centre Dr., Suite 500, San Diego, CA (Address of principal executive offices)	92130 (Zip Code)

(858) 552-0866

(Registrant's telephone number, including area code)

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

Title of each class:	Name of each exchange on which registered:
Common Stock, par value $0.001 per share	NYSE MKT LLC

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. Yes ¨ No x

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

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 periods that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes x No ¨

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

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statement incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. x

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

Large accelerated filer	¨	Accelerated filer	x
Non-accelerated filer	¨	Smaller reporting company	x

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant as of June 30, 2015 was approximately $77.0 million based upon the closing price of the registrant's common stock on the NYSE MKT reported for such date.

As of March 10, 2016, the registrant had 192,836,367 shares of its common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement to be filed subsequent to the date hereof with the Securities and Exchange Commission pursuant to Regulation 14A in connection with the registrant's 2016 annual meeting of stockholders are incorporated by reference into Part III of this report. Such definitive proxy statement will be filed with the Commission not later than 120 days after the end of the registrant's fiscal year ended December 31, 2015.

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Forward-Looking Statements

This Annual Report on Form 10-K, particularly in Item 1 "Business," and Item 7 "Management's Discussion and Analysis of Financial Condition and Results of Operations," and the information incorporated herein by reference, include forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including, but not limited to, statements regarding our business strategy, expectations and plans, our objectives for future operations and our future financial position. When used in this report, the words "believe," "may," "could," "will," "estimate," "continue," "anticipate," "intend," "indicate," "seek," "should," "would" and similar expressions are intended to identify forward-looking statements, though not all forward-looking statements contain these identifying words. We cannot guarantee that we actually will achieve the plans, intentions or expectations expressed in our forward-looking statements and you should not place undue reliance on them. Among the factors that could cause or contribute to material differences between our actual results and expectations indicated or implied by the forward-looking statements in this report include, but are not limited to: the risk that results from our Phase 3 study of vepoloxamer in sickle cell disease will not be positive or that the study may demonstrate statistical significance in the primary endpoint but that regulatory authorities determine it does not demonstrate sufficient magnitude of clinical relevance or provide adequate safety and tolerability data to provide the basis for submission of a new drug application; the risk that we are unable to raise sufficient additional capital on a timely basis or on acceptable terms, or at all, and are required to significantly reduce the scope of our operations, including by delaying or discontinuing investment in development and commercialization efforts for vepoloxamer in sickle cell disease and heart failure, and/or are not able to continue as a going concern; the risk that we may be required to repay our outstanding debt obligations on an accelerated basis and/or at a time that could be detrimental to our financial condition, operations and/or business strategy; our ability, or that of a future partner, to successfully develop, obtain regulatory approval for and then successfully commercialize our product candidates on our planned timeline, or at all; delays in the commencement or completion of clinical studies or manufacturing and regulatory activities necessary to obtain regulatory approval to commercialize our product candidates; suspension or termination of an ongoing clinical study, including due to patient safety concerns or capital constraints; the ability of our product candidates to demonstrate acceptable safety and efficacy in clinical studies; the risk that, even if our clinical trials are successful, the FDA or other regulatory authorities determine that additional studies or other development activities are required to support submission or approval of a new drug application; our ability to maintain our relationships with the single-source third-party manufacturers and suppliers for our clinical trial material and commercial products, to the extent we receive the requisite regulatory approvals, and the ability of such manufacturers and suppliers to successfully and consistently meet our manufacturing and supply requirements; the satisfactory performance of other third parties, including contract research organizations, on whom we rely significantly to conduct or assist in the conduct of our nonclinical testing, clinical studies, regulatory activities, and other aspects of our development programs; the potential for us to delay, reduce or discontinue development of a product candidate, partner it or sell our assets at inopportune times, or pursue less expensive but higher-risk and/or lower-return development paths if we are unable to raise sufficient additional capital as needed; the potential that we may enter into one or more collaborative arrangements, including partnering and licensing arrangements, for a product candidate, and the terms of any such arrangements; the extent to which we increase our workforce and our ability to attract and retain qualified personnel and manage internal growth; the extent of market acceptance of any of our product candidates for which we receive regulatory approval; the level of competition our product candidates face in the marketplace, if approved; the extent to which we acquire new technologies and/or product candidates and our ability to integrate them successfully into our operations; our ability to obtain and maintain effective patent coverage or other market exclusivity protections for our products and technologies without infringing the proprietary rights of others; claims against us for infringing the proprietary rights of third parties; healthcare reform measures and reimbursement policies that, if not favorable to our products, could hinder or prevent our products' commercial success; potential product liability exposure and, if successful claims are brought against us, liability for a product or product candidate; our ability to maintain compliance with NYSE MKT continued listing standards and maintain the listing of our common stock on the NYSE

MKT or another national securities exchange; and other risks and uncertainties described in Part I, Item 1A “Risk Factors” of this report.

We have based the forward-looking statements we make on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy, short-term and long-term business operations and objectives, and financial needs. However, in light of the risks and uncertainties outlined above, actual results may differ materially from expectations indicated by the forward-looking statements contained in, or incorporated by reference into, this report. We cannot guarantee future results, events, levels of activity, performance or achievement. Accordingly, you are cautioned not to place undue reliance on forward-looking statements. Except as required by law, we do not intend to update the forward-looking statements discussed in this report publicly or to update the reasons actual results could differ materially from those anticipated in these forward-looking statements, even if new information becomes available in the future.

Unless context requires otherwise, all references in this report to “our company,” “we,” “us,” “our,” or similar words refer to Mast Therapeutics, Inc. together with its consolidated subsidiaries.

PART I

Item 1. Business.

Overview

We are a biopharmaceutical company developing novel, clinical-stage therapies for serious or life-threatening diseases with significant unmet needs. We have built our product pipeline through the strategic acquisition of privately-held companies with clinical-stage assets and we currently are focused on developing new therapies for sickle cell disease, a chronic, genetic disorder classified as a rare, or orphan, disease in the United States and European Union, and for heart failure, a condition with a high unmet need for innovative treatment options.

We are leveraging our Molecular Adhesion & Sealant Technology, or MAST, platform, derived from over two decades of clinical, nonclinical, and manufacturing experience with purified and non-purified poloxamers, to develop vepoloxamer (also known as MST-188), our lead product candidate. Vepoloxamer has demonstrated multiple pharmacologic effects that may provide clinical benefit in a wide range of diseases and conditions typically characterized by impaired microvascular blood flow and/or damaged cell membranes. We initially focused on development of vepoloxamer for sickle cell disease and recently completed enrollment in a pivotal Phase 3 clinical study of vepoloxamer for the treatment of vaso-occlusive crisis in patients with sickle cell disease.

Our Phase 3 clinical study of vepoloxamer in sickle cell disease, known as the EPIC study, completed patient enrollment in February 2016 and we expect to report top-line data in the second quarter of 2016. The primary objective of the EPIC study is to demonstrate that vepoloxamer reduces the duration of vaso-occlusive crisis, a severely painful, debilitating, and recurring condition for which patients are hospitalized on average four to five days. An estimated 90,000 to 100,000 people in the United States have sickle cell disease and there are between 80,000 to 100,000 hospitalizations annually in the U.S. related to vaso-occlusive crisis and no approved treatment option for patients in the U.S. or outside of the U.S. to shorten the duration or reduce the severity of a crisis once underway. Treatment centers for sickle cell patients are concentrated in a relatively small number of metropolitan areas in the U.S. and European Union (EU) and, as a result, we believe we can use a small, focused sales force to effectively commercialize our product in the U.S. and EU, if approved. Vepoloxamer has orphan drug designation in the U.S. and EU for the treatment of sickle cell disease.

Vepoloxamer also is in Phase 2 clinical development for the treatment of heart failure with reduced ejection fraction, or HFrEF, also known as systolic heart failure or heart failure with reduced systolic function. Nonclinical studies of vepoloxamer in an animal model of advanced heart failure suggest that vepoloxamer can directly improve left ventricle contractile function by restoring cardiomyocyte membrane integrity, which can be expected to minimize calcium overload injury and improve cardiomyocyte survival. Our ongoing randomized, double-blind, placebo-controlled, multicenter Phase 2 study in which we plan to enroll approximately 150 patients, is evaluating a new formulation of vepoloxamer for the treatment of patients with chronic heart failure. In this study, vepoloxamer is being administered over three hours in an outpatient setting, with the intention of helping to demonstrate vepoloxamer’s practical utility for chronic heart failure patients. In addition, we have filed provisional patent applications claiming a new composition of matter and uses for the new formulation of vepoloxamer being tested in the study.

Our second product candidate, AIR001, is in Phase 2 clinical development for the treatment of heart failure with preserved ejection fraction, or HFpEF, also known as diastolic heart failure or heart failure with preserved systolic function. Data show there are approximately 5.7 million individuals with heart failure in the U.S. and that approximately 50% of patients hospitalized for heart failure have HFpEF. In February 2016, we announced positive top-line results from a 30-patient, randomized, double-blind, placebo-controlled Phase 2a study of AIR001 in patients with HFpEF. The study met its pre-specified primary endpoint, with the AIR001 treatment group showing a

statistically significant decrease in pulmonary capillary wedge pressure during exercise compared to the control group. Another investigator-sponsored Phase 2a study of AIR001 is ongoing and we anticipate interim data on a cohort of patients in May 2016. In addition, we are supporting a multicenter, randomized, double-blind, placebo-controlled crossover Phase 2 study of AIR001 in HFpEF designed by the Heart Failure Clinical Research Network (HFN) and sponsored by its Coordinating Center. The HFN is made up of premier clinical centers located across North America and was established to expedite clinical research on treatments and strategies to improve the management of acute and chronic heart failure. The Phase 2 study, known as the Inorganic Nitrite Delivery to Improve Exercise Capacity in HFpEF (INDIE-HFpEF) study, will enroll approximately 100 patients and is expected to begin in the third quarter of 2016.

Business Strategy

Our goal is to become a leading biopharmaceutical company developing, and in some cases commercializing, novel therapies for serious or life-threatening diseases with significant unmet needs. Near-term activities that underlie our business strategy include the following:

Complete the EPIC study and seek regulatory approval of vepoloxamer for the treatment of sickle cell crisis in the U.S. and EU. Our 388-patient EPIC study is the largest placebo-controlled clinical trial in sickle cell disease concluded to date. Following study conclusion and analysis of results, we plan to request one or more meetings with the U.S. Food and Drug Administration, or FDA, to help us gain alignment with the FDA on the contents and process for submission of a new drug application, or NDA, for vepoloxamer based in large part on the data from EPIC. Pending the outcome of our discussions with the FDA, assuming agreement to use the FDA's rolling review process potentially afforded by vepoloxamer's fast track designation for the treatment of vaso-occlusive crisis of sickle cell disease, we plan to submit portions of the NDA for vepoloxamer beginning in the fourth quarter of 2016 and complete the submission in the first quarter of 2017. We currently are planning for a six-month NDA review period following the FDA's filing decision, based on receiving a priority review designation. Concurrently with FDA review of our NDA, we intend to seek advice from the European Medicines Agency, or EMA, on submission of a Marketing Authorisation Application, or MAA, for vepoloxamer. Pending the outcome of those discussions, we currently plan to submit a MAA for vepoloxamer in the fourth quarter of 2017.

Independently commercialize vepoloxamer for the treatment of sickle cell crisis in the U.S. and EU. We intend to independently commercialize vepoloxamer, if approved, in the U.S. and EU. Data show that in the U.S. about 500 hospitals located in a relatively small number of metropolitan areas serve nearly 80% of sickle cell patients treated for vaso-occlusive crisis, and, in the EU, more than 50% of sickle cell patients reside in the United Kingdom and France, with most patients concentrated in the London and Paris metropolitan areas. Given this market concentration, we plan to build our own highly-focused hospital sales force of approximately 30 representatives and, assuming vepoloxamer receives FDA approval in the third quarter of 2017, launch in the U.S. by the end of 2017. We plan to hire approximately 10 additional sales representatives for the EU if vepoloxamer is approved by the EMA and would anticipate a 2018 launch in that territory. For additional discussion, see "Commercialization Strategy" below.

Advance clinical development of vepoloxamer in heart failure. As described above, we believe vepoloxamer may offer a new therapeutic approach for patients with heart failure and believe that our ongoing Phase 2 study of vepoloxamer in patients with chronic heart failure will help define the potential clinical utility of vepoloxamer for treatment of heart failure patients.

Advance clinical development of AIR001 in HFpEF. Results from prior clinical studies of AIR001, demonstrating decreases in right atrial and pulmonary capillary wedge pressures, as well as improvements observed in pulmonary vascular resistance and cardiac lusitrophy, support the potential benefit of AIR001 treatment for HFpEF patients and we plan to continue to advance its development in HFpEF. We anticipate interim data from a second investigator-sponsored Phase 2a study in HFpEF patients in May 2016. In addition, the HFN's INDIE-HFpEF study of AIR001 in approximately 100 patients is expected to begin in the third quarter of 2016. The HFN is recognized for robust enrollment in heart failure clinical trials and high scientific productivity and we expect this study to define the potential efficacy of AIR001 for the treatment of HFpEF.

Vepoloxamer

Vepoloxamer is purified poloxamer 188, a nonionic, block copolymer comprised of a central linear chain of hydrophobic polyoxypropylene flanked on both sides by linear hydrophilic polyoxyethylene chains. As discussed further below, we believe that for patient safety reasons, it is important to clearly identify and distinguish vepoloxamer

from non-purified poloxamers. Drug products with non-purified poloxamer 188 as the active pharmaceutical ingredient, or API, may have serious toxicity consequences and should not be substituted for or confused with drug products containing purified poloxamer 188. Accordingly, we sought a unique generic name from the United States Adopted Names (USAN) Council, and USAN subsequently assigned "vepoloxamer" as the unique generic name for purified poloxamer 188.

Studies have shown that vepoloxamer's mechanism of action is biophysical and driven by its ability to modulate cell membrane surface tension. Its hydrophobic polyoxypropylene core is believed to adhere to hydrophobic domains exposed on damaged cell membranes, restoring membrane integrity and reducing surface tensions that otherwise promote pathological adhesive interactions. Data suggest vepoloxamer does not interact with healthy cell membranes, which have a hydrophilic exterior surface. As the damaged area of the cell membrane repairs, vepoloxamer is removed from the cell surface and ultimately is excreted from the body, unchanged, primarily in the urine.

We are leveraging the MAST platform to develop vepoloxamer. Vepoloxamer is manufactured through a proprietary supercritical fluid extraction purification process applied to poloxamer 188. As described below, vepoloxamer was designed to preserve the activity of poloxamer 188, but eliminate certain impurities and other substances that we believe were the cause of the acute renal dysfunction observed in clinical studies of poloxamer 188 (non-purified) conducted by a prior sponsor.

The MAST Platform

The MAST platform describes the repository of both proprietary (to us) and non-proprietary poloxamer-related data, know-how, and other information that has been developed over the course of several decades by numerous sponsors, most recently by us. It reflects the accumulated knowledge of over 100 pharmacology studies, more than 15 clinical studies in multiple indications in which over 2,500 subjects have been exposed to poloxamer 188 or vepoloxamer, and experience manufacturing and purifying poloxamers. This knowledge, and those aspects that are proprietary to us in particular, provide us with unique insight into the mechanism of action of, and areas of potential clinical benefit with, vepoloxamer.

We believe the MAST platform provides us with key benefits as we develop vepoloxamer, including the ability to leverage existing data for its development in new indications and to protect the market for our products, if approved, not only through patent coverage but manufacturing-related trade secrets. For example, proof-of-concept in pharmacologic studies or experimental models has been demonstrated in a wide range of diseases and conditions and, for most new indications we pursue, we believe we will not need to re-conduct many of the preclinical activities that consume substantial time and resources in drug development (e.g., IND-enabling toxicology, pharmacokinetic, absorption/distribution/metabolism/excretion studies). By leveraging already-completed pre-clinical and Phase 1 clinical activities and safety data from the more than 2,500 subjects that have received poloxamer 188 or vepoloxamer in more than 15 clinical studies, we can focus on later-stage, higher-value activities, as well as save time and money (both in terms of the costs to conduct these activities and by maintaining a more streamlined infrastructure). In addition, unlike discrete small molecules, polymers (including vepoloxamer) are molecularly diverse; that is, polymers contain chemical species with varying structural characteristics. This molecule diversity makes polymers difficult to characterize, both chemically and physically. Without access to our testing methods and acceptance criteria for starting material and in-process and release specifications, and other know-how which we protect as trade secrets, generic and other follow-on manufacturers may be unable to adequately characterize products that are equivalent to vepoloxamer in the manner that regulatory agencies will require. As a result, we believe that generic and other follow-on manufacturers will be required to invest in and take the time to conduct large clinical studies to demonstrate the safety and efficacy of their follow-on products. We also are evaluating the development of a proprietary process for manufacturing API starting material, which we expect would further protect the markets for our vepoloxamer products, if approved.

Mechanism of Action

The cell membrane is comprised primarily of phospholipids, which form the fundamental structure of the cell membrane the phospholipid bilayer. This structure is critical to living cells because it forms a selectively-permeable barrier between the aqueous environments of the cell interior and exterior. The exterior surface of healthy cell membranes normally is hydrophilic. When a cell membrane is damaged, the interior hydrophobic regions of the lipid bilayer become exposed.

The cell membrane serves many functions, but one of its primary roles is to regulate the passage of ions and large molecules into and out of the cell and, in particular, to maintain critical transmembrane ion concentrations. Damaged cell membranes can result in unregulated diffusion of ions between the intracellular and extracellular environments. The integrity of a cell membrane can be compromised by chemical agents (e.g., air pollutants, free radicals, poisons),

physical trauma (e.g., electric shock, frostbite, radiation, thermal burns, hypovolemia) and disease. Cells have endogenous mechanisms for membrane repair, but membrane injury can exceed the cell's natural repair capacity. If the damage is not repaired, cell ion pumps become overwhelmed and subsequently deplete the cell's energy stores, leading to cell death.

After intravenous administration, vepoloxamer's hydrophobic polyoxypropylene core is believed to adhere to hydrophobic domains on cell membranes, which, as described above, become exposed when the membrane is damaged. At sites of adhesion, it physically occupies the available area, minimizing or preventing other hydrophobic adhesive interactions, while displacing water and causing lipid molecules to pack more tightly, effectively "sealing" the damaged area and arresting unchecked transport of ions across the membrane. Vepoloxamer does not bond covalently with the cell membrane and the adhesive interaction is reversible. When membrane phospholipid density is normalized, vepoloxamer is displaced from the cell membrane and returns to circulation where it is cleared through normal excretion pathways as described below under "Safety." While vepoloxamer adheres specifically to hydrophobic domains, these domains may be widespread in sick or injured patients. As a result, vepoloxamer's activity broadly targets hydrophobic domains, without regard to the cause of the underlying damage, and, as described below, simultaneously may resolve multiple pathophysiologic processes. At the same time, vepoloxamer has demonstrated little or no affinity for hydrophilic domains and, thus, does not interact with healthy cells.

Pharmacodynamics

Vepoloxamer is believed to exert multiple pharmacologic effects as a result of its adhesion to hydrophobic domains.

Hemorheologic. In nonclinical studies as well as in a sub-study of the Phase 3 study of vepoloxamer in patients with sickle cell disease experiencing vaso-occlusive crisis discussed below, vepoloxamer demonstrated that it improved blood flow, particularly in the microcirculation where the vast majority of oxygen and nutrient exchange occurs, and improved blood flow can be expected to improve tissue perfusion (and reperfusion following ischemia). Vepoloxamer is believed to impede the aggregation of red blood cells, or RBCs, by inhibiting the fibrin/fibrinogen cross-bridges that form between RBCs, causing them to aggregate. Since RBCs traverse microcapillaries in "single file," the presence in the circulation of RBC aggregates can significantly impair microvascular blood flow. Inhibiting RBC aggregation also reduces blood viscosity, allowing it to flow more readily, particularly in the low shear environment of the microcirculation. The anti-inflammatory and antithrombotic/pro-fibrinolytic properties described below also contribute to improved blood flow.

Cytoprotective. Vepoloxamer may protect cells by interrupting the pathological cascade associated with cell membrane dysfunction and the resulting unregulated diffusion of ions across the membrane. This cytoprotective effect provides time for the cell's natural repair mechanisms to restore the cell to normal functioning, of importance during reperfusion, when viable but damaged cells may not survive the oxidative stress resulting from the reintroduction of oxygenated blood.

Anti-inflammatory. Vepoloxamer may inhibit adhesion of circulating blood cells to the endothelium by competing for and physically occupying hydrophobic domains on vessel walls, which has anti-inflammatory effects. Endothelial cells line the interior surface of blood vessels, provide a smooth surface for the flow of blood and regulate the movement of water and dissolved materials between the blood and tissues. The initial step in the inflammatory cascade is adhesion of white blood cells to the endothelium. By blocking adhesive interactions between white blood cells and the vessel wall, vepoloxamer may help prevent an inflammatory process from beginning.

Antithrombotic/pro-fibrinolytic. Vepoloxamer may help reduce the pro-thrombotic state that may result from disease or injury. A thrombus, or blood clot, results from aggregation of platelets and clotting factors. Platelet activation, triggered by damage to a vessel wall, causes a cascade of further platelet activation eventually leading to formation of a thrombus. Disease or injury may cause this normal response to turn pathologic, leading to thrombosis, where the thrombus grows to the point of obstructing the flow of blood through the occluded vessel. Studies suggest that vepoloxamer inhibits weak platelet-activation stimuli (e.g., shear activation of platelets) and release of adenosine di-phosphate from RBCs, minimizing the self-perpetuating response that leads to thrombosis. However, vepoloxamer does not inhibit strong platelet-activation stimuli (e.g., platelet/receptor interactions directly at the endothelium). Accordingly, we believe vepoloxamer does not negatively affect normal hemostatic function, which is supported by data from multiple nonclinical studies. Further, vepoloxamer may facilitate fibrinolysis, the body's natural process of dissolving a thrombus. Vepoloxamer adheres to fibrin monomers during clot formation, making them larger and more readily degraded by plasmin, the endogenous fibrinolytic enzyme that dissolves formed clots.

Clinical Application

We believe the pharmacodynamic properties of vepoloxamer enable it simultaneously to address, or prevent activation of, multiple biochemical pathways that are central to the pathophysiology of a wide range of diseases. The microcirculation is responsible for the delivery of blood through the smallest blood vessels (arterioles and capillaries) embedded within tissues. A healthy endothelium is critical to a functional microcirculation. Without the regular delivery of blood and transfer of oxygen to tissue from the microcirculation, individual cells (in both the endothelium and tissue) are unable to maintain aerobic metabolism and, through a series of complex and interrelated events,

eventually die. If the microcirculatory insufficiency continues, the individual will suffer tissue necrosis, organ damage, and eventually, death.

Treatment with vepoloxamer can be expected to be most clinically impactful in diseases where improving microcirculatory insufficiency is central to improving clinical outcomes. Vepoloxamer may also have clinical utility in diseases where damaged cell membranes are unable to prevent the unregulated passage of calcium leading to calcium overload toxicity. Vepoloxamer has shown effectiveness in experimental models of heart failure and stroke. Poloxamer 188 has shown effectiveness in experimental models of hemorrhagic shock, muscular dystrophy, bypass surgery, deep hypothermic circulatory arrest, spinal cord injury, amniotic fluid embolism, acute ischemic bowel disease and burns.

Safety

As described above, vepoloxamer has little or no affinity for undamaged, hydrophilic domains and, thus, has no measurable interaction with healthy cells and tissues. In addition, the carbon/oxygen ether bonds that comprise the vepoloxamer backbone generally are accepted as insusceptible to metabolic pathways in humans. Thus, following administration, essentially all of the drug is recovered, unchanged, in the urine. A small amount is recovered in fecal biliary excretion, presumably following uptake by the reticuloendothelial system. The lack of metabolic breakdown and elimination by normal excretion pathways reduces concern over active metabolites driving unintended toxicities.

The safety of poloxamer 188 (both purified and non-purified) has been evaluated in more than 15 clinical studies in multiple indications in which over 2,500 subjects have received active drug. In these studies, it was generally well-tolerated, with the exception of renal toxicities associated with poloxamer 188 (non-purified); in particular, in a 2,950-patient, randomized, controlled study in acute myocardial infarction conducted by Burroughs Wellcome (now, GlaxoSmithKline), referred to as the CORE study. The therapeutic potential of non-purified poloxamer 188 was and is limited by these renal toxicities. A series of nonclinical studies conducted after the CORE study identified low molecular weight substances generated during the chemical process by which the poloxamer is synthesized that were associated with renal dysfunction. We believe these substances were primarily responsible for the acute renal dysfunction observed in clinical studies of poloxamer 188, including the CORE study, and are a principal reason why clinical development of poloxamer 188 was discontinued by Burroughs Wellcome.

To address the renal toxicity associated with poloxamer 188, a proprietary manufacturing and purification process was developed to remove certain low molecular weight substances present in poloxamer 188. In nonclinical studies, compared to poloxamer 188, vepoloxamer resulted in less accumulation in kidney tissue, lower levels of serum creatinine, less vacuolization of proximal tubular epithelium, and more rapid recovery from vacuolar lesions. No difference was observed in the efficacy of vepoloxamer compared to poloxamer 188.

In the seven clinical studies of vepoloxamer completed before the EPIC study, including the 255-patient, Phase 3 study in sickle cell disease known as Study C97-1248, which is discussed in more detail below, vepoloxamer was generally well-tolerated. Transient elevations in liver enzymes have been observed, though in each case levels returned to baseline during the follow-up period, except in subjects whose liver enzymes had been elevated at baseline. Importantly, in contrast to the acute renal dysfunction observed with poloxamer 188 (non-purified) in prior studies, including the CORE study, the effects on serum creatinine reported as adverse events among subjects who received vepoloxamer were comparable to those among subjects who received placebo.

Additionally, our thorough QT/QTc clinical study of vepoloxamer, or the TQT study, met its primary endpoint and demonstrated that, based on analysis of electrocardiograms, vepoloxamer did not have an adverse effect on cardiac repolarization, as measured by prolongation of the QT interval. Sixty four healthy volunteers received vepoloxamer and it was generally well-tolerated at both therapeutic and supratherapeutic doses. The TQT study was a four-period, four-arm, crossover design, randomized, placebo- and active-controlled clinical trial for the evaluation of the effect of therapeutic and supratherapeutic single-dose vepoloxamer on the QT/QTc intervals. No clinically significant elevations in creatinine were noted in any vepoloxamer arm.

Vepoloxamer – Phase 3 Product Candidate for the Treatment of Sickle Cell Disease

Overview of Sickle Cell Disease

Sickle cell disease is an inherited genetic disorder that affects millions of people worldwide. It is the most common inherited blood disorder in the U.S., where it is estimated to affect approximately 90,000 to 100,000 people. The annual cost of medical care in the U.S. for patients with sickle cell disease is estimated to exceed $1.0 billion.

Sickle cell disease is characterized by the “sickling” of red blood cells, which normally are disc-shaped, deformable and move easily through the microvasculature carrying oxygen from the lungs to the rest of the body. Sickled, or crescent-shaped, red blood cells, on the other hand, are rigid and sticky and tend to adhere to each other and the walls of blood vessels (the vascular endothelium).

The hallmark of the disease is recurring episodes of severe pain commonly known as sickle cell crisis or vaso-occlusive crisis. Vaso-occlusive crisis occurs when the proportion of sickled cells rises, leading to obstruction of small blood vessels and reduced blood flow to organs and bone marrow. This obstruction results in intense pain and tissue damage, including necrosis (tissue death). The frequency, severity and duration of these acute crises can vary considerably. Frequency may range from infrequent to more than monthly and duration is typically four to five days and may last a week or longer. Over a lifetime, the accumulated burden of damaged tissue frequently results in the loss of vital organ function and a greatly reduced lifespan. The average age of death of an individual with sickle cell disease is around 45 years.

In addition to vaso-occlusive crises, sickle cell patients can suffer many additional complications, including: acute chest syndrome, a respiratory distress syndrome that may arise in the course of an acute crisis; stroke, including silent stroke, which can result from a progressive narrowing of blood vessels, preventing oxygen from reaching the brain; pulmonary hypertension and heart failure; kidney dysfunction and chronic renal failure; bone necrosis of the hip and other major joints; frequent infections due to loss of splenic function and decreased immune function; leg ulcers; blindness; increased rate of complications from pregnancy; and chronic deep muscle and bone pain, even in the absence of acute vaso-occlusive pain.

Significant Unmet Need

Based on data available from the Healthcare Cost and Utilization Project (HCUP) group of databases, we estimate that there are approximately 80,000 to 100,000 hospitalizations related to vaso-occlusive crisis in the U.S. each year. In addition, although the number is difficult to measure, we estimate that the number of untreated vaso-occlusive crisis events is substantial and in the hundreds of thousands in the U.S. each year. If vepoloxamer is approved and as people with sickle cell disease are made aware of the new therapy, we believe that people who would otherwise suffer through a crisis at home may seek treatment.

We are not aware of any approved therapeutic agents for shortening the duration or reducing the severity of an ongoing vaso-occlusive crisis. For patients experiencing a vaso-occlusive crisis, treatment typically consists of hydration, oxygen and analgesia for pain, usually using narcotics. By improving microvascular blood flow and reducing tissue ischemia, vepoloxamer has the potential to reduce the severity and shorten the duration of vaso-occlusive crisis and improve patient outcomes.

Vepoloxamer Clinical Development in Sickle Cell Disease

Overview

In February 2016, we completed patient enrollment in our Phase 3 clinical study of vepoloxamer for the treatment of vaso-occlusive crisis in patients with in sickle cell disease, known as the EPIC study. We do not yet have results from EPIC. In prior-sponsor clinical studies, vepoloxamer was administered to 211 patients with sickle cell disease over four studies, three of which were for vaso-occlusive crisis, including the Phase 3 study known as Study C97-1248. The fourth study involved patients with acute chest syndrome. Encouraging results in early clinical studies warranted continued development.

In these prior-sponsor studies, vepoloxamer was generally well-tolerated. Based on an integrated analysis of all four clinical studies, the majority of adverse events reported were mild or moderate. The most common adverse events (incidence >20%) were fever, bilirubinemia direct, pruritus, vomiting, nausea, constipation, headache, tachycardia, pain, weight loss, bilirubinemia, and anemia. The tolerability of vepoloxamer did not change significantly with increasing exposure (increasing dose and/or duration). The safety profile was similar in children (ages 18 and younger) compared to adults. In Study C97-1248, which is discussed in detail below, no difference in the overall incidence of adverse events or serious adverse events was observed between the vepoloxamer and placebo (control) groups.

Ongoing and Planned Clinical Studies

Phase 3 Study (EPIC). The EPIC study was a randomized, double-blind, two-arm, placebo-controlled Phase 3 study. We expect to report top-line data from EPIC in the second quarter of 2016. The primary objective is to demonstrate that vepoloxamer reduces the duration of vaso-occlusive crisis, with the duration of crisis measured from the time a patient is randomized to the time at which the patient receives the last dose of parenteral opioid analgesic for the

treatment of vaso-occlusive crisis prior to hospital discharge. A total of 388 patients, ages four to 46, who have sickle cell disease and were experiencing acute pain typical of vaso-occlusive crisis and required treatment with parenteral opioid analgesia were randomized in EPIC. Using a two-sided alpha of 0.05, the study has approximately 90% power to detect a 16-hour difference between treatment arms, assuming an average crisis duration of 96 hours in the control arm and a coefficient of variation of greater than 50%. These assumptions were derived in part from proprietary analyses of the Preventing Acute Chest Syndrome by Transfusion Feasibility Study (PROACTIVE), which we believe enrolled a study population similar to that which would be enrolled in EPIC, and publicly available data on average duration of hospitalization for vaso-occlusive crisis. Using a two-sided alpha of 0.01, the study has approximately 85% power to detect a 24-hour difference between treatment arms. Secondary endpoints will compare the rate of re-hospitalization for vaso-occlusive crisis within 14 days of initial discharge from the hospital and the occurrence of acute chest syndrome within 120 hours of randomization. More than 75 study sites in 14 countries participated in EPIC, with approximately two-thirds of the sites located in the U.S. The average age of patients randomized in EPIC was 15 years and patients under age 18 accounted for approximately 71% of total subjects. Approximately 61% of patients randomized in EPIC were concurrently being treated with hydroxyurea.

Open-Label, Repeat-Exposure Extension Study (EPIC-E). During the second quarter of 2015, we initiated an open-label, multicenter extension study known as EPIC-E to expand our existing safety database regarding repeat exposure to vepoloxamer. The study is enrolling patients who have completed the EPIC study and are hospitalized for subsequent vaso-occlusive crisis. Other objectives of the study will be to assess the rate of re-hospitalization for recurrence of vaso-occlusive crisis and the occurrence of acute chest syndrome.

EPIC Sub-Study. It is generally believed that the long-term morbidity and early mortality associated with sickle cell disease is the consequence of a lifetime of repeated vaso-occlusive events and the ensuing ischemic end-organ damage. In fact, organ failure is the leading cause of premature death in adults with sickle cell disease. Vepoloxamer's hemorheologic and cytoprotective effects can be expected to improve tissue oxygenation, shorten the duration of vaso-occlusive crisis and limit the impact of each vaso-occlusive crisis that ultimately leads to end-organ dysfunction and failure. In 2014, we began enrolling patients participating in EPIC at selected U.S. study sites in a sub-study to investigate and quantify the effect of vepoloxamer on tissue oxygenation, utilizing a non-invasive, FDA-approved device, along with various biomarkers of tissue injury. At the time we completed EPIC enrollment, 22 EPIC patients had also participated in the sub-study. Although a multi-year or even multi-decade study would likely be required to demonstrate vepoloxamer's ability to improve long-term end-organ function in sickle cell patients, by measuring its effect on tissue oxygenation and tissue injury biomarkers during a vaso-occlusive crisis, we hope to gain insight into vepoloxamer's ability to reduce tissue damage during vaso-occlusive crisis.

Special Population Study. To further enhance the safety database for vepoloxamer in support of our NDA submission and to help guide dosage adjustments for renally impaired patients, we are enrolling a clinical pharmacokinetics study of vepoloxamer in approximately 40 patients with varying degrees of renal insufficiency. The study began in January 2016 and we expect to complete enrollment in the summer of 2016.

Prior-Sponsor Studies in Sickle Cell Disease

Phase 3 Study in Vaso-Occlusive Crisis (Study C97-1248). A Phase 3, multicenter, randomized, double-blind, placebo-controlled study of vepoloxamer enrolled 255 patients with sickle cell disease experiencing vaso-occlusive crisis. The study had initially planned to enroll 350 subjects. Signs of efficacy were observed in the primary endpoint, duration of crisis, but it did not reach statistical significance. An 8-hour decrease in the duration of crisis (approximately 132 hours in the treatment group compared to approximately 140 hours in the control group (p=0.072)) was observed in the intent-to-treat population (n=249). Notably, post hoc analyses identified a statistically significant and greater treatment effect in patients under 16 years of age. Among patients under 16 years of age (n=73), there was a 21.6-hour decrease in the duration of vaso-occlusive crisis in the treatment group compared to the control group (p=0.010), and among patients who received concomitant hydroxyurea (HU) (n=54), there was a 16-hour decrease in the duration of vaso-occlusive crisis in the treatment group compared to the control group (p=0.024).

A potentially significant limitation of Study C97-1248 is that it did not follow subjects until crisis resolution; rather, subjects were followed for 168 hours from randomization and any subject whose crisis had not resolved by 168 hours was, for purposes of determining that patient's duration of crisis, attributed a duration of exactly 168 hours. This truncation had a potentially significant effect on the duration of crisis reported in Study C97-1248, particularly because a substantial number of subjects did not achieve crisis resolution within 168 hours. However, a "responder's analysis," which analyzes the proportion of subjects who had achieved crisis resolution at 168 hours (without attribution), would not be affected by this truncation and may provide a more accurate picture of vepoloxamer's treatment effect in this setting. In a post-hoc responder's analysis of the intent-to-treat population (n=249), over 50% of subjects receiving study drug achieved crisis resolution within 168 hours, compared to 37% in the control group (p=0.02). In the under-16 age group, 60% of the treatment group achieved crisis resolution within 168 hours, compared to under 28% of the control group (p=0.009), and in the HU group, 46% of the treatment group achieved

crisis resolution within 168 hours compared to 22% of the control group (p=0.016).

Study C97-1248 was the first large, interventional clinical trial in sickle cell disease. We believe features of the study's design and the study enrolling only 255 patients, which was fewer than the originally-planned 350 patients, may have further diluted the treatment effect observed in the study, and its significance. In addition to eliminating arbitrary observation periods (e.g., 168 hours), which will allow us to minimize the truncation effect described above, other lessons that we learned from Study C97-1248 include: simplifying the primary endpoint to minimize protocol violations and "left censored" data; avoiding subjective endpoints, which increase variability; standardizing pain management practices across study sites; improving data collection techniques; increasing homogeneity in terms of cumulative disease burden; and controlling the duration of crisis prior to randomization.

In terms of safety, no clinically significant differences in the overall incidence of adverse events or adverse events defined as serious were observed between the treatment and control groups. Notably, the effects on serum creatinine reported as adverse events among subjects in the active treatment arm were comparable to those among subjects in the control arm. The active treatment arm was associated with transient elevations of liver enzymes (total and direct bilirubin, AST (aspartate aminotransferase), and ALT (alanine

aminotransferase)), each of which returned to its respective baseline level by the day-35 follow-up visit, except in patients whose liver enzymes had been elevated at baseline. Adverse events with a greater than 5% increased incidence in the treatment group compared to the control group and their incidences for treatment and control groups, respectively, were as follows: bilirubinemia direct (54% vs. 37%), bilirubinemia (21% vs. 13%), ALT increased (12% vs. 2%), thrombocytopenia (25% vs. 16%), nausea (41% vs. 34%), vomiting (36% vs. 28%), weight loss (28% vs. 15%), and urticaria (6% vs. 0%). Serious adverse events were reported for 23% and 22% of the patients in the treatment and control groups, respectively. Six patients in the treatment group discontinued treatment due to adverse events that included fever, bilirubinemia, tachycardia, pruritus, anemia, embolus, thrombocytopenia, acute chest syndrome, hypoxia, and dyspepsia. One patient in the treatment group died due to cardiopulmonary arrest, which was considered secondary to a fat embolism based on autopsy. The study investigator believed the underlying cause of death was due to sickle cell disease and not to treatment with vepoloxamer.

Phase 3 Sub-Study. The effect of vepoloxamer on microvascular blood flow was evaluated in a randomized, double-blind, placebo-controlled sub-study conducted as part of Study C97-1248 (described above). Nine patients with sickle cell disease who were hospitalized for vaso-occlusive crisis were studied to objectively, longitudinally and quantitatively investigate the in vivo effects of vepoloxamer on real-time microcirculation in the bulbar conjunctiva during vaso-occlusive crisis. Subjects were randomly assigned to receive vepoloxamer or placebo (control). Following treatment, compared to control, all four patients treated with vepoloxamer showed significant improvement in red blood cell velocity at both approximately two hours ($p=0.001$) and at seven hours ($p=0.000032$) after initiation of treatment. In the case of the patients who received vepoloxamer, the velocity values observed at seven hours after initiation of treatment were similar to historical steady-state (non-crisis) values for sickle cell patients.

Phase 1 Study in Vaso-Occlusive Crisis (Study C96-1237). A Phase 1, multicenter study was conducted to evaluate the safety and pharmacokinetics of vepoloxamer in patients with sickle cell disease experiencing vaso-occlusive crisis. The study enrolled 17 adults (ages 19 and older) and 15 received study drug but two discontinued prior to completing the full dose due to breakthrough crisis pain and a problem with the IV line administration, respectively. The most common adverse events (incidence >20%) were vomiting, nausea, headache, bilirubinemia, fever, anemia, and abdominal pain. Serious adverse events were reported in six patients. The serious adverse events experienced by five of the six patients were considered unrelated to vepoloxamer. The serious adverse events experienced by the sixth patient were nausea, vomiting, and abdominal pain that were considered possibly related to vepoloxamer. No clinically significant changes in renal function were observed.

Repeat Exposure Study in Vaso-Occlusive Crisis (Study C97-1273). An open-label, multicenter study was conducted to evaluate the safety of repeat exposure of vepoloxamer in patients with sickle cell disease experiencing vaso-occlusive crisis. The study enrolled 28 patients, 16 of whom were children (ages 18 and younger). Vepoloxamer was administered as a treatment for up to six episodes of vaso-occlusive crisis occurring within a period of one year from enrollment. Seventeen patients received two or more exposures and one patient received six exposures. The most common adverse events (incidence >20%) were fever, pruritis, bilirubinemia direct, constipation, nausea, vomiting, tachycardia, abdominal pain, headache, thrombocytopenia, ALT increase, urine abnormality, jaundice, and dyspnea. Serious adverse events were reported in five patients. Only one patient experienced serious adverse events considered to be related to treatment with study drug (increased AST and ALT). One study patient died sixteen days after the completion of treatment. The cause of this patient’s death is not known, but the study investigator attributed it to sickle cell disease and considered it to be unrelated to study treatment. Two other subjects discontinued treatment due to adverse events. No clinically significant changes in renal function were observed.

Acute Chest Syndrome (Study C97-1243). A dose-escalating, multicenter study was conducted to evaluate the safety and pharmacokinetics of vepoloxamer in patients with sickle cell disease experiencing acute chest syndrome. The study enrolled 43 patients who were under 65 years of age and 42 received study drug. The median age of the patients was 19 years (range of one to 38 years). Patients were randomized to one of five dose groups and vepoloxamer was

administered as a continuous, two-stage, intravenous infusion over 24 hours. All patients received a loading dose of 200 mg/kg given over one hour, followed by one of the following maintenance doses given over 23 hours: 40 mg/kg/hr, 60 mg/kg/hr, 80 mg/kg/hr, 100 mg/kg/hr or 120 mg/kg/hr. Secretory phospholipase A2 (sPLA2) was measured as an efficacy biomarker. sPLA2 has been shown in clinical studies to correlate with the onset and resolution of acute chest syndrome. Among the 34 patients who had elevated sPLA2 levels at baseline, levels returned to steady-state levels by the end of the 24-hour infusion period and remained at steady-state through follow-up. All doses appeared equally effective.

Notably, the mean duration of hospitalization for patients in Study C97-1243 was shorter compared to historical controls. Specifically, in a 538-subject, 30-center study of patients with sickle cell disease experiencing acute chest syndrome published in the New England Journal of Medicine (2000) mean duration of hospitalization was 12.8 days for patients older than 19 years (n=128) and 9.9 days for patients 19 years and younger (n=409). In Study C97-1243, the mean duration of hospitalization of patients older than 19 years (n=14) was 7.2 days for patients in the low dose groups (maintenance doses of 40, 60 or 80 mg/kg/hr, n=10) and 6.3 days for patients in the high dose groups (maintenance doses of 100 or 120 mg/kg/hr, n=4) and the mean duration of hospitalization of patients 19 years and younger (n=27) was 7.9 days for patients in the low dose groups (n=20) and 4.1 days for patients in the high dose groups (n=7).

In terms of safety, vepoloxamer was generally well-tolerated at all dose levels. The most common adverse events (incidence of >20%) were fever, pain, tachycardia, constipation, vomiting, bilirubinemia, bilirubinemia-direct, weight loss and rhinitis. Serious adverse events were reported in eight patients (19%), and two patients had serious adverse events considered related to study treatment (abnormal gait, bilirubinemia and bilirubinemia-direct), but no patients discontinued treatment due to adverse events. One patient died during the study due to acute respiratory distress syndrome. That patient had a cardiac arrest and was resuscitated, but developed acute respiratory distress syndrome and died on day 8 post-treatment. The study investigator considered the patient's death unlikely to be attributable to the study drug. Importantly, results from the renal function test did not reveal any pattern or dose-related effects suggestive of renal dysfunction across the range of doses studied.

Phase 2 Study of Poloxamer 188 (Non-Purified) in Vaso-Occlusive Crisis (Study 130-005). Prior to development of vepoloxamer, poloxamer 188 (non purified) was evaluated in a Phase 1 study in patients with sickle cell disease (n=7) (Study 02) and a randomized, double-blind, placebo-controlled, multicenter Phase 2 study in patients with sickle cell disease experiencing vaso-occlusive crisis (Study 130-005). Study 130-005 enrolled 50 patients ages 15 and older, with 28 randomized to receive poloxamer 188 and 22 to receive placebo. Study medication was administered as a continuous, two-stage, intravenous infusion over 48 hours. In the efficacy analyses, three subgroups of patients were considered: subgroup 1 (n=49) was the intent-to-treat population, subgroup 2 (n=45) excluded patients with a study drug infusion duration of less than 24 hours, and subgroup 3 (n=31) excluded patients who did not receive the full dose of study drug or for whom the end-of-painful episode time was estimated. Safety data were analyzed in all 50 patients. The primary endpoint in Study 130-005 was duration of crisis and secondary endpoints were pain intensity, total analgesic use, and days of hospitalization. Median duration of crisis was reduced in the treatment group compared to the control group by 13 hours in subgroup 1 (67 vs 80 hours, p=0.147), by 28 hours in subgroup 2 (60 vs 88 hours, p=0.097), and by 36 hours in subgroup 3 (44 vs 80 hours, p=0.020). Duration of hospitalization was reduced in the treatment group compared to the control group by one day in subgroup 1 (5 vs 6 days, p=0.298), by two days in subgroup 2 (5 vs 7 days, p=0.261), and by two days in subgroup 3 (5 vs 7 days, p=0.145). Total analgesic use (measured by morphine equivalent units, or MEU) was reduced in the treatment group compared to the control group by 102 mg in subgroup 1 (median MEU of 57 mg vs 159 mg, p=0.055), by 120 mg in subgroup 2 (median MEU of 49 mg vs 169 mg, p=0.037), and by 111 mg in subgroup 3 (median MEU of 34 mg vs 145 mg, p=0.014). Parenteral analgesic use was reduced in the treatment group compared to the control group by 102 mg in subgroup 1 (median MEU of 47 mg vs 149 mg, p=0.075), by 110 mg in subgroup 2 (median MEU of 40 mg vs 150 mg, p=0.048), and by 106 mg in subgroup 3 (median MEU of 27 mg vs 133 mg, p=0.014).

In terms of safety, poloxamer 188 was generally well-tolerated. Adverse events were similar in both groups and most were either mild or moderate in intensity. The most common adverse events (incidence >5%) were headache, nausea, injection site pain, abdominal pain, vomiting and constipation. One adverse event was considered serious and attributable to study medication – a subject in the poloxamer 188 with mild underlying renal dysfunction (baseline creatinine 1.5 mg/dL) had a transient increase in serum creatinine concentration during infusion (peak concentration = 2.7 mg/dL). No treatment was required and his creatinine returned to baseline by the time of the follow-up assessment.

Vepoloxamer – Phase 2 Product Candidate for the Treatment of Heart Failure

Overview of Heart Failure and the Significant Unmet Need for New Therapies

Heart failure is a chronic, progressive condition in which heart muscle is unable to pump sufficient blood to meet the body's needs. A healthy heart pumps blood continuously through the circulatory system to deliver oxygen and nutrient-rich blood to the body's cells and enable normal functioning. Heart failure due to left ventricular dysfunction is categorized according to left ventricular ejection fraction into heart failure with reduced ejection fraction, or HFrEF (also known as systolic heart failure), and heart failure with preserved ejection fraction, or HFpEF (also known as diastolic heart failure). In HFrEF, the left ventricle of the heart loses its ability to contract with enough force for the circulation to meet the metabolic needs of the body. In HFpEF, the left ventricle loses its ability to relax normally because the muscle has become stiff and the heart can't properly fill with blood during the resting period between each beat.

It is estimated that more than 20 million individuals worldwide suffer from heart failure, with approximately 5.7 million in the U.S. alone. Heart failure is the most common diagnosis for hospital admission in the U.S. among patients over age 65. The American Heart Association estimates that total medical costs of heart failure in the U.S. will increase from approximately $21 billion in 2012 to approximately $31 billion in 2020 and $53 billion in 2030, with the vast majority of such costs related to hospitalization.

Most existing therapies target indirect methods that reduce the workload on the heart, but may not directly improve heart function. For example, ACE inhibitors widen blood vessels (vasodilate) to lower blood pressure and reduce the resistance against which the heart must pump. However, they do not directly improve the heart's ability to contract normally. These indirect approaches provide symptomatic relief and have improved mortality, but there remains an urgent need for new therapies, as evidenced by the more than one million hospitalizations each year in the U.S. with a primary diagnosis of heart failure. Further, Medicare patients hospitalized for heart failure have median 30-day readmission and mortality rates of approximately 22% and 12%, respectively.

Vepoloxamer may offer a new mechanistic approach for treating heart failure that improves heart function directly through its membrane-sealing activity and indirectly through its hemorheologic activity. In a failing heart, it is thought that dysfunctional cardiac cell membranes result in unregulated entry of calcium into cells leading to calcium overload toxicity. Vepoloxamer's membrane-sealing activity may help restore dysfunctional cardiac cell membranes, thus minimizing calcium overload injury and directly improving heart contractility. Vepoloxamer's hemorheologic activity may minimize the heart's workload by reducing blood viscosity and improving microvascular blood flow and oxygen delivery within the heart. If vepoloxamer can alter the trajectory of heart failure, whether by preserving heart tissue or decreasing cardiac workload, it has the potential to minimize cardiac myocyte damage and improve clinical outcomes, such as hospital readmission and survival.

Nonclinical Proof-of-Concept and Repeat Treatment Studies

Proof-of-Concept Study

To investigate the utility of vepoloxamer as a treatment for heart failure, we conducted a randomized, placebo-controlled, nonclinical study of vepoloxamer in an experimental model of chronic, stable heart failure. A single dose of vepoloxamer (low dose (225 mg/kg) or high dose (450 mg/kg)) or placebo was administered intravenously over two hours. Hemodynamic, ventriculographic, echocardiographic and electrocardiographic measurements were taken at baseline (prior to study drug administration) and at the following time-points after the start of study drug administration: two hours (end of administration), 24 hours, one week and two weeks. Peripheral venous blood samples were obtained at the same time-points. The study was conducted under the supervision of Dr. Hani N. Sabbah at Henry Ford Health System. The improvements described below were calculated as the difference between baseline and mean values of each study group at each time-point using a one-way analysis of variance, with $p<0.05$ considered significant.

The study demonstrated that a single, two-hour infusion of vepoloxamer improved left ventricular (LV) systolic function that was significant immediately (at the end of vepoloxamer administration) and remained significant at one week (and, in some cases, at two weeks) after vepoloxamer administration. In particular, vepoloxamer demonstrated a statistically significant improvement in LV ejection fraction, end-systolic volume, stroke volume and cardiac output.

In addition, the single, two-hour infusion of vepoloxamer resulted in prolonged (one to two week) improvement in biomarkers of LV remodeling, cell death, inflammation and collagen deposition, while saline infusion in the control group had no effect on any of the biomarkers.

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Vepoloxamer resulted in statistically significant and progressive reductions in troponin-I, at both one week and two weeks after vepoloxamer administration. Specifically, at two weeks post-administration, compared to baseline values, mean reduction (improvement) in troponin was 46.7% for the low-dose group and 48.8% for the high-dose group. In contrast, in the control group, troponin increased 7.7%. Troponin is an intracellular protein that is released from cardiomyocytes (heart muscle cells) following injury to and/or death of these cells. In patients with heart failure, elevated troponin levels have been associated with more severe disease and a worse clinical prognosis. A recent clinical study confirmed that increasing troponin during hospital stay is associated with increased 180-day all-cause mortality and hypothesized that preventing myocardial damage, as evidenced by reduced levels of troponin, might favorably influence survival.

- Vepoloxamer also resulted in statistically significant and progressive reductions in plasma N-terminal pro-brain natriuretic peptide (NT-proBNP), at both one week and two weeks after vepoloxamer administration. Specifically, at two weeks post-administration, compared to baseline values, mean reduction (improvement) in NT-proBNP was 54.5% for the low-dose group and 61.4% for the high-dose group. In contrast, in the control group, NT-proBNP increased 3.5%. NT-proBNP is released from the heart during periods of increased cardiac wall stress, typically as a result of the increased fluid volumes that are common in heart failure. Studies have associated persistently elevated natriuretic peptide concentrations during hospital stay with poor prognosis. A recent clinical study found that higher NT-proBNP levels are associated with increased 180-day all-cause mortality.
- Additionally, vepoloxamer significantly reduced plasma levels of tumor necrosis factor- (TNF-), interlukin-6 (IL-6), C reactive protein (CRP) and matrix metalloproteinase-2 (MMP-2), at both one week and two weeks after vepoloxamer administration.

Repeat Treatment Study

Following the single administration, proof-of-concept study, the effects of repeat-administration of vepoloxamer on LV systolic and diastolic function were evaluated in a second randomized, placebo-controlled, study in the same model of chronic, stable heart failure as discussed above. In this study, vepoloxamer (450 mg/kg) or placebo was administered over two hours at the start of the study and a repeat treatment was administered three weeks after the first administration, with the study concluding six weeks after the first administration. The study was conducted under the supervision of Dr. Hani N. Sabbah at Henry Ford Health System. Consistent with results of the proof-of-concept study, the first treatment of vepoloxamer in this study resulted in robust improvements that persisted for one to two weeks in key parameters of heart function, including LV end-systolic volume, ejection fraction, stroke volume, and cardiac output. LV ejection fraction was improved by approximately 20% for up to two weeks, returning to baseline values by three weeks post-administration. Diastolic function also was improved. The second treatment resulted in similar improvements in LV systolic and diastolic function. However, the effects observed after the second treatment persisted for at least three weeks post-administration to the end of the study. Following the second treatment of vepoloxamer, LV ejection fraction had not returned to baseline values by the end of the six-week study, but was still improved by approximately 20% above baseline values. Vepoloxamer had no statistically significant effect on heart rate, blood pressure or end-diastolic volume after either administration. The study also demonstrated that troponin-I and NT-proBNP were improved following both the first and second administrations of vepoloxamer. The effect on these biomarkers was of similar magnitude and duration as observed in the single administration study discussed above.

Clinical Development

Encouraged by the results of the nonclinical studies discussed above, as well as recommendations from medical experts in heart failure, we commenced clinical development of vepoloxamer in heart failure in October 2015. Our ongoing, randomized, double-blind, placebo-controlled, multicenter Phase 2 study of vepoloxamer will enroll approximately 150 ambulatory patients with chronic heart failure (LV ejection fraction ≤ 35%). Patients in this study are randomized into one of three approximately 50-patient study arms and receive one of two dose levels of a new formulation of vepoloxamer or placebo control intravenously over three hours in an outpatient setting or short-stay inpatient unit, depending on local practice and resource availability. We designed the new formulation of vepoloxamer being evaluated in this study to be more suitable for heart failure patients. The study will evaluate the safety and efficacy of a single, three-hour infusion of vepoloxamer compared to placebo, including vepoloxamer's effect on markers of cardiac injury (troponin) and wall stress (NT-proBNP), as well as clinical outcomes such as changes in echocardiographic measurements, exercise tolerance, and quality of life.

Vepoloxamer – Other Clinical Development Opportunities

Ischemic Stroke

We also are evaluating vepoloxamer's potential in acute ischemic cerebrovascular infarction, known as "stroke." Stroke is the fourth leading cause of death in the U.S. and a leading cause of long-term disability. Over 85% of all strokes are ischemic strokes, meaning they occur when a blood vessel that supplies blood to the brain is occluded, or blocked, by a clot. Timely restoration of blood flow is critical for stroke patients as brain damage is a rapid, progressive process. In a typical large-vessel acute ischemic stroke, 1.9 million neurons may be lost each minute. Recombinant tissue plasminogen activator, or tPA, is approved for treatment of acute ischemic stroke. However, in stroke patients, due to bleeding risks, tPA should not be administered until intracranial hemorrhage has been excluded by a cranial computerized tomography, or CT, scan, which can delay treatment. At the same time, tPA has not demonstrated improved outcomes for stroke patients if administered more than three hours after onset of stroke symptoms.

There is a significant need for a pharmacologic agent that enhances the breakdown of blood clots, or thrombolysis. The mechanistic activities of vepoloxamer facilitate thrombolysis and suggest potential to shorten the time to clot lysis or attain similar thrombolysis at a reduced dosage of thrombolytic, such as tPA. In addition, vepoloxamer's cytoprotective properties may reduce reperfusion injury, with the potential to limit tissue necrosis. Further, improving microvascular flow and distal tissue reperfusion should also reduce untoward events from the no-reflow phenomenon, relieving persistent tissue ischemia despite restoration of large vessel patency. Additionally, because the risk of hemorrhagic complications from thrombolytics is associated with the dose and duration of infusion, more rapid thrombolysis and/or lower dosage of thrombolytic agent has the potential to decrease the risk of bleeding.

In 2015, we announced positive data from a nonclinical study of vepoloxamer in ischemic stroke. In an experimental model of delayed administration of tPA treatment following embolic middle cerebral artery occlusion (MCAO), vepoloxamer, both alone and in combination with tPA, reduced neurological function deficits, lesion volume and intravascular fibrin deposition without increased incidence of gross hemorrhage compared to treatment with tPA alone and saline controls. In the study, tPA was administered four hours after MCAO. Treatment with vepoloxamer in combination with tPA significantly ($p<0.05$) improved neurologic function (measured with adhesive removal test and modified neurological severity scores at one and seven days after MCAO) and reduced ischemic brain lesion volume and microvascular fibrin deposition compared to treatment with tPA alone or saline. Importantly, vepoloxamer was not associated with any increase in hemorrhagic risk. No significant differences of the incidence of gross hemorrhage were detected among groups.

Based on our nonclinical data, as well as published data from third party studies of poloxamer 188, we believe, and several medical experts in the field have agreed, that sufficient data now exists to support clinical development of vepoloxamer in stroke. Consequently, during the third quarter of 2015, we elected to discontinue our Phase 2 clinical study of vepoloxamer in combination with tPA for the treatment of acute limb ischemia and directly pursue the opportunity for clinical development of vepoloxamer in stroke. However, we do not anticipate commencing clinical development in stroke without further evaluation of the opportunity and not prior to our analysis of results from our Phase 3 EPIC study of vepoloxamer in sickle cell disease.

Resuscitation Following Major Trauma

We believe that vepoloxamer also has potential as a resuscitation fluid to improve outcomes for patients who experience shock following major trauma. However, currently, we do not plan to initiate a clinical study in this indication without funding from the U.S. government or some other third-party collaborator. In 2014, we signed a Cooperative Research and Development Agreement with a branch of the U.S. military to evaluate the utility of vepoloxamer in nonclinical models of trauma of interest to the U.S. government. If the results of such studies are positive, the U.S. government may have interest in developing vepoloxamer as a therapy in major trauma.

AIR001 – Phase 2 Product Candidate for the Treatment of HFpEF

AIR001 is a sodium nitrite solution for intermittent inhalation via nebulization. Nitrite is a direct vasodilator and can be recycled in vivo to form nitric oxide (NO) independent of the classical NO synthase (NOS) pathway. Nitrite mediated NO formation has several beneficial effects, including dilation of blood vessels and reduction of inflammation and undesirable cell growth. Generation of NO from sodium nitrite is not dependent upon endothelial function and is enhanced in the setting of tissue hypoxia and acidosis, conditions in which NOS activity typically is depressed. In experimental models, nitrite use has demonstrated improved remodeling both in the pulmonary vasculature and right ventricle. Hemodynamic effects include venodilation with reductions in right atrial pressures, pulmonary and systemic vasodilation with reductions in pulmonary vascular resistance and left atrial pressures, and improved cardiac relaxation. In addition, nonclinical studies have demonstrated that nitrite can stimulate mitochondrial biogenesis and mitochondrial fusion and decrease mitochondrial oxygen consumption through a

mechanism distinct from that of NO, which may have utility in treating heart failure.

We obtained the AIR001 program through our acquisition of Aires Pharmaceuticals, Inc. in February 2014. Prior to the acquisition, AIR001 had been tested in more than 120 healthy volunteers and patients with various forms of pulmonary hypertension in three Phase 1 studies and one Phase 2 study and was generally well-tolerated. While the Phase 2 study in patients with pulmonary arterial hypertension, known as Study CS05, was prematurely terminated due to Aires' capital constraints prior to the acquisition, data from the 29 patients who enrolled in the study were positive, showing a trend towards improvements in hemodynamic parameters and change in exercise capacity from baseline, and AIR001 was generally well-tolerated, with no drug-related serious adverse events. In particular, methemoglobin levels remained normal (< 1.5%), which distinguishes AIR001 from safety concerns associated with intravenously-administered nitrite.

Significant Unmet Need in HFpEF and Development Rationale

We are developing AIR001 for the treatment of patients with HFpEF. Data show that approximately 50% of patients hospitalized for heart failure have HFpEF and the prevalence of HFpEF is expected to increase as the population ages. To date, no pharmacologic agents have shown convincing evidence of efficacy in HFpEF and few interventions have been observed to improve symptoms or quality of life for HFpEF patients.

People with HFpEF suffer from dyspnea and fatigue with activity, limiting exercise tolerance. The pathophysiology of HFpEF is complex and includes left ventricular systolic and diastolic dysfunction, pulmonary vascular disease, endothelial dysfunction, and peripheral abnormalities. In HFpEF patients, cardiac pressures are often normal at rest but elevated with stress (exercise), creating a major barrier to treatment because interventions that reduce filling pressures during exercise also reduce resting pressures, increasing vulnerability to hypotension. While HFpEF is a heterogeneous syndrome, which may explain the failure of clinical studies testing therapies that have shown efficacy in treating HFrEF, elevation in left ventricular (LV) filling pressures and pulmonary artery pressures during exercise has been a universal finding in HFpEF patients.

Evidence points to impaired nitric oxide-cyclic guanosine monophosphate (NO-cGMP) bioavailability as playing a central role in the abnormalities that limit exercise capacity in HFpEF patients. NO-cGMP levels can be increased using direct NO donors, such as the organic nitrates. However, organic nitrates have shown several shortcomings, including the development of tolerance, greater vulnerability to hypotension in patients with HFpEF, development of "pseudo-tolerance," where chronic venodilation leads to renal sodium retention, and increases in oxidative stress and endothelial dysfunction. Inorganic nitrite is an alternative strategy to restoring NO-cGMP levels. Notably, because generation of NO from nitrite is enhanced with tissue hypoxia and acidosis, as occur during exercise, it becomes most active at the time of greatest need for HFpEF patients.

Clinical Development in HFpEF

We have supported two investigator-sponsored Phase 2a studies of AIR001 in patients with HFpEF, one of which is ongoing. In February 2016, we reported positive top-line results from the first Phase 2a study, a randomized, double-blind, placebo-controlled study of AIR001 in 30 patients with HFpEF. In the study, AIR001 showed statistically significant improvement for the pre-specified primary endpoint: change in pulmonary capillary wedge pressure (PCWP) at 20 Watts exercise after drug treatment relative to PCWP at 20 Watts exercise in the initial assessment prior to drug treatment, compared to placebo-treated patients. Study data show that nebulized AIR001 attenuates the hemodynamic derangements of cardiac failure that occur during exercise in HFpEF patients. AIR001 was generally well-tolerated, with no drug-related serious adverse events.

In February 2016, we also announced that AIR001 had been selected by the Heart Failure Clinical Research Network for evaluation in a multicenter, randomized, double-blind, placebo-controlled crossover Phase 2 study of AIR001 in approximately 100 patients with HFpEF, known as the INDIE-HFpEF study. The primary objective of the study is to evaluate whether AIR001, as compared to placebo, improves maximal exercise capacity as assessed by cardiopulmonary exercise testing. The study is expected to begin in the third quarter of 2016. We believe this study can provide evidence and rationale for pursuing a Phase 3 clinical study in HFpEF.

Commercialization Strategy

We intend to independently commercialize vepoloxamer for sickle cell crisis, if approved, in the United States and the European Union. Treatment centers for patients with sickle cell disease are concentrated in a relatively small number of metropolitan areas in the U.S. and EU and, as a result, we believe a sales force of approximately 30 representatives in the U.S. and approximately 10 representatives in the EU can effectively market our product in those territories, if

approved. Given the current stage of our product candidates' development and anticipated regulatory approval timelines, we have not yet established a commercial infrastructure, including a sales force. In building our sales force, we intend to recruit representatives with experience in the acute care and/or hospital setting, particularly with hematology products. For other key global markets, such as in the Middle East and North Africa, we will seek to partner with one or more organizations that have expertise selling in those regions.

Our commercial strategy for vepoloxamer, if approved, will include promoting its clinical benefits and a concerted effort to raise awareness in the sickle cell patient community about the existence of a treatment option for shortening the duration of a vaso-occlusive crisis, of which there currently are none. Recent data from the Health Care Utilization Project (HCUP) indicate that approximately 95% of patients with sickle cell disease have medical insurance and more than 75% are in public plans (Medicaid or Medicare). Based upon the treatment setting, which is hospital inpatient, and the payer mix, which is majority public plans, we expect the patient's share of costs for an episode of care to be minimal and not adversely impact potential utilization. We believe the combination of our commercial effort, the high unmet need, and vepoloxamer's product profile will facilitate rapid and extensive penetration in the sickle cell market.

Manufacturing

We do not have, and have not made plans to establish, our own manufacturing facilities. We meet our requirements for nonclinical and clinical trial material (including manufacturing API, formulating and assembling final drug product, labeling, testing and release, packaging, storing API and finished drug product and similar activities) by establishing relationships with third-party manufacturers and other service providers to perform these services for us.

In the case of clinical trial material for our vepoloxamer programs, currently, we have a single-source supplier of the drug substance, vepoloxamer, and single-source suppliers of the finished drug products for our sickle cell disease program and heart failure program, respectively. We have an agreement with Pierre Fabre Médicament (PFM) for supply of vepoloxamer for clinical development. As we position toward commercialization in sickle cell disease, we expect to enter into commercial supply agreements with PFM and the third-party supplier of finished drug product for sickle cell disease, Patheon Inc. There are a limited number of manufacturers with the technical capabilities and desire to perform the specialized, proprietary processes required to produce vepoloxamer, however, to support commercialization of vepoloxamer in sickle cell disease we are pursuing alternative supply sources.

In addition, although it is commercially available, there are a limited number of sources of poloxamer 188, the starting material for vepoloxamer. BASF, the current supplier of our starting material, has extensive, worldwide operations and poloxamer 188 is part of its standard product portfolio; however, we do not have any control over BASF's production of poloxamer 188 and BASF may change its manufacturing process and/or limit the availability of its poloxamer 188 product in the future.

In the case of AIR001 clinical trial material, we also have single-source, third-party suppliers of API and finished drug product and there are a limited number of manufacturers with the technical capabilities and desire to produce AIR001. In addition, AIR001 is administered via nebulization and the proprietary nebulizer device currently validated for use in clinical studies of AIR001 is manufactured and supplied by a single third-party.

We are investigating manufacturing-related opportunities to enhance our proprietary position around vepoloxamer, including those involving proprietary API starting material, alternative purification processes, unique analytical methods and new drug product formulations, and AIR001, including those involving alternative drug product formulations and delivery systems.

In the future, establishing supply agreements, particularly with respect to commercial manufacturing and supply, may require us to agree to substantial investment in infrastructure, minimum volume requirements, exclusivity arrangements, and/or other restrictive or potentially costly terms. As discussed above, our alternatives may be limited due to the specialized nature of the technologies and methods used to manufacture our product candidates and, in the case of ARI001, the specialized and proprietary device needed for administration of our product candidate. In addition, if we seek to make certain changes to the manufacturing process, including changing our sources of API starting material, API, or finished drug product, or to the drug delivery device, we may need FDA review and approval before a change can be implemented. Among other things, the FDA may require clinical, stability or other data for any product candidate manufactured with new materials or by new manufacturers, which data will take time and is costly to generate, and the delay associated with generating this data would increase our costs and may delay completion of development of a product candidate and/or its commercial launch or, once launched, our ability to meet market demand for the product.

Intellectual Property

Our commercial success depends in part on our ability to prevent competitors from duplicating or developing equivalent versions of our product candidates. To protect our proprietary compounds, we have implemented and will

continue to pursue a multi-faceted approach that relies on a combination of patent protection, proprietary know-how, trade secrets, and data and market exclusivity. We seek to establish and protect our proprietary rights through confidentiality, licensing and other agreements, including those with our contract manufacturers, such as PFM.

We have filed patent applications claiming vepoloxamer as a novel composition of poloxamer material. We also have filed for patent protection covering a process of manufacture of vepoloxamer, various methods of therapeutic use of poloxamers, including vepoloxamer, and our new formulation of vepoloxamer for the treatment of heart failure patients. We anticipate making additional patent filings, including around vepoloxamer's therapeutic uses, administration and formulation. In addition, we plan to file patent applications claiming priority to the initial applications in various countries, as determined in consultation with our patent professionals with the goal of obtaining relevant coverage in territories that are commercially important to us or potential partners. As of March 10, 2016, we owned one granted patent covering our vepoloxamer product candidate, which was issued by a country other than the U.S. and relates to methods of use of purified poloxamers to treat storage-lesioned compromised blood and compositions of purified poloxamers and storage-lesioned blood.

In addition to the patent protection we are seeking, we continue to expand our manufacturing know-how, which we maintain as a trade secret. For macromolecules, such as vepoloxamer, testing methods and acceptance criteria for starting materials and in-process and release specifications are critical to the quality of drug product. Without these proprietary specifications, we believe competitors will be unable to adequately characterize products that are equivalent to our vepoloxamer products in the manner that regulatory agencies will require. Further, we are evaluating the development of a proprietary process for manufacturing API starting material, which we expect would further protect the markets for our vepoloxamer products, if approved.

For particular indications, such as rare or orphan diseases, our products may benefit from periods of post-approval "marketing exclusivity." Vepoloxamer has orphan drug designation in the United States and European Union for the treatment of sickle cell disease. As described below under "Government Regulation – Orphan Drug Designation," due to our orphan designation, if our vepoloxamer product receives FDA approval for the treatment of sickle cell disease, the FDA will not approve any other application to market a drug product with the same active moiety for the same indication for a period of seven years, except in limited circumstances, such as another drug product showing clinical superiority to ours. With regard to the European Union, our vepoloxamer product may benefit from ten years of market exclusivity for the treatment of sickle cell disease with the potential for an additional two years of market exclusivity if a paediatric investigation plan, or PIP, is completed. Orphan drug designation does not necessarily convey any advantage in the regulatory review and approval process. In addition, competitors may receive approval of different drugs or biologics for the same indication for which our orphan drug product is approved.

In the case of AIR001, we have filed for patent protection covering various methods of therapeutic use of inorganic nitrite, and under the NIH License (discussed below), we have certain exclusive rights to issued and pending patents related to various methods of therapeutic use of inorganic nitrite salts. We may also seek to obtain other licenses to third party patents and other rights to the extent we determine they relate to potential therapeutic uses of AIR001. Additionally, we believe there is potential to establish exclusivity around the combination of AIR001 and its inhalation delivery system.

We are aware of a substantial number of patents issued and patent applications filed in our technical areas or fields, and we may want or determine that we need to obtain licenses to patents or other rights owned by third parties. There is a risk that third parties may allege that they have patent rights encompassing our products or methods and no assurance can be given that patents do not exist, have not been filed, or could not be filed or issued, that contain claims covering our product candidates or methods.

We cannot provide assurance that our pending patent applications will issue as patents, that any issued patents will provide us with significant competitive advantages, or that the validity or enforceability of any of our patents will not be challenged or, if instituted, that these challenges will not be successful. The cost of litigation to uphold the validity and prevent infringement of our patents could be substantial. Furthermore, we cannot provide assurance that others will not independently develop similar technologies or methods, duplicate our technologies or methods, or design around the patented aspects of our products, technologies or methods. We can provide no assurance that our proposed technologies will not infringe patents or rights owned by others, licenses to which might not be available to us.

In addition, the approval process for patent applications in different countries may differ significantly. The patent authorities in each country administer that country's laws and regulations relating to patents independently of the laws and regulations of any other country and the patents must be sought and obtained separately, which can add substantial cost and expense. Further, a favorable outcome or approval in one country does not necessarily indicate that a favorable outcome or approval will be obtained in other countries.

In-Licensing Agreements

License Agreement with CytRx Corporation

As discussed in more detail below, in April 2011, we acquired SynthRx, Inc. Under a 2004 agreement, CytRx granted SynthRx an exclusive license, with the right to sublicense, certain intellectual property, including as related to surface-active copolymers, exemplified by poloxamer 188, to use, offer and sell covered products in all of the countries in the world and in all fields, except those fields that, at the time of the agreement, were or would be licensed pursuant to certain identified agreements. We believe that the field limitation does not prevent us from developing or commercializing vepoloxamer in the fields in which we are pursuing its development.

In partial consideration of the license grant, SynthRx agreed to pay CytRx certain non-refundable and non-creditable milestone payments based on the approval of each covered product in a major market, which includes the United States. The amount of each milestone payment is $2 million, half of which is due on the first commercial sale of the approved product and half of which is payable over time at a rate of 25% of quarterly net sales. In addition, SynthRx would pay a 5% royalty on quarterly net sales of covered products on a country-by-country, subject to up to 50% reduction in certain circumstances, for the longer of seven years from the date of first commercial sale of the covered product in a country or the expiration of the last applicable patent for a covered

product. However, in the event of a sublicense under the specified patents, in lieu of the foregoing milestone and royalty payments, SynthRx, in its sole discretion, may elect to pay CytRx an amount equal to 20% of any sublicensing income received by SynthRx within 30 days of receipt thereof. Sublicense income includes, without limitation, license fees, royalties, milestone payments, license maintenance fees and strategic alliance payments, whether in cash, equity or other property, with the payment by SynthRx to CytRx to be in the same form as the payment received by SynthRx. In December 2014, we merged SynthRx, then our wholly-owned subsidiary, with and into Mast Therapeutics and assumed the rights and obligations under the license agreement with CytRx.

License Agreement with The National Institutes of Health

We, through our wholly-owned subsidiary, Aires Pharmaceuticals, Inc., have exclusive, sublicensable, worldwide rights to issued and pending patents related to nitrite salts and their uses, under which it may develop and commercialize inhaled nitrite formulations to treat pulmonary arterial hypertension, ischemia reperfusion injury and reperfusion injury associated with organ transplantation pursuant to a Public Health Service Patent License Agreement – Exclusive, which we refer to as the NIH License. Under the terms of the NIH License, Aires agreed to make a minimum annual payment of $15,000. Aires may also be obligated to make “benchmark” payments of up to $7.0 million, with (a) $0.2 million upon dosing of first patient in a Phase 3 clinical study in pulmonary arterial hypertension, (b) $0.1 million related to the issuance of the first U.S. patent in the licensed field of use, and (c) an aggregate of $6.8 million related to the filing of the first NDA, regulatory approval, and commercial sales of a covered product in pulmonary arterial hypertension. In addition to these benchmark payments, to the extent a covered product is approved for commercial sale, under the NIH License, Aires will pay annual royalties ranging from 4% to 5% of its annual net sales of covered products. Because the NIH License currently is limited by fields of use, we are exploring expansion of its scope, including a field of use expansion that would include heart failure.

Competition

The industries in which we operate (biopharmaceutical, specialty pharmaceutical, biotechnology and pharmaceutical) are highly competitive and subject to rapid and significant change. If any of our product candidates are approved by regulatory authorities, we expect they will face significant competition. We may not be able to compete successfully against organizations with competitive products, particularly large pharmaceutical companies. Many of our potential competitors have greater clinical, regulatory, manufacturing, marketing, distribution, compliance and financial resources and experience than do we.

Over the longer term, our ability, independently or otherwise, to successfully manufacture, market, distribute and sell any approved products, expand their usage or bring additional new products to the marketplace will depend on many factors, including, but not limited to, FDA and foreign regulatory agency approval of new products and of new indications for existing products, the efficacy and safety of our products (alone and relative to other treatment options), the degree of patent or other protection afforded to particular products, and reimbursement for use of those products.

Many other organizations are developing drug products and other therapies intended to treat the same diseases and conditions for which our product candidates are in development, and the success of others may render potential application of our product candidates obsolete or noncompetitive, even prior to completion of its development.

Further, there is increasing interest in developing drugs for rare diseases, which may have the effect of increasing the development of agents to treat sickle cell disease and other rare diseases we may pursue. Legislative action may generate further interest.

Sickle Cell Disease

Currently, there are few options for patients suffering complications of sickle cell disease. Patients experiencing vaso-occlusive crisis typically are treated with hydration, oxygen, and analgesia for pain, usually consisting of narcotics, such as morphine. Hydroxyurea, a form of chemotherapy used for myeloproliferative disease and approved for sickle cell disease in 1998, is an approved product that has been shown to decrease the frequency of vaso-occlusive crisis. It is not approved to intervene during an ongoing a vaso-occlusive crisis to reduce its duration or severity; it has not been shown to treat the crisis itself. To date, no therapeutic agents have been approved to reduce the duration or severity of an ongoing vaso-occlusive crisis.

There is, however, substantial interest in developing agents to treat various aspects of sickle cell disease. We are aware of numerous companies with product candidates in varying stages of development for the prevention and treatment of vaso-occlusive crisis, including mechanisms that target the P2Y12 ADP receptor, increase oxygen binding of hemoglobin or stimulate production of fetal hemoglobin. Some of these companies are large, well-financed and experienced pharmaceutical and biotechnology companies or have partnered with such companies, which may give them development, regulatory and/or marketing advantages over us. For example, Pfizer and Novartis have each invested in companies, GlycoMimetics, Inc. and Selexys Pharmaceuticals Corporation, respectively, with clinical-stage agents for the treatment of vaso-occlusive crisis. Pfizer is enrolling a Phase 3 clinical study of

GlycoMimetics' rivipansel in adult and adolescent patients with sickle cell disease experiencing vaso-occlusive crisis and estimates completion of the study in July 2018. Emmaus Life Sciences, Inc. completed a Phase 3 study of its L-glutamine treatment for sickle cell patients in 2013, but the study did not meet its primary efficacy endpoint for reduction in the number of sickle cell crises during a 48-week period. However, based on statements in its most recent periodic report filed with the SEC in May 2015, Emmaus is preparing to submit an NDA to the FDA for marketing approval of its L-glutamine product candidate for sickle cell patients ages five and older. Global Blood Therapeutics Inc. is conducting what it characterizes as a Phase 1/2 clinical study of its product candidate GBT440, an oral, once-daily therapy intended to prevent the sickling of red blood cells in sickle cell patients, and estimates completion of this early stage study in May 2016. Further, numerous non-profit or non-commercial foundations and interest groups are committed to improving outcomes for patients with sickle cell disease. Advances in the understanding of the signaling pathways associated with sickle cell disease may lead to further interest and development of treatment options.

More broadly, vepoloxamer may compete against agents designed to treat the underlying pathology of sickle cell disease, of which vaso-occlusive crisis is the hallmark complication. On the other hand, it may be used in combination with any such therapies. Bone marrow and stem cell transplantation have been shown to be effective to treat and, in some cases, cure sickle cell disease, but current methods are not available to the majority of patients due to the risk of serious complications, including graft versus host disease and infection, the high cost of the procedures, and the unavailability of a well-matched donor. Forms of gene therapy are being pursued to correct sickle cell disease by halting production of sickled cells, but they are in preclinical or early-stage clinical development and for only patients with the more severe forms of sickle cell disease. For example, bluebird bio, Inc. is conducting a Phase 1 clinical study of its LentiGlobin® BB305 product candidate for patients with severe sickle cell disease and estimates completion of this Phase 1 study in March 2019.

Heart Failure

Treatment options in heart failure vary depending on disease severity, patient-specific factors such as age and comorbidities, the underlying cause of failure, and whether the condition is compensated (stable) or decompensated (deteriorating). Lifestyle changes (e.g., heart healthy diet, stopping smoking, controlling weight, monitoring fluid in-take) can reduce risk factors for coronary heart disease, high blood pressure and diabetes, all of which can contribute to heart failure. Lifestyle changes or medications, such as cholesterol-lowering statins, that address these risk factors may reduce the prevalence of heart failure.

In addition, a variety of medications are commonly used to treat heart failure. These include diuretics, ACE (angiotensin-converting enzyme) inhibitors and angiotensin receptor blockers, beta blockers, aldosterone antagonists and inotropes (such as digoxin). Depending on symptoms, many patients take a combination of two or more of these drugs. Surgery and medical devices also can treat the underlying causes of heart failure. Coronary bypass surgery, heart valve repair/replacement, implantable cardioverter-defibrillators, pacemakers, left ventricular assist devices, heart pumps and heart transplant all may improve symptoms, quality of life and survival in patients with heart failure. More potent diuretics and vasodilators, such as nitroglycerin, may be used to relieve symptoms by reducing congestion in the body's tissues.

Despite the wide range of treatment options, heart failure remains the leading cause of hospital admission in the U.S. for people over age 65 and morbidity and mortality from heart failure remain high. Numerous companies are working to address this unmet medical need and some products have either recently received approval or are in late-stage clinical studies. Most notably, Novartis' Entresto™ (formerly, LCZ696), a dual-acting angiotensin receptor/neprilysin inhibitor, was approved by the FDA in July 2015 and by the European regulatory agency in November 2015 as a treatment for patients with HFrEF. Novartis is also evaluating RLX030 (serelaxin), a relaxin receptor agonist, in a second Phase 3 study in patients with acute heart failure with cardiovascular mortality as the primary endpoint.

Although the product was approved for sale and launched in Russia in 2014 (under a different trade name), U.S. and EU regulatory agencies required further data for approval. Other development approaches include myofilament calcium sensitizers, stem cell therapy, gene therapy and drugs that enhance the uptake of calcium by the sarcoplasmic reticulum.

We are not aware of any pharmacologic therapy of proven benefit for patients with HFpEF. Therapies that have demonstrated efficacy in HFrEF have thus far failed to demonstrate improved outcomes in patients with HFpEF. A Phase 3 study of Novartis' LCZ696 in patients with HFpEF is underway, with an estimated completion date of May 2019. We are aware of other therapies under investigation in earlier stage clinical studies for the treatment of HFpEF.

If vepoloxamer is approved as a treatment for patients with HFrEF, it may compete with Novartis' Entresto and other treatment options currently available. In addition, should any therapy that receives approval prior to our product candidates become entrenched in the standard of care, the need for our product candidates may be diminished and/or such competing products may be difficult to displace.

Acquisition of SynthRx, Inc.

We acquired our vepoloxamer program through the acquisition of SynthRx, Inc. in April 2011. Pursuant to an agreement and plan of merger, upon completion of the acquisition, SynthRx became a wholly-owned subsidiary of ours. In December 2014, we effected a roll-up of SynthRx with and into Mast Therapeutics through a short-form merger under Delaware law.

The merger consideration related to the 2011 acquisition of SynthRx consisted solely of shares of our common stock. Additional payments of up to 12,478,050 shares of our common stock to the former stockholders of SynthRx may be triggered if and when the development of vepoloxamer for the treatment of sickle cell crisis in children achieves certain milestones. For additional information regarding these potential milestone share issuances, see "Acquisition of SynthRx" under Item 7 "Management's Discussion and Analysis of Financial Condition and Results of Operations" of this report.

Acquisition of Aires Pharmaceuticals

We acquired our AIR001 program through the acquisition of Aires Pharmaceuticals, Inc. in February 2014. Pursuant to an agreement and plan of merger, upon completion of the acquisition, Aires became a wholly-owned subsidiary of ours. The merger consideration related to the acquisition consisted solely of shares of our common stock. All of the shares issuable to former stockholders of Aires as merger consideration were issued during 2014. There are no milestone or earn-out payments under the merger agreement. For additional information regarding the merger consideration, see "Acquisition of Aires Pharmaceuticals" under Item 7 "Management's Discussion and Analysis of Financial Condition and Results of Operations" of this report.

Government Regulation

Governmental authorities in the U.S. and other countries extensively regulate the testing, manufacturing, labeling and packaging, storage, recordkeeping, advertising, promotion, import, export, marketing and distribution, among other things, of pharmaceutical products. In the U.S., the FDA, under the Federal Food, Drug and Cosmetic Act, or FDCA, and other federal statutes and regulations, subjects pharmaceutical products to rigorous review. If we do not comply with applicable requirements, we may be fined, the government may refuse to approve our marketing applications or allow us to manufacture or market our products, and we may be criminally prosecuted.

We and our third-party manufacturers, distributors and CROs may also be subject to regulations under other federal, state, and local laws, including the Occupational Safety and Health Act, the Environmental Protection Act, the Clean Air Act, the Health Insurance Portability and Accountability Act, privacy laws and import, export and customs regulations, as well as the laws and regulations of other countries.

FDA Approval Process

To obtain approval of a new drug product from the FDA, we must, among other requirements, submit data supporting its safety and efficacy, as well as detailed information on the manufacture and composition of the drug and proposed product labeling. The testing and collection of data and the preparation of necessary applications are expensive and time-consuming. The FDA may not act quickly or favorably in reviewing these applications, and we may encounter significant difficulties or costs in our efforts to obtain FDA approvals that could delay or preclude us from marketing our product candidates, including vepoloxamer and AIR001.

The process required by the FDA before a new drug may be marketed in the U.S. generally involves the following:

completion of nonclinical laboratory and animal testing performed in compliance with FDA regulations;
submission of an investigational new drug application, or IND, which must become effective before human clinical trials may begin and must be updated annually;
performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the product candidate for its intended use;
submission of an NDA after completion of pivotal clinical trials;
a determination by the FDA within 60 days of its receipt of the NDA to file the NDA for review;
satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities at which the API and finished drug product are produced and tested to assess compliance with current good manufacturing practices, or cGMP;

- possible inspection of selected clinical sites to confirm compliance with good clinical practices, or GCP, requirements and data integrity; and
- FDA review and approval of the NDA prior to any commercial marketing or sale of the drug product in the U.S.

Clinical studies are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety, and the efficacy criteria to be evaluated. A protocol for each clinical study and any subsequent protocol amendments must be submitted to the FDA as part of the IND.

The clinical investigation of an investigational new drug is generally divided into three phases that typically are conducted sequentially, but may overlap. The three phases are as follows:

- Phase 1. Phase 1 includes initial clinical studies introducing an investigational new drug into humans, and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. The number of participants included in Phase 1 studies is generally in the range of 20 to 80.
- Phase 2. Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.
- Phase 3. Phase 3 studies are typically expanded trials, which may be controlled or uncontrolled (which refers to a study that does not have a control, or comparison, group). They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information about the effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling and product approval. Phase 3 studies usually are conducted at geographically dispersed clinical study sites and include from several hundred to several thousand subjects.

A clinical study may combine the elements of more than one phase and the FDA generally requires two or more Phase 3 studies to support approval of a product candidate. A company’s designation of a clinical study as being of a particular phase is not necessarily indicative that the study will be sufficient to satisfy the FDA requirements of that phase because this determination cannot be made until the protocol and data have been submitted to and reviewed by the FDA. In addition, a clinical study may contain elements of more than one phase notwithstanding the designation of the study as being of a particular phase.

A pivotal study is a clinical study that is believed to satisfy FDA requirements for the evaluation of a product candidate’s safety and efficacy such that it can be used, alone or with other pivotal or non-pivotal studies, to justify regulatory approval. Generally, pivotal studies are Phase 3 studies, but they may be Phase 2 studies if the study design provides a well-controlled and reliable assessment of clinical benefit, particularly in an area of unmet medical need.

Clinical trials must be conducted in accordance with the FDA’s good clinical practices, or GCP, requirements. The FDA may order the temporary or permanent discontinuation of a clinical study at any time or impose other sanctions if it believes that the clinical study is not being conducted in accordance with FDA requirements or that the participants are being exposed to an unacceptable health risk. An institutional review board, or IRB, generally must approve the clinical trial design and process for obtaining patient informed consent at study sites that the IRB oversees and also may halt a study, either temporarily or permanently, for failure to comply with the IRB’s requirements, or may impose other conditions. Additionally, some clinical studies are overseen by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board or committee. This group recommends whether or not a trial may continue based on access to certain data from the study at designated check points.

As a product candidate moves through the clinical testing phases, manufacturing processes are further defined, refined, controlled and validated. The level of control and validation required by the FDA increases as clinical studies progress. We and the third-party manufacturers on which we rely for the manufacture of our product candidates and their respective components (including API) are subject to requirements that drugs be manufactured, packaged and labeled in conformity with cGMP. To comply with cGMP requirements, manufacturers must continue to spend time, money and effort to meet requirements relating to personnel, facilities, equipment, production and process, labeling and packaging, quality control, recordkeeping and other requirements.

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, detailed information on the product candidate is submitted to the FDA in the form of an NDA requesting approval to market the drug for one or more indications, together with payment of a significant user fee, unless waived. An NDA includes all relevant data available from pertinent nonclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information on the chemistry, manufacture, controls (CMC) and proposed labeling, among other things. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and efficacy of the product candidate for its intended use to the satisfaction of the FDA. In addition, under the Pediatric Research Equity Act, or PREA, an NDA or supplement to an NDA must contain data to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which orphan designation has been granted. However, if only one indication for a product has orphan drug designation, a pediatric assessment may still be required for any applications to market that same product for the non-orphan indication(s).

The FDA reviews all NDAs submitted to ensure that they are sufficiently complete for substantive review before it accepts them for filing. It may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. The FDA has 60 days after submission of an NDA to conduct an initial review to determine whether it is sufficient to accept for filing.

If an NDA submission is accepted for filing, the FDA begins an in-depth review of the NDA. Under the Prescription Drug User Fee Act, or PDUFA, the FDA sets a goal date by which it plans to complete its review. For a standard review, this goal date typically is 12 months from the date of submission of the NDA application. If the NDA application relates to an unmet medical need in a serious or life-threatening indication and is designated for priority review, the FDA’s goal date typically is eight (8) months from the date of NDA submission. However, PDUFA goal dates are not legal mandates and FDA response often occurs several months beyond the original PDUFA goal date. Further, the review process and the target response date under PDUFA may be extended if the FDA requests, or the NDA sponsor otherwise provides, additional information or clarification regarding information already provided in the NDA. The NDA review process can, accordingly, be very lengthy. During its review of an NDA, the FDA may refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it typically follows such recommendations. Data from clinical studies are not always conclusive and the FDA and/or any advisory committee it appoints may interpret data differently than the NDA sponsor.

After the FDA evaluates the NDA and inspects manufacturing facilities where the drug product and/or its API will be produced, it will either approve commercial marketing of the drug product with prescribing information for specific indications or issue a complete response letter indicating that the application is not ready for approval and stating the conditions that must be met in order to secure approval of the NDA. If the complete response letter requires additional data and the applicant subsequently submits that data, the FDA nevertheless may ultimately decide that the NDA does not satisfy its criteria for approval. The FDA could also approve the NDA with a Risk Evaluation and Mitigation

Strategy, or REMS, which could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling, development of adequate controls and specifications, or a commitment to conduct post-marketing testing. Such post-marketing testing may include Phase 4 clinical studies and surveillance to further assess and monitor the product's safety and efficacy after approval. Regulatory approval of products for serious or life-threatening indications may require that participants in clinical studies be followed for long periods to determine the overall survival benefit of the drug.

If the FDA approves any of our product candidates, we will be required to comply with a number of post-approval regulatory requirements. We would be required to report, among other things, certain adverse reactions and production problems to the FDA, provide updated safety and efficacy information and comply with requirements concerning advertising and promotional labeling for any of our products. Also, quality control and manufacturing procedures must continue to conform to cGMP after approval, and the FDA periodically inspects manufacturing facilities to assess compliance with cGMP, which imposes extensive procedural, substantive and record keeping requirements. If we seek to make certain changes to an approved product, such as certain manufacturing changes, we will need FDA review and approval before the change can be implemented. For example, if we change the manufacturer of a product or its API, the FDA may require stability or other data from the new manufacturer, which data will take time and is costly to

generate, and the delay associated with generating this data may cause interruptions in our ability to meet commercial demand, if any. While physicians may use products for indications that have not been approved by the FDA, we may not label or promote the product for an indication that has not been approved. Securing FDA approval for new indications is similar to the process for approval of the original indication and requires, among other things, submitting data from adequate and well-controlled studies that demonstrate the product's safety and efficacy in the new indication. Even if such studies are conducted, the FDA may not approve any change in a timely fashion, or at all.

We rely on third parties for the manufacture of our clinical trial material and we expect to rely on third-party manufacturers to produce commercial quantities of our drugs, should they receive regulatory approval in the future. Future FDA, state and/or foreign governmental agency inspections may identify compliance issues at these third-party facilities that may disrupt production or distribution or require substantial resources to correct. In addition, discovery of previously unknown problems with a product or the failure to comply with applicable requirements may result in restrictions on a product, manufacturer or holder of an approved NDA, including withdrawal or recall of the product from the market or other voluntary, FDA-initiated or judicial action that could delay or prohibit further marketing. Newly discovered or developed safety or efficacy data may require changes to a product's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. Many of the foregoing could limit the commercial value of a product or require us to commit substantial additional resources in connection with the approval of an investigational drug. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

Expedited Review Programs

Investigational drugs intended to treat serious or life-threatening conditions with unmet medical needs may be eligible for certain programs intended to expedite or facilitate the process for FDA review, such as the fast track and priority review designations. Fast track and priority review designations do not change the standards for FDA approval but may expedite the approval process.

Investigational drugs are eligible for fast track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast track designation applies to the combination of the drug and the specific indication for which it is being studied. For a drug with fast track designation, the FDA may consider a "rolling review" of the NDA, meaning it may agree to review sections of the NDA on a rolling basis before the complete application is submitted, which could expedite the FDA's review of the NDA. Fast track designation, however, does not guarantee that the FDA will agree to a rolling review of the NDA. An investigational drug is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an NDA for a drug product candidate designated for priority review in an effort to facilitate the review.

Orphan Drug Designation

The Orphan Drug Act, or ODA, provides for granting special status, referred to as orphan designation, to a drug intended to treat, diagnose or prevent a rare disease or condition that affects fewer than 200,000 people in the U.S. at the time of application for orphan designation. Orphan designation qualifies the sponsor of the product for the tax credit and marketing incentives of the ODA. Orphan designation must be requested by an applicant before submitting its marketing application for that drug for an orphan disease or condition. After the FDA grants orphan designation, the generic identity of the orphan drug and its potential use are disclosed publicly by the FDA. The first sponsor to receive FDA marketing approval for a drug with an orphan designation is entitled to a seven-year exclusive marketing period in the U.S. for that product for that indication and, typically, a waiver of the prescription drug user fee for its

marketing application. However, a drug that the FDA considers to be clinically superior to, or different from, another approved orphan drug, even though for the same indication, may also obtain approval in the U.S. during the seven-year exclusive marketing period. Orphan drug exclusive marketing rights may also be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug. The approval of an orphan designation request does not alter the standard regulatory requirements and process for obtaining marketing approval. Safety and efficacy of the product candidate must be established through adequate and well-controlled studies.

Legislation similar to the Orphan Drug Act has been enacted in countries other than the U.S., including the European Union. The legislation in the European Union is available for therapies addressing conditions that affect five or fewer out of 10,000 persons. The marketing exclusivity period is for ten years, although that period can be reduced to six years if, at the end of the fifth year, available evidence establishes that the product is sufficiently profitable not to justify maintenance of market exclusivity.

Pharmaceutical Pricing and Reimbursement

Sales of our products, if approved, will depend, in part, on the extent to which the costs of our products will be covered by third-party payors, such as government healthcare programs, private health insurers, managed healthcare providers, and other organizations. These third-party payors are increasingly challenging drug prices and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. If these third-party payors do not consider our products to be cost-effective compared to other therapies, they may not cover our products after approval as a benefit under their plans or, even if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis. In the case of products administered in an inpatient hospital setting, a level of payment that is inadequate to cover the cost to hospitals of providing and administering our products to patients, could delay acceptance of or limit our ability to penetrate the markets for our products.

Significant uncertainty exists as to the reimbursement status for newly approved drug products, including coding, coverage and payment. Sales of any products for which we obtain marketing approval will depend in part on coverage and adequate payment from third-party payors. There is no uniform policy requirement for coverage and reimbursement for drug products among third-party payors in the United States, therefore coverage and reimbursement for drug products can differ significantly from payor to payor. 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 products to each payor separately, with no assurance that coverage and adequate payment will be applied consistently or obtained. The process for determining whether a payor will cover and how much it will reimburse a product may be separate from the process of seeking approval of the product or for setting the price of the product. Even if reimbursement is provided, market acceptance of our products may be adversely affected if the amount of payment for our products proves to be unprofitable for healthcare providers or less profitable than alternative treatments or if administrative burdens make our products less desirable to use. Third-party payor reimbursement to providers of our products, if approved, may be subject to a bundled payment that also includes the procedure of administering our products. To the extent there is no separate payment for our product(s), there may be further uncertainty as to the adequacy of reimbursement amounts.

Additionally, the containment of healthcare costs has become a priority of federal and state governments and the prices of drug products have been a focus in this effort. For example, there have been several recent U.S. Congressional inquiries and proposed bills designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. We expect that federal, state and local governments in the U.S. will continue to consider legislation directed at lowering the total cost of healthcare. In addition, in certain foreign markets, the pricing of drug products is subject to government control and reimbursement may in some cases be unavailable or insufficient.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, collectively referred to as the ACA, enacted in March 2010, has had and is expected to continue to have a significant impact on the healthcare industry. The ACA, among other things, imposes a significant annual fee on certain companies that manufacture or import branded prescription drug products. The ACA also increased the Medicaid rebate rate and the volume of rebated drugs has been expanded to include beneficiaries in Medicaid managed care organizations. The ACA also expanded the 340B drug discount program (excluding orphan drugs), included a 50% discount on brand name drugs for Medicare Part D participants in the coverage gap, and revised the definition of “average manufacturer price” for reporting purposes, which could increase the amount of the Medicaid drug rebates paid to states. It also contains substantial provisions intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against healthcare fraud and abuse, add new transparency requirements for the healthcare industry, impose new taxes and fees on pharmaceutical manufacturers, and impose additional health policy reforms, any or all of which may affect our business. Since its enactment there

have been judicial and Congressional challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. Certain provisions of the ACA are not yet, or have only recently become, effective, and others have been temporarily suspended, but the ACA is likely to continue the downward pressure on pharmaceutical pricing, and may also increase our regulatory burdens and operating costs.

Other legislative changes have also been proposed and adopted since the ACA was enacted. For example, the Budget Control Act of 2011 resulted in aggregate reductions in Medicare payments to providers of up to 2% per fiscal year, which went into effect in 2013 and, following passage of the Bipartisan Budget Act of 2015, will stay in effect through 2025 unless additional Congressional action is taken. Additionally, the American Taxpayer Relief Act of 2012, 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. These new laws may result in additional reductions in Medicare and other healthcare funding.

It is uncertain whether and how future legislation, whether domestic or abroad, could affect prospects for our product candidates or what actions federal, state, or commercial payors for healthcare treatment and services may take in response to any such healthcare reform proposals or legislation. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures reforms may prevent or limit our ability to generate revenue, attain profitability or commercialize our product candidates.

Other Healthcare Laws and Compliance Requirements

In addition to FDA requirements, several other types of state and federal laws apply and will apply to our operations. These laws include, among others, healthcare information and data privacy protection laws, transparency laws, and fraud and abuse laws, such as anti-kickback and false claims laws.

The federal healthcare program anti-kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item, good, facility or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exceptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor.

Federal false claims laws and civil monetary penalties laws prohibit, among other things, any person or entity from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to have a false claim paid. Pharmaceutical and other healthcare companies have been prosecuted under these laws for, among other things, allegedly promoting their products for uses for which they were not approved and causing the submission of claims for payment for such use under federal healthcare programs. In addition, the Health Insurance Portability and Accountability Act of 1996, or HIPAA, prohibits persons and entities from knowingly and willfully executing a scheme to defraud any health care benefit program, including private payors, or 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 health care benefits, items or services.

HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, on certain types of individuals and entities, with respect to safeguarding the privacy, security and transmission of individually identifiable health information.

The federal transparency requirements under the ACA, requires certain manufacturers of drug products, medical devices, biologics and medical supplies to annually report to the Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals and physician ownership and investment interests. Compliance with such reporting requirements may be costly.

The majority of states also have statutes or regulations similar to the aforementioned federal anti-kickback and false claims laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor. We may be subject to state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. In addition, we may be subject to reporting requirements under state transparency laws, as well as state laws that require pharmaceutical companies to comply with the industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government that otherwise restricts certain payments that may be made to healthcare providers and entities.

Because we intend to commercialize products that could be reimbursed under federal and other governmental healthcare programs, we plan to develop a compliance program that establishes internal controls to facilitate

adherence to the rules and healthcare program requirements. Although compliance programs and adherence thereto may mitigate the risk of violation of and subsequent investigation and prosecution for violations of the laws described above, the risks cannot be eliminated entirely. In addition, due to the breadth of these laws and the narrowness of available statutory and regulatory exceptions, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If we or our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, individual imprisonment, disgorgement, exclusion of products from reimbursement under U.S. federal or state healthcare programs, contractual damages, reputational harm, administrative burdens, diminished profits and future earnings and/or the curtailment or restructuring of our operations.

Government Regulation Outside the U.S.

In addition to regulations in the U.S., we may be subject to a variety of regulations in foreign jurisdictions that govern, among other things, clinical studies and any commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product candidate, we must obtain the requisite approvals from regulatory authorities in foreign jurisdictions prior to the commencement of clinical studies or marketing and sale of the product in those countries. The foreign regulatory approval process

includes all of the risks associated with the FDA approval described above. Some foreign jurisdictions have a drug product approval process similar to that in the U.S., which requires the submission of a clinical trial application much like the IND prior to the commencement of clinical studies. In Europe, for example, a clinical trial application, or CTA, must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is approved in accordance with a country's requirements, clinical trial development may proceed.

To obtain regulatory approval of a product candidate under European Union regulatory systems, we would be required to submit a Marketing Authorisation Application, which is similar to the NDA, except that, among other things, there are country-specific document requirements. For countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical studies, product approval, pricing and reimbursement vary from country to country. In addition, regulatory approval of prices is required in most countries other than the U.S. We face the risk that the resulting prices would be insufficient to generate an acceptable return to us or any future partner of ours. If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Research and Development Expenses

Our research and development expenses were $28.3 million in 2015 and $19.4 million in 2014. Our research and development expenses for 2015 and 2014 consisted primarily of costs associated with the EPIC study, our Phase 2 study of vepoloxamer in heart failure, our discontinued Phase 2 study of vepoloxamer in acute limb ischemia, and research-related manufacturing for vepoloxamer and AIR001. See Item 7 "Management's Discussion and Analysis of Financial Condition and Results of Operations" in this report for more information regarding our research and development expenses.

Employees

As of March 10, 2016, Mast Therapeutics has 28 employees, all of which are full time. Our employees are not unionized and we believe that our relationship with our employees is good.

Formation

Our company was incorporated in Delaware in December 1995. In October 2000, we merged our wholly-owned subsidiary, Biokeys Acquisition Corp., with and into Biokeys, Inc. and changed our name to Biokeys Pharmaceuticals, Inc. In May 2003, we merged Biokeys, Inc., a wholly-owned subsidiary, with and into us and changed our name to ADVENTRX Pharmaceuticals, Inc. In March 2013, we merged Mast Therapeutics, Inc., a wholly-owned subsidiary, with and into us and changed our name to Mast Therapeutics, Inc.

Trademarks

"Mast Therapeutics," the Mast Therapeutics logo, "VOICE Crisis Alert," "Aironite," "SynthRx" and "Exelbine" are trademark or service marks of Mast Therapeutics, Inc. or its subsidiaries. This report contains additional trademarks, services marks or trade names of others, which are the property of their respective owners. Use or display by us of other parties' trademarks, service marks, trade names, trade dress or products is not intended to and does not imply a relationship with, or endorsements or sponsorship of, us by the trademark, service mark, trade name, trade dress or product owners.

Available Information

Our website is located at http://www.masttherapeutics.com. Information found on our website is not incorporated by reference into this annual report on Form 10-K. We make our filings with the U.S. Securities and Exchange Commission, or SEC, including our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and any amendments and exhibits to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, available free of charge on or through our website, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Copies of our SEC filings are located at the SEC's Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. Information on the operation of the Public Reference Room can be obtained by calling the SEC at 1-800-SEC-0330. In addition, the SEC maintains a website that contains reports, proxy and information statements, and other information regarding our filings at http://www.sec.gov.

Item 1A. Risk Factors.

Investment in our securities involves a high degree of risk and uncertainty. Our business, operating results, growth prospects and financial condition are subject to various risks, many of which are not exclusively within our control, that may cause actual performance to differ materially from historical or projected future performance. We urge investors to consider carefully the risks

described below, together with all of the information in this report and our other public filings, before making investment decisions regarding our securities. Each of these risk factors, as well as additional risks not presently known to us or that we currently deem immaterial, could adversely affect our business, operating results, growth prospects or financial condition, as well as the trading price of our common stock, in which case you may lose all or part of your investment.

RISKS RELATED TO OUR BUSINESS

Risks Related to Our Capital Requirements, Finances and Operations

We recently announced completion of patient enrollment in our Phase 3 clinical study of vepoloxamer in sickle cell crisis (EPIC) and expect to receive and announce top-line results in the second quarter of 2016. If EPIC results are not positive, our business, financial condition and results of operations could be materially adversely affected and the price of our common stock could decline significantly.

None of our product candidates has been approved for sale by any regulatory agency or is available for commercial sale. Since 2012, we have focused our resources primarily on the development of vepoloxamer and the success of our business currently is highly dependent on the success of our Phase 3 clinical study of vepoloxamer for treatment of vaso-occlusive crisis in patients with sickle cell disease and our ability to obtain regulatory approval to market vepoloxamer in the United States. However, results from the EPIC study, which we expect to announce in the second quarter of 2016, may not be positive or, even if the study demonstrates statistical significance in the primary endpoint, regulatory authorities may determine it does not demonstrate sufficient magnitude of clinical relevance or provide adequate safety and tolerability data to provide the basis for submission of a new drug application. If results from the EPIC study do not provide substantial evidence of vepoloxamer's efficacy and safety for the treatment of vaso-occlusive crisis, we would expect the FDA to require another Phase 3 study before accepting a NDA for vepoloxamer. Even if the FDA does not require another Phase 3 study, it may require other additional clinical or nonclinical studies to provide sufficient evidence of vepoloxamer's safety and tolerability for the treatment of vaso-occlusive crisis. If results from the EPIC study are not positive in the sense that we or other market participants determine they are unlikely to provide a sufficient basis for FDA review or approval of a vepoloxamer NDA, we expect the price of our common stock to decline significantly and you could lose all of your investment. In addition, if Hercules, in its discretion, determines that EPIC results are not positive, we will be required to prepay to Hercules $10 million of the principal balance under our debt facility on July 31, 2016. Further, in the event EPIC results are not positive, we plan to implement severe cost saving measures that likely would significantly delay our ability to complete development of vepoloxamer in sickle cell disease and to progress development of vepoloxamer and AIR001 in heart failure, and we may be compelled to not only to reduce the scope of our operations but also to sell or license our assets, including intellectual property assets, at less than we believe they should be valued. If EPIC results are not viewed as positive by us and others, our business, financial condition and results of operations will be significantly adversely impacted.

We have incurred net losses since our inception, we expect our operating expenses to continue to exceed revenue for the foreseeable future, and we may never generate revenue sufficient to achieve profitability. In addition, the report of our independent registered public accounting firm included in this Annual Report contains an emphasis of a matter explanatory paragraph with respect to our liquidity.

We are a clinical-stage biopharmaceutical company and have not generated sustainable revenue from operations or been profitable since inception, and we may never achieve profitability. We have devoted our resources to acquiring and developing proprietary product candidates, but such product candidates cannot be marketed until the regulatory process is completed and governmental approvals have been obtained. For the years ended December 31, 2015 and 2014, we incurred losses from operations of $39.4 million and $29.3 million, respectively, and our net cash used in

operating activities was $32.9 million and $24.6 million, respectively. At December 31, 2015, we had an accumulated deficit of $275.0 million, our cash, cash equivalents and investment securities were $41.0 million, and our working capital was $19.1 million. We expect to continue to incur substantial operating losses for the next several years as we advance our product candidates through clinical studies and other development activities and seek approval from the FDA and regulatory authorities outside of the U.S. to commercialize them. Accordingly, there is no current source of revenue from operations, much less profits, to sustain our present activities. Further, no revenue from operations will likely be available until, and unless, one of our product candidates is approved by the FDA or another regulatory agency and successfully marketed, or we enter into an arrangement that provides for licensing revenue or other partnering-related funding, outcomes which we may not achieve. If we obtain FDA approval of vepoloxamer in sickle cell disease, we may incur significant sales, marketing, and external manufacturing expenses, as well as continued research and development expenses. In addition, if by July 31, 2016, we have not demonstrated, to the reasonable satisfaction of Hercules, positive results from the EPIC study, we will be required to prepay to Hercules $10 million of the principal balance under our debt facility on July 31, 2016.

As more fully discussed in Note 1 to the consolidated financial statements included in this Annual Report and Item 7 “Management’s Discussion and Analysis of Financial Condition and Results of Operations” of this Annual Report, based on our anticipated operating expenses and current limited capital resources, we plan to raise additional capital before the fourth quarter of

2016 through equity or debt financings and/or through collaborations, including licensing arrangements, to fund our operations. As a result of the uncertainty surrounding our ability to raise additional capital and as to our future liquidity, the report of our independent registered public accounting firm included in this Annual Report includes an emphasis of a matter explanatory paragraph with respect to our liquidity. The consolidated financial statements included in this Annual Report have been prepared on a going concern basis, which contemplates the realization of assets and the satisfaction of liabilities in the normal course of business. However, if we are not successful in raising sufficient additional capital as needed, we may be compelled to reduce the scope of our operations and planned capital expenditures and/or sell or license certain assets at inopportune times, which could have a material and adverse effect on our ability to pursue our business strategy and our future financial condition.

Our management plans to take actions to raise additional capital to fund cash requirements after results of the EPIC study are known. However, there is no assurance that we will be able to obtain additional capital on favorable terms, or at all, or to successfully reduce costs in such a way that would continue to allow us to operate our business. If we are compelled to reduce the scope of our operations because we are unable to raise adequate additional capital as needed, which may be the case even if EPIC results are positive, our cost saving measures may delay our ability to seek approval for vepoloxamer in sickle cell disease and/or to commercialize vepoloxamer for sickle cell crisis, if approved, and could adversely affect our ability to meet future market demand.

We cannot predict the extent of our future operating losses and accumulated deficit, and we may never generate sufficient revenues to achieve or sustain profitability. To become and remain profitable, we must succeed in developing and obtaining required regulatory approvals and commercializing our product candidates. This will require us to succeed in a range of challenging activities, including all of the activities listed above. We may never succeed in these activities, and we may never obtain the FDA's or another regulatory authority's approval to market our product candidates or otherwise generate revenues sufficient to achieve profitability. If we do achieve profitability, we may not be able to sustain it.

The success of our business currently is dependent largely on the success of vepoloxamer and if regulatory approval is delayed or not granted or, if granted, but our product is not commercially successful, our business, financial condition and results of operations may be materially adversely affected and the price of our common stock may decline.

None of our product candidates has been approved for sale by any regulatory agency or is available for commercial sale. We are focusing our resources primarily on the development of vepoloxamer. Accordingly, the success of our business currently is highly dependent on our ability, or that of a future partner, to successfully develop, obtain regulatory approval for and then successfully commercialize vepoloxamer and our efforts, or those of a future partner, in this regard may prove unsuccessful. The regulatory approval and successful commercialization of vepoloxamer is subject to many risks, including the risks discussed in other risk factors below, and vepoloxamer may not receive marketing approval from the FDA or any regulatory agency. If the results or timing of our clinical or nonclinical studies, regulatory filings, the regulatory process, regulatory developments, commercialization, and other activities, actions or decisions related to vepoloxamer do not meet our expectations or those of securities market participants, the market price of our common stock could decline significantly. If the FDA determines that the EPIC study does not provide sufficient efficacy and safety data for marketing approval, vepoloxamer may require costly additional clinical development prior to approval for treatment of vaso-occlusive crisis in patients with sickle cell disease in the United States. Even if the EPIC study is successful and additional studies are not required prior to approval in sickle cell disease, regulatory approval and commercialization of vepoloxamer may be delayed or denied for a variety of reasons, including difficulties and/or delays in manufacturing and related activities or commercial launch activities, including hiring sales and marketing personnel and creating commercial infrastructure. If any of our product candidates is approved by the FDA or any foreign regulatory agency, our ability to generate revenue will depend in substantial part on the extent to which that drug product is accepted by the medical community and reimbursed by third-party payors, as well as our ability to market and sell the product and ensure that our third-party manufacturers produce it in

quantities sufficient to meet commercial demand, if any.

The terms of our debt facility place restrictions on our operating and financial flexibility, and failure to comply with covenants or to satisfy certain conditions of the agreement governing the debt facility may result in acceleration of our repayment obligations and foreclosure on our pledged assets, which could significantly harm our liquidity, financial condition, operating results, business and prospects and cause the price of our common stock to decline.

We have an outstanding principal balance of $15 million under our debt facility with Hercules Technology Growth Capital, Inc. and Hercules Technology III, L.P. (collectively referred to as Hercules) that is secured by a lien covering substantially all of our assets, excluding intellectual property, but including proceeds from the sale, licensing or disposition of our intellectual property. The loan and security agreement governing the debt facility requires us to comply with a number of covenants (affirmative and negative), including restrictive covenants that limit our ability to: incur additional indebtedness; encumber the collateral securing the loan; acquire, own or make investments; repurchase or redeem any class of stock or other equity interest; declare or pay any cash dividend or make a cash distribution on any class of stock or other equity interest; transfer a material portion of our assets; acquire other businesses; and merge or consolidate with or into any other organization or otherwise suffer a change in control, in each case subject to exceptions. Our intellectual property also is subject to customary negative covenants. In addition, subject to limited exceptions, Hercules could declare an event of default upon the occurrence of any event that it interprets as having a material adverse effect upon our business, operations, properties, assets, or financial condition or upon our ability to perform or pay the secured obligations under the loan and security agreement or upon the collateral or Hercules' liens on the collateral under the agreement, thereby requiring us to repay the loan immediately, together with a prepayment charge of up to 3% of the then outstanding principal balance and end-of-term charge of $712,500, or renegotiate the terms of the agreement. Although, in and of itself, the occurrence of adverse results or delays in any clinical study or the denial, delay or limitation of approval of or taking of any other regulatory action by the FDA or another governmental entity will not constitute a material adverse effect under our loan and security agreement with Hercules, Hercules may determine that such an event together with contemporaneous events or circumstances constitutes a material adverse effect upon our business, operations, properties, assets, or financial condition or upon our ability to perform or pay the secured obligations under the loan and security agreement. If we default under the facility, Hercules may accelerate all of our repayment obligations and, if we are unable to access funds to meet those obligations or to renegotiate our agreement, Hercules could take control of our pledged assets and we could immediately cease operations. If we were to renegotiate our agreement under such circumstances, the terms may be significantly less favorable to us. If we were liquidated, Hercules' right to repayment would be senior to the rights of our stockholders to receive any proceeds from the liquidation. Any declaration by Hercules of an event of default could significantly harm our liquidity, financial condition, operating results, business, and prospects and cause the price of our common stock to decline.

In addition, our loan and security agreement with Hercules requires us to prepay $10 million of the principal balance on July 31, 2016, unless we demonstrate, to the reasonable satisfaction of Hercules, positive results from the EPIC study by July 31, 2016. If this prepayment obligation is triggered, the payment of $10 million to Hercules that would be required by July 31, 2016 could not only significantly harm our liquidity, financial condition and operating results and cause the price of our common stock to decline, but also significantly impair our ability to raise adequate additional capital to fund our operations and pursue our business strategy.

The process of developing and seeking regulatory approval of, and ultimately commercializing, investigational new drug products requires expenditure of substantial resources, and we cannot estimate with reasonable certainty the duration of or costs to complete our development programs.

Our capital requirements for the foreseeable future will depend in large part on, and could increase significantly as a result of, our expenditures on our development programs. Future expenditures on our development programs are subject to many uncertainties, and will depend on, and could increase significantly as a result of, many factors, including:

the number, size, complexity, results and timing of our drug development programs;
the number of clinical and nonclinical studies necessary to demonstrate acceptable evidence of the safety and efficacy of a product candidate in a particular indication;
the number of patients who participate, the rate of enrollment, and the ratio of randomized to evaluable patients in each clinical study;
the number and location of sites and the rate of site initiation in each study;
the duration of patient treatment and follow-up;
the potential for additional safety monitoring or other post-marketing studies that may be requested by regulatory agencies;

- the time and cost to manufacture clinical trial material and commercial product, including process development and scale-up activities, and to conduct stability studies, which can last several years;
- the costs, requirements, timing of, and the ability to, secure regulatory approvals;
- the timing and terms of any collaborative or other strategic arrangement that we may establish;
- the extent to which we increase our workforce and the costs involved in recruiting, training and incentivizing new employees;
- the costs related to developing, acquiring and/or contracting for sales, marketing and distribution capabilities, supply chain management capabilities, and regulatory compliance capabilities, if we obtain regulatory approval for a product candidate and commercialize it without a partner;
- competing technologies and market developments; and
- the costs involved in establishing, enforcing or defending patent claims and other proprietary rights.

We may not be able to raise capital when needed or reduce other expenditures to offset expenditures on our development programs, which could have a material adverse effect on our financial condition and ability to pursue our business strategy.

We will need to obtain additional funding to pursue our current business strategy and continue as a going concern and we may not be able to obtain such funding on a timely basis, or on commercially reasonable terms, or at all. Any capital-raising transaction we are able to complete may result in substantial dilution to our existing stockholders, require us to relinquish significant rights, or restrict our operations.

As discussed above, based on our projected operating expenses and capital needs, our cash, cash equivalents and investment securities as of December 31, 2015, together with the net proceeds from the underwritten public offering we completed in February 2016, we intend to raise additional capital before the fourth quarter of 2016 through equity or debt financings and/or through collaborations, including licensing arrangements. If we are unable to raise sufficient additional capital before that time, or in the event of negative results in the EPIC study and prepayment to Hercules on July 31, 2016 of $10 million of the principal balance under our debt facility, we intend to reduce the scope of our planned operations. In that case, we expect that our current cash, cash equivalents and investment securities will be sufficient to fund our operations, as reduced in scope, into the first quarter of 2017. The cost saving measures we would implement in the event of results from EPIC are positive but we are unable to raise additional capital or in the event results from EPIC are negative, likely would delay our ability to complete development of vepoloxamer in sickle cell disease, obtain regulatory approvals to commercialize vepoloxamer, and, if approved, may adversely affect our ability to meet market demand, as well as impair progress on our other development programs. In addition, we may utilize our current financial resources sooner than we currently expect if we incur unanticipated expenses or the assumptions on which we have based our forecasts and contingency plans prove to be wrong.

Although we were able to raise significant funds in the past through equity financings and a debt financing, the conditions of and our access to capital markets are highly variable and adequate additional equity or debt financing may not be available to us in the future on acceptable terms, or on a timely basis, or at all. Further, each of these financing alternatives carries risks. Raising capital through the issuance of our common stock, or securities convertible into or exercisable for our common stock, may depress the market price of our stock and may substantially dilute our existing stockholders. If instead we seek to raise capital through strategic transactions, such as licensing arrangements or sales of one or more of our technologies or product candidates, we may be required to relinquish valuable rights and dilute the current and future value of our assets. For example, any licensing arrangement likely would require us to share with our licensee a significant portion of any revenues generated by our licensed technologies. Additionally, our control over the development and/or marketing of any products or product candidates licensed or sold to third parties likely would be reduced and thus we may not realize the full value of any such products or product candidates. Debt financings would likely involve covenants and/or repayment provisions that would restrict our operations. These restrictive covenants may include limitations on additional borrowing and specific restrictions on the use of our assets, including requirements to maintain specified amounts of cash or restrictions on our ability to license or sell our

intellectual property assets, as well as prohibitions on our ability to create liens or make investments and may, among other things, preclude us from making distributions to stockholders (either by paying dividends or redeeming stock) and taking other actions beneficial to our stockholders. In addition, investors could impose more one-sided investment terms and conditions on companies that have or are perceived to have limited remaining funds or limited ability to raise additional funds. The lower our cash balance, the more difficult it is likely to be for us to raise additional capital on commercially reasonable terms, or at all.

For particular development programs, such as development of vepoloxamer for resuscitation following major trauma, we plan to seek funding from the U.S. government. The process of obtaining government contracts is lengthy and uncertain and highly competitive. In addition, changes in government budgets and agendas may result in decreased availability of funding for drug research and development. If we do secure government funding, the contracts for such funding may contain termination and audit provisions that are unfavorable to us and cause us to incur significant additional administrative expense. In addition, the U.S. government may require "march-in" rights that allow it to grant licenses to inventions that arise from development programs it funds if, for example, we do not commercialize the technology within a certain timeframe or the government deems such action necessary to alleviate health or safety needs that are not being reasonably satisfied by us. If the government exercises its march-in rights, we could be obligated to license intellectual property developed by us on terms unfavorable to us and we may not receive compensation from the government for its exercise of such rights.

Notwithstanding efforts on our part to raise additional capital, adequate additional funding may not be available on acceptable terms, or on a timely basis, or at all. Even if we incur costs in pursuing, evaluating and negotiating particular capital-raising and/or strategic or partnering transactions, our efforts may not prove successful. We believe global economic conditions, such as volatility in the U.S. and international equity markets, may adversely impact our ability to raise additional capital. Our failure to raise capital as needed would have a material adverse effect on our financial condition and ability to pursue our business strategy and we potentially may be unable to continue as a going concern and required to liquidate our assets and dissolve our company.

Our ability to raise capital may be limited by applicable laws and regulations.

Historically, we have raised capital primarily through the sale of our equity securities. In recent years, we have raised substantial funding through equity offerings conducted under "shelf" registration statements on Form S-3. Using a shelf registration statement on Form S-3 to raise additional capital generally takes less time and is less expensive than other means, such as conducting an offering under a Form S-1 registration statement. However, our ability to raise capital using a shelf registration statement may be limited by, among other things, current SEC rules and regulations. Under current SEC rules and regulations, we must meet certain requirements to use a Form S-3 registration statement to raise capital without restriction as to the amount of the market value of securities sold thereunder. One such requirement is that the market value of our outstanding common stock held by non-affiliates, or public float, be at least $75.0 million as of a date within 60 days prior to the date of filing the Form S-3. If we do not meet that requirement, then the aggregate market value of securities sold by us or on our behalf under the Form S-3 in any 12-month period is limited to an aggregate of one-third of our public float. Moreover, even if we meet the public float requirement at the time we file a Form S-3, SEC rules and regulations require that we periodically re-evaluate the value of our public float, and if, at a re-evaluation date, our public float is less than $75.0 million, we would become subject to the one-third of public float limitation described above. If our ability to utilize a Form S-3 registration statement for a primary offering of our securities is limited to one-third of our public float, we may conduct such an offering pursuant to an exemption from registration under the Securities Act or under a Form S-1 registration statement, which we have done in the past, including in June 2013, and we would expect either of those alternatives to increase the cost of raising additional capital relative to utilizing a Form S-3 registration statement.

In addition, under current SEC rules and regulations, our common stock must be listed and registered on a national securities exchange in order to utilize a Form S-3 registration statement (i) for a primary offering, if our public float is not at least $75.0 million as of a date within 60 days prior to the date of filing the Form S-3, or a re-evaluation date, whichever is later, and (ii) to register the resale of our securities by persons other than us (i.e., a resale offering). While currently our common stock is listed on the NYSE MKT equities market, there can be no assurance that we will be able to maintain such listing. The NYSE MKT reviews the appropriateness of continued listing of any issuer that falls below the exchange's continued listing standards. Previously, including during part of 2010, we were not in compliance with certain NYSE MKT continued listing standards and were at risk of having our common stock

delisted from the NYSE MKT equities market. For additional information regarding this risk, see the risk factor below titled “If we are unable to maintain compliance with NYSE MKT continued listing standards, our common stock may be delisted from the NYSE MKT equities market, which would likely cause the liquidity and market price of our common stock to decline.”

Our ability to timely raise sufficient additional capital also may be limited by the NYSE MKT’s stockholder approval requirements for transactions involving the issuance of our common stock or securities convertible into our common stock. For instance, the NYSE MKT requires that we obtain stockholder approval of any transaction involving the sale, issuance or potential issuance by us of our common stock (or securities convertible into our common stock) at a price less than the greater of book or market value, which (together with sales by our officers, directors and principal stockholders) equals 20% or more of our then outstanding common stock, unless the transaction is considered a “public offering” by the NYSE MKT staff. Based on 192,836,367 shares of our common stock outstanding as of March 10, 2016 and the closing price per share of our common stock on such date, which was $0.28, we could not raise more than approximately $10.8 million without obtaining stockholder approval, unless the transaction is deemed a public offering or does not involve the sale, issuance or potential issuance by us of our common stock (or securities convertible into our common stock) at a price less than the greater of book or market value. In addition, certain prior sales by us may be aggregated with any offering we may propose in the future, further limiting the amount we could raise in any future offering that is not considered a public offering by the NYSE MKT staff and involves the sale, issuance or potential issuance by us of

our common stock (or securities convertible into our common stock) at a price less than the greater of book or market value. The NYSE MKT also requires that we obtain stockholder approval if the issuance or potential issuance of additional shares will be considered by the NYSE MKT staff to result in a change of control of our company.

Obtaining stockholder approval is a costly and time-consuming process. If we are required to obtain stockholder approval for a potential transaction, we would expect to spend substantial additional money and resources. In addition, seeking stockholder approval would delay our receipt of otherwise available capital, which may materially and adversely affect our ability to execute our current business strategy, and there is no guarantee our stockholders ultimately would approve a proposed transaction. A public offering under the NYSE MKT rules typically involves broadly announcing the proposed transaction, which often times has the effect of depressing the issuer's stock price, as occurred following our issuance of a press release on February 9, 2016 announcing a proposed underwritten public offering. Accordingly, the price at which we could sell our securities in a public offering may be less, and the dilution existing stockholders experience may in turn be greater, than if we were able to raise capital through other means.

If we are unable to raise sufficient additional capital as needed, we may be forced to delay, reduce or discontinue development of our product candidates and commercialization efforts, partner them or dispose of our assets at inopportune times or pursue less expensive but higher-risk and/or lower-return development paths.

If we are not able to raise sufficient additional capital as needed, we may be required to delay, reduce or discontinue one or more of our development programs and commercialization efforts, to seek collaborators or buyers at an earlier stage than otherwise would be desirable or on terms less favorable than might otherwise be available, or to liquidate our assets and dissolve our company. For example, if we do not have sufficient capital, we may determine to delay or suspend planned or ongoing clinical or nonclinical studies or other development activities and/or not to investigate certain additional indications for vepoloxamer or to conduct other studies or activities intended to enhance our intellectual property position, improve the probability of regulatory approval, or expand the scope of vepoloxamer's clinical benefit and market potential, or we may not make investments desirable for commercial success of vepoloxamer as a treatment for sickle cell crisis, if approved. Delays in and/or reduction of development and commercial-readiness activities could impair our ability to realize the full clinical and market potential of a product candidate and have a material adverse effect on our business and financial condition. In addition, suspension or discontinuation of a development program may be viewed negatively, which could adversely affect our stock price.

To the extent we discontinue independent development of a product candidate, we may not realize any value from our investment in the discontinued program. Even if we pursue a strategic option, such as partnering, selling or exclusively licensing the program to a third party, such an option may be not be available on acceptable terms or at all. For example, in prior years, we were focused on developing Exelbine and ANX-514 and expended significant resources on their development; however, in 2011 and 2012, respectively, we elected to discontinue independent development of those programs. Although from time to time we evaluate other opportunities for further development of those agents, such as partnering and licensing arrangements, none may be available and we may not realize any return on our investment in those programs.

In addition, if we determine our financial resources are insufficient to fund our operations even after implementing significant cost saving measures and reducing the scope of our operations, we may be required to dispose of or liquidate our assets at values significantly less than what we believe their values to be and at which they are carried on our financial statements.

Our business may suffer if we are unable to retain and attract highly qualified personnel and manage internal growth.

Currently, we have a small number of employees and we rely on third parties to perform many essential services for us. Our ability to execute on our business strategy and compete in the highly competitive biopharmaceutical, specialty

pharmaceutical, pharmaceutical and biotechnology industries depends, in part, on our ability to attract and retain highly qualified personnel. Our industries in general and our company in particular historically have experienced a high rate of turnover of management personnel. Loss of key employees, including any of our executive officers, could adversely affect our ability to successfully execute our current business strategy, which could negatively affect our stock price. Replacing key employees may be a difficult, costly and protracted process, particularly due to the fact that we may not have other personnel with the capacity to assume all of the responsibilities of a key employee. In addition, we may seek to increase the size of our organization as development of our product candidates progresses, and in particular, in connection with independent commercialization of vepoloxamer as a therapy for patients with sickle cell disease, if approved by the FDA. There is intense competition from other companies and organizations for qualified personnel in the areas of our activities. Other companies and organizations with which we compete for personnel may have greater financial and other resources and different risk profiles than we do, and a history of successful development and commercialization of their product candidates, which may make them more attractive employers. Our ability to compete for qualified personnel also may be adversely affected by our highly volatile stock price. The value of stock options we offer to candidates to induce their employment and to our employees to retain and incentivize them is significantly affected by movements in our stock price that we cannot control and may at any time be insufficient to counteract more lucrative offers from other companies. All of our employees, including our executive

officers, may terminate their employment with us at any time without notice. If we cannot attract and retain skilled personnel, as needed, we may not achieve our development and other goals.

Future internal growth could impose significant added responsibilities on our management, including the need to identify, recruit, maintain, motivate and integrate additional employees. We may need to devote a significant amount of time to managing these activities and may not be able to do so effectively. If we are unable to effectively manage future internal growth, our expenses may increase more than expected, we may not be able to achieve our development goals, and our ability to generate and/or grow revenue could be diminished. In the meantime, the success of our business also depends, in part, on our ability to develop and maintain relationships with respected service providers and industry-leading consultants and advisers. If we cannot develop and maintain such relationships, as needed, the rate and success at which we can develop and commercialize product candidates may be limited. In addition, our outsourcing strategy, which has included engaging consultants that spend considerable time in our office to manage key functional areas, may subject us to scrutiny under labor laws and regulations, which may divert management time and attention and have an adverse effect on our business and financial condition.

If we determine to grow our business through the acquisition of new technologies and/or product candidates, our existing stockholders may experience substantial dilution, we may fail to realize the benefits of any future strategic acquisition or investment, and we may incur unexpected costs and disruptions to our business.

From time to time, we may evaluate pipeline expansion opportunities and execute the acquisition of new technologies and/or product candidates that we believe will increase the long-term value of our company. The process of identifying, evaluating, negotiating and implementing the purchase or license of new assets is lengthy and complex and may be disruptive to our operations and/or distracting for our personnel. We have limited resources with respect to identifying, evaluating, negotiating and implementing the acquisition of new assets or rights thereto and integrating them into our current infrastructure. Supplementing our current resources to complete one or more of these transactions may be costly.

We may use cash, shares of our common stock, securities convertible into or exercisable for shares of our common stock or a combination of cash and our securities to pay the purchase price or license fee for any future strategic transaction. The use of cash could negatively impact our financial position and ability to advance our current development programs. The use of shares of our common stock or securities convertible into or exercisable for shares of our common stock would dilute the holdings of our existing stockholders and such dilution could be substantial. For example, to acquire SynthRx we agreed to issue up to such number of shares that represented a 41% ownership stake in our company at the time we completed the acquisition in April 2011, if development of vepoloxamer fully achieved the milestones under the merger agreement. The issuance of shares in connection with future strategic transactions, if any, may result in the stockholders who own the majority of our voting securities prior to one or more of such transactions owning less than a majority after such transactions.

Further, strategic transactions may entail numerous operational and financial risks, including:

- exposure to unknown liabilities;
- disruption of our business and diversion of our management’s time and attention to develop and/or commercialize acquired technologies and/or products candidates;
- incurrence of substantial debt to pay for acquisitions;
- greater than anticipated difficulty and cost in combining the operations and personnel of any acquired businesses with our operations and personnel;
- impairment of relationships with key suppliers of any acquired business due to changes in management and ownership; and
- inability to retain key employees of any acquired business.

Our stockholders will be required to rely on the judgment of our management and board of directors as to which new product candidates and/or technologies we pursue and may have limited or no opportunity to evaluate potential new assets prior to completion of a transaction, including the terms of acquisition, the costs of their future development and their commercial potential. We may devote resources to potential acquisition or in-licensing opportunities that are never completed, or we may fail to realize the anticipated benefits of such efforts. Any technology and/or product candidate that we acquire or to which we acquire rights likely will require additional development efforts prior to commercial sale, including extensive clinical testing and approval by the FDA and applicable foreign regulatory authorities. All product candidates are subject to risks of failure typical of pharmaceutical product

development, including the possibility that a product candidate will not be shown to be sufficiently safe and effective for approval by regulatory authorities and other risks described under the section titled “Risks Related to Drug Development and Commercialization.”

We expend substantial resources to comply with laws and regulations relating to public companies, and any failure to maintain compliance could subject us to regulatory scrutiny and cause investors to lose confidence in our company, which could harm our business and have a material adverse effect on our stock price.

Laws and regulations affecting public companies, including provisions of the Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010 and the Sarbanes-Oxley Act of 2002, or SOX, and the related rules and regulations adopted by the SEC and by the NYSE MKT have resulted in, and will continue to result in, significant costs to us as we evaluate the implications of these rules and respond to their requirements. For example, compliance with Section 404 of SOX, including performing the system and process documentation and evaluation necessary to issue our annual report on the effectiveness of our internal control over financial reporting and, if applicable, obtain the required attestation report from our independent registered public accounting firm, requires us to incur substantial expense and expend significant management time. Further, we have in the past discovered, and may in the future discover, areas of internal controls that need improvement. If we identify deficiencies in our internal controls that are deemed to be material weaknesses, we could become subject to scrutiny by regulatory authorities and lose investor confidence in the accuracy and completeness of our financial reports, which could have a material adverse effect on our stock price. Internal control over financial reporting cannot provide absolute assurance of achieving financial reporting objectives because of its inherent limitations, including the possibility of human error and circumvention by collusion or overriding of controls. Accordingly, even an effective internal control system may not prevent or detect material misstatements on a timely basis, or at all. Also, previously effective controls may become inadequate over time as a result of changes in our business or operating structure, and we may fail to take measures to evaluate the adequacy of and update these controls, as necessary, which could lead to a material misstatement.

In addition, new laws and regulations could make it more difficult or more costly for us to obtain certain types of insurance, including director and officer liability insurance, and we may be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the coverage that is the same or similar to our current coverage. The impact of these events could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors or board committees, and as our executive officers. We cannot predict or estimate with any reasonable accuracy the total amount or timing of the costs we may incur to comply with these laws and regulations.

Our ability to use net operating loss carry forwards and research and development tax credits to offset future taxable income or future tax will be limited, and may be limited further in the future, due to changes in ownership (within the meaning of IRC Section 382) that have occurred and may occur in the future.

In general, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or IRC, a corporation that undergoes an “ownership change” is subject to limitations on its ability to utilize its pre-change net operating losses, or NOLs, and certain other tax assets to offset future taxable income, and an ownership change is generally defined as a cumulative change of 50% or more in the ownership positions of certain stockholders during a rolling three year period. In 2012, we had identified an ownership change within the meaning of IRC Section 382 that occurred on November 11, 2011 as a result of an equity financing we completed on that date and, consequently, we do not expect to be eligible to utilize the NOL carry forwards and research and development tax credits we had accumulated as of November 11, 2011. We completed a formal study to determine if any ownership changes within the meaning of IRC Section 382 had occurred during the years ended December 31, 2012, 2013 and 2014. None were identified. However, other ownership changes within the meaning of IRC Section 382 may occur in the future or may already have occurred in connection with the public offering of our common stock and warrants completed in February 2016, which could eliminate or restrict our ability to use NOL carry forwards and research and development

tax credits generated after November 11, 2011. Limitations on our ability to use NOL carry forwards and research and development tax credits to offset future taxable income could require us to pay U.S. federal income taxes earlier than would be required if such limitations were not in effect. Similar rules and limitations may apply for state income tax purposes.

Our business and operations would suffer in the event of computer system failures, cyber-attacks on our systems or deficiency in our cyber security.

Despite the implementation of security measures, our internal computer systems, and those of third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, malware, natural disasters, fire, terrorism, war and telecommunication, electrical failures, cyber-attacks or cyber-intrusions over the Internet, attachments to emails, persons inside our organization, or persons with access to systems inside our organization. The risk of a security breach or disruption, particularly through cyber-attacks or cyber intrusion, including by computer hackers, foreign governments, and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. In addition, our systems or those of third parties on which we rely safeguard important confidential personal data regarding our

employees and patients enrolled in our clinical trials. If a disruption event were to occur and cause interruptions in our operations, it could result in a disruption of our drug development programs. For example, the loss of clinical trial data from completed, 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 results 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 vepoloxamer, AIR001 and any future product candidates we may develop could be delayed.

Our employees, independent contractors and consultants, principal investigators, CROs, CMOs and other vendors, and any future commercial partners may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation.

We are exposed to the risk that our employees, independent contractors and consultants, principal investigators, CROs, CMOs and other vendors, and any future commercial partners may engage in fraudulent conduct or other misconduct, including intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, to provide accurate information to the FDA or comparable foreign regulatory authorities, to comply with manufacturing standards required by cGMP or that we establish, to comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, and to report financial information or data accurately or disclose unauthorized activities to us. The misconduct of our employees and others we engage to provide services to us 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 maintain a code of business conduct and ethics for our directors, officers and employees, but it is not always possible to identify and deter such misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

Laws and regulations governing conduct of international operations may negatively impact our development, manufacture and sale of products outside of the United States and require us to develop and implement costly compliance programs.

Currently, except for our clinical study sites and manufacturing activities performed by third party vendors located outside of the United States, substantially all of our operations are in the U.S.; however, we may seek to expand our operations outside of the U.S., particularly as we seek to commercialize our product candidates outside of the U.S., and we must comply with numerous laws and regulations in each jurisdiction in which we plan to operate. The creation and implementation of international business practices compliance programs is costly and such programs are difficult to enforce, particularly where we must rely on third parties.

The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring such companies 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. The anti-bribery provisions of the FCPA are enforced primarily by the U.S. Department of Justice. The SEC is involved with enforcement of the books and records provisions of the FCPA.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the pharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

Various laws, regulations and executive orders also restrict the use and dissemination outside of the U.S., or the sharing with certain foreign nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. Expanding our presence outside of the U.S. will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling our product candidates outside of the U.S., which could limit our growth potential and increase our development costs.

The failure to comply with laws governing international business practices may result in substantial penalties, including suspension or debarment from government contracting. Violation of the FCPA can result in significant civil and criminal penalties. Indictment alone under the FCPA can lead to suspension of the right to do business with the U.S. government until the pending claims are resolved. Conviction of a violation of the FCPA can result in long-term disqualification as a government contractor. The termination of a government contract or relationship as a result of our failure to satisfy any of our obligations under laws governing international business practices would have a negative impact on our operations and harm our reputation and ability to procure government contracts. Additionally, the SEC also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

Our operations might be interrupted by the occurrence of a natural disaster or other catastrophic event.

Our corporate headquarters are located in a single commercial facility in San Diego, California. Important documents and records, including copies of our regulatory documents and other records for our product candidates, are located at our facilities and we depend on our facilities for the continued operation of our business. Natural disasters and other catastrophic events, such as wildfires and other fires, earthquakes and extended power interruptions, which have impacted San Diego businesses in the past, and terrorist attacks or severe weather conditions, could significantly disrupt our operations and result in additional, unplanned expense. As a small company with limited resources, we have not prepared or implemented a formal business continuity or disaster recovery plan and any natural disaster or catastrophic event could disrupt our business operations and result in setbacks to our development programs. Even though we believe we carry commercially reasonable insurance, we might suffer losses that are not covered by or exceed the coverage available under these insurance policies.

Risks Related to Drug Development and Commercialization

There is significant uncertainty regarding the regulatory approval process for any investigational drug, including vepoloxamer, further testing and validation of our product candidates and related manufacturing processes are required, and regulatory approval may be conditioned, delayed or denied, which could delay or prevent us from successfully marketing our product candidates and substantially harm our business.

Human pharmaceutical products generally are subject to rigorous nonclinical testing and clinical studies and other approval procedures mandated by the FDA and foreign regulatory authorities. Various federal and foreign statutes and regulations also govern or influence the manufacturing, safety, labeling, storage, record keeping and marketing of pharmaceutical products. The process of obtaining these approvals and the subsequent compliance with appropriate U.S. and foreign statutes and regulations is time-consuming and requires the expenditure of substantial resources.

Significant uncertainty exists with respect to the regulatory approval process for any investigational drug, including vepoloxamer for patients with sickle cell disease. Regardless of guidance the FDA may give a drug's sponsor during its development, the FDA retains complete discretion in deciding whether to accept a NDA for filing or, if accepted, approve an NDA. There will be many components to our NDA submission for vepoloxamer beyond the data from the EPIC and EPIC-E studies. For example, in addition to reviewing the safety and efficacy data from EPIC and EPIC-E and from clinical and nonclinical studies of poloxamer 188 and/or vepoloxamer completed, in some cases, more than 20 years ago, the FDA will review our internal systems and processes, as well as those of our CROs, CMOs and other vendors, related to development of our product candidate, including those pertaining to our clinical studies and manufacturing processes. Before accepting an NDA for vepoloxamer or before approving the NDA, the FDA may request that we provide significant additional information and there is no guarantee that our product candidate will be approved for the treatment of vaso-occlusive crisis in patients with sickle cell disease or any other indication. The FDA may choose not to approve our NDA for vepoloxamer for any of a variety of reasons, including a decision related to the safety or efficacy data, manufacturing controls or systems, or for any other issues that the agency may

identify related to the development of our product candidate. Even if the EPIC study is successful in providing statistically significant evidence of the efficacy and safety of vepoloxamer to treat vaso-occlusive crisis of sickle cell disease, the FDA may not consider efficacy and safety data from a single Phase 3 study adequate scientific support for a conclusion of effectiveness and/or safety and may require an additional Phase 3 or other studies prior to granting marketing approval. If this were to occur, the overall development cost for vepoloxamer in sickle cell disease would be substantially increased and an alternative therapy could be approved and introduced to the market in the meantime, which could adversely affect our business, financial condition and results of operations.

We expect our MAST platform to accelerate development of vepoloxamer as compared to other new molecular entities for therapeutic use in humans. However, this expectation is predicated on the belief that regulatory authorities, such as the FDA, will consider clinical and nonclinical studies of vepoloxamer and poloxamer 188 conducted by prior sponsors supportive of our clinical development of vepoloxamer, which may not be the case for a variety of reasons, including that an agency may not agree that the test material in prior-sponsor studies was the same as or similar enough to the test material in our studies. If regulatory agencies take the position that prior-sponsor studies of vepoloxamer and poloxamer 188 do not support the safety and efficacy of our vepoloxamer-

based product candidates, they may require further testing of our product candidates prior to granting marketing approval, which could require us to expend substantial additional resources and significantly delay commercialization of our product candidates.

Further, development of our product candidates and/or regulatory approval may be delayed for reasons beyond our control. For example, U.S. federal government shut-down or budget sequestration, such as occurred during 2013, may result in significant reductions to the FDA's budget and operations, which may lead to slower response times and longer review periods, potentially affecting our ability to progress development of or obtain regulatory approval for our product candidates.

Even if the FDA grants approval, the conditions or scope of the approval may limit our ability to commercialize our product, and in turn, limit our ability to generate substantial sales revenue. For example, the FDA may not approve the labeling claims for our vepoloxamer product that we believe are necessary or desirable for successful commercialization as a treatment for sickle cell disease, or may grant approval contingent on the performance of costly post-approval clinical trials or subject to warnings or contraindications. Additionally, even after granting approval, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for our product will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, and continued compliance with current good manufacturing processes, or cGMP, good clinical practices, international conference on harmonization regulations and good laboratory practices, which are regulations and guidelines that are enforced by the FDA for all of our clinical development and for any clinical studies that we conduct post-approval. The FDA may decide to withdraw approval, add warnings or narrow the approved indications in the product label, or establish risk management programs that could restrict distribution of our products. These actions could result from, among other things, safety concerns, including unexpected side effects or drug-drug interaction problems, or concerns over misuse of a product. If any of these actions were to occur following approval, we may have to discontinue commercialization of the product, limit our sales and marketing efforts, and/or conduct post-approval studies, which in turn could result in significant expense and delay or limit our ability to generate sales revenues.

Clinical studies typically involve a lengthy and expensive process with an uncertain outcome.

Clinical testing typically is expensive and can take years to complete, and its outcome is inherently uncertain. Clinical studies may not commence on time or be completed on schedule, if at all. The commencement and completion of clinical studies can be delayed for a variety of reasons, including difficulties and delays related to:

- obtaining regulatory approval to commence a clinical study;
- obtaining institutional review board, or IRB, approval to conduct a clinical study at a prospective site;
- identifying appropriate study sites and reaching agreements with prospective study sites and investigators, on acceptable terms, which can be subject to extensive negotiation and may vary significantly among study sites;
- reaching agreements with prospective contract research organizations, or CROs, for the conduct of clinical studies and contract manufacturing organizations, or CMOs, for the production of clinical trial material, the terms of which agreements can be subject to extensive negotiation and may vary significantly among different CROs and CMOs;
- failures on the part of our CROs, CMOs, and other third-party contractors in developing procedures and protocols or otherwise conducting activities in accordance with applicable policies and procedures and on timelines requested by us;
- identifying and hiring or engaging, as applicable, additional employees or consultants to assist us in managing CRO and/or CMO activities, managing a clinical study and analyzing the data resulting from a study;
- recruiting and enrolling patients to participate in a clinical study;
- manufacturing sufficient quantities of clinical trial material due, among other things, to lack of availability of capacity at a CMO or of the component materials, including the active pharmaceutical ingredient, or API;

- having patients complete a study and/or return for and complete post-treatment follow-up; and
- unforeseen results from other clinical studies or nonclinical testing that require us to amend a study design or halt or terminate a clinical study.

Patient enrollment, a critical component to successful completion of a clinical study, is affected by many factors, including the size and nature of the study subject population, the proximity of patients to clinical sites, the eligibility criteria for the study, the design of the clinical study, competing clinical studies and clinicians' and patients' perceptions as to the potential advantages of the

drug being studied in relation to available alternatives, including therapies being investigated by other companies. Further, completion of a clinical study and/or its results may be adversely affected by failure to retain subjects who enroll in a study but withdraw due to adverse side effects, lack of efficacy, improvement in condition before treatment has been completed or for personal issues or who fail to return for or complete post-treatment follow-up.

In addition, a clinical study may be suspended or terminated by us, an IRB, a data safety monitoring board, the FDA or other regulatory authorities due to a number of factors, including:

- failure to conduct the study in accordance with regulatory requirements or the study's protocol;
- inspection of clinical study operations or sites by the FDA or other regulatory authorities resulting in the imposition of a clinical hold;
- unforeseen safety issues, including adverse side effects;
- changes in governmental regulations or administrative actions; or
- lack of adequate funding to continue the study.

Changes in governmental regulations and guidance relating to clinical studies may occur and we may need to amend study protocols to reflect these changes, or we may amend study protocols for other reasons. Amendments may require us to resubmit protocols to IRBs for reexamination or renegotiate terms with CROs, study sites and investigators, all of which may adversely impact the costs or timing of or our ability to successfully complete a trial.

Clinical studies may not begin on time or be completed in the timeframes we anticipate and may be more costly than we anticipate for a variety of reasons, including one or more of those described above. For example, although we expect to move vepoloxamer directly into Phase 2 studies for most new indications we plan to pursue, an IRB or the FDA or another regulatory agency may require additional clinical or nonclinical studies prior to initiation of any planned Phase 2 study, which likely would increase the total time and cost of development in that indication. The length of time necessary to complete clinical studies varies significantly and is difficult to predict accurately. We may make statements regarding anticipated timing for completion of enrollment in and/or availability of results from our clinical studies, but such predictions are subject to a number of significant assumptions and actual timing may differ materially for a variety of reasons, including patient enrollment rates, length of time needed to prepare raw study data for analysis and then to review and analyze it, and other factors described above. In addition, in the case of AIR001, we are supporting but are not the sponsor of the ongoing Phase 2 clinical studies and, as a result, the initiation and completion of and receipt of data from those studies is outside of our control. If we experience delays in the completion of a clinical study, if a clinical study is terminated, or if failure to conduct a study in accordance with regulatory requirements or the study's protocol leads to deficient safety and/or efficacy data, the regulatory approval and/or commercial prospects for our product candidate may be harmed and our ability to generate product revenue will be delayed. In addition, any delays in completing our clinical studies likely will increase our development costs. Further, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical studies may ultimately lead to the denial of regulatory approval of a product candidate. Even if we are able to ultimately commercialize our product candidates, other therapies for the same indications may be introduced to the market in the interim and establish a competitive advantage or diminish the need for our products.

We do not have, and do not have plans to establish, any manufacturing facilities and are dependent on third parties for the manufacture and supply of our product candidates, and the loss of any of these manufacturers, or their failure to provide us with an adequate supply of drug product in a timely manner and on commercially acceptable terms, or at all, could harm our business.

We do not have, and do not have plans to establish, our own manufacturing facilities. For clinical trial material, we have entered into supply agreements with third parties for both API and finished drug product, but our current agreements may not cover all of our clinical trial material needs and we may need to negotiate new or amended agreements with these CMOs or rely on individual proposals or statements of work, which inherently involves

uncertainty as to ongoing supply and may result in delays in the completion of ongoing clinical studies or initiation of new studies. In addition, as development of our product candidates progress, we will need to negotiate agreements for commercial supply, including with respect to vepoloxamer for patients with sickle cell disease; however, we may not be able to reach an agreement containing terms that are acceptable to us, or at all.

If we fail to maintain relationships with our current CMOs, we may not be able to complete development of our product candidates, including vepoloxamer, or market them, if approved, on a timely basis, or at all, which would have a material and adverse effect on our business. Third-party manufacturers and suppliers may not perform as agreed or may terminate their agreements with us. For example, because these third parties provide manufacturing services to a number of other pharmaceutical companies, they may experience capacity constraints or choose to prioritize one or more of their other customers over us. Any significant problem that our

manufacturers or suppliers experience could delay or interrupt our supply of clinical trial material or commercial product until the manufacturer or supplier cures the problem or until we locate, negotiate for and validate an alternative source of supply, if one is available.

In addition to our reliance on third parties to manufacture clinical trial material, we rely on them to conduct or assist us in conducting key manufacturing development activities, including qualification of equipment, developing and validating methods, defining critical process parameters, releasing component materials and conducting stability testing, among other things. If these third parties are unable to perform successfully in a timely manner, whether for technical, financial or other reasons, we may be unable to secure clinical trial material, which likely would delay the initiation, conduct or completion of our clinical studies, which, in turn, likely would have a material and adverse effect on our business.

All manufacturers of our clinical trial material and, as applicable, commercial product, including API manufacturers, must comply with cGMP requirements enforced by the FDA through its facilities inspection program and applicable requirements of foreign regulatory authorities. These requirements include quality control, quality assurance and the maintenance of records and documentation. Manufacturers of our clinical trial material may be unable to comply with these cGMP requirements and with other FDA, state and foreign regulatory requirements. While we or our representatives generally monitor and audit our manufacturers' systems, we have little control over their ongoing compliance with these regulations. Failure to comply with these requirements may result in fines and civil penalties, suspension of production, suspension or delay in product approval, product seizure or recall, or withdrawal of product approval.

Currently, we do not have alternative sources to backup our primary sources of clinical trial material. Identification of and discussions with other vendors may be protracted and/or unsuccessful. Therefore, if our primary sources become unable or unwilling to perform, we could experience protracted delays or interruptions in the supply of clinical trial material and, ultimately, product for commercial sale, which could materially and adversely affect our development programs, commercial activities, operating results and financial condition. For example, if we are unable to maintain our relationship with our current supplier of vepoloxamer, we may be unable to identify or establish a relationship with an alternate CMO that has the technical capabilities and desire to perform the development and supply services that we require for vepoloxamer on commercially reasonable terms, or at all. Production of vepoloxamer requires application of our proprietary fluid extraction process. This extraction process is complex and requires highly specialized equipment and there are a limited number of CMOs capable of performing and willing to perform the process as we require, which makes identifying and establishing relationships with CMOs more difficult and may provide them with leverage over us in any negotiations. In addition, we use commercially-available poloxamer 188 as API starting material. There are a limited number of sources of poloxamer 188, and we are not aware of any that currently manufacture it to cGMP requirements applicable to API. The current supplier of our starting material manufactures it under excipient-grade cGMP conditions. Prior to approval of any vepoloxamer-based product, the FDA or other regulatory agencies may require our starting material to be manufactured consistent with cGMP requirements applicable to API, in which case regulatory approval and commercialization of our product candidate could be delayed significantly and require substantial additional financial resources as we seek to contract with a third party to manufacture the starting material consistent with cGMP requirements applicable to API or undertake to manufacture it ourselves, and conduct any additional clinical or nonclinical activities with such material as the FDA may require. Even if the FDA accepts our current approach with respect to API starting material, we do not have any control over its production and the third-party supplier may change its manufacturing process and/or limit the availability of its poloxamer 188 product in the future. If we cannot reach an agreement with the supplier to establish quality assurance controls around the API starting material or if the supplier makes changes to its poloxamer 188 product, the FDA may determine that it is not acceptable API starting material and we may have difficulty obtaining an alternate supply of API starting material that the FDA finds acceptable without our conducting additional clinical or nonclinical activities or taking other remedial measures, which could require substantial time and financial

resources. As a result, we could experience significant disruption in our ability to manufacture vepoloxamer, which likely would add significantly to its overall development and commercialization costs and adversely affect our business and financial condition.

Any new manufacturer or supplier of finished drug product or its component materials, including API, would be required to qualify under applicable regulatory requirements and would need to have sufficient rights under applicable intellectual property laws to the method of manufacturing such product or ingredients. The FDA may require us to conduct additional clinical studies, collect stability data and provide additional information concerning any new supplier, or change in a validated manufacturing process, including scaling-up production, before we could distribute products from that manufacturer or supplier or revised process. For example, if we were to engage a third party other than our current CMO to supply vepoloxamer for future clinical trial material or commercial product, the FDA may require us to conduct additional clinical and nonclinical studies to ensure comparability of the drug substance manufactured by our current CMO to drug substance manufactured by the new supplier. In addition to the potential for such requirements to result in significant interruption to development and commercialization of vepoloxamer, we likely would incur substantial additional costs to comply with the additional requirements.

The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products often encounter difficulties in production, particularly in scaling-up initial production. These problems include difficulties with production costs and yields, quality control, including stability of the product candidate and quality assurance testing, and shortages of qualified personnel. None of our product candidates has been manufactured at the scale we believe will be necessary to maximize its commercial value and, accordingly, we may encounter difficulties in attempting to scale-up production and may not succeed in that effort on a timely basis or at all, including as a result of delaying activities necessary to establish commercial-scale production due to capital constraints. In addition, the FDA or other regulatory authorities may impose additional requirements as we scale-up initial production capabilities, which may delay our scale-up activities or add expense.

If our manufacturers encounter any of these difficulties or otherwise fail to comply with their contractual obligations or we delay in entering into commercial supply agreements due to capital constraints, we may have insufficient quantities of material to support ongoing and/or planned clinical studies or to meet commercial demand for vepoloxamer, if approved. In addition, any delay or interruption in the supply of materials necessary or useful to manufacture our product candidates could delay the completion of our clinical studies, increase the costs associated with our development programs and, depending upon the period of delay, require us to commence new clinical studies at significant additional expense or terminate the studies completely. Delays or interruptions in the supply of commercial product could result in increased cost of goods sold and lost sales. We cannot ensure that manufacturing or quality control problems will not arise in connection with the manufacture of our clinical trial material or commercial product, if approved, or that third-party manufacturers will be able to maintain the necessary governmental licenses and approvals to continue manufacturing such clinical trial material or commercial product, as applicable. In addition, vepoloxamer currently is manufactured outside the U.S. and, as a result, we may experience interruptions in supply due to shipping or customs difficulties or regional instability. Any of the above factors could cause us to delay or suspend anticipated or ongoing trials, regulatory submissions or commercialization of our product candidates, entail higher costs or result in our being unable to effectively commercialize our products. Our dependence upon third parties for the manufacture of our clinical trial material may adversely affect our future costs and our ability to develop and commercialize our product candidates on a timely and competitive basis.

Positive results in nonclinical testing and prior clinical studies do not ensure that ongoing or future clinical studies will be successful or that our product candidates will receive the regulatory approvals necessary for their commercialization.

Before obtaining regulatory approval for the commercial sale of any of our product candidates, we must demonstrate through nonclinical testing and clinical studies that each product is safe and effective for use in each target indication. Based on extensive nonclinical testing, we believe we understand our product candidates' respective mechanisms of action; however, previously observed pharmacologic effects and clinical benefits may not be observed in ongoing or future nonclinical or clinical studies. Success in nonclinical testing and prior clinical studies does not ensure that subsequent or larger-scale studies will be successful. For example, poloxamer 188 (non-purified) was tested in more than 2,000 human subjects in various indications before its development was discontinued, principally due to concerns regarding acute renal dysfunction observed in patients who received it. In contrast, vepoloxamer was generally well-tolerated in seven completed clinical studies and the effects on serum creatinine reported as adverse events among subjects who received vepoloxamer were comparable to those among subjects who received placebo. However, patient safety concerns, including renal dysfunction, may be observed in ongoing or future clinical studies, including EPIC. With respect to efficacy, although there is encouraging data from nonclinical and clinical studies of poloxamer 188 and vepoloxamer in multiple indications, ongoing and future studies of vepoloxamer may fail to demonstrate clinical benefits to human subjects, or the demonstrated benefits may be judged by regulatory agencies as not clinically meaningful.

Clinical study results frequently are susceptible to varying interpretations. Medical professionals, investors and/or regulatory authorities may analyze or weigh study data differently than we do. For example, even if a study drug demonstrates a statistically significant treatment effect in its primary objective in a Phase 3 study, a regulatory agency could determine that the study data are not sufficient to support approval and require additional testing prior to granting approval. In addition, determining the value of clinical data typically requires application of assumptions and extrapolations to raw data. Alternative methodologies may lead to differing conclusions, including with respect to the safety or efficacy of our product candidates. For example, alternative methods for applying missing or imputed data may have impacted the treatment effect observed in the prior-sponsor Phase 3 study of vepoloxamer in sickle cell disease. If regulatory authorities disagree with us as to the appropriate methods for analyzing study data, regulatory approval for our product candidates may be delayed, limited or withheld.

If we license to third parties rights to develop our product candidates in other geographic areas or in other indications or otherwise permit third-parties to evaluate our product candidates in clinical studies, such as in the case of AIR001, we may have limited control over nonclinical testing or clinical studies that may be conducted by such third-parties. If data from third-party testing identifies a safety or efficacy concern, it could adversely affect our or another licensee’s development of the product candidate and prospects for regulatory approval.

There is significant risk that our product candidates could fail to show anticipated results in ongoing and future nonclinical testing and/or clinical studies, including the EPIC study, and, as a result, we may be required to conduct additional costly testing or we may elect to discontinue one or more of our development programs. A failure to obtain requisite regulatory approvals or to obtain approvals of the scope requested will delay or preclude us from marketing our products or limit the commercial use of the products, and would have a material adverse effect on our business, financial condition and results of operations.

We rely significantly on third parties to conduct our nonclinical testing and clinical studies and other aspects of our development programs and if those third parties do not satisfactorily perform their contractual obligations or meet anticipated deadlines, the development of our product candidates could be adversely affected.

We do not employ personnel or possess the facilities necessary to conduct many of the activities associated with our programs. We engage consultants, advisors, CROs, CMOs and others to assist in the design and conduct of nonclinical and clinical studies of our product candidates, with interpretation of the results of those studies and with regulatory activities, and we expect to continue to outsource a significant amount of such activities. As a result, many important aspects of our development programs are and will continue to be outside our direct control, and our third-party service providers may not perform as required or expected. Further, such third parties may not be as committed to the success of our programs as employees and, therefore, may not devote the same time, thoughtfulness or creativity to completing projects or problem-solving as would an employee. To the extent we are unable successfully manage the performance of third-party service providers, our business may be adversely affected.

The CROs that we engage to execute our clinical studies play a significant role in the conduct of the studies and subsequent collection and analysis of data, and we likely will depend on CROs and clinical investigators to conduct future clinical studies and to assist in analyzing data from completed studies and developing regulatory strategies for our product candidates. Individuals working at the CROs with which we contract, as well as investigators at the sites at which our studies are conducted, are not our employees, and we have limited control over the amount or timing of resources that they devote to our programs. With respect to our AIR001 program, AIR001 is being tested in third-party-sponsored clinical studies and, because we are not the study sponsor, our control over these studies is further limited. If CROs and/or investigators fail to devote sufficient time and resources to studies of our product candidates, if they do not comply with all regulatory and contractual requirements, or if their performance is substandard, it may delay commencement and/or completion of these studies, submission of our new drug applications to the FDA and other regulatory agencies, approval of our applications by those agencies, and commercialization of our products. Failure of these CROs to meet their obligations could adversely affect development of our product candidates. For example, in 2006, we engaged a CRO to assist with the primary conduct of our bioequivalence study of Exelbine, including monitoring participating clinical sites to ensure compliance with regulatory requirements. FDA guidance recommends that clinical sites randomly select and retain reserve samples of study drugs used in bioequivalence studies. However, the clinical sites that participated in our bioequivalence study of Exelbine failed to do so. In August 2011, we received a complete response letter from the FDA stating that the authenticity of the study drugs used in that bioequivalence study could not be verified and, consequently, the study would need to be repeated to address that deficiency.

In addition, CROs we engage may have relationships with other commercial entities, some of which may compete with us. If they assist our competitors at our expense, it could harm our competitive position. Moreover, if any of our current CRO relationships were to terminate, particularly those with the CROs we have engaged to conduct the EPIC study, we may not be able to enter into arrangements with alternative CROs on acceptable terms or in a timely manner, or at all. Switching CROs would involve additional cost and divert management time and attention. In addition, there likely would be a transition period when a new CRO commences work. These challenges could result in delays in the commencement or completion of our clinical studies, which could materially impact our ability to meet our desired development timelines and have a material adverse impact on our business and financial condition.

Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their clinical development, regulatory approval or commercialization.

Undesirable side effects caused by our product candidates could interrupt, delay or halt clinical studies and could result in the denial of regulatory approval by the FDA or other regulatory authorities for any or all indications, and in turn prevent us from commercializing our product candidates. For example, while we believe our proprietary purification process has addressed the cause of the acute renal dysfunction observed in clinical studies of poloxamer 188 (non-purified), we cannot provide assurance that the purification process has fully addressed the issue or that renal toxicity will not be observed in ongoing or future studies of vepoloxamer, particularly if we conduct studies in patients with impaired renal function. In addition, transient, generally mild to moderate elevations in liver enzymes were associated with treatment with vepoloxamer in prior clinical studies. If in our clinical studies of vepoloxamer we observe more pronounced increases in liver enzymes, or we observe other previously unidentified adverse events, whether or not statistically significant, we may be required to conduct additional clinical studies of vepoloxamer or to investigate the clinical significance of the adverse event and vepoloxamer may not receive regulatory approval.

If any of our product candidates receive marketing approval and we or others later identify undesirable side effects caused by the product or, if applicable, the reference product:

- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication;
- regulatory authorities may withdraw their approval of the product;
- we may be required to change the way the product is administered, conduct additional clinical studies or change the labeling of the product; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the affected product or could substantially increase the costs and expenses of commercializing the product, which in turn could delay or prevent us from generating significant revenue from its sale.

We may not achieve our projected development goals in the time frames we announce.

We set goals for and make public statements regarding our estimates of the timing for accomplishing certain objectives material to successful development of our product candidates. The actual timing of these events can vary, sometimes dramatically, due to many factors, including delays or failures in our nonclinical testing, clinical studies and manufacturing and regulatory activities and the uncertainties inherent in the regulatory approval process. For example, we had expected to initiate the EPIC study in 2012, but unforeseen delays related to the manufacture of clinical trial material delayed initiation of the study to 2013. In addition, from time to time we estimate the timeframe for completion of enrollment of or announcement of data from our clinical studies. However, predicting the rate of enrollment or the time from completion of enrollment to announcement of data for any clinical study, including EPIC, requires us to make a number of significant assumptions that may prove to be incorrect. If, as a clinical study progresses, we gain reliable information that materially impacts our assumptions, we will adjust our estimates. Even so, as discussed in other risk factors above, our estimated enrollment rates and the actual rates may differ materially and the time required to complete enrollment of any clinical study may be considerably longer than we estimate. In addition, even if we complete enrollment as expected, it may take longer than anticipated to prepare the data for review and then to review, analyze and announce the data.

Even if we complete a clinical study with successful results, we may not achieve our projected development goals in the time frames we initially anticipate or announce. As discussed above, the FDA may require nonclinical testing and/or clinical studies prior to its review or approval of a NDA for vepoloxamer in sickle cell disease in addition to the EPIC study and the other testing that we are conducting. If a development plan for a product candidate becomes more extensive and costly than anticipated, we may determine that the associated time and cost are not financially justifiable and, as a result, discontinue development in a particular indication or of the product candidate as a whole. Any such action may be viewed negatively, which could adversely affect our stock price.

In addition, changes may occur in regulatory requirements or policy during the period of product development and/or regulatory review of an NDA that relate to the data required to be included in NDAs. For example, despite including in our initial Exelbine NDA submission in December 2009 data that we believe met the filing requirements for a new drug promulgated by the International Conference on Harmonization, or ICH, as well as site-specific stability data from lots manufactured at the intended commercial manufacturing site, we received a refusal-to-file letter from the FDA indicating that the data included in that submission was insufficient to support a commercially-viable expiration dating period. Consequently, we had to generate 12 months of stability data from material manufactured at our intended commercial manufacturing site before resubmitting the Exelbine NDA, which we did in November 2010. A change in regulatory policy, which may not have been formalized or publicly disseminated, may have been a factor underlying the FDA’s refusal to file our December 2009 submission.

Further, throughout development, we must provide adequate assurance to the FDA and other regulatory authorities that we can consistently produce our product candidates in conformance with cGMP and other regulatory standards. As discussed above, we rely on CMOs for the manufacture of clinical, and future commercial, quantities of our product candidates. If future FDA or other regulatory authority inspections identify cGMP compliance issues at these third-party facilities, production of our clinical trial material or, in the future, commercial product, could be disrupted, causing potentially substantial delay in development or commercialization of our product candidates.

Even if we receive regulatory approval for a product candidate, we may face development and regulatory difficulties that could materially and adversely affect our business, financial condition and results of operations and cause our stock price to decline.

Even if initial regulatory approval is obtained, or as a condition to the initial approval, the FDA or a foreign regulatory agency may impose significant restrictions on a product's indicated uses or marketing or impose ongoing requirements for potentially costly post-approval studies or marketing surveillance programs, any of which would limit the commercial potential of the product. Our product candidates also will be subject to ongoing FDA requirements related to the manufacturing processes, labeling, packaging, storage, distribution, advertising, promotion, record-keeping and submission of safety and other post-market information regarding the product. For instance, the FDA may require changes to approved drug labels, require post-approval clinical studies and impose distribution and use restrictions on certain drug products. In addition, approved products, manufacturers and manufacturers' facilities are subject to continuing regulatory review and periodic inspections. If previously unknown problems with a product are discovered, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, the FDA may impose restrictions on that product or us, including requiring withdrawal of the product from the market. If we or a CMO of ours fail to comply with applicable regulatory requirements, a regulatory agency may:

- issue warning letters or untitled letters;
- impose civil or criminal penalties;
- suspend or withdraw regulatory approval;
- suspend or terminate any ongoing clinical studies;
- refuse to approve pending applications or supplements to approved applications;
- exclude our product from reimbursement under government healthcare programs, including Medicaid or Medicare;
- impose restrictions or affirmative obligations on our or our CMO's operations, including costly new manufacturing requirements;
- close the facilities of a CMO; or
- seize or detain products or require a product recall.

Even though we have obtained orphan drug designation for vepoloxamer for the treatment of sickle cell disease, we may not be able to obtain orphan drug marketing exclusivity for our products.

Vepoloxamer has orphan drug designation from the FDA and the European Commission for the treatment of sickle cell disease. Generally, if a drug with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the drug is entitled to a multi-year period of marketing exclusivity, which precludes the FDA or the European Commission from approving another marketing application for the same drug for that time period. However, orphan drug marketing exclusivity may not effectively protect our product candidates, even if our product candidates are the first to receive regulatory approved for the rare disease or condition. The FDA can subsequently approve another drug or biologic for the same indication if the FDA concludes that the competing product is clinically superior (safer and/or more effective) or makes a major contribution to patient care. The European Commission may reduce the exclusivity period in the EU if a drug no longer meets the criteria for orphan drug designation or if the drug is sufficiently profitable so that market exclusivity is no longer justified. Further, orphan drug exclusivity may be lost if the FDA or European Commission determines that the request for designation was materially defective or if the manufacturer of the drug is unable to assure a quantity of the drug sufficient to meet the needs of patients with the rare disease or condition. In addition, orphan drug designation does not shorten the regulatory review process for obtaining marketing approval.

Even though vepoloxamer has FDA fast track designation for the treatment of vaso-occlusive crisis of sickle cell disease, we may not experience a faster regulatory review process.

The FDA has granted vepoloxamer fast track designation for the treatment of vaso-occlusive crisis of sickle cell disease. For a product candidate with track designation, the FDA may agree to more frequent interactions with us during our development of vepoloxamer and to initiate review of sections of an NDA before the application is complete, which could expedite the FDA review process for granting marketing approval. However, fast track designation does not guarantee that the FDA will agree to this "rolling review" process. In addition, the FDA may withdraw a drug's fast track designation if it determines that the drug no longer demonstrates a potential to address unmet medical need or is not being studied in a manner that shows the drug can treat a serious condition and meets an unmet medical need. A drug may no longer demonstrate a potential to address unmet medical need, for

example, if the FDA approved a different product that addressed the same need or if emerging clinical data failed to show that the drug with fast track designation had the anticipated advantage over an available therapy. In spite of vepoloxamer's fast track designation, ultimately, the FDA may not agree to a rolling review process for an NDA for vepoloxamer for the treatment of vaso-occlusive crisis of sickle cell disease. In addition, although there are no approved therapies for the treatment of an ongoing vaso-occlusive crisis in sickle cell disease and our vepoloxamer NDA may be eligible for priority review, the FDA may determine to review our NDA on a standard review basis.

We have never commercialized a product candidate and we may lack the necessary expertise, personnel and resources to successfully commercialize any of our product candidates that receive regulatory approval on our own or together with suitable partners, which could delay and/or limit our ability to generate revenue in the event we receive regulatory approval to market one of our product candidates.

Our operations to date have been limited to business planning, raising capital, acquiring our product candidates and nonclinical and clinical development of our product candidates. We have never commercialized a product candidate and currently have limited marketing capabilities and no sales force or distribution capabilities. To achieve commercial success of our vepoloxamer product candidate or any other product candidate, if approved, we will have to develop our own marketing, distribution, sales and associated regulatory compliance capabilities, or outsource one or more of these activities to a third party. There is no guarantee that we will be able to establish adequate marketing, distribution or sales capabilities or make arrangements with third parties to perform those activities on terms satisfactory to us, or at all, or that any internal capabilities or third-party arrangements will be cost-effective.

Factors that may affect our ability to commercialize our product candidates on our own include recruiting and retaining adequate numbers of effective sales and marketing personnel, obtaining access to or persuading adequate numbers of physicians to prescribe our product candidates and other unforeseen expenses, difficulties, complications and delays associated with building an independent sales and marketing organization. Developing commercialization and associated regulatory compliance capabilities requires substantial investment, is time consuming, and could delay launch of any product candidate for which we receive regulatory approval. We may not be able to build an effective sales and marketing organization in the United States, the European Union or other key global markets in which our product candidates may be approved. If we are unable to build our own marketing, sales or distribution capabilities or to find suitable third parties to perform these activities for us, the launch of an approved product may be delayed and we may not generate revenues from them in the timeframes in which we expect, or at all.

To the extent we outsource marketing, distribution or sales activities to third parties, those third parties may hold significant control over important aspects of the commercialization of our products, including market identification, marketing methods, pricing, composition of sales force and promotional activities. Even if we are successful in establishing and maintaining these arrangements, there can be no assurance that we will be able to control the amount and timing of resources that any third party may devote to our products or prevent any third party from pursuing alternative technologies or products that could result in the development of products that compete with, or the withdrawal of support for, our products. If we retain third-party service providers to perform functions related to the marketing, distribution and sale of our products, key aspects of those functions that may be out of our direct control could include warehousing and inventory management, distribution, contract administration and chargeback processing, accounts receivable management and call center management. In this event, we would place substantial reliance on third-party providers to perform services for us, including entrusting our inventories of products to their care and handling. If these third-party service providers fail to comply with applicable laws and regulations, fail to meet expected deadlines, encounter natural or other disasters at their facilities or otherwise fail to perform in a satisfactory manner, or at all, our ability to deliver product to meet commercial demand could be significantly impaired. In addition, we may use third parties to perform various other services for us relating to sample accountability and regulatory monitoring, including adverse event reporting, safety database management and other product maintenance services. If the quality or accuracy of the data maintained by these service providers is

insufficient, our ability to continue to market our products could be jeopardized or we could be subject to regulatory sanctions.

If any of our product candidates for which we receive regulatory approval fails to achieve significant market acceptance among the medical community, patients or third-party payors, the revenue we generate from its sales will be limited and our business may not be profitable.

Our success will depend in substantial part on the extent to which our products candidates, if approved, are accepted by the medical community and patients and reimbursed by third-party payors, including government payors. The degree of market acceptance with respect to each of our approved products, if any, will depend upon a number of factors, including:

- the safety and efficacy of our product demonstrated in clinical studies;
- acceptance in the medical and patient communities of our product as a safe and effective treatment;

- the perceived advantages of our product over alternative treatments, including with respect to the incidence and severity of any adverse side effects and the cost of treatment;
- the indications for which our product is approved;
- claims or other information (including limitations or warnings) in our product's approved labeling;
- reimbursement and coverage policies of government and other third-party payors;
- pricing and cost-effectiveness of our product relative to alternative treatments;
- availability of alternative treatments;
- the prevalence of off-label substitution of chemically equivalent products or alternative treatments; and
- the resources we devote to marketing our product and restrictions on promotional claims we can make with respect to the product.

We cannot predict with reasonable accuracy whether physicians, patients, healthcare insurers or maintenance organizations, or the medical community in general, will accept or utilize any of our products. If our product candidates are approved but do not achieve an adequate level of acceptance by these parties, we may not generate sufficient revenue to become or remain profitable. In addition, our efforts to educate the medical community and third-party payors regarding benefits of our products may require significant resources and may never be successful.

If we determine that a product candidate may not achieve adequate market acceptance or that the potential market size does not justify additional expenditure on the program, we may reduce our expenditures on the development and/or the process of seeking regulatory approval of the product candidate while we evaluate whether and on what timeline to move the program forward.

Even if we receive regulatory approval to market one or more of our product candidates in the U.S., we may never receive approval or commercialize our products outside of the U.S., which would limit our ability to realize the full commercial potential of our product candidates.

In order to market any products outside of the U.S., we must establish and comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy. Approval procedures vary among countries and can involve additional product testing and validation and additional administrative review periods. The time required to obtain approval in other countries might differ from that required to obtain FDA approval. The regulatory approval process in other countries may include all of the risks detailed above regarding FDA approval in the U.S., as well as other risks. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in others. Failure to obtain regulatory approval in other countries or any delay or setback in obtaining such approval could have the same adverse effects detailed above regarding FDA approval in the U.S. As described above, such effects include the risks that our product candidates may not be approved for all indications requested, which could limit the uses of our product candidates and have an adverse effect on product sales, and that such approval may be subject to limitations on the indicated uses for which the product may be marketed or require costly, post-marketing follow-up studies.

Risks Related to Our Intellectual Property

Our success will depend in part on obtaining and maintaining effective patent and other intellectual property protection for our product candidates and proprietary technology.

Our success will depend in part on our ability to:

- obtain and maintain patent and other exclusivity with respect to our products and their use;

prevent third parties from infringing upon our proprietary rights;
maintain proprietary know-how and trade secrets;
operate without infringing upon the patents and proprietary rights of others; and
obtain appropriate licenses to patents or proprietary rights held by third parties if infringement would otherwise occur or if necessary to secure exclusive rights to them, both in the U.S. and in foreign countries.

The patent and intellectual property positions of biopharmaceutical companies generally are highly uncertain, involve complex legal and factual questions, and have been and continue to be the subject of much litigation. There is no guarantee that we have or will develop or obtain the rights to products or processes that are patentable, that patents will issue from any pending applications or that claims allowed will be sufficient to protect the technology we develop or have developed or that is used by us, our CMOs or our other service providers. In addition, any patents that are issued to us may be limited in scope or challenged, invalidated, infringed or circumvented, including by our competitors, and rights we have under issued patents may not provide competitive advantages to us. If competitors can develop and commercialize technology and products similar to ours, our ability to successfully commercialize our technology and products may be impaired.

Patent applications in the U.S. are confidential for a period of time until they are published, and publication of discoveries in scientific or patent literature typically lags actual discoveries by several months. As a result, we cannot be certain that the inventors listed in any patent or patent application owned by us were the first to conceive of the inventions covered by such patents and patent applications (for U.S. patent applications filed before March 16, 2013), or that such inventors were the first to file patent applications for such inventions outside the United States and, after March 15, 2013, in the United States. In addition, changes in or different interpretations of patent laws in the United States and foreign countries may affect our patent rights and limit the number of patents we can obtain, which could permit others to use our discoveries or to develop and commercialize our technology and products without any compensation to us.

We also rely on unpatented know-how and trade secrets and continuing technological innovation to develop and maintain our competitive position, which we seek to protect, in part, through confidentiality agreements with employees, consultants, collaborators and others. We also have invention or patent assignment agreements with our employees and certain consultants. The steps we have taken to protect our proprietary rights, however, may not be adequate to preclude misappropriation of or otherwise protect our proprietary information or prevent infringement of our intellectual property rights and we may not have adequate remedies for any such misappropriation or infringement. In addition, it is possible that inventions relevant to our business could be developed by a person not bound by an invention assignment agreement with us or independently discovered by a competitor.

We also intend to rely on regulatory exclusivity for protection of our product candidates, if approved for commercial sale. Implementation and enforcement of regulatory exclusivity, which may consist of regulatory data protection and market protection, varies widely from country to country. Failure to qualify for regulatory exclusivity, or failure to obtain or maintain the extent or duration of such protections that we expect for our product candidates, if approved, could affect our decision on whether to market the products in a particular country or countries or could otherwise have an adverse impact on our revenue or our results of operations.

We may rely on trademarks, trade names and brand names to distinguish our products, if approved for commercial sale, from the products of our competitors. However, our trademark applications may not be approved. Third parties may also oppose our trademark applications or otherwise challenge our use of the trademarks in which case we may expend substantial resources to defend our trademarks and may enter into agreements with third parties that may limit our use of our trademarks. In the event that our trademarks are successfully challenged, we could be forced to rebrand our product, which could result in loss of brand recognition and could require us to devote significant resources to advertising and marketing these new brands. Further, our competitors may infringe our trademarks or we may not have adequate resources to enforce our trademarks.

Our success depends in large part on our ability to prevent competitors from duplicating or developing equivalent versions of our product candidates, but patent protection, including for vepoloxamer, may be difficult to obtain and any issued claims may be limited.

The potential therapeutic benefits of poloxamer 188 have been known for decades and there is substantial prior art describing the use of poloxamer 188 in a wide range of diseases and conditions. As a result, our ability to find novel and non-obvious uses of vepoloxamer is limited. Further, a patent examiner may combine numerous, disparate references in order to reject a claimed use for obviousness. If the prior art suggests, even implicitly, the desirability of combining previously known elements, such as the use of poloxamer 188 in a particular indication, the subsequent use of vepoloxamer in that indication may be unpatentable.

We have filed for patent protection of vepoloxamer as a novel composition of poloxamer material as well as to cover various methods of therapeutic use of poloxamers, including vepoloxamer. However, our pending patent applications may not issue as patents, any issued patents may not provide us with significant competitive advantages, the validity or enforceability of any of our patents may be challenged and, if instituted, one or more of these challenges may be successful. For instance, our patent application covering a purportedly novel composition of poloxamer material may be limited to the specific method by which we manufacture the material. Even if claims issue, a competitor may develop a method to manufacture our poloxamer material using a different process, in which case the competitor may not infringe our “product-by-process” claims.

The patent prosecution process is expensive and time-consuming. We and any future licensors and licensees may not apply for or prosecute patents on certain aspects of our product candidates at a reasonable cost, in a timely fashion, or at all. We may not

have the right to control the preparation, filing and prosecution of some patent applications related to our product candidates or technologies. As a result, these patents and patent applications may not be prosecuted and enforced in a manner consistent with the best interests of our company. It is also possible that we or any future licensors or licensees will fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. Further, it is possible that defects of form in the preparation or filing of our patent applications may exist, or may arise in the future, such as with respect to proper priority claims, inventorship, assignment, or claim scope. If there are material defects in the form or preparation of our patents or patent applications, such patents or applications may be invalid or unenforceable. In addition, one or more parties may independently develop similar technologies or methods, duplicate our technologies or methods, or design around the patented aspects of our products, technologies or methods. Any of these circumstances could impair our ability to protect our products, if approved, in ways which may have an adverse impact on our business, financial condition and operating results.

Furthermore, the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in and outside of the United States. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical products or technology, or limit the duration of the patent protection of our technology and drugs. Given the amount of time required for the development, testing and regulatory review of new drug candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing drugs similar or identical to ours.

Enforcement of intellectual property rights in countries outside the U.S., including China in particular, has been limited or non-existent. Future enforcement of patents and proprietary rights in many other countries will likely be problematic or unpredictable. Moreover, the issuance of a patent in one country does not assure the issuance of a similar patent in another country. Claim interpretation and infringement laws vary by nation, so the extent of any patent protection is uncertain and may vary in different jurisdictions.

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

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and applications are required to be paid to the U.S. Patent and Trademark Office, or USPTO, and various governmental patent agencies outside of the U.S. in several stages over the lifetime of the patents and applications. The USPTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process and after a patent has issued. There are situations in which non-compliance can result in decreased patent term adjustment or in abandonment or lapse of the patent or patent application, leading to partial or complete loss of patent rights in the relevant jurisdiction.

If we are sued for infringing the proprietary rights of third parties or our patents rights are otherwise challenged in administrative proceedings, defending such actions may be costly and time consuming, and an unfavorable outcome would have an adverse effect on our business.

Our commercial success depends on our ability and the ability of our CMOs and component suppliers to develop, manufacture, market and sell our products and product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are or may be developing products. As

the industries in which we operate (biopharmaceutical, specialty pharmaceutical, biotechnology and pharmaceutical) expand and more patents are issued, the risk increases that we will be subject to claims that our products or product candidates, or their use or manufacture, infringe the rights of others. Because patent applications can take many years to publish and issue, there currently may be pending applications, unknown to us, that may later result in issued patents that our products, product candidates or technologies infringe, or that the process of manufacturing our products or any of their respective component materials, or the component materials themselves, infringe, or that the use of our products, product candidates or technologies infringe.

We or our CMOs or component material suppliers may be exposed to, or threatened with, litigation by third parties alleging that our products, product candidates and/or technologies infringe their patents and/or other intellectual property rights, or that one or more of the processes for manufacturing our products or any of their respective component materials, or the component materials themselves, or the use of our products, product candidates or technologies, infringe their patents and/or other intellectual property rights. If a third-party patent or other intellectual property right is found to cover our products, product candidates, technologies or their uses, or any of the underlying manufacturing processes or components, we could be required to pay damages and could be unable

to commercialize our products or use our technologies or methods unless we are able to obtain a license to the patent or intellectual property right. A license may not be available to us in a timely manner or on acceptable terms, or at all. In addition, during litigation, the third-party alleging infringement could obtain a preliminary injunction or other equitable remedy that could prohibit us from making, using or selling our products, technologies or methods.

There generally is a substantial amount of litigation involving patent and other intellectual property rights in the industries in which we operate and the cost of such litigation is may be substantial. We can provide no assurance that our product candidates or technologies will not infringe patents or rights owned by others, licenses to which might not be available to us in a timely manner or on acceptable terms, or at all. If a third party claims that we or our CMOs or component material suppliers infringe its intellectual property rights, we may face a number of issues, including, but not limited to:

- infringement and other intellectual property claims which, with or without merit, may be expensive and time consuming to litigate and may divert our management's time and attention from our core business;
- substantial damages for infringement, including the potential for treble damages and attorneys' fees, which we may have to pay if it is determined that the product at issue infringes or violates the third party's rights;
- a court prohibiting us from selling or licensing the product unless the third-party licenses its intellectual property rights to us, which it may not be required to do;
- if a license is available from the third party, we may have to pay substantial royalties, fees and/or grant cross-licenses to the third party; and
- redesigning our products or processes so they do not infringe, which may not be possible or may require substantial expense and time.

No assurance can be given that patents do not exist, have not been filed, or could not be filed or issued, which contain claims covering our products, product candidates or technology or those of our CMOs or component material suppliers or the use of our products, product candidates or technologies. Because of the large number of patents issued and patent applications filed in the industries in which we operate, there is a risk that third parties may allege they have patent rights encompassing our products, product candidates or technologies, or those of our CMOs or component material suppliers, or uses of our products, product candidates or technologies.

In addition, it may be necessary for us to enforce our proprietary rights, or to determine the scope, validity and unenforceability of other parties' proprietary rights, through litigation or other dispute proceedings, which may be costly, and to the extent we are unsuccessful, adversely affect our rights. In these proceedings, a court or administrative body could determine that our claims, including those related to enforcing patent rights, are not valid or that an alleged infringer has not infringed our rights. The uncertainty resulting from the mere institution and continuation of any patent- or other proprietary rights-related litigation or interference proceeding could have a material and adverse effect on us.

RISKS RELATED TO OUR INDUSTRY

We expect intense competition in the marketplace for our product candidates, should any of them receive regulatory approval.

The industries in which we operate (biopharmaceutical, specialty pharmaceutical, biotechnology and pharmaceutical) are highly competitive and subject to rapid and significant change. We are aware of many other organizations developing drug products and other therapies intended to treat or cure the diseases or conditions in which we are developing or plan to develop our product candidates. Developments by others may render potential application of any of our product candidates in a particular indication obsolete or noncompetitive, even prior to completion of its development and approval for that indication. If successfully developed and approved, we expect our product candidates will face intense competition. We may not be able to compete successfully against organizations with

competitive products, particularly large pharmaceutical companies. Many of our potential competitors have significantly greater financial, technical and human resources than we do, and may be better equipped to develop, manufacture, market and distribute products. Many of these companies operate large, well-funded research, development and commercialization programs, have extensive experience in nonclinical and clinical studies, obtaining FDA and other regulatory approvals and manufacturing and marketing products, and have multiple products that have been approved or are in late-stage development. Smaller companies may also prove to be significant competitors, particularly through collaborative arrangements with large pharmaceutical and biotechnology companies. Furthermore, heightened awareness on the part of academic institutions, government agencies and other public and private research organizations of the potential commercial value of their inventions have led them to actively seek to commercialize the technologies they develop, which increases competition for investment in our programs. In addition, there is increasing interest in developing drugs for rare diseases, which may have the effect of increasing the development of agents to treat sickle cell disease and

other orphan indications we may pursue. Legislative action may generate further interest. Competitive products may be more effective, or more effectively marketed and sold, than ours, which would have a material adverse effect on our ability to generate revenue.

With respect to competition for vepoloxamer in sickle cell disease, we are aware of numerous companies with product candidates in varying stages of development for the prevention and treatment of vaso-occlusive crisis, including mechanisms that target the P2Y12 ADP receptor, increase oxygen binding of hemoglobin or stimulate production of fetal hemoglobin. Some of these companies are large, well-financed and experienced pharmaceutical and biotechnology companies or have partnered with such companies, which may give them development, regulatory and/or marketing advantages over us. For example, Pfizer and Novartis have each invested in companies, GlycoMimetics, Inc. and Selexys Pharmaceuticals Corporation, respectively, with clinical-stage agents for the treatment of vaso-occlusive crisis. Pfizer is enrolling a Phase 3 clinical study of GlycoMimetics' rivipansel in adult and adolescent patients with sickle cell disease experiencing vaso-occlusive crisis and estimates completion of the study in July 2018. Emmaus Life Sciences, Inc. completed a Phase 3 study of its L-glutamine treatment for sickle cell patients in 2013 and is preparing to submit an NDA to the FDA for marketing approval of its L-glutamine product candidate for sickle cell patients ages five and older. Global Blood Therapeutics Inc. is conducting what it characterizes as a Phase 1/2 clinical study of its product candidate GBT440, an oral, once-daily therapy intended to prevent the sickling of red blood cells in sickle cell patients, and estimates completion of this early stage study in May 2016. Emmaus Life Sciences, Inc. has announced its plans to submit an NDA to the FDA in 2015 for marketing approval of its L-glutamine treatment for patients with sickle cell disease. Further, numerous non-profit or non-commercial foundations and interest groups are committed to improving outcomes for patients with sickle cell disease. Advances in the understanding of the signaling pathways associated with sickle cell disease may lead to further interest and development of treatment options. Forms of gene therapy are being pursued to correct sickle cell disease by halting production of sickled cells. For example, bluebird bio, Inc. is in Phase 1 development of its LentiGlobin® BB305 drug product for patients with severe sickle cell disease. If an effective treatment or cure for vaso-occlusive crisis or sickle cell disease receives regulatory approval, the potential commercial success of vepoloxamer could be severely jeopardized.

We are subject to uncertainty relating to healthcare reform measures and reimbursement policies that, if not favorable to our products, could hinder or prevent our products' commercial success, if any of our product candidates are approved.

The unavailability or inadequacy of third-party payor coverage and reimbursement could negatively affect the market acceptance of our product candidates and the future revenues we may expect to receive from those products. The commercial success of our product candidates, if approved, will depend in part on the extent to which the costs of such products will be covered by third-party payors, such as government health programs, commercial insurance and other organizations. These third-party payors are increasingly challenging the prices and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. If these third-party payors do not consider our products to be cost-effective compared to other therapies, they may not cover our products after approval as a benefit under their plans or, even if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis. In the case of products administered in an inpatient hospital setting, a level of payment that is inadequate to cover the cost to hospitals of providing and administering our products to patients, could delay market acceptance of or limit our ability to penetrate the markets for our products.

Significant uncertainty exists as to the reimbursement status for newly approved drug products, including coding, coverage and payment. There is no uniform policy requirement for coverage and reimbursement for drug products among third-party payors in the United States, therefore coverage and reimbursement for drug products can differ significantly from payor to payor. 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 products to each payor separately, with

no assurance that coverage and adequate payment will be applied consistently or obtained. The process for determining whether a payor will cover and how much it will reimburse a product may be separate from the process of seeking approval of the product or for setting the price of the product. Even if reimbursement is provided, market acceptance of our products may be adversely affected if the amount of payment for our products proves to be unprofitable for healthcare providers or less profitable than alternative treatments or if administrative burdens make our products less desirable to use. Third-party payor reimbursement to providers of our products, if approved, may be subject to a bundled payment that also includes the procedure of administering our products. To the extent there is no separate payment for our product(s), there may be further uncertainty as to the adequacy of reimbursement amounts.

The continuing efforts of the government, private insurance companies, and other organizations to contain or reduce costs of healthcare may adversely affect:

- our ability to set an appropriate price for our products;
- the rate and scope of adoption of our products by healthcare providers;
- our ability to generate revenue or achieve or maintain profitability;

the future revenue and profitability of our potential customers, suppliers and collaborators; and
our access to additional capital.

Our ability to successfully commercialize our products will depend in part on the extent to which governmental authorities, private health insurers and other organizations establish what we believe are appropriate coverage and reimbursement for our products. The containment of healthcare costs has become a priority of federal and state governments and the prices of drug products have been a focus in this effort. For example, there have been several recent U.S. Congressional inquiries and proposed bills designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs.. We expect that federal, state and local governments in the U.S. will continue to consider legislation directed at lowering the total cost of healthcare. In addition, in certain foreign markets, the pricing of drug products is subject to government control and reimbursement may in some cases be unavailable or insufficient. It is uncertain whether and how future legislation, whether domestic or abroad, could affect prospects for our product candidates or what actions federal, state, or private payors for healthcare treatment and services may take in response to any such healthcare reform proposals or legislation. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures reforms may prevent or limit our ability to generate revenue, attain profitability or commercialize our product candidates.

We face potential product liability exposure and, if successful claims are brought against us, we may incur substantial liability for a product or product candidate and may have to limit its commercialization. In the future, we anticipate that we will need to obtain additional or increased product liability insurance coverage and it is uncertain whether such increased or additional insurance coverage can be obtained on commercially reasonable terms, if at all.

Our business (in particular, the use of our product candidates in clinical studies and the sale of any products for which we obtain marketing approval) will expose us to product liability risks. Product liability claims might be brought against us by patients, healthcare providers, pharmaceutical companies or others selling our products. If we cannot successfully defend ourselves against any such claims, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

decreased demand for our products and loss of revenue;
impairment of our business reputation;
delays in enrolling patients to participate in our clinical studies;
withdrawal of clinical study participants;
a “clinical hold,” suspension or termination of a clinical study or amendments to a study design;
significant costs of related litigation;
substantial monetary awards to patients or other claimants; and
the inability to commercialize our products and product candidates.

We maintain limited product liability insurance for our clinical studies, but our insurance coverage may not reimburse us or may not be sufficient to reimburse us for all expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive and, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses.

We expect that we will expand our insurance coverage to include the sale of commercial products if we obtain marketing approval of any of our product candidates, but we may be unable to obtain product liability insurance on commercially acceptable terms or may not be able to maintain such insurance at a reasonable cost or in sufficient amounts to protect us against potential losses. Large judgments have been awarded in class action lawsuits based on drug products that had unanticipated side effects. A successful product liability claim or series of claims brought against us could cause our stock price to fall and, if judgments exceed our insurance coverage, could decrease our cash and adversely affect our business.

RISKS RELATED TO OUR COMMON STOCK

If we are unable to maintain compliance with NYSE MKT continued listing standards, our common stock may be delisted from the NYSE MKT equities market, which would likely cause the liquidity and market price of our common stock to decline.

Our common stock currently is listed on the NYSE MKT equities market. The NYSE MKT will consider suspending dealings in, or delisting, securities of an issuer that does not meet its continued listing standards, including specified stockholders' equity levels. In addition, the NYSE MKT will consider suspending dealings in, or delisting, securities selling for a substantial period of time at a low price per share if the issuer fails to effect a reverse split of such stock within a reasonable time after being notified that the NYSE MKT deems such action to be appropriate under the circumstances.

In the past, though not since 2010, we were notified of non-compliance with certain NYSE MKT stockholders' equity continued listing standards; specifically, (1) Section 1003(a)(ii) of the NYSE MKT Company Guide, or the Company Guide, because we reported stockholders' equity of less than $4,000,000 and losses from continuing operations and net losses in three of our four most recent fiscal years, and (2) Section 1003(a)(iii) of the Company Guide, because we reported stockholders' equity of less than $6,000,000 and losses from continuing operations and net losses in our five most recent fiscal years. In addition, we were notified, in accordance with Section 1003(f)(v) of the Company Guide, that the NYSE MKT determined it was appropriate for us to effect a reverse stock split of our common stock to address our low selling price per share. In April 2010, we announced that we had resolved the stockholders' equity continued listing deficiencies and we implemented a 1-for-25 reverse split of our common stock, in part to address the NYSE MKT's requirement that we address our low stock price.

There is no assurance, however, that we will continue to maintain compliance with NYSE MKT continued listing standards. As of December 31, 2015, our stockholders' equity was $23.9 million. If we are unable to raise additional capital before the fourth quarter of 2016, our stockholders' equity could fall below the level required to maintain compliance with NYSE MKT continued listing standards. In addition, the market price for our common stock historically has been highly volatile, as more fully described below under the risk titled "The market price of our common stock historically has been and likely will continue to be highly volatile." The NYSE MKT may again determine that the selling price per share of our common stock is low and require that we effect a reverse stock split of our common stock, which would require stockholder approval that we may be unable to obtain. Our failure to maintain compliance with NYSE MKT continued listing standards could result in the delisting of our common stock from the NYSE MKT.

The delisting of our common stock from the NYSE MKT likely would reduce the trading volume and liquidity in our common stock and may lead to decreases in the trading price of our common stock and may also materially impair our stockholders' ability to buy and sell shares. In addition, the delisting of our common stock could significantly impair our ability to raise additional capital, which we expect will be required in order to execute our current business strategy.

If our common stock were delisted and determined to be a "penny stock," a broker-dealer may find it more difficult to trade our common stock and an investor may find it more difficult to acquire or dispose of our common stock in the secondary market.

If our common stock were removed from listing with the NYSE MKT, it may be subject to the so-called "penny stock" rules. The SEC has adopted regulations that define a "penny stock" to be any equity security that has a market price per share of less than $5.00, subject to certain exceptions, such as any securities listed on a national securities exchange. For any transaction involving a "penny stock," unless exempt, the rules impose additional sales practice requirements on

broker-dealers, subject to certain exceptions. If our common stock were delisted and determined to be a "penny stock," a broker-dealer may find it more difficult to trade our common stock and an investor may find it more difficult to acquire or dispose of our common stock on the secondary market.

The market price of our common stock historically has been and likely will continue to be highly volatile.

The market price for our common stock historically has been highly volatile, and the market for our common stock has from time to time experienced significant price and volume fluctuations, based both on our operating performance and for reasons that appear to us unrelated to our operating performance. For instance, on August 10, 2011, the market price for our common stock dropped almost 60% following our announcement of our receipt of a complete response letter to our NDA for Exelbine, which letter stated that the FDA could not approve Exelbine in its present form. Conversely, the market price for our common stock increased by more than 55% during one trading day in January 2014, in the absence of any news release by us or rumors of which we were aware. The market price of our common stock may fluctuate significantly in response to a number of factors, including:

- the level of our financial resources;
- announcements of entry into or consummation of a financing or strategic transaction;

- changes in the regulatory status of our product candidates, including results of any clinical studies and other research and development programs;
- delays in the completion of our clinical studies or termination of a clinical study, including due to difficulties with patient enrollment or safety issues or inability to produce sufficient quantities of clinical trial material;
- FDA or international regulatory actions and regulatory developments in the U.S. and foreign countries;
- announcements of new products or technologies, commercial relationships or other events (including clinical study results and regulatory events and actions) by us or our competitors;
- announcements of difficulties or delays in commercial manufacture or supply of our drug products;
- market conditions in the pharmaceutical, biopharmaceutical, specialty pharmaceutical and biotechnology sectors;
- developments concerning intellectual property rights generally or those of us or our competitors;
- changes in securities analysts' estimates of our financial performance or deviations in our business and the trading price of our common stock from the estimates of securities analysts;
- events affecting any future collaborations, commercial agreements and grants;
- fluctuations in stock market prices and trading volumes of similar companies;
- sales of large blocks of our common stock, including sales by significant stockholders, our executive officers or our directors or pursuant to shelf or resale registration statements that register shares of our common stock that may be sold by us or certain of our current or future stockholders;
- discussion of us or our stock price by the financial and scientific press and in online investor communities;
- commencement of delisting proceedings by the NYSE MKT;
- additions or departures of key personnel; and
- changes in third-party payor coverage or reimbursement policies.

As evidenced by the August 10, 2011 decline, the realization of any of the foregoing could have a dramatic and adverse impact on the market price of our common stock. In addition, class action litigation has often been instituted against companies whose securities have experienced a substantial decline in market price. Moreover, regulatory entities often undertake investigations of investor transactions in securities that experience volatility following an announcement of a significant event or condition. Any such litigation brought against us or any such investigation involving our investors could result in substantial costs and a diversion of management's attention and resources, which could hurt our business, operating results and financial condition.

Our stock price could decline significantly based on progress with and results of our clinical studies and regulatory agency decisions affecting development of our product candidates.

We expect announcements of progress with and results of clinical studies of our product candidates and regulatory decisions (by us, the FDA, or another regulatory agency) to affect our stock price. Stock prices of companies in our industry have declined significantly when such results and decisions were unfavorable or perceived to be negative or discouraging or when a product candidate did not otherwise meet expectations. If progress in clinical studies or study results are not viewed favorably by us or third parties, including investors, analysts, potential collaborators, the academic and medical communities and regulators, our stock price could decline significantly and you could lose your investment in our common stock.

We may report top-line clinical and nonclinical study data from time to time, which is based on preliminary analysis of then-available data. Such preliminary findings and conclusions are subject to change following a more comprehensive review of the study data. In addition, results of clinical and nonclinical studies often are subject to different interpretations. We may interpret or weigh the importance of study data differently than third parties, including those noted above. Others may not accept or agree with our analysis of study data, which could impact the approvability of our product candidates and/or the value of our development programs and our company in general.

Sales of substantial amounts of our common stock or the perception that such sales may occur could cause the market price of our common stock to decline significantly, even if our business is performing well.

The market price of our common stock could decline as a result of sales by, or the perceived possibility of sales by, us or our existing stockholders of shares of our common stock. Sales by our existing stockholders might also make it more difficult for us to sell equity securities at a time and price that we deem appropriate. In August 2015, we entered into a new sales agreement under which we may, from time to time, sell shares of our common stock having an aggregate offering price of up to $30 million through an "at the market" equity offering program, or ATM program. As of December 31, 2015, we had sold only a small fraction of the shares we may sell under the ATM program. The shelf registration statement on Form S-3 under which the ATM program is registered may be used to register the sale and issuance of more than $99 million of additional securities, subject to limitations if our public float is less than $75 million. In addition, as of March 10, 2016, we have outstanding warrants to purchase more than 105.1 million additional shares of our common stock and warrants to purchase more than 13 million of those shares have an exercise price of $0.01 per share and warrants to purchase all but 10.6 million of those shares have an exercise price of less than $1.00 per share. Collectively, the ATM program, the shelf registration statement and the outstanding, in-the-money warrants, may increase the likelihood of sales of substantial amounts of our shares, or the perception that substantial sales may occur, by us or our existing securityholders from time to time, which could cause the market price of our common stock to decline significantly.

We have voting control over shares held by the former principal stockholders of SynthRx and Aires Pharmaceuticals and we will have voting control over shares issuable to former SynthRx stockholders in the future, and we may determine to cause those shares to be voted in such a manner that does not necessarily coincide with the interests of individual stockholders or particular groups of stockholders.

We have voting control with respect to approximately 1.9% of our outstanding common stock (based on shares outstanding as of March 10, 2016), pursuant to agreements we entered into with the former principal stockholders of each of SynthRx and Aires Pharmaceuticals in connection with our acquisition of those companies. Pursuant to the voting and transfer restriction agreement between us and each of the former principal stockholders of SynthRx, we have an irrevocable proxy to vote the shares of our common stock beneficially owned by those stockholders with respect to every action or approval by written consent of our stockholders in such manner as directed by us, except in limited circumstances. If the development of vepoloxamer achieves the remaining milestones set forth in our merger agreement with SynthRx, we will issue an additional 12,478,050 shares of our common stock to the former stockholders of SynthRx and the amount of those shares held by the stockholder parties to the voting and transfer restriction agreement will also be subject to the irrevocable proxy held by us. In addition, pursuant to the stockholder agreements between us and the former principal stockholders of Aires, we have an irrevocable proxy to vote the shares of our common stock issued to such stockholders as merger consideration and then held by such stockholders with respect to every action or approval by written consent of our stockholders in such manner as directed by us, except in limited circumstances, until August 2016. Accordingly, pursuant to our agreements with the former principal stockholders of SynthRx and Aires, assuming achievement of the remaining milestones under our merger agreement with SynthRx and issuance of all 12,478,050 milestone shares, based on 192,836,367 shares of our common stock outstanding as of March 10, 2016, we would have voting control with respect to approximately 7.6% of our outstanding common stock. As a result, in the future, we may have significant control over substantially all matters requiring approval by our stockholders, including the election of directors and the approval of certain mergers and other business combination transactions. Even if less than all potential milestone-related and holdback shares are issued, our ability to control a potentially significant block of stockholder votes pursuant to these voting agreements may enable us to substantially affect the outcome of proposals brought before our stockholders. Although our board of directors acts in a manner it believes is in the best interest of our stockholders as a whole, the interests of our stockholders as a whole may not always coincide with the interests of individual stockholders or particular groups of stockholders.

Anti-takeover provisions in our charter documents and under Delaware law may make an acquisition of us, which may be beneficial to our stockholders, more difficult, which could depress our stock price.

We are incorporated in Delaware. Certain anti-takeover provisions of Delaware law and our charter documents as currently in effect may make a change in control of our company more difficult, even if a change in control would be beneficial to our stockholders. Our bylaws limit who may call a special meeting of stockholders and establish advance notice requirements for nomination of individuals for election to our board of directors or for proposing matters that can be acted upon at stockholders' meetings. Delaware law also prohibits corporations from engaging in a business combination with any holders of 15% or more of their capital stock until the holder has held the stock for three years unless, among other possibilities, the board of directors approves the transaction. Our board of directors may use these provisions to prevent changes in the management and control of our company. Also, under applicable Delaware law, our board of directors may adopt additional anti-takeover measures in the future. In addition, provisions of certain compensatory contracts with our management, such as equity award agreements, may have an anti-takeover effect by resulting in accelerated vesting of outstanding equity securities held by our executive officers. In particular, in the event of a change in control, the vesting of options we granted from July 2009 through March 2016 to our chief executive officer will accelerate with respect to fifty percent of the then unvested shares on the day prior to the date of the change in control and, subject to his

continuous service, with respect to the remaining fifty percent of the then unvested shares on the one year anniversary of the date of the change in control, and could accelerate in full at the time of the change in control if the acquirer does not assume or substitute for the options. As a result, if an acquirer desired to retain the services of our chief executive officer following an acquisition, it may be required to provide additional incentive to him, which could increase the cost of the acquisition to the acquirer and may deter or adversely affect the terms of the potential acquisition.

Because we do not expect to pay dividends with respect to our common stock in the foreseeable future, you must rely on stock appreciation for any return on your investment.

We have paid no cash dividends on any of our common stock to date, and we currently intend to retain our future earnings, if any, to fund the development and growth of our business. As a result, with respect to our common stock, we do not expect to pay any cash dividends in the foreseeable future, and payment of cash dividends, if any, will also depend on our financial condition, results of operations, capital requirements and other factors and will be at the discretion of our board of directors. Furthermore, we are subject to various laws and regulations that may restrict our ability to pay dividends and we may in the future become subject to contractual restrictions on, or prohibitions against, the payment of dividends. Currently, our debt facility with Hercules prohibits us from declaring and paying any cash dividend on any class of stock or other equity interest. Due to our intent to retain any future earnings rather than pay cash dividends on our common stock and applicable laws, regulations and contractual obligations that may restrict our ability to pay dividends on our common stock, the success of your investment in our common stock will likely depend entirely upon any future appreciation and our common stock may not appreciate.

If we were to issue shares of our common stock or preferred stock that are available for issuance, our stock price could decline.

We have 500,000,000 shares of authorized common stock and, as of March 10, 2016, approximately 145 million of such authorized shares were not outstanding or reserved for issuance under outstanding warrants, options, equity incentive plans or other rights. Subject to applicable securities laws and stock exchange listing requirements, our board of directors is authorized under our charter documents to sell and issue our authorized, but unissued, common stock without stockholder approval and may do so to satisfy our capital requirements or finance the expansion of our product pipeline. Our board of directors also is authorized to issue and sell up to 1,000,000 shares of preferred stock without stockholder approval, at a purchase price approved by the board. The preferred stock may have rights that are superior to the rights of the holders of our common stock. The sale or the proposed sale of substantial amounts of our common stock, preferred stock and/or securities convertible into shares of our common or preferred stock in the public markets may adversely affect the market price of our common stock. Our stockholders may also experience substantial dilution.

Item 1B. Unresolved Staff Comments.

We do not have any unresolved comments issued by the SEC staff.

Item 2. Properties.

We sublease approximately 13,700 square feet of office space for our headquarters in San Diego, California. Approximately four years remain on the sublease term. We believe that these facilities are adequate to meet our current requirements. We have no laboratory, research or manufacturing facilities.

Item 3. Legal Proceedings.

From time to time, we may become involved in various claims and legal proceedings. Regardless of outcome, litigation and other legal proceedings can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors. We are not currently a party to any material pending litigation or other material legal proceeding.

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 trades under the symbol "MSTX" on the NYSE MKT equities market. The following table sets forth the high and low sale prices for our common stock in each full quarterly period within the two most recent fiscal years.

	Sales Price			
	2015		2014	
	High	Low	High	Low
First Quarter	$0.63	$0.42	$1.10	$0.45
Second Quarter	$0.58	$0.46	$0.73	$0.52
Third Quarter	$0.60	$0.38	$0.69	$0.53
Fourth Quarter	$0.59	$0.37	$0.60	$0.40

As of March 10, 2016, we had approximately 117 record holders of our common stock. The number of beneficial owners is substantially greater than the number of record holders because a large portion of our common stock is held of record through brokerage firms in "street name."

Dividend Policy

We have never declared or paid any cash dividends on our common stock and do not anticipate declaring or paying any cash dividends on our common stock in the foreseeable future. We expect to retain all available funds and any future earnings to support operations and fund the development and growth of our business. Our board of directors will determine whether we pay and the amount of future dividends (including cash dividends), if any.

In connection with previous preferred stock financings, we have agreed to charter restrictions on our ability to pay cash dividends or distributions on our common stock for so long as any shares of such preferred stock are outstanding, unless we obtain prior written consent from the holders of such preferred stock. Although currently there are no such restrictions on our ability to pay dividends on our common stock, we may agree to similar restrictions in the future.

Recent Sales of Unregistered Securities

In August 2015, we entered into a Loan and Security Agreement with Hercules Technology III, L.P. and Hercules Capital, Inc. (formerly known as, Hercules Technology Growth Capital, Inc.) pursuant to which Hercules agreed to lend us up to $15 million in two tranches. The Loan and Security Agreement with Hercules was amended in September 2015 (the "First Amendment"), December 2015, and February 2015 (the "Third Amendment"). In connection with, and as partial consideration for the debt facility provided under the Loan and Security Agreement, as amended, in August 2015, we entered into a Warrant Agreement with Hercules Technology III, L.P., which was amended in September 2015 in connection with the First Amendment and in February 2016 in connection with the Third Amendment. Pursuant to the Warrant Agreement, as amended, Hercules has a right to purchase up to an aggregate of 2,272,727 shares of our common stock at an exercise price of $0.275 per share, at any time, from time to time, through August 11, 2020. Upon exercise, the aggregate exercise price may be paid, at Hercules' election, in cash or on a net

issuance basis, based upon the fair market value of our common stock at the time of exercise. Under the terms of the Warrant Agreement, as amended, Hercules received a warrant exercisable for 853,658 shares as of August 11, 2015, a warrant exercisable for an additional 670,732 shares as of September 28, 2015, and a warrant exercisable for an additional 748,337 shares as of February 25, 2016, which, in the aggregate, represent the right to purchase 2,272,727 shares of our common stock.

We offered and sold the warrants described above to Hercules in reliance upon the exemption from the registration requirements of the Securities Act of 1933, as amended, or the Securities Act, provided by Section 4(a)(2) of the Securities Act. We relied on this exemption based in part on representations made to us by Hercules, including Hercules' intention to acquire the securities for investment only and not with a view to, or a present intention of, selling or distributing any part thereof in violation of applicable laws, and Hercules' status as an "accredited investor," as such term is defined in Rule 501 of Regulation D promulgated under the Securities Act. Appropriate legends were affixed to securities certificates issued in these transactions. Hercules had adequate access to information about our company.

Item 6. Selected Financial Data.

Under SEC rules and regulations, because the aggregate worldwide market value of our common stock held by non-affiliates was more than $75 million, but less than $700 million, as of June 30, 2015, the last business day of our most recently completed second fiscal quarter, we are considered to be an "accelerated filer." We were considered to be a "smaller reporting company" when we determined our filing status for purposes of our annual report on Form 10-K for our fiscal year ended December 31, 2014. SEC rules and regulations provide that a smaller reporting company transitioning to the larger reporting system, as we are doing this year, may finish reporting as a smaller reporting company for the rest of the fiscal year, including in its annual report on Form 10-K, and is not required to satisfy the larger reporting company disclosure requirements until the first quarterly report for the new fiscal year following the determination date. Accordingly, we are not required to provide the information required by this item in this report.

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

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with the consolidated financial statements and related notes appearing elsewhere in this report. In addition to historical information, this discussion and analysis contains forward-looking statements that involve risks, uncertainties, and assumptions. Our actual results may differ materially from those anticipated in these forward-looking statements as a result of certain factors, including but not limited to those identified under Item 1A "Risk Factors" in this report.

Overview

We are a biopharmaceutical company developing clinical-stage therapies for serious or life-threatening diseases with significant unmet needs and we currently are focused on developing new therapies for sickle cell disease and heart failure. Our lead product candidate, vepoloxamer (also known as MST-188), is in Phase 3 clinical development for sickle cell disease and Phase 2 clinical development for heart failure with reduced ejection fraction. We are leveraging our Molecular Adhesion & Sealant Technology, or MAST, platform, derived from over two decades of clinical, nonclinical and manufacturing experience with purified and non-purified poloxamers, to develop vepoloxamer, which has demonstrated multiple pharmacologic effects that may provide clinical benefit in a wide range of diseases and conditions typically characterized by impaired microvascular blood flow and/or damaged cell membranes. Our second product candidate, AIR001, a sodium nitrite solution for inhalation via nebulization, has demonstrated positive hemodynamic benefits in patients with pulmonary hypertension and heart failure with preserved ejection fraction, or HFpEF, and currently is in Phase 2 clinical development for HFpEF.

We have devoted substantially all of our resources to research and development, or R&D, and to acquisition of our product candidates. We have not yet marketed or sold any products or generated any significant revenue and we have incurred significant annual operating losses since inception. We incurred losses from operations of $39.4 million and $29.3 million for the years ended December 31, 2015 and December 31, 2014, respectively. As of December 31, 2015, we had an accumulated deficit of $275.0 million. Our cash, cash equivalents and investment securities were $41.0 million and our working capital was $19.1 million as of December 31, 2015.

Our development efforts have been funded primarily through the offering and sale of our equity securities from time to time and a debt facility under which we have a principal balance of $15 million. The process of developing and seeking regulatory approval for investigational new drug products and marketing such products, if approved, requires significant capital investment. We expect to continue to incur substantial operating losses for the next several years as we advance our product candidates through clinical development and, if successful, seek regulatory approval to market and sell them. Until such time as we obtain regulatory approval and are subsequently able to generate positive cash flow, we plan to continue to fund our operations with our current cash, cash equivalents and investment securities and by raising additional capital through equity or debt financings and/or through collaborations, including licensing arrangements. If we are not successful in raising sufficient additional capital as needed, we may be compelled to

reduce the scope of our operations and planned capital expenditures and/or sell or license certain assets at inopportune times, which could have a material and adverse effect on our ability to pursue our business strategy. As discussed below under "Management Outlook," if we are unable to raise additional capital before the fourth quarter of 2016 or if we are required to prepay $10 million of the principal balance of our debt facility on July 31, 2016, we plan to reduce the scope of our operations, including by delaying or discontinuing investment in development and commercialization efforts for vepoloxamer in sickle cell disease and heart failure.

In February 2016, we completed enrollment in our 388-patient Phase 3 clinical study of vepoloxamer in sickle cell disease, known as the EPIC study, and we expect to report top-line data in the second quarter of 2016. Vepoloxamer also is currently being evaluated in a randomized, double-blind, placebo-controlled, multicenter Phase 2 study in patients with chronic heart failure. In addition, we continue to evaluate the opportunity for clinical development of vepoloxamer in ischemic stroke and our vepoloxamer pipeline includes a preclinical development program in resuscitation following major trauma (i.e., restoration of circulating blood volume and pressure). We obtained the MAST platform and vepoloxamer program through our acquisition of SynthRx, Inc. in April 2011.

Our second product candidate, AIR001, is in Phase 2 clinical development for HFpEF. In February 2016, we announced positive top-line results from a 30-patient, randomized, double-blind, placebo-controlled Phase 2a study of AIR001 in patients with HFpEF. The study met its pre-specified primary endpoint, with the AIR001 treatment group showing a statistically significant decrease in pulmonary capillary wedge pressure during exercise compared to the control group and AIR001 was generally well-tolerated. Another institution-sponsored Phase 2a clinical study of AIR001 in patients with HFpEF is ongoing. In addition, we are supporting a multicenter, randomized, double-blind, placebo-controlled crossover Phase 2 study designed by the Heart Failure Clinical Research Network (HFN) and sponsored by its Coordinating Center. The study, which is known as the INDIE-HFpEF study, is expected to begin in the third quarter of 2016. We obtained the AIR001 program through our acquisition of Aires Pharmaceuticals, Inc. in February 2014.

Acquisition of Aires Pharmaceuticals

In February 2014, we acquired Aires Pharmaceuticals, Inc., a privately-held corporation, in a merger transaction , which resulted in Aires becoming our wholly-owned subsidiary. Upon completion of the merger, we issued an aggregate of 1,049,706 unregistered shares of our common stock to former Aires stockholders and, in September 2014, following a six-month “holdback” period, we issued an aggregate of 4,053,996 additional unregistered shares of our common stock to former Aires stockholders in accordance with the merger agreement. There are no milestone or earn-out payments under the merger agreement. Accordingly, the total merger consideration was 5,103,702 shares, which represented approximately 5% of our outstanding common stock as of the acquisition date.

Acquisition of SynthRx

Merger Consideration. In April 2011, we acquired SynthRx, Inc. as a wholly-owned subsidiary through a merger transaction in exchange for shares of our common stock and rights to additional shares of our common stock upon achievement of specified milestones related to vepoloxamer. We have issued an aggregate of 3,050,851 shares of our common stock to the former SynthRx stockholders, 1,454,079 of which we repurchased in December 2012 for $0.001 per share pursuant to our exercise of a repurchase right under the merger agreement. We could issue up to an aggregate of 12,478,050 additional shares of our common stock to the former SynthRx stockholders if and when the development of vepoloxamer achieves certain milestones, with 3,839,400 shares issuable upon the FDA’s acceptance for review of a NDA covering the use of vepoloxamer for the treatment of sickle cell crisis in children, which we refer to as the Second Milestone, and 8,638,650 shares issuable upon approval of such NDA by the FDA, which we refer to as the Third Milestone.

Stockholders’ Agreement. In connection with our acquisition of SynthRx, each of the former principal stockholders of SynthRx entered into a stockholders’ voting and transfer restriction agreement with us. This agreement became effective upon completion of the acquisition and will remain in effect until all of the shares of our common stock issued pursuant to the merger agreement to those stockholders and their affiliates have been transferred to non-affiliates. The transfer restriction aspect of the agreement, among other things, limits the amount of shares acquired pursuant to the merger agreement that the stockholder parties and their affiliates, as a group, can sell or transfer to non-affiliates on any trading day to an aggregate number of shares of our common stock of up to 10% of the average daily trading volume of our common stock. The agreement provides, however, that once in any 12-month period, the stockholder parties and their affiliates, as a group, may sell or transfer to non-affiliates up to an aggregate number of such shares of our common stock as is equal to five times the average daily trading volume of our common stock.

Critical Accounting Policies and Significant Judgments and Estimates

Our discussion and analysis of our financial condition and results of operations included in this annual report is based upon consolidated financial statements that we have prepared in accordance with U.S. generally accepted accounting principles, or U.S. GAAP. The preparation of these financial statements requires us to make a number of estimates and assumptions that affect the reported amounts of assets, liabilities, revenues and expenses in these financial statements and accompanying notes. On an ongoing basis, we evaluate these estimates and assumptions, including those related to determination of the fair value of goodwill and acquired in-process research and development, or IPR&D, and recognition of R&D expenses and share-based compensation. We base our estimates on historical information, when available, and assumptions believed to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities not readily apparent from other sources. Actual results may differ materially from these estimates under different assumptions or conditions.

We believe the following accounting estimates are those that can have a material impact on our financial condition or operating performance and involve substantial subjectivity and judgment in the application of our accounting policies to account for highly uncertain matters or the susceptibility of such matters to change. The following is not intended to be a comprehensive discussion of all of our significant accounting policies. See the notes accompanying our financial statements appearing in this report for a summary of all of our significant accounting policies and other disclosures required by U.S. GAAP.

Accrued Research and Development Expenses. As part of the process of preparing our 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 on our behalf 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. Many 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 financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments, if necessary. The majority of our accrued expenses relate to R&D services and related expenses. Examples of estimated accrued R&D expenses include:

- fees paid to contract research organizations, or CROs, in connection with clinical studies;
- fees paid to investigative sites and investigators in connection with clinical studies;
- fees paid to contract manufacturing organizations, or CMOs, in connection with process development activities and production of nonclinical and clinical trial material;
- fees paid to vendors in connection with nonclinical development activities; and
- fees paid to consultants for regulatory-related advisory and data management services.

We base our accrued expenses related to CROs and CMOs on our estimates of the services received and efforts expended pursuant to purchase orders or contracts with multiple service providers that we engage to conduct and manage our clinical studies and manufacture our clinical trial material on our behalf. The financial terms of our arrangements with our CROs and CMOs are subject to negotiation, vary from contract to contract and may result in uneven payment flows. Payments under some of these contracts depend on factors such as the successful completion of specified process development activities or the successful enrollment of patients and the completion of clinical study milestones. In accruing these service fees, we estimate, as applicable, the time period over which services will be performed (e.g., enrollment of patients, activation of clinical sites, etc.). If the actual timing varies from our estimate, we adjust the accrual accordingly. In addition, there may be instances in which payments made to service providers will exceed the level of services provided and result in a prepayment of R&D expense, which we report as an asset. The actual costs and timing of clinical studies and research-related manufacturing are uncertain and subject to change depending on a number of factors. Differences between actual costs of these services and the estimated costs that we have accrued in a prior period are recorded in the subsequent period in which the actual costs become known to us. Historically, these differences have not resulted in material adjustments, but such differences may occur in the future and have a material impact on our consolidated results of operations or financial position.

Business Combinations. We account for business combinations, such as our acquisitions of SynthRx in April 2011 and Aires Pharmaceuticals in February 2014, in accordance with Accounting Standards Codification, or ASC, Topic 805, Business Combinations, which requires the purchase price to be measured at fair value. When the purchase consideration consists entirely of shares of our common stock, we calculate the purchase price by determining the fair value, as of the acquisition date, of shares issued in connection with the closing of the acquisition and, if the transaction involves contingent consideration based on achievement of milestones or earn-out events, the probability-weighted fair value, as of the acquisition date, of shares issuable upon the occurrence of future events or conditions pursuant to the terms of the agreement governing the business combination. If the transaction involves such contingent consideration, our calculation of the purchase price involves probability inputs that are highly judgmental due to the inherent unpredictability of drug development, particularly by development-stage companies such as ours. We recognize estimated fair values of the tangible assets and intangible assets acquired, including IPR&D, and liabilities assumed as of the acquisition date, and we record as goodwill any amount of the fair value of the tangible and intangible assets acquired and liabilities assumed in excess of the purchase price.

Goodwill and Acquired IPR&D. In accordance with ASC Topic 350, Intangibles – Goodwill and Other, or ASC Topic 350, our goodwill and acquired IPR&D are determined to have indefinite lives and, therefore, are not amortized.

Instead, they are tested for impairment annually and between annual tests if we become aware of an event or a change in circumstances that would indicate the carrying value may be impaired. We perform our annual impairment testing as of September 30 of each year, or, in the case of initially acquired IPR&D, on the first anniversary of the date we acquired it and subsequently on September 30. Pursuant to Accounting Standards Update, or ASU, No. 2011-08, Intangibles – Goodwill and Other (Topic 350): Testing Goodwill for Impairment, and No. 2012-02, Intangibles – Goodwill and Other (Topic 350): Testing Indefinite-Lived Intangible Assets for Impairment, we have the option to first assess qualitative factors to determine whether the existence of events or circumstances leads us to determine that it is more likely than not (that is, a likelihood of more than 50%) that our goodwill or our acquired IPR&D is impaired. If we choose to first assess qualitative factors and we determine that it is not more likely than not goodwill or acquired IPR&D is impaired, we are not required to take further action to test for impairment. We also have the option to bypass the qualitative assessment and perform only the quantitative impairment test, which we may choose to do in some periods but not in others.

If we perform a quantitative assessment of goodwill, we utilize the two-step approach prescribed under ASC Topic 350. Step 1 requires a comparison of the carrying value of a reporting unit, including goodwill, to its estimated fair value. We test for impairment at the entity level because we operate on the basis of a single reporting unit. If our carrying value exceeds our fair value, we then perform Step 2 to measure the amount of impairment loss, if any. In Step 2, we estimate the fair value of our individual assets, including identifiable intangible assets, and liabilities to determine the implied fair value of goodwill. We then compare the carrying value of our goodwill to its implied fair value. The excess of the carrying value of goodwill over its implied fair value, if any, is recorded as an impairment charge.

If we perform a quantitative assessment of IPR&D, we calculate the estimated fair value of acquired IPR&D by using the Multi-Period Excess Earnings Method, or MPEEM, which is a form of the income approach. Under the MPEEM, the fair value of an intangible asset is equal to the present value of the asset's projected incremental after-tax cash flows (excess earnings) remaining after deducting the market rates of return on the estimated value of contributory assets (contributory charge) over its remaining useful life.

Our determinations as to whether, and, if so, the extent to which, goodwill and acquired IPR&D become impaired are highly judgmental and based on significant assumptions regarding our projected future financial condition and operating results, changes in the manner of our use of the acquired assets, development of our acquired assets or our overall business strategy, and regulatory, market and economic environment and trends.

Share-based Compensation Expenses. We account for share-based compensation awards granted to employees, including non-employee members of our board of directors, in accordance with ASC Topic 718, Compensation – Stock Compensation. Compensation expense for all share-based awards is based on the estimated fair value of the award on its date of grant and recognized on a straight-line basis over its vesting period. As share-based compensation expense is based on awards ultimately expected to vest, it is reduced for estimated forfeitures. We estimate forfeitures at the time of grant based on the expected forfeiture rate for our unvested stock options, which is based in large part on our historical forfeiture rates, but also on assumptions believed to be reasonable under the circumstances. We revise our estimates in subsequent periods if actual forfeitures differ from those estimates. Although share-based compensation expense can be significant to our consolidated financial statements, it does not involve the payment of any cash by us.

We estimate the grant date fair value of a stock option award using the Black-Scholes option-pricing model, or Black-Scholes model. In determining the grant date fair value of a stock option award under the Black-Scholes model, we must make a number of assumptions, including the term of the award, the volatility of the price of our common stock over the term of the award, and the risk-free interest rate. Changes in these or other assumptions could have a material impact on the compensation expense we recognize.

Results of Operations – Overview

We operate our business and evaluate our company on the basis of a single reportable segment, which is the business of developing therapies for serious or life-threatening diseases.

Revenue

We have not generated any revenue from product sales to date, and we do not expect to generate revenue from product sales until such time, if any, that we have obtained approval from a regulatory agency to sell one or more of our product candidates, which we cannot predict with certainty will occur. If we enter into any licensing or other collaborative arrangements regarding our development programs, we may recognize revenue from those arrangements prior to commercial sale of any products.

Operating Expenses

Research and Development Expenses. We maintain and evaluate our R&D expenses by the type of cost incurred rather than by project. We do this primarily because we outsource a substantial portion of our work and our R&D personnel and consultants work across multiple programs rather than dedicating their time to one particular program. We categorize our R&D expenses as external clinical study fees and expenses, external nonclinical study fees and expenses, personnel costs and share-based compensation expense. The major components of our external clinical study fees and expenses are fees and expenses related to CROs and clinical study investigative sites and investigators. The major components of our external nonclinical study fees and expenses are fees and expenses related to preclinical studies and other nonclinical testing, research-related manufacturing, and quality assurance and regulatory affairs services. Research-related manufacturing expenses include costs associated with producing and/or purchasing active pharmaceutical ingredient (API), conducting process development activities, producing clinical trial material, producing material for stability testing to support regulatory filings, related labeling, testing and release, packaging and storing services and related consulting fees. Impairment losses on R&D-related manufacturing equipment are also considered research-related manufacturing expenses. Personnel costs relate to employee salaries, benefits and related costs.

A general understanding of drug development is critical to understanding our results of operations and, particularly, our R&D expenses. Drug development in the U.S. and most countries throughout the world is a process that includes several steps defined by the U.S. Food and Drug Administration, or FDA, and similar regulatory authorities in foreign countries. The FDA approval processes relating to new drug products differ depending on the nature of the particular product candidate for which approval is sought. With respect to any product candidate with active ingredients not previously approved by the FDA, a prospective drug product manufacturer is required to submit a new drug application, or NDA, that includes complete reports of pre-clinical, clinical and laboratory studies and extensive manufacturing information to demonstrate the product candidate's safety and effectiveness. Generally, an NDA must be supported by at least phase 1, 2 and 3 clinical studies, with each study typically more expensive and lengthy than the previous study.

Future expenditures on R&D programs are subject to many uncertainties, including the number of clinical studies required to be conducted for each development program and whether we will develop a product candidate with a partner or independently. At this time, due to such uncertainties and the risks inherent in drug product development and the associated regulatory process, we cannot estimate with any reasonable certainty the duration of or costs to complete our R&D programs, or whether or when or to what extent revenues will be generated from the commercialization and sale of any of our product candidates. The duration and costs of our R&D programs, in particular, the duration and costs associated with clinical studies and research-related manufacturing, can vary significantly as a result of a variety of factors, including:

- the number of clinical and nonclinical studies necessary to demonstrate the safety and efficacy of a product candidate in a particular indication;
- the number of patients who participate in each clinical study;
- the number and location of sites included and the rate of site approval in each clinical study;
- the rate of patient enrollment and ratio of randomized to evaluable patients in each clinical study;
- the duration of patient treatment and follow-up;
- the potential additional safety monitoring or other studies requested by regulatory agencies;
- the time and cost to manufacture clinical trial material and commercial product, including process development and scale-up activities, and to conduct stability studies, which can last several years;
- the availability and cost of comparative agents used in clinical studies;
- the timing and terms of any collaborative or other strategic arrangements that we may establish; and
- the cost, requirements, timing of and the ability to secure regulatory approvals.

We regularly evaluate the prospects of our R&D programs, including in response to available scientific, nonclinical and clinical data, our assessments of a product candidate's market potential and our available resources, and make determinations as to which programs to pursue and how much funding to direct to each one.

We expect our R&D expenses to increase approximately 5% to 15% (excluding share-based compensation expense) in 2016 compared to 2015 if results from the EPIC study are positive and we determine they will support an NDA submission for vepoloxamer in sickle cell disease. Such an increase would be primarily due to increased external costs related to preparing our vepoloxamer NDA, conducting our Phase 2 clinical study of vepoloxamer in heart failure, supporting the INDIE-HFpEF Phase 2 study of AIR001, and increased compensation expenses for the full year impact of employees hired in 2015. These increases are expected to be offset by decreased external costs related to the EPIC study, research-related manufacturing for vepoloxamer, and the Phase 2 study of vepoloxamer in acute limb ischemia, or ALI, which we discontinued in the third quarter of 2015.

Selling, General and Administrative Expenses. Selling, general and administrative, or SG&A, expenses primarily consist of salaries, benefits and related costs for personnel in executive, finance and accounting, legal and marketing functions, and professional and consulting fees for accounting, legal, investor relations, business development, commercial strategy and research, human resources and information technology services. Other SG&A expenses

include facility lease and insurance costs and in-licensing costs for third-party intellectual property, if any.

We expect SG&A expenses to increase approximately 10% to 20% (excluding share-based compensation expense) in 2016 relative to 2015 if results from the EPIC study are positive and we determine they will support an NDA submission for vepoloxamer in sickle cell disease. Such an increase would be primarily due to increased external costs related to commercial-readiness activities, including medical communications, brand development and other market preparation activities.

Transaction-Related Expenses. Transaction-related expenses consist of legal, accounting, financial and business development advisory fees associated with the evaluation of potential acquisition targets and execution of acquisition transactions, including our acquisition of Aires.

Interest Income. Interest income includes interest earned on our cash, cash equivalent and investment security balances.

Interest Expense. Interest expense consists of interest payments made and interest expense related to debt issuance costs and debt discount under our debt facility with Hercules and interest expense associated with payments under capital leases of equipment.

Other Income, Net. Other income, net includes the bargain purchase gain related to the acquisition of Aires in 2014, as well as unrealized and realized gains and losses from foreign currency transactions and other non-operating gains and losses.

Results of Operations – Comparison of 2015 and 2014

Revenue. We recognized no revenue for the years ended December 31, 2015 and 2014.

Operating Expenses. The following table illustrates the types of operating expenses we incurred in 2015 and 2014 and their respective percent of our total operating costs for those periods:

	Operating Expenses Years Ended			
	2015		2014	
Research and development	72	%	66	%
Selling, general and administrative	28	%	33	%
Transaction-related expenses	0	%	1	%
Depreciation and amortization	0	%	0	%
Total operating expenses	100	%	100	%

R&D Expenses. In 2015, our most significant R&D expenses were external costs associated with the EPIC study, our Phase 2 studies of vepoloxamer in ALI, which we discontinued in the third quarter of 2015, and heart failure, which is ongoing, and research-related manufacturing for vepoloxamer and AIR001. These expenses consisted primarily of CRO and CMO expenses, clinical study-related consulting and study site expenses, which include start-up costs as well as patient expenses. In 2014, our most significant R&D expenses were external costs associated with the EPIC study, our Phase 2 study of vepoloxamer in ALI, and research-related manufacturing for vepoloxamer.

The following table summarizes our consolidated R&D expenses by type for each of the periods listed and their respective percent of our total R&D expenses for 2015 and 2014 (in thousands, except for percentages):

	Years Ended December 31,				
	2015	%		2014	%	
External clinical study fees and expenses	$14,089	50	%	$11,158	57	%
External nonclinical study fees and expenses	9,519	34	%	4,451	23	%
Personnel costs	4,058	14	%	3,401	18	%
Share-based compensation expense	598	2	%	425	2	%
Total	$28,264	100	%	$19,435	100	%

R&D expenses increased by $8.8 million, or 45.4%, to $28.3 million for the year ended December 31, 2015, compared to $19.4 million for the year ended December 31, 2014. The increase in R&D expenses in 2015 compared to 2014 was due to a $5.1 million increase in external nonclinical study fees and expenses, a $2.9 million increase in external clinical study fees and expenses, a $0.7 million increase in personnel costs and a $0.2 million increase in share-based compensation expense.

The $5.1 million increase in external nonclinical study fees and expenses resulted primarily from increases of: 1) $2.9 million in research-related manufacturing costs for vepoloxamer, 2) $1.8 million primarily related to nonclinical toxicology studies of vepoloxamer to support our NDA submission, and 3) $0.4 million in consulting expenses for NDA-readiness activities related to vepoloxamer. The $2.9 million increase in external clinical study fees and expenses was related primarily to increases of $3.3 million

in EPIC study costs and $0.9 million in costs for our Phase 2 study of vepoloxamer in heart failure, offset by decreases of $0.8 million in costs for the discontinued Phase 2 study of vepoloxamer in ALI and $0.5 million in costs related to AIR001 clinical study expenses. The $0.7 million increase in personnel costs resulted primarily from additional regulatory, clinical operations, and research-related manufacturing staff hired in 2015.

Selling, General and Administrative Expenses. In 2015 and 2014, our SG&A expenses primarily consisted of employee salaries and benefits, share-based compensation expense, facility lease and insurance costs, and professional and consulting fees for accounting, legal, investor relations, market strategy and research, human resources, facilities, internal systems support, and share-based compensation expense.

SG&A expenses increased by $1.5 million, or 15.6%, to $11.0 million for the year ended December 31, 2015, compared to $9.5 million for the year ended December 31, 2014. This increase was due primarily to a $0.7 million increase in professional and consulting fees and a $0.5 million increase in personnel costs. Personnel costs for 2015 include $0.4 million of severance expense and $0.3 million of share-based compensation expense resulting from the termination of employment of our former president and chief operating officer in February 2015 and the acceleration of stock option vesting pursuant to the terms of his option agreements.

Transaction-Related Expenses. There were no transaction-related expenses for the year ended December 31, 2015. Transaction-related expenses of $0.3 million for the year ended December 31, 2014 consisted primarily of legal fees associated with the acquisition of Aires.

Interest Income. Interest income for the year ended December 31, 2015 was $130,000 compared to $69,000 for the year ended December 31, 2014.

Interest Expense. Interest expense for the year ended December 31, 2015 was $603,000, $601,000 of which was related to the debt facility with Hercules. There was no interest expense in the year ended December 31, 2014.

Other Income, Net. Other income, net for the year ended December 31, 2015 was negligible. Other income, net for the year ended December 31, 2014 consisted primarily of a $0.5 million bargain purchase gain associated with the acquisition of Aires.

Net Loss. Net loss was $39.8 million, or $0.25 per share (basic and diluted), for the year ended December 31, 2015, compared to a net loss of $28.7 million, or $0.23 per share (basic and diluted), for the year ended December 31, 2014.

Liquidity and Capital Resources

We have a history of annual losses from operations and we anticipate that we will continue to incur losses for at least the next several years. For the years ended December 31, 2015 and 2014, we incurred losses from operations of $39.4 million and $29.3 million, respectively. Our cash, cash equivalents and investment securities were $41.0 million and our working capital was $19.1 million at December 31, 2015.

We historically have funded our operations principally through proceeds from sales of our equity securities.

In February 2016, we completed an underwritten public offering with gross proceeds of $8.0 million from the sale and issuance of 29,090,910 units, each consisting of one share of our common stock and one warrant to purchase one share of our common stock. Net proceeds, after deducting underwriting discounts and commissions and other estimated offering expenses, were approximately $7.3 million. The warrants have an exercise price of $0.42 per share, are exercisable any time on or after August 17, 2016 and will expire on February 16, 2021.

In November 2014, we completed an underwritten public offering with gross proceeds of $21.0 million from the sale and issuance of units consisting of shares of our common stock and warrants to purchase our common stock at an exercise price of $0.75 per share and units consisting of “pre-funded” warrants to purchase shares of our common stock at an exercise price of $0.01 per share and warrants to purchase shares of our common stock at an exercise price of $0.75 per share. We issued and sold an aggregate of 30,941,102 shares of our common stock, 13,081,428 pre-funded warrants exercisable for up to 13,081,428 shares, and 22,011,265 warrants exercisable for up to 22,011,265 shares. Net proceeds, after deducting underwriting discounts and commissions and other offering expenses, were $19.7 million. The pre-funded warrants and the warrants are exercisable at any time on or before November 12, 2019, subject to certain beneficial ownership limitations.

We may receive up to $11.7 million, $18.3 million, $0.1 million, $16.5 million, and $12.2 million of additional net proceeds from the exercise of warrants issued in the underwritten public offerings we completed in November 2011, June 2013, November 2014, and February 2016, respectively. However, the timing of the exercise and extent to which any of these warrants are exercised before they expire are beyond our control and depend on a number of factors, including certain beneficial ownership limitations and the market price of our common stock. The exercise prices of these warrants are $1.10, $0.65, $0.01, $0.75, and $0.42 per share,

respectively. In comparison, the closing sale price of our common stock on March 10, 2016 was $0.28 per share and we do not expect the holders of the warrants to exercise them unless and until our common stock trades at or above the exercise price of their warrants. In addition, if at the time of exercise there is not an effective registration statement available for the issuance of the shares subject to the warrants, they may be exercised on a "cashless" net issuance basis, in which case we would not receive any proceeds from the exercise of these warrants.

In February 2014, we entered into a sales agreement with Cowen and Company, LLC, or Cowen, to sell shares of our common stock, with aggregate gross sales proceeds of up to $30 million, from time to time, through an "at the market," or ATM, equity offering program, under which Cowen acts as sales agent. We refer to that agreement as the 2014 Sales Agreement. In August 2015, we terminated the 2014 Sales Agreement upon entry into a new sales agreement with Cowen to sell shares of our common stock, with aggregate gross sales proceeds of up to $30 million, from time to time, through an ATM program. As of December 31, 2015, we had sold and issued an aggregate of 24,859,107 shares at a weighted-average sales price of $0.70 per share under the ATM programs for aggregate gross proceeds of $17.5 million and $16.6 million in net proceeds, after deducting sales agent commission and discounts and our other offering costs.

We have borrowed $15 million under a debt facility and have received proceeds of approximately $14.8 million, net of fees. The debt facility is governed by a loan and security agreement, as amended, among our company, Hercules Technology III, L.P., and Hercules Capital, Inc. (formerly known as Hercules Technology Growth Capital, Inc.), together referred to as Hercules. Under the loan and security agreement, as amended, we are required to prepay $10 million of the principal balance to Hercules on July 31 ,2016 unless on or before such date we demonstrate, to the reasonable satisfaction of Hercules, positive results in the EPIC study. To date, we have been making interest-only payments to Hercules. However, our first principal payment of approximately $430,000 is due on July 1, 2016, unless we demonstrate positive results in the EPIC study on or before such date and no event of default has occurred, in which case our first principal payment will not be due until March 1, 2017. If we do not have EPIC results before July 1, but demonstrate positive results in EPIC between July 2 and July 31, 2016, inclusive, and no event of default has occurred, then on July 1, 2016, we will be required to make a single principal payment of approximately $430,000, but then resume making interest-only payments until March 1, 2017. See Note 9, "Debt Facility," of the Notes to the Condensed Consolidated Financial Statements in this report for additional information regarding our debt facility with Hercules. Our obligations under our agreement with Hercules are secured by substantially all of our assets other than our intellectual property, but including proceeds from the sale, licensing or other disposition of our intellectual property. Our intellectual property is subject to negative covenants, which, among other things, prohibit us from selling, transferring, assigning, mortgaging, pledging, leasing, granting a security interest in or otherwise encumbering our intellectual property, subject to limited exceptions. The agreement includes a number of other restrictive covenants that may limit our ability to raise capital through other debt or equity financing. The debt facility also includes events of default, the occurrence and continuation of which would provide Hercules with the right to exercise remedies against us and the collateral securing our indebtedness, which include declaring payment of all or any part of the debt, together with a prepayment charge of 1%, 2% or 3% of the then outstanding principal balance, immediately due and payable. These events of default include, among other things, our failure to pay any amount due on the due date, our breach or default in the performance of any covenant under the debt facility, our insolvency, the attachment, seizure, or filing of a levy against our assets or a judgment entered against us in an amount greater than $250,000, the occurrence of any default under certain other indebtedness, and, subject to limited exceptions, the occurrence of an event or circumstance that would reasonably be expected to have a material adverse effect on our business, operations, assets or financial condition, our ability to repay our indebtedness in accordance with the terms of the credit facility, or on the collateral securing our indebtedness.

For a discussion of our liquidity and capital resources outlook, see "Management Outlook" below.

The following table sets forth a summary of the primary sources and uses of cash and cash equivalents for each of the years presented below (in thousands):

	Years Ended December 31,	
	2015	2014
Net cash (used in) provided by:		
Operating activities	$(32,949)	$(24,645)
Investing activities	$3,395	$481
Financing activities	$16,798	$34,291
Net (decrease)/increase in cash and cash equivalents	$(12,756)	$10,127

Operating activities. Net cash used in operating activities was $32.9 million in 2015 and consisted primarily of a net loss of $39.8 million adjusted for non-cash items, including share-based compensation expense of $2.7 million, a net increase of $3.9 million due to changes in assets and liabilities, and $0.2 million of amortization of debt issuance costs and debt discount. Net cash used in operating activities was $24.6 million in 2014 and consisted primarily of a net loss of $28.7 million adjusted for non-cash items,

including share-based compensation expense of $2.0 million, a net increase of $2.4 million due to changes in assets and liabilities, offset by a gain on bargain purchase for the Aires acquisition of $0.5 million.

Investing activities. Net cash provided by investing activities was $3.4 million in 2015, compared to $0.5 million in 2014. The difference was due primarily to a decrease of $5.7 million in purchases of certificates of deposit, an increase of $0.4 million in proceeds from maturities of certificates of deposit, offset by $3.5 million in cash obtained in our acquisition of Aires in 2014.

Financing activities. Net cash provided by financing activities was $16.8 million in 2015, compared to $34.3 million in 2014. The cash provided by financing activities in 2015 consisted of net proceeds of $14.8 million under our debt facility with Hercules and $2.0 million from sales of our shares of common stock through our ATM program. Net cash provided by financing activities in 2014 consisted of net proceeds of $19.7 million from the underwritten public offering of our equity securities completed in November 2014 and net proceeds of $14.6 million from sales of our common stock under the ATM program.

Management Outlook

If results from the EPIC study are positive and we determine they will support an NDA submission for vepoloxamer in sickle cell disease, we expect our operating expenses for the year ending December 31, 2016 will be approximately $38 to $43 million, excluding share-based compensation expense. Based on our projected capital needs, which assume positive results from the EPIC study, and our current cash, cash equivalents and investment securities and working capital, we intend to raise additional capital before the fourth quarter of 2016 through equity or debt financings and/or through collaborations, including licensing arrangements, to pursue our current business strategy and planned operations. If we are unable to raise sufficient additional before the fourth quarter of 2016, or in the event of negative results in the EPIC study and prepayment to Hercules on July 31, 2016 of $10 million of the principal balance under our debt facility, we anticipate that we would immediately reduce the scope of our planned operations, including by delaying or discontinuing investment in development and commercialization efforts for vepoloxamer in sickle cell disease and heart failure. In that case, we expect that our cash, cash equivalents and investment securities as of December 31, 2015, together with the net proceeds from the underwritten public offering we completed in February 2016, will be sufficient to fund our operations, as reduced in scope, into the first quarter of 2017. In the case of either positive or negative results in the EPIC study, adequate additional capital may not be available to us on acceptable terms, on a timely basis, or at all.

Our estimate of our 2016 operating expenses and of the period of time through which our current financial resources will be adequate to support our operations are forward-looking statements based on significant assumptions, including that results from the EPIC study are positive and we determine they will support an NDA submission. We could utilize our financial resources sooner than we currently expect. Forward-looking statements involve a number of risks and uncertainties and actual results could differ materially if the assumptions on which we have based our forward-looking statements prove to be wrong. Factors that will affect our 2016 operating expenses and future capital requirements include, but are not limited to:

- the results from the EPIC study;
- feedback from the FDA regarding the content and process for submission of an NDA for vepoloxamer, including whether the FDA will require a second Phase 3 study or other clinical or nonclinical studies to demonstrate substantial evidence of effectiveness of vepoloxamer for the treatment of sickle cell crisis, such as greater statistical significance or magnitude of clinical relevance, or to provide additional safety and tolerability data, or whether the FDA will require the starting material for vepoloxamer to be manufactured consistent with cGMP requirements applicable to API or that we have control over excipient-grade cGMP conditions under which it currently is manufactured;

- our ability to secure adequate supply of API and finished drug product from our CMOs to meet market demand and manage our costs related to commercial manufacture of our products, should any of our product candidates obtain regulatory approval;
- the design, initiation, scope, rate of progress, results and timing of our clinical and nonclinical studies of our product candidates;
- the successful completion of our development programs and our ability to manage costs associated with clinical and nonclinical development of our product candidates, including research-related manufacturing activities;
- our ability to obtain and maintain regulatory approvals of our product candidates, the scope of regulatory approval we pursue, and the extent to which we do so independently or through collaborations;

- the extent to which we increase our workforce, including in connection with establishing a commercial infrastructure to support independent commercialization of vepoloxamer in the U.S. and EU, if approved;
- our ability to obtain and maintain effective patent coverage or other market exclusivity protections for our products, if approved, and to operate our business without infringing upon the intellectual property rights of others;
- the extent of commercial success of any of our product candidates for which we receive regulatory approval; and
- the extent to which we seek to expand our product pipeline through acquisitions and execute on transactions intended to do so.

Vepoloxamer

We are focusing our resources primarily on development of vepoloxamer. In February 2016, we completed patient enrollment in the EPIC study and we expect to report top-line data in the second quarter of 2016. If results are positive and, based on subsequent discussions with the FDA we determine to submit an NDA for vepoloxamer for the treatment of vaso-occlusive crisis in patients with sickle cell disease utilizing the FDA's rolling review process, we plan to begin submitting portions of the NDA in the fourth quarter of 2016 and complete our submission in the first quarter of 2017. We currently are planning for a six-month review period following the FDA's filing decision (or eight months from the date we complete the NDA submission), based on an assumption of receiving priority review designation. If vepoloxamer is approved on this timeline, we anticipate commercial launch in the U.S. by the end of 2017. We plan to build a commercial infrastructure to support U.S. launch, including a sales force of approximately 30 representatives, in 2017. In order to take advantage of vepoloxamer's potential to be the first and only approved therapy to shorten the duration of a vaso-occlusive crisis, we are conducting and plan to continue to conduct during 2016 other commercial-readiness activities, including medical communications, brand development and other market preparation activities.

To support our NDA submission, we also are conducting an open-label, multicenter EPIC extension study known as EPIC-E, a sub-study of patients participating in EPIC and EPIC-E at selected U.S. study sites, and a clinical pharmacokinetics study of vepoloxamer in approximately 40 individuals with varying degrees of renal insufficiency. EPIC-E will provide data to expand our existing safety database regarding repeat exposure to vepoloxamer. Through the EPIC sub-study we hope to gain insight into vepoloxamer's ability to reduce tissue damage during vaso-occlusive crisis. The special population study will further enhance the safety database for vepoloxamer and help guide dosage adjustments for renally impaired patients. We intend to continue enrolling these studies as we prepare our NDA submission for vepoloxamer in sickle cell disease.

Vepoloxamer also is in Phase 2 clinical development for the treatment of heart failure. Our ongoing randomized, double-blind, placebo-controlled, multicenter Phase 2 study in which we plan to enroll approximately 150 patients, is evaluating a new formulation of vepoloxamer for the treatment of patients with chronic heart failure. As of March 10, 2016, we had opened a total of nine study sites in the U.S. and Australia. Pending positive data from the EPIC study, we plan to open additional study sites within and outside of the U.S. Although predicting the rate and timing of enrollment for any clinical study including this study is subject to a number of significant assumptions and completion of the study may differ materially, we expect to complete patient enrollment in the first quarter of 2018.

We also are evaluating vepoloxamer's potential in stroke. Based on nonclinical study data we announced in 2015, as well as published data from third party studies of poloxamer 188, we believe, and several medical experts in the field have agreed, that sufficient data now exists to support clinical development of vepoloxamer in stroke. We continue to assess the opportunity and believe it is a Phase 2-ready program. However, we do not plan to commence clinical development in stroke prior to analysis of results from the EPIC study.

Further, we are conducting or plan to conduct a number of other ex vivo, nonclinical in vivo and in vitro studies of vepoloxamer to further understand its pharmacologic effects and support our intellectual property positions.

AIR001

AIR001 is in Phase 2 clinical development for the treatment of patients with HFpEF. Since acquiring the program in 2014, we have supported two investigator-sponsored Phase 2a studies of AIR001 in patients with HFpEF, one of which is ongoing and the other reported positive top-line results in February 2016, as discussed above. In addition, as we announced in February 2016, we are supporting the Heart Failure Clinical Research Network's (HFN) INDIE-HFpEF study, a multicenter, randomized, double-blind, placebo-controlled crossover Phase 2 study of AIR001 in approximately 100 patients with HFpEF. The study is expected to begin in the third quarter of 2016. We expect to enter into an agreement with the HFN's Coordinating Center to provide the test materials,

nebulizers, regulatory and technical support for the study, as well as approximately $3 million in financial support at specified milestones over the course of the study. We expect to pay the majority of such amount in 2017.

In parallel with our independent development of vepoloxamer and AIR001, from time to time, we evaluate opportunities for strategic collaborations, including with respect to country-specific development and regulatory or commercial expertise that would enhance the value of our programs.

As discussed above, based on our projected capital needs, which assume positive results from the EPIC study, and our current cash, cash equivalents and investment securities and working capital, we intend to raise additional capital before the fourth quarter of 2016 through equity or debt financings and/or through collaborations, including licensing arrangements, to pursue our current business strategy and planned operations. Subject to limited exceptions, our loan and security agreement with Hercules prohibits us from incurring indebtedness without Hercules' prior written consent. If we are unable to raise sufficient additional capital before the fourth quarter of 2016, or in the event of negative results in the EPIC study and prepayment to Hercules on July 31, 2016 of $10 million of the principal balance under our debt facility, we anticipate that we would immediately reduce the scope of our planned operations, including by delaying or discontinuing investment in development and commercialization efforts for vepoloxamer in sickle cell disease and heart failure. In that case, we expect that our cash, cash equivalents and investment securities as of December 31, 2015, together with the net proceeds from the underwritten public offering we completed in February 2016, would be sufficient to fund our operations, as reduced in scope, into the first quarter of 2017. If we implement significant cost saving measures, it could delay our ability to seek approval for vepoloxamer in sickle cell disease even if EPIC results are positive, and our ability to commercialize vepoloxamer for sickle cell crisis, if approved, and could adversely affect our ability meet future market demand.

We may utilize our current financial resources sooner than we currently expect if we incur unanticipated expenses or the assumptions on which we've based our forecasts and contingency plans prove to be wrong. If we are unable to raise sufficient additional capital as needed and we reduce the scope of our operations, we may also be compelled to repay all of our outstanding debt to Hercules and sell certain assets, including intellectual property assets, which would have a further material and adverse effect on our financial condition and ability to pursue our business strategy.

Recent Accounting Pronouncements

See Note 2, "Summary of Significant Accounting Policies — Recent Accounting Pronouncements," of the Notes to Consolidated Financial Statements in this report for a discussion of recent accounting pronouncements and their effect, if any, on us.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.
Under SEC rules and regulations, as a smaller reporting company transitioning to the larger reporting company disclosure requirements, we are not required to provide the information required by this item. See "Item 6. Selected Financial Data," above.

Item 8. Financial Statements and Supplementary Data.

The consolidated financial statements and supplementary financial information required by this item are filed with this report as described under Item 15.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure.
None.

Item 9A. Controls and Procedures.

Disclosure Controls and Procedures

We maintain disclosure controls and procedures that are designed to provide reasonable assurance that information required to be disclosed by us in the reports we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognized that any controls and procedures, no matter how well designed and operated, can only provide reasonable assurance of achieving the desired control objectives, and in reaching a reasonable level of assurance, management necessarily was required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Under the supervision and with the participation of our management, including our principal executive officer and principal financial officer, we have evaluated the effectiveness of our disclosure controls and procedures (as defined under Exchange Act Rule

13a-15(e)) as of December 31, 2015. Based on that evaluation, our principal executive officer and principal financial officer have concluded that as of December 31, 2015 these disclosure controls and procedures were effective at the reasonable assurance level.

Management's Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Exchange Act Rule 13a-15(f). Under the supervision and with the participation of our management, including our principal executive officer and principal financial officer, we conducted an evaluation of the effectiveness of our internal control over financial reporting as of December 31, 2015 based on the framework in Internal Control — Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on our evaluation under the framework in Internal Control — Integrated Framework (2013), our management concluded that our internal control over financial reporting was effective as of December 31, 2015.

The effectiveness of our internal control over financial reporting as of December 31, 2015 has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report, which appears on page F 2 of this annual report.

Changes in Internal Control over Financial Reporting

There was no change in our internal control over financial reporting identified in connection with the evaluation required by Exchange Act Rules 13a-15(d) and 15d-15(d) that occurred during the fiscal quarter ended December 31, 2015 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.
Not applicable.

PART III

Certain information required by Part III of this report is omitted from this report pursuant to General Instruction G(3) of Form 10-K because we will file a definitive proxy statement pursuant to Regulation 14A for our 2016 annual meeting of stockholders (the "Proxy Statement") not later than 120 days after the end of the fiscal year covered by this report, and the information included in the Proxy Statement that is required by Part III of this report is incorporated herein by reference.

Item 10. Directors, Executive Officers and Corporate Governance.
Code of Ethics

We have adopted a code of ethics that applies to our principal executive officer, principal financial officer, principal accounting officer or persons performing similar functions, as well as all of our other officers, directors and employees. This code of ethics is a part of our code of business conduct and ethics, and is available on our corporate website at www.masttherapeutics.com. We intend to disclose future amendments to, or waivers of, certain provisions of our code of ethics that apply to our principal executive officer, principal financial officer, principal accounting officer or persons performing similar functions on our corporate website within four business days following such amendment or waiver.

The other information required by this item will be set forth in the Proxy Statement and is incorporated into this report by reference.

Item 11. Executive Compensation.
The information required by this item will be set forth in the Proxy Statement and is incorporated into this report by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.
The information required by this item will be set forth in the Proxy Statement and is incorporated into this report by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence.
The information required by this item will be set forth in the Proxy Statement and is incorporated into this report by reference.

Item 14. Principal Accounting Fees and Services.
The information required by this item will be set forth in the Proxy Statement and is incorporated into this report by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(a) Documents Filed. The following documents are filed as part of this report:

(1) Financial Statements. The following reports of PricewaterhouseCoopers LLP and financial statements:

Report of PricewaterhouseCoopers LLP, Independent Registered Public Accounting Firm

Consolidated Balance Sheets as of December 31, 2015 and 2014

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

Consolidated Statements of Stockholders' Equity for the years ended December 31, 2015 and 2014

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

Notes to Consolidated Financial Statements

(2) Financial Statement Schedules. See subsection (c) below.

(3) Exhibits. See subsection (b) below.

(b) Exhibits. The exhibits filed or furnished with this report are set forth on the Exhibit Index immediately following the signature page of this report, which Exhibit Index is incorporated herein by reference.

(c) Financial Statement Schedules. All schedules are omitted because they are not applicable, the amounts involved are not significant or the required information is shown in the financial statements or notes thereto.

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.

Date: March 14, 2016 Mast Therapeutics, Inc.

By: /s/ Brian M. Culley
Brian M. Culley
Chief Executive Officer and Director

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Brian M. Culley and Brandi L. Roberts, and each of them acting individually, as his/her true and lawful attorneys-in-fact and agents, each with full power to act alone, with full powers of substitution and resubstitution, for him/her and in his/her name, place and stead, in any and all capacities, to sign any and all amendments to this annual report on Form 10-K, and to file the same, with all exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully for all intents and purposes as he/she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or any of them or their substitute or resubstitute, may lawfully do or cause to be done by virtue hereof.

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 and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Brian M. Culley	Chief Executive Officer and Director	March 14, 2016
Brian M. Culley	(Principal Executive Officer)	
/s/ Brandi L. Roberts	Chief Financial Officer and Senior Vice President	March 14, 2016
Brandi L. Roberts	(Principal Financial and Accounting Officer)	
/s/ Howard C. Dittrich	Director	March 14, 2016
Howard C. Dittrich		
/s/ Peter Greenleaf	Director	March 14, 2016
Peter Greenleaf		
/s/ Matthew Pauls	Director	March 14, 2016
Matthew Pauls		

/s/ David A. Ramsay	Director	March 14, 2016
David A. Ramsay		

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Financial Statement Schedules:	

Financial statement schedules have been omitted for the reason that the required information is presented in financial statements or notes thereto, the amounts involved are not significant or the schedules are not applicable.
See accompanying notes to consolidated financial statements.

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Stockholders of

Mast Therapeutics, Inc.

In our opinion, the accompanying consolidated balance sheets and the related consolidated statements of operations and comprehensive loss, of stockholders' equity and of cash flows present fairly, in all material respects, the financial position of Mast Therapeutics, Inc. and its subsidiaries at December 31, 2015 and 2014, and the results of their operations and their cash flows for the years then ended in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2015, based on criteria established in Internal Control - Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). The Company's management is responsible for these financial statements, for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in Management's Report on Internal Control over Financial Reporting appearing under Item 9A. Our responsibility is to express opinions on these financial statements and on the Company's internal control over financial reporting based on our audits (which was an integrated audit in 2015). We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the financial statements are free of material misstatement and whether effective internal control over financial reporting was maintained in all material respects. Our audits of the financial statements included examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

As discussed in Note 1 to the consolidated financial statements, the Company has incurred significant operating losses since inception and will require additional financing to fund future operations. Management's plans in regard to these matters are also described in Note 1.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) 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 of the company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ PricewaterhouseCoopers LLP

San Diego, California

March 14, 2016

Mast Therapeutics, Inc. and Subsidiaries

Consolidated Balance Sheets

(in thousands, except for share and par value data)

	December 31, 2015	December 31, 2014
Assets		
Current assets:		
Cash and cash equivalents	$23,052	$35,808
Investment securities	17,929	21,481
Prepaid expenses and other current assets	1,271	1,114
Total current assets	42,252	58,403
Property and equipment, net	226	188
In-process research and development	8,549	8,549
Goodwill	3,007	3,007
Other assets	183	353
Total assets	$54,217	$70,500
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$2,600	$1,370
Accrued liabilities	8,152	5,625
Accrued compensation and payroll taxes	1,430	1,443
Debt facility	10,991	-
Total current liabilities	23,173	8,438
Long-term lease obligation	25	-
Debt facility, net of current portion	3,726	-
Deferred income tax liability	3,404	3,404
Total liabilities	30,328	11,842
Commitments (Note 12)		
Stockholders' equity:		
Common stock, $0.001 par value; 500,000,000 shares authorized; 163,614,297 and 159,458,376 shares issued and outstanding at December 31, 2015 and 2014, respectively	164	159
Additional paid-in capital	298,715	293,655
Accumulated other comprehensive loss	(17)	(25)
Accumulated deficit	(274,973)	(235,131)
Total stockholders' equity	23,889	58,658
Total liabilities and stockholders' equity	$54,217	$70,500

See accompanying notes to consolidated financial statements.

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Mast Therapeutics, Inc. and Subsidiaries

Consolidated Statements of Operations and Comprehensive Loss

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

	Years ended December 31,	
	2015	2014
Revenues	$—	$—
Operating expenses:		
Research and development	28,264	19,435
Selling, general and administrative	10,963	9,488
Transaction-related expenses	-	271
Depreciation and amortization	146	85
Total operating expenses	39,373	29,279
Loss from operations	(39,373)	(29,279)
Interest income	130	69
Interest expense	(603)	-
Other income, net	4	508
Net loss	$(39,842)	$(28,702)
Net loss per share - basic and diluted	$(0.25)	$(0.23)
Weighted average shares outstanding - basic and diluted	162,219,116	122,409,183
Comprehensive Loss:		
Net loss	$(39,842)	$(28,702)
Other comprehensive income/(loss)	8	(4)
Comprehensive loss	$(39,834)	$(28,706)

See accompanying notes to consolidated financial statements.

Mast Therapeutics, Inc. and Subsidiaries

Consolidated Statements of Stockholders' Equity

(in thousands, except for share data)

	Common stock		Additional paid-in	Accumulated other comprehensive	Accumulated	Total stockholders'
	Shares	Amount	capital	loss	deficit	equity
Balances at January 1, 2014	102,710,286	$ 103	$ 254,155	$ (21)	$ (206,429)	$ 47,808
Net loss	-	-	-	-	(28,702)	(28,702)
Sale of common stock and pre-funded warrants, net of offering costs of $2,095	51,644,288	51	34,203	-	-	34,254
Issuance of stock in Aires acquisition	5,103,702	5	3,265	-	-	3,270
Share-based compensation expense - employee options	-	-	2,032	-	-	2,032
Warrant exercise	100	0	0	-	-	0
Other comprehensive loss	-	-	-	(4)	-	(4)
Balances at December 31, 2014	159,458,376	159	293,655	(25)	(235,131)	58,658
Net loss	-	-	-	-	(39,842)	(39,842)
Sale of common stock, net of offering costs of $142	4,155,921	5	1,993	-	-	1,998
Issuance of warrants in connection with debt facility	-	-	392	-	-	392
Share-based compensation expense - employee options	-	-	2,675	-	-	2,675
Other comprehensive income	-	-	-	8	-	8
Balances at December 31, 2015	163,614,297	$ 164	$ 298,715	$ (17)	$ (274,973)	$ 23,889

See accompanying notes to consolidated financial statements.

Mast Therapeutics, Inc. and Subsidiaries

Consolidated Statements of Cash Flows

(in thousands)

	Years ended December 31,	
	2015	2014
Cash flows from operating activities:		
Net loss	$(39,842)	$(28,702)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	146	85
Gain on bargain purchase	—	(486)
Share-based compensation expense related to employee stock options	2,675	2,032
Write-off of fixed assets	6	—
Amortization of debt issuance costs and debt discount	185	—
Changes in assets and liabilities, net of effect of acquisitions:		
Increase/(decrease) in prepaid expenses and other assets	13	(58)
Increase in accounts payable	1,230	406
Increase in accrued liabilities	2,638	2,078
Net cash used in operating activities	(32,949)	(24,645)
Cash flows from investing activities:		
Purchases of certificates of deposit	(13,713)	(19,435)
Proceeds from maturities of certificates of deposit	17,024	16,659
Proceeds from sales of certificates of deposit	249	—
Purchases of property and equipment	(165)	(147)
Security deposit for new lease	—	(130)
Cash obtained through acquisition	—	3,534
Net cash provided by investing activities	3,395	481
Cash flows from financing activities:		
Proceeds from borrowings under debt facility	15,000	—
Costs paid in connection with debt facility	(193)	—
Proceeds from sale of common stock	2,140	30,201
Proceeds from sale and exercise of warrants	—	6,148
Payments for offering costs	(142)	(2,058)
Payments for capital lease	(7)	—
Net cash provided by financing activities	16,798	34,291
Net (decrease)/increase in cash and cash equivalents	(12,756)	10,127
Cash and cash equivalents at beginning of period	35,808	25,681
Cash and cash equivalents at end of period	$23,052	$35,808

See accompanying notes to consolidated financial statements.

Mast Therapeutics, Inc. and Subsidiaries

Notes to Consolidated Financial Statements

December 31, 2015

1. Description of Business

Mast Therapeutics, Inc., a Delaware corporation ("Mast Therapeutics," "we" or "our company"), is a biopharmaceutical company focused on developing clinical-stage therapies for serious or life-threatening diseases. We have devoted substantially all of our resources to research and development ("R&D") and acquisition of our product candidates. We have not yet marketed or sold any products or generated any significant revenue. Through our acquisition of SynthRx, Inc. ("SynthRx") in 2011, we acquired our Membrane Adhesion & Sealant Technology (MAST) platform, which includes proprietary poloxamer-related data and know-how developed over two decades of clinical, nonclinical and manufacturing experience, and we are leveraging the MAST platform to develop vepoloxamer (also known as MST-188) for serious or life-threatening diseases and conditions typically characterized by impaired microvascular blood flow and damaged cell membranes. Through our acquisition of Aires Pharmaceuticals, Inc. ("Aires") in February 2014, we acquired AIR001, a sodium nitrite inhalation solution for intermittent inhalation via nebulization, which we are developing for the treatment of heart failure with preserved ejection fraction (HFpEF).

The accompanying consolidated financial statements have been prepared on a going concern basis, which contemplates the realization of assets and the satisfaction of liabilities in the normal course of business. We have incurred significant operating losses since inception and have relied on our ability to fund our operations primarily though equity financings and a debt financing. For the years ended December 31, 2015 and 2014, we incurred losses from operations of $39.4 million and $29.3 million, respectively, and our net cash used in operating activities was $32.9 million and $24.6 million, respectively. At December 31, 2015, we had an accumulated deficit of $275.0 million, our cash, cash equivalents and investment securities totaled $41.0 million, and our working capital was $19.1 million. Given our planned operating activities in the case of positive results from the EPIC study that we determine will support proceeding with an NDA submission for vepoloxamer, our current cash, cash equivalents and investment securities balances, and our working capital, we intend to raise additional capital before the fourth quarter of 2016 through equity or debt financings and/or through collaborations, including licensing agreements. There can be no assurance that we will be successful in raising sufficient additional capital or that such capital, if available, will be on terms that are acceptable to us. Subject to limited exceptions, our loan and security agreement with Hercules prohibits us from incurring indebtedness without Hercules' prior written consent. If we are unable to raise sufficient additional capital before the fourth quarter of 2016, or in the case of negative results from the EPIC study and prepayment to Hercules on July 31, 2016 of $10 million of the principal balance under our debt facility, we anticipate that we would immediately reduce the scope of our planned operations, including by delaying or discontinuing investment in development and commercialization efforts for vepoloxamer in sickle cell disease and heart failure. In this case, we expect that our cash, cash equivalents and investment securities as of December 31, 2015, together with the net proceeds from the underwritten public offering we completed in February 2016, would be sufficient to fund our operations, as reduced in scope, into the first quarter of 2017.

Our business, operating results, financial condition, and growth prospects are subject to significant risks and uncertainties, including failing to obtain regulatory approval to commercialize our product candidates and failing to secure additional funding to complete development of and to successfully commercialize our product candidates.

2. Summary of Significant Accounting Policies

Basis of Presentation

The consolidated financial statements include the accounts of Mast Therapeutics and its wholly-owned subsidiaries, Aires and SD Pharmaceuticals, Inc. (“SD Pharmaceuticals”). All intercompany accounts and transactions have been eliminated in consolidation.

We account for business combinations, such as our acquisitions of SynthRx in April 2011 and Aires in February 2014, in accordance with Accounting Standards Codification (“ASC”) Topic 805, Business Combinations (“ASC Topic 805”). ASC Topic 805 establishes principles and requirements for recognizing and measuring the total consideration transferred to and the assets acquired, liabilities assumed and any non-controlling interests in the acquired target in a business combination. ASC Topic 805 also provides guidance for recognizing and measuring goodwill acquired in a business combination; requires purchased in-process research and development (“IPR&D”) to be capitalized at fair value as an intangible asset at the time of acquisition; requires acquisition-related expenses and restructuring costs to be recognized separately from the business combination; expands the definition of what constitutes a business; and requires the acquirer to disclose information that users may need to evaluate and understand the financial effect of the business combination.

Use of Estimates

The preparation of financial statements in conformity with United States generally accepted accounting principles ("U.S. GAAP") requires management to make estimates and assumptions that affect the amounts reported in our consolidated financial statements and accompanying notes. On an ongoing basis, we evaluate our estimates, including estimates related to R&D expenses, IPR&D, goodwill, and share-based compensation expenses. We base our estimates on historical experience and various other relevant assumptions we believe to be reasonable under the circumstances. Actual results may differ from these estimates.

Fair Value of Financial Instruments

Our investment securities and debt facility are carried at fair value (see Note 6). Cash equivalents, prepaid expenses and other current assets, accounts payable and accrued liabilities, are carried at cost, which we believe approximates fair value due to the short-term maturities of these instruments.

Cash Equivalents

We consider all highly liquid investments with original maturities of three months or less at the date of purchase to be cash equivalents. Cash equivalents are carried at cost, which we believe approximates fair value due to the short-term maturities of these instruments. At December 31, 2015 and 2014, we had $15.8 million and $16.6 million of cash equivalents, respectively.

Investment Securities

Investment securities are marketable equity or debt securities. All of our investment securities are "available-for-sale" securities and carried at fair value (see Note 6). Fair value for securities with short maturities and infrequent secondary market trades typically is determined by using a curve-based evaluation model that utilizes quoted prices for similar securities. The evaluation model takes into consideration the days to maturity, coupon rate and settlement date convention. Net unrealized gains or losses on these securities are included in accumulated other comprehensive income/(loss), which is a separate component of stockholders' equity. Realized gains and realized losses are included in other income, net while amortization of premiums and accretion of discounts are included in interest income. Interest and dividends on available-for-sale securities are included in interest income. We periodically evaluate our investment securities for impairment. If we determine that a decline in fair value of any investment security is other than temporary, then the cost basis would be written down to fair value and the decline in value would be charged to earnings.

Our investment securities are under the custodianship of a major financial institution and consist of FDIC-insured certificates of deposit. We have classified all of our available-for-sale investment securities, including those with maturities beyond one year from the date of purchase, as current assets on our consolidated balance sheets because we consider them to be highly liquid and available for use, if needed, in current operations. As of December 31, 2015, $2.7 million, or approximately 15%, of our investment securities had contractual maturity dates of more than one year and less than or equal to 18 months and none were greater than 18 months.

Property and Equipment

Property and equipment are stated at cost, less accumulated depreciation. Property and equipment are depreciated using the straight-line method over the estimated useful lives of the assets, which generally is three to five years. Leasehold improvements are amortized over the economic life of the asset or the lease term, whichever is shorter. Repairs and maintenance are expensed as incurred.

In accordance with ASC Topic 360-10, Property, Plant and Equipment – Overall, we test for recoverability of long-lived assets, including property and equipment, if events or changes in circumstances indicate that the carrying amount for the assets may not be recoverable. If our assessment indicates impairment, we measure the impairment loss as the amount by which the carrying amount exceeds fair value of the assets. Fair value determinations are based on an undiscounted cash flow model or independent appraisals, as appropriate.

Intangible Assets – Goodwill and Acquired In-Process Research & Development

In accordance with ASC Topic 350, Intangibles – Goodwill and Other ("ASC Topic 350"), our goodwill and acquired IPR&D are determined to have indefinite lives and, therefore, are not amortized. Instead, they are tested for impairment annually and between annual tests if we become aware of an event or a change in circumstances that would indicate the carrying value may be impaired. Pursuant to Accounting Standards Update, or ASU, No. 2011-08, Intangibles – Goodwill and Other (Topic 350): Testing Goodwill for Impairment, and No. 2012-02, Intangibles – Goodwill and Other (Topic 350): Testing Indefinite-Lived

Intangible Assets for Impairment, we have the option to first assess qualitative factors to determine whether the existence of events or circumstances leads us to determine that it is more likely than not (that is, a likelihood of more than 50%) that our goodwill or our acquired IPR&D is impaired. If we choose to first assess qualitative factors and we determine that it is not more likely than not goodwill or acquired IPR&D is impaired, we are not required to take further action to test for impairment. We also have the option to bypass the qualitative assessment and perform only the quantitative impairment test, which we may choose to do in some periods but not in others.

If we perform a quantitative assessment of goodwill, we utilize the two-step approach prescribed under ASC Topic 350. Step 1 requires a comparison of the carrying value of a reporting unit, including goodwill, to its estimated fair value. We test for impairment at the entity level because we operate on the basis of a single reporting unit. If our carrying value exceeds our fair value, we then perform Step 2 to measure the amount of impairment loss, if any. In Step 2, we estimate the fair value of our individual assets, including identifiable intangible assets, and liabilities to determine the implied fair value of goodwill. We then compare the carrying value of our goodwill to its implied fair value. The excess of the carrying value of goodwill over its implied fair value, if any, is recorded as an impairment charge.

If we perform a quantitative assessment of acquired IPR&D, we calculate the estimated fair value of acquired IPR&D by using the Multi-Period Excess Earnings Method, or MPEEM, which is a form of the income approach. Under the MPEEM, the fair value of an intangible asset is equal to the present value of the asset's projected incremental after-tax cash flows (excess earnings) remaining after deducting the market rates of return on the estimated value of contributory assets (contributory charge) over its remaining useful life. This method requires us to make long-term projections of revenues and expenses related to development and commercialization of the acquired assets and assumptions regarding the rate of return on contributory assets, the weighted average cost of capital and the probability adjustment factor for estimated future after-tax cash flows. The excess of the carrying value over its estimated fair value is recorded as an impairment charge.

Any impairment charges are recorded to our consolidated statements of operations and comprehensive loss. Our determinations as to whether, and, if so, the extent to which, goodwill and acquired IPR&D become impaired are highly judgmental and based on significant assumptions regarding our projected future financial condition and operating results, changes in the manner of our use or development of the acquired assets, our overall business strategy, and regulatory, market and economic environment and trends. We perform our annual impairment testing as of September 30 each year, or, in the case of initially acquired IPR&D, on the first anniversary of the date we acquired it and subsequently on September 30. As of September 30, 2015, no impairment of goodwill or acquired IPR&D was identified. We are not aware of an event or change in circumstances that would indicate the carrying value may be impaired.

Concentration of Credit Risk and Significant Sources of Supply

Financial instruments that potentially subject us to concentrations of credit risk are primarily cash, cash equivalents and investment securities. We have a board-approved investment policy that sets our investment parameters and limitations with objectives of preserving principal and liquidity. Our cash and cash equivalent balances consist primarily of money market accounts under the custodianship of major financial institutions. Investment securities are invested in accordance with our investment policy. We do not have any financial instruments with off-balance-sheet risk of accounting loss.

We rely on single-source, third-party manufacturers and suppliers for production and supply of key components of our product candidates, and for production of the final drug products themselves. If these single-source, third-party manufacturers and suppliers are unable to continue providing a key component or the final drug products, the initiation or progress of any clinical studies of our product candidates may be severely impeded.

Research and Development Expense

R&D costs are charged to expense as incurred and include, but are not limited to, clinical and nonclinical study costs, research-related manufacturing and related costs, employee salaries and benefits, consulting services fees and share-based compensation cost. Clinical study costs include, but are not limited to, clinical research organization fees, investigator fees, site costs and, as applicable, comparator drug costs. Costs for certain R&D activities, such as research-related manufacturing and clinical studies, are recognized based on an evaluation of the percentage of work completed or the progress to completion of specific tasks using data such as patient enrollment, clinical site activations, duration of the study and/or information provided to us by our vendors on their actual costs incurred. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are reflected in the financial statements as prepaid expenses or accrued R&D costs.

Advance payments to third parties, including nonrefundable amounts, for goods and services that will be used or rendered for future R&D activities are deferred and capitalized, then expensed as the services are performed or as the underlying goods are

delivered. If we do not expect the services to be rendered or goods to be delivered, any remaining capitalized amounts for nonrefundable advance payments are charged to expense immediately.

Milestone payments that we make in connection with in-licensed technology or product candidates are expensed as incurred when there is uncertainty in receiving future economic benefits from the licensed technology or product candidates. We consider the future economic benefits from the licensed technology or product candidates to be uncertain until such licensed technology is incorporated into products that, or such product candidates, are approved for marketing by the FDA or when other significant risk factors are abated. For accounting purposes, management has viewed future economic benefits for all of our licensed technology or product candidates to be uncertain.

Share-Based Compensation

Share-based compensation cost is measured at the grant date, based on the estimated fair value of the award using the Black-Scholes valuation model, and is recognized as expense over the vesting period on a straight-line basis. Share-based compensation expense recognized in the consolidated statements of operations for the years ended December 31, 2015 and 2014 is based on awards ultimately expected to vest and has been reduced for estimated forfeitures. This estimate will be revised in subsequent periods if actual forfeitures differ from those estimates. None of our outstanding share-based awards have market or performance conditions.

Patent Costs

Legal costs and other fees incurred in connection with patent prosecution and maintenance are expensed as incurred, as recoverability of such expenditures is uncertain. These costs are recorded as selling, general and administrative expenses in our consolidated statement of operations and comprehensive loss.

Income Taxes

We account for income taxes and the related accounts under the liability method. Deferred tax assets and liabilities are determined based on the differences between the financial statement carrying amounts and the income tax basis of assets and liabilities. A valuation allowance is applied against any net deferred tax asset if, based on available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

The tax effects from an uncertain tax position can be recognized in our consolidated financial statements only if the position is more likely than not of being sustained upon an examination by tax authorities. An uncertain income tax position will not be recognized if it has less than a 50% likelihood of being sustained.

We account for interest and penalties related to income tax matters, if any, in income tax expense.

Comprehensive Income/(Loss)

Comprehensive income or loss is defined as the change in equity of a business enterprise during a period from transactions and other events and circumstances from non-owner sources, including unrealized gains and losses on marketable securities and foreign currency translation adjustments. We present comprehensive income/(loss) in our consolidated statement of operations and comprehensive loss.

Net Loss per Common Share

Basic and diluted net loss per common share is calculated by dividing the net loss applicable to common stock for the periods presented by the weighted-average number of common shares outstanding during those periods, respectively,

without consideration for outstanding common stock equivalents because their effect would have been anti-dilutive. Common stock equivalents are included in the calculation of diluted earnings per common share only if their effect is dilutive. For the years ended December 31, 2015 and 2014, our outstanding common stock equivalents consisted of options and warrants to purchase shares of our common stock. The weighted-average number of those common stock equivalents outstanding for each of the periods presented is set forth in the table below:

	Years ended December 31,	
	2015	2014
Warrants	77,355,271	49,217,355
Options	21,514,699	11,760,113

Supplemental Cash Flow Information

	Years ended December 31,	
	2015	2014
	(in thousands)	
Cash paid for interest on debt facility	298	-
Supplemental disclosures of non-cash investing and financing activities:		
Issuance of common stock for acquisitions	-	3,270
Assumptions of liabilities in acquisitions	-	1,069
Unrealized loss on investment securities	(8)	(4)
Warrants issued in connection with debt facility	392	-
Purchase of equipment under capital lease	40	-
Purchases of property and equipment in accounts payable	2	17
Offering costs included in accounts payable	-	36

Recent Accounting Pronouncements

In February 2016, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") No. 2016-02, Leases (ASC 842) ("ASU 2016-02"), ASU 2016-02 sets out the principles for the recognition, measurement, presentation and disclosure of leases for both parties to a contract (i.e., lessees and lessors). The new standard requires lessees to classify leases as either finance or operating leases based on the principle of whether or not the lease is effectively a financed purchase by the lessee. This classification will determine whether lease expense is recognized based on an effective interest method or on a straight line basis over the term of the lease, respectively. A lessee is also required to record a right-of-use asset and a lease liability for all leases with a term of greater than 12 months regardless of their classification. Leases with a term of 12 months or less will be accounted for similar to existing guidance for operating leases today. ASC 842 supersedes the previous leases standard, ASC 840 Leases. The standard is effective on January 1, 2019, with early adoption permitted. The Company is in the process of evaluating the impact of this new guidance.

In November 2015, the FASB issued ASU No. 2015-17, Balance Sheet Classification of Deferred Taxes ("ASU 2015-17"). Currently deferred taxes for each tax jurisdiction are presented as a net current asset or liability and net noncurrent asset or liability on the balance sheet. To simplify the presentation, the new guidance requires that all deferred tax assets and liabilities for each jurisdiction, along with any related valuation allowance, be classified as noncurrent on the balance sheet. The new guidance becomes effective for public business entities in fiscal years beginning after December 15, 2016. We elected to early adopt this new standard prospectively for the year ended December 31, 2015 and it did not have a material impact on our financial statements.

In April 2015, the FASB issued ASU No. 2015-03, Simplifying the Presentation of Debt Issuance Costs ("ASU 2015-03"). The new standard requires debt issuance costs to be presented on the balance sheet as a direct reduction of the carrying value of the associated debt liability, consistent with the presentation of debt discounts. The recognition

and measurement requirements will not change as a result of this guidance. ASU 2015-03 is effective for the annual reporting periods beginning after December 15, 2015 and requires a retrospective application. We elected to early adopt this guidance and it did not have a material impact on our financial statements.

In August 2014, the FASB issued ASU No. 2014-15, Presentation of Financial Statements - Going Concern (Subtopic 205-40): Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern ("ASU 2014-15"). The amendments in ASU 2014-15 will require management to assess, at each annual and interim reporting period, the entity's ability to continue as a going concern and, if management identifies conditions or events that raise substantial doubt about the entity's ability to continue as a going concern within one year after the date that the financial statements are issued, to disclose in the notes to the entity's financial statements the principal conditions or events that raised substantial doubt about the entity's ability to continue as a going concern, management's evaluation of their significance, and management's plans that alleviated or are intended to alleviate substantial doubt about the entity's ability to continue as a going concern. ASU 2014-15 is effective for annual periods ending after December 15, 2016 and early application is permitted. The amendments in ASU 2014-15 do not have any application to an entity's financial statements, but only to the related notes. We plan to adopt ASU 2014-15 in the first quarter of 2017 for the annual period ending December 31, 2016.

3. Acquisition of Aires

On February 27, 2014, we completed the acquisition of Aires in an all-stock transaction pursuant to the terms of an agreement and plan of merger, dated February 7, 2014, by and among us, AP Acquisition Sub, Inc., a wholly-owned subsidiary of ours, Aires, and a stockholders' representative (the "Merger Agreement"). Aires was a clinical-stage company with its lead product candidate, AIR001 (sodium nitrite) inhalation solution, in Phase 2 studies in pulmonary hypertension. Aires survived the merger transaction as a wholly-owned subsidiary of ours.

Upon completion of the merger, we issued an aggregate of 1,049,706 unregistered shares of our common stock to former Aires stockholders and, in September 2014 after the six-month "holdback" period, we issued an aggregate of 4,053,996 additional unregistered shares of our common stock to former Aires stockholders, all in accordance with the merger agreement. There are no milestone or earn-out payments under the merger agreement; therefore, the total merger consideration was 5,103,702 shares.

We accounted for the acquisition of Aires in accordance with ASC Topic 805. The total purchase price of the acquisition is approximately $3.3 million. We calculated the purchase price by first multiplying the total number of shares of our common stock issued by $0.80, which was the closing price per share of our common stock on February 27, 2014, the acquisition date. Then, we applied a discount factor to account for lack of market liquidity due to the restrictions on transfer of the securities for a period of six months following the acquisition in accordance with stockholder agreements we entered into with the former Aires stockholders and the fact that the shares are unregistered and we have no obligation to register them for resale.

Under the acquisition method of accounting, the total purchase price is allocated to Aires' net tangible and intangible assets and liabilities based on their estimated fair values as of the acquisition date. The table below summarizes the estimated fair values of Aires' net tangible and intangible assets and liabilities on the acquisition date (in thousands).

Cash and cash equivalents	$3,534
Prepaid expenses and other assets	86
In-process research and development	2,000
Total assets:	5,620
Accounts payable and accrued liabilities	1,069
Deferred tax liability	795
Total liabilities:	1,864
Net assets acquired	$3,756

The estimated fair value of the net assets acquired exceeds the purchase price by approximately $0.5 million. Accordingly, we recognized the $0.5 million excess as a bargain purchase gain in other income/(expense), net in our condensed consolidated statements of operations and comprehensive income/(loss). We were able to realize a gain because Aires was in a distressed sale situation. Aires lacked sufficient capital to continue operations and was unable to secure additional capital in the timeframe it required.

Acquired In-Process Research and Development

Acquired IPR&D is the estimated fair value of the AIR001 program as of the acquisition date. We determined that the estimated fair value of the AIR001 program was $2.0 million as of the acquisition date using the Multi-Period Excess Earnings Method, or MPEEM, which is a form of the income approach. Under the MPEEM, the fair value of an intangible asset is equal to the present value of the asset's projected incremental after-tax cash flows (excess earnings)

remaining after deducting the market rates of return on the estimated value of contributory assets (contributory charge) over its remaining useful life.

To calculate fair value of the AIR001 program under the MPEEM, we used probability-weighted, projected cash flows discounted at a rate considered appropriate given the significant inherent risks associated with drug development by clinical-stage companies. Cash flows were calculated based on estimated projections of revenues and expenses related to AIR001 and then reduced by a contributory charge on requisite assets employed. Contributory assets included debt-free working capital, net fixed assets and assembled workforce. Rates of return on the contributory assets were based on rates used for comparable market participants. Cash flows were assumed to extend through a seven-year market exclusivity period. The resultant cash flows were then discounted to present value using a weighted-average cost of capital for companies with profiles substantially similar to that of Aires, which we believe represents the rate that market participants would use to value the assets. We compensated for the phase of development of the program by applying a probability factor to our estimation of the expected future cash flows. The projected cash flows were based on significant assumptions, including the indication in which we will pursue development of AIR001, the time and resources needed to complete the development and regulatory approval of AIR001, estimates of revenue and operating profit related to the program considering its stage of development, the life of the potential commercialized product, market penetration and competition, and risks associated with achieving commercialization,

including delay or failure to obtain regulatory approvals to conduct clinical studies, failure of clinical studies, delay or failure to obtain required market clearances, and intellectual property litigation.

Deferred Income Tax Liability

The $0.8 million recorded as deferred income tax liability resulting from the acquisition reflects the tax impact of the difference between the book basis and tax basis of acquired IPR&D. Such deferred income tax liability cannot be used to offset deferred tax assets when analyzing our valuation allowance as the acquired IPR&D is considered to have an indefinite life until we complete or abandon development of AIR001.

4. Goodwill and IPR&D

At December 31, 2015 and 2014, our goodwill and IPR&D consisted of the following (in thousands):

Goodwill	$3,007
IPR&D	
Acquired IPR&D related to SynthRx acquisition	6,549
Acquired IPR&D related to Aires acquisition	2,000
Total goodwill and IPR&D	$11,556

Our goodwill represents the difference between the total purchase price for SynthRx and the aggregate fair values of tangible and intangible assets acquired, less liabilities assumed.

Our IPR&D consists of the estimated fair values of the vepoloxamer and AIR001 programs as of the dates we acquired SynthRx and Aires, respectively.

We test our goodwill and acquired IPR&D for impairment annually as of September 30, or, in the case of initially acquired IPR&D, on the first anniversary of the date we acquired it and subsequently on September 30, and between annual tests if we become aware of an event or a change in circumstances that would indicate the carrying value may be impaired. We performed a qualitative assessment for our goodwill and our acquired IPR&D as of September 30, 2015. We concluded that it is not more likely than not that the carrying value of our goodwill or our acquired IPR&D exceeds its fair value. Therefore, we concluded that no impairment charge is required.

5. Investment Securities

At December 31, 2015 and 2014, our investment securities were as follows (in thousands):

	December 31,	
	2015	2014
Fair value of investment securities	$17,929	$21,481
Cost basis of investment securities	17,946	21,506

	Years ended December 31,	
	2015	2014
Net unrealized losses on investment securities	17	25

6. Fair Value of Financial Instruments

Our cash equivalents are recorded at cost plus accrued interest, which approximates fair value. Our investment securities are carried at fair value. The fair value of financial assets and liabilities is measured under a framework that establishes “levels” which are defined as follows: (i) Level 1 fair value is determined from observable, quoted prices in active markets for identical assets or liabilities; (ii) Level 2 fair value is determined from inputs, other than Level 1 inputs, that are observable, either directly or indirectly, such as quoted prices for similar assets or liabilities, quoted prices in markets that are not active, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the asset or liability; and (iii) Level 3 fair value is determined using the entity’s own assumptions about the inputs that market participants would use in pricing an asset or liability.

The fair values at December 31, 2015 and 2014 of our cash equivalents and investment securities are summarized in the following tables (in thousands):

	Total Fair Value	Fair Value Determined Under: (Level 1)	(Level 2)	(Level 3)
At December 31, 2015:				
Cash equivalents	$15,799	$15,799	$—	$ —
Investment securities	$17,929	$—	$17,929	$ —
At December 31, 2014:				
Cash equivalents	$16,626	$16,626	$—	$ —
Investment securities	$21,481	$—	$21,481	$ —

We believe that our debt facility bears interest at a rate that approximates prevailing market rates for instruments with similar characteristics and, accordingly, the carrying value of the debt facility approximates fair value. The fair value of our debt facility is determined under Level 2 in the fair value hierarchy.

7. Property and Equipment

Property and equipment at December 31, 2015 and 2014 were as follows (in thousands):

		December 31,	
	Useful Lives	2015	2014
Office furniture, computer and lab equipment	3 - 5 years	$493	$416
Computer software	3 years	16	58
Leasehold improvements	1 year	44	35
Equipment in progress	n/a	12	23
		565	532
Less: accumulated depreciation and amortization		(339)	(344)
Property and equipment, net		$226	$188

Equipment in progress represents the cost of lab equipment and/or leasehold improvements not yet available for service as of December 31, 2015 and 2014. These items are depreciated over their applicable useful lives once they are available for service.

Depreciation and amortization expense was $146,000 and $85,000 for the years ended December 31, 2015 and 2014, respectively.

We lease certain office equipment under leases classified as capital leases. As of December 31, 2015, the total amount of leased equipment was $40,000 with interest rates ranging from 8% to 14% per annum. The equipment is being amortized over the life of the leases, which range from three to five years.

Future commitments under capital leases are as follows (in thousands):

Year Ending December 31,	
2016	11
2017	10
2018	10
2019	8
2020	-
Thereafter	-
Total	$39

Total imputed interest over the life of the capital leases is $8,000.

8. Accrued Liabilities

Accrued liabilities at December 31, 2015 and 2014 were as follows (in thousands):

	December 31,	
	2015	2014
Accrued R&D agreements and study expenses	$7,898	$5,383
Other accrued liabilities	254	242
Total accrued liabilities	$8,152	$5,625

9. Debt Facility

Hercules Loan and Security Agreement

We have borrowed an aggregate of $15 million pursuant to a Loan and Security Agreement, dated August 11, 2015, with Hercules Technology III, L.P. and Hercules Capital, Inc. (formerly known as, Hercules Technology Growth Capital, Inc.) (together, "Hercules"), as amended by the First Amendment thereto dated September 28, 2015, the Second Amendment thereto dated December 31, 2015, and the Third Amendment thereto dated February 25, 2016, (collectively, the "Loan Agreement"). Pursuant to the terms and conditions of the Loan Agreement we received the first advance of $5 million on August 11, 2015 and the second advance of $10.0 million (the "Second Advance") on September 28, 2015.

Under the Loan Agreement, the Second Advance is required to be prepaid to Hercules on July 31, 2016, without any prepayment penalty, unless on or before such date, we demonstrate, to the reasonable satisfaction of Hercules, positive results in our Phase 3 clinical study of vepoloxamer in patients with sickle cell disease, known as the EPIC study. Due to numerous factors, we are not able to predict with any reasonable certainty the probability of meeting this condition by July 31, 2016; therefore, we have classified the Second Advance as a current liability on the balance sheet.

The interest rate for the principal balance under the Loan Agreement is the greater of (i) 8.95% plus the prime rate as reported in The Wall Street Journal minus 3.25%, and (ii) 8.95%, determined on a daily basis. The interest rate as of December 31, 2015 was 9.20%. Monthly payments under the amended Loan Agreement are interest only until July 1, 2016, followed by equal monthly payments of principal and interest through the scheduled maturity date of January 1, 2019. The interest-only period will be extended to March 1, 2017 if we have demonstrated positive results in the EPIC study by July 1, 2016, we have not prepaid the Second Advance, and no event of default has occurred. If we demonstrate positive results in the EPIC study during the period between July 2, 2016 and July 31, 2016, inclusive, we have not prepaid the Second Advance and no event of default has occurred, then on July 1, 2016, we will be required to make a single payment against the principal balance of approximately $430,000 and, beginning August 1, 2016, we will resume making interest-only payments until March 1, 2017. If our interest-only payment period is extended to March 1, 2017, the maturity date would extend to October 1, 2019. An end of term charge of $712,500 will be due on the scheduled maturity date and is being accrued through interest expense using the effective interest method.

If we elect to prepay the principal balance under the amended Loan Agreement prior to maturity, a prepayment charge of 1%, 2% or 3%, of the then outstanding principal balance also will be due, depending upon when the prepayment occurs.

Our obligations under the amended Loan Agreement are secured by a first priority security interest in substantially all of our assets, excluding our intellectual property but including the proceeds from the sale, licensing or disposition of

our intellectual property. Our intellectual property is subject to customary negative covenants.

In connection with the Loan Agreement, through December 31, 2015, we had paid facility charges of $112,500 and a commitment charge of $25,000. Such charges were accounted for as debt issuance costs and are being amortized to interest expense using the effective interest method through the scheduled maturity date.

In connection with the Loan Agreement, we entered into a Warrant Agreement with Hercules, dated August 11, 2015, as amended by the First Amendment thereto dated September 28, 2015 and the Second Amendment thereto dated February 25, 2016, pursuant to which Hercules has a right to purchase up to 2,272,727 shares of our common stock at an exercise price of $0.275 per share. Prior to the Second Amendment to Warrant Agreement and as of December 31, 2015, the Warrant Agreement, as amended, provided Hercules a right to purchase up to 1,524,390 shares of our common stock at an exercise price of $0.41 per share. The warrants issued to Hercules were valued using the Black-Scholes option pricing model with the following assumptions: volatility of 77%, expected term of five years, risk-free interest rate of 1.5% and a zero dividend yield. The warrant fair value of $0.4 million has been recorded as a debt discount and is being amortized through interest expense using the

effective interest method through the scheduled maturity date. See Note 10 “Capital Stock and Warrants” and Note 17 “Subsequent Events” for further description of the terms of the warrants.

Summary of Carrying Value

The following table summarizes the components of the debt facility carrying value.

	As of December 31, 2015	
	Short-Term	Long-Term
Potential prepayment to lender	$10,000	$ -
Principal payments to lender and end of term charge	874	4,839
Accrued interest	117	-
Debt issuance costs	-	(776)
Debt discount related to warrants	-	(337)
Carrying value	$10,991	$ 3,726

10. Capital Stock and Warrants

Our certificate of incorporation, as amended, authorizes us to issue 500,000,000 shares of common stock, par value $0.001 per share, and 1,000,000 shares of preferred stock, par value $0.001 per share. As of December 31, 2015, 163,614,297 shares of common stock were outstanding and no shares of preferred stock were outstanding.

Underwritten Public Offering of Common Stock, Pre-funded Warrants and Warrants

In November 2014, we completed an underwritten public offering of 30,941,102 shares of our common stock, 13,081,428 “pre-funded” warrants exercisable for up to 13,081,428 shares of our common stock, and 22,011,265 warrants exercisable for up to 22,011,265 shares of our common stock. These securities were offered and sold to the underwriters and the public in units with each Series A unit consisting of one share of our common stock and one-half (0.5) of a warrant and each Series B unit consisting of one pre-funded warrant and one-half (0.5) of a warrant. Each whole warrant is exercisable for one share of our common stock. We sold an aggregate of 30,941,102 Series A units and 13,081,428 Series B units. The gross proceeds from this financing were $21.0 million and, after deducting underwriting discounts and commissions and other offering expenses, our net proceeds were $19.7 million. We may receive up to $0.1 million and $16.5 million of additional proceeds from the exercise of the pre-funded warrants and warrants, respectively, issued in the offering. The exercise price of the pre-funded warrants is $0.01 per share and exercise price of the warrants is $0.75 per share. Subject to certain beneficial ownership limitations, the pre-funded warrants and warrants are exercisable at any time on or before November 12, 2019.

“At the Market” Equity Offering Program

In February 2014, we entered into a sales agreement with Cowen and Company, LLC (“Cowen”), to sell shares of our common stock, with aggregate gross sales proceeds of up to $30 million, from time to time, through an “at the market,” or ATM, equity offering program (the “2014 Sales Agreement”), under which Cowen acted as sales agent. In August 2015, we terminated the 2014 Sales Agreement upon entry into a new sales agreement with Cowen to sell shares of our common stock, with aggregate gross sales proceeds of up to $30 million, from time to time, through an ATM program. As of December 31, 2015, we had sold and issued an aggregate of 24,859,107 shares at a weighted-average sales price of $0.70 per share under the ATM programs for aggregate gross proceeds of $17.5 million and $16.6

million in net proceeds, after deducting sales agent commission and discounts and our other offering costs.

Warrants

At December 31, 2015, outstanding warrants to purchase shares of common stock are as follows:

Shares Underlying Outstanding Warrants	Exercise Price	Expiration Date
2,046,139	$ 2.75	January 2016
10,625,000	$ 1.10	November 2016
28,097,400	$ 0.65	June 2018
13,081,428	$ 0.01	November 2019
22,011,265	$ 0.75	November 2019
1,524,390	$ 0.41	August 2020
77,385,622		

Warrants Issued to Hercules

In connection with the Loan Agreement, we entered into a Warrant Agreement with Hercules Technology III, L.P., dated August 11, 2015, as amended by the First Amendment thereto dated September 28, 2015 and the Second Amendment thereto dated February 25, 2016, pursuant to which Hercules has a right to purchase up to 2,272,727 shares of our common stock at an exercise price of $0.275 per share. Prior to the Second Amendment to Warrant Agreement and as of December 31, 2015, the Warrant Agreement, as amended, provided Hercules a right to purchase up to 1,524,390 shares of our common stock at an exercise price of $0.41 per share. Hercules may exercise its warrants at any time, or from time to time, through August 11, 2020. The Warrant Agreement, as amended, provides for adjustment to the exercise price and number of shares subject to Hercules' warrants in the event of a merger event, reclassification of our common stock, subdivision or combination of our common stock, or certain dividend payments. Upon exercise, the aggregate exercise price may be paid, at Hercules' election, in cash or on a net issuance basis, based upon the fair market value of our common stock at the time of exercise. If the fair market value of our common stock is greater than the exercise price of the warrants as of immediately before their expiration, to the extent the warrants are not previously exercised in full, the warrants shall be deemed automatically exercised on a net issuance basis as of immediately before their expiration.

11. Equity Incentive Plans

Our equity-based incentive plan, which is stockholder-approved, is intended to encourage ownership of shares of common stock by our directors, officers, employees, consultants and advisors and to provide additional incentive for them to promote the success of our business through the grant of share-based awards. At December 31, 2015, our equity-based incentive plan consisted of the 2005 Equity Incentive Plan (the "2005 Plan") and the 2008 Omnibus Incentive Plan (the "Original 2008 Plan"), which has been amended, restated and renamed four times, first in June 2011 as the Amended and Restated 2008 Omnibus Incentive Plan, then in June 2013 as the 2013 Omnibus Incentive Plan, then in June 2014 as the 2014 Omnibus Incentive Plan and finally in June 2015 as the 2015 Omnibus Incentive Plan (the "2015 Plan"). Following approval by our stockholders of each amendment and restatement of the Original 2008 Plan, no awards have been or will be granted under the terms of the plan in effect immediately prior to such amendment and restatement. In prior years, our stockholder-approved, equity-based incentive plans included the 2005 Employee Stock Purchase Plan. In May 2015, our 2005 Employee Stock Purchase Plan, which had never been implemented, expired.

During the years ended December 31, 2015 and 2014, all awards granted under our equity-based incentive plans were stock options. The share-based compensation expense from all stock options granted that has been charged to our consolidated statements of operations and comprehensive loss in those periods was as follows (in thousands):

	Years ended December 31,	
	2015	2014
Selling, general and administrative expense	$2,077	$1,607
Research and development expense	598	425
Share-based compensation expense	$2,675	$2,032

For the year ended December 31, 2015, we recognized a $0.3 million expense in our selling, general and administrative expenses related to share-based compensation expense as a result of the departure of our former president and chief operating officer in February 2015. Termination of the former officer's employment triggered accelerated vesting of a portion of his outstanding, unvested stock options that resulted in $0.4 million of additional share-based compensation expense, but this additional expense was offset by a $0.1 million reduction in share-based

compensation expense that resulted from cancellation of the remaining, unvested portion of the former officer's outstanding stock options.

2015 Omnibus Incentive Plan

The 2015 Plan provides for the grant of incentive and non-statutory stock options, as well as share appreciation rights, restricted shares, restricted share units, performance units, shares and other share-based awards. Share-based awards are subject to terms and conditions established by our board of directors or the compensation committee of our board of directors.

As of December 31, 2015, the maximum aggregate number of shares of our common stock available for grant under the 2015 Plan was 21,583,541 shares. Shares of common stock that are subject to awards granted under the 2015 Plan shall be counted against the shares available for issuance under this plan as one share for each share subject to a stock option or stock appreciation right and as 1.34 shares for each share subject to an award other than a stock option or a stock appreciation right. If any shares of common stock subject to an award granted under any of our stockholder-approved, equity-based incentive plans are forfeited, or an award expires or is settled for cash pursuant to the terms of an award, the shares subject to the award may be

used again for awards under the 2015 Plan to the extent of the forfeiture, expiration or cash settlement. The shares of common stock will be added back as one share for every share of common stock if the shares were subject to a stock option or stock appreciation right, and as 1.34 shares for every share of common stock if the shares were subject to an award other than a stock option or stock appreciation right. However, the following shares of common stock will not be added to the shares available for issuance under the 2015 Plan: (i) shares tendered or withheld in payment of the purchase price of a stock option, (ii) shares tendered or withheld to satisfy any tax withholding obligation with respect toany award, (iii) shares subject to a stock appreciation right that are not issued in connection with the stock settlement of the stock appreciation right on exercise thereof, and (iv) shares reacquired by us on the open market or otherwise using cash proceeds from the exercise of stock options. Shares of common stock under awards made in assumption of or in substitution or exchange for awards previously granted, or the right or obligation to make future awards, in each case by a company acquired by us, or with which we combine, will not reduce the number of shares available for issuance under the 2015 Plan. In addition, if a company acquired by us, or with which we combine, has shares available under a pre-existing plan approved by its stockholders and not adopted in contemplation of such acquisition or combination, the shares available for issuance under such plan (as adjusted, to the extent appropriate, using the exchange or other adjustment or valuation ratio of formula applied to determine the consideration payable to stockholders in the acquisition or combination) may be used for awards under the 2015 Plan and will not reduce the number of shares of common stock available for issuance under the 2015 Plan; provided, however that awards using such available shares shall not be made after the date awards or grants could have been made under the pre-existing plan, absent the acquisition or combination, and shall only be made to individuals who were not our employees or directors prior to the acquisition or combination.

Under the 2015 Plan, the purchase price of shares of common stock covered by a stock option cannot be less than 100% of the fair market value of the common stock on the date the stock option is granted. Fair market value of the common stock is generally equal to the closing price for the common stock on the principal securities exchange on which the common stock is traded on the date the stock option is granted (or if there was no closing price on that date, on the last preceding date on which a closing price was reported). Stock option awards generally have ten-year contractual terms and vest over four years based on continuous service; however, the 2015 Plan allows for other vesting periods.

Summary of 2015 Stock Option Activity

The following table summarizes our stock option activity for the year ended December 31, 2015:

	Shares Underlying Option Awards	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Years	Aggregate Intrinsic Value (in thousands)
Outstanding at January 1, 2015	13,616,137	$ 1.00		
Granted	13,114,372	$ 0.55		
Exercised	-	$ —		
Expired/cancelled/forfeited	(3,827,782)	$ 0.65		
Outstanding at December 31, 2015	22,902,727	$ 0.80	7.46	$ 4

Options exercisable at December 31, 2015	10,428,421	$ 1.10	5.72	$ -
Vested and expected to vest at December 31, 2015	21,897,047	$ 0.81	7.38	$ 3

The weighted-average grant-date fair value of options granted during the years ended December 31, 2015 and 2014 was $0.42 and $0.50, respectively. As of December 31, 2015, there was approximately $4.6 million of unamortized compensation cost related to unvested stock option awards, which is expected to be recognized over a weighted-average period of approximately 2.8 years.

Our determination of fair value is affected by our stock price as well as a number of assumptions that require judgment. The fair value of each option award is estimated on the date of grant using the Black-Scholes option-valuation model. The assumptions used in the Black-Scholes option-valuation model and the calculation of share-based compensation for option grants to employees and non-employee directors during the years ended December 31, 2015 and 2014 are as follows:

	Years ended December 31,	
	2015	2014
Risk-free interest rate	1.6 - 1.9%	1.9 - 2.1%
Dividend yield	0.0%	0.0%
Expected volatility	78 - 99%	104 - 112%
Expected term (in years)	5.3 - 6.2 years	5.4 - 6.2 years
Forfeiture rate	7%	9%

The risk-free interest rate assumption is based on the U.S. Treasury yield for a period consistent with the expected term of the option in effect at the time of the grant. We have not paid any dividends on common stock since our inception and do not anticipate paying dividends on our common stock in the foreseeable future. The expected option term is computed using the "simplified" method as permitted under the provisions of Staff Accounting Bulletin ("SAB") 107. SAB 107's guidance was extended indefinitely by SAB 110. The expected volatility is based on the historical volatility of our common stock based on the daily closing prices. Forfeiture rates are based on the expected forfeiture rates for our unvested stock options, which are based in large part on our historical forfeiture rates, but also on assumptions believed to be reasonable under the circumstances.

In accordance with ASC 718, Compensation – Stock Compensation, share-based compensation expense associated with the non-employee director options is included with employee share-based compensation expense.

12. Commitments

SynthRx Merger Consideration Milestone Payments

In April 2011, we acquired SynthRx in a merger transaction in exchange of shares of our common stock and rights to additional shares of our common stock. Pursuant to the merger agreement, we could issue up to an aggregate of 12,478,050 shares of our common stock to the former SynthRx stockholders if and when the development of vepoloxamer achieves the following milestones: (a) 3,839,400 shares upon acceptance for review by the U.S. Food and Drug Administration ("FDA") of a new drug application ("NDA") covering the use of vepoloxamer for the treatment of sickle cell crisis in children and (b) 8,638,650 shares upon approval of such NDA by the FDA.

Operating Leases

We are obligated under operating leases for office space and equipment. We sublease approximately 13,700 square feet of office space for our corporate headquarters in San Diego, California. Our sublease commenced on January 20,

2015 and expires on May 31, 2020. Our monthly rent of $41,000 escalates by 3% each year on January 20th. During the first year of the sublease, the monthly base rent for approximately 2 1/3 months, or approximately $96,000, was abated. In July 2014, we made a payment of $300,000 to the landlord, up to approximately $170,000 of which will be applied to our monthly base rent for months 13, 16, 19 and 24 of the sublease term, subject to certain conditions. The remaining $130,000 will be held by the landlord as a security deposit. Rent expense for our office space is recognized on a straight-line basis.

We lease office equipment under a lease that expires in 2019.

Rent expense was approximately $508,000 and $334,000 during the years ended December 31, 2015 and 2014, respectively.

Future rental commitments under all operating leases are as follows (in thousands):

Year Ending December 31,	
2016	$389
2017	489
2018	547
2019	557
2020	237
Thereafter	-
Total	$2,219

13. Income Taxes

Due to our historical net loss position, and as we have recorded a full valuation allowance against net deferred tax assets, there is no provision or benefit for income taxes recorded for the years ended December 31, 2015 and 2014.

The income tax benefit is different from that which would be obtained by applying the statutory Federal income tax rate of 34% to income before income tax expense. The items causing this difference for the years ended December 31, 2015 and 2014 are as follows:

	Years ended December 31,	
	2015	2014
	(in thousands)	
Income tax benefit at federal statutory rate	$(13,546)	$(9,758)
Orphan drug credit / R&D credit	(7,530)	(4,575)
Stock options	594	278
Other	187	(213)
Change in federal valuation allowance	20,295	14,268
Total	$-	$-

Deferred income taxes reflect the net tax effect of temporary differences between the carrying amount of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. Significant components of deferred tax assets and liabilities at December 31, 2015 and 2014 are as follows:

	Years ended December 31,	
	2015	2014
	(in thousands)	
Deferred tax assets:		
Accrued expenses	$619	$592
Stock options under ASC 718	2,610	2,240
Net operating loss carry forwards	31,649	20,583
Income tax credit carry forwards	19,369	8,109
Property and equipment	20	12
Intangibles	895	1,793
Other	69	33
Total deferred tax assets	55,231	33,362
Less: valuation allowance	(55,231)	(33,362)
Total deferred tax assets, net of valuation allowance	$-	$-
Deferred tax liabilities:		
Acquired intangibles	(3,404)	(3,404)
Total deferred tax assets/liabilities, net of valuation	$(3,404)	$(3,404)

allowance

We have established a full valuation allowance against our net deferred tax assets due to uncertainty surrounding the realization of such assets. Management has determined it is more likely than not that the deferred tax assets are not realizable due to our historical loss position.

As a result of our acquisitions of SynthRx and Aires during 2011 and 2014, respectively, we recorded deferred tax liabilities. These deferred tax liabilities reflect the tax impact of the differences between the book basis and tax basis of acquired IPR&D that has not yet reached feasibility. Such deferred tax liabilities cannot be used to offset deferred tax assets when analyzing our end of year valuation allowance as the acquired IPR&D is considered to have an indefinite life until we complete or abandon development. The deferred tax liabilities were recorded as an offset to goodwill or gain on bargain purchase, recorded as part of the SynthRx and Aires acquisitions, respectively.

Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or IRC, limit our ability to use net operating loss carry forwards and R&D tax credit carry forwards ("tax attribute carry forwards") to offset future taxable income or income tax, respectively, if we experience a cumulative change in ownership of more than 50% within a three-year testing period. We completed a formal study through the year ended December 31, 2011 and determined ownership changes within the meaning of IRC Section 382 had occurred. We adjusted our tax attribute carry forwards and deferred tax assets accordingly. As the deferred tax assets associated with the tax attribute carry forwards were fully offset by a valuation allowance, a corresponding reduction in the Company's valuation allowance was also recorded, resulting in no income tax impact. We completed a formal study to determine whether an ownership change, within the meaning of IRC Section 382, occurred during 2012, 2013 or 2014, and no ownership changes were identified.

As of December 31, 2015, we had federal and California net operating loss carry forwards of $80.3 million and $74.4 million, respectively. These tax loss carry forwards begin to expire in 2031 if unused. As of December 31, 2015, we also had federal R&D/orphan drug and California R&D tax credit carry forwards of $18.8 million and $0.9 million, respectively. The aforementioned federal tax credits will begin to expire in 2031. The California R&D tax credits do not expire.

In accordance with authoritative guidance, the impact of an uncertain income tax position on the income tax return must be recognized at the largest amount that is more-likely-than-not to be sustained upon audit by the relevant taxing authority. An uncertain income tax position will not be recognized if it has less than a 50% likelihood of being sustained. As of December 31, 2015, we continue to have no unrecognized tax benefits. There are no unrecognized tax benefits included on the balance sheet that would, if recognized, impact the effective tax rate. We do not anticipate there will be a significant change in unrecognized tax benefits within the next 12 months.

Our policy is to recognize interest and/or penalties related to income tax matters in income tax expense. Because we have generated net operating losses since inception, no tax liability, penalties or interest has been recognized for balance sheet or income statement purposes as of and for the years ended December 31, 2015 and 2014.

We are subject to income taxation in the U.S. and the state of California. All of our tax years are subject to examination by the tax authorities due to the carry forward of unutilized net operating losses and R&D tax credits.

14. 401(k) Plan

We have a defined contribution savings plan pursuant to Section 401(k) of the IRC. The plan is for the benefit of all qualifying employees and permits voluntary contributions by employees up to 100% of eligible compensation, subject to the Internal Revenue Service ("IRS") imposed maximum limits. The terms of the plan require us to make matching contributions equal to 100% of employee contributions up to 6% of eligible compensation, limited by the IRS-imposed maximum. We incurred total expenses of $246,000 and $212,000 in employer matching contributions in 2015 and 2014, respectively.

15. Segment Information

We operate our business on the basis of a single reportable segment, which is the business of developing therapies for serious or life-threatening diseases. We evaluate our Company as a single operating segment. The majority of our operating activities and work performed by our employees are currently conducted from a single location in the U.S. We recognized no revenues in 2015 and 2014.

16. Summary of Quarterly Financial Data (unaudited)

The following is a summary of the unaudited quarterly results of operations for the years ended December 31, 2015 and 2014 (in thousands, except per share data):

Quarterly statements of operations data

	Quarters Ended			
2015 (unaudited)	March 31	June 30	September 30	December 31
Revenue	$-	$-	$-	$-
Loss from operations	(9,650)	(10,181)	(9,828)	(9,714)
Net loss	(9,616)	(10,151)	(9,912)	(10,162)
Net loss applicable to common stock	(9,616)	(10,151)	(9,912)	(10,162)
Basic and diluted net loss per share	$(0.06)	$(0.06)	$(0.06)	$(0.06)
Basic and diluted weighted average number of shares of common stock outstanding	159,459	162,128	163,614	163,614

	Quarters Ended			
2014 (unaudited)	March 31	June 30	September 30	December 31
Revenue	$-	$-	$-	$-
Loss from operations	(6,839)	(7,202)	(7,884)	(7,354)
Net loss	(6,371)	(7,152)	(7,866)	(7,313)
Net loss applicable to common stock	(6,371)	(7,152)	(7,866)	(7,313)
Basic and diluted net loss per share	$(0.06)	$(0.06)	$(0.06)	$(0.05)
Basic and diluted weighted average number of shares of common stock outstanding	105,054	115,587	123,287	145,257

17. Subsequent Events

Underwritten Public Offering of Common Stock

In February 2016, we completed an underwritten public offering with gross proceeds of $8.0 million from the sale and issuance of 29,090,910 units, each consisting of one share of our common stock and one warrant to purchase one share of our common stock. Net proceeds, after deducting underwriting discounts and commissions and other estimated offering expenses, were approximately $7.3 million. The warrants have an exercise price of $0.42 per share, are exercisable any time on or after August 17, 2016 and will expire on February 16, 2021.

Amendments to Loan and Security Agreement and Warrant Agreement with Hercules

In February 2016, we entered into a Third Amendment to Loan and Security Agreement primarily to amend the conditions under which we are required to prepay $10 million of the principal balance and the deadline for meeting the required condition, as well as to extend the interest-only payment period and provide for further extension of the interest-only payment period under certain circumstances. Pursuant to the Third Amendment to Loan Agreement, we paid an additional facility charge to Hercules of $37,500 and agreed to further amend our Warrant Agreement with Hercules Technology III, L.P. See Note 9 “Debt Facility” for additional information.

In February 2016, in connection with the Third Amendment to Loan and Security Agreement, we entered into a Second Amendment to Warrant Agreement with Hercules Technology III, L.P. Pursuant to the Second Amendment to Warrant Agreement, the warrant issued to Hercules was amended such that the exercise price was decreased from $0.41 per share to $0.275 per share, resulting in the warrant becoming exercisable for an additional 748,337 shares of our common stock, for a total of up to 2,272,727 shares of our common stock. See Note 9 “Debt Facility” and Note 10 “Capital Stock and Warrants” for additional information.

Exhibit Index

Exhibit No.	Description	Filed Herewith	Incorporated by Reference		
			Form	File/Film No.	Date Filed
2.1†	Agreement and Plan of Merger, dated February 12, 2011, by and among the registrant, SRX Acquisition Corporation, SynthRx, Inc. and, solely with respect to Sections 2 and 8, the Stockholders' Agent		Form 8-K	001-32157-11752769	04/11/11
2.2†	Agreement and Plan of Merger, dated February 7, 2014, by and among the registrant, AP Acquisition Sub, Inc., Aires Pharmaceuticals, Inc. and, solely with respect to Sections 2.8(b) and 6.3 and Article IX, the Stockholders' Representative, as amended by the Waiver of Closing Conditions, dated February 26, 2014		Form 10-Q	001-32157-14813538	05/05/14
3.1	Composite Amended and Restated Certificate of Incorporation, as amended, of the registrant		Form S-1	333-188870-13873232	05/28/13
3.2	Composite Amended and Restated Bylaws, as amended, of the registrant		Form 10-K	001-32157-14717498	03/26/14
4.1	Form of common stock certificate of the registrant		Form 10-K	001-32157-13702619	03/19/13
4.2	Warrant Agent Agreement, dated November 11, 2011, by and between the registrant and American Stock Transfer & Trust Company, including the form of Common Stock Purchase Warrant as Exhibit A		Form 8-K	001-32157-111203681	11/14/11
4.3	Warrant Agent Agreement, dated June 14, 2013, between the registrant and American Stock Transfer & Trust		Form 8-K	001-32157-13917371	06/17/13

	Company, LLC, including the Form of Common Stock Purchase Warrant as Exhibit A			
4.4	Form of Pre-Funded Warrant Agent Agreement, dated as of November 6, 2014, between the registrant and American Stock Transfer & Trust Company, LLC	Form 8-K	001-32157-141202528	11/07/14
4.5	Form of Pre-Funded Warrant issued by the registrant on November 12, 2014	Form 8-K	001-32157-141202528	11/07/14
4.6	Form of Warrant Agent Agreement, dated as of November 6, 2014, between the registrant and American Stock Transfer & Trust Company, LLC	Form 8-K	001-32157-141202528	11/07/14
4.7	Form of Warrant issued by the registrant on November 12, 2014	Form 8-K	001-32157-141202528	11/07/14
4.8	Warrant Agreement, dated as of August 11, 2015, between the registrant and Hercules Technology III, L.P.	Form 10-Q	001-32157-151224926	11/12/15
4.9	First Amendment to Warrant Agreement, dated as of September 28, 2015, between the registrant and Hercules Technology III, L.P.	Form 10-Q	001-32157-151224926	11/12/15
4.10	Second Amendment to Warrant Agreement, dated as of February 25, 2016, between the registrant and Hercules Technology III, L.P.	Form 8-K	001-32157-161468225	02/29/16

			Incorporated by Reference		
Exhibit No.	Description	Filed Herewith	Form	File/Film No.	Date Filed
4.11	Form of Warrant Agreement entered into on February 16, 2016 between the registrant and American Stock Transfer & Trust Company, LLC		Form 8-K	001-32157-161407765	02/11/16
4.12	Form of Warrant Certificate for warrants to acquire common stock of the registrant issued by the registrant on February 16, 2016		Form 8-K	001-32157-161407765	02/11/16
10.1	Sales Agreement, dated August 21, 2015, between the registrant and Cowen and Company, LLC		Form 8-K	001-32157-151069175	08/21/15
10.2	Loan and Security Agreement, dated as of August 11, 2015, among the registrant, Hercules Technology III, L.P. and Hercules Technology Growth Capital, Inc.		Form 10-Q	001-32157-151224926	11/12/15
10.3	First Amendment to Loan and Security Agreement, dated as of September 28, 2015, among the registrant, Hercules Technology III, L.P. and Hercules Technology Growth Capital, Inc.		Form 10-Q	001-32157-151224926	11/12/15
10.4	Second Amendment to Loan and Security Agreement, dated as of December 31, 2015, among the registrant, Hercules Technology III, L.P. and Hercules Technology Growth Capital, Inc.		Form 8-K	001-32157-161328864	01/07/16
10.5	Third Amendment to Loan and Security Agreement, dated as of February 25, 2016, among the registrant, Hercules Technology III, L.P. and Hercules Technology Growth Capital, Inc.		Form 8-K	001-32157-161468225	02/29/16

10.6†	Stockholders' Voting and Transfer Restriction Agreement, dated February 12, 2011, by and among the registrant, each of the principal stockholders of SynthRx, Inc. and, solely with respect to Section 3(c), the Stockholders' Agent	Form 8-K	001-32157-11752769	04/11/11
10.7†	Form of Stockholder Agreement, dated February 7, 2014, by and among the registrant each of the principal stockholders of Aires Pharmaceuticals, Inc.	Form 10-Q	001-32157-14813538	05/05/14
10.8	License Agreement, dated December 10, 2005, among SD Pharmaceuticals, Inc., Latitude Pharmaceuticals, Inc. and Andrew Chen, including a certain letter, dated November 20, 2007, clarifying the scope of rights thereunder	Form 10-K	001-32157-08690952	03/17/08
10.9†	License Agreement, dated June 8, 2004, between SynthRx, Inc. and CytRx Corporation, as amended by that certain Letter Agreement Re: Amendment to License Agreement, dated August 3, 2006, and that certain Agreement and Amendment No. 2 to License Agreement, dated December 1, 2010	Form 8-K	001-32157-11752769	04/11/11
10.10#	2005 Equity Incentive Plan	Form 10-K	001-32157-07697283	03/15/07
10.11#	Form of Stock Option Agreement under the 2005 Equity Incentive Plan	Form S-8	333-126551-05951362	07/13/05

			Incorporated by Reference		
Exhibit No.	Description	Filed Herewith	Form	File/Film No.	Date Filed
10.12#	Form of Stock Option Agreement under the 2005 Equity Incentive Plan (for director option grants beginning in 2008)		Form 10-K	001-32157-08690952	03/17/08
10.13#	Form of Stock Option Agreement under the 2005 Equity Incentive Plan (for option grants to employees approved in March 2008)		Form 10-Q	001-32157-08820541	05/12/08
10.14#	2008 Omnibus Incentive Plan		Form 8-K	001-32157-08874724	06/02/08
10.15#	Form of Non-Statutory Stock Option Grant Agreement (for directors) under the 2008 Omnibus Incentive Plan		Form 10-Q	001-32157-081005744	08/11/08
10.16#	Form of Non-Statutory/Incentive Stock Option Grant Agreement (for consultants/employees) under the 2008 Omnibus Incentive Plan		Form 10-Q	001-32157-081005744	08/11/08
10.17#	Form of Incentive Stock Option Grant Agreement under the 2008 Omnibus Incentive Plan (for grant to Brian M. Culley in July 2009)		Form 8-K	001-32157-09957353	07/22/09
10.18#	Form of Incentive Stock Option Grant Agreement under the 2008 Omnibus Incentive Plan (for grant to Patrick L. Keran in July 2009)		Form 8-K	001-32157-09957353	07/22/09
10.19#	Form of letter, dated January 20, 2010, modifying options granted to Brian M. Culley and Patrick L. Keran in July 2009		Form 8-K	001-32157-10547818	01/26/10
10.20#	Form of Incentive Stock Option Grant Agreement under the 2008 Omnibus		Form 8-K	001-32157-10547818	01/26/10

	Incentive Plan (for grant to Brian M. Culley in January 2010)			
10.21#	Form of Incentive Stock Option Grant Agreement under the 2008 Omnibus Incentive Plan (for grant to Patrick L. Keran in January 2010)	Form 8-K	001-32157-10547818	01/26/10
10.22#	Incentive Stock Option Grant Agreement under the 2008 Omnibus Incentive Plan, effective as of February 1, 2011, by and between the registrant and Brian M. Culley	Form 10-Q	001-32157-11823538	05/09/11
10.23#	Incentive Stock Option Grant Agreement under the 2008 Omnibus Incentive Plan, effective as of February 1, 2011, by and between the registrant and Patrick L. Keran	Form 10-Q	001-32157-11823538	05/09/11
10.24#	Amended and Restated 2008 Omnibus Incentive Plan	Form S-8	333-174940-11914946	06/16/11
10.25#	Form of Non-Statutory Stock Option Grant Agreement — Director under the Amended and Restated 2008 Omnibus Incentive Plan	Form S-8	333-174940-11914946	06/16/11
10.26#	Form of Incentive Stock Option Grant Agreement (for grants to the registrant's Chief Executive Officer and President and Chief Operating Officer made in July 2011) under the Amended and Restated 2008 Omnibus Incentive Plan	Form 10-Q	001-32157-111186142	11/08/11

			Incorporated by Reference		
Exhibit No.	Description	Filed Herewith	Form	File/Film No.	Date Filed
10.27#	Form of Senior Executive Incentive Stock Option Grant Agreement (for grants to the registrant's Chief Executive Officer and President and Chief Operating Officer made beginning in December 2011) under the Amended and Restated 2008 Omnibus Incentive Plan		Form 10-K	001-32157-12677367	03/08/12
10.28#	2013 Omnibus Incentive Plan		Form 8-K	001-32157-13927320	06/21/13
10.29#	Form of Non-Statutory Stock Option Grant Agreement—Director (for grants to non-employee directors) under the 2013 Omnibus Incentive Plan		Form 8-K	001-32157-13927320	06/21/13
10.30#	Form of Incentive Stock Option Grant Agreement (for grants to employees) under the 2013 Omnibus Incentive Plan		Form 8-K	001-32157-13927320	06/21/13
10.31#	Form of Senior Executive Incentive Stock Option Grant Agreement (for grants to the registrant's chief executive officer and president and chief operating officer) under the 2013 Omnibus Incentive Plan		Form 8-K	001-32157-13927320	06/21/13
10.32#	2014 Omnibus Incentive Plan		Form 8-K	001-32157-14933081	06/20/14
10.33#	Form of Non-Statutory Stock Option Grant Agreement—Director (for grants to non-employee directors) under the 2014 Omnibus Incentive Plan		Form 8-K	001-32157-14933081	06/20/14
10.34#	Form of Incentive Stock Option Grant Agreement (for grants to employees) under the 2014 Omnibus Incentive Plan		Form 8-K	001-32157-14933081	06/20/14
10.35#	Form of Senior Executive Incentive Stock Option Grant Agreement (for grants to the registrant's chief executive officer and		Form 8-K	001-32157-14933081	06/20/14

	president and chief operating officer) under the 2014 Omnibus Incentive Plan			
10.36#	Form of CMO Incentive Stock Option Grant Agreement (for grants to the registrant's chief medical officer) under the 2014 Omnibus Incentive Plan	Form 8-K	001-32157-14933081	06/20/14
10.37#	Amendment of Stock Option Agreements, dated March 18, 2015, between the registrant and Patrick L. Keran	Form 10-Q	001-32157-15851050	05/11/15
10.38#	2015 Omnibus Incentive Plan	Form 8-K	001-32157-15934477	06/16/15
10.39#	Form of Non-Statutory Stock Option Grant Agreement—Director (for grants to non-employee directors) under the 2015 Omnibus Incentive Plan	Form 8-K	001-32157-15934477	06/16/15
10.40#	Form of Incentive Stock Option Grant Agreement – Exempt Employees under the 2015 Omnibus Incentive Plan	Form 8-K	001-32157-15934477	06/16/15
10.41#	Form of Incentive Stock Option Grant Agreement – Non-Exempt Employees under the 2015 Omnibus Incentive Plan	Form 8-K	001-32157-15934477	06/16/15
10.42#	Form of CEO Incentive Stock Option Grant Agreement under the 2015 Omnibus Incentive Plan	Form 8-K	001-32157-15934477	06/16/15

			Incorporated by Reference		
Exhibit No.	Description	Filed Herewith	Form	File/Film No.	Date Filed
10.43#	Form of CMO Incentive Stock Option Grant Agreement under the 2015 Omnibus Incentive Plan		Form 8-K	001-32157-15934477	06/16/15
10.44#	Offer letter, dated November 15, 2004, to Brian M. Culley		Form 10-KSB	001-32157-05719975	03/31/05
10.45#	Offer letter, dated February 11, 2011, to Brandi L. Roberts		Form 8-K	001-32157-11704394	03/22/11
10.46#	Offer letter, dated March 28, 2011, to R. Martin Emanuele		Form 10-Q	001-32157-11823538	05/09/11
10.47#	Offer letter, dated July 21, 2011, to Gregory D. Gorgas		Form 10-K	001-32157-12677367	03/08/12
10.48#	Offer letter, dated September 29, 2014, to Edwin L. Parsley		Form 10-Q	001-32157-141186781	10/31/14
10.49#	Retention and Severance Plan (as of July 21, 2009) for Brian M. Culley and Patrick L. Keran		Form 8-K	001-32157-09957353	07/22/09
10.50#	Change in Control Severance Plan, effective as of December 6, 2012		Form 8-K	001-32157-121250022	12/07/12
10.51#	2014 Executive Incentive Plan		Form 8-K	001-32157-14933081	06/20/14
10.52#	2015 Executive Incentive Plan		Form 8-K	001-32157-15934477	06/16/15
10.53#	Director Compensation Policy, effective January 1, 2015		Form 10-K	001-32157-15722085	03/24/15
10.54#	Form of Director and Officer Indemnification Agreement		Form 8-K	001-32157-061156993	10/23/06
10.55	Sublease Agreement by and between the registrant and Santarus, Inc., effective as of June 19, 2014		Form 8-K	001-32157-14949388	06/30/14
21.1	List of Subsidiaries	X			
23.1	Consent of PricewaterhouseCoopers LLP, Independent Registered Public Accounting Firm	X			

31.1	Certification of principal executive officer pursuant to Rule 13a-14(a)/15d-14(a)	X
31.2	Certification of principal financial officer pursuant to Rule 13a-14(a)/15d-14(a)	X
32.1±	Certification of principal executive officer and principal financial officer pursuant to 18 U.S.C. 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002	X
101.INS	XBRL Instance Document	X
101.SCH	XBRL Taxonomy Extension Schema Document	X
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document	X
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document	X
101.LAB	XBRL Taxonomy Extension Label Linkbase Document	X
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document	X

† Indicates that confidential treatment has been requested or granted to certain portions, which portions have been omitted and filed separately with the SEC

# Indicates management contract or compensatory plan

± These certifications are being furnished solely to accompany this report pursuant to 18 U.S.C. 1350, and are not being filed for purposes of Section 18 of the Securities Exchange Act of 1934 and are not to be incorporated by reference into any filing of the registrant, whether made before or after the date hereof, regardless of any general incorporation by reference language in such filing.