UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

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

For the fiscal year ended December 31, 2014

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

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 ☒

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 ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ 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. ☒

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	☐
Non-accelerated filer	☐	Smaller reporting company	☒

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant as of June 30, 2014 was approximately $74.0 million based upon the closing price of the registrant's common stock on the NYSE MKT reported for such date.

As of March 20, 2015, the registrant had 159,458,376 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 2015 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, 2014.

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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," "expect," "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: our ability, or that of a future partner, to successfully develop, obtain regulatory approval for and then successfully commercialize our product candidates; 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; our ability to maintain our relationships with the single-source third-party manufacturers and suppliers for our clinical trial material 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 and other aspects of our development programs; our ability to obtain additional capital as needed on acceptable terms or at all; the potential for us to delay, scale back or discontinue development of a product candidate, partner it 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 protect our intellectual property rights and prevent competitors from duplicating or developing equivalent versions of our product candidates; 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.

PART I

Item 1. Business.

Overview

We are a clinical-stage, biopharmaceutical company developing novel therapies for serious or life-threatening diseases with significant unmet needs. 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 MST-188 (vepoloxamer) Injection, 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 currently are developing vepoloxamer for the treatment of sickle cell disease, arterial disease (in combination with thrombolytics), and heart failure. We also are developing AIR001, a sodium nitrite solution for intermittent inhalation via nebulizer. AIR001 has demonstrated positive hemodynamic effects in patients with pulmonary hypertension and we are developing it for the treatment of heart failure with preserved ejection fraction, or HFpEF.

For purposes of this report, "MST-188 Injection" refers to the investigational drug product of which vepoloxamer is the investigational drug substance. Vepoloxamer is purified poloxamer 188. 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 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.

Vepoloxamer is being tested in a pivotal Phase 3 clinical study called EPIC for the treatment of vaso-occlusive crisis in patients with sickle cell disease. As of early January 2015, enrollment in EPIC was more than one-third complete. Although predicting the rate of enrollment for any clinical study is subject to a number of significant assumptions and the actual rate may differ materially, we expect to complete enrollment around the end of this year and announce top-line data in the first quarter of 2016. Vepoloxamer has orphan drug status for the treatment of sickle cell disease in the U.S. and European Union. We have filed a provisional patent application claiming vepoloxamer as a novel composition of poloxamer material with the U.S. Patent and Trademark Office, as well as provisional and non-provisional patent applications covering various methods of therapeutic use of poloxamers, including vepoloxamer.

We also are enrolling patients with acute limb ischemia in a Phase 2 clinical study of vepoloxamer in combination with recombinant tissue plasminogen activator, or tPA, to evaluate whether vepoloxamer improves the effectiveness of thrombolytic therapy. In addition, we plan to initiate a Phase 2 clinical study of vepoloxamer for the treatment of heart failure in the third quarter of this year.

Our second product candidate, AIR001, is being tested in multiple institution-sponsored Phase 2a clinical studies that will provide us with data on AIR001's potential to treat patients with HFpEF. These Phase 2a studies will evaluate AIR001's acute hemodynamic effects, its acute effects versus placebo on submaximal oxygen consumption and exercise hemodynamics, its effects versus intravenous administration of nitrite, and the safety of multiple doses of AIR001 in HFpEF patients. We anticipate preliminary data from one of these Phase 2a studies in the second half of this year.

Summary of Our Key Development Programs

· *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. Studies have shown that vepoloxamer's mechanism of action is biophysical and driven by its ability to modulate surface tension of cell membranes. 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, the physical adhesion of vepoloxamer to the membrane reverses and vepoloxamer dislodges and returns to the circulation. Essentially all of it is recovered, unchanged, in the urine. In clinical and nonclinical studies, vepoloxamer has demonstrated hemorheologic (flow), cytoprotective, anti-inflammatory and antithrombotic/pro-fibrinolytic pharmacodynamic effects.

· *Vepoloxamer for sickle cell disease*. Sickle cell disease is a chronic, genetic disorder classified as a rare, or orphan, disease in the U.S. and European Union. The hallmark of sickle cell disease, and the primary reason for hospitalization, is recurring episodes of severe pain commonly known as sickle cell crisis or vaso-occlusive crisis, which occur when the proportion of sickled red blood cells rises, leading to obstruction of small blood vessels and reduced blood flow to organs and bone marrow. There

are no approved agents to shorten the duration or severity of vaso-occlusive crisis and only one FDA-approved agent for sickle cell disease, which is a treatment to reduce the frequency of crisis and was approved over 17 years ago. Vepoloxamer's hemorheologic and cytoprotective effects have potential to shorten the duration and severity of vaso-occlusive crisis by restoring blood flow, especially in the microcirculation. The primary objective of the EPIC study is to demonstrate that vepoloxamer reduces the duration of vaso-occlusive crisis. As of early January 2015, enrollment in EPIC was more than one-third complete with more than 130 patients enrolled and we expect to announce top-line results in the first quarter of 2016. In addition to EPIC, we are conducting other activities to evaluate vepoloxamer's potential in sickle cell disease, including preparing to initiate an open-label EPIC extension study in the first half of this year to expand our existing safety database regarding repeat exposure to vepoloxamer. The study will enroll patients who have completed EPIC. We also are conducting a sub-study at select EPIC study sites in the U.S. to investigate and quantify the effect of vepoloxamer on tissue oxygenation.

· *Vepoloxamer in combination with thrombolytics for acute complications of arterial disease*. Acute complications of arterial disease, such as acute ischemic cerebrovascular infarction (known as "stroke"), acute myocardial infarction (known as "heart attack"), and acute limb ischemia, occur when obstructions in the arteries severely and suddenly reduce blood flow to tissues. Timely restoration of blood flow is central to the treatment of these acute events. Current treatments target dissolution of blood clots and improving blood flow in large arteries, but are considered suboptimal for a number of reasons, including inadequate or slow reperfusion and risk of hemorrhage and reperfusion injury. We believe vepoloxamer's potential to improve blood flow in the microcirculation as well as its antithrombotic/profibrinolytic and cytoprotective properties can improve time to reperfusion while inhibiting reperfusion injury in patients experiencing acute complications of arterial disease. While we believe vepoloxamer may be useful as a stand-alone agent, it has demonstrated synergy with thrombolytics and we initially are pursuing its development in arterial disease as an adjunct to thrombolytic therapy. In 2014, we initiated a Phase 2 study of vepoloxamer in combination with recombinant tPA in patients with acute limb ischemia, or ALI, and we expect to complete enrollment in the study in the second half of 2016. In addition to evaluating vepoloxamer's safety in this patient population, a key objective of the study is to evaluate whether treatment with vepoloxamer in addition to recombinant tPA results in more rapid thrombolysis and improved tissue perfusion. Vepoloxamer has orphan drug designation for treatment of ALI in the U.S. If results of the study are positive, we believe it not only would progress development in ALI, but also support development of vepoloxamer in other acute complications of arterial disease, such as thrombotic stroke. Therefore, in parallel with the Phase 2 study, we are conducting nonclinical studies to evaluate vepoloxamer's potential in that indication, including its ability to expand the therapeutic window for tPA after onset of stroke symptoms. Earlier this year, we announced new data supporting development of vepoloxamer in this indication. In a nonclinical study of vepoloxamer in a model of embolic stroke with delayed administration of tPA, treatment with vepoloxamer, both alone and in combination with tPA, improved neurologic function and reduced brain tissue loss compared to treatment with tPA alone and saline controls. Importantly, vepoloxamer was not associated with any increase in hemorrhagic (bleeding) risk. No significant differences in the incidence of gross hemorrhage were detected among treatment groups.

· *Vepoloxamer for heart failure*. Heart failure is a chronic, progressive condition in which heart muscle is unable to pump sufficient blood to meet the body's needs. There are an estimated five to six million individuals with heart failure in the U.S. and heart failure accounts for more than one million hospitalizations each year in the U.S. In contrast with current treatments, such as vasodilators and beta blockers, which reduce the symptoms of heart failure, but may not directly improve heart function, vepoloxamer's cytoprotective properties may preserve cardiac tissue by helping to restore damaged cell membranes, thereby minimizing calcium overload injury, preserving cardiomyocytes and directly improving heart contractility and function. Based on encouraging results of our proof-of-concept and repeat treatment nonclinical studies in a model of advanced heart failure, which we discuss in detail below, as well as recommendations from medical experts in heart failure, we plan to initiate a Phase 2 study of vepoloxamer in patients with chronic heart failure in the third quarter of this year.

· *AIR001 for the treatment of HFpEF*. We are developing AIR001 (sodium nitrite) inhalation solution, which is administered intermittently via nebulizer, for the treatment of heart failure with preserved ejection fraction, or HFpEF. Approximately 50% of patients hospitalized for heart failure have HFpEF and there is no proven effective treatment. We acquired AIR001 in February 2014 through our acquisition of Aires Pharmaceuticals, Inc. 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 well-tolerated. While the Phase 2 study was prematurely terminated by Aires due to Aires' capital constraints prior to the acquisition, preliminary data from the study showed improvements in hemodynamic parameters and change in exercise capacity from baseline. We believe the data from these prior studies, in particular the reductions observed in right atrial pressure, pulmonary capillary wedge pressure, and pulmonary vascular resistance, support development of AIR001 in HFpEF. We are supporting multiple institution-sponsored Phase 2a studies of AIR001 in HFpEF patients to evaluate: (1) its acute hemodynamic effects, (2) its acute effects versus placebo on submaximal oxygen consumption and exercise hemodynamics, and (3) inhaled versus intravenous administration of nitrite, as well as the safety of multiple doses of AIR001. We anticipate preliminary data from one of these Phase 2a studies in the second half of this year.

Business Strategy

Our goal is to become a leading biopharmaceutical company developing 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 MST-188 Injection in sickle cell disease*. Enrolling subjects in EPIC is one of our top priorities. We have approximately 70 EPIC study sites open in ten countries, with more than 50 of those sites in the U.S. and, as of early January 2015, enrollment was more than one-third complete. We expect to announce top-line results in the first quarter of 2016. If results are positive, we plan to submit a new drug application, or NDA, to the U.S. Food and Drug Administration, or FDA, based in large part on the data from EPIC. Vepoloxamer has fast track designation with the FDA for the treatment of vaso-occlusive crisis of sickle cell disease.

- *Advance clinical development of vepoloxamer in combination with thrombolytics for treatment of acute complications of arterial disease*. We plan to complete enrollment of our Phase 2 study in ALI in the second half of 2016. In addition, we recently reported positive results of a nonclinical study of vepoloxamer in combination with tPA in an embolic stroke model and we plan to conduct additional nonclinical studies to evaluate vepoloxamer's potential in thrombotic stroke. We believe that positive data from the Phase 2 study in ALI together with data from the nonclinical studies in stroke would be supportive of clinical development of vepoloxamer in stroke.

- *Initiate Phase 2 clinical study of vepoloxamer in heart failure*. As described above, we believe vepoloxamer may offer a new therapeutic approach for patients with heart failure and we plan to initiate a Phase 2 study in the third quarter of this year to evaluate the safety and efficacy of vepoloxamer in patients with chronic heart failure. While still in the planning process, we expect the study will enroll approximately 150 patients.

- *Advance clinical development of AIR001 in HFpEF*. We are supporting multiple institution-sponsored Phase 2a studies of AIR001 that will provide us with data on AIR001's potential to treat patients with HFpEF. If data are positive, we plan to conduct a Phase 2b proof-of-concept clinical study of AIR001 in HFpEF.

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 both poloxamer 188 and 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.

The MAST platform provides us with several key benefits as we develop vepoloxamer. In particular, we believe it:

- *Accelerates development of vepoloxamer in new indications, at reduced cost*. 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 plan to 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). Further, we already have evaluated vepoloxamer in healthy volunteers and our thorough QT/QTc study of vepoloxamer in 64 healthy volunteers met its primary endpoint and demonstrated that, based on an analysis of electrocardiograms, vepoloxamer did not have an adverse effect on cardiac repolarization, as measured by the QT interval. In addition, we have successfully manufactured multiple batches of clinical trial material. As a result, we expect to move vepoloxamer directly into Phase 2 studies and generate clinical proof-of-concept data in new indications in relatively short time frames at relatively modest cost. 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).

- *Provides broad-based, indication-agnostic exclusivity for vepoloxamer*. We have filed for patent protection and continue to develop patent positions that we expect will provide us with exclusivity around the use of vepoloxamer in new indications and in combination with other therapies. In addition, the MAST platform allows us to augment our proprietary position around broadly-applicable, indication-agnostic activities that we believe will provide additional barriers-to-entry for competitors. For example, 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 adequately characterizing the active ingredient, and without access to our acceptance criteria for starting material and in-process and release specifications, which we protect as trade secrets, generic and other follow-on

manufacturers may be unable to develop 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 clinical studies to demonstrate the safety and efficacy of their follow-on products. We also are evaluating the use of proprietary analytical standards and bioanalytical assays to further augment our control over product quality, as well as exploring development of our own proprietary process for manufacturing API starting material, which we expect would further enhance our proprietary position around vepoloxamer, without regard to indication.

- *Increases partnering interest in and value of vepoloxamer*. We believe that we increase our ability to attract collaborators by pursuing multiple development programs within the vepoloxamer franchise and, if advantageous, partnering different indications in different jurisdictions. We intend to structure all partnering transactions, whether indication- or product-based and whether regional or global, to ensure that we realize the financial benefit of the development, regulatory and commercial success of vepoloxamer, regardless of the partnered indication, including through milestones, royalties and, possibly, equity arrangements.

- *Reduces our overall risk profile*. Pursuing multiple development programs reduces the risk associated with any one program, assuming vepoloxamer has an acceptable safety profile in each indication. Importantly, this diversification can be achieved without the costs typically associated with product pipeline expansion. By leveraging the MAST platform to move vepoloxamer directly into Phase 2 studies, we expect to be able to expand into new indications without the time, expense and distraction needed to identify, negotiate and acquire new product candidates.

Vepoloxamer

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, 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. Substantial research has demonstrated that poloxamer 188 has cytoprotective and hemorheologic properties and inhibits inflammatory processes and thrombosis.

Composition and Mechanism of Action

Vepoloxamer is a nonionic, block copolymer comprised of a central linear chain of hydrophobic polyoxypropylene flanked on both sides by linear hydrophilic polyoxyethylene chains. The activity of vepoloxamer is believed to be based on hydrophobic adhesive interactions, driven in part by its hydrophobic core.

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 evolved 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 adhere to 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 patient 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 and poloxamer 188 have shown effectiveness in experimental models of heart failure and stroke and poloxamer 188 also 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 under "Composition and Mechanism of Action," vepoloxamer has little or no affinity for undamaged, hydrophilic domains and, thus, has little or no 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. In contrast, as discussed below, in the more than 300 healthy volunteers and sickle cell patients treated with vepoloxamer in these prior studies, no clinically significant elevations in serum creatinine have been observed.

The therapeutic potential of non-purified poloxamer 188 is limited by toxicities associated with low molecular weight substances generated during the chemical process by which the poloxamer is synthesized. 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 to date, including the 255-patient, Phase 3 study in sickle cell disease 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), no clinically significant elevations in serum creatinine have been observed in patients treated with vepoloxamer.

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.

Sickle Cell Disease

Overview

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, but 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 MST-188 Injection 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, oxygenation 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.

Clinical Development

Overview

Vepoloxamer currently is being evaluated in a Phase 3 study in sickle cell disease called the EPIC study. 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 a 255-patient Phase 3 study. The fourth study involved patients with acute chest syndrome. Encouraging results in early clinical studies warranted continued development.

In these 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, the prior Phase 3 study discussed 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). In May 2013, we began enrolling subjects in EPIC, a randomized, double-blind, two-arm, placebo-controlled, Phase 3 study of vepoloxamer in patients with sickle cell disease. 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 65, who have sickle cell disease and are experiencing acute pain typical of vaso-occlusive crisis and require treatment with parenteral opioid analgesia will be enrolled. 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%, which 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 will enroll in EPIC. 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. The study will enroll subjects from approximately 70 study sites. More than 50 EPIC sites are located in the U.S. As of early January 2015, enrollment was more than one-third complete. While predicting the rate of enrollment in any clinical study, including EPIC, is subject to a number of assumptions and the actual enrollment rate may differ materially from our estimates, we expect to complete enrollment of EPIC around the end of 2015 and announce top-line results in the first quarter of 2016.

Open-Label, Repeat-Exposure Extension Study (EPIC-E). We plan to initiate an open-label, multicenter extension study called EPIC-E in the first half of this year to expand our existing safety database regarding repeat exposure to vepoloxamer. The study will enroll patients who have completed the EPIC study and are hospitalized for subsequent vaso-occlusive crises. 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 ischemia and 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 cumulative tissue damage, end-organ dysfunction and failure. While it is impractical to conduct multi-decade, interventional studies to evaluate the ability of an agent to improve long-term outcomes in sickle cell patients, it is possible to measure the effect of an agent on tissue ischemia, which is widely accepted as the physiologic basis for organ damage in sickle cell disease. Last year, 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, which is measured utilizing a non-invasive, FDA-approved device.

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. 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 were receiving 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, in 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=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, there were no clinically significant changes in renal function following treatment with study drug compared to placebo. The 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, while the mean duration of hospitalization 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) 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 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 005). Study 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 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.

Arterial Disease – Vepoloxamer as Adjunctive Therapy to Thrombolytics for Acute Complications

Introduction

As discussed more fully below, data from nonclinical and clinical studies demonstrate the potential of vepoloxamer to improve outcomes in patients experiencing acute complications of arterial disease. For these indications, we believe vepoloxamer may be useful as a stand-alone agent or as an adjunct to thrombolytics. We plan first to study its potential in acute limb ischemia, or ALI, a complication of peripheral arterial disease and an advanced form of atherosclerosis. Ultimately, we plan to leverage the data generated in our ongoing Phase 2 clinical study in patients with ALI to support development of vepoloxamer in other market segments within arterial disease, such as thrombotic stroke.

Overview

Arterial disease resulting from atherosclerotic and thromboembolic processes is associated with significant morbidity and mortality. It is a common circulatory problem in which plaque-obstructed arteries reduce the flow of blood to tissues. Atherosclerosis occurs with advanced age, smoking, hypertension, diabetes and dyslipidemia.

Arterial disease resulting in obstruction of blood flow to the brain can cause ischemic cerebrovascular infarction, or stroke, while arterial disease resulting in obstruction of blood flow to the heart can cause myocardial infarction, or heart attack. Peripheral arterial disease, or PAD, refers to disease affecting arteries outside the brain and heart and often refers to blockage of arteries in the lower extremities. Progression of PAD is associated with ongoing obstruction, or occlusion, of the peripheral arteries, which can occur slowly over time or may lead to a sudden, acute occlusion.

Acute limb ischemia is a sudden decrease in perfusion of a limb, typically in the legs, that often threatens viability of the limb. A patient is considered to have ALI when the symptoms develop suddenly and the patient presents for treatment within 14 days after symptom onset. Critical limb ischemia, or CLI, occurs after chronic and severe lack of blood flow to an artery that leads to leg pain while resting, ulcers and gangrene. In contrast to CLI, in which collateral blood vessels may circumvent an occluded artery, ALI rapidly threatens limb viability because there is insufficient time for new blood-vessel growth to compensate for loss of perfusion.

Timely restoration of blood flow is central to the treatment of acute events associated with arterial disease. A well-known adage in this field is “time is tissue.” Timely restoration of blood flow is particularly 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. However, brain cells in the “ischemic penumbra,” areas that have been denied oxygen but that remain metabolically active, may be salvageable with timely reperfusion.

Significant Unmet Need

There are an estimated 8 to 12 million people with PAD in the United States. This prevalence is expected to increase, not only in the U.S., but throughout the world, as the population ages, cigarette smoking persists, and the prevalence of diabetes mellitus and obesity grows. Acute limb ischemia is an orphan disease within PAD with significant unmet needs. Sudden occlusion of a major artery in the leg is associated with significant morbidity and mortality. In the U.S., there were approximately 16,800 hospital admissions for ALI in 2012, and the in-hospital mortality rate has not changed significantly since the late 1990s. Only about 50% of patients hospitalized for ALI have a routine discharge and more than 25% of hospitalized patients require care in a nursing home or rehabilitation center after discharge.

Current treatments for acute complications of arterial disease focus on dissolution of the blood clots and improving blood flow in large arteries. The principal goal is to restore blood flow and tissue perfusion as rapidly as possible because rapid restoration of tissue perfusion is critical to regaining clinical function. Treatment options for ALI include revascularization with thrombolytics, endovascular treatment, open surgery, or various combinations of these approaches. However, current treatment options are considered suboptimal.

Recombinant tPA is FDA-approved and indicated for the management of acute myocardial infarction, acute ischemic stroke and acute pulmonary embolism. No thrombolytics, including recombinant tPA, have been approved for the treatment of ALI. Despite lack of specific approval, the preferred current treatment for patients with ALI, for whom thrombolytic therapy is not contraindicated, is catheter-directed thrombolysis, and the use of recombinant tPA as an intra-arterial thrombolytic treatment for ALI is part of routine clinical practice and recommended by international and national scientific vascular surgeon associations in their guidelines. However, in ALI patients, arterial reperfusion with thrombolytics is slow—it typically takes many hours. Moreover, major hemorrhagic complications are frequent, both locally at the site of catheter insertion and distant. While lowering the dose of the thrombolytic agent may decrease the risk of bleeding, albeit at the cost of slower reperfusion, the risk of major bleeding is associated with the duration of thrombolytic administration, offsetting the potential safety benefits of lower dose therapy. Consequently, new pharmacologic therapies that can achieve more rapid thrombolysis and arterial reperfusion with similar or less risk of bleeding complications would address an area of significant medical need.

While ALI is an orphan disease, stroke is the fourth leading cause of death in the U.S. and a leading cause of serious 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. Thrombotic stroke is a type of ischemic stroke that occurs when a thrombus, or blood clot, forms in a blood vessel of the brain restricting or blocking blood flow to the brain. Treatment options for ischemic stroke are similar to those for ALI, except that surgical intervention is less viable in stroke due to proximity of the occluded artery to the brain, making intravenous or intra-arterial thrombolytic therapy the dominant treatment modalities. Recombinant t-PA is approved for acute ischemic stroke. However, in stroke patients, due to bleeding risks, it 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.

While current therapies target large vessel reperfusion, reperfusion of large vessels alone may not be adequate to prevent tissue loss. Further, the reintroduction of blood flow can initiate reactive hyperemia, leading to reperfusion injury. Reperfusion injury is the paradoxical damage to tissues caused by the restoration of blood flow following a period of ischemia. It is believed to result from activation of inflammatory and oxidative processes upon ischemia-injured cells. Existing treatments are not targeted to treat reperfusion injury and are suboptimal at limiting it. Many patients also suffer re-thrombosis/re-stenosis, in which new clots form in a previously treated blood vessel. An adjunctive agent that improves blood flow in the microcirculation, where the majority of oxygen and nutrient transport occurs, and limits reperfusion injury may globally improve thrombolytic outcomes.

There is a significant need for a pharmacologic agent that enhances thrombolysis. The mechanistic activities of vepoloxamer, which facilitate thrombolysis and inhibit reperfusion injury and re-occlusion, have potential to increase the speed of thrombolysis. In addition, vepoloxamer's cytoprotective properties may reduce reperfusion injury, with the potential to limit tissue necrosis. Further, improved microvascular flow and distal tissue reperfusion has the potential to 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 duration of infusion, more rapid thrombolysis has the potential to decrease the risk of bleeding.

Nonclinical Data

Vepoloxamer's utility as an adjunct to thrombolytics has been demonstrated in experimental studies, as discussed below.

Effects on neurologic function, brain tissue loss and microvascular fibrin deposition in embolic 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.

Effect on thrombolysis, blood flow and re-thrombosis/re-stenosis

To assess whether poloxamer 188 accelerates the time required to achieve thrombolysis the extent of blood flow following thrombolysis and the time to and incidence of re-thrombosis, it was evaluated in an experimental femoral artery thrombolysis model. Tissue plasminogen activator, or t-PA, was administered either in combination with saline (control) or poloxamer 188. The time to restoration of flow, or reperfusion, and the extent of flow following reperfusion were measured using a calibrated electromagnetic flow probe. Treatment with poloxamer 188 resulted in a 38% faster time-to-reperfusion, compared to t-PA plus saline (26 ± 3 minutes v. 42 ± 6 minutes, respectively) ($p<0.04$). Blood flow following reperfusion was also significantly increased (by 28%) over t-PA plus saline ($p<0.02$) and the time to re-occlusion was also significantly prolonged (50 ± 13 min vs. 22 ± 2 min) ($p<0.04$).

Effect on reperfusion injury

To determine its effect on reperfusion injury, poloxamer 188 was evaluated relative to sham and saline controls in a reperfusion model following one hour of ischemia. Treatment effects were evaluated based on histopathology, myeloperoxidase and heme-oxygenase activity and edema score, and gene expression arrays covering the spectrum of genes associated with ischemia/reperfusion injury. Study treatments were administered during reperfusion.

Compared to sham, histopathology following saline control showed marked damage to tissue cyto-architecture, as well as hemorrhage, edema, ulceration and inflammatory cell infiltration. In contrast, histopathology following treatment with poloxamer 188 appeared nearly identical to sham, with little damage to tissue architecture and none of the changes observed with saline control. Quantification of these observations using the Chui score showed the differences were statistically significant (2.66 ± 0.3 vs. 1.16 ± 0.16 for saline and poloxamer 188, respectively) ($p<0.05$).

Consistent with histopathology, myeloperoxidase and heme-oxygenase activity and edema all were significantly elevated following reperfusion injury. These markers were significantly reduced following treatment with poloxamer 188, but not saline control. Gene expression arrays further validated the histopathological observations. Compared to sham, expression of important injury pathways (including acute phase reactants, adhesion receptors, coagulation enzymes, chemokines, matrix metaloproteinases, apoptosis and VEGF signaling) remained altered in saline controls. However, in almost every case, gene expression returned toward sham levels following treatment with poloxamer 188 in those instances where gene expression was altered by ischemia/reperfusion injury.

Effect on re-thrombosis/re-stenosis

Poloxamer 188 was evaluated for its effect on acute thrombosis in a model of experimental angioplasty and stent placement. Specifically, this model measured the extent of artery occlusion following placement of a coiled wire stent under excessive angioplasty pressure. Control treatment (saline plus heparin) resulted in average occlusion of about 63%. Test treatment (poloxamer 188 plus heparin) resulted in significantly less occlusion (mean of about 13%) ($p=0.001$).

Electron micrographs of the occlusive thrombi revealed that platelets adhered to areas damaged by the angioplasty with both control and test treatments. However, platelets degranulated and accumulated to form large thrombi with control treatment while, with test treatment, platelets did not de-granulate or accumulate and a smaller layer of adherent platelets was observed. These observations suggest that poloxamer 188 cannot overcome the highly specific platelet/vessel wall interactions needed to stop bleeding associated with injury. However, it is able to inhibit the extension of a platelet thrombus, when the stimulus for the growing thrombus is the thrombus itself.

Effect on blood flow in experimental ischemic stroke

The effect of poloxamer 188 on cerebral artery blood flow was measured over four hours following experimentally induced arterial occlusion. Blood flow was measured using a well-established hydrogen wash-out technique. Poloxamer 188, but not placebo, increased blood flow by an average of 121% in areas with severe or moderate ischemia, but had little effect in areas with mild or no ischemia. These observations suggest poloxamer 188 improves flow in ischemic tissues without "stealing" flow from non-ischemic tissues. The overall difference in blood flow between poloxamer 188 and placebo at four hours following occlusion was statistically significant (p=0.001).

Clinical Data

Other than our ongoing Phase 2 study in ALI, clinical trials directly evaluating the effect of vepoloxamer on clinical outcomes in ALI or stroke have not been conducted. However, its synergy with thrombolytics and its pharmacological effects on arterial and microvascular blood flow and reperfusion injury have been observed in studies of poloxamer 188 and vepoloxamer in patients with acute myocardial infarction and sickle cell disease. We believe the effects observed in those studies have potential to translate into clinically meaningful benefits in ALI, stroke and other conditions where thrombolytics are indicated or useful.

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, a Phase 3 study of vepoloxamer in sickle cell disease (described above). As discussed above, compared to placebo (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.

The effect of poloxamer 188 on early coronary patency and reperfusion injury was evaluated in a randomized, multicenter, placebo-controlled Phase 2 study in patients receiving thrombolytic therapy for acute myocardial infarction, which we refer to as the Pre-CORE study. One hundred fourteen patients with symptoms consistent with acute myocardial infarction were randomized immediately after the initiation of thrombolytic therapy to receive poloxamer 188 (test) or placebo (control). Myocardial infarct size was assessed through SPECT imaging. Global LV ejection fraction was assessed through radionuclide angiography performed 5 to 7 days after randomization. Median infarct size was significantly smaller in the test group than in the control group (p=0.031). Median LV ejection fraction was significantly higher in the test group than in the control group (p=0.020). In addition, the incidence of in-hospital reinfarction was significantly lower in the test group than in the control group (p=0.016). The study investigators concluded that poloxamer 188 may enhance early coronary patency (time to reperfusion) by accelerating thrombolysis and may reduce reperfusion injury (as evidenced by reduced myocardial infarct size and improved LV function).

The effect of poloxamer 188 on coronary artery patency also was evaluated in a randomized sub-study conducted as part of the CORE study, an approximately 2,950-patient Phase 2 study in acute myocardial infarction. In the sub-study, 71 patients with symptoms consistent with acute myocardial infarction were randomized shortly after initiating thrombolytic therapy to receive poloxamer 188 or placebo (control). Patency was assessed in the infarct-related artery with angiograms completed 70 to 100 minutes after randomization. All angiograms were analyzed in a central laboratory without knowledge of treatment assignment or clinical outcome and assigned a thrombolysis in myocardial infarction, or TIMI, grade flow score. TIMI grade flow is a scoring system from 0-3 referring to levels of coronary blood flow assessed during percutaneous coronary angioplasty. The rates of TIMI grade 2 or 3 (partial or complete perfusion) were 74% in the test group and 54% in the control group (p=0.11). These data suggest that treatment with poloxamer 188 results in greater proportion of patients achieving clinically significant reperfusion (TIMI grades 2 or 3) compared to control. For the overall CORE study, outcomes were equivocal in the primary endpoint – a composite outcome of death, reinfarction and cardiogenic shock at 35 days post-randomization. However, the comparable dosing regimens that were evaluated and found effective in the Pre-CORE study (described in the preceding paragraph) were discontinued within months of initiation of the CORE study as a result of the acute renal dysfunction described above under "Safety." We believe discontinuation of the two high-dose regimens and the low-dose/longer-duration regimen in the CORE study, and that 92.5% of patients who received active drug in the CORE study received a low-dose/shorter-duration regimen, negatively impacted the overall study results.

Ongoing and Planned Development

Acute Limb Ischemia

In 2014, we initiated a Phase 2, randomized, double-blind, placebo-controlled, multicenter, clinical proof-of-concept study to evaluate the safety and efficacy of vepoloxamer in combination with recombinant tPA in patients with ALI. The study will enroll approximately 60 patients with Rutherford Category IIa and IIb acute lower limb ischemia receiving catheter-directed recombinant tPA. We plan to conduct the study at approximately 35 sites within and outside the U.S. The primary objectives of the study are to evaluate the safety and efficacy of vepoloxamer in combination with recombinant tPA against recombinant tPA alone and whether

vepoloxamer results in more rapid thrombolysis and tissue perfusion. The secondary objectives are to assess the clinically-meaningful benefit of vepoloxamer in combination with recombinant tPA by measures such as duration of thrombolytic therapy, amputation-free survival, target limb re-interventions, and the need for endovascular or open surgical re-interventions. These objectives will be measured through up to 90 days of follow-up. We expect to complete enrollment in the study in the second half of 2016.

Thrombotic Stroke

There may be substantial growth opportunities for vepoloxamer within other acute thrombotic arterial diseases, such as stroke. We believe that, based on the similar pathophysiology of thrombotic arterial disease (thrombus-obstructed arteries reducing the flow of blood to tissue), an agent that is effective in one form of thrombotic arterial disease also may be effective in its other manifestations. Our strategy in arterial disease is first to demonstrate the utility of vepoloxamer in patients with ALI, where we believe the potential to demonstrate a treatment effect is greatest. However, in parallel, we are conducting nonclinical studies in thrombotic stroke to evaluate vepoloxamer's potential to improve the therapeutic effect of tPA and expand the window in which it is effective. Results of the Phase 2 study in ALI and data from our nonclinical studies in stroke will help guide our assessment of opportunities for vepoloxamer in stroke.

Heart Failure

Overview

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. However, a variety of diseases and conditions can weaken the heart and reduce its ability to deliver an adequate blood supply.

Common causes of heart failure include: coronary artery disease, such as atherosclerosis, in which cholesterol and fatty deposits build up in the heart's arteries, limiting blood from reaching heart muscle; myocardial infarction, or heart attack, in which arteries that supply blood to heart muscle are blocked, resulting in death of heart muscle tissue and weakening of the heart's ability to pump blood; and hypertension, or high blood pressure, which causes the heart to pump harder (to overcome increased resistance) to keep blood circulating, which causes the heart's chambers to enlarge and weaken.

The body employs various "compensatory" mechanisms to assist a failing heart and overcome factors that otherwise may cause symptoms. The heart may enlarge or develop more mass (pathologic hypertrophy) or pump faster (chronotropic response), all of which increase the heart's ability to pump blood, at least initially. The body may respond by narrowing blood vessels (vasoconstriction), which maintains blood pressure and offsets the heart's loss of pumping power, but which also puts additional strain on the heart. The body also may divert blood away from less important tissues and organs to maintain flow to the heart and brain. Ultimately, however, if the underlying strain on the heart is not resolved, these compensatory mechanisms will exacerbate the underlying problem and begin to fail.

Symptoms of heart failure include shortness of breath, persistent coughing or wheezing, edema (buildup of excess fluid in body tissues), fatigue, lack of appetite or nausea, impaired thinking and increased heart rate. Everyday activities such as walking, climbing stairs or carrying groceries can become difficult. When blood returning to the heart through veins backs-up due to the heart's decreased ability to pump blood, fluid may accumulate and cause congestion in the body's tissues (often referred to as "congestive" heart failure). Fluid accumulation in the lungs (pulmonary edema) can interfere with breathing, causing shortness of breath, and often results in hospitalization. Left untreated, pulmonary edema may cause respiratory distress.

Significant Unmet Need

It is estimated that more than 20 million individuals worldwide, including five to six million in the U.S., suffer from heart failure, which is the most common diagnosis for hospital admission in the U.S. for 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 $53 billion in 2030, with the majority (80%) 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 (vasodilation) 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 short-term symptomatic relief, 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 estimated 30-day readmission and mortality rates of approximately 27% and 11%, 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 contribute to loss of cardiac function due to unregulated entry of calcium into cells. Vepoloxamer's membrane-sealing activity may help restore weakened cardiac cell membranes, thus minimizing calcium overload injury and directly improving heart contractility and function. 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 organ damage and improve 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: 2 hours (end of administration), 24 hours, 1 week and 2 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.

- 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-α (TNF-α), 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

In March 2015, we announced preliminary results of a second randomized, placebo-controlled, nonclinical study of vepoloxamer in the same model of chronic, stable heart failure as the proof-of-concept study discussed above. While the first study investigated the effects of a single administration of vepoloxamer, the primary objective of the second study was to examine the

effects of repeat intravenous administration of vepoloxamer on LV systolic and diastolic function. 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 or blood pressure compared to the control.

Data from these nonclinical studies are consistent with prior studies showing vepoloxamer directly improved cardiac function without increasing cardiac energy requirements. We believe this nonclinical data supports development of vepoloxamer for treatment of acute and chronic heart failure.

Planned Clinical Development

Encouraged by the results of the nonclinical studies discussed above, as well as recommendations from medical experts in heart failure, we are planning to study the effects of vepoloxamer in patients with chronic heart failure and expect to initiate a Phase 2 study in the third quarter of this year. While we are still in the planning process, we expect the study will be a randomized, double-blind, two-arm, placebo-controlled Phase 2 study of the safety and efficacy of a single administration of vepoloxamer in patients with chronic heart failure, including its effect on markers of cardiac injury (troponin) and wall stress (NT-proBNP), as well as clinical outcomes. We expect that the study will be conducted on an outpatient basis and estimate that it will enroll approximately 150 patients at sites in and outside of the U.S.

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

AIR001 is a sodium nitrite solution for intermittent inhalation via nebulizer. Nitrite is a physiological signaling molecule with roles in intravascular endocrine nitric oxide (NO) production, hypoxic vasodilation signaling, and cytoprotection after ischemia-reperfusion. Nitrite serves as the largest physiologic reservoir of NO and can be converted to NO independent of nitric oxide synthase (NOS) activity. 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 plan to develop AIR001 for treatment of patients experiencing heart failure with preserved ejection fraction (HFpEF). Approximately 50% of patients hospitalized for heart failure have HFpEF (also known as diastolic heart failure or heart failure with preserved diastolic function) and, as the population ages, the prevalence of HFpEF is expected to increase. No proven effective therapeutic agent is available. Pharmacologic therapies that have demonstrated efficacy in heart failure with reduced ejection fraction have failed to demonstrate improved outcomes in HFpEF patients.

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 well-tolerated. While the Phase 2 study, which we refer to as Study CS05, was prematurely terminated due to Aires' capital constraints prior to the acquisition, preliminary data from the study were positive, showing improvements in hemodynamic parameters and change in exercise capacity from baseline.

Study CS05 was a multicenter, open-label, randomized, parallel-dose Phase 2 study to evaluate the safety and efficacy of AIR001 in patients with pulmonary arterial hypertension. Subjects were randomized into one of three treatment arms and treated with

AIR001 for 16 weeks: 80 mg once daily after a 2-week "run-in" period of 46 mg once daily; 46 mg four times daily after a 2-week run-in period of 46 mg four times daily; or 80 mg four times daily after a 2-week run-in period of 46 mg four times daily. The primary objective of the study was to evaluate the efficacy of inhaled nebulized AIR001 as determined by change in pulmonary vascular resistance (PVR) from baseline to week 16, measured immediately post-completion of AIR001 nebulization. Secondary endpoints included change from baseline to week 16 in: 6-Minute Walk Distance (6MWD) assessed immediately post-completion of AIR001 nebulization (peak), but no more than 40 minutes after completion of AIR001 nebulization; hemodynamic measurements of cardiac output, mean right atrial pressure and pulmonary capillary wedge pressure at peak; NT-proBNP; hemodynamics and 6MWD at trough; and quality of life measures. The study was powered to enroll 90 patients, however, as a result of Aires' premature termination of the study due to capital constraints, data is available from 29 patients who enrolled in the study. In the primary efficacy analysis, all doses showed improvement in median pulmonary vascular resistance (PVR). In the secondary efficacy analysis, all doses showed improvements in the median distances obtained in the 6MWD, including clinically-meaningful improvements at the highest dose level. Additionally, AIR001 was well-tolerated, with no treatment related serious adverse events. In particular, methemoglobin levels remained normal (< 1.5%), which distinguishes AIR001 from safety concerns associated with intravenously-administered nitrite.

We believe data from Study CS05, together with data from earlier studies of AIR001, support continued clinical development. Given the hemodynamic improvements observed, we believe AIR001 may be uniquely suitable to address the serious unmet need of HFpEF patients. We are supporting multiple institution-sponsored Phase 2a studies of AIR001 in patients with HFpEF to evaluate: (1) its acute hemodynamic effects, (2) its acute effects versus placebo on submaximal oxygen consumption and exercise hemodynamics, and (3) inhaled versus intravenous administration of nitrite, as well as the safety of multiple doses of AIR001. Patient dosing in Phase 2a studies of AIR001 at Mayo Clinic and the University of Pittsburgh began in early 2015 and we expect a third Phase 2a study to begin later this year. We anticipate reporting preliminary data from one of these studies in the second half of this year. If results are positive, we expect to conduct a Phase 2b proof-of-concept study of AIR001 in HFpEF.

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 active pharmaceutical ingredient, or 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 single-source suppliers of the drug substance and finished drug product. We have entered into supply agreements with Pierre Fabre Médicament (PFM) and Patheon Inc. for drug substance and finished drug product, respectively. There are a limited number of manufacturers with the technical capabilities and desire to perform the specialized, proprietary processes required to produce vepoloxamer. As development of vepoloxamer progresses, we plan to pursue commercial supply agreements.

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.

We are investigating manufacturing-related opportunities to enhance our proprietary position around MST-188 Injection including those involving proprietary API starting material, alternative purification processes, unique analytical methods and new drug product formulations.

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 the future, establishing supply agreements, particularly with respect to commercial manufacturing, may require us to agree to minimum volume requirements, exclusivity arrangements, substantial investment in infrastructure and/or other restrictive and 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. 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, we will need FDA review and approval before the 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 commercialization.

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 "marketing 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 a provisional patent application claiming vepoloxamer as a novel composition of poloxamer material. We also have filed for patent protection covering various methods of therapeutic use of poloxamers, including vepoloxamer. We anticipate making additional patent filings, including around vepoloxamer's therapeutic uses, administration and formulation.

In addition to the patent protection we are seeking, we believe that our proprietary purification process for making vepoloxamer, which we maintain as a trade secret, will help provide exclusivity for our products, and we continue to expand our proprietary manufacturing know-how. For macromolecules, such as vepoloxamer, 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 manufacture compounds that are equivalent to vepoloxamer in the manner that regulatory agencies will require. Further, we are evaluating the use of proprietary analytical standards and bioanalytical assays to further augment our control over product quality, as well as evaluating development of a proprietary process for manufacturing API starting material, which we expect would further enhance our proprietary position around vepoloxamer.

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 U.S. and European Union for the treatment of sickle cell disease and in the U.S. for the treatment of acute limb ischemia. We plan to pursue orphan designation for vepoloxamer for the treatment of acute limb ischemia in the European Union after we have data from our ongoing Phase 2 study in acute limb ischemia. As described below under "Government Regulation – Orphan Drug Designation," for example, if MST-188 Injection is the first drug product in which vepoloxamer is the active ingredient to receive FDA approval for reducing the duration of vaso-occlusive crisis in patients with sickle cell disease, the FDA may not approve any other application to market a drug product in which vepoloxamer is the active ingredient for the same indication for a period of seven years, except in limited circumstances, such as another drug product showing clinical superiority to MST-188 Injection. With regard to the European Union, MST-188 Injection may benefit from ten years of market exclusivity. 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 MST-188 Injection 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. 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. There is a risk that third parties may allege that they have patent rights encompassing our product candidates 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. In addition, a favorable outcome or approval in one country does not necessarily indicate that a favorable outcome or approval will be obtained in other countries.

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 U.S. 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 based on a percentage of quarterly net sales. In addition, SynthRx would pay a single-digit royalty on net sales of covered products. 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

Aires has 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 also agreed to make "benchmark" payments of up to $7.2 million, with (a) $0.3 million related to clinical development milestones 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.

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 agencies' approvals of new products and indications, 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.

We are focusing our resources primarily on development of vepoloxamer and currently have clinical-stage programs in sickle cell disease, acute limb ischemia and heart failure. We also are developing AIR001 in HFpEF. Many other organizations are developing drug products and other therapies intended to treat such diseases and conditions and developments by others may render potential application of our product candidates in a particular indication obsolete or noncompetitive, even prior to completion of its development for that indication.

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, acute limb ischemia, and other indications we may pursue. Legislative action may generate further interest.

Vepoloxamer Programs

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, oxygenation, 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, but it is not approved to intervene after onset of a vaso-occlusive crisis; it has not been shown to treat the crisis itself. We are not aware of any therapeutic agents that have been approved to reduce the duration or severity of an ongoing vaso-occlusive crisis.

However, there is substantial interest in developing agents to treat sickle cell disease-related complications. We are aware of numerous companies with product candidates in varying stages of development for the 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 was expected to initiate a Phase 3 clinical study of GlycoMimetics' rivipansel compound in adult and pediatric patients with sickle cell disease experiencing vaso-occlusive crisis in 2014, but the study has been significantly delayed due to an undisclosed manufacturing issue. In addition, Eli Lilly and Company is conducting a Phase 3 study of prasugrel in pediatric patients to assess whether it reduces the rate of vaso-occlusive crisis. 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.

More broadly, vepoloxamer would compete against agents designed to treat the underlying pathology of sickle cell disease, of which vaso-occlusive crisis is a complication. 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 drug product for patients with severe sickle cell disease.

Thrombotic Arterial Disease

Current treatment options for arterial disease depend on disease severity and patient-specific factors. Some forms of thrombotic arterial disease may be addressed through lifestyle changes (e.g., smoking cessation, regular physical activity, heart healthy diet) and medication to control high cholesterol, high blood pressure and blood glucose. To the extent patients are able to control symptoms and prevent disease progression with lifestyle changes and medical therapy, the potential market for vepoloxamer in arterial disease will be reduced.

Acute limb ischemia and stroke typically require revascularization to restore blood flow, but current treatment options, which include open surgery, endovascular procedures, administration of thrombolytics and various combinations of these approaches, are considered suboptimal. As discussed above, in ALI patients, arterial reperfusion with tPA is slow and major hemorrhagic complications are frequent. In stroke patients, due to bleeding risks associated with tPA, tPA should not be administered until intracranial hemorrhage has been excluded by a CT scan, which can delay administration beyond the three-hour window in which it has demonstrated effectiveness. Dissatisfaction with currently available thrombolytics led to the emergence of mechanical thrombectomy, such as with the AngioJet rheolytic device, which has demonstrated reasonable efficacy. However, with that approach, thrombus removal is often incomplete, requiring subsequent infusion of traditional intra-arterial thrombolytics in a large proportion of cases. We believe vepoloxamer, if approved, would be compatible with the standard of care and we are first developing it as an adjunct to thrombolytics, but some medical professionals could perceive vepoloxamer as competitive with their current treatment methods and/or be adverse to a new approach.

We are aware of a number of investigational therapies for severe forms of thrombotic arterial disease, such as angiogenic growth factors, vasoactive drugs, anticoagulants, thrombolytics, anti-platelet agents, cytoprotectives, blood substitutes and devices to effect mechanical thrombectomy. If approved, vepoloxamer could compete with these therapies, certain of which are in late-stage clinical development. Should any of these other investigational therapies receive regulatory approval prior to vepoloxamer, they may become entrenched in the standard of care, diminish the need for vepoloxamer, or be difficult to displace.

Heart Failure

Similar to arterial disease, treatment options in heart failure depend on disease severity and patient-specific factors, as well as the underlying cause of failure and whether the condition is compensated or decompensated. 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, which often 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. During periods of decompensation (when mechanisms the body has employed to assist a failing heart fail), the immediate goal is to address symptoms (dyspnea, or shortness of breath, following fluid build-up in the lungs) and re-establish adequate perfusion and oxygen delivery to end-organs. 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. in people over age 65 and morbidity and mortality from heart failure remain high. Numerous companies are working to address this unmet medical need and we are aware of several agents in development for heart failure, certain of which have completed or are in late-stage clinical studies. Most notably, Novartis has submitted regulatory applications in both the U.S. and EU for approval of LCZ696 (valsartan and sacubitril), an angiotensin receptor/neprilysin inhibitor, as a treatment for patients with heart failure with reduced ejection fraction. Novartis' Phase 3 study of LCZ696 in this indication was stopped early after results showed that LCZ696 reduced cardiovascular death and heart failure hospitalizations compared to patients who received enalapril in the study. In addition, Novartis' RLX030 (serelaxin), a relaxin receptor agonist, is being evaluated in a second Phase 3 study in patients with acute heart failure with cardiovascular mortality as the primary endpoint. Results from the Phase 3 RELAX-AHF study of RLX030 show that it improved symptoms and reduced mortality in patients with acute heart failure, but U.S. and EU regulatory agencies required further data for approval. RLX030 was launched in Russia in 2014 under the trade name Reasanz. Other development approaches include myofilament calcium sensitizers, stem cell therapy, gene therapy and drugs that enhance the uptake of calcium by the sarcoplasmic reticulum. If approved as a treatment for heart failure, vepoloxamer could compete with one or more of these therapies. Should any of these other investigational therapies receive approval prior to vepoloxamer, they may become entrenched in the standard of care, diminish the need for vepoloxamer, or be difficult to displace.

AIR001 Program

We are not aware of any pharmacologic therapy of proven benefit for patients with HFpEF. Therapies that have demonstrated efficacy in heart failure with reduced ejection fraction have thus far failed to demonstrate improved outcomes in patients with HFpEF. A Phase 3 study of Novartis' LCZ696, which was discussed above, in patients with HFpEF is underway, with an estimated completion date of May 2019. We are aware of other therapies under investigation for HFpEF and, should any of them receive regulatory approval prior to AIR001, they may become entrenched in the standard of care, diminish the need for AIR001, or 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 MST-188 Injection or any of our other product candidates.

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 testing of a drug product candidate generally is conducted in three sequential phases, but the phases may overlap or be combined. The three phases are as follows:

- *Phase 1*. In Phase 1 clinical studies, the product is tested in a small number of patients with the target condition or disease or in healthy volunteers. These studies are designed to evaluate the safety, dosage tolerance, metabolism and pharmacologic actions of the product candidate in humans, side effects associated with increasing doses, and, in some cases, to gain early evidence on efficacy. The number of participants included in Phase 1 studies is generally in the range of 20 to 80.

- *Phase 2*. In Phase 2 studies, in addition to safety, the sponsor evaluates the efficacy of the product candidate on targeted indications to determine dosage tolerance and optimal dosage and to identify possible adverse effects and safety risks. Phase 2 studies typically are larger than Phase 1 but smaller than Phase 3 studies and may involve several hundred participants.

- *Phase 3*. Phase 3 studies typically involve an expanded patient population at geographically-dispersed test sites. They are performed after preliminary evidence suggesting effectiveness of the product candidate has been obtained and are designed to further evaluate clinical efficacy and safety, to establish the overall benefit-risk relationship of the product candidate and to provide an adequate basis for product approval. Phase 3 studies usually involve several hundred to several thousand participants.

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 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 move forward at designated check points based on access to certain data from the study.

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. 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.

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's goal is to complete its initial review and respond to the applicant within 12 months of submission, unless the application relates to an unmet medical need in a serious or life-threatening indication and is designated for priority review, in which case the goal is within eight months 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 Strategies, or REMS, plan to mitigate risks, 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 programs. Fast track designation and priority review 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 an unmet medical need 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 health programs, commercial insurance and managed healthcare organizations. These third-party payors are increasingly challenging the prices charged for medical products and services. 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, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

Significant uncertainty exists as to the coverage and reimbursement status of 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 reimbursement from third-party payors. Third-party payors include government health administrative authorities, managed care providers, private health insurers and other organizations. 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 would 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.

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. Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. Even if reimbursement is provided, market acceptance of our products would 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. There have been federal and state proposals to subject the pricing of healthcare goods and services to government control and to make other changes to the U.S. healthcare system. 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, is expected 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. It also contains substantial new 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. A significant number of provisions are not yet, or have only recently become, effective, but the ACA is likely to continue the downward pressure on pharmaceutical pricing, especially under the Medicare program, 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 will stay in effect through 2024 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 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.

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 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. Violations of the anti-kickback statute are punishable by imprisonment, criminal fines, civil monetary penalties and exclusion from participation in federal healthcare programs. 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.

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 laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

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 authorization 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 $19.4 million in 2014 and $12.9 million in 2013. Our research and development expenses for 2014 and 2013 consisted primarily of costs associated with the EPIC study, our Phase 2 study of vepoloxamer in acute limb ischemia and the QT/QTc study of vepoloxamer, and research-related manufacturing for vepoloxamer. 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 24, 2015, Mast Therapeutics has 23 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

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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 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 have incurred losses since our inception, we expect our operating expenses to continue to exceed our revenue for the foreseeable future, and we may never generate revenue sufficient to achieve profitability.

We are a clinical-stage 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 year ended December 31, 2014, we incurred a loss from operations of $29.3 million and, as of December 31, 2014, we had an accumulated deficit of $235.1 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 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, we enter into an arrangement that provides for licensing revenue or other partnering-related funding or one of our product candidates is approved by the FDA or another regulatory agency and successfully marketed, outcomes which we may not achieve.

The success of our business currently is dependent largely on the success of vepoloxamer and it may not receive regulatory approval or be successfully commercialized.

None of our product candidates has been approved for sale by any regulatory agency. We are focusing our resources primarily on the development of vepoloxamer. Accordingly, the success of our business currently depends on our ability, or that of a future partner, to successfully develop, obtain regulatory approval for and then successfully commercialize it and our efforts, or those of a future partner, in this regard may prove unsuccessful. Vepoloxamer may require considerable additional clinical development and significant manufacturing and related activities prior to commencing any commercial manufacturing, which activities require us to expend significant resources and with which we, as a company, have limited experience. Vepoloxamer may not be successful in the EPIC study or in other clinical studies, and, even if successful in clinical studies, may not receive regulatory approval in a timely manner, or at all. 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 process of developing and seeking regulatory approval of 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 and scope of development programs we pursue;
- 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 and the rate of site initiation in each 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 for 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 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; 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 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 dilution to our existing stockholders, require us to relinquish significant rights or restrict our operations.

We anticipate that our cash, cash equivalents and investment securities, which were approximately $57.3 million as of December 31, 2014, will be sufficient to fund our currently planned level of operations for at least the next 12 months. However, we may determine to grow our organization and/or pursue development activities for our product candidates at levels or on timelines, or we may incur unexpected expenses, that shorten the period through which our current operating funds will sustain us. Additionally, we may seek to further expand our product pipeline through acquisition of additional product candidates and/or technologies and the cost to acquire and develop such new product candidates and/or technologies may shorten the period through which our current operating funds will sustain us. We do not expect to generate any substantial revenue from operations until, and unless, one of our product candidates receives regulatory approval and we commence commercial sales or we enter into an arrangement that provides for licensing revenue or other partnering-related funding.

For the foreseeable future, we likely will seek to fund our operations through public or private equity and debt financings and/or through collaborations, such as licensing arrangements or partnering transactions, and may execute any such transaction at any time, subject to applicable laws and regulations. Although we were able to raise significant funds in the past through equity financings, the conditions of and our access to capital markets are highly variable and adequate additional 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 may be reduced and thus we may not realize the full value of any such products or product candidates. Debt financings would likely involve covenants that would restrict our operations. These restrictive covenants may include limitations on additional borrowing and specific restrictions on the use of our 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 any effort 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.

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

Historically, we have raised capital 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 159,458,376 shares of our common stock outstanding as of March 20, 2015 and the closing price per share of our common stock on such date, which was $0.49, we could not raise more than approximately $15.6 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. 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, scale back or discontinue development of our product candidates, partner them 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, scale back or discontinue one or more of our development programs, or to seek collaborators at an earlier stage than otherwise would be desirable or on terms less favorable than might otherwise be available. For example, if we do not have sufficient capital, we may determine 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. Delays in and/or reduction of development 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, 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.

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 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. Competition for qualified personnel, particularly for key positions, is intense among companies in our field, universities and other research organizations, particularly in the San Diego, California area, and many of the organizations against which we compete for qualified personnel have greater financial and other resources and different risk profiles than our company, which may make them more attractive employers. Our ability to compete for qualified personnel 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 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, 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 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

Further testing and validation of our product candidates and related manufacturing processes are required and regulatory approval may be delayed or denied, which would delay or prevent us from 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. In addition, these requirements and processes vary widely from country to country. Government regulation and the need for FDA and other regulatory agency approval will delay commercialization of our product candidates, impose costly procedures upon our activities, and may put us at a disadvantage relative to other companies with which we compete. There can be no assurance that FDA or any other regulatory agency will grant marketing approval for any of our product candidates on a timely basis, or at all, including due to factors not within our control. For example, 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 approval for our product candidates.

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 agreement on acceptable terms with prospective study sites and investigators, the terms of which can be subject to extensive negotiation and may vary significantly among study sites;
- reaching agreement on acceptable terms 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 and CMOs in developing procedures and protocols or otherwise conducting activities 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 and other factors described above. If we experience delays in the completion of a clinical study or if a clinical study is terminated, the 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 to 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.

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 current good manufacturing practices, or 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 MST-188 Injection, 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 MST-188 Injection 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 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. 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, we may have insufficient quantities of clinical trial material for our ongoing and/or planned clinical studies, including EPIC. 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. We cannot ensure that manufacturing or quality control problems will not arise in connection with the manufacture of our clinical trial material, or that third-party manufacturers will be able to maintain the necessary governmental licenses and approvals to continue manufacturing such clinical trial material. 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 no clinically significant changes in renal function were observed. However, patient safety concerns 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 may fail to demonstrate clinical benefits to human subjects.

Further, 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, a regulatory agency could determine that the study did not demonstrate sufficient clinical significance 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.

In addition, if we license to third parties rights to develop our product candidates in other geographic areas or in other indications, we may have limited control over nonclinical testing or clinical studies that may be conducted by such third-party licensees in those territories or indications. 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.

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 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 and with interpretation of the results of those studies, 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. Consultants and contractors may not be as committed to the success of our programs as employees and, therefore, may not be willing to devote the same time, thoughtfulness or creativity as would an employee. There can be no assurance that such third parties will perform all of their obligations under arrangements with us or will perform those obligations satisfactorily.

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 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 currently is being tested in institution-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 and approval of our applications by those agencies, and commercialization of our products. Moreover, 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. 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.

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, 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. For additional discussion of these risks, see the risk factors above in this section, “Risks Related to Drug Development and Commercialization.”

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. The FDA may require nonclinical testing and/or clinical studies prior to its review or approval of a new drug application for MST-188 Injection in sickle cell disease in addition to the EPIC study and the other testing that we are conducting or are planning to conduct in parallel with EPIC. 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 and acute limb ischemia, we may not be able to obtain orphan drug marketing exclusivity for MST-188 Injection.

Vepoloxamer has orphan drug designation from the FDA and the European Commission for the treatment of sickle cell disease and from the FDA for the treatment of acute limb ischemia. 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.

We currently have limited marketing capabilities and no sales capability and our failure to acquire or develop these and related capabilities internally or contract with third parties to perform these activities successfully could delay and/or limit our ability to generate revenue in the event we receive regulatory approval to market one of our product candidates.

We currently have limited marketing capabilities and no sales capability and our company has never marketed or sold products. To commercialize MST-188 Injection or any other product candidate, we will have to acquire or develop marketing, distribution, sales and associated regulatory compliance capabilities, or rely on marketing partners or other third parties for the marketing, distribution and sale of our products. 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. The acquisition or development of commercialization and associated regulatory compliance capabilities likely will require substantial financial and other resources and divert the attention of our management and key personnel, and, if not completed on time, could delay the launch of an approved product, and otherwise negatively impact our product development and commercialization efforts.

To the extent we establish marketing, distribution or sales arrangements with 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 patents and other intellectual property protection we obtain that cover 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;
- 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, both in the U.S. and in foreign countries.

The patent and intellectual property positions of biopharmaceutical companies, including ours, are uncertain and involve complex legal and factual questions. 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 challenged, invalidated, infringed or circumvented, including by our competitors, and rights we have under issued patents may not provide competitive advantages to us.

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.

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. There can be no assurance, however, that binding agreements will not be breached, that we will have adequate remedies for any breach, or that trade secrets or other proprietary information will not otherwise become known or be independently discovered by competitors. 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.

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 cost of litigation to uphold the validity and prevent infringement of our patents could be substantial. Furthermore, 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. We can provide no assurance that our 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 we are sued for infringing the proprietary rights of third parties, it will 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. 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, acute limb ischemia and other orphan indications we may pursue. Legislative action, such as the Food and Drug Administration Safety and Innovation Act, which was signed into law in 2012, 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. Some of our potential competitors in sickle cell disease 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 was expected to initiate a Phase 3 clinical study of GlycoMimetics' rivipansel compound in adult and pediatric patients with sickle cell disease experiencing vaso-occlusive crisis in 2014. The study has been delayed due to a manufacturing issue, but once it begins it likely will compete with EPIC for patients and may adversely affect enrollment in EPIC, which could delay completion of our study. In addition, Eli Lilly and Company is conducting a Phase 3 study of prasugrel in pediatric patients with sickle cell disease to assess whether it reduces the rate of vaso-occlusive crisis. 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.

With respect to competition for vepoloxamer for complications of arterial disease, although we intend first to develop vepoloxamer as an adjunct to thrombolytics, it could compete with current revascularization methods, including thrombolytics. In addition, we are aware of a number of potentially competitive investigational therapies for severe forms of thrombotic arterial disease, including angiogenic growth factors, vasoactive drugs, anticoagulants, thrombolytics, anti-platelet agents, cytoprotectives, and blood substitutes, some of which are in late-stage clinical development. Should any of these other investigational therapies receive regulatory approval prior to vepoloxamer, they may become entrenched in the standard of care, diminish the need for vepoloxamer, or be difficult to displace.

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.

Our ability to commercialize our products successfully 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 managed healthcare organizations. These third-party payors are increasingly challenging the prices charged for medical products and services and, if they do not consider our products to be cost-effective compared to other therapies, they may not cover them as a benefit under their plans or, if covered, the level of reimbursement may not be sufficient to allow us to sell our products on a profitable basis. Significant uncertainty exists as to the coverage and reimbursement status of newly approved drug products, including coding, coverage and

payment. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services 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 drugs have been a focus in this effort. Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. Even if reimbursement is provided, market acceptance of our products would 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. There have been federal and state proposals to subject the pricing of healthcare goods and services to government control and to make other changes to the U.S. healthcare system. 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. For example, we may determine to pursue development or other activities or grow our organization or product pipeline or at levels or on timelines that reduces our stockholders' equity 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 February 2014, we commenced a $30 million "at the market" offering program, or ATM program. As of December 31, 2014, we had raised gross proceeds of $15.3 million 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 up to an additional $82.4 million of our securities, subject to limitations if our public float is less than $75 million. In addition, we have outstanding warrants to purchase more than 79 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 another 50.1 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 4.1% of our outstanding common stock (based on shares outstanding as of March 20, 2015), 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. 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 159,458,376 shares of our common stock outstanding as of March 20, 2015, we would have voting control with respect to approximately 10.8% 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 since July 2009 to certain key executives 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 the respective executive's 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 those executives following an acquisition, it may be required to provide additional incentive to them, 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. 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 December 31, 2014, more than 224 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 five 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. During the first quarter of 2013, it traded under the symbol "ANX" on the same 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			
	2014		2013	
	High	Low	High	Low
First Quarter	$ 1.10	$ 0.45	$ 0.82	$ 0.56
Second Quarter	$ 0.73	$ 0.52	$ 0.76	$ 0.41
Third Quarter	$ 0.69	$ 0.53	$ 0.52	$ 0.40
Fourth Quarter	$ 0.60	$ 0.40	$ 0.55	$ 0.40

As of March 20, 2015, we had approximately 139 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 April 2011, we acquired SynthRx, Inc. through a merger transaction in exchange for shares of our common stock and rights to additional shares of our common stock contingent upon achievement of certain milestones. On June 4, 2013, pursuant to the terms of our merger agreement with SynthRx and as a result of the achievement of the first milestone under the merger agreement, we issued an aggregate of 250,000 shares of our common stock to the former stockholders of SynthRx on a pro rata basis based on each such stockholder's ownership percentage of SynthRx immediately prior to the effective time of the merger.

In February 2014, we acquired Aires Pharmaceuticals, Inc. through a merger transaction in exchange for shares of our common stock. Pursuant to the terms of the merger agreement, on February 28, 2014, we issued an aggregate of 1,049,706 shares of our common stock to former stockholders of Aires, and, following a six-month "holdback" period, we issued an aggregate of 4,053,996 additional shares of our common stock to former stockholders of Aires, 4,000,340 of which we issued on September 4, 2014 and 53,656 we issued on September 15, 2014.

The securities described above were offered and sold by us in reliance upon exemptions from the registration requirements of the Securities Act of 1933, as amended, or the Securities Act. Such securities were issued pursuant to Section 4(2) of the Securities Act, and/or Regulation D promulgated thereunder as transactions by an issuer not involving a public offering. The recipients of the securities represented their intention to acquire the securities for investment only and not with a view to or for sale in connection with any distribution thereof and appropriate legends were affixed to share certificates issued in these transactions. All recipients 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 less than $75 million, as of June 30, 2014, we are considered to be a "smaller reporting company." 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 clinical-stage, biopharmaceutical company developing novel therapies for serious or life-threatening diseases with significant unmet needs. 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 MST-188 (vepoloxamer) Injection, 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 currently are developing vepoloxamer for the treatment of sickle cell disease, arterial disease (in combination with thrombolytics), and heart failure. We also are developing AIR001, a sodium nitrite solution for intermittent inhalation via nebulizer. AIR001 has demonstrated positive hemodynamic effects in patients with pulmonary hypertension and we are developing it for the treatment of heart failure with preserved ejection fraction, or 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 $29.3 million and $21.5 million for the years ended December 31, 2014 and December 31, 2013, respectively. As of December 31, 2014, we had an accumulated deficit of $235.1 million. Our cash, cash equivalents and investment securities were $57.3 million as of December 31, 2014.

We continue to focus our resources primarily on the development of vepoloxamer. In May 2013, we began enrolling subjects in EPIC, a pivotal Phase 3 study of vepoloxamer in patients with sickle cell disease, and enrollment of that study is one of our top priorities. We also are enrolling patients with acute limb ischemia in a Phase 2 study of vepoloxamer in combination with recombinant tissue plasminogen activator (tPA) to evaluate whether vepoloxamer improves effectiveness of thrombolytic therapy. In addition, we are planning to initiate a Phase 2 study of vepoloxamer in patients with heart failure in the third quarter of 2015. Our vepoloxamer pipeline also includes preclinical development programs in thrombotic stroke and resuscitation following major trauma (i.e., restoration of circulating blood volume and pressure).

Our second product candidate, AIR001, is being tested in multiple institution-sponsored Phase 2a clinical studies in patients with HFpEF. 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 and it demonstrated positive hemodynamic effects and was well-tolerated. If data from the Phase 2a studies are positive, we expect to conduct a Phase 2b proof-of-concept study in HFpEF.

Acquisition of Aires Pharmaceuticals

On February 27, 2014, we completed the acquisition of Aires Pharmaceuticals, Inc., a privately-held corporation, in an all-stock transaction pursuant to 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 Pharmaceuticals, and a stockholders' representative, 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 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 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 is not related to 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 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 35% to 45% (excluding share-based compensation expense) in 2015 compared to 2014 primarily due to increased CRO, study site and patient costs associated with increased enrollment in the EPIC study and our Phase 2 study of vepoloxamer in acute limb ischemia, and initiation of a Phase 2 study of vepoloxamer in heart failure, as well as increases in research-related manufacturing expenses, primarily related to generating additional material for clinical trials and to support regulatory filings and conducting process development activities, and in nonclinical study expenses, primarily to support our vepoloxamer development programs.

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 market research functions, and professional and consulting fees for accounting, legal, investor relations, business development, market research, human resources and information technology services. Other SG&A expenses include facility lease and insurance costs.

We expect SG&A expenses to increase approximately 10% to 20% (excluding share-based compensation expense) in 2015 relative to 2014, primarily due to increased consulting fees related to commercial-readiness activities for vepoloxamer in sickle cell disease.

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 acquisitions of Aires and SynthRx. Transaction-related expenses for 2013 also include the changes in the fair value of the contingent liability related to our acquisition of SynthRx, which we remeasured as of the end of each quarter and as of the date the contingent arrangement was settled.

Interest and Other Income/(Expense). Interest and other income/(expense) includes interest income, interest expense, gains and losses from foreign currency exchanges, and other non-operating gains and losses.

Results of Operations – Comparison of 2014 and 2013

Revenue. We recognized no revenue for the years ended December 31, 2014 and 2013.

Operating Expenses. The following table illustrates the types of operating expenses we incurred in 2014 and 2013 and their respective percent of our total operating costs for those periods:

	Operating Expenses Years Ended	
	2014	2013
Research and development	66%	60%
Selling, general and administrative	33%	40%
Transaction-related expenses	1%	0%
Depreciation and amortization	0%	0%
Total operating expenses	100%	100%

R&D 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. 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 2013, our most significant R&D expenses were external costs associated with the EPIC study and our QT/QTc study of 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 2014 and 2013 (in thousands, except for percentages):

	Years Ended December 31,			
	2014	%	2013	%
External clinical study fees and expenses	$ 11,158	57%	$ 7,524	58%
External nonclinical study fees and expenses	4,451	23%	2,798	22%
Personnel costs	3,401	18%	2,409	19%
Share-based compensation expense	425	2%	171	1%
Total	$ 19,435	100%	$ 12,902	100%

R&D expenses increased by $6.5 million, or 50.6%, to $19.4 million for the year ended December 31, 2014, compared to $12.9 million for the year ended December 31, 2013. The increase in R&D expenses in 2014 compared to 2013 was due to a $3.6 million increase in external clinical study fees and expenses, a $1.6 million increase in external nonclinical study fees and expenses, a $1.0 million increase in personnel costs and a $0.3 million increase in share-based compensation expense.

The $3.6 million increase in external clinical study fees and expenses was related primarily to increases of 1) $3.3 million in EPIC study costs, 2) $1.1 million related to our Phase 2 study of vepoloxamer in ALI, and 3) $1.0 million related to the wind-down of the AIR001 studies in pulmonary arterial hypertension, all offset by a $1.8 million decrease due to lack of costs related to the thorough QT/QTc clinical study of vepoloxamer that was completed in 2013. The $1.6 million increase in external nonclinical study fees and expenses resulted primarily from a $1.2 million increase in research-related manufacturing costs for vepoloxamer and a $0.2 million increase for research-related manufacturing costs for AIR001. The $1.0 million increase in personnel costs resulted primarily from additional clinical and research-related manufacturing staff hired after the first half of 2013 and severance expenses related to the departure of our former chief medical officer.

Selling, General and Administrative Expenses. In 2014 and 2013, our SG&A expenses primarily consisted of employee salaries and benefits, consulting fees for investor relations, market strategy and research, human resources, facilities, internal systems support, business development and accounting services, and share-based compensation expense.

SG&A expenses increased by $1.0 million, or 11.4%, to $9.5 million for the year ended December 31, 2014, compared to $8.5 million for the year ended December 31, 2013. This increase resulted primarily from an increase in personnel costs and consulting expenses.

Transaction-Related Expenses. Transaction-related expenses were $0.3 million for the year ended December 31, 2014, compared to $0.1 million for the year ended December 31, 2013. We recognized transaction-related expenses for the year ended December 31, 2014 related to legal and accounting fees associated with the acquisition of Aires Pharmaceuticals in February 2014. We recognized transaction-related expenses for the year ended December 31, 2013 related to legal fees associated with the acquisition of Aires Pharmaceuticals in February 2014 and as a result of an increase in the fair value of the contingent liability related to the consideration for our acquisition of SynthRx at its settlement date, May 30, 2013, relative to December 31, 2012, which increase was due to the increase in our stock price at the settlement date ($0.71 per share) relative to December 31, 2012 ($0.57 per share).

Other Income/(Expense), Net. Other income (net) was $0.5 million for the year ended December 31, 2014 and was primarily attributable to $0.5 million of bargain purchase gain resulting from the acquisition of Aires Pharmaceuticals in February 2014.

Net Loss. Net loss was $28.7 million, or $0.23 per share (basic and diluted), for the year ended December 31, 2014, compared to a net loss of $21.5 million, or $0.28 per share (basic and diluted), for the year ended December 31, 2013.

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, 2014 and 2013, we incurred losses from operations of $29.3 million and $21.5 million, respectively. Our cash, cash equivalents and investment securities were $57.3 million at December 31, 2014.

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

In June 2013, we completed an underwritten public offering with gross proceeds of $28.1 million from the sale and issuance of units consisting of 56,195,000 shares of our common stock and warrants to purchase 28,097,500 shares of our common stock. Net proceeds, after deducting underwriting discounts and commissions and other offering expenses, were $25.7 million. The warrants have an exercise price of $0.65 per share and, subject to certain beneficial ownership limitations, are exercisable at any time on or before June 19, 2018.

We may receive up to $0.8 million, $6.6 million, $5.6 million, $11.7 million, $18.3 million, $0.1 million, and $16.5 million of additional net proceeds from the exercise of warrants issued in the registered direct equity financings we completed in October 2009, May 2010 and January 2011 and the underwritten public offerings we completed in November 2011, June 2013 and November 2014, 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 $3.67, $3.65, $2.75, $1.10, $0.65, $0.01, and $0.75 per share, respectively. In comparison, the closing sale price of our common stock on March 20, 2015 was $0.49 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 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" equity offering program, or ATM program, under which Cowen acts as sales agent. Since commencement of the ATM program more than 12 months ago, we have sold and issued an aggregate of 20,703,186 shares at a weighted-average sales price of $0.74 per share for aggregate gross proceeds of $15.3 million. After deducting sales agent commission and discounts, such proceeds totaled $14.9 million. During the fourth quarter of 2014, we utilized the ATM program only in October and we have not utilized the ATM program during the first quarter of 2015.

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,	
	2014	2013
Net cash (used in) provided by:		
Operating activities	$ (24,645)	$ (17,788)
Investing activities	$ 481	$ (4,766)
Financing activities	$ 34,291	$ 25,737
Net increase in cash and cash equivalents	$ 10,127	$ 3,181

Operating activities. Net cash used in operating activities was $24.6 million in 2014, compared to $17.8 million in 2013. The increase in cash used in operating activities in 2014 was due primarily to a higher net loss in 2014 as compared to 2013 ($7.2 million), which was attributable primarily to increases in cash used for R&D expenses related to our vepoloxamer development activities. Adjustments for non-cash charges included a decrease related to the gain on bargain purchase for the Aires acquisition ($0.5 million) and an increase in share-based compensation expense ($0.4 million). Net cash was also impacted favorably by a decrease in prepaid and other assets ($0.4 million).

Investing activities. Net cash provided by investing activities was $0.5 million in 2014, compared to net cash used in investing activities of $4.8 million in 2013. The difference was due primarily to $3.5 million in cash obtained in our acquisition of Aires and a decrease of $2.5 million in purchases of certificates of deposit, offset by a $0.6 million decrease in proceeds from maturities of certificates of deposits.

Financing activities. Net cash provided by financing activities was $34.3 million in 2014, compared to $25.7 million in 2013. The 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. The cash provided by financing activities in 2013 consisted of proceeds from the underwritten public offering of our equity securities completed in June 2013.

Management Outlook

We anticipate that our cash, cash equivalents and investment securities as of December 31, 2014 will be sufficient to fund our currently planned level of operations for at least the next 12 months. We expect our operating expenses for the year ending December 31, 2015 will be approximately $35 million to $38 million, excluding share-based compensation expense.

Our estimate of our 2015 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 and 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've based our forward-looking statements prove to be wrong. Factors that will affect our 2015 operating expenses and future capital requirements include, but are not limited to:

- 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;
- our ability to manage costs related to commercial manufacture of our products, should any of our product candidates obtain regulatory approval;
- the extent to which we increase our workforce, including in connection with establishing or acquiring sales and distribution capabilities;
- our ability to protect our intellectual property and 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 2013, we initiated the EPIC study and enrolling subjects in that study is one of our top priorities. We expect to enroll 388 subjects in the study from approximately 70 medical centers, including over 50 centers in the U.S. As of early January 2015, enrollment was more than one-third complete. Although predicting the rate of enrollment for any clinical study, including EPIC, is subject to a number of significant assumptions and the actual rate may differ materially, we expect to complete enrollment around the end of 2015 and announce top-line results in the first quarter of 2016. We estimate that external clinical study fees and expenses from January 2015 through completion of the EPIC study will be approximately $16 million.

In addition to enrolling subjects in EPIC, we are conducting other activities to evaluate vepoloxamer's potential in sickle cell disease. 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 using non-invasive methods and evaluate the relationship between tissue oxygenation and clinical outcomes, such as the duration of vaso-occlusive crisis. We are seeking data that will provide insight into the potential for vepoloxamer to reduce end-organ damage and improve long-term outcomes for individuals with sickle cell disease. We believe we may obtain that data from the EPIC sub-study, together with data from an earlier clinical study in which vepoloxamer significantly improved microvascular blood flow in patients with sickle cell disease and from nonclinical studies we have conducted, are conducting or are planning to conduct in parallel with the EPIC study. Further, we plan to initiate an open-label, multicenter extension study called EPIC-E in the first half of 2015 to expand our existing safety database regarding repeat exposure to vepoloxamer. The study will enroll patients who have completed the EPIC study and are hospitalized for subsequent vaso-occlusive crisis. The estimated external clinical study fees and expenses to conduct the sub-study and EPIC-E are included in the estimated cost of EPIC stated above.

We also are advancing our other vepoloxamer programs. In 2014, we initiated a Phase 2 study of vepoloxamer in combination with recombinant tPA. The study will enroll approximately 60 patients with acute lower limb ischemia (ALI) and compare treatment with vepoloxamer in combination with recombinant tPA against recombinant tPA alone. We estimate that enrollment of this Phase 2 study will complete in the second half of 2016. As noted above, predicting the rate of enrollment of a clinical study is necessarily subject to a number of significant assumptions and the actual rate may differ materially. We estimate that external clinical study fees and expenses from January 2015 through completion of this study will be approximately $5 million. If the Phase 2 study in ALI demonstrates that the combination of vepoloxamer and recombinant tPA results in more rapid thrombolysis than recombinant tPA alone, we believe it not only would progress development in ALI, but also support development of vepoloxamer in other manifestations of occlusive arterial disease, such as thrombotic stroke. Therefore, in parallel to the Phase 2 study in ALI, we have conducted and are planning to conduct nonclinical studies to evaluate vepoloxamer's potential in thrombotic stroke, including its ability to expand the therapeutic window for recombinant tPA after the onset of stroke symptoms.

We also are evaluating vepoloxamer's potential in heart failure, another area of significant unmet medical need. Encouraged by positive results from randomized, placebo-controlled, nonclinical proof-of-concept and repeat-treatment studies of vepoloxamer in a model of advanced heart failure, as well as recommendations from medical experts in heart failure, we are planning to initiate a Phase 2 study of vepoloxamer for the treatment of chronic heart failure in the third quarter of 2015. While we are still in the planning process, we expect the study will evaluate the safety and efficacy of a single administration of vepoloxamer, including its effect on markers of cardiac injury (troponin) and wall stress (NT-proBNP), as well as clinical outcomes, in approximately 150 patients with chronic heart failure. We expect to conduct the study on an outpatient basis at medical centers within and outside of the U.S. We estimate that external clinical study fees and expenses from January 2015 through completion of this study will be approximately $10 million, but that only approximately $1 million will be incurred in 2015.

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. We also are conducting and plan to conduct additional research-related manufacturing activities.

AIR001

Based on the positive hemodynamic effects observed in Phase 1 and Phase 2 studies of AIR001 in more than 120 healthy volunteers and patients with various forms of pulmonary hypertension and data showing AIR001 was well tolerated in those studies, we believe AIR001 may be uniquely suitable to address the serious unmet need of patients with heart failure with preserved ejection fraction (HFpEF). We are supporting multiple institution-sponsored Phase 2a studies of AIR001 in patients with HFpEF to better understand AIR001's potential in that patient population. Patient dosing in Phase 2a studies of AIR001 at Mayo Clinic and the University of Pittsburgh began in early 2015 and we expect a third Phase 2a study to begin later this year. We anticipate reporting preliminary data from one of these studies in the second half of 2015. We estimate that, from January 2015 through their respective completion, the combined external clinical study fees and expenses and external nonclinical study fees and expenses for these studies will be less than $1 million. If results are positive, we expect to conduct a Phase 2b proof-of-concept study of AIR001 in HFpEF.

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.

Although we anticipate that our cash, cash equivalents and investment securities will be sufficient to fund our operations for at least the next 12 months, we do not anticipate that such capital alone will be sufficient to fund our operations through the completion of development and commercialization of our product candidates. In addition, we may utilize our financial resources sooner than we currently expect if we incur unanticipated expenses or we pursue development or commercial-readiness activities for our product candidates at levels or on timelines other than currently planned or we expand our product pipeline through acquisition of new product candidates and/or technologies. For the foreseeable future, we plan to fund our operations through public or private equity and/or debt financings and through collaborations, including licensing arrangements. However, adequate additional capital may not be available to us in the future on acceptable terms, on a timely basis, or at all. Our failure to raise capital as and when needed would have a 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, 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, 2014. Based on that evaluation, our principal executive officer and principal financial officer have concluded that as of December 31, 2014 these disclosure controls and procedures were effective at the reasonable assurance level.

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, 2014 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

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, 2014 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, 2014.

This annual report does not include an attestation report of our independent registered public accounting firm regarding our internal control over financial reporting. Management's report on internal control over financial reporting was not subject to attestation by our independent registered public accounting firm pursuant to the rules of the SEC because we are neither an accelerated filer nor a larger accelerated filer.

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 2015 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, 2014 and 2013
- Consolidated Statements of Operations and Comprehensive Income/(Loss) for the years ended December 31, 2014 and 2013
- Consolidated Statements of Stockholders' Equity (Deficit) for the years ended December 31, 2014 and 2013
- Consolidated Statements of Cash Flows for the years ended December 31, 2014 and 2013
- 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 24, 2015

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 Brian M. Culley	Chief Executive Officer and Director (Principal Executive Officer)	March 24, 2015
/s/ Brandi L. Roberts Brandi L. Roberts	Chief Financial Officer and Senior Vice President (Principal Financial and Accounting Officer)	March 24, 2015
/s/ Jack Lief Jack Lief	Chair of the Board	March 24, 2015
/s/ Howard C. Dittrich Howard C. Dittrich	Director	March 24, 2015
/s/ David A. Ramsay David A. Ramsay	Director	March 24, 2015
/s/ Lewis J. Shuster Lewis J. Shuster	Director	March 24, 2015

Index to Consolidated Financial Statements

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, comprehensive loss, stockholders' equity and cash flows present fairly, in all material respects, the financial position of Mast Therapeutics, Inc. and its subsidiaries at December 31, 2014 and 2013, the results of their operations and their cash flows for each of the two years in the period ended December 31, 2014 in conformity with accounting principles generally accepted in the United States of America. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits. We conducted our audits of these statements in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

/s/ PricewaterhouseCoopers LLP

San Diego, California
March 24, 2015

Mast Therapeutics, Inc. and Subsidiaries
Consolidated Balance Sheets
(in thousands, except for share and par value data)

	December 31, 2014	December 31, 2013
Assets		
Current assets:		
Cash and cash equivalents	$ 35,808	$ 25,681
Investment securities	21,481	18,711
Prepaid expenses and other current assets	1,114	1,136
Total current assets	58,403	45,528
Property and equipment, net	188	106
In-process research and development	8,549	6,549
Goodwill	3,007	3,007
Other assets	353	60
Total assets	$ 70,500	$ 55,250
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 1,370	$ 964
Accrued liabilities	5,625	2,495
Accrued compensation and payroll taxes	1,443	1,374
Total current liabilities	8,438	4,833
Deferred income tax liability	3,404	2,609
Total liabilities	11,842	7,442
Commitments (Note 11)		
Stockholders' equity:		
Common stock, $0.001 par value; 500,000,000 shares authorized; 159,458,376 and 102,710,286 shares issued and outstanding at December 31, 2014 and 2013, respectively	159	103
Additional paid-in capital	293,655	254,155
Accumulated other comprehensive loss	(25)	(21)
Accumulated deficit	(235,131)	(206,429)
Total stockholders' equity	58,658	47,808
Total liabilities and stockholders' equity	$ 70,500	$ 55,250

See accompanying notes to consolidated financial statements.

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,	
	2014	**2013**
Revenues	$ —	$ —
Operating expenses:		
Research and development	19,435	12,902
Selling, general and administrative	9,488	8,518
Transaction-related expenses	271	79
Depreciation and amortization	85	40
Total operating expenses	29,279	21,539
Loss from operations	(29,279)	(21,539)
Interest income	69	60
Other income/(expense), net	508	(1)
Net loss	$ (28,702)	$ (21,480)
Net loss per share - basic and diluted	$ (0.23)	$ (0.28)
Weighted average shares outstanding - basic and diluted	122,409,183	76,585,752
Comprehensive Loss:		
Net loss	$ (28,702)	$ (21,480)
Other comprehensive losses	(4)	(19)
Comprehensive loss	$ (28,706)	$ (21,499)

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 capital	Accumulated other comprehensive loss	Accumulated deficit	Treasury stock, at cost	Total stockholders' equity
	Shares	Amount					
Balances at January 1, 2013	46,265,286	$ 48	$ 226,697	$ (2)	$ (184,949)	$ (1)	$ 41,793
Net loss	-	-	-	-	(21,480)	-	(21,480)
Sale of common stock, net of offering costs of $2,361	56,195,000	56	25,681	-	-	-	25,737
Elimination of treasury stock in connection with offering	-	(1)	-	-	-	1	-
Share-based compensation expense - employee options	-	-	1,600	-	-	-	1,600
Issuance of stock pursuant to achievement of milestone in SynthRx acquisition	250,000	0	0	-	-	-	-
Elimination of contingent liability	-	-	177	-	-	-	177
Other comprehensive loss	-	-	-	(19)	-	-	(19)
Balances at December 31, 2013	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

See accompanying notes to consolidated financial statements.

Mast Therapeutics, Inc. and Subsidiaries
Consolidated Statements of Cash Flows
(in thousands)

	Years ended December 31,	
	2014	2013
Cash flows from operating activities:		
Net loss	$ (28,702)	$ (21,480)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	85	40
Loss on change in fair value of contingent consideration	—	35
Gain on bargain purchase	(486)	—
Share-based compensation expense related to employee stock options	2,032	1,600
Changes in assets and liabilities, net of effect of acquisitions:		
Increase in prepaid expenses and other assets	(58)	(490)
Increase in accounts payable and accrued liabilities	2,484	2,507
Net cash used in operating activities	(24,645)	(17,788)
Cash flows from investing activities:		
Purchases of certificates of deposit	(19,435)	(21,967)
Proceeds from maturities of certificates of deposit	16,659	17,248
Purchases of property and equipment	(147)	(47)
Security deposit for new lease	(130)	—
Cash obtained through acquisition	3,534	—
Net cash provided by/(used in) investing activities	481	(4,766)
Cash flows from financing activities:		
Proceeds from sale of common stock	30,201	28,098
Proceeds from sale and exercise of warrants	6,148	—
Payments for offering costs	(2,058)	(2,361)
Net cash provided by financing activities	34,291	25,737
Effect of exchange rate changes on cash	—	(2)
Net increase in cash and cash equivalents	10,127	3,181
Cash and cash equivalents at beginning of period	25,681	22,500
Cash and cash equivalents at end of period	$ 35,808	$ 25,681

See accompanying notes to consolidated financial statements.

1. Description of Business

Mast Therapeutics, Inc., a Delaware corporation ("Mast Therapeutics," "we" or "our company"), is a biopharmaceutical company focused on developing 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 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 nebulizer, which we are developing for the treatment of heart failure with preserved ejection fraction (HFpEF).

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, SD Pharmaceuticals, Inc. ("SD Pharmaceuticals") and Aires. All intercompany accounts and transactions have been eliminated in consolidation. SynthRx, which became a wholly-owned subsidiary of Mast Therapeutics upon completion of the acquisition in 2011, was merged with and into Mast Therapeutics in December 2014.

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.

We previously were classified as a "development stage entity" under the Master Glossary of the Accounting Standards Codification and, as such, were required to present inception-to-date information in our statements of operations and income, stockholders' equity, and cash flows. In June 2014, the Financial Accounting Standards Board ("FASB") issued an accounting standards update that eliminates the concept of a development stage entity from United States generally accepted accounting principles ("U.S. GAAP") and removes the related incremental reporting requirements. See "Recent Accounting Pronouncements" below in this Note 2 for additional information on this new standard. We elected to early adopt the new standard. Accordingly, the financial statements contained in this report do not include inception-to-date information.

Use of Estimates

The preparation of financial statements in conformity with 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 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, 2014 and 2013, we had $16.6 million and $1.3 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/(expense), 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, 2014, $4.7 million, or approximately 22%, 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 income/(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 and 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, 2014, no impairment of goodwill or acquired IPR&D related to the SynthRx acquisition was identified.

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, 2014 and 2013 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 income/(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 income/(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, 2014 and 2013, 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,	
	2014	2013
Warrants	49,217,355	31,576,405
Options	11,760,113	5,742,168

Supplemental Cash Flow Information

	Years ended December 31, 2014	2013
	(in thousands)	
Supplemental disclosures of non-cash investing and financing activities:		
Issuance of common stock for acquisitions	3,270	0
Assumptions of liabilities in acquisitions	1,069	-
Unrealized loss on investment securities	4	19
Disposal of equipment in conjunction with settlement of a liability	-	100
Purchases of property and equipment in accounts payable	17	-
Offering costs included in accounts payable	36	-

Recent Accounting Pronouncements

In August 2014, the FASB issued Accounting Standards Update ("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.

In June 2014, the FASB issued ASU No. 2014-10, *Development Stage Entities (Topic 915), Elimination of Certain Financial Reporting Requirements, Including an Amendment to Variable Interest Entities Guidance in Topic 810, Consolidation* ("ASU 2014-10"). The amendments in ASU 2014-10 remove the definition of a development stage entity from the Master Glossary of the Accounting Standards Codification, thereby removing the financial reporting distinction between development stage entities and other reporting entities from U.S. GAAP. In addition, the amendments eliminate the requirements for development stage entities to: (a) present inception-to-date information in the statements of income, cash flows, and shareholder equity; (b) label the financial statements as those of a development stage entity; (c) disclose a description of the development stage activities in which the entity is engaged; and (d) disclose in the first year in which the entity is no longer a development stage entity that in prior years it had been in the development stage. The amendments also clarify that the guidance in ASC Topic 275, *Risks and Uncertainties*, is applicable to entities that have not commenced planned principal operations. For public business entities, the removal of the development stage entity reporting requirements in ASC Topic 915, *Development Stage Entities*, and the clarification to the risks and uncertainties disclosure requirements in ASC Topic 275 are effective for annual and interim reporting periods beginning after December 15, 2014. In addition, ASU 2014-10 changes the current guidance in ASC Topic 810, *Consolidation*, in that it eliminates the exception provided to development stage entities for determining whether an entity is a variable interest entity on the basis of the amount of investment equity that is at risk. For public business entities, the revised consolidation standards are effective for annual and interim reporting periods beginning after December 15, 2015. Early adoption of ASU 2014-10 is permitted and we elected to early adopt the provisions of ASU 2014-10 beginning with the interim reporting period ended June 30, 2014.

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.

Pro Forma Information

The following unaudited pro forma information presents our condensed consolidated results of operations as if the acquisition of Aires had occurred on January 1, 2013 (in thousands):

	Years ended December 31,	
	2014	2013
	Unaudited	
Revenues	$ —	$ 7,305
Loss from operations	$ (29,728)	$ (24,520)
Net loss applicable to common stock	$ (29,637)	$ (24,457)

The $7.3 million of revenues consists of amounts recognized by Aires during the year ended December 31, 2013 as a result of a payment by a third-party partner pursuant to a collaboration agreement. The agreement was terminated in the fourth quarter of 2013. Aires recognized no revenues in 2014.

The above unaudited pro forma information includes the following nonrecurring adjustments directly attributable to the acquisition (in thousands):

	Years ended December 31,	
	2014	2013
Transaction-related expenses	$ 1,364	$ (1,364)

Transaction-related expenses include $0.9 million of severance payments to former executive officers of Aires pursuant to employment agreements between such persons and Aires.

The above unaudited pro forma condensed consolidated financial information is presented for illustrative purposes only. It is not necessarily indicative of what the results of operations actually would have been had the acquisition been completed on the date indicated. In addition, it does not purport to project the future operating results of the combined entity.

The operations of Aires were consolidated with our operations as of the closing of the acquisition on February 27, 2014. Accordingly, Aires' total operating expenses of $1.8 million for the period from February 27 through December 31, 2014 were included in our condensed consolidated statements of operations and comprehensive income/(loss).

4. Goodwill and IPR&D

At December 31, 2014 and 2013, our goodwill and IPR&D consisted of the following (in thousands):

	December 31,	
	2014	2013
Goodwill	$ 3,007	$ 3,007
IPR&D		
Acquired IPR&D related to SynthRx acquisition	6,549	6,549
Acquired IPR&D related to Aires acquisition	2,000	-
Total goodwill and IPR&D	$ 11,556	$ 9,556

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 related to the SynthRx acquisition as of September 30, 2014 and we concluded that it is not more likely than not that the carrying value of our goodwill or our acquired IPR&D related to the SynthRx acquisition exceeds its fair value. Therefore, we concluded that no impairment charge is required. We will test acquired IPR&D related to the Aires acquisition as of February 27, 2015, which is the first anniversary of the date we completed the acquisition, and in between annual tests if we become aware of an event or change in circumstances that would indicate the carrying value may be impaired. We are not aware of an event or change in circumstances in our acquired IPR&D related to the Aires acquisition that would indicate the carrying value may be impaired.

5. Investment Securities

At December 31, 2014 and 2013, our investment securities were as follows (in thousands):

	December 31,	
	2014	2013
Fair value of investment securities	$ 21,481	$ 18,711
Cost basis of investment securities	21,506	18,730

	Years ended December 31,	
	2014	2013
Net unrealized losses on investment securities	25	19

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, 2014 and 2013 of our cash equivalents and investment securities are summarized in the following tables (in thousands):

		Fair Value Determined Under:		
	Total Fair Value	(Level 1)	(Level 2)	(Level 3)
At December 31, 2014:				
Cash equivalents	$ 16,626	$ 16,626	$ —	$ —
Investment securities	$ 21,481	$ —	$ 21,481	$ —
At December 31, 2013:				
Cash equivalents	$ 1,340	$ 1,340	$ —	$ —
Investment securities	$ 18,711	$ —	$ 18,711	$ —

7. Property and Equipment

Property and equipment at December 31, 2014 and 2013 were as follows (in thousands):

	Useful Lives	December 31, 2014	2013
Office furniture, computer and lab equipment	3 - 5 years	$ 416	$ 275
Computer software	3 years	58	58
Leasehold improvements	1 year	35	35
Equipment in progress	n/a	23	-
		532	368
Less: accumulated depreciation and amortization		(344)	(262)
Property and equipment, net		$ 188	$ 106

Equipment in progress represents expenses for lab equipment and leasehold improvements that had not gone into service as of December 31, 2014. These items are depreciated over their applicable useful lives once they are placed in service.

Depreciation and amortization expense was $85,000 and $40,000 for the years ended December 31, 2014 and 2013, respectively.

8. Accrued Liabilities

Accrued liabilities at December 31, 2014 and 2013 were as follows (in thousands):

	December 31, 2014	2013
Accrued R&D agreements and study expenses	$ 5,383	$ 2,274
Other accrued liabilities	242	221
Total accrued liabilities	$ 5,625	$ 2,495

9. 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, 2014, 159,458,376 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" equity offering program (the "ATM program"), under which Cowen acts as sales agent. As of December 31, 2014, we had sold and issued an aggregate of 20,703,186 shares at a weighted-average sales price of $0.74 per share under the ATM program for aggregate gross proceeds of $15.3 million and $14.6 million in net proceeds, after deducting sales agent commission and discounts and our other offering costs.

Underwritten Public Offering of Common Stock and Warrants

In June 2013, we completed an underwritten public offering of 56,195,000 shares of our common stock and warrants to purchase up to 28,097,500 additional shares of our common stock. Of the 56,195,000 shares of our common stock issued, 1,454,079 of such shares were issued from our treasury stock. These securities were offered and sold to the underwriters and the public in units with each unit consisting of one share of common stock and one warrant to purchase up to 0.5 of a share of common stock. The gross proceeds from this financing were $28.1 million and, after deducting underwriting discounts and commissions and other offering expenses, our net proceeds were $25.7 million. We may receive up to $18.3 million of additional proceeds from the exercise of the warrants issued in the financing. The exercise price of the warrants is $0.65 per share. Subject to certain beneficial ownership limitations, the warrants are exercisable at any time on or before June 19, 2018.

Warrants

At December 31, 2014, outstanding warrants to purchase shares of common stock are as follows:

Shares Underlying Outstanding Warrants		Exercise Price	Expiration Date
409,228	$	3.440	April 2015
1,062,500	$	1.000	April 2015
1,816,608	$	3.650	May 2015
2,046,139	$	2.750	January 2016
10,625,000	$	1.100	November 2016
28,097,400	$	0.650	June 2018
13,081,428	$	0.010	November 2019
22,011,265	$	0.750	November 2019
79,149,568			

10. Equity Incentive Plans

At December 31, 2014, our equity-based incentive plans consisted of the 2005 Equity Incentive Plan (the "2005 Plan"), the 2005 Employee Stock Purchase Plan (the "Purchase Plan") and the 2008 Omnibus Incentive Plan (the "Original 2008 Plan"), which has been amended, restated and renamed three times, first in June 2011 as the Amended and Restated 2008 Omnibus Incentive Plan, then in June 2013 as the 2013 Omnibus Incentive Plan and again in June 2014 as the 2014 Omnibus Incentive Plan (the "2014 Plan").

Our equity-based incentive plans, which are stockholder-approved, are 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. Following approval of the Original 2008 Plan by our stockholders in May 2008, no awards have been or will be granted under the 2005 Plan, and, 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.

During the years ended December 31, 2014 and 2013, 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 income/(loss) in those periods was as follows (in thousands):

	Years ended December 31,	
	2014	2013
Selling, general and administrative expense	$ 1,607	$ 1,429
Research and development expense	425	171
Share-based compensation expense	$ 2,032	$ 1,600

For the year ended December 31, 2014, we recognized a $0.1 million reduction in our research and development related share-based compensation expense as a result of the departure of our former chief medical officer in September 2014. Termination of the former officer's employment triggered accelerated vesting of a portion of his outstanding, unvested stock options that resulted in $0.3 million of additional share-based compensation expense, but this additional expense was more than offset by a $0.4 million reduction in share-based compensation expense that resulted from cancellation of the remaining, unvested portion of the former officer's outstanding stock options.

2014 Omnibus Incentive Plan

The 2014 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, 2014, the maximum aggregate number of shares of our common stock available for grant under the 2014 Plan was 10,388,691 shares. Shares of common stock that are subject to awards granted under the 2014 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 1.2 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 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 2014 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 1.2 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 2014 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 to an option or stock appreciation right, (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 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 2014 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 2014 Plan and will not reduce the number of shares of common stock available for issuance under the 2014 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 2014 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 2014 Plan allows for other vesting periods.

The following table summarizes our stock option activity for the year ended December 31, 2014:

	Shares Underlying Option Awards	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Years	Aggregate Intrinsic Value (in thousands)
Outstanding at January 1, 2014	7,304,828	$ 1.38		
Granted	7,475,095	$ 0.60		
Exercised	-	$ —		
Expired/cancelled/forfeited	(1,163,786)	$ 0.78		
Outstanding at December 31, 2014	13,616,137	$ 1.00	8.06	$ 374
Options exercisable at December 31, 2014	5,456,110	$ 1.58	6.71	$ 130
Vested and expected to vest at December 31, 2014	12,716,125	$ 1.03	7.98	$ 350

The weighted-average grant-date fair value of options granted during the years ended December 31, 2014 and 2013 was $0.50 and $0.41, respectively. As of December 31, 2014, there was approximately $3.3 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, 2014 and 2013 are as follows:

	Years ended December 31,	
	2014	2013
Risk-free interest rate	1.9 - 2.1%	1.0 - 2.0%
Dividend yield	0.0%	0.0%
Expected volatility	104 - 112%	113 - 132%
Expected term (in years)	5.4 - 6.2 years	5.3 - 6.1 years
Forfeiture rate (officers and directors)	9%	0%
Forfeiture rate (employees)	9%	10%

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. We updated the forfeiture rate for our officers and directors in 2014 to better reflect what we believe are reasonable assumptions for the future due to recent forfeitures.

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.

Employee Stock Purchase Plan

The Purchase Plan was approved by our stockholders in 2005; however, we have not implemented the Purchase Plan. The Purchase Plan, if implemented, allows all eligible employees to purchase shares of common stock at 85% of the lower of the fair market value on the first or the last day of each offering period. Employees may authorize us to withhold up to 15% of their compensation during any offering period, subject to certain limitations. As of December 31, 2014, a maximum of 306,945 shares of common stock would have been issuable under the Purchase Plan had it been in effect as of that date. This maximum number is subject to an annual automatic increase on January 1 of each year (whether or not we have implemented the Purchase Plan) equal to the lesser of (i) 1% of the number of outstanding shares of common stock on such day, (ii) 30,000 shares or (iii) such other amount as our board of directors may specify.

11. 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, will be 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.

We lease a copier and phone system under leases that expire in 2019.

Rent expense was approximately $334,000 and $288,000 during the years ended December 31, 2014 and 2013, respectively.

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

Year Ending December 31,	
2015	$ 374
2016	397
2017	496
2018	554
2019	565
Thereafter	237
Total	$ 2,623

12. 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, 2014 and 2013.

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, 2014 and 2013 are as follows:

	Years ended December 31,	
	2014	2013
	(in thousands)	
Income tax benefit at federal statutory rate	$ (9,758)	$ (7,303)
Orphan drug credit / R&D credit	(4,575)	(804)
Stock options	278	207
Other	(213)	37
Change in federal valuation allowance	14,268	7,863
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, 2014 and 2013 are as follows:

	Years ended December 31, 2014	2013
	(in thousands)	
Deferred tax assets:		
Accrued expenses	$ 592	$ 171
Stock options under ASC 718	2,240	1,750
Net operating loss carry forwards	20,583	12,994
Income tax credit carry forwards	8,109	1,078
Property and equipment	12	4
Intangibles	1,793	1,124
Other	33	20
Total deferred tax assets	33,362	17,141
Less: valuation allowance	(33,362)	(17,141)
Total deferred tax assets, net of valuation allowance	$ -	$ -
Deferred tax liabilities:		
Acquired intangibles	(3,404)	(2,609)
Total deferred tax assets/liabilities, net of valuation allowance	$ (3,404)	$ (2,609)

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, 2014, we had federal and California net operating loss carry forwards of $55.1 million and $31.2 million, respectively. These tax loss carry forwards begin to expire in 2031 if unused. As of December 31, 2014, we also had federal R&D/orphan drug and California R&D tax credit carry forwards of $7.7 million and $0.6 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, 2014, 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, 2014 and 2013.

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.

13. 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 $212,000 and $182,000 in employer matching contributions in 2014 and 2013, respectively.

14. 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 2014 and 2013.

15. Summary of Quarterly Financial Data (unaudited)

The following is a summary of the unaudited quarterly results of operations for the years ended December 31, 2014 and 2013 (in thousands, except per share data):

Quarterly statements of operations data

	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

	Quarters Ended			
2013 (unaudited)	**March 31**	**June 30**	**September 30**	**December 31**
Revenue	$ -	$ -	$ -	$ -
Loss from operations	(5,593)	(4,953)	(5,271)	(5,722)
Net loss	(5,581)	(4,941)	(5,254)	(5,705)
Net loss applicable to common stock	(5,581)	(4,941)	(5,254)	(5,705)
Basic and diluted net loss per share	$ (0.12)	$ (0.09)	$ (0.05)	$ (0.06)
Basic and diluted weighted average number of shares of common stock outstanding	46,265	53,750	102,710	102,710

16. Subsequent Events

Severance Expense

On February 28, 2015, the employment of our president and chief operating officer, Patrick L. Keran, terminated. Pursuant to a Retention and Severance Plan, effective as of July 21, 2009, in which Mr. Keran was a participant, if Mr. Keran delivers and does not revoke a general release of claims, he will receive a lump sum severance payment of approximately $0.4 million, less applicable withholdings, which is equal to 12 months of his base salary and the estimated cost of continuing his healthcare coverage and the coverage of his dependents for 12 months under the Consolidated Omnibus Budget Reconciliation Act of 1985, as amended. In addition, pursuant to the terms of Mr. Keran's stock option awards, an additional 25% of the shares underlying his outstanding, unvested stock options will vest and become exercisable as of the date of termination. Provided that Mr. Keran delivers to us and does not revoke a general release of claims, he may have until November 15, 2016 to exercise the vested portion of his outstanding stock options.

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
10.1	Form of Series A and B Common Stock Purchase Warrants issued on May 6, 2010 by the registrant to the purchasers of the registrant's 2.19446320054018% Series F Convertible Preferred Stock		Form 8-K	001-32157-10790486	05/03/10
10.2	Form of [Series A/B] Common Stock Purchase Warrant issued on January 11, 2011 by the registrant to the purchasers of the registrant's common stock and to Rodman & Renshaw, LLC		Form 8-K	001-32157-11515655	01/07/11
10.3	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
10.4	Form of Common Stock Purchase Warrant issued on November 16, 2011 to Rodman & Renshaw, LLC and its designees		Form 8-K	001-32157-111203681	11/14/11
10.5	Warrant Agent Agreement, dated June 14, 2013, between the registrant and American Stock Transfer & Trust Company, LLC, including the Form of Common Stock Purchase Warrant as Exhibit A		Form 8-K	001-32157-13917371	06/17/13
10.6	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
10.7	Form of Pre-Funded Warrant issued by the registrant on November 12, 2014		Form 8-K	001-32157-141202528	11/07/14
10.8	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

Exhibit No.	Description	Filed Herewith	Incorporated by Reference		
			Form	File/Film No.	Date Filed
10.9	Form of Warrant by the registrant on November 12, 2014		Form 8-K	001-32157-141202528	11/07/14
10.10	Sales Agreement, dated February 10, 2014, between the registrant and Cowen and Company, LLC		Form 8-K	001-32157-14586244	02/10/14
10.11†	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
10.12†	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
10.13	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
10.14†	License Agreement, dated March 25, 2009, among the registrant, SD Pharmaceuticals, Inc. and Shin Poong Pharmaceutical Co., Ltd.		Form 10-Q	001-32157-09829059	05/15/09
10.15†	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
10.16#	2005 Equity Incentive Plan		Form 10-K	001-32157-07697283	03/15/07
10.17#	Form of Stock Option Agreement under the 2005 Equity Incentive Plan		Form S-8	333-126551-05951362	07/13/05
10.18#	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
10.19#	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
10.20#	2008 Omnibus Incentive Plan		Form 8-K	001-32157-08874724	06/02/08
10.21#	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
10.22#	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
10.23#	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

Exhibit No.	Description	Filed Herewith	Incorporated by Reference		
			Form	File/Film No.	Date Filed
10.24#	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
10.25#	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
10.26#	Form of Incentive Stock Option Grant Agreement under the 2008 Omnibus Incentive Plan (for grant to Brian M. Culley in January 2010)		Form 8-K	001-32157-10547818	01/26/10
10.270#	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
10.28#	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
10.29#	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
10.30#	Amended and Restated 2008 Omnibus Incentive Plan		Form S-8	333-174940-11914946	06/16/11
10.31#	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
10.32#	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
10.33#	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
10.34#	Form of Incentive Stock Option Grant Agreement for grants to the registrant's Chief Medical Officer under the Amended and Restated 2008 Omnibus Incentive Plan		Form 10-Q	001-32157-121180752	11/05/12
10.35#	2013 Omnibus Incentive Plan		Form 8-K	001-32157-13927320	06/21/13
10.36#	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
10.37#	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
10.38#	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

Exhibit No.	Description	Filed Herewith	Incorporated by Reference		
			Form	File/Film No.	Date Filed
10.39#	Form of CMO Incentive Stock Option Grant Agreement (for grants to the registrant's chief medical officer) under the 2013 Omnibus Incentive Plan		Form 8-K	001-32157-13927320	06/21/13
10.40#	2014 Omnibus Incentive Plan		Form 8-K	001-32157-14933081	06/20/14
10.41#	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
10.42#	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
10.43#	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 2014 Omnibus Incentive Plan		Form 8-K	001-32157-14933081	06/20/14
10.44#	Form of CMO Incentive Stock Option Grant Agreement (for grants to the registrant's chief medical officer) under the 2013 Omnibus Incentive Plan		Form 8-K	001-32157-14933081	06/20/14
10.45#	Offer letter, dated November 15, 2004, to Brian M. Culley		Form 10-KSB	001-32157-05719975	03/31/05
10.46#	Offer letter, dated February 11, 2011, to Brandi L. Roberts		Form 8-K	001-32157-11704394	03/22/11
10.47#	Offer letter, dated March 28, 2011, to R. Martin Emanuele		Form 10-Q	001-32157-11823538	05/09/11
10.48#	Offer letter, dated July 21, 2011, to Gregory D. Gorgas		Form 10-K	001-32157-12677367	03/08/12
10.49#	Offer letter, dated July 20, 2012, to Santosh Vetticaden		Form 10-Q	001-32157-121180752	11/05/12
10.50#	Offer letter, dated September 29, 2014, to Edwin L. Parsley		Form 10-Q	001-32157-141186781	10/31/14
10.51#	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
10.52#	Change in Control Severance Plan, effective as of December 6, 2012		Form 8-K	001-32157-121250022	12/07/12
10.53#	2013 Executive Incentive Plan		Form 8-K	001-32157-13587943	02/08/13
10.54#	2014 Executive Incentive Plan		Form 8-K	001-32157-14933081	06/20/14
10.55#	Director Compensation Policy, adopted March 21, 2013		Form 10-Q	001-32157-13847400	05/15/13
10.56#	Director Compensation Policy, adopted December 11, 2014	X			
10.57	Form of Director and Officer Indemnification Agreement		Form 8-K	001-32157-061156993	10/23/06
10.58	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			

Exhibit No.	Description	Filed Herewith	Incorporated by Reference		
			Form	File/Film No.	Date Filed
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.

MAST THERAPEUTICS, INC.

DIRECTOR COMPENSATION POLICY
(adopted December 11, 2014)

Non-employee members of the board of directors (the "Board") of Mast Therapeutics, Inc. (the "Company") shall, beginning January 1, 2015, be eligible to receive cash and equity compensation as set forth in this Director Compensation Policy. The cash compensation described in this Director Compensation Policy shall be paid automatically and without further action of the Board or any committee of the Board, to each member of the Board who is not an employee of the Company or any parent or subsidiary of the Company (each, a "Non-Employee Director") who is eligible to receive such cash compensation, unless such Non-Employee Director declines the receipt of such cash compensation by written notice to the Company. The equity compensation described in this policy shall not be granted automatically but shall require action by the Board, or a duly authorized committee of the Board, approving the equity award pursuant to the terms and conditions set forth herein. This Director Compensation Policy shall remain in effect until it is revised or rescinded by further action of the Board. This Director Compensation Policy shall be administered and interpreted by the Board, in its sole and absolute discretion, and the Board retains full discretion to modify its terms or cancel it at any time.

1. Cash Compensation.

(a) Annual Retainers. Non-Employee Directors shall be eligible to receive annual cash retainers as set forth below, payable in equal quarterly installments and in arrears after the end of each fiscal quarter in which the service occurred. If a Non-Employee Director joins the Board or a committee of the Board or is appointed to serve as Chair of the Board (or Lead Independent Director) or chair of a committee of the Board effective as of a date other than the first day of a fiscal quarter, the applicable annual retainer(s) set forth below shall be pro-rated based on days served in the applicable fiscal year (based on a 365-day year), with the pro-rated amount paid for the fiscal quarter in which the Non-Employee Director began providing the service, and regular (full) quarterly payments thereafter. If a Non-Employee Director's service as a member of the Board, Chair of the Board (or Lead Independent Director), or chair of a committee of the Board ends on a date other than the last day of a fiscal quarter, the applicable annual retainer(s) set forth below will be pro-rated based on days served in the applicable fiscal year (based on a 365-day year), with the pro-rated amount paid for the fiscal quarter in which the Non-Employee Director's service ended.

(i) Annual Board Service Retainer: $35,000

(ii) Annual Board Chair Service Retainer: $25,000 (payable in addition to the Annual Board Service Retainer). If the Chair of the Board is not a Non-Employee Director, the Annual Board Chair Service Retainer shall be paid to the Non-Employee Director appointed to serve as Lead Independent Director.

(iii) Annual Committee Chair Service Retainer:

(A) Chair of the Audit Committee: $15,000

(B) Chair of the Compensation Committee: $10,000

(C) Chair of the Nominating and Governance Committee: $10,000

(iv) Annual Committee Service Retainer (payable only to non-chair members of the committee):

(A) Member of the Audit Committee: $7,500

(B) Member of the Compensation Committee: $5,000

(C) Member of the Nominating and Governance Committee: $5,000

(b) Meeting Stipend for Other Committee Service. Each Non-Employee Director appointed to serve on an *ad hoc* or special committee of the Board shall be eligible to receive a $1,000 stipend for each committee meeting attended (whether in person or by telephone, videoconference or other communication technology that allows remote participants to hear and be heard during the meeting), payable quarterly and in arrears after the end of each fiscal quarter. For clarity, the meeting stipend is not applicable to meetings of the Board's Audit Committee, Compensation Committee or Nominating and Governance Committee.

2. Equity Compensation.

(a) Definitions. For purposes of this Section 2, the following terms shall have the following meanings:

(i) "Current Allocation" shall mean the product of (A) 0.0396%, multiplied by (B) the number of shares of common stock issued and outstanding as of the applicable date. For clarity, (X) the applicable date for each newly elected/appointed director shall be the Appointment Date and (Y) the applicable date for each Annual Option shall be the date of the applicable annual meeting of stockholders.

(ii) "Make-Up Amount" shall mean the difference between (A) the Current Allocation as of the date of the current-year annual meeting of stockholders, minus (B) the Current Allocation applicable to the prior year's annual meeting of stockholders (or, for Non-Employee Directors who were not Non-Employee Directors at the time of the prior year's annual meeting of stockholders, the Current Allocation as of the date of such Non-Employee Director's Appointment Date (as defined in Section 2(c))).

(b) Omnibus Incentive Plan. Anything in this Director Compensation Policy to the contrary notwithstanding, the options described in this Director Compensation Policy shall be granted under and shall be subject to the terms and provisions of the Company's 2014 Omnibus Incentive Plan, as amended and/or restated from time to time (the "Incentive Plan"), and shall be granted subject to the execution and delivery of option agreements, including attached exhibits, if any, in substantially the same forms previously approved by the Board or a committee of the Board, setting forth the vesting schedule applicable to such options and such other terms as may be required by the Incentive Plan. In addition, the approval and granting of the options described below shall be subject to and contingent upon the Company's compliance with, or the waiver thereof, of any contractual obligations applicable to the Company's approval or granting of such options (all as determined by the Company in its sole and absolute discretion).

(c) New Non-Employee Directors. Each newly elected or appointed Non-Employee Director or member of the Board who becomes a Non-Employee Director(each, a "New Non-Employee Director") shall be eligible to receive, in connection with such New Non-Employee Director's election or appointment to the Board or change in status (the "Appointment Date"), the following:

(i) a non-qualified stock option (each, an "Inducement Option") to purchase such number of shares of common stock as is equal to the Current Allocation (subject to adjustment as provided in the Incentive Plan); and

(ii) provided the New Non-Employee Director was not initially elected at an annual meeting of stockholders and such New Non-Employee Director's Appointment Date is more than 30 days before the date of the next annual meeting of stockholders, a non-qualified stock option (each, a "Pro-Rated Annual Option") to purchase that number of shares of common stock as is equal to (A) x (B), where:

(A) = the quotient of (I) the Current Allocation, divided by (II) 12; subject to adjustment as provided in the Incentive Plan; and

(B) = The number of full 30-day periods between such New Non-Employee Director's Appointment Date and the date of the next annual meeting of stockholders (or, if, on the Appointment Date, the date of the next annual meeting of stockholders has not been set by the Board, the one-year anniversary of the prior year's annual meeting of stockholders) (such number of 30-day periods, the "Number of Months Until Meeting").

(d) Annual Options. In connection with each annual meeting of stockholders, each Non-Employee Director shall be eligible to receive a non-qualified stock option (each, an "Annual Option") to purchase such number of shares of common stock as is equal to the Current Allocation (subject to adjustment as provided in the Incentive Plan), plus, if applicable, the Make-Up Amount.

The "Make-Up Amount" shall be included in the Annual Option for a Non-Employee Director only if: (i) the Make-Up Amount with respect to such Non-Employee Director exceeds 20% of the Current Allocation as of the date of the current-year annual meeting of stockholders; (ii) the Company's market capitalization (shares outstanding multiplied by stock price) has not exceeded $100 million for a sustained period (e.g., 20 trading days), as determined unanimously by the Board; and (iii) the Board unanimously determines to include the Make-Up Amount in such Annual Option.

(e) Termination of Employment of Employee Directors. Members of the Board who are employees of the Company or any parent or subsidiary of the Company who subsequently terminate their employment with the Company and any parent or subsidiary of the Company and remain on the Board will, to the extent that they are otherwise eligible, be eligible to receive, after termination from employment with the Company and any parent or subsidiary of the Company, an Inducement Option, a Pro-Rated Annual Option and an Annual Option, all as described in this Section 2.

(f) Terms of Options Granted to Non-Employee Directors.

(i) Exercise Price. The per share exercise price of each option granted to a Non-Employee Director shall equal 100% of the Fair Market Value (as defined in the Incentive Plan) of a share of common stock on the date the option is granted.

(ii) Vesting.

(A) Each Inducement Option granted to a New Non-Employee Director shall become vested and exercisable in 36 substantially equal monthly installments of approximately 1/36th of the shares subject to such option on each monthly anniversary of the Appointment Date of such New Non-Employee Director, subject to such director's continuing Services (as defined in the Incentive Plan) through such dates.

(B) Each Pro-Rated Annual Option granted to a New Non-Employee Director shall become vested and exercisable in such number of substantially equal monthly installments (which number shall be equal to the Number of Months Until Meeting) of such fraction of the shares subject to such option (which fraction shall be equal to 1/the Number of Months Until Meeting) on each monthly anniversary of the Appointment Date of such New Non-Employee Director, subject to such director's continuing Services (as defined in the Incentive Plan) through such dates.

(C) Each Annual Option granted to a Non-Employee Director shall become vested and exercisable in 12 substantially equal monthly installments of approximately 1/12th of the shares subject to such option on each monthly anniversary of the date of the applicable annual meeting of stockholders, subject to such director's continuing Services (as defined in the Incentive Plan) through such dates.

(iii) Term. The term of each option granted to a Non-Employee Director shall be the shorter or (A) ten years from the date the option is granted (subject to a 30-day extension in accordance with the terms of the Incentive Plan in the event the exercise of the option is prohibited by applicable law or the Non-Employee Director cannot purchase or sell shares of the Company's common stock due to a "black-out period" under the Company's insider trading policy) and (B) three years from the date such Non-Employee Director ceases to provide Services (as defined in the Incentive Plan) for any reason other than such Non-Employee Director's death or disability.

Exhibit 21.1

Subsidiary	Jurisdiction of Incorporation
Aires Pharmaceuticals, Inc.	Delaware
SD Pharmaceuticals, Inc.	Delaware

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the registration statements of Mast Therapeutics, Inc. on Form S-8 (Nos. 333-126551, 333-151903, 333-174940, 333-190376 and 333-198046) and the registration statements on Form S-3 (Nos. 333-188870, 333-179989, 333-174203, 333-165691, 333-164177, 333-159376, 333-133824, 333-127857 and 333-117022) of our report dated March 24, 2015 relating to the financial statements, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP

San Diego, California
March 24, 2015

Exhibit 31.1

CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER PURSUANT TO SECURITIES EXCHANGE ACT RULES 13a-14(a) AND 15d-14(a) AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Brian M. Culley, certify that:

1. I have reviewed this Annual Report on Form 10-K of Mast Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

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

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

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

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

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

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

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

Date: March 24, 2015

/s/ Brian M. Culley
Brian M. Culley
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION OF PRINCIPAL FINANCIAL OFFICER PURSUANT TO SECURITIES EXCHANGE ACT RULES 13a-14(a) AND 15d-14(a) AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Brandi L. Roberts, certify that:

1. I have reviewed this Annual Report on Form 10-K of Mast Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

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

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

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

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

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

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

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

Date: March 24, 2015

/s/ Brandi L. Roberts
Brandi L. Roberts
Chief Financial Officer and Senior Vice President
(Principal Financial and Accounting Officer)

Exhibit 32.1

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

In connection with the Annual Report of Mast Therapeutics, Inc. (the "Company") on Form 10-K for the year ended December 31, 2014, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Brian M. Culley, principal executive officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

(i) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and

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

Date: March 24, 2015

/s/ Brian M. Culley
Brian M. Culley
Chief Executive Officer
(Principal Executive Officer)

In connection with the Annual Report of Mast Therapeutics, Inc. (the "Company") on Form 10-K for the year ended December 31, 2014, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Brandi L. Roberts, principal financial and accounting officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

(i) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and

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

Date: March 24, 2015

/s/ Brandi L. Roberts
Brandi L. Roberts
Chief Financial Officer and Senior Vice President
(Principal Financial and Accounting Officer)